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IRIS Toxicological Review of Inorganic Arsenic

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Integrated Risk Information System
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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
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

AUTHORS | CONTRIBUTORS | REVIEWERS

Assessment Managers (Lead Authors)

J. Allen Davis, M.S.	U.S. EPA/Office of Research and Development/Center for Public Health and Environmental Assessment
Janice S. Lee, Ph.D.	

Authors

Ingrid L. Druwe, Ph.D.	U.S. EPA/Office of Research and Development/Center for Public Health and Environmental Assessment
Jeff Gift, Ph.D.	
Ellen Kirrane, Ph.D.	
Alexandra Larsen, Ph.D.	
Tom Luben, Ph.D.	
Martha Powers, Ph.D.	
Rachel M. Shaffer, Ph.D.	

Contributors

Bevin E. Blake, Ph.D.	U.S. EPA/Office of Research and Development/Center for Public Health and Environmental Assessment
Ila Cote, Ph.D. (retired)	
Hisham El-Masri, Ph.D.	
Michele Taylor, Ph.D.	
David Thomas, Ph.D. (retired)	
Brittany Schulz	Oak Ridge Associated Universities
Andrew Rooney, Ph.D.	U.S. National Institute for Environmental Health Sciences

Production Team

Maureen Johnson	U.S. EPA/Office of Research and Development/Center for Public Health and Environmental Assessment
Ryan Jones	
Dahnish Shams	
Vicki Soto	
Jessica Soto Hernandez	
Samuel Thacker	
Garland Waleko	

Contractor Support

Robyn Blain, Ph.D.	ICF International
Audrey DeLucia	
Sorina Eftim, Ph.D.	
Susan Goldhaber	
Ali Goldstone	
Pamela Hartman	
Cara Henning, Ph.D.	
Kevin Hobbie	
Michelle Mendez	
William Mendez, Jr., Ph.D.	
Nicole Vetter	
Bruce Allen	Allen Consulting LLC

Executive Direction	
Wayne Cascio	CPHEA Center Director
V. Kay Holt	CPHEA Deputy Center Director
Samantha Jones	CPHEA Associate Director
Andrew Kraft	CPHEA/CPAD Associate Division Director
Viktor Morozov	CPHEA/CPAD/Quantitative Assessment Branch Chief
Kathleen Newhouse	CPHEA/CPAD/ActingToxic Effects Assessment (DC) Branch
Elizabeth Radke	Chief
Kristina Thayer	CPHEA/CPAD/Science Assessment Methods Branch Chief
Paul White	CPHEA/CPAD Division Director
	CPHEA/CPAD Senior Science Advisor
Internal Review Team	
General Toxicology Workgroup	U.S. EPA/Office of Research and Development/ Center for
Inhalation Workgroup	Public Health and Environmental Assessment
Neurotoxicity Workgroup	
Pharmacokinetics Workgroup	
Reproductive and Developmental	
Toxicology Workgroup	
Statistical Workgroup	
Toxicity Pathways Workgroup	
Executive Review Committee	

Reviewers

Agency Reviewers

This assessment was provided for review to scientists in EPA's program and regional offices. Comments were submitted by:

Office of the Administrator/Office of Children's Health Protection
Office of Air and Radiation/Office of Air Quality Planning and Standards
Office of Chemical Safety and Pollution Prevention/Office of Pollution Prevention and Toxics
Office of Land and Emergency Management
Office of Water
Region 2, New York City, NY
Region 3, Philadelphia, PA
Region 4, Atlanta, GA
Region 8, Denver, CO
Region 10, Seattle, WA

Interagency Reviewers

This assessment was provided for review to other federal agencies and the Executive Office of the President (EOP). Comments were submitted by:

The White House

- Office of Science and Technology Policy
- Office of Management and Budget

Department of Defense

Department of Health and Human Services

- National Institute of Environmental Health Sciences
- National Institute of Occupational Safety and Health
- National Library of Medicine

Office of Homeland Security

U.S. Department of Agriculture

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, semi-conductors, 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); (WHO, 2011b); (WHO, 2011a); (ATSDR, 2007); (IARC, 2012); (FDA, 2005); (U.S. EPA, 2002a); (IARC, 2004a); (IARC, 2012); (NTP, 2016).

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, pregnancy and birth 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).

Based on 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 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 diabetes mellitus (Type 1 and Type 2 diabetes). 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 pregnancy and birth outcomes and neurodevelopmental effects, and the currently available **evidence indicates** that inorganic arsenic likely causes pregnancy and birth outcomes and neurodevelopmental effects in humans given sufficient exposure conditions. For pregnancy and birth 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 pregnancy and birth outcomes but given limitations in the ability to derive a quantitative estimate (described in Section 4.5), no RfD was derived for neurodevelopmental effects. Table ES-1 summarizes the organ/system-specific RfDs derived for the health outcomes.

ES.2 TOXICITY VALUES FOR CANCER AND NONCANCER EFFECTS

The risk estimates from EPA's multiple study Bayesian meta-regression analyses of bladder cancer, lung cancer, diseases of the circulatory system (CVD and IHD), and diabetes represent predicted extra risk above a zero dose. To estimate the risk at zero dose, U.S. lifetime background risks reported in CDC lifetables 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).[1] As discussed in the Section 4.3 Bayesian meta-regression summaries, sensitivity analyses indicate that inhalation exposures would not have a significant impact on extra risk estimates. Therefore, risk estimates for oral exposures are calculated assuming zero inhalation exposure. The bladder cancer, lung cancer, DCS, and diabetes meta-regression analyses include studies with total iAs intake and iAs drinking water exposure levels in the range of U.S. levels, predominantly < 1 μg/kg-day to 100 μg/L.

Lifetime extra risks of 7.9 and 24 were estimated for bladder cancer and lung cancer, respectively, for a hypothetical U.S. cohort of 10,000 individuals[2] 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-1 represent estimates of the 95% upper bound on the lifetime extra

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

[2]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).

risk associated with a daily 1 µg/kg dose. These CSF values can be multiplied by other estimates of lifetime daily µg/kg-day dose to estimate the 95% upper bound on lifetime extra risk for the endpoint in question. As noted in Table ES-1 (footnote b), these cancer slope factors are estimated from the risk estimates in the low dose region (corresponding to <0.22 µg/kg-day for bladder and lung cancer), which displays an approximately linear dose-response relationship. Above that dose level, the relationship becomes non-linear and risk estimates should not be obtained using the CSF. Instead, at higher doses, the polynomial equations in Figure 4-7 and Figure 4-9 should be used. A combined cancer slope factor of 5.3×10^{-2} $(\mu g/kg\text{-}day)^{-1}$ was also estimated according the the method described in footnote c of Table ES-1.

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

Health Outcome	Hazard Descriptor	Cancer Slope factor (CSF) 1/(µg/kg-d) [a, b]
Bladder cancer	Accepted hazard	1.3E-2
Lung cancer		4.6E-2
Combined cancer risk		5.3E-2[c]

[a]Estimate of the 95% upper bound lifetime extra risk per daily µg/kg 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 from diet, 0.0165 µg/kg from water and 0 µg/kg from air (see Section 4.3.4).

[b]EPA estimates of lifetime extra risk per µg/kg-day dose above background are nonlinear above 0.22 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 figures.

[c]Calculated as described in the Toxicological Review of Chloroprene (U.S. EPA, 2010) using 95% UCL and MLE linear slope estimates shown in Figure 4-7 (bladder cancer) and Figure 4-9 (lung cancer). The combined CSF is the sum of MLE slopes + 1.645*composite SD. The composite SD is the square root of the sum of the SD2 values (SQRT (((0.0127-0.0061)/1.645))^2+((0.0462-0.0186)/1.645))^2) = 0.0175. Thus, the combined CSF is (0.0186+0.0061) + 1.645*0.01725 = 5.31E-2.

Lifetime extra risks of 208, 178 and 179 were estimated for CVD incidence, IHD incidence and diabetes, respectively, for a hypothetical U.S. cohort of 10,000 individuals (see footnote 2 above) exposed for a lifetime at the U.S. drinking water standard of 10 µg/L. Possible explanations for the CVD and IHD observations are a high U.S. prevalence of strong DCS risk factors such as high cholesterol, high blood pressure, diabetes, and a low prevalence (relative to high exposure populations) of mutations or polymorphisms that can reduce DCS risk by affecting arsenic methylation efficiency (see Section 3.3).

For non-cancer effects, candidate toxicity values of 0.031 µg/kg-day, 0.047 µg/kg-day, and 0.047 µg/kg-day were estimated for CVD incidence, IHD incidence and diabetes, respectively, using the Bayesian meta-regression approach described in Sections 4.3.7 and 4.3.8 (see Table ES-2). For pregnancy and birth outcomes (decreased birth weight) a candidate toxicity value of 0.077 µg/kg-day was estimated using the methods described in Section 4.4. Overall, an RfD of **0.031 µg/kg-day**

based on increased CVD incidence in humans was selected. Confidence in the RfD is *high*, based on *high* confidence in the DCS organ/system-specific RfD. The DCS organ/system-specific RfD is based on the lowest POD_{HED} using a meta-regression approach that included *medium-high* confidence studies. The DCS organ/system-specific RfD is expected to be protective across all life stages.

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

Health Outcome	Hazard Descriptor	$BMDL_{05}$ (µg/kg-d)	UFc	RfD (µg/kg-d)	Confidence in RfD
CVD Incidence	Evidence demonstrates	0.094[a]	3	0.031	*High*
IHD Incidence		0.0140[a]	3	0.047	*High*
Diabetes		0.140[a]	3	0.047	*High*
Pregnancy and birth outcomes	Evidence indicates (likely)	0.210[b]	3	0.077	*Medium-low*
Overall RfD	--	--	--	**0.031**	*High*

[a]BMDL estimated using the 95th upper bound of the meta-regression logistic slope.

[b]The pregnancy and birth outcome POD is a BMDL (the 17.3 µg/L BMDL05 reported in Section 4.4 was converted to a µg/kg-day total dose by multiplying by 0.012 L/kg-day (median water consumption rate for pregnant women) and adding a 0.02 µg/kg-day U.S. median dietary background dose).

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 the NASEM (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).

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 non-metal (IARC, 2009). Arsenic can exist in 4 oxidation states: -3, 0, +3, or +5. Because of its reactivity, elemental arsenic (oxidation state 0) is rarely found in the environment (ATSDR, 2007); (U.S. EPA, 2006). Instead, arsenic is often found combined with other elements 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 (ATSDR, 2007); (U.S. EPA, 2006); (OEHHA, 1996). 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 et al., 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, gray 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/cm3)	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); (ATSDR, 2007); (Health Canada, 2006). Natural sources of inorganic arsenic result in naturally occurring, or "background," levels of inorganic arsenic in soil. Natural sources can also contribute to inorganic arsenic in water, particularly groundwater from wells in arsenic-rich geological formations. Volcanic activity releases, volatilization, and dusts are some natural sources of inorganic arsenic released in the atmosphere. It is estimated that approximately one-third of atmospheric inorganic arsenic comes from natural sources.

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 refuses 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 (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) (ATSDR, 2000)(USGS, 2014) . The average arsenic content in drinking water in the United States (U.S.) is 2 µg/L with 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 (ATSDR, 2007) (USGS, 2014). 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). Inorganic arsenic has also been found in fruit juices and the FDA currently recommends an "action level" of 10 ppb for inorganic arsenic in apple juice (FDA, 2013). 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 placenta (Concha et al., 1998); (Hall et al., 2007). With advancing gestation, the efficiency of maternal arsenic methylation increases resulting in lower exposure of the fetus to inorganic arsenic and MMA (Concha et al., 1998); (Li et al., 2008); (Gardner et al., 2011). The transfer of arsenic into breast milk is limited and breastfeeding, which results in efficient methylation of arsenic, protects the infants from arsenic exposure (Concha et al., 1998); (Fängström et al., 2008).

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

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

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 (ATSDR, 2007)(USGS, 2014).

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 $\mu g/m^3$. Smokers can reach up to 10 μg/day of arsenic exposure (IARC, 2009); (ATSDR, 2007). Inhalation is the principal route of exposure in occupational exposure settings. Industries with potential inorganic arsenic exposure include smelting, coal-fired power plants, pressure-treated wood, glass manufacturing, and electronics industry. It is likely that ingestion and dermal exposure occurs simultaneously in certain occupational settings (IARC, 2009). Since oral exposure is the primary route of exposure for the general population, inhalation exposure to inorganic arsenic was not evaluated further. 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.

It Is recognized that dermal exposure is a potential route of exposure for inorganic arsenic, but it is 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, the fact that it is a minimal exposure compared to 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. Hence, dermal exposure to inorganic arsenic was not evaluated further.

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 (Lynch et al., 2017a); (Lynch et al., 2017b); (Vahter, 1994); (Vahter and Norin, 1980). 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 (NRC, 2013) and NASEM (NASEM, 2019), and consistent with assessments by others (ATSDR, 2007); (EFSA, 2009);(TCEQ, 2017).

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 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 particular, relevant health outcomes (bladder cancer, lung cancer, DCS, diabetes, pregnancy and birth outcomes, and neurodevelopmental effects [see Section 3.2 for more details on the focus of these health outcomes), which was supported by a 2019 NASEM review of the iAs protocol (NASEM, 2019). The literature search was first conducted in 2012 and regular updates were performed. 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).
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/kg-d. 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 pf 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, etc.).
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, pregnancy and birth 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).

[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.

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 6 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-16 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 meta-regression dose-response approach [see the iAs Protocol (link provided in Appendix A), Section 5.2.2]. EPA characterized the strength of the evidence base to be *moderate* for pregnancy and birth 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 pregnancy and birth outcomes and neurodevelopmental effects.

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 1-1. Epidemiologic studies containing exposure- 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)[5] with arsenic-specific clarifications as needed (see Protocol (link provided in Appendix A),). An overall study determination was based on these domain level judgments. Risk of bias was assessed for each study question using a rating system with four categories as follows: 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). Some of the key arsenic-specific evaluation considerations are described here.

[5]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).

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 to 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).

In addition to temporality, 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, 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. Due to 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.

With regard to exposure measurement methods, 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 iAs concentration 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, the distribution of arsenic metabolites in urine ranges from 10-30% inorganic arsenic, 10-20% monomethylarsonic acid (MMA) and 60-80% dimethylarsinic acid (DMA) (Vahter and Concha, 2001). Seafood, the main source of organic arsenic compounds including arsenobetaine, a non-toxic arsenical, can also contribute to total urinary arsenic. While hair and nail biomarkers may give an indication of past exposure due to their slow growth, there may also be concerns with external contamination (NRC, 1999). With all methods to assess exposure, there may be non-differential 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 (Cohen et al., 2006; NRC, 1999). 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. Studies with creatinine corrected urinary intake biomarker data were preferred, as urine creatinine is one practical approach to correct arsenic concentrations for urine dilution as compared to 24-h or 12-h urine samples (Hsieh et al., 2019).

Once all evaluation domains were evaluated, the identified strengths and limitations were collectively considered by the reviewers to reach a final study confidence classification:

- *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.

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.

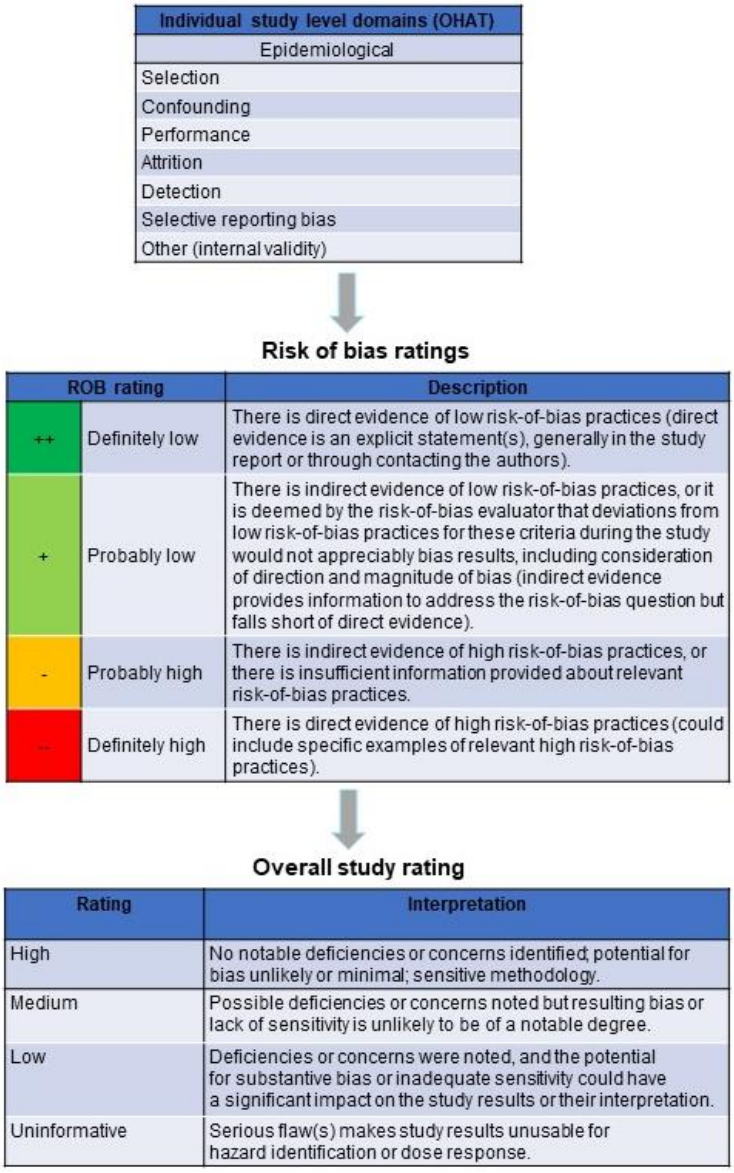


Figure 1-1. Study evaluation overview of epidemiological studies.

1.6.3. Data Extraction

The detailed data extraction approach is provided in the iAs Protocol (link provided in Appendix A), Section 3.10. 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: studies evaluated as being overall *uninformative* were not considered further and therefore did not undergo data extraction. All findings are considered for extraction, regardless of the statistical significance of their findings. 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.

1.6.4. Evidence Synthesis of Epidemiological Evidence

As indicated in the updated problem formulation and protocol (link provided in Appendix A), skin, bladder, and lung cancer and skin lesions are acknowledged as known hazard outcomes for inorganic arsenic (ATSDR, 2007); (Health Canada, 2006); (IARC, 2004b);(IARC, 2012);(NRC, 2013) and were considered to have *robust* human evidence. Skin cancer and skin lesions were not considered for further dose-response analyses based on initial screening analyses (see Section 5.1 of the protocol, link provided in Appendix A). EPA already recognizes arsenic as a known human carcinogen (U.S. EPA, 1995). New evidence synthesis conclusions were developed for diseases of the circulatory system, pregnancy and birth outcomes, neurodevelopmental effects, and diabetes

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);(U.S. EPA, 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 (Hobbie et al., 2020); (Mendez et al., 2020); (Allen et al., 2020a); (Allen et al., 2020b). The dose-response methods used are consistent with 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 (NASEM, 2021); (NASEM, 2019); (NRC, 2014);(NRC, 2013);(NRC, 2011);(NRC, 2009);(NRC, 2001).

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 meta-regression 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). Based on the screening analysis results, more complex Bayesian meta-regression (Allen et al., 2020a);(Allen et al., 2020b) dose-response analyses 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)[6]. Additionally, pregnancy and birth 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 pregnancy and birth outcomes and neurodevelopmental, neurocognitive effects were not amenable to the Bayesian meta-regression approach, they contained dose-response data that could be evaluated by other methods.

The meta-regression approach used in this assessment involves the application of a flexible, nonlinear, logistic model to derive upper-bound U.S. population-specific extra risk estimates with confidence intervals that reflect the uncertainty in the logistic 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 approximates 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 extra risk at any dose, the lifetable approach can be applied using the dose of interest.[7]

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 meta-regression analyses 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 meta-regressions. In this assessment, EPA's meta-regressions estimate a health outcome-specific average (logistic model) slope for that relationship across studies, then uses it to predict 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 meta-regression analysis and assuming that U.S. lifetime background risks are associated with EPA's U.S. background dose

[6] 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.

[7]EPA has provided the endpoint-specific lifetables as supplemental materials so that these calculations can be performed.

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 multiple DCS outcomes (CVD incidence and IHD incidence), diabetes, and pregnancy and birth outcomes. 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]Based on 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. 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, pregnancy and birth 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.

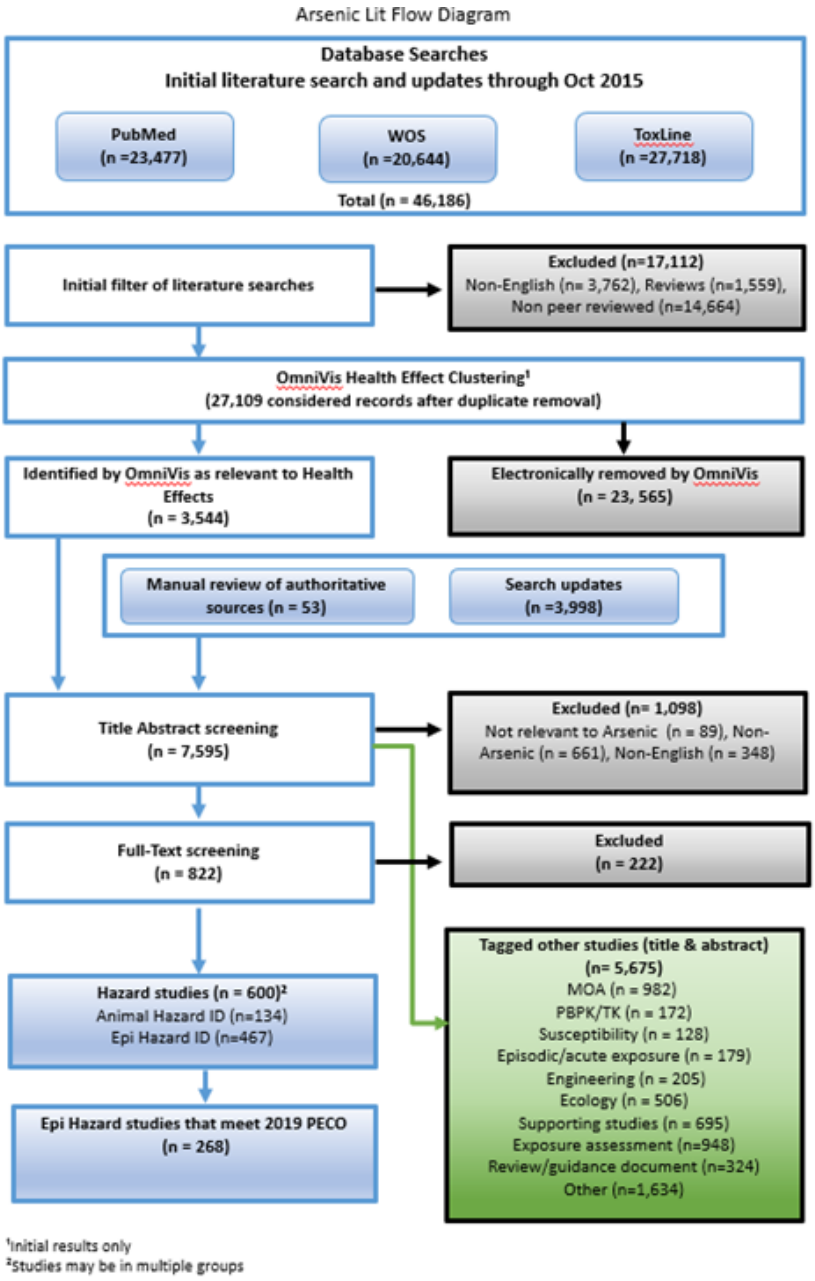


Figure 2-1. Literature search and screening flow diagram for inorganic arsenic (initial database search and updates through 2015).

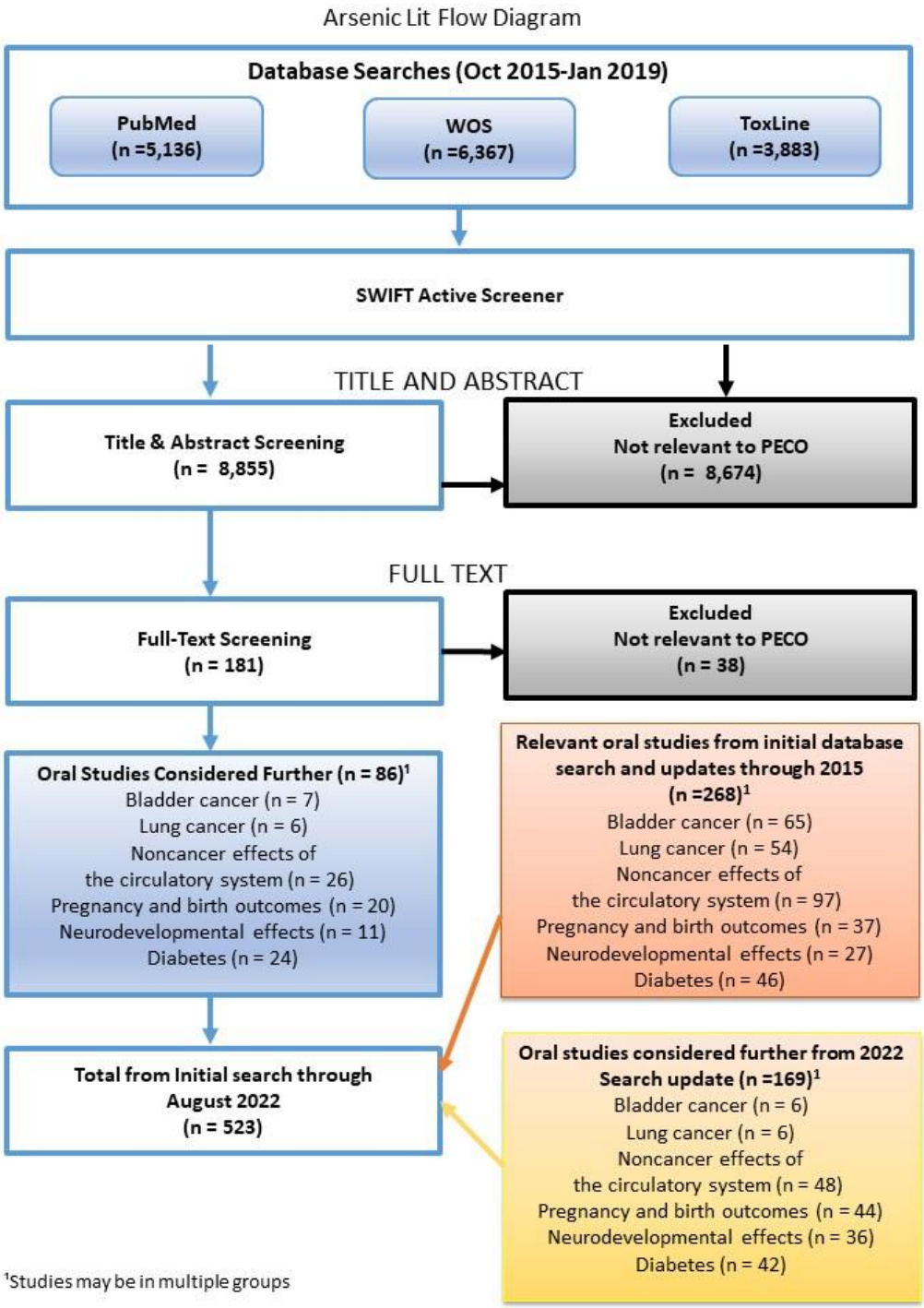


Figure 2-2. Literature search and screening flow diagram for inorganic arsenic (October 2015 to January 2019; 2022 search update).

3. PHARMACOKINETICS AND EVIDENCE SYNTHESIS

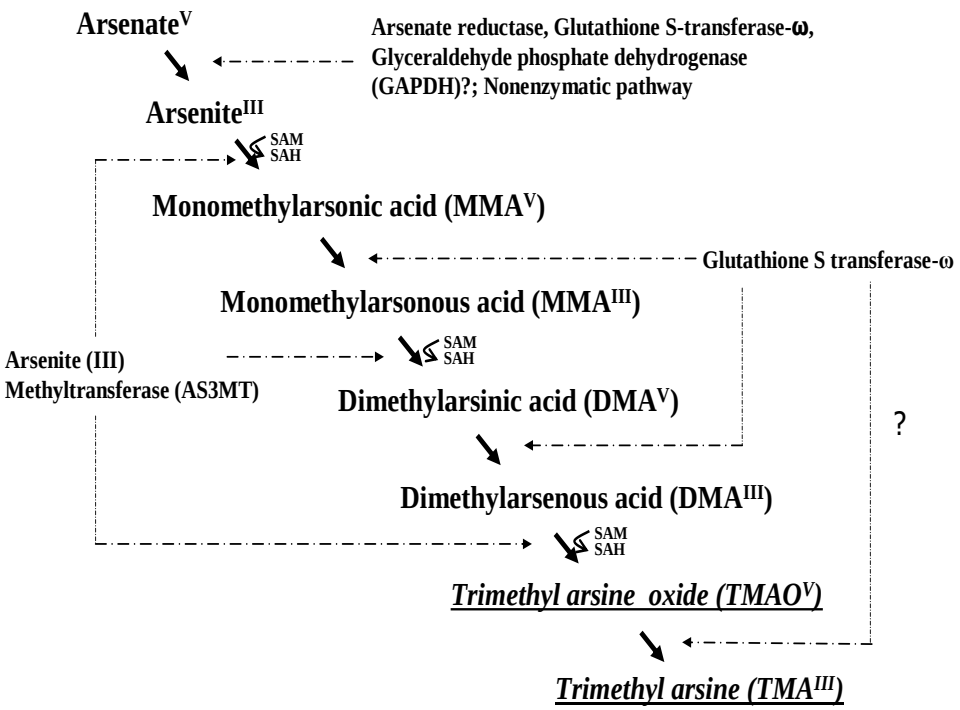
3.1. PHARMACOKINETICS

The behavior of arsenic in the body is complex. After absorption, inorganic arsenic undergoes a complicated series of enzymatic and non-enzymatic 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, 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 (Engström et al., 2013; Pierce et al., 2012; Wood et al., 2006).

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.



Source: Sams et al. (2007)

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

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 by Mann et al. (1996a); (Mann et al., 1996b), (Yu, 1999), (Gentry et al., 2004); (Gentry et al., 2005); (Kenyon et al., 2008) and (El-Masri and Kenyon, 2008); (El-Masri et al., 2018b); (El-Masri et al., 2018a). 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., 2018b); (El-Masri et al., 2018a) (see Figure 3-2, Bangladesh data shown).

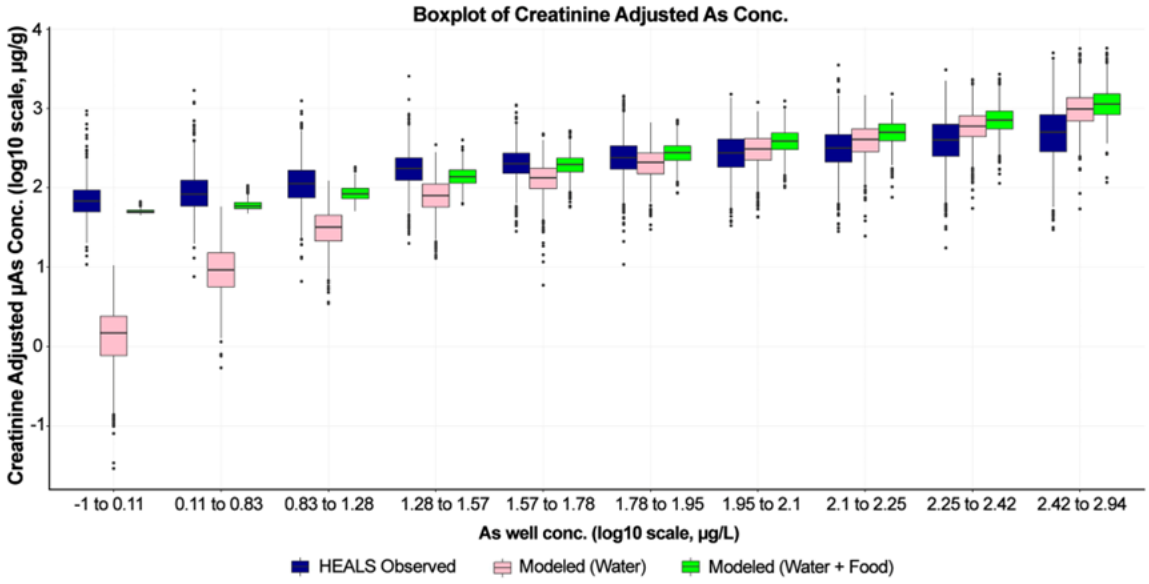


Figure 3-2. El-Masri-Kenyon PBPK model calibration against measured iAs total urinary concentrations and drinking water concentrations.

3.2. EVIDENCE SYNTHESIS

This assessment focuses on cancer and noncancer outcomes including bladder cancer, lung cancer, DCS, pregnancy and birth outcomes, neurodevelopmental effects, and diabetes. The prioritization of these health outcomes was based on prior feedback from (NRC, 2014); (NRC, 2013); (NRC, 2009); (NASEM, 2019) and availability of evidence. Because bladder cancer and lung cancer are accepted hazards of inorganic arsenic exposure (NTP, 2016);(ATSDR, 2007);(ATSDR, 2016);(IARC, 2004b);(IARC, 2012);(WHO, 2011b);(WHO, 2011a);(Lynch et al., 2017b);(Lynch et al., 2017a), 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, pregnancy and birth outcomes, neurodevelopmental effects, and diabetes.

Noncancer

3.2.1. Diseases of the Circulatory System

Database Overview

In 2013, the NRC concluded that low-to-moderate 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. Based 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 available evidence demonstrating a conclusion that exposure to iAs causes diseases of the circulatory system.

There are 171 epidemiological publications that examined the relationship between iAs exposures and diseases of the circulatory system (see Figure 3-3). One hundred and twenty three of these publications underwent study evaluation; 94 of the 123 studies were considered *medium* or *high* confidence and the remaining 29 were considered *low* or *uninformative*. Forty eight studies were identified in the 2022 search update and were considered further for dose-response but were not factored into the qualitative considerations and synthesis (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.

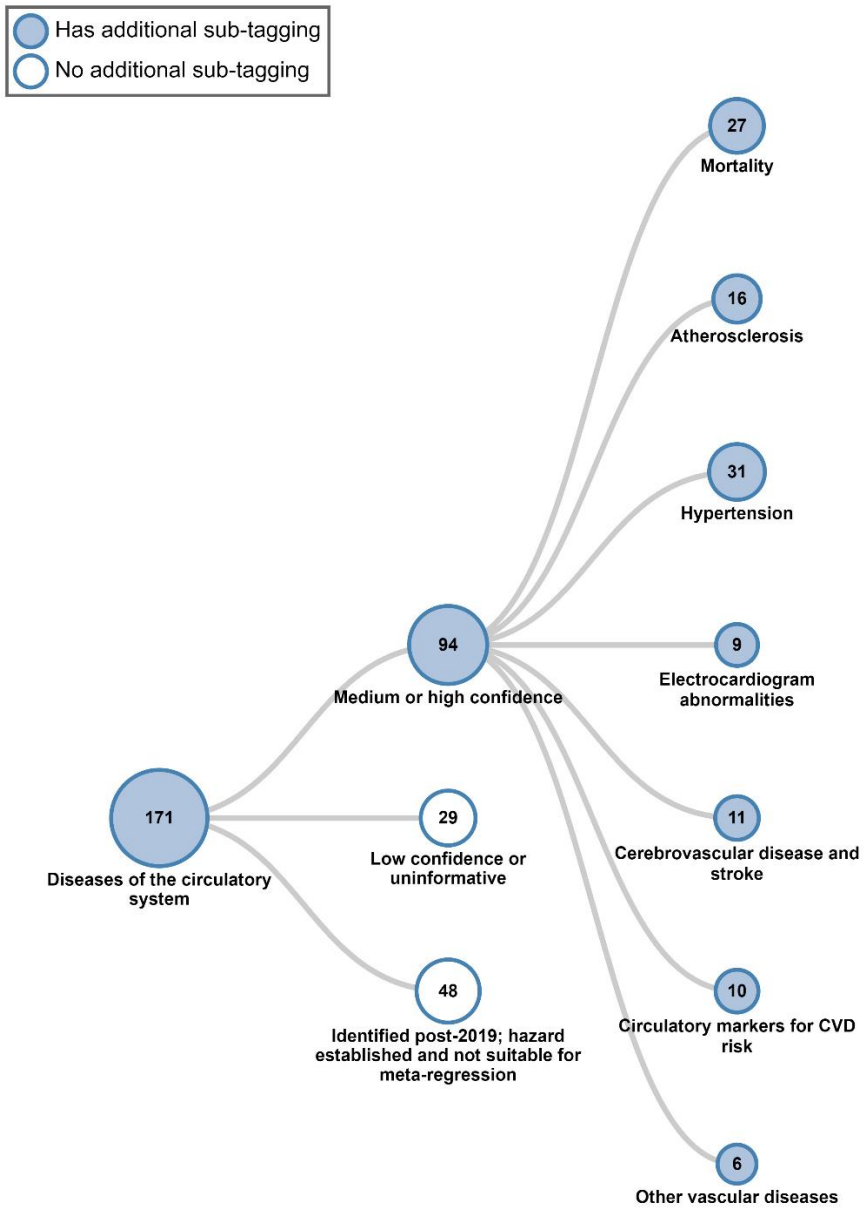


Figure 3-3. Literature tree of epidemiological studies assessing diseases of the circulatory system (see interactive version in HAWC).

In many of these studies, individual exposure was measured by using current arsenic concentrations in drinking water in prediction of past exposure. These exposure methods are limited by potential nondifferential misclassification bias due to using a proxy for previous years of exposure; this is expected to be a potential bias towards the null on average (i.e., attenuated effect estimates). 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. A potential benefit to using external arsenic exposure as a

proxy for exposure is potentially avoiding confounding from physiologic or personal behavior factors that affect the concentration of urinary arsenic. 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 iAs concentration 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. 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. For dose-response purposes, studies that allow for the estimation of risk at U.S.-relevant exposure levels (e.g., concentrations < 50 µg/L) are particularly informative. Key confounders include BMI, smoking status, and education level, potential risk factors for cardiovascular disease that may be related to the distribution of arsenic or influence health effects of arsenic exposure, such as through methylation efficiency.

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. The studies in Taiwan include large exposure contrasts and are defined by a clearly identified intervention, providing a natural experiment for evaluation of health hazards. Observed associations from this type of ecological study, particularly in combination with other studies using individual-level data, provide elevated confidence in the observed associations. 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) and coronary heart disease (CHD),[11] hypertension, cerebrovascular, peripheral vascular diseases (PVDs), and cardiovascular-related mortality. Studies describing inorganic arsenic exposure and related intermediate endpoints and/or risk factors for CVDs are also considered.

Among the most common CVDs that are studied in relation to inorganic arsenic exposure are IHD, CHD and associated mortality. IHD typically refers to conditions that result in deprivation of oxygen to the heart, tissue death and myocardial infarction (MI). CHD is a chronic IHD

[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.

characterized by coronary artery atherosclerosis, which can be assessed prior to manifesting clinically using ultrasonography to measure carotid intima media thickness (cIMT). The atherogenic effect of inorganic arsenic exposure is also 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.

The arsenic literature also includes studies of exposure to inorganic arsenic and 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 IHD and stroke and is itself 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.

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., 1993); (Chen et al., 1988). Due to 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.

Incidence of and Mortality from Cardiovascular Disease and Ischemic Heart Disease

The literature review identified 27 epidemiological studies that were considered medium or high confidence that evaluated the association between iAs exposure and incidence of or mortality from cardiovascular disease and ischemic heart disease. A selection of these studies will be discussed by study design. A selection of studies that reported effect estimates are summarized in Figure 3-4.

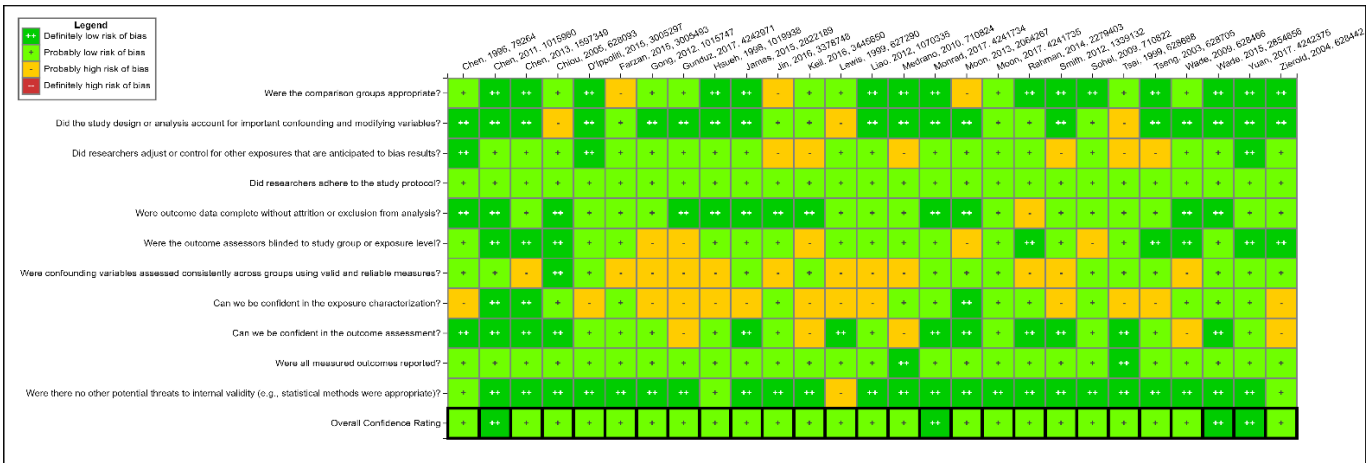


Figure 3-4. Study evaluation ratings for references evaluating incidence of mortality from cardiovascular disease and ischemic heart disease (see interactive version in HAWC).

Some of the strongest evidence for an association between iAs exposure and CVD/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 coronary heart disease and mortality, cardiovascular disease mortality, ischemic heart disease, and circulatory system disease mortality. A potential limitation occurs when arsenic speciation information is not available during exposure assessment, as total arsenic may not reflect inorganic arsenic exposure specificallyIn humans, the distribution of arsenic metabolites in urine ranges from 10–30% inorganic arsenic, 10–20% monomethylarsonic acid (MMA) and 60–80% dimethylarsinic acid (DMA) (Vahter and Concha, 2001). Temporal and local arsenic contamination variation could introduce a nondifferential bias; some of the studies examined a subset of drinking water wells or residential history over years without finding major differences in arsenic exposure concentrations over time to further support use of the individual proxy exposure value (Sohel et al., 2009); (Wade et al., 2015). However, these limitations were balanced by the strength of almost every other study domain, including large sample sizes and availability of data on arsenic exposure in both a biomarker and water in many studies, allowing for overall medium and high confidence ratings.

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 incidence and mortality from CVD and IHD. This includes low-moderate exposure levels, such as the dose-dependent relationship between iAs exposure and IHD morbidity and mortality observed by Chen et al. (1996);(Sohel et al., 2009), China (Wade et al., 2009), 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 21 case-control and cohort *medium* or *high* confidence studies that evaluated the association between iAs exposure and CHD/IHD incidence and mortality. Exposure measurements of arsenic included drinking water iAs measurements (15 studies) (Chen et al., 1996); (Lewis et al., 1999); (Chiou et al., 2005); (Wade et al., 2009); (Sohel et al., 2009); (Gong and O'Bryant, 2012); (Chen et al., 2011b); (Hsueh et al., 1998); (Liao et al., 2012); (Chen et al., 2013b); (Rahman et al., 2014); (James et al., 2015); (Wade et al., 2015);(D'Ippoliti et al., 2015); (Monrad et al., 2017), and biomarkers including urine, plasma, hair, and toenail (8 studies) (Chen et al., 2011b); (Chen et al., 2013b); (Moon et al., 2013); (Wade et al., 2015); (Farzan et al., 2015a); (Jin et al., 2016); (Moon et al., 2017a); (Yuan et al., 2017), with some of these studies using both water and biomarker measurements (Chen et al., 2011b); (Chen et al., 2013b);(Wade et al., 2015) and one using air measurements (Keil and Richardson, 2016).

Two large prospective cohort studies with urinary arsenic concentrations, , a cohort of 3575 rural American Indian men and women enrolled in the U.S. Strong Heart Study,(2013) and Chen et al., (2011b), a cohort of 11,746 men and women in Bangladesh enrolled in the Health Effect of Arsenic Longitudinal Study (HEALS), reported significant associations with CVD and IHD incidence and mortality and total arsenic or its metabolites. (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 ratios for cardiovascular disease, coronary heart disease, and stroke mortality were 1.65 (95% CI, 1.20 to 2.27; P for trend < 0.001), 1.71 (CI, 1.19 to 2.44; P for trend < 0.001), and 3.03 (CI, 1.08 to 8.50; P for trend = 0.061), respectively (see Figure 3-5c). The authors also found a statistically significant dose-response relationship of urinary arsenic concentrations with CVD and CHD incidence and mortality; for stroke incidence and mortality the dose-response relationship was positive but not statistically significant. (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 relation between exposure to arsenic in well water, which was also measured in HEALS, assessed at baseline and mortality from ischemic heart disease 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 only 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 for the study population (Karagas et al., 2001); (Ryan et al., 2000); (Steinmaus et al., 2005) and in urine (Navas-Acien et al., 2009b); (Karagas et al., 2001) 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.

Also conducted in HEALS, a case-cohort analysis reported increased risk of CHD-related mortality among those with lower methylation capacity (Chen et al., 2013b).

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—an arsenic-related peripheral vascular disease—and controls were without blackfoot disease, in order to examine ischemic heart disease (ISHD) mortality. Significant associations with ISHD mortality were observed for arsenic-exposure indices, including average arsenic concentration in drinking water and cumulative exposure from drinking artesian well water (Chen et al., 1996). (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; and (Hsueh et al., 1998) observed an association between duration of consumption of high-arsenic artersian well water and risk of ISHD. In another cohort study, an association was reported between cumulative arsenic exposure (ppm-years) and abnormal lactate dehydrogenase activity, a marker of CVD risk in this highly exposed population (Liao et al., 2012).

Studies examining drinking water arsenic concentrations from other countries were consistent with the southwestern Taiwan findings. A large cohort of 61,074 men and women in Bangladesh observed arsenic exposure measured in well water to be associated with increased stroke mortality risk (Rahman et al., 2014). 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 in (Sohel et al., 2009), with arsenic exposure determined from a survey of past and current water use of tubewells and arsenic concentrations in the tubewells, and increased stroke mortality (Rahman et al., 2014)

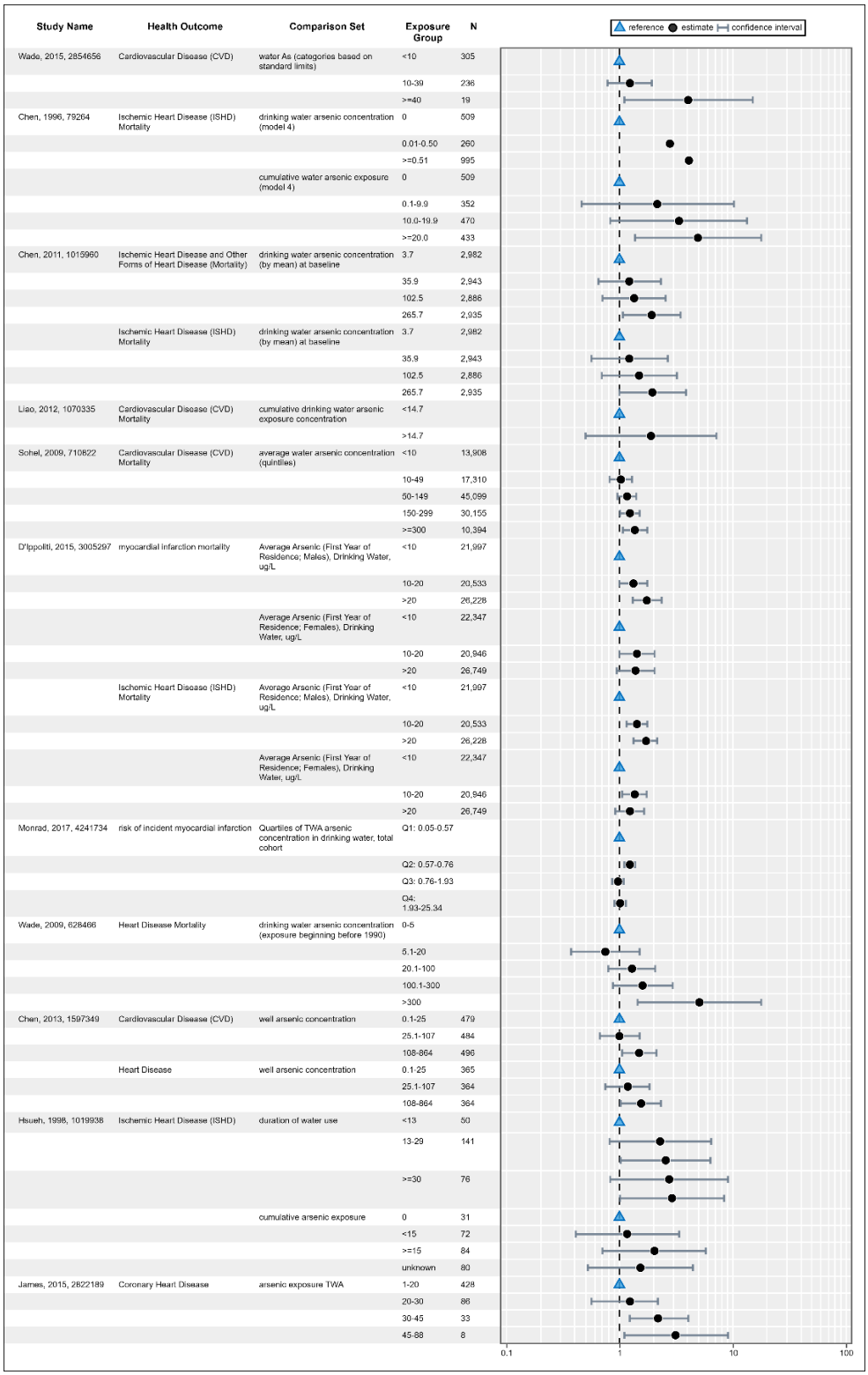
A case-cohort study, which examined exposure to iAs in drinking water using a geospatial model of arsenic concentrations combined with residential histories in the San Luis Valley Diabetes Study in Colorado, U.S. to calculate lifetime exposure (James et al., 2015). The study population (n = 555) was 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 (CHD risk HR = 1.38, 95% CI: 1.09, 1.78 per 15 µg/L). The study population was exposed to iAs concentrations in drinking water ranging from 10 to 100 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, finding that coronary heart disease was associated with low-level arsenic exposure; and in Utah, (Lewis et al., 1999) used residence history and median drinking water arsenic concentration, authors observed increased mortality from hypertensive heart disease. 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 yrs. 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. No association between 20-year average concentration and MI was observed among the study population overall. An association between ever compared to never living at a residence with ≥10 µg/L was observed, however [IRR: 1.26 (95% CI: 0.89–1.79)]. The concentration of arsenic levels in drinking water at the participants' baseline address ranged from 0.03 to 25.34 µg/L. Consistent results were also seen in an airborne arsenic—one study used air measurements to estimate arsenic exposure via inhalation in an occupational cohort of male copper smelter workers (Keil and Richardson, 2016). The authors determined that arsenic exposure was associated with an increase in the risk of heart disease at age 70.

Two toenail biomarker studies, conducted in the U.S. (Farzan et al., 2015a)and Inner Mongolia, China (Wade et al., 2015), provide additional supporting evidence that arsenic is a contributing risk factor for IHD and CVD, respectively, 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 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). As shown in Figure 3-5, they reported no significant increase in HRs with increasing toenail arsenic concentration with CVD- or 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 IHD mortality and toenail arsenic 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). In another 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

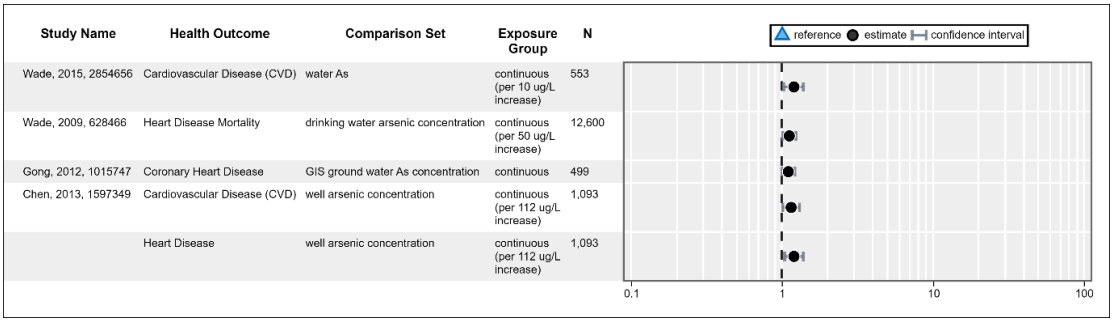
primary drinking water source as exposure metrics. As shown in Figure 3-5, arsenic concentrations in drinking water and toenails were associated with CVD incidence. The drinking-water arsenic concentration ranged from less than the limit of detection to 208 µg/L (mean 8.9 µg/L) among study participants. Congruent findings were seen across biomarkers, with maternal hair arsenic associated with congenital heart defects (Jin et al., 2016).

A nested case control study of Chinese adults (Dongfeng-Tongji Cohort), Yuan et al. (2017) examined the association of plasma arsenic concentration with incident CHD events (i.e., nonfatal MI, fatal CHD, stable and unstable angina, or coronary revascularization) confirmed by physician adjudication. 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 of plasma arsenic concentration]. Blood samples were obtained between 2008 and 2010 and follow-up exams were conducted in 2013.

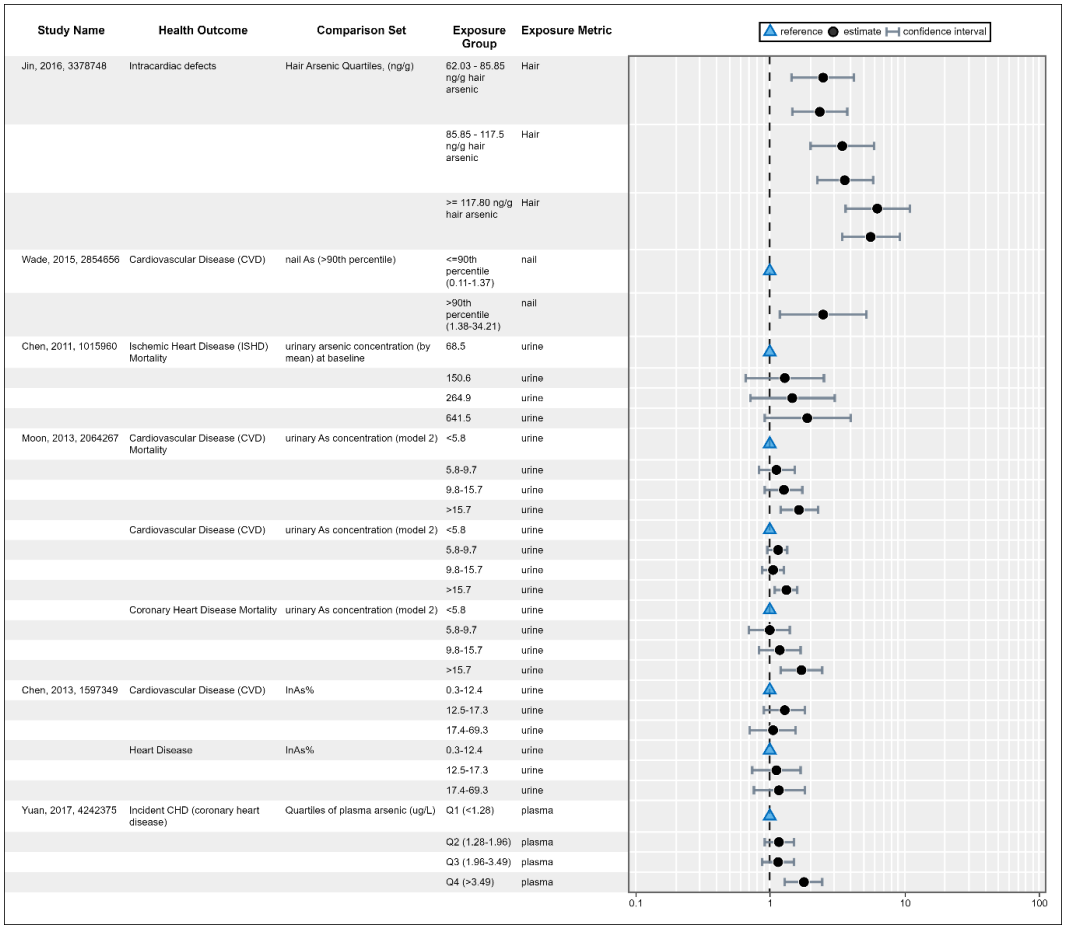


Study Name	Health Outcome	Comparison Set	Exposure Group	N
Wade, 2015, 2854656	Cardiovascular Disease (CVD)	water As (categories based on standard limits)	<10	305
			10-39	236
			>=40	19
Chen, 1996, 79264	Ischemic Heart Disease (ISHD) Mortality	drinking water arsenic concentration (model 4)	0	509
			0.01-0.50	260
			>=0.51	995
		cumulative water arsenic exposure (model 4)	0	509
			0.1-9.9	352
			10.0-19.9	470
			>=20.0	433
Chen, 2011, 1019960	Ischemic Heart Disease and Other Forms of Heart Disease (Mortality)	drinking water arsenic concentration (by mean) at baseline	3.7	2,982
			35.9	2,943
			102.5	2,886
			265.7	2,935
	Ischemic Heart Disease (ISHD) Mortality	drinking water arsenic concentration (by mean) at baseline	3.7	2,982
			35.9	2,943
			102.5	2,886
			265.7	2,935
Liao, 2012, 1070335	Cardiovascular Disease (CVD) Mortality	cumulative drinking water arsenic exposure concentration	<14.7	
			>14.7	
Sohel, 2009, 710822	Cardiovascular Disease (CVD) Mortality	average water arsenic concentration (quintiles)	<10	13,908
			10-49	17,310
			50-149	45,099
			150-299	30,155
			>=300	10,394
D'Ippoliti, 2015, 3005297	myocardial infarction mortality	Average Arsenic (First Year of Residence; Males), Drinking Water, ug/L	<10	21,997
			10-20	20,533
			>20	26,228
		Average Arsenic (First Year of Residence; Females), Drinking Water, ug/L	<10	22,347
			10-20	20,946
			>20	26,749
	Ischemic Heart Disease (ISHD) Mortality	Average Arsenic (First Year of Residence; Males), Drinking Water, ug/L	<10	21,997
			10-20	20,533
			>20	26,228
		Average Arsenic (First Year of Residence; Females), Drinking Water, ug/L	<10	22,347
			10-20	20,946
			>20	26,749
Monrad, 2017, 4241734	risk of incident myocardial infarction	Quartiles of TWA arsenic concentration in drinking water, total cohort	Q1: 0.05-0.57	
			Q2: 0.57-0.76	
			Q3: 0.76-1.93	
			Q4: 1.93-25.34	
Wade, 2009, 628466	Heart Disease Mortality	drinking water arsenic concentration (exposure beginning before 1990)	0-5	
			5.1-20	
			20.1-100	
			100.1-300	
			>300	
Chen, 2013, 1597349	Cardiovascular Disease (CVD)	well arsenic concentration	0.1-25	479
			25.1-107	484
			108-864	496
	Heart Disease	well arsenic concentration	0.1-25	365
			25.1-107	364
			108-864	364
Hsueh, 1998, 1019938	Ischemic Heart Disease (ISHD)	duration of water use	<13	50
			13-29	141
			>=30	76
		cumulative arsenic exposure	0	31
			<15	72
			>=15	84
			unknown	80
James, 2015, 2822189	Coronary Heart Disease	arsenic exposure TWA	1-20	428
			20-30	86
			30-45	33
			45-88	8

(a) Adj OR, Adj RR, or HR—drinking water—categorical exposure



(b) Regression coefficient—drinking water—continuous exposure



(c) Regression coefficient—biomarker—categorical exposure

Figure 3-5. Thumbnail schematic of case-control and cohort studies with CVD/IHD outcomes in relation to inorganic arsenic exposure (a) Adj OR, Adj RR, or HR—drinking water— categorical exposure, (b) Regression coefficient —drinking water—continuous exposure, (c) Regression coefficient— biomarker—categorical exposure (see interactive data graphics). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Cross-sectional studies

Three cross-sectional studies of *medium* confidence examined the association between arsenic exposure and CHD/IHD outcomes in Turkey, the U.S., and Taiwan, respectively (Gunduz et al., 2017); (Tseng et al., 2003); (Zierold et al., 2004). All 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 ≥10µg/L) and heart attack (OR (95%CI): 2.08 (1.10, 4.31)); and (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, when compared with no drinking water arsenic exposure (see Figure 3-6). (Gunduz et al., 2017) examined the distribution of chronic diseases in villages with high arsenic levels in drinking water supplies in Turkey and found diseases of the circulatory system to have the highest prevalence.

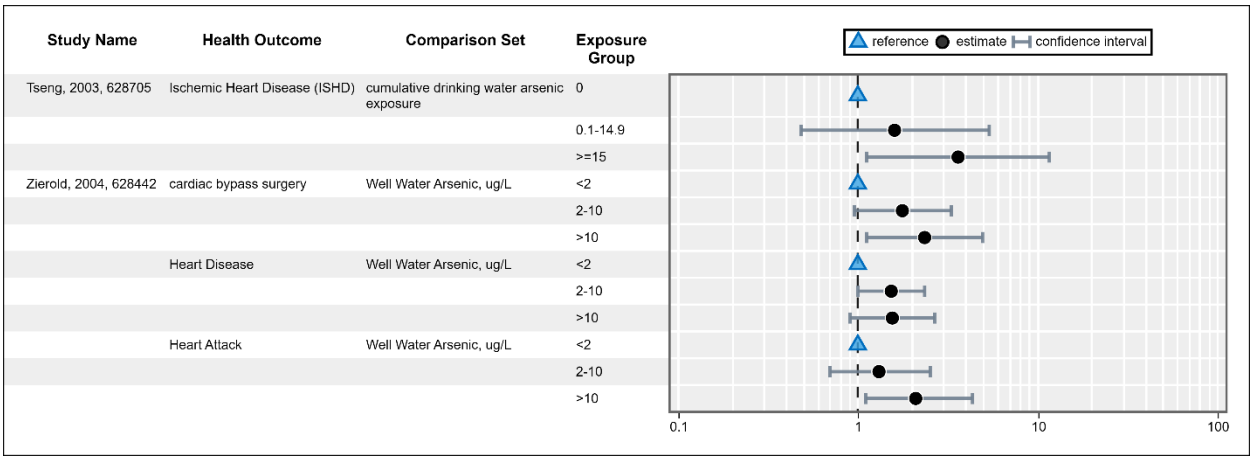


Figure 3-6. Thumbnail schematic of cross-sectional epidemiological studies addressing the association between iAs exposure (drinking water) and CHD/IHD outcomes- odds ratios (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Ecological studies

Three ecological studies of medium confidence were included, examining CVD-related mortality in Chile, Taiwan, and Spain, respectively (see Figure 3-7) (Smith et al., 2012); (Tsai et al., 1999); (Medrano et al., 2010). Statistically significant positive associations were observed for acute myocardial infarction mortality in Chile, IHD mortality in Taiwan, and CVD mortality in Spain.

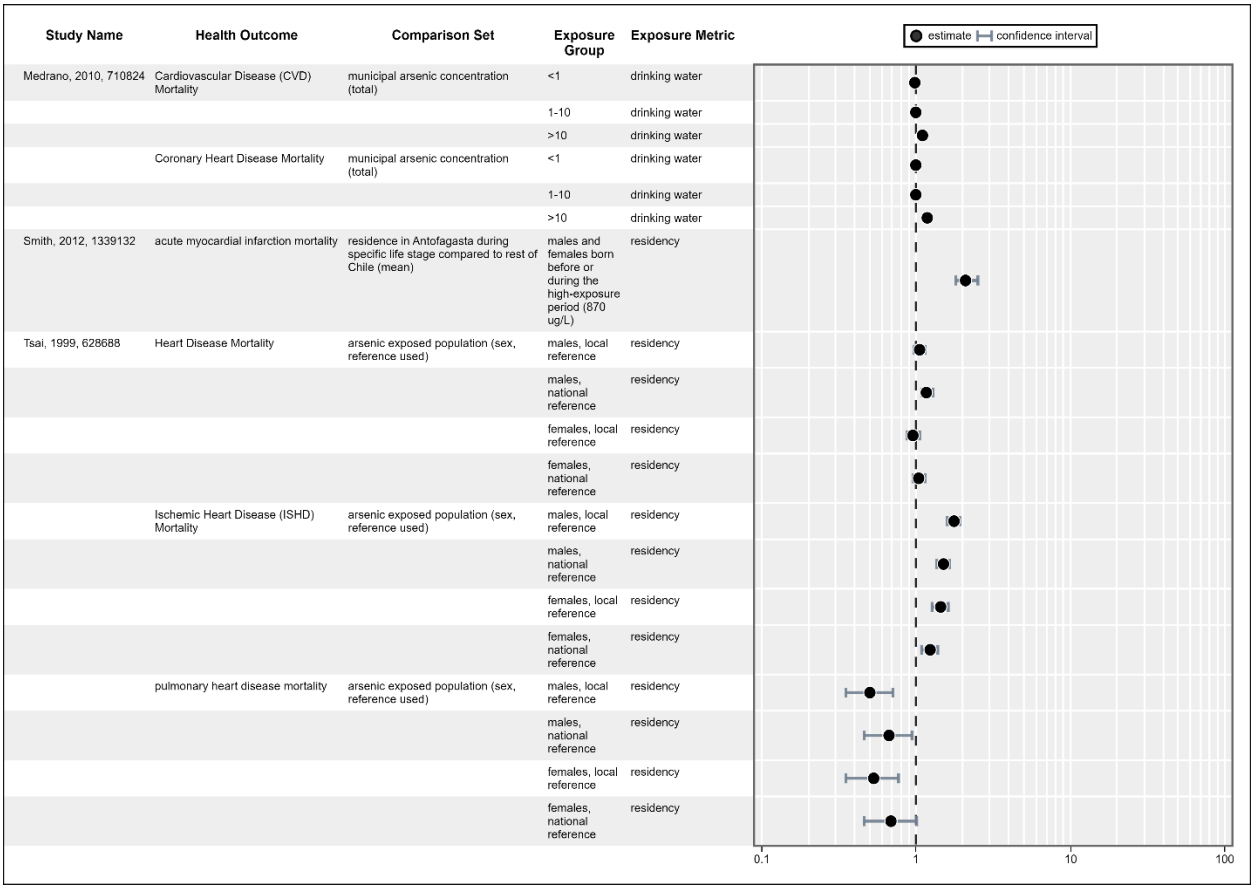


Figure 3-7. Thumbnail schematic of ecological epidemiological studies addressing the association between iAs exposure (drinking water) and CHD/IHD outcomes- SMRs (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Natural Experiment: Highly Exposed Population in Southwest Taiwan

The studies reporting the strongest exposure-dependent positive associations examined the effect of cumulative arsenic exposure ([mg/L-yr]) on CVD-related morbidity or mortality in the southwestern coastal region of Taiwan, where chronic arsenic poisoning was endemic (Chen et al., 1996);(Hsueh et al., 1998);(Tseng et al., 2003). 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. Ecological studies in this Southwest Taiwan area found

elevated mortality rates from cardiovascular causes from high pre-1975 exposures (Wu et al., 1989); (Chang et al., 2004);(Gunduz et al., 2017) but reported substantial declines in IHD mortality (i.e., 3-year moving average SMRs) 17–21 years after the interventions to reduce arsenic exposure were implemented (post-1975), providing support for a causal association between iAs and cardiovascular effects (Chang et al., 2004);(Chang et al., 2004).

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 including from the Newcastle-Ottawa Scale to assess study quality (see Appendix C, Table C-43) 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 meta-regression 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 multiple CVD endpoints (all CVD, CHD, and stroke). Compared with 10 mg/l, the estimated pooled relative risks [95% confidence interval (CI)] for 20 mg/l water arsenic were 1.09 (1.03, 1.14) for CVD incidence, 1.07 (1.01, 1.14) for CVD mortality, 1.11 (1.05, 1.17) for CHD incidence, 1.16 (1.07, 1.26) for CHD mortality, and 1.08 (0.99, 1.17) for stroke incidence.

[12]The Moon et al. (2017b) meta-analysis is discussed further in Appendix C, Section C.1.2 Diseases of the Circulatory System; Comparison of studies selected for EPA meta-regression 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); (2012) and the EPA meta-analyses of CVD and IHD outcomes with respect to study selection, data adjustments/pre-analysis and modeling methods.

[13](2017b); 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."

Summary

Overall, epidemiological studies provide robust evidence for exposure-dependent associations between arsenic exposure and the cardiovascular-related morbidity and mortality outcomes examined. 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 CVD/IHD-related outcomes in association with iAs exposure, dose-response gradient associations observed in many studies, 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, "natural experiment" studies from southwest Taiwan, and meta-analyses. These studies are medium to high confidence, with adequate control of important confounders and consideration of other potential biases (see Appendix B.2 and HAWC).

Intermediate Endpoints and/or Risk Factors for Cardiovascular Disease and Ischemic Heart 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: atherosclerosis, hypertension, and electrocardiogram abnormalities.

Atherosclerosis

The literature review identified 16 epidemiological studies, 6 case-control/cohort and 10 cross-sectional studies, considered *medium* or *high* confidence that evaluated the association between iAs exposure and atherosclerosis (see Figure 3-8). 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.

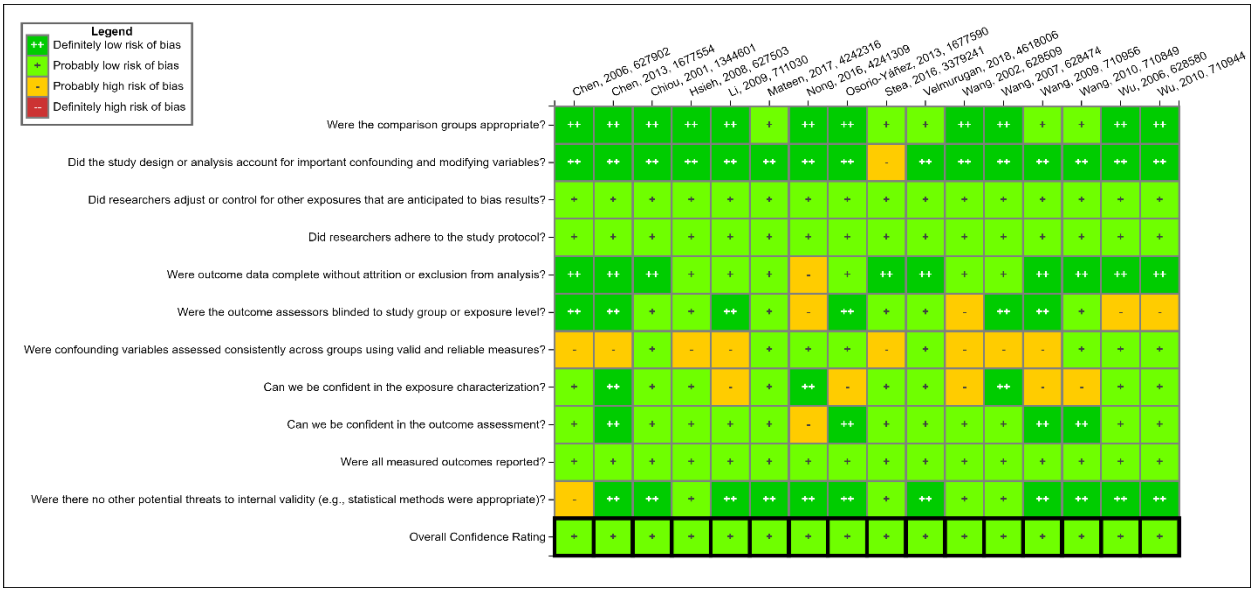


Figure 3-8. Study evaluation ratings for references evaluating atherosclerosis (see interactive version in HAWC).

The epidemiological studies presented in Figure 3-9 and Figure 3-10 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. (2013a) 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 and an 11.7-mm (95% CI 1.8–21.6) increase in cIMT per SD increase in baseline urinary iAs concentration in the HEALS cohort. In this cohort, a sizeable proportion of the population is exposed to low or moderate arsenic concentrations (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. (2001), 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 was generally from pesticides [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., 2001) 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.

Overall, these studies indicate that low-to-moderate arsenic concentrations are associated with increased cIMT, supporting the associations of arsenic with CHD observed in 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.

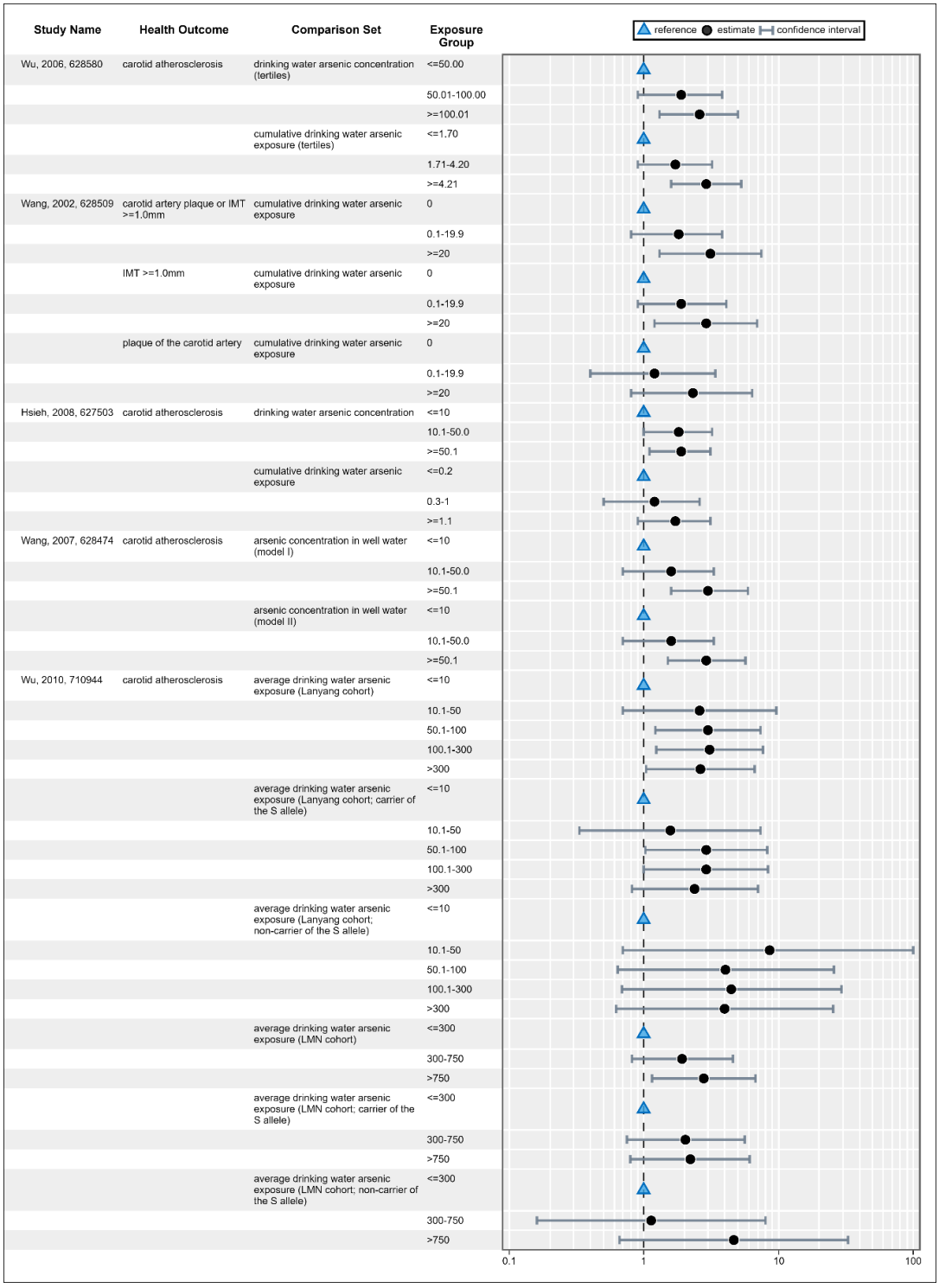
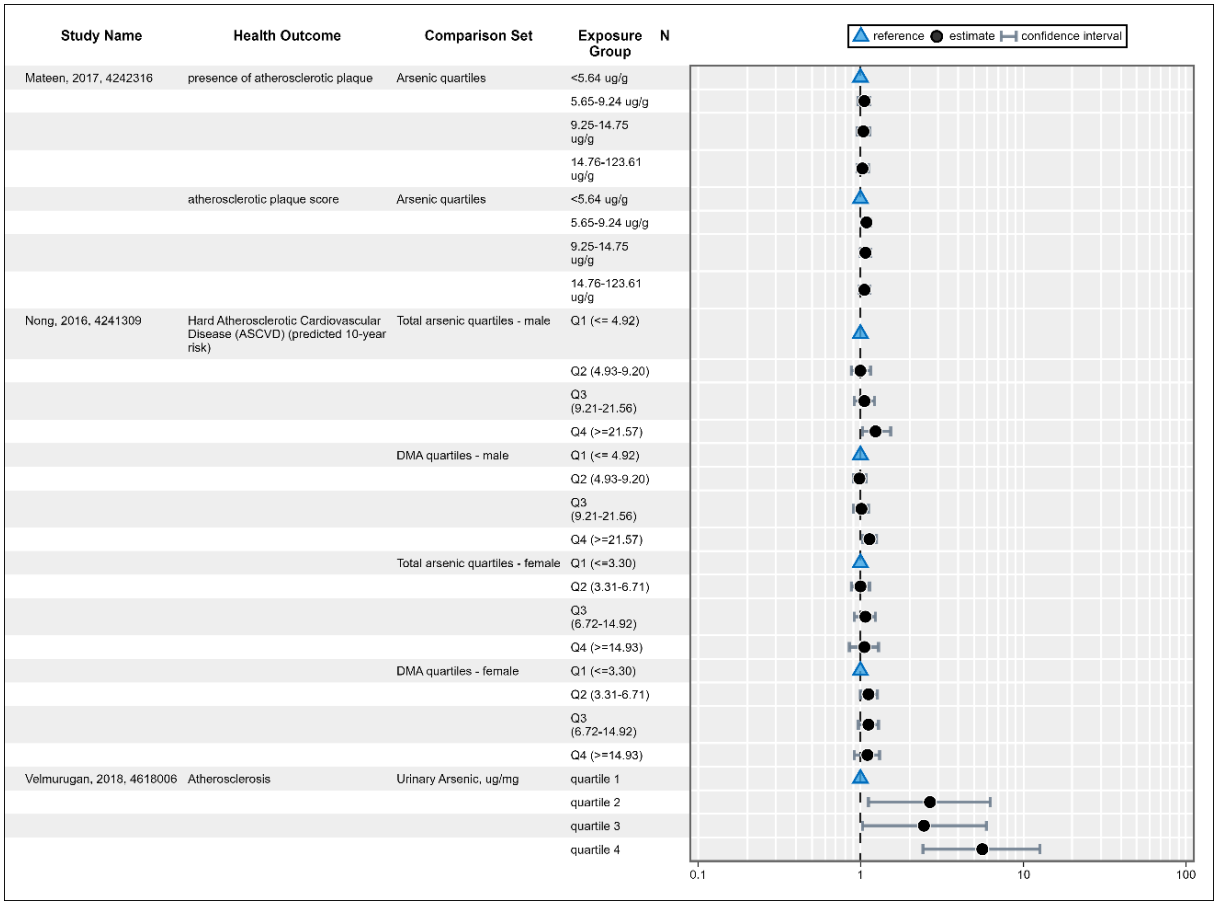
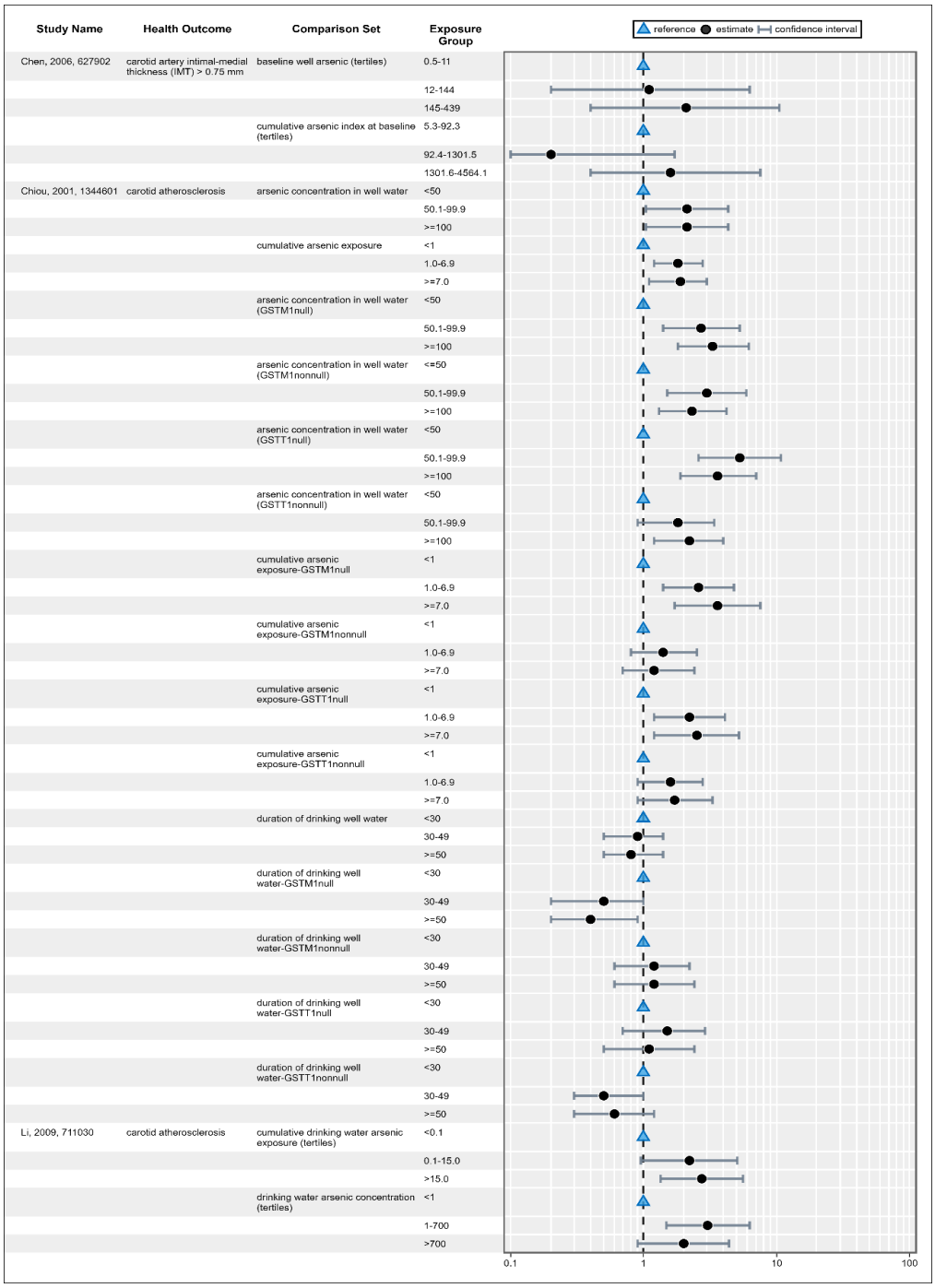


Figure 3-9. Thumbnail schematic of case-control and cohort studies of atherosclerosis in response to inorganic arsenic exposure (OR) drinking water—categorical exposure (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.



(a) Regression coefficient—urine—categorical exposure



(b) Regression coefficient drinking water—categorical exposure

Figure 3-10. Thumbnail schematic of cross-sectional studies of atherosclerosis in response to inorganic arsenic exposure (a) urine—categorical exposure; (b) drinking water—categorical exposure (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Hypertension and increased blood pressure

The literature review identified 31 epidemiological studies, 12 case-control/cohort and 19 cross-sectional studies, considered medium or high confidence that evaluated the association between iAs exposure and hypertension (see Figure 3-11). Hypertension typically is defined as systolic blood pressure (SBP) ≥130 mmHg and diastolic blood pressure (DBP) ≥80 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 also a risk factor for heart disease and stroke. The results from studies of hypertension are summarized in Figure 3-12 and Figure 3-13.

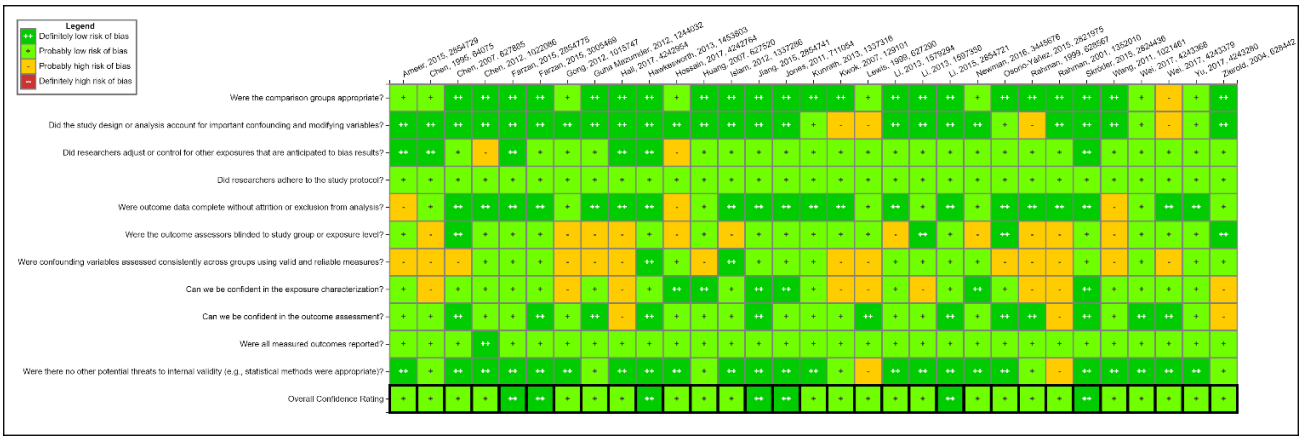


Figure 3-11. Study evaluation ratings for references evaluating hypertension and increased blood pressure (see interactive version in HAWC).

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 in the U.S. (Jones et al., 2011), and in southwest Taiwan where long-term exposure was identified by sampling in previously-Blackfoot disease endemic areas (Chen et al., 1995) (see Figure 3-13).

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 4 villages in the districts of Faridpur, Nawabgong, Bangladesh, Jessore, and Narayongong (Rahman et al., 1999) (see Figure 3-12). 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 the risk of hypertension was higher among those with skin lesions related to arsenic exposures compared to 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 range from 10-1400 µg/L, Islam et al. (2012a) reported an association of arsenic exposure with pulse pressure (PP) but not with hypertension (see Figure 3-13). Another cross-sectional study, (Hossain et al., 2017), observed chronic arsenic exposure was 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.

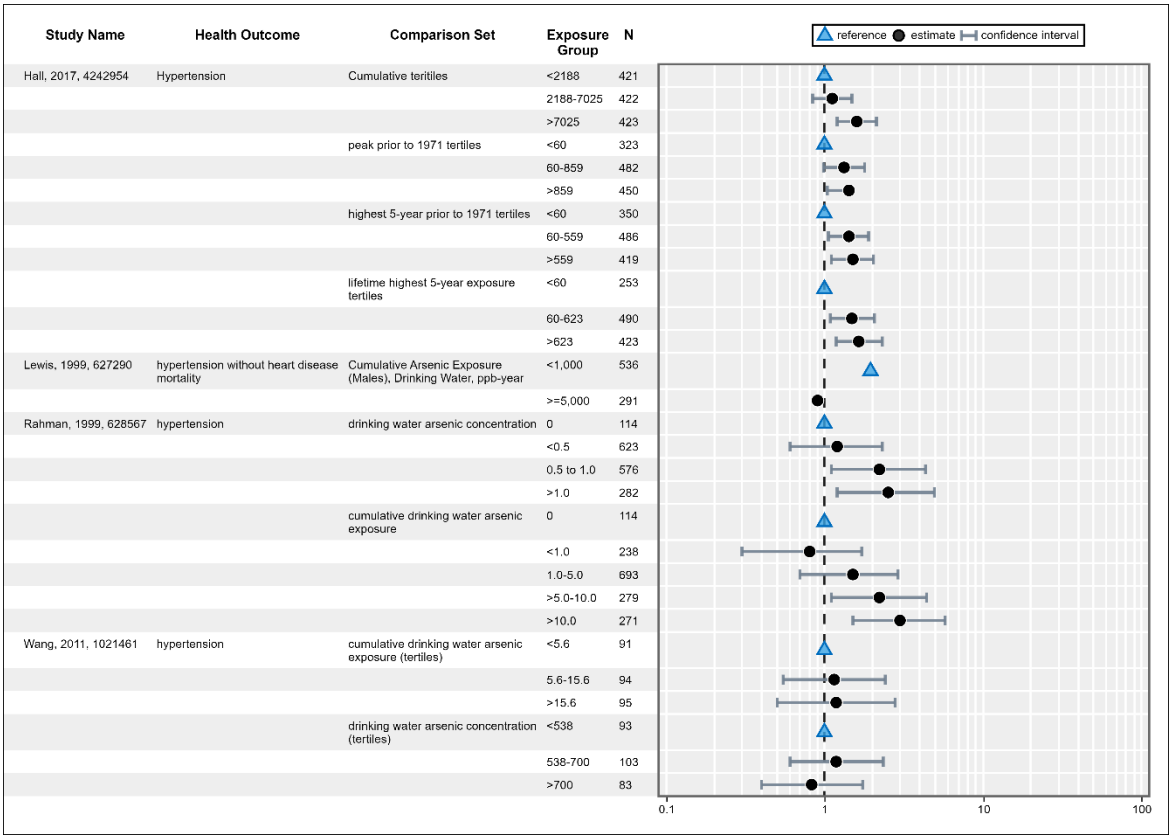
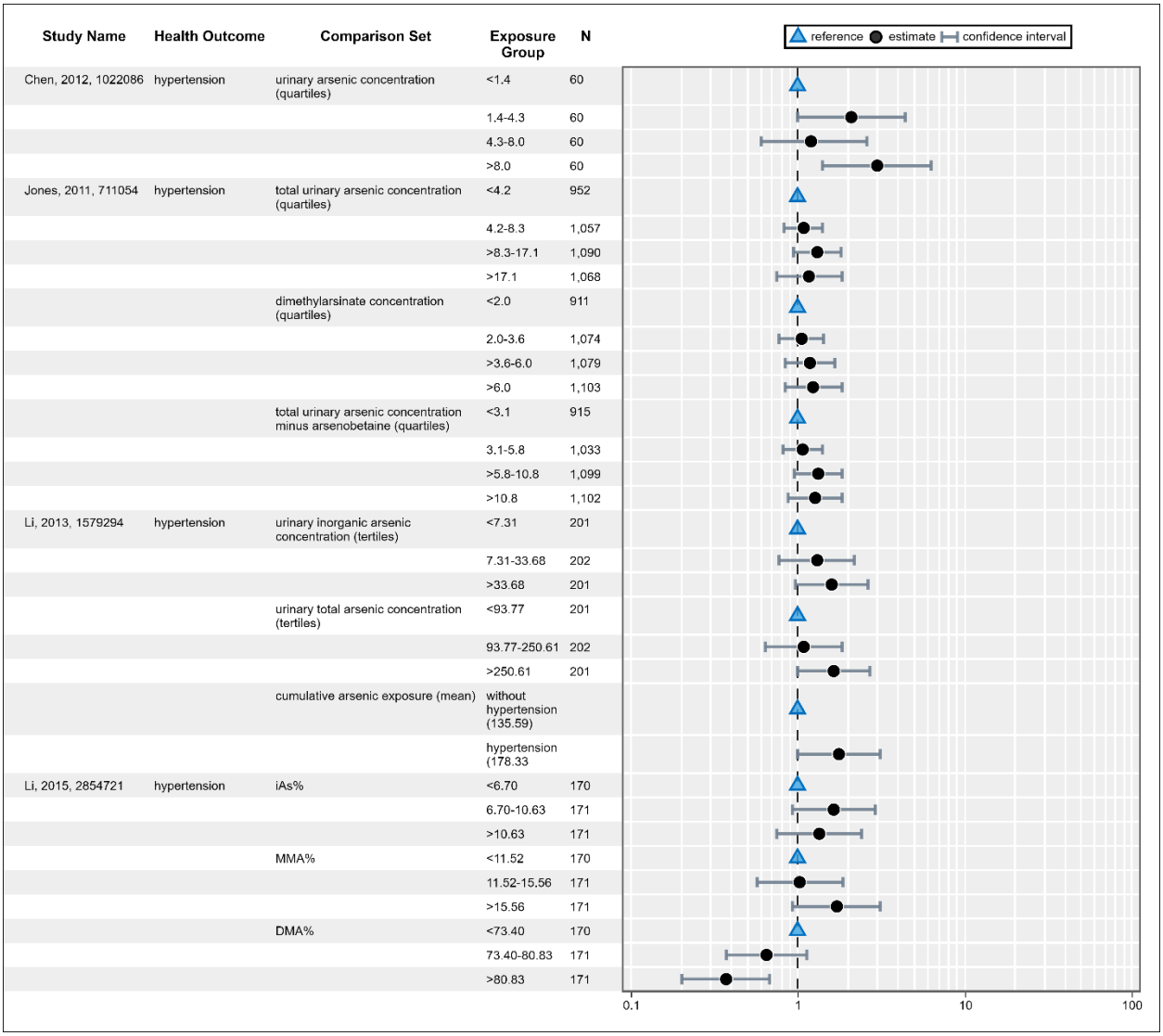
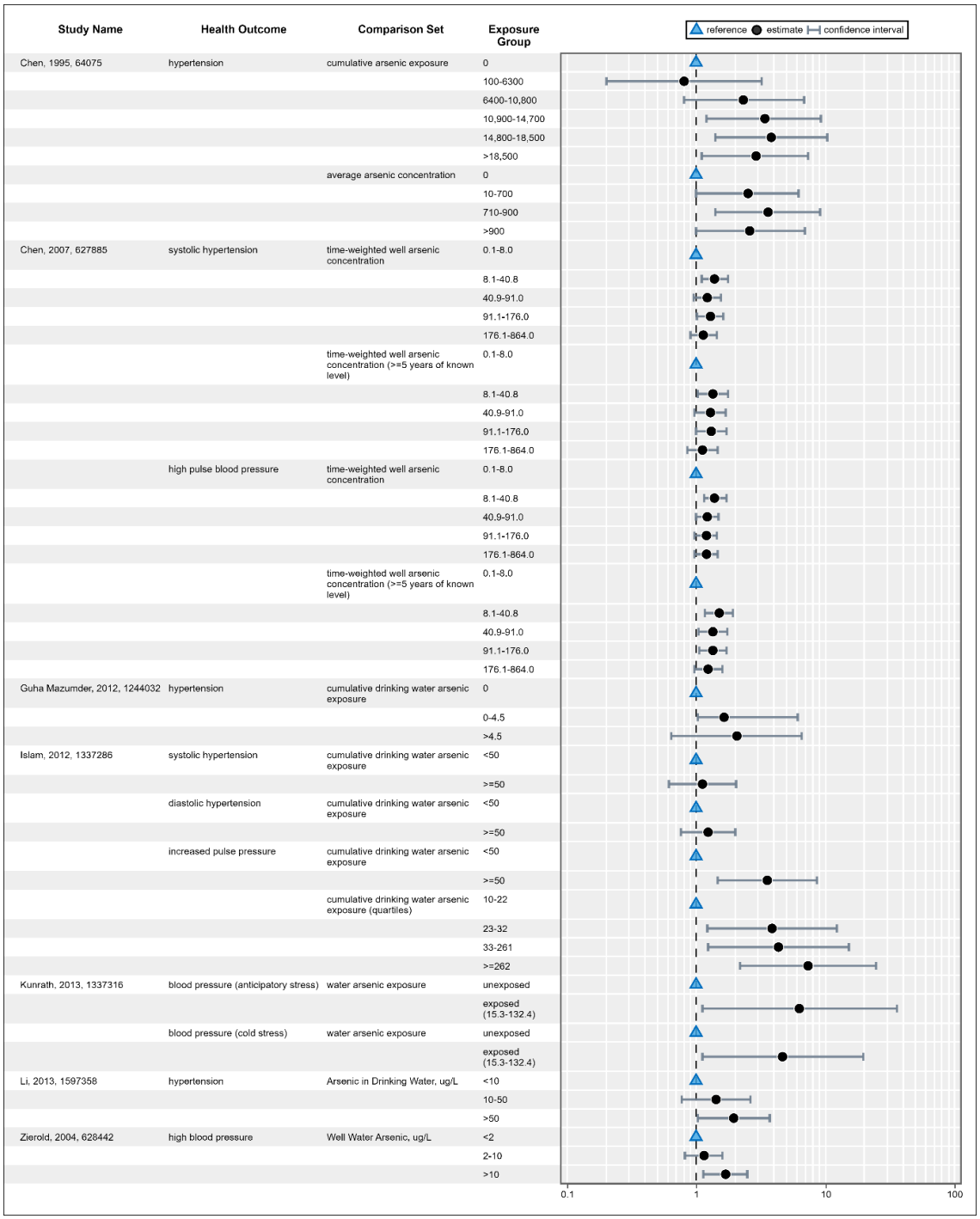


Figure 3-12. Thumbnail schematic of case-control/cohort studies of hypertension in response to inorganic arsenic exposure (OR or similar) drinking water—categorical exposure (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.



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

(a) urine—categorical exposure (odds ratios)



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

(b) drinking water—categorical exposure (odds ratios)

Figure 3-13. Thumbnail schematic of cross-sectional studies of hypertension in response to inorganic arsenic exposure (a) urine—categorical (odds ratios); (b) water—categorical (odds ratios) (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Also in Bangladesh, the association of inorganic arsenic exposure and hypertension was also examined in a cross-sectional study among participants in the HEALS cohort, a large study (n=11,746) of adults (≥18 years old) who have 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 in this study. No association of time-weighted average exposure to arsenic 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 and arsenic concentration in urine with small statistically significant annual increases in both SBP and DBP (Jiang et al., 2015) and (Wei et al., 2017b) reported an increase in SBP and DBP in association with cumulative arsenic exposure. Modification of the longitudinal association of water arsenic concentration with blood pressure 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 to those without arsenic associated skin lesions (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 and third tertiles to the reference category, 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 this study (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); (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 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 arsenic exposure 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 and peripheral arterial disease markers in American Indians (Newman et al., 2016); arsenic in drinking water and mortality from hypertensive heart disease in residents from Utah (Lewis et al., 1999); and arsenic in private well-water 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. Based on pooling of extracted odds ratios (OR) 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, 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 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 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. This evidence indicates that the effect of arsenic exposure on hypertension and blood pressure might be more pronounced among those with higher exposure (>50 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.

Electrocardiogram abnormalities

The literature review identified 9 epidemiological studies, 4 case-control/cohort and 5 cross-sectional, considered *medium* or *high* confidence that evaluated the association between iAs exposure and electrocardiogram abnormalities (see Figure 3-14 and Figure 3-15). 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).

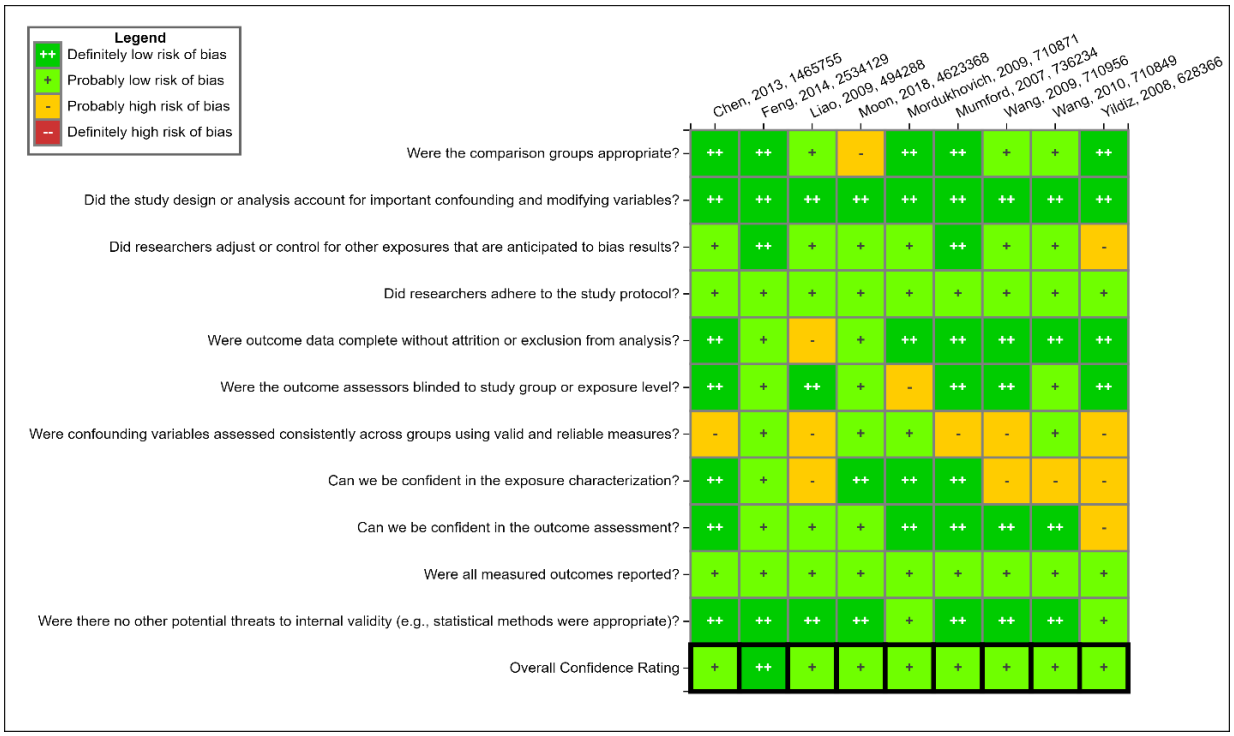


Figure 3-14. Study evaluation ratings for references evaluating electrocardiogram abnormalities (see interactive version in HAWC).

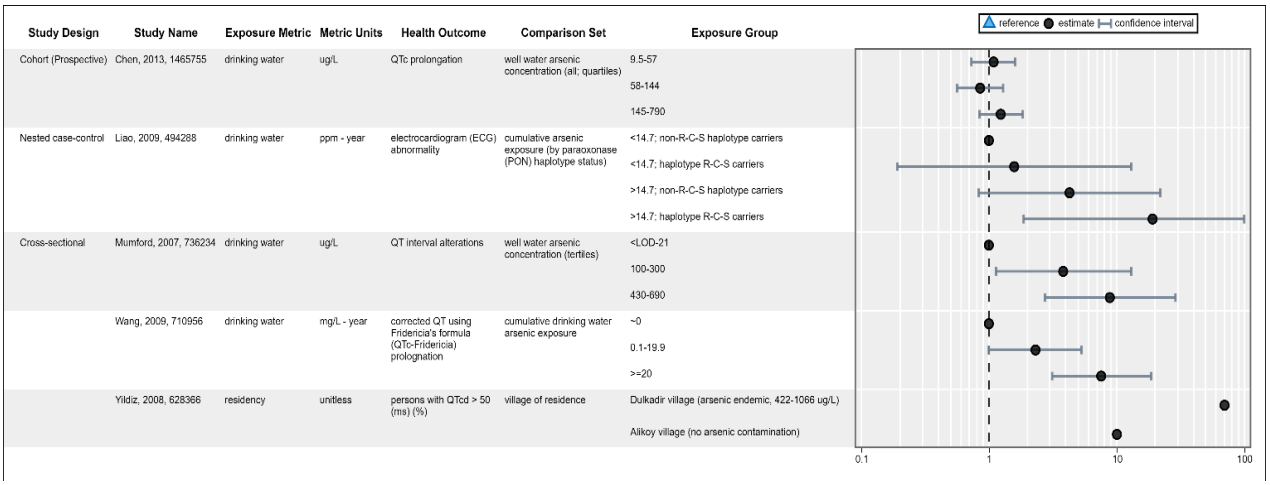


Figure 3-15. Thumbnail schematic of studies addressing the association between iAs exposure and electrocardiogram abnormalities—odds ratios, prevalence ratios —water (see interactive graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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 Native Americans in the SHS and the Strong Heart Family Study (SHFS). 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 was associated with an increase in QTc. Arsenic exposure is presumed to be "low" in this cohort of residents of greater Boston. 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. (2013c) observed associations of both drinking water arsenic concentration and urinary arsenic concentration 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 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., 2013c).

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. Association 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 (Ahmad et al., 2006); (Yildiz et al., 2008).

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 CHD, 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. There is limited evidence that the association with QT prolongation may be stronger in women. Findings were generally unchanged after adjustment for confounders such as age, BMI, and smoking status, with some studies also considering additional confounders such as educational attainment and pesticide exposure.

Cerebrovascular Disease and Stroke

The literature review identified 11 epidemiological studies, 7 case-control/cohort and 4 cross-sectional/ecological, considered medium or high confidence that evaluated the association between iAs exposure and cerebrovascular disease and stroke (see Figure 3-16). 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 fully adjusted models (see Figure 3-17). 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, including those considered relevant to the US. After adjustment for confounders, 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 3-17). 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. soil and streams) 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]. 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=2486 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 to the lowest quintile] 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 (see Figure 3-17). 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 CHD- and stroke-related mortality were elevated in higher exposed groups over the lower, reference group (Moon et al., 2017b).

In the large study of Italian municipalities described previously, ''Ippoliti et al. (2015); (2015) reported positive associations of cumulative arsenic dose indicator, which accounted for lifetime intensity and duration 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) to the reference category (≤204.9 µg). 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 3-17).

Several additional studies assessed the association of iAs exposure with stroke or cerebrovascular outcomes. 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. 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, US (Lewis et al., 1999).

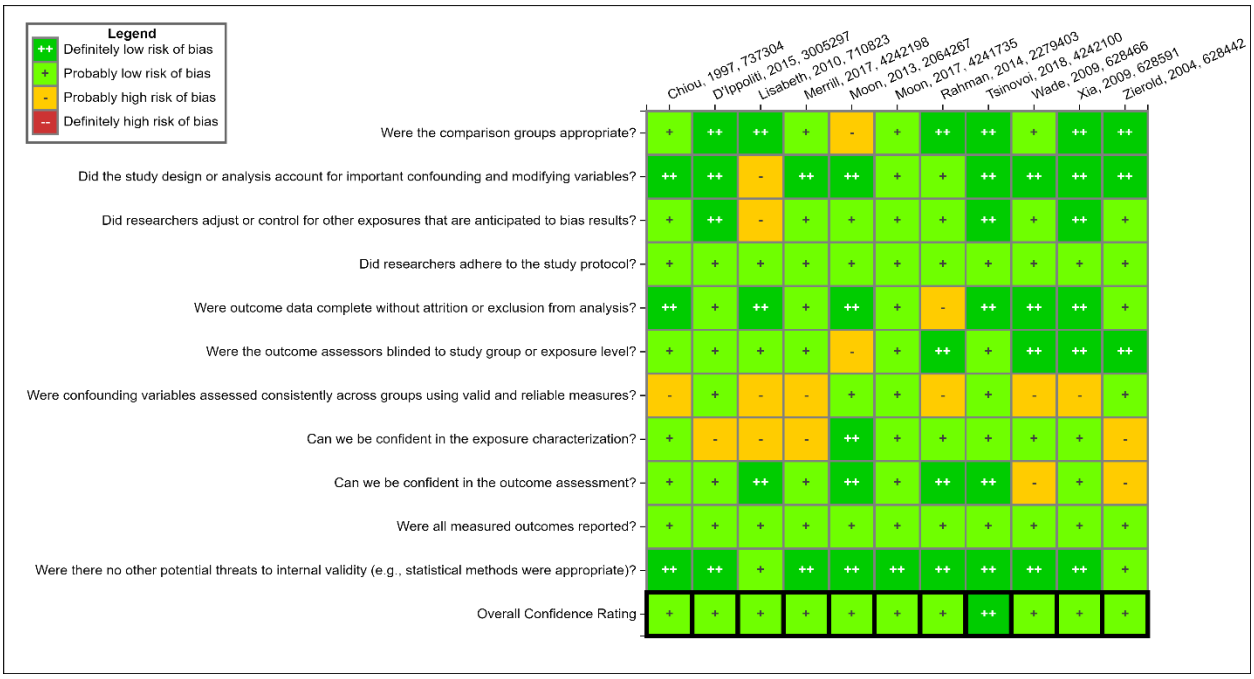
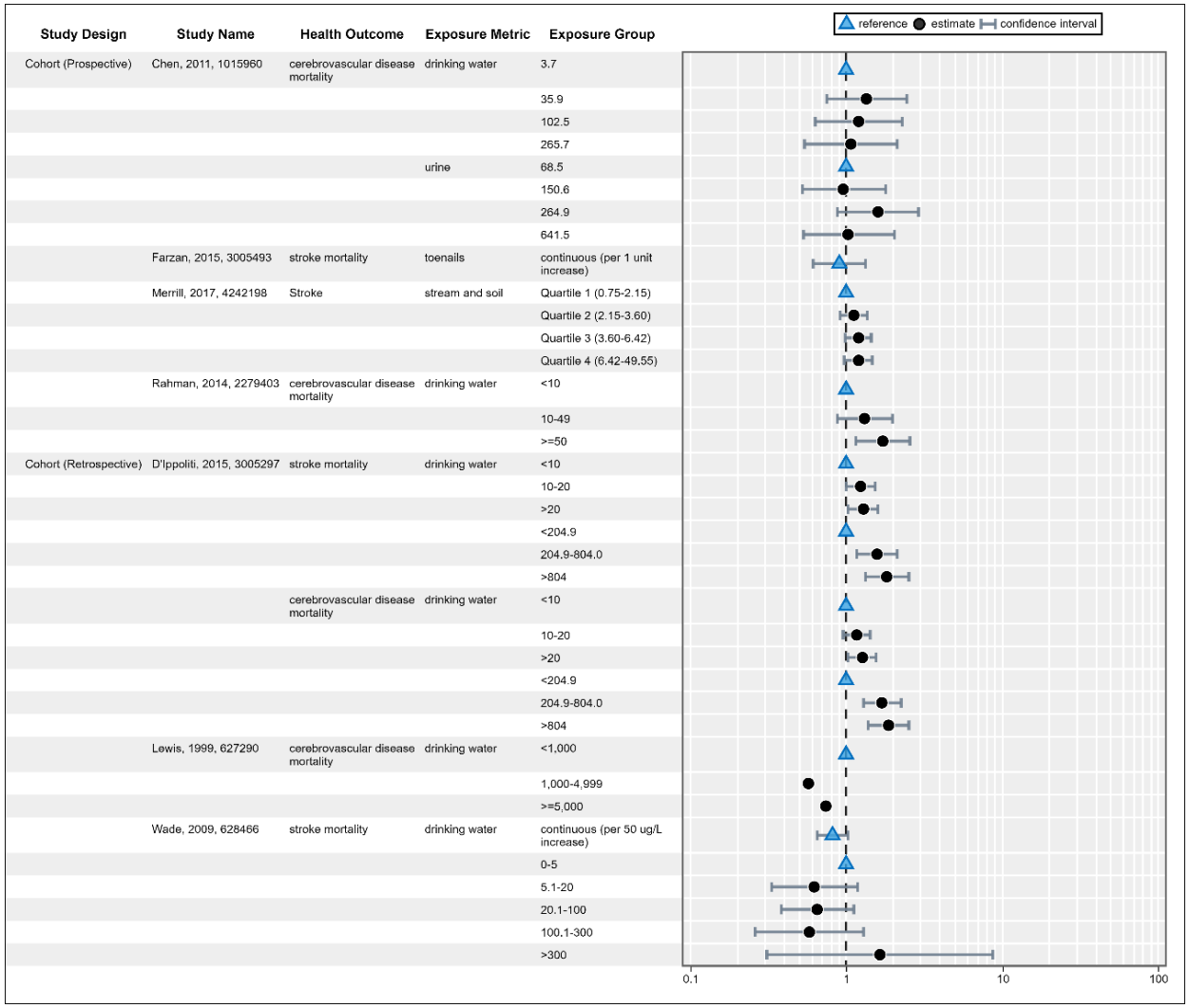


Figure 3-16. Study evaluation ratings for references evaluating cerebrovascular disease and stroke (see interactive version in HAWC).



Study Design	Study Name	Health Outcome	Exposure Metric	Exposure Group
Cohort (Prospective)	Chen, 2011, 1015960	cerebrovascular disease mortality	drinking water	3.7
				35.9
				102.5
				265.7
			urine	68.5
				150.6
				264.9
				641.5
	Farzan, 2015, 3005493	stroke mortality	toenails	continuous (per 1 unit increase)
	Merrill, 2017, 4242198	Stroke	stream and soil	Quartile 1 (0.75-2.15)
				Quartile 2 (2.15-3.60)
				Quartile 3 (3.60-6.42)
				Quartile 4 (6.42-49.55)
	Rahman, 2014, 2279403	cerebrovascular disease mortality	drinking water	<10
				10-49
				>=50
Cohort (Retrospective)	D'Ippoliti, 2015, 3005297	stroke mortality	drinking water	<10
				10-20
				>20
				<204.9
				204.9-804.0
				>804
		cerebrovascular disease mortality	drinking water	<10
				10-20
				>20
				<204.9
				204.9-804.0
				>804
	Lewis, 1999, 627290	cerebrovascular disease mortality	drinking water	<1,000
				1,000-4,999
				>=5,000
	Wade, 2009, 628466	stroke mortality	drinking water	continuous (per 50 ug/L increase)
				0-5
				5.1-20
				20.1-100
				100.1-300
				>300

Figure 3-17. Thumbnail schematic of case-control and cohort studies of stroke in response to inorganic arsenic exposure (OR or similar) (see interactive data graphic and rationale for study evaluations for cardiovascular effects in HAWC) Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

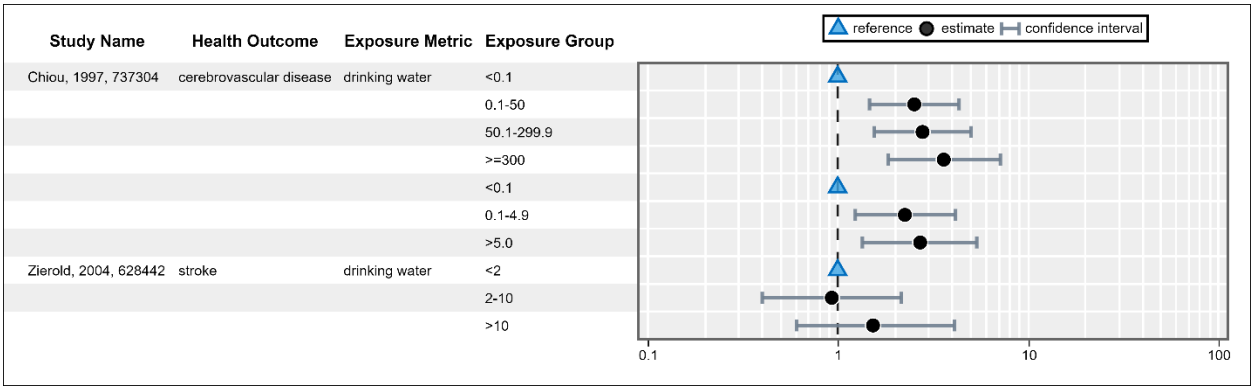


Figure 3-18. Thumbnail schematic of cross-sectional studies of stroke in response to inorganic arsenic exposure (OR or similar) (see interactive data graphic and rationale for study evaluations for cardiovascular effects in HAWC). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Supplemental information: Meta-analysis

In the meta-analysis by Moon et al. (2012), relatively weak (compared to 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, 1.07 (95% CI: 0.96, 1.20).

Summary

Findings from the epidemiological studies is limited and not entirely consistent. Overall, provides suggestive evidence for an association between arsenic exposure and cerebrovascular diseases and mortality from cerebrovascular causes but does not contribute significantly to the overall determination of robust for diseases of the circulatory system .

Other Vascular Diseases

The literature review identified 6 epidemiological studies, 4 case-control/cohort and 2 cross-sectional, considered medium or high confidence that evaluated the association between iAs exposure and other vascular disease (see Figure 3-19). 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., 2005; Tseng et al.,

1996), 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 (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. These few studies of vascular endpoints provide consistent evidence for an array of effects of arsenic on the vascular system at high concentrations.

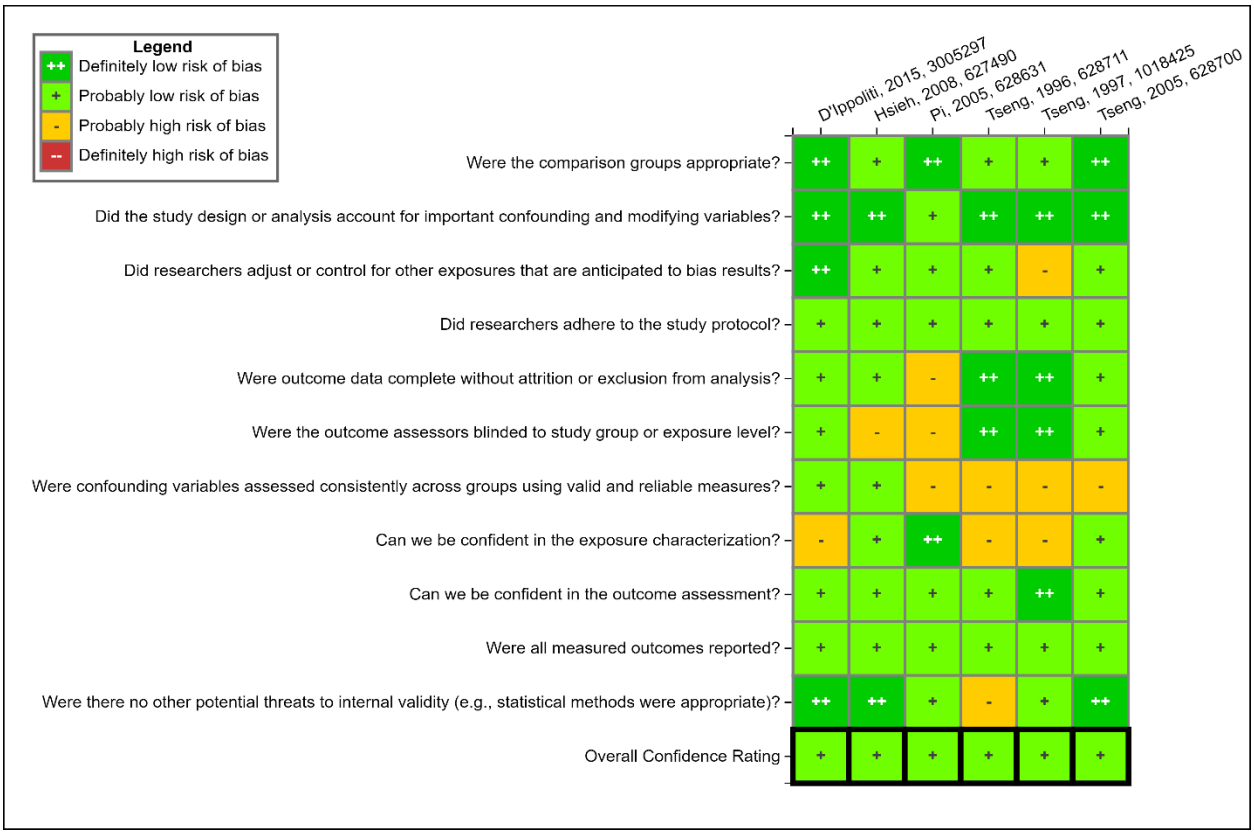


Figure 3-19. Study evaluation ratings for references evaluating other vascular diseases (see interactive version in HAWC).

Circulatory Markers of Cardiovascular Risk

Circulating blood or serum markers of CVD risk were examined in 10 epidemiological studies, 3 cohort and 7 cross-sectional (see Figure 3-20). Moon et al. (2017a) examined the association of iAs in urine with plasma fibrinogen, PAI-1 and CRP among Native Americans 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 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 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. 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 vs. unexposed 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.

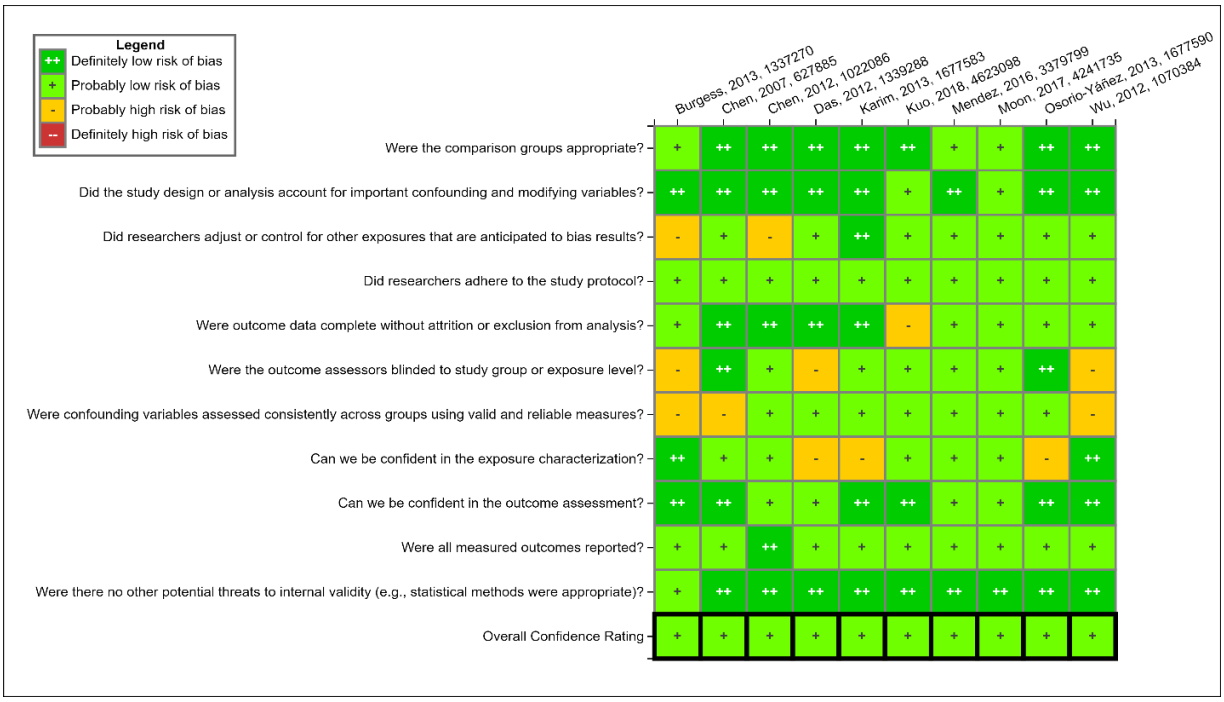


Figure 3-20. Study evaluation outcomes for references evaluating circulatory markers for CVD risk (see interactive version in HAWC).

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

Researchers have proposed that arsenic exposure may cause DCS through a multifactorial process, with most studies evaluating oxidative stress and effects on vascular tissue (see MOA Appendix A in protocol). Arsenic exposure results in the production of reactive oxygen species in vascular endothelial cells, causing endothelial inflammation (Bunderson et al., 2004); (Barchowsky et al., 1999). Further, arsenic exposure (in vitro in primary aorta endothelial and smooth muscle cells or in human lymphocytes) induces 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). Arsenic-induced vascular leakage also has been proposed to be instrumental in induction of CVD. Chen and Chen (2008) reported increased vascular permeability in the skin of rats after intradermal injections of arsenic. The increased permeability resulted from increased production of nitric oxide, hydroxyl radical, and peroxynitrite. In an in vitro study in mouse brain endothelial cells, Bao and Shi (2010) reported increased vascular permeability after treatment with 5-μM arsenic. The vascular permeability was mediated by inducing reactive oxygen species, resulting in the release of vascular endothelial growth factor. Arsenic stimulates the expression of vascular endothelial growth factor 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). Finally, arsenic has been found to cause dysfunction in blood vessel relaxation and to cause vascular constriction (Lee et al., 2003).

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 3.11 of iAs Protocol) identified in Table 3-1, 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 CHD 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 CHD-related mortality among those with lower methylation capacity, suggesting that low

methylation capacity may increase the risk of arsenic associated mortality (Chen et al., 2013b)

- **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 was 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., 2013a).

- **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 3-1) 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 3-1) 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 or 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 to 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 3-1. 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 (adjusted 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 to those with plasma homocysteine levels <12.7 µmol/L and MMA <16.5% (adjusted 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-year and for PMI >1.77 and SMI >6.93 (adjusted OR = 2.93 95% CI 0.90–9.52), PMI >1.77 and SMI ≤6.93 (adjusted OR = 2.85, 95% CI 1.05–7.73), PMI ≤ 0.77 and SMI ≤ 6.93 (adjusted 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. (2013a)	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 (adjusted OR = 1.693, 95% CI 1.028–2.787) compared to those with lower MMA levels, and those with higher DMA levels had decreased risk of hypertension (adjusted OR = 1.549, 95% CI 0.938–2.559) compared to those with lower levels of DMA	China, 0–650 µg/L
	Li et al. (2015)	Significantly higher odds of hypertension among individuals with low methylation capacity (indicated by lower DMA% and SMI) compared to 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)

Modifying factor	Key reference	Effect	Population, exposure level
	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 to never smokers, and those reporting ≥31 years or ≥30 pack-years of smoking, respectively, compared to 0 pack-years 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-year associated with increased risk of electrocardiogram abnormality	Taiwan, 350–1,140 µg/L (water, 1960's)
	Li et al. (2009)	No significant association between atherosclerosis and cumulative arsenic exposure >15,000 µg/L-year 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. (2001)	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)
	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)

Modifying factor	Key reference	Effect	Population, exposure level
	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 to 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 to those without the S allele	Taiwan, <50–>750 µg/L (water)
	Gong and O'Bryant (2012)	Significant association between coronary heart disease, arsenic exposure, and AS3MT genotype GG (compared to AA); significant association between hyperlipidemia and AS3MT genotype AG (compared to AA); hypertension not significantly associated with genotypes studied	United States, 2.2–15.3 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-year 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 years of age exposed in utero or in childhood to approximately 580 µg/L arsenic compared to 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 to 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 years of age exposed in utero or in childhood during the high exposure period (1958-1970) compared to 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 to 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 years <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 years (# years spent at residence)
	Tseng et al. (2005)	Significantly increased risk for peripheral artery disease in men compared to 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 (adjusted HR = 1.35, 95% CI 1.04–1.75) and women alone (adjusted HR = 1.72, 95% CI 1.15–2.57) but not for men alone (adjusted 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 to men	Italy, 0.5-80.4 µg/L (water)

1

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 3-2) given sufficient exposure conditions[14]. 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, while the results for hypertension were also largely consistent. These large studies were conducted in different countries and studied populations with high and low arsenic concentrations in drinking water. The studies adjusted for key confounders including BMI, smoking status, and education level, potential risk factors for cardiovascular disease that may be related to the distribution of arsenic or influence health effects of arsenic exposure.

As shown in Figure 3-5, consistent exposure-dependent associations of iAs concentration in drinking water with IHD-related morbidity and mortality were observed. 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 CHD-related morbidity and mortality (Chen et al., 2013a); (Osorio-Yáñez et al., 2013); (Chiou et al., 2001); (Chen et al., 2013a); (Chiou et al., 2001); (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., 2012c); (Huang et al., 2009); (Li et al., 2009).

As shown in Figure 3-12 and Figure 3-13, associations between iAs exposure and hypertension, which is a risk factor for CHD, 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 ecological studies of pregnant women in the New Hampshire Birth Cohort (Farzan et al., 2015b); (Farzan et al., 2015b) (well-water concentration of 4.3 µg/L) and of children in Mexico (Osorio-Yáñez et al., 2015) (drinking water-arsenic concentrations ranging from 3 to135 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, is reported

[14] The "sufficient exposure conditions" are more fully evaluated and defined for the identified health effects through dose-response analysis in Section 4.

in an arsenic-exposed population of normotensive men in Romania (Kunrath et al., 2013); (Pi et al., 2005); (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., 2013c); (Mordukhovich et al., 2009); (Wang et al., 2009).

Some evidence from epidemiological studies indicates iAs exposure could be associated with 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); (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 quality and 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 diseases of the circulatory system in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <10 μg/L to 930 μg/L. The strongest evidence derives from studies of IHD 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 3-2. 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/Ischemic heart disease incidence and mortality 27 *medium* or *high* confidence studies (21 case-control/cohort; 3 cross-sectional; 3 ecological)	Large, prospective cohort studies support exposure-dependent associations of relatively low exposures to iAs in drinking water (<100 µg/L).	• Most studies are *medium* or *high* confidence • Consistency - across study types, including cross-sectional, and ecological "natural experiments;" across populations including U.S., Bangladesh, China, Taiwan, and Mexico. • Dose-response gradient - observed in many studies. • Large or concerning magnitude of effect - large odds ratios in some studies. • Coherence with findings for related endpoints/CHD risk factors such as hypertension, atherosclerosis.	• No factors noted	⊕⊕⊕ *Robust* Based on consistent evidence with individual-level exposure data including studies with exposure gradients spanning relatively low (<100 ug/L) concentrations of iAs in drinking water, and associations with related CVD endpoints such as atherosclerosis and hypertension.
Hypertension 31 *medium* or *high* confidence studies (12 case-control/cohort; 19 cross-sectional)	Some, but not all, well-designed cohort studies report positive associations. Results are sensitive to the choice of exposure metric.	• Most studies are *medium* or *high* confidence • Consistency - with metrics indicating recent exposure to iAs (or cumulative exposure in currently exposed	• No factors noted	⊕⊕⊕ *Robust* Based on consistent evidence between iAs and hypertension with exposure-dependent changes. Findings further supported by studies showing the effect of iAs

		populations) are generally reported; across different life stages, including adults, pregnant women, and children. • Dose-response gradient observed in many studies. • Large or concerning magnitude of effect • Coherence across markers of hypertension as well as related endpoints such as QT prolongation.		exposure across related endpoints or risk factors.
Cerebrovascular disease and stroke 11 *medium* or *high* confidence studies (7 case-control/cohort; 3 cross-sectional; 1 ecological)	Some well-conducted studies report positive associations. However, imprecise or null associations were also observed across other studies of varying quality and design.	• Most studies are *medium* or *high* confidence • Dose-response gradient observed, though more consistently observed in populations with higher (>50 µg/L) concentrations of iAs in drinking water.	• Unexplained inconsistency across cross-sectional studies.	⊕⊕⊙ *Moderate* Based on some evidence indicating iAs exposure is associated with stroke, although some findings are inconsistent.

1

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. Based 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 diabetes in humans.

There are 112 epidemiologic publications that report on the relationship between arsenic exposure and diabetes (see Figure 3-21). Fifty seven of the 112 studies were considered medium or high confidence, 14 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). Due to the abundance of the evidence base, the subsequent synthesis is focused on the medium and high confidence studies (see Figure 3-22 and Figure 3-23). 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. For cross-sectional studies, the ability to infer temporality (e.g., based on the specific exposure assessment methods used and duration of anticipated exposures) and adjustment for confounding were considered when determining whether they would be considered medium or high confidence versus low. Most of these cross-sectional studies evaluated populations that had experienced chronic or lifelong exposure to arsenic, and thus the concurrent exposure measurements are expected to be a reasonable proxy for exposure during an etiologically relevant period. Further, epidemiologic data related to risk modifiers (e.g., genetic variation, cigarette smoking) are also presented. The information below is organized by study design.

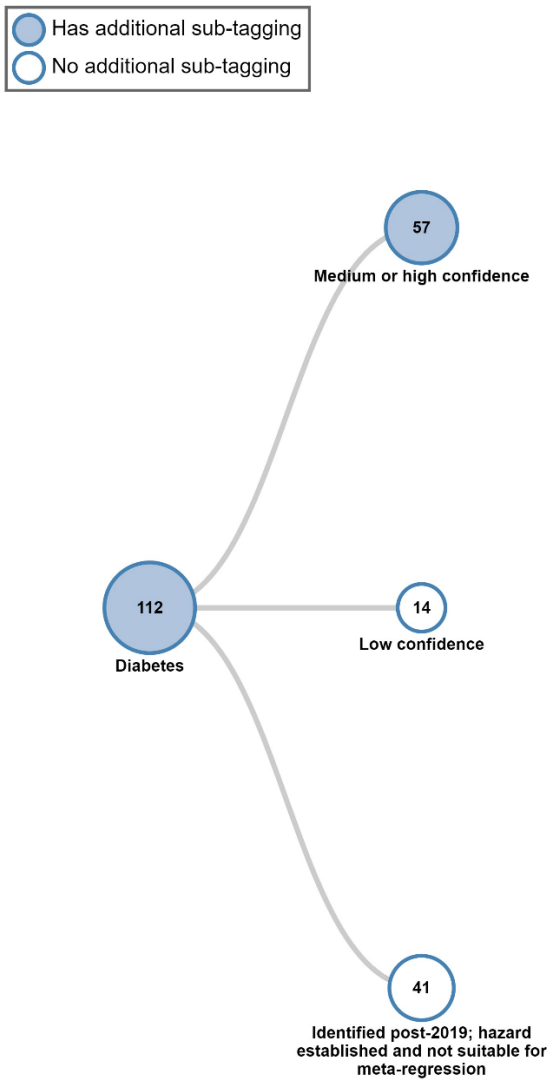


Figure 3-21. Literature tree of epidemiological studies that assessed diabetes (see interactive version in HAWC).

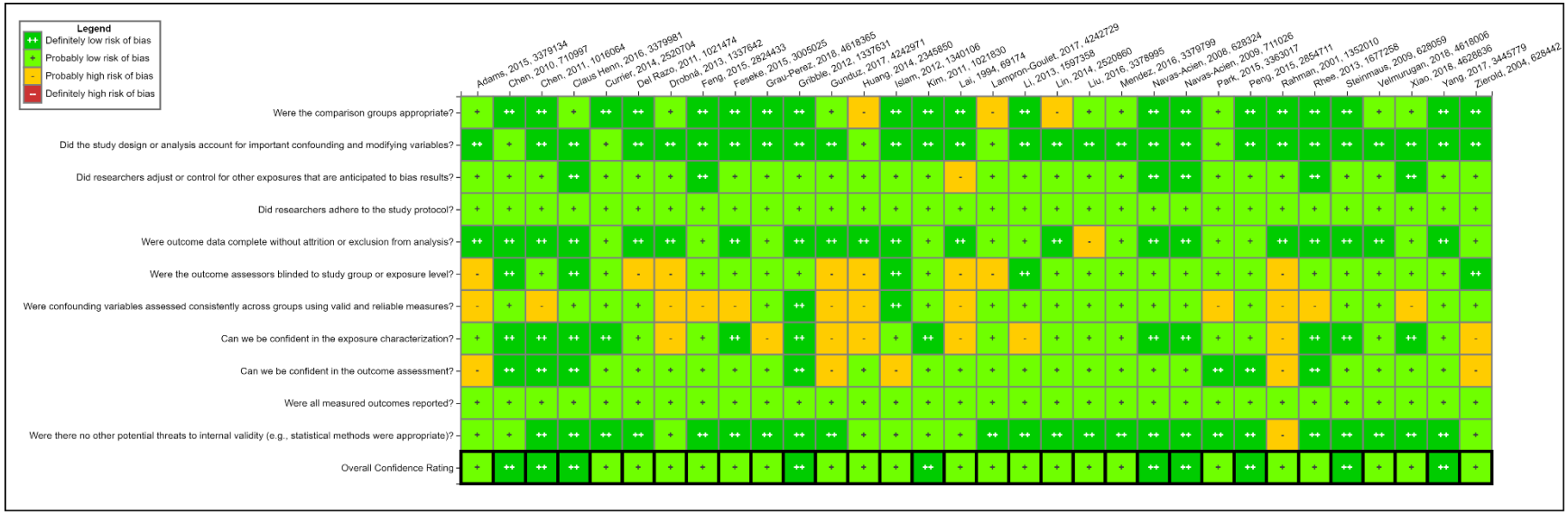


Figure 3-22. Study evaluation ratings for cross-sectional studies evaluating diabetes (see interactive version in HAWC).

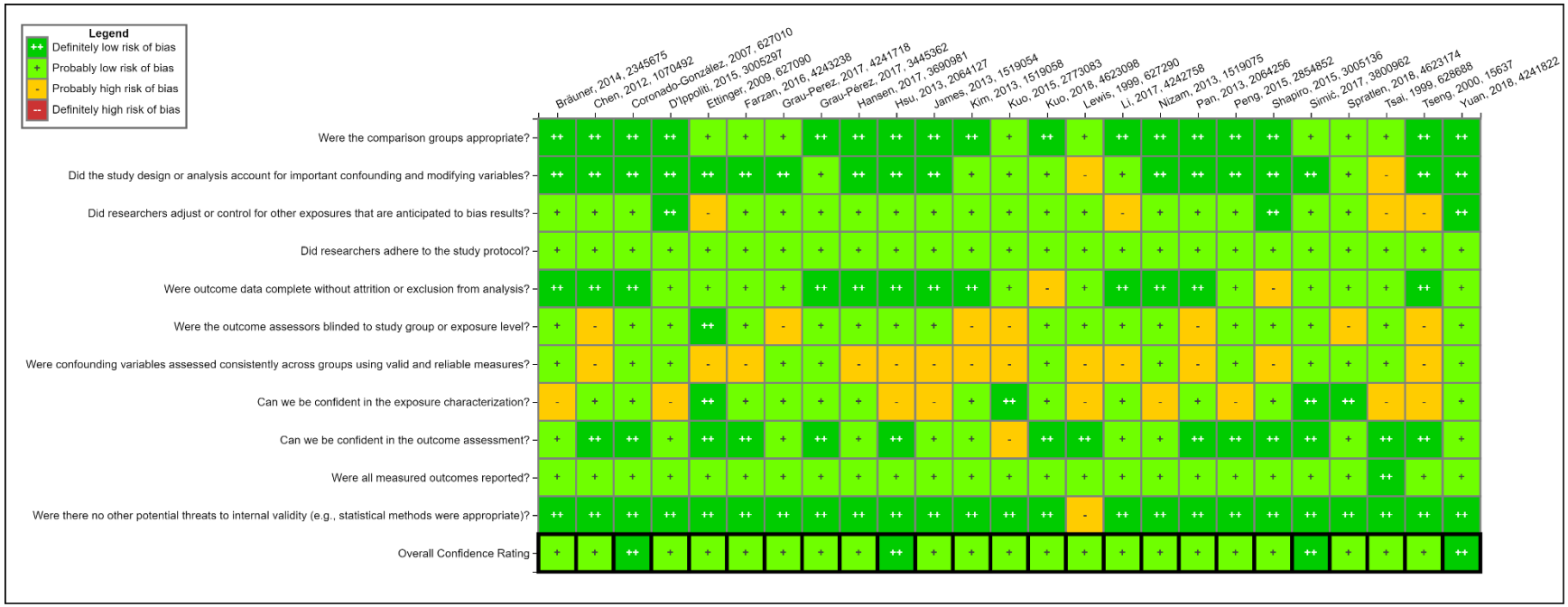


Figure 3-23. Study evaluation ratings for case-control, cohort, and ecological studies evaluating diabetes (see interactive version in HAWC).

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).

Exposure assessment included internal biomarkers of exposure, such as in urine, blood, toenail, hair, or meconium, or drinking water arsenic concentration by water consumption level. The use of urinary biomarkers of arsenic exposure could be affected by creatinine output, which varies based on age, body mass index (BMI), and muscle mass. As summarized in supporting materials from the 2011 NTP workshop evaluating the association between arsenic and diabetes (Maull et al., 2012), adjustment of urinary arsenic concentrations by creatinine may lead to bias because creatinine excretion is reduced in diabetics, and the direction of the overall bias cannot be predicted. Studies with creatinine corrected urinary intake biomarker data were preferred, as urine creatinine is one practical approach to correct arsenic concentrations for urine dilution as compared to 24-h or 12-h urine samples (Hsieh et al., 2019). Other important confounders considered in analyses include diabetes risk factors, such as body mass or percent body fat indices, and smoking and alcohol statuses, and seafood. Seafood is the main source of organic arsenic compounds including arsenobetaine, a non-toxic arsenical that contributes to total urinary arsenic. Approximately half of the studies either adjusted for seafood consumption or arsenobetaine, confirmed low seafood consumption in the study population, or asked participants not to consume seafood prior to study inclusion, while the other studies did not address potential confounding by organic arsenic by seafood intake, some due to confirmed low consumption of seafood intake in the population(s).

Overall, the association between arsenic exposure and diabetes was mostly positive and consistent across studies (see Figure 3-24 and Figure 3-25). The strongest evidence comes from cohort and case-control studies, which generally demonstrated a positive association between arsenic exposure and incidence of diabetes mellitus, diabetes-related mortality (D'Ippoliti et al., 2015), or gestational diabetes (Ettinger et al., 2009); (Shapiro et al., 2015); (Peng et al., 2015b); (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 24 case-control and cohort *medium* or *high* confidence studies that evaluated the association between iAs exposure and diabetes. The findings generally demonstrated a positive association between arsenic exposure and incidence of diabetes; the hazard ratios were usually around 2 when compared to those in lowest exposure category, often ≤10 µg/L (see Figure 3-24). 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 an adjusted relative risk (RR) of 2.1 (95% CI 1.1, 4.2) for cumulative drinking water exposures ≥17,000 µg/L-year. Bräuner et al. (2014) conducted a prospective cohort study that identified an adjusted 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 adjIRRs were somewhat attenuated (IRR = 1.02; 95% CI 0.99, 1.05). When the study population was evaluated by quartiles, the adjIRR 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. A more recent prospective cohort study by Spratlen (2018) evaluated the associations of baseline arsenic exposure (i.e., urinary arsenic levels) and metabolism (relative percentage of arsenic species over their sum, (σAs)) 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)[15]. The authors found that an interquartile-range increase in arsenic exposure (σAs) 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. In a Chinese population, a case-control study (Li et al., 2017) found plasma arsenic to be associated with diabetes mortality, while (Yuan et al., 2018) observed a null association between plasma arsenic concentrations 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 II 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 σAs at baseline was 5.9 µg/L.

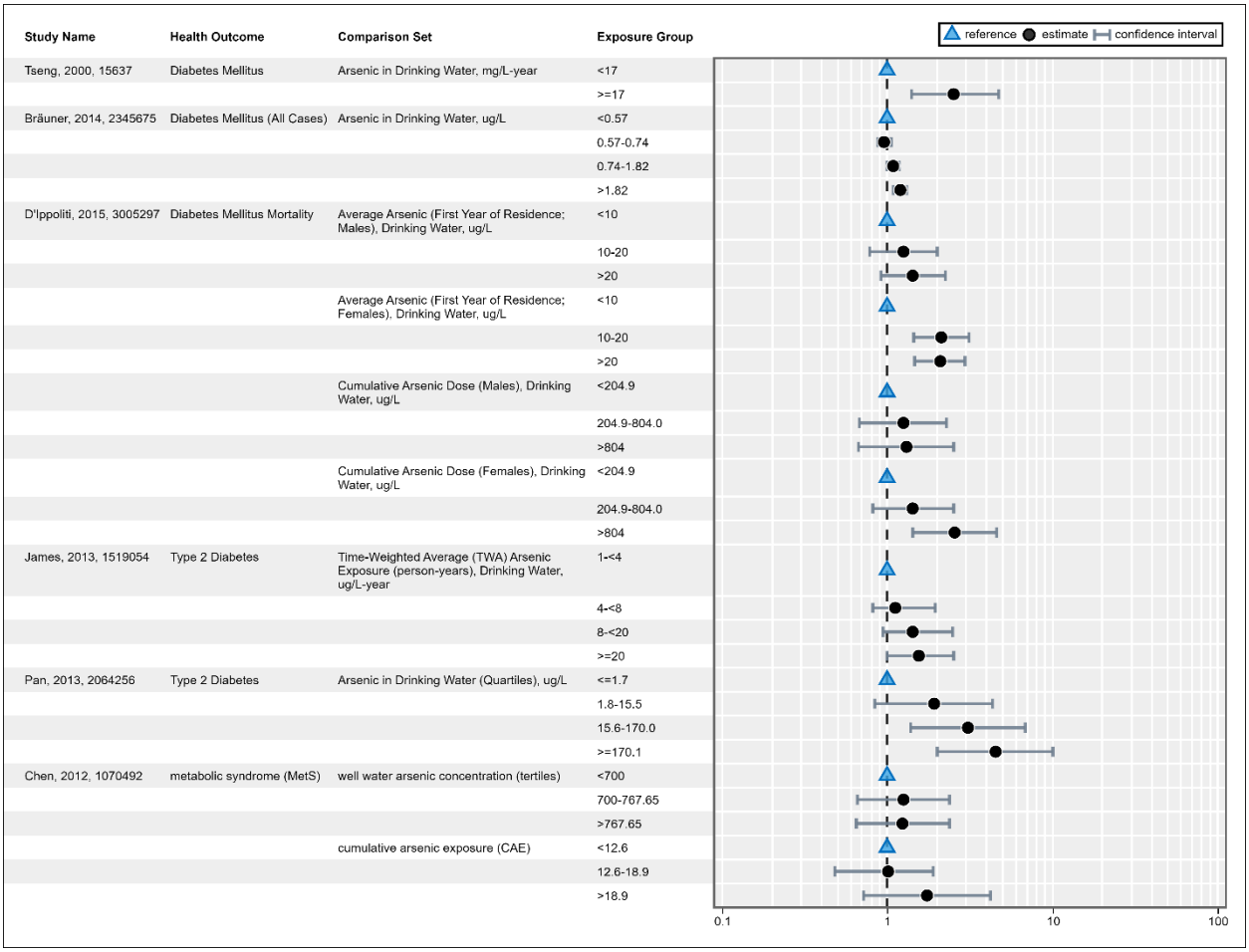
[15]The SHFS is an extension of the Strong Heart Study (SHS), a population-based study of American Indian adults in which relatives of the SHS participants were recruited.

The authors reported that over 10,327 person-years of follow-up, 252 participants developed diabetes (N=1838). Median HOMA2-IR at baseline was 1.5. The fully adjusted hazard ratio [95% (CI)] for incident diabetes per an interquartile range increase in σAs 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, they did observe that 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, σAs 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.

Although the majority of the prospective cohorts observed a statistically significant association between arsenic and diabetes, one study reported no association (Chen et al., 2012b). However, the study by (Chen et al., 2012b) was not specifically evaluating diabetes and iAs exposure, rather evaluating metabolic syndrome (defined as having at least three of five risk factors: large waistline, high triglycerides, low HDL, high blood pressure, and high fasting blood sugar) and insulin sensitivity (Chen et al., 2012b). While an increase was observed in the adjOR 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.

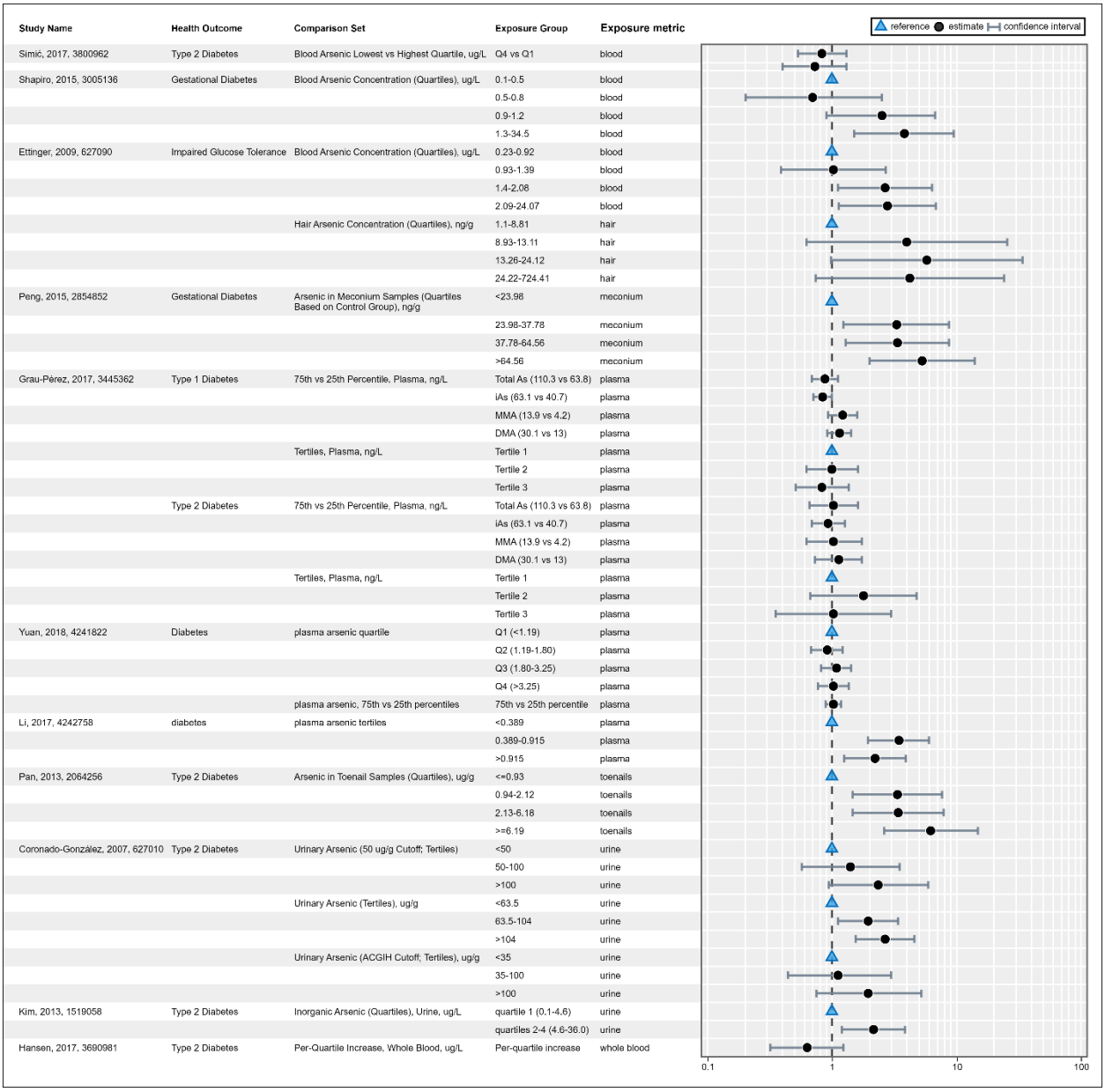
Evidence from retrospective cohort studies also largely reported a positive association between arsenic exposure and diabetes. ''Ippoliti (2015) reported an association between cumulative arsenic (CAI) exposure levels >804.0 µg with diabetes mortality in females (Hazard Ratio (HR) of 2.56 CI 95% 1.43, 4.57 p<0.001)[16].

[16]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
Tseng, 2000, 15637	Diabetes Mellitus	Arsenic in Drinking Water, mg/L-year	<17
			>=17
Bräuner, 2014, 2345675	Diabetes Mellitus (All Cases)	Arsenic in Drinking Water, ug/L	<0.57
			0.57-0.74
			0.74-1.82
			>1.82
D'Ippoliti, 2015, 3005297	Diabetes Mellitus Mortality	Average Arsenic (First Year of Residence; Males), Drinking Water, ug/L	<10
			10-20
			>20
		Average Arsenic (First Year of Residence; Females), Drinking Water, ug/L	<10
			10-20
			>20
		Cumulative Arsenic Dose (Males), Drinking Water, ug/L	<204.9
			204.9-804.0
			>804
		Cumulative Arsenic Dose (Females), Drinking Water, ug/L	<204.9
			204.9-804.0
			>804
James, 2013, 1519054	Type 2 Diabetes	Time-Weighted Average (TWA) Arsenic Exposure (person-years), Drinking Water, ug/L-year	1-<4
			4-<8
			8-<20
			>=20
Pan, 2013, 2064256	Type 2 Diabetes	Arsenic in Drinking Water (Quartiles), ug/L	<=1.7
			1.8-15.5
			15.6-170.0
			>=170.1
Chen, 2012, 1070492	metabolic syndrome (MetS)	well water arsenic concentration (tertiles)	<700
			700-767.65
			>767.65
		cumulative arsenic exposure (CAE)	<12.6
			12.6-18.9
			>18.9

(a) Regression coefficient—drinking water—categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	Exposure metric
Simić, 2017, 3800962	Type 2 Diabetes	Blood Arsenic Lowest vs Highest Quartile, ug/L	Q4 vs Q1	blood
Shapiro, 2015, 3005136	Gestational Diabetes	Blood Arsenic Concentration (Quartiles), ug/L	0.1-0.5	blood
			0.5-0.8	blood
			0.9-1.2	blood
			1.3-34.5	blood
Ettinger, 2009, 627090	Impaired Glucose Tolerance	Blood Arsenic Concentration (Quartiles), ug/L	0.23-0.92	blood
			0.93-1.39	blood
			1.4-2.08	blood
			2.09-24.07	blood
		Hair Arsenic Concentration (Quartiles), ng/g	1.1-8.81	hair
			8.93-13.11	hair
			13.26-24.12	hair
			24.22-724.41	hair
Peng, 2015, 2854852	Gestational Diabetes	Arsenic in Meconium Samples (Quartiles Based on Control Group), ng/g	<23.98	meconium
			23.98-37.78	meconium
			37.78-64.56	meconium
			>64.56	meconium
Grau-Pérez, 2017, 3445362	Type 1 Diabetes	75th vs 25th Percentile, Plasma, ng/L	Total As (110.3 vs 63.8)	plasma
			iAs (63.1 vs 40.7)	plasma
			MMA (13.9 vs 4.2)	plasma
			DMA (30.1 vs 13)	plasma
		Tertiles, Plasma, ng/L	Tertile 1	plasma
			Tertile 2	plasma
			Tertile 3	plasma
	Type 2 Diabetes	75th vs 25th Percentile, Plasma, ng/L	Total As (110.3 vs 63.8)	plasma
			iAs (63.1 vs 40.7)	plasma
			MMA (13.9 vs 4.2)	plasma
			DMA (30.1 vs 13)	plasma
		Tertiles, Plasma, ng/L	Tertile 1	plasma
			Tertile 2	plasma
			Tertile 3	plasma
Yuan, 2018, 4241822	Diabetes	plasma arsenic quartile	Q1 (<1.19)	plasma
			Q2 (1.19-1.80)	plasma
			Q3 (1.80-3.25)	plasma
			Q4 (>3.25)	plasma
		plasma arsenic, 75th vs 25th percentiles	75th vs 25th percentile	plasma
Li, 2017, 4242758	diabetes	plasma arsenic tertiles	<0.389	plasma
			0.389-0.915	plasma
			>0.915	plasma
Pan, 2013, 2064256	Type 2 Diabetes	Arsenic in Toenail Samples (Quartiles), ug/g	<=0.93	toenails
			0.94-2.12	toenails
			2.13-6.18	toenails
			>=6.19	toenails
Coronado-González, 2007, 627010	Type 2 Diabetes	Urinary Arsenic (50 ug/g Cutoff; Tertiles)	<50	urine
			50-100	urine
			>100	urine
		Urinary Arsenic (Tertiles), ug/g	<63.5	urine
			63.5-104	urine
			>104	urine
		Urinary Arsenic (ACGIH Cutoff; Tertiles), ug/g	<35	urine
			35-100	urine
			>100	urine
Kim, 2013, 1519058	Type 2 Diabetes	Inorganic Arsenic (Quartiles), Urine, ug/L	quartile 1 (0.1-4.6)	urine
			quartiles 2-4 (4.6-36.0)	urine
Hansen, 2017, 3690981	Type 2 Diabetes	Per-Quartile Increase, Whole Blood, ug/L	Per-quartile increase	whole blood

(b) Regression coefficient—biomarker (blood, hair, meconium, plasma, toenail, urine, whole blood)—categorical exposure

Figure 3-24. Case-control/Cohort epidemiologic studies examining the association between arsenic and diabetes. (a) drinking water—categorical exposure; (b) biomarker—categorical exposure (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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 (adjusted hazard ratio = 1.27; 95% CI 1.02, 1.64). Kim et al. (2013) observed that arsenic exposure was associated with an increased adjOR (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, adjOR = 3.07, 95% CI 1.38, 6.85; ≥170.1 µg/L in drinking water, adjOR = 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 arsenic is not expected to fluctuate substantially over time. In a population in Bangladesh, measurement of arsenic exposure occurred prior to diabetes development, with similar associations seen with both drinking water exposure and toenail biomarker Pan et al. (2013b). From another study in Bangladesh, (Nizam et al., 2013) examined the metabolism of arsenic in diabetes as compared to non-diabetics 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 (adjOR = 2.16; 95% CI 1.23, 3.79), and a three times greater risk for those with >100 µg/g creatinine (adjOR = 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. with null results observed in Utah, U.S. (Lewis et al., 1999).

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 (adjOR = 3.28; 95% CI 1.24, 8.71); 3rd (adjOR = 3.35; 95% CI 1.28, 8.75); and 4th (adjOR = 5.25; 95% CI 1.99, 13.86) quartiles of arsenic. 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).

Grau-Pérez et al. (2017) 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 either type 1 diabetes (T1D) or type 2 diabetes (T2D). However, the methylarsonite (MMA)% OR of T1D showed an

association between arsenic metabolism and T1D (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 (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).

Cross-sectional studies

Thirty-two (*medium* and *high* confidence) cross-sectional studies 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 (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.

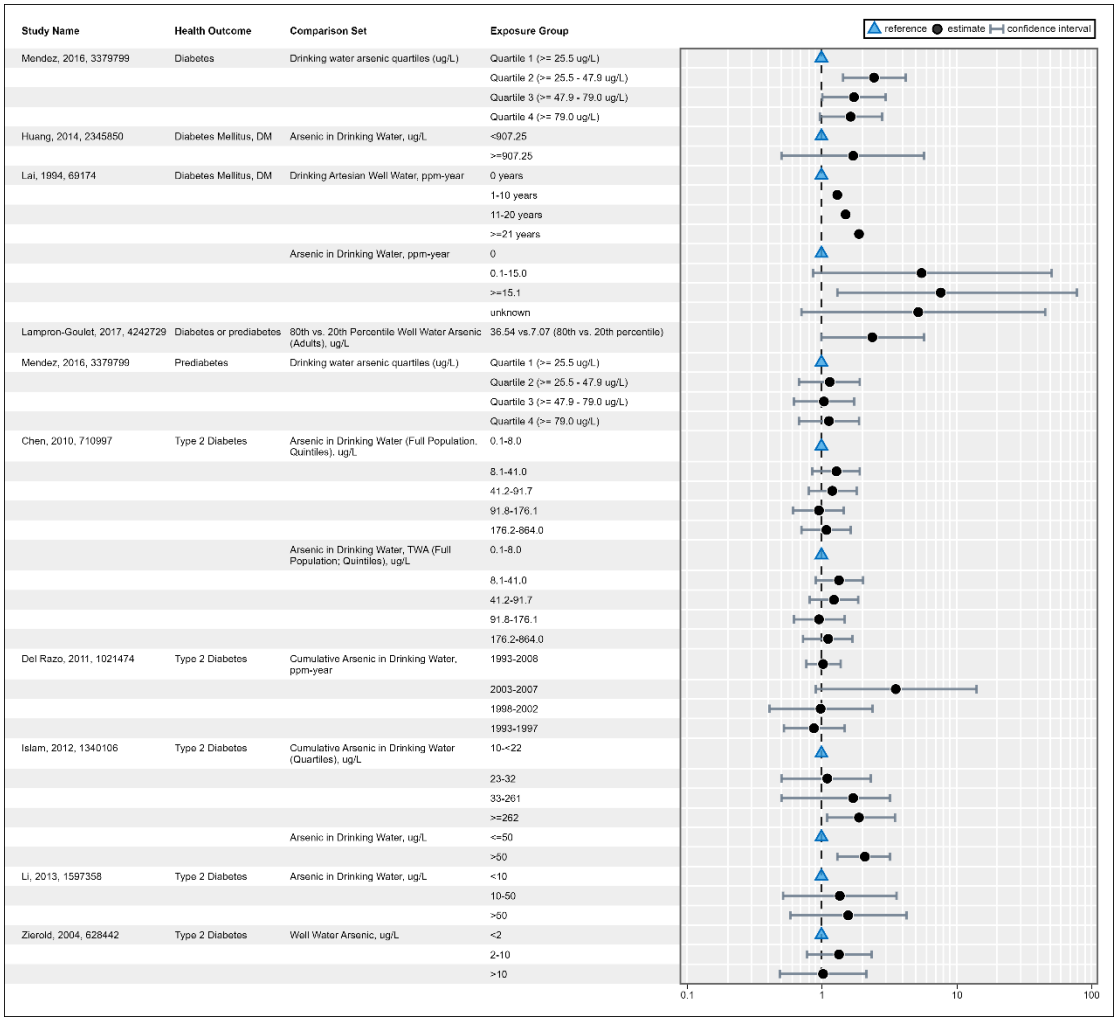
Currier et al. (2014) examined associations between arsenic species (including 3-60ethylarsonate [MAIII) and dimethylarsinite [DMAIII]) in exfoliated urothelial cells (EUC) (an alternative to the measures of iAs in urine) and the prevalence of diabetes among residents of Chihuahua, Mexico. They found 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.Del Razo et al. (2011) 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 United States (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 T2 diabetes (Navas-Acien et al., 2009a); (Navas-Acien et al., 2008); and (Adams et al., 2015) observed an association between urinary arsenic and diabetes in older Hispanic adults living in southern New Mexico. However, (Steinmaus et al., 2009) saw no increased risk of diabetes with arsenic exposure in NHANES adults; and (Peng et al., 2015a), when examining urinary arsenic and insulin resistance in NHANES adolscents, did not observe an association. In rural Oklahoma, U.S., (Claus Henn et al., 2016) inverse associations between arsenic and birth outcomes were observed to be stronger among women with impaired glucose tolerance.

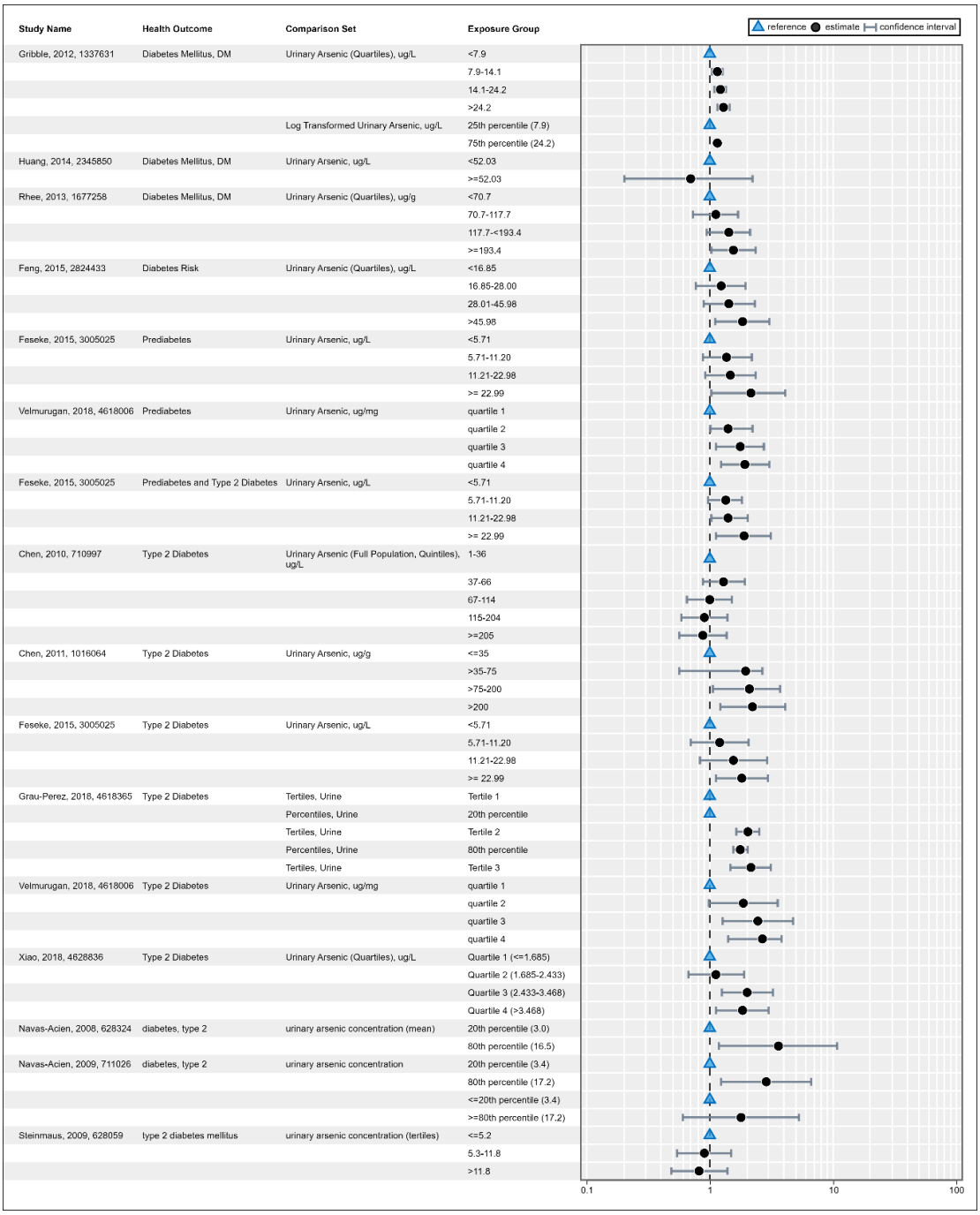
In Korea, Rhee et al. (2013) reported a statistically significant adjusted OR in the highest quartile of arsenic exposure (≥193.4 µg/g-creatinine urinary total arsenic; adjOR = 1.56; 95% CI 1.03, 2.36) compared with the lowest exposure group; adjusted Ors exhibited a positive linear trend when comparing 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 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 adjOR (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; however, arsenic exposure was measured using creatinine-adjusted urinary arsenic which reduced confidence in the results (Chen et al., 2011a). In Cambodia, drinking water with arsenic levels above the median 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 and found an association between exposure to arsenic and glucosuria. In China, (Li et al., 2013a) did not observe an association between arsenic exposure and T2 diabetes.



Study Name	Health Outcome	Comparison Set	Exposure Group
Mendez, 2016, 3379799	Diabetes	Drinking water arsenic quartiles (ug/L)	Quartile 1 (>= 25.5 ug/L)
			Quartile 2 (>= 25.5 - 47.9 ug/L)
			Quartile 3 (>= 47.9 - 79.0 ug/L)
			Quartile 4 (>= 79.0 ug/L)
Huang, 2014, 2345850	Diabetes Mellitus, DM	Arsenic in Drinking Water, ug/L	<907.25
			>=907.25
Lai, 1994, 69174	Diabetes Mellitus, DM	Drinking Artesian Well Water, ppm-year	0 years
			1-10 years
			11-20 years
			>=21 years
		Arsenic in Drinking Water, ppm-year	0
			0.1-15.0
			>=15.1
			unknown
Lamprон-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)
Mendez, 2016, 3379799	Prediabetes	Drinking water arsenic quartiles (ug/L)	Quartile 1 (>= 25.5 ug/L)
			Quartile 2 (>= 25.5 - 47.9 ug/L)
			Quartile 3 (>= 47.9 - 79.0 ug/L)
			Quartile 4 (>= 79.0 ug/L)
Chen, 2010, 710997	Type 2 Diabetes	Arsenic in Drinking Water (Full Population, Quintiles), ug/L	0.1-8.0
			8.1-41.0
			41.2-91.7
			91.8-176.1
			176.2-864.0
		Arsenic in Drinking Water, TWA (Full Population; Quintiles), ug/L	0.1-8.0
			8.1-41.0
			41.2-91.7
			91.8-176.1
			176.2-864.0
Del Razo, 2011, 1021474	Type 2 Diabetes	Cumulative Arsenic in Drinking Water, ppm-year	1993-2008
			2003-2007
			1998-2002
			1993-1997
Islam, 2012, 1340106	Type 2 Diabetes	Cumulative Arsenic in Drinking Water (Quartiles), ug/L	10-<22
			23-32
			33-261
			>=262
		Arsenic in Drinking Water, ug/L	<=50
			>50
Li, 2013, 1597358	Type 2 Diabetes	Arsenic in Drinking Water, ug/L	<10
			10-50
			>50
Zierold, 2004, 628442	Type 2 Diabetes	Well Water Arsenic, ug/L	<2
			2-10
			>10

(a) Drinking water—categorical exposure (odds ratios)



Study Name	Health Outcome	Comparison Set	Exposure Group
Gribble, 2012, 1337631	Diabetes Mellitus, DM	Urinary Arsenic (Quartiles), ug/L	<7.9
			7.9-14.1
			14.1-24.2
			>24.2
		Log Transformed Urinary Arsenic, ug/L	25th percentile (7.9)
			75th percentile (24.2)
Huang, 2014, 2345850	Diabetes Mellitus, DM	Urinary Arsenic, ug/L	<52.03
			>=52.03
Rhee, 2013, 1677258	Diabetes Mellitus, DM	Urinary Arsenic (Quartiles), ug/g	<70.7
			70.7-117.7
			117.7-<193.4
			>=193.4
Feng, 2015, 2824433	Diabetes Risk	Urinary Arsenic (Quartiles), ug/L	<16.85
			16.85-28.00
			28.01-45.98
			>45.98
Feseke, 2015, 3005025	Prediabetes	Urinary Arsenic, ug/L	<5.71
			5.71-11.20
			11.21-22.98
			>= 22.99
Velmurugan, 2018, 4618006	Prediabetes	Urinary Arsenic, ug/mg	quartile 1
			quartile 2
			quartile 3
			quartile 4
Feseke, 2015, 3005025	Prediabetes and Type 2 Diabetes	Urinary Arsenic, ug/L	<5.71
			5.71-11.20
			11.21-22.98
			>= 22.99
Chen, 2010, 710997	Type 2 Diabetes	Urinary Arsenic (Full Population, Quintiles), ug/L	1-36
			37-66
			67-114
			115-204
			>=205
Chen, 2011, 1016064	Type 2 Diabetes	Urinary Arsenic, ug/g	<=35
			>35-75
			>75-200
			>200
Feseke, 2015, 3005025	Type 2 Diabetes	Urinary Arsenic, ug/L	<5.71
			5.71-11.20
			11.21-22.98
			>= 22.99
Grau-Perez, 2018, 4618365	Type 2 Diabetes	Tertiles, Urine	Tertile 1
		Percentiles, Urine	20th percentile
		Tertiles, Urine	Tertile 2
		Percentiles, Urine	80th percentile
		Tertiles, Urine	Tertile 3
Velmurugan, 2018, 4618006	Type 2 Diabetes	Urinary Arsenic, ug/mg	quartile 1
			quartile 2
			quartile 3
			quartile 4
Xiao, 2018, 4628836	Type 2 Diabetes	Urinary Arsenic (Quartiles), ug/L	Quartile 1 (<=1.685)
			Quartile 2 (1.685-2.433)
			Quartile 3 (2.433-3.468)
			Quartile 4 (>3.468)
Navas-Acien, 2008, 628324	diabetes, type 2	urinary arsenic concentration (mean)	20th percentile (3.0)
			80th percentile (16.5)
Navas-Acien, 2009, 711026	diabetes, type 2	urinary arsenic concentration	20th percentile (3.4)
			80th percentile (17.2)
			<=20th percentile (3.4)
			>=80th percentile (17.2)
Steinmaus, 2009, 628059	type 2 diabetes mellitus	urinary arsenic concentration (tertiles)	<=5.2
			5.3-11.8
			>11.8

(b) Urine—categorical exposure (odds ratios)

Figure 3-25. Cross-sectional epidemiologic studies examining the association between arsenic and diabetes. (a) drinking water—categorical exposure (odds ratios); (b) urine—categorical exposure (odds ratios) (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Mechanistic Observations

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 (see the iAs Protocol (link provided in Appendix A) for details on possible modes of action). In their 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 chonic 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 indiced 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.

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 3.11 of iAs Protocol) identified in Table 3-3, 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 US (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 to non-smokers exposed to lower levels (<15.5 µg/L) (Pan et al., 2013b). Smoking history data was only available in men.

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

Risk Modifiers	References	Finding	Population, exposure level
Genetic variation	Chen et al. (2012b) 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. (2012b)	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)
	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, Native American 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 T1D due to increase %MMA	USA, Native American Population, 5.9 µg/L total urinary arsenic

Risk Modifiers	References	Finding	Population, exposure level
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 diabetes in humans (see Table 3-4) given sufficient exposure conditions[17]. 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 from arsenic-endemic areas (e.g., Bangladesh, Taiwan; >150 µg/L arsenic in drinking water) and those from geographical areas with comparatively lower levels of arsenic exposure (e.g., Denmark, United States; <150 µg/L arsenic in drinking water).

A strong evidence base demonstrating arsenic exposure causes diabetes in humans comes from cohort, case-control studies, and cross-sectional studies which were largely consistent in demonstrating a positive association between arsenic exposure and incidence of diabetes mellitus, diabetes-related mortality, or gestational diabetes. Trivalent arsenic species may also be responsible for associations between chronic iAs exposure and diabetes. Several studies reported a strong exposure response gradient, and a temporal relationship was evident in several prospective cohort studies in which prolonged arsenic exposure was associated with diabetes. 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.

Overall, the currently available epidemiologic **evidence demonstrates** that iAs causes diabetes in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <150µg/L to >150µg/L. 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).

[17]The "sufficient exposure conditions" are more fully evaluated and defined for the identified health effects through dose-response analysis in Section 4.

Table 3-4. Evidence profile table for epidemiological evidence on iAs and 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)**
56 *medium* or *high* confidence studies	Generally consistent, positive associations across diverse populations. Some evidence for exposure-dependent changes within and across studies with well-characterized exposures, long duration exposures with sufficient follow-up for latency.	• Most studies are *medium* or *high* confidence • *Consistency* - of strong positive associations in populations across 3 continents, primarily at > 10 ug/kg-day. • *Dose-response gradient* - observed across studies. • *Large* or *concerning magnitude* of effect- Hazard ratios ~ 2 were observed.	• No factors noted	⊕⊕⊕ *Robust* Based on consistent, reliable evidence from cohort and case-control studies with coherence across diverse study designs.

3.2.3. Pregnancy and Birth 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 pregnancy and birth outcomes was recommended for consideration for dose-response analysis in the IRIS Toxicological Review. Based on 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 pregnancy and birth outcomes in humans.

A systematic literature search identified 102 epidemiological studies that evaluated the association between exposure to inorganic arsenic (iAs) and pregnancy and birth outcomes (see Figure 3-26). These publications underwent study evaluation, and 68 studies were considered

medium or *high* confidence while 22 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.

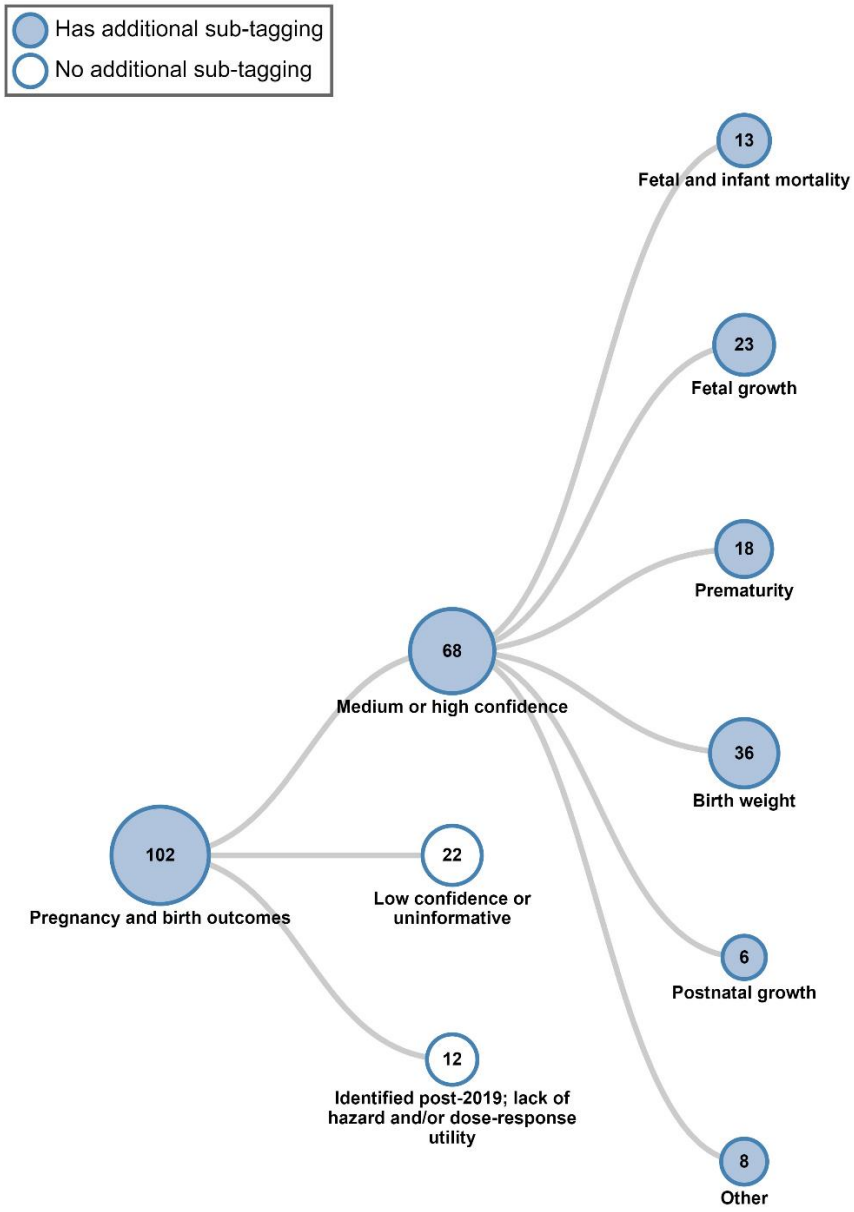


Figure 3-26. Literature tree of epidemiological studies assessing pregnancy and birth outcomes (see interactive version in HAWC).

This section presents a review of the evidence for an association between iAs exposure and fetal and postnatal 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.[18] 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 to typical cross-sectional study scenarios. Ecological studies (with long well-defined exposure periods, limited population 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, 3 mg/kg in soil) from cohort and cross-sectional studies on pregnancy and birth outcomes in the United States, Chile, and China (e.g., (Wang et al., 2022a; Almberg et al., 2017; Claus Henn et al., 2016; Mcdermott et al., 2014; Hopenhayn et al., 2003)

Finally, this section summarizes mechanistic observations and also discusses how an association between iAs and pregnancy and birth outcomes might be influenced by potential risk modifiers (e.g., timing of early-life exposure, 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 noted throughout the text.

Fetal and infant mortality

The literature review identified thirteen *medium* or *high* confidence epidemiological studies that evaluated the association between iAs exposure and fetal and infant mortality. (see Figure 3-27). The most commonly assessed outcomes in these studies were spontaneous abortion, stillbirth, and infant death (death in the first year of life), neonatal death (death that occurred in the first

[18]Neurodevelopmental outcomes are discussed in Section 3.2.4.

month 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 3-28 and Figure 3-29.

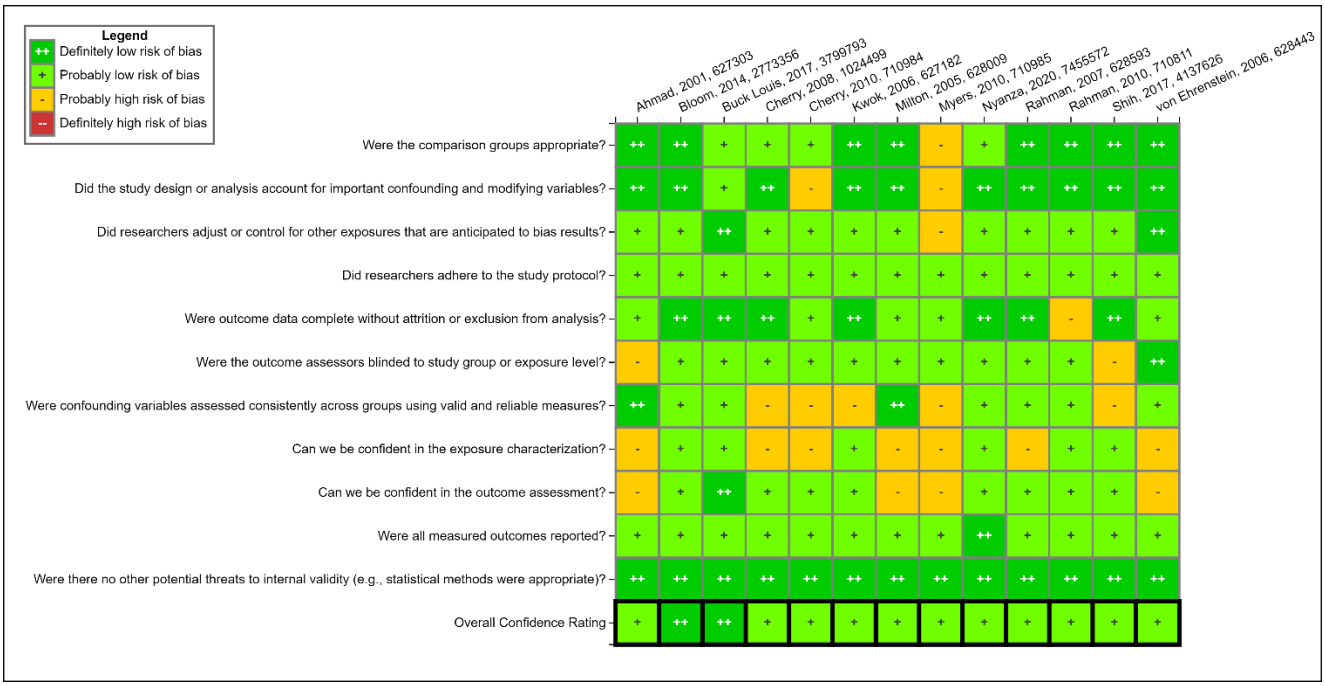


Figure 3-27. Study evaluation ratings for references evaluating fetal and infant mortality (see interactive version in HAWC).

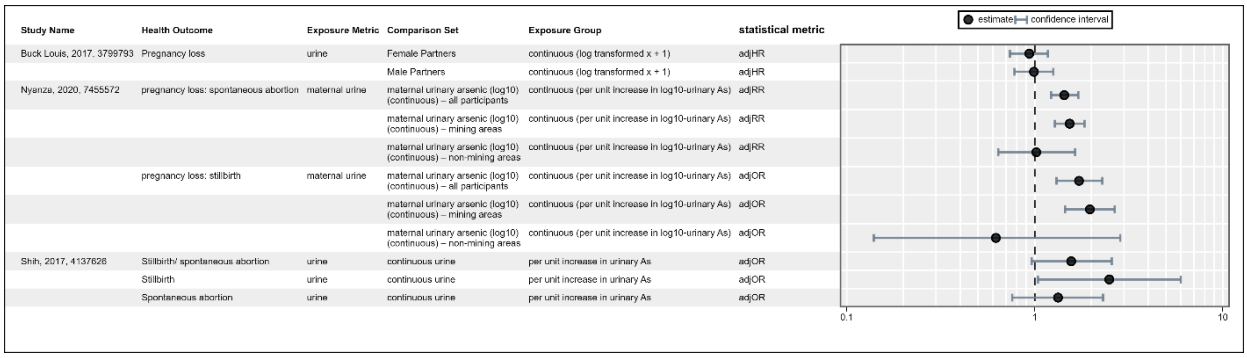
The strongest evidence for an association between iAs exposure and fetal and infant mortality comes from cohort and cross-sectional studies conducted in Bangladesh (Ahmad et al., 2001); (Milton et al., 2005); (Rahman et al., 2007); (Rahman et al., 2010); (Shih et al., 2017) and India (von Ehrenstein 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. The primary limitation is that most of these studies did not report individual data on water consumption and instead relied on iAs concentrations measured in drinking water to assign exposure. The resulting exposure misclassification likely was nondifferential since availability of alternative drinking water sources would have been less common in those locations, with bias expected to be towards the null. An additional limitation is that the gestational age at which arsenic exposure occurred was rarely reported., although it is assumed that exposure occurred throughout gestation. Yet overall, these deficiencies in the individual exposure and outcome domains were balanced by other strengths in these studies (e.g. minimal concern for selection bias, appropriate control for key confounders, appropriate statistical analyses), allowing for overall medium and high confidence ratings.

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 3-28 and Figure 3-29). 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 3-29). 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 (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 3-28). 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 "tudy'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 3-28).

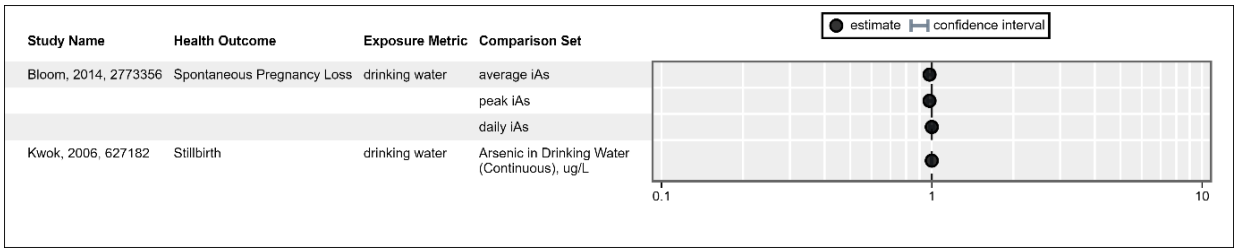
In a cross-sectional study conducted in Bangladesh, Milton et al. (2005) used a single well-water measurement from village tube wells to estimate iAs exposure during pregnancy among a group of mothers. The authors reported a strong, statistically significant association between drinking water iAs levels >50 μg/L (measured after pregnancy) and neonatal mortality, spontaneous abortion, and stillbirth (see Figure 3-28). 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 non-significant, positive association between arsenic and infant mortality . No association was observed between arsenic exposure and spontaneous abortion (see Figure 3-28). 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.



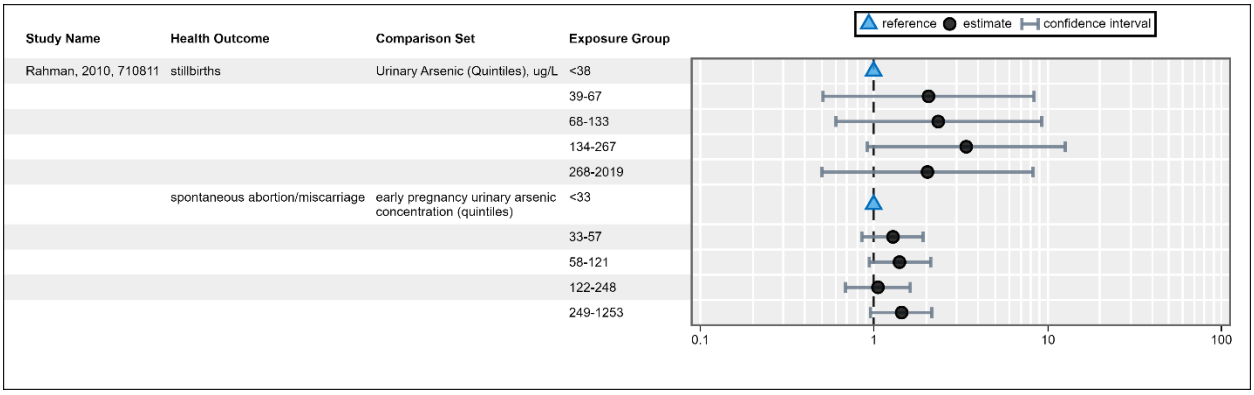
Study Name	Health Outcome	Exposure Metric	Comparison Set	Exposure Group	statistical metric
Buck Louis, 2017, 3799793	Pregnancy loss	urine	Female Partners	continuous (log transformed x + 1)	adjHR
			Male Partners	continuous (log transformed x + 1)	adjHR
Nyanza, 2020, 7455572	pregnancy loss: spontaneous abortion	maternal urine	maternal urinary arsenic (log10) (continuous) – all participants	continuous (per unit increase in log10-urinary As)	adjRR
			maternal urinary arsenic (log10) (continuous) – mining areas	continuous (per unit increase in log10-urinary As)	adjRR
			maternal urinary arsenic (log10) (continuous) – non-mining areas	continuous (per unit increase in log10-urinary As)	adjRR
	pregnancy loss: stillbirth	maternal urine	maternal urinary arsenic (log10) (continuous) – all participants	continuous (per unit increase in log10-urinary As)	adjOR
			maternal urinary arsenic (log10) (continuous) – mining areas	continuous (per unit increase in log10-urinary As)	adjOR
			maternal urinary arsenic (log10) (continuous) – non-mining areas	continuous (per unit increase in log10-urinary As)	adjOR
Shih, 2017, 4137626	Stillbirth/ spontaneous abortion	urine	continuous urine	per unit increase in urinary As	adjOR
	Stillbirth	urine	continuous urine	per unit increase in urinary As	adjOR
	Spontaneous abortion	urine	continuous urine	per unit increase in urinary As	adjOR

(a) OR, HR, RR—continuous, biomarkers



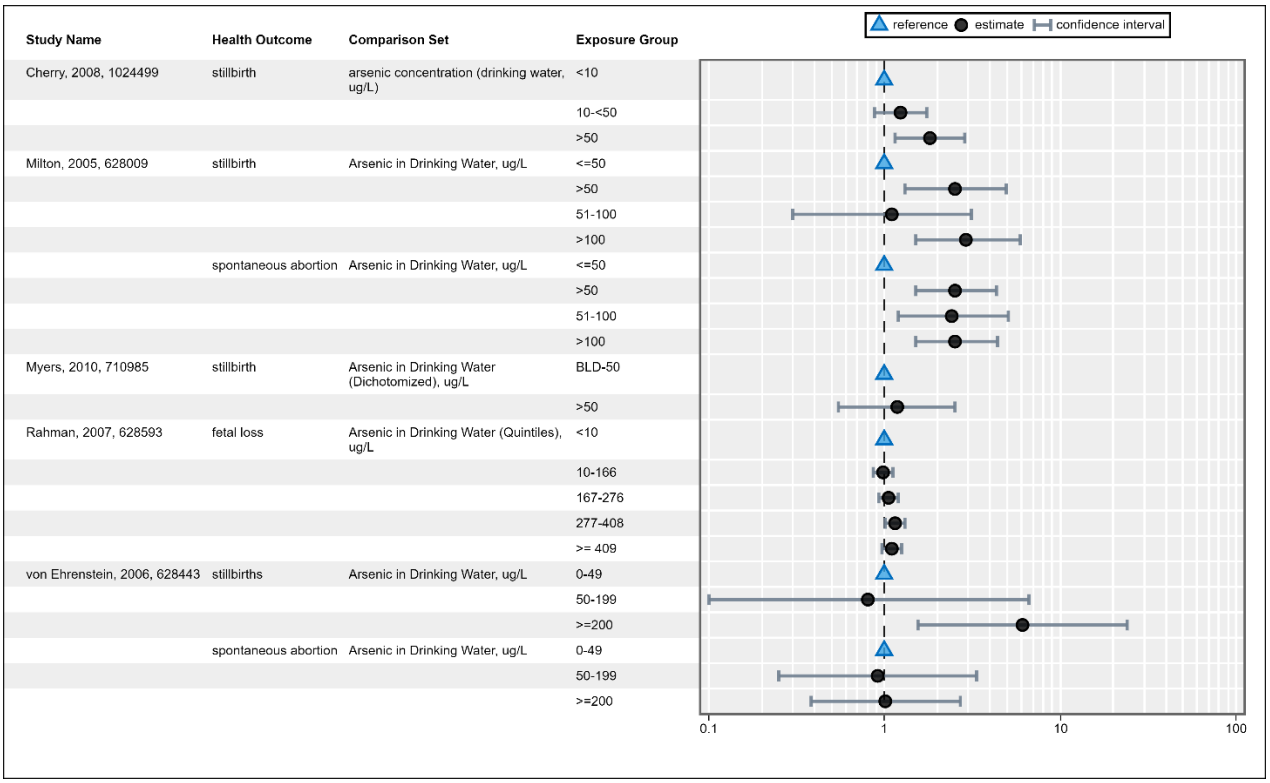
Study Name	Health Outcome	Exposure Metric	Comparison Set
Bloom, 2014, 2773356	Spontaneous Pregnancy Loss	drinking water	average iAs
			peak iAs
			daily iAs
Kwok, 2006, 627182	Stillbirth	drinking water	Arsenic in Drinking Water (Continuous), ug/L

(b) OR—continuous, drinking water



Study Name	Health Outcome	Comparison Set	Exposure Group
Rahman, 2010, 710811	stillbirths	Urinary Arsenic (Quintiles), ug/L	<38
			39-67
			68-133
			134-267
			268-2019
	spontaneous abortion/miscarriage	early pregnancy urinary arsenic concentration (quintiles)	<33
			33-57
			58-121
			122-248
			249-1253

(c) OR—categorical, biomarkers



(d) OR, RR, PR—categorical, drinking water

Figure 3-28. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and stillbirth, fetal loss, and spontaneous abortion (a) OR, HR, RR—continuous, biomarkers; (b) OR, HR, RR—continuous, drinking water; (c) OR—categorical, biomarkers; (d) OR, PR, RR—categorical, drinking water (see Adjusted Prevalence in the interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

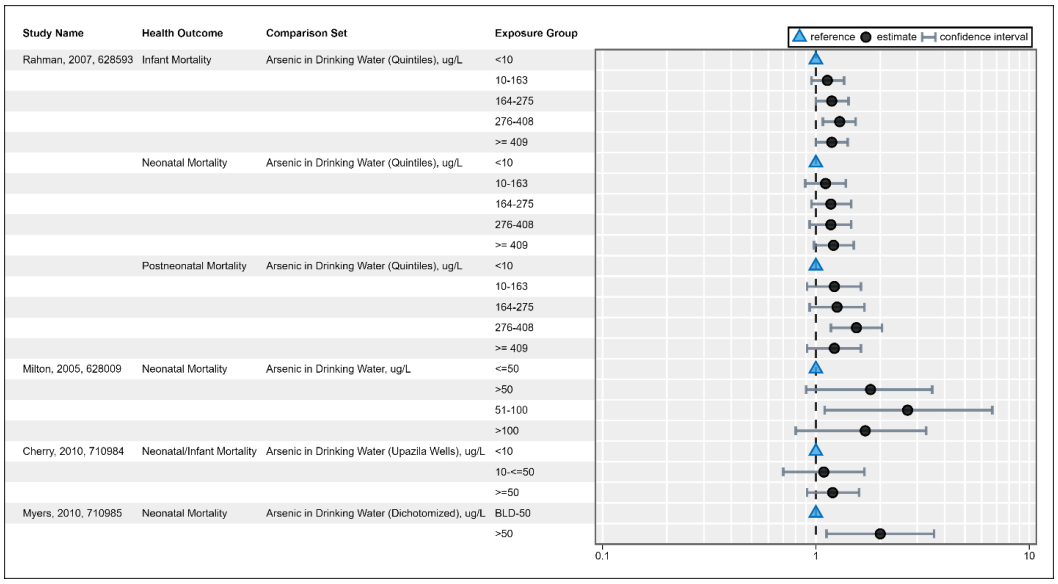
The systematic literature review also identified one case-control study. This study, conducted in Romania by Bloom et al. (2014), observed no association between arsenic and spontaneous pregnancy loss based on estimated iAs exposure from residential drinking water.

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 3-28 and Figure 3-29). At iAs drinking water levels >50 µg/L, Cherry et al. (2008) and Myers et al. (2010) reported statistically significant

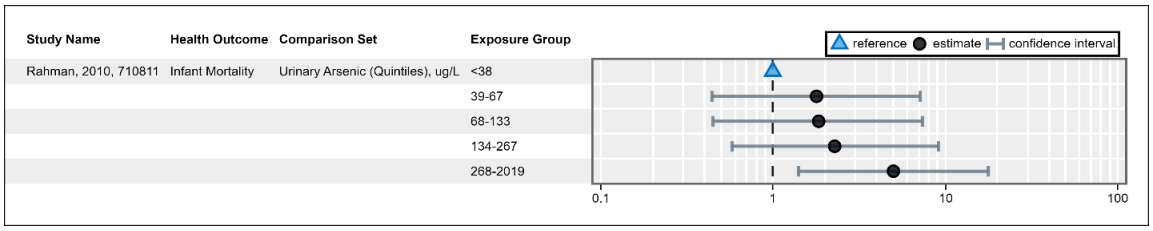
associations between stillbirth and neonatal mortality, respectively. Cherry et al. (2010) found a nonsignificant, dose-dependent increase in neonatal/infant mortality within the first year of life.

Summary

Across varying geographic regions and study designs, there is general consistency in the association between arsenic exposure and fetal and infant mortality. The strongest evidence is from areas with the highest exposure levels (e.g., > 200 µg/L arsenic in drinking water), but there also also effects observed at lower exposure levels.



(a) OR, RR—categorical, drinking water



(b) HR—categorical, biomarkers

Figure 3-29. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and infant/neonatal death (a) OR, RR—categorical, drinking water; (b) HR—categorical, biomarkers (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Birth weight

The systematic literature review identified 36 *medium* or *high* confidence epidemiological studies that evaluated the relationship between iAs and birth weight (see Figure 3-30). 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 3-31).

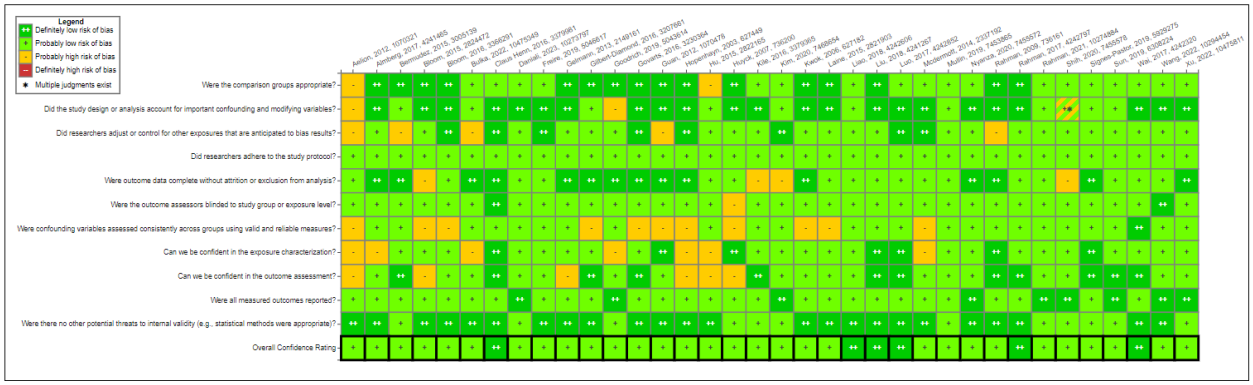


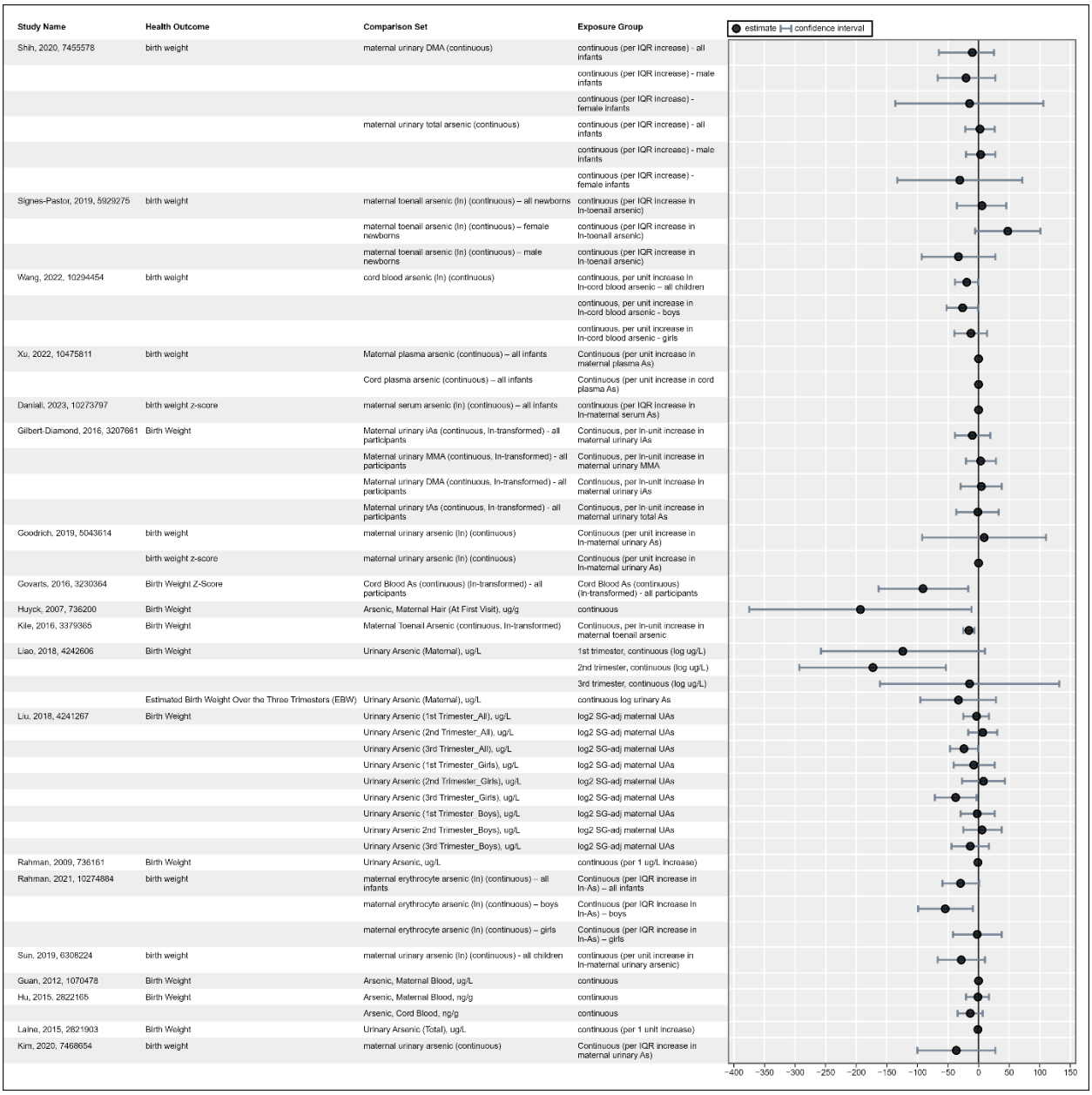
Figure 3-30. Thumbnail schematic of study evaluation ratings for references evaluating birth weight (see interactive version in HAWC).

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

Twenty 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 (Daniali et al., 2023; Bulka et al., 2022; Rahman et al., 2021; Kim et al., 2020; Nyanza et al., 2020; Freire et al., 2019; Mullin et al., 2019; Sun et al., 2019; Liao et al., 2018; Liu et al., 2018; Almberg et al., 2017; Rahman et al., 2017b; Bloom et al., 2016; Gilbert-Diamond et al., 2016; Govarts et al., 2016; Kile et al., 2016; Mcdermott et al., 2014; Rahman et al., 2009; Huyck et al., 2007; Hopenhayn et al., 2003); (see Figure 3-31). 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 of GW 8 and GW 30) and birth weight. 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 using multivariate linear regression (Huyck et

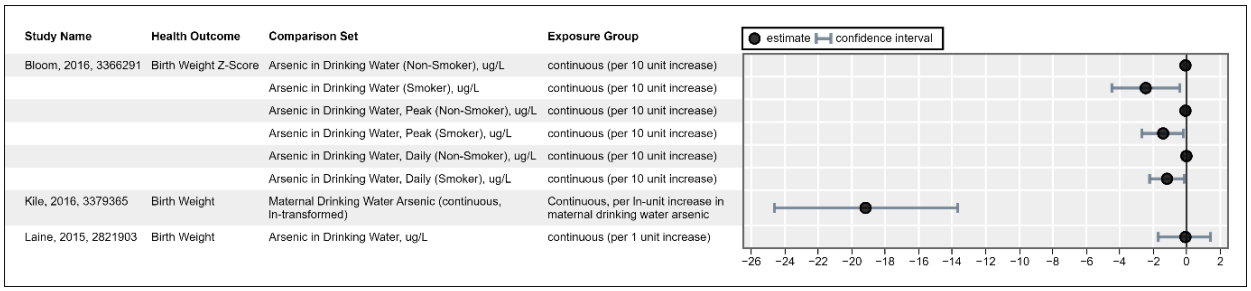
al., 2007). Rahman et al. (2017b) observed inverse associations between concentrations of arsenic in drinking water (mean=2.2 µg/L) and birth weight in a prospective cohort conducted in Bangladesh; these results were similar when arsenic measured in toenail samples were used to assign exposure. The decreases in birth weight associated with arsenic exposure were greater in magnitude for babies with lower birth weight. Kile et al. (2016)measured arsenic in drinking water at the time of enrollment (gestational age <16 weeks) and in toenails collected ≤ 1 month postpartum. They observed decreased birth weight for every unit increase in natural log water arsenic and toenail arsenic, 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 and reported a decrease in estimated birth weight associated with increased arsenic exposure (mean arsenic concentrations in maternal urine were ~40 µg/L). Using a similar study design, Liu et al. (2018) measured arsenic in maternal urine samples from 1390 women in Wuhan, China during each trimester of pregnancy. They observed decreases in birth weight associated with arsenic concentrations measured in maternal urine during the third trimester of pregnancy. In stratified analyses, this association persisted for girls, but was attenuated for boys.



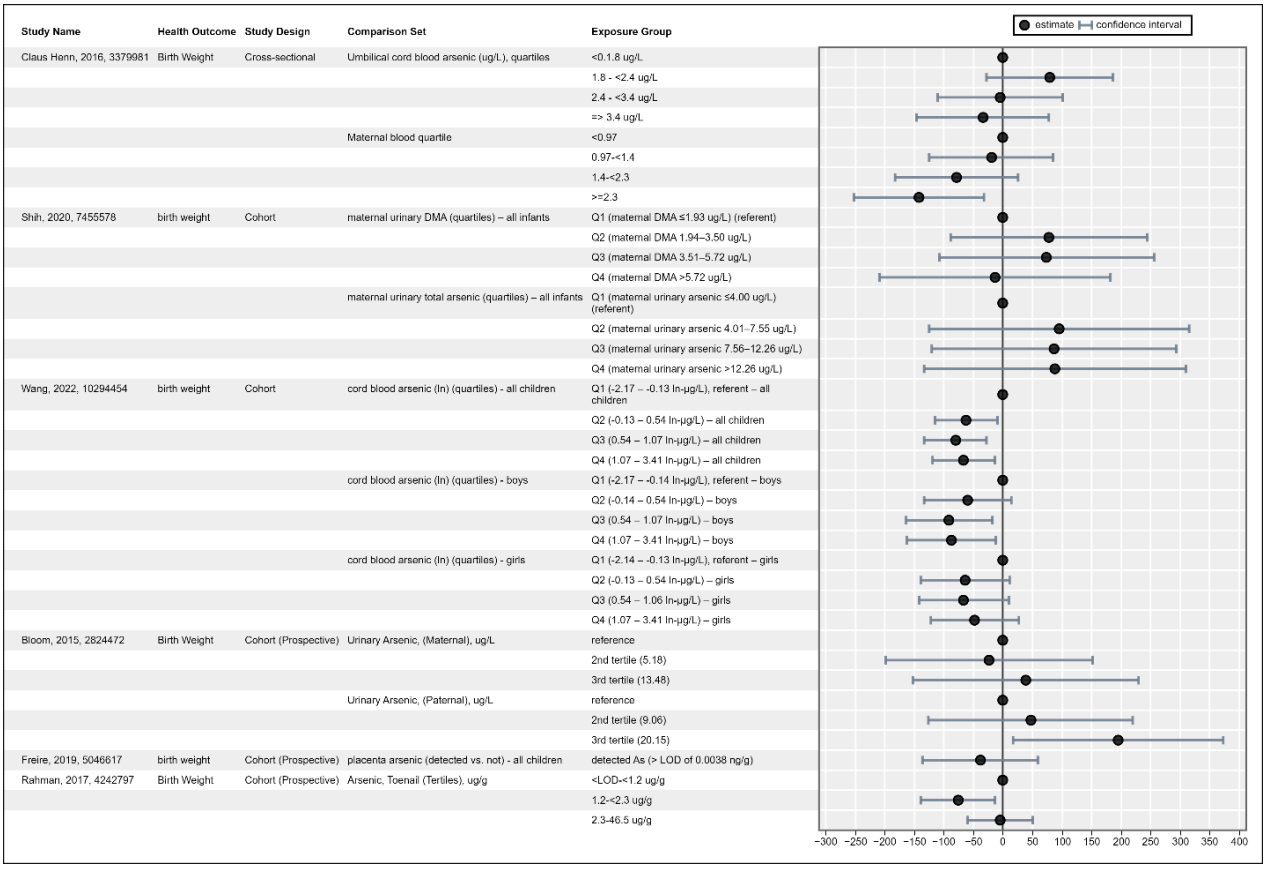
Study Name	Health Outcome	Comparison Set	Exposure Group
Shih, 2020, 7455578	birth weight	maternal urinary DMA (continuous)	continuous (per IQR increase) - all infants
			continuous (per IQR increase) - male infants
			continuous (per IQR increase) - female infants
		maternal urinary total arsenic (continuous)	continuous (per IQR increase) - all infants
			continuous (per IQR increase) - male infants
			continuous (per IQR increase) - female infants
Signes-Pastor, 2019, 5929275	birth weight	maternal toenail arsenic (ln) (continuous) – all newborns	continuous (per IQR increase in ln-toenail arsenic)
		maternal toenail arsenic (ln) (continuous) – female newborns	continuous (per IQR increase in ln-toenail arsenic)
		maternal toenail arsenic (ln) (continuous) – male newborns	continuous (per IQR increase in ln-toenail arsenic)
Wang, 2022, 10294454	birth weight	cord blood arsenic (ln) (continuous)	continuous, per unit increase in ln-cord blood arsenic – all children
			continuous, per unit increase in ln-cord blood arsenic - boys
			continuous, per unit increase in ln-cord blood arsenic - girls
Xu, 2022, 10475811	birth weight	Maternal plasma arsenic (continuous) – all infants	Continuous (per unit increase in maternal plasma As)
		Cord plasma arsenic (continuous) – all infants	Continuous (per unit increase in cord plasma As)
Daniali, 2023, 10273797	birth weight z-score	maternal serum arsenic (ln) (continuous) – all infants	continuous (per IQR increase in ln-maternal serum As)
Gilbert-Diamond, 2016, 3207661	Birth Weight	Maternal urinary iAs (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary iAs
		Maternal urinary MMA (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary MMA
		Maternal urinary DMA (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary iAs
		Maternal urinary tAs (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary total As
Goodrich, 2019, 5043614	birth weight	maternal urinary arsenic (ln) (continuous)	Continuous (per unit increase in ln-maternal urinary As)
	birth weight z-score	maternal urinary arsenic (ln) (continuous)	Continuous (per unit increase in ln-maternal urinary As)
Govarts, 2016, 3230364	Birth Weight Z-Score	Cord Blood As (continuous) (ln-transformed) - all participants	Cord Blood As (continuous) (ln-transformed) - all participants
Huyck, 2007, 736200	Birth Weight	Arsenic, Maternal Hair (At First Visit), ug/g	continuous
Kile, 2016, 3379365	Birth Weight	Maternal Toenail Arsenic (continuous, ln-transformed)	Continuous, per ln-unit increase in maternal toenail arsenic
Liao, 2018, 4242606	Birth Weight	Urinary Arsenic (Maternal), ug/L	1st trimester, continuous (log ug/L)
			2nd trimester, continuous (log ug/L)
			3rd trimester, continuous (log ug/L)
	Estimated Birth Weight Over the Three Trimesters (EBW)	Urinary Arsenic (Maternal), ug/L	continuous log urinary As
Liu, 2018, 4241267	Birth Weight	Urinary Arsenic (1st Trimester_All), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (2nd Trimester_All), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (3rd Trimester_All), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (1st Trimester_Girls), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (2nd Trimester_Girls), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (3rd Trimester_Girls), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (1st Trimester_Boys), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic 2nd Trimester_Boys), ug/L	log2 SG-adj maternal UAs
		Urinary Arsenic (3rd Trimester_Boys), ug/L	log2 SG-adj maternal UAs
Rahman, 2009, 736161	Birth Weight	Urinary Arsenic, ug/L	continuous (per 1 ug/L increase)
Rahman, 2021, 10274884	birth weight	maternal erythrocyte arsenic (ln) (continuous) – all infants	Continuous (per IQR increase in ln-As) – all infants
		maternal erythrocyte arsenic (ln) (continuous) – boys	Continuous (per IQR increase in ln-As) – boys
		maternal erythrocyte arsenic (ln) (continuous) – girls	Continuous (per IQR increase in ln-As) – girls
Sun, 2019, 6308224	birth weight	maternal urinary arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-maternal urinary arsenic)
Guan, 2012, 1070478	Birth Weight	Arsenic, Maternal Blood, ug/L	continuous
Hu, 2015, 2822165	Birth Weight	Arsenic, Maternal Blood, ng/g	continuous
		Arsenic, Cord Blood, ng/g	continuous
Laine, 2015, 2821903	Birth Weight	Urinary Arsenic (Total), ug/L	continuous (per 1 unit increase)
Kim, 2020, 7468654	birth weight	maternal urinary arsenic (continuous)	Continuous (per IQR increase in maternal urinary As)

(a) Regression coefficient—continuous, biomarkers



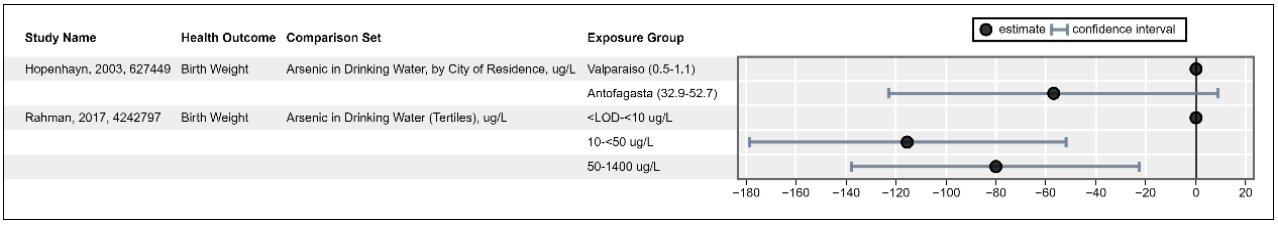
Study Name	Health Outcome	Comparison Set	Exposure Group
Bloom, 2016, 3366291	Birth Weight Z-Score	Arsenic in Drinking Water (Non-Smoker), ug/L	continuous (per 10 unit increase)
		Arsenic in Drinking Water (Smoker), ug/L	continuous (per 10 unit increase)
		Arsenic in Drinking Water, Peak (Non-Smoker), ug/L	continuous (per 10 unit increase)
		Arsenic in Drinking Water, Peak (Smoker), ug/L	continuous (per 10 unit increase)
		Arsenic in Drinking Water, Daily (Non-Smoker), ug/L	continuous (per 10 unit increase)
		Arsenic in Drinking Water, Daily (Smoker), ug/L	continuous (per 10 unit increase)
Kile, 2016, 3379365	Birth Weight	Maternal Drinking Water Arsenic (continuous, ln-transformed)	Continuous, per ln-unit increase in maternal drinking water arsenic
Laine, 2015, 2821903	Birth Weight	Arsenic in Drinking Water, ug/L	continuous (per 1 unit increase)

(b) Regression coefficient—continuous, drinking water



Study Name	Health Outcome	Study Design	Comparison Set	Exposure Group
Claus Henn, 2016, 3379981	Birth Weight	Cross-sectional	Umbilical cord blood arsenic (ug/L), quartiles	<0.1.8 ug/L
				1.8 - <2.4 ug/L
				2.4 - <3.4 ug/L
				=> 3.4 ug/L
			Maternal blood quartile	<0.97
				0.97-<1.4
				1.4-<2.3
				>=2.3
Shih, 2020, 7455578	birth weight	Cohort	maternal urinary DMA (quartiles) – all infants	Q1 (maternal DMA ≤1.93 ug/L) (referent)
				Q2 (maternal DMA 1.94–3.50 ug/L)
				Q3 (maternal DMA 3.51–5.72 ug/L)
				Q4 (maternal DMA >5.72 ug/L)
			maternal urinary total arsenic (quartiles) – all infants	Q1 (maternal urinary arsenic ≤4.00 ug/L) (referent)
				Q2 (maternal urinary arsenic 4.01–7.55 ug/L)
				Q3 (maternal urinary arsenic 7.56–12.26 ug/L)
				Q4 (maternal urinary arsenic >12.26 ug/L)
Wang, 2022, 10294454	birth weight	Cohort	cord blood arsenic (ln) (quartiles) - all children	Q1 (-2.17 – -0.13 ln-µg/L), referent – all children
				Q2 (-0.13 – 0.54 ln-µg/L) – all children
				Q3 (0.54 – 1.07 ln-µg/L) – all children
				Q4 (1.07 – 3.41 ln-µg/L) – all children
			cord blood arsenic (ln) (quartiles) - boys	Q1 (-2.17 – -0.14 ln-µg/L), referent – boys
				Q2 (-0.14 – 0.54 ln-µg/L) – boys
				Q3 (0.54 – 1.07 ln-µg/L) – boys
				Q4 (1.07 – 3.41 ln-µg/L) – boys
			cord blood arsenic (ln) (quartiles) - girls	Q1 (-2.14 – -0.13 ln-µg/L), referent – girls
				Q2 (-0.13 – 0.54 ln-µg/L) – girls
				Q3 (0.54 – 1.06 ln-µg/L) – girls
				Q4 (1.07 – 3.41 ln-µg/L) – girls
Bloom, 2015, 2824472	Birth Weight	Cohort (Prospective)	Urinary Arsenic, (Maternal), ug/L	reference
				2nd tertile (5.18)
				3rd tertile (13.48)
			Urinary Arsenic, (Paternal), ug/L	reference
				2nd tertile (9.06)
				3rd tertile (20.15)
Freire, 2019, 5046617	birth weight	Cohort (Prospective)	placenta arsenic (detected vs. not) - all children	detected As (> LOD of 0.0038 ng/g)
Rahman, 2017, 4242797	Birth Weight	Cohort (Prospective)	Arsenic, Toenail (Tertiles), ug/g	<LOD-<1.2 ug/g
				1.2-<2.3 ug/g
				2.3-46.5 ug/g

(c) Regression coefficient—categorical, biomarkers



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

(d) Regression coefficient—categorical, drinking water

Figure 3-31. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and birth weight. (a) regression coefficient—continuous, biomarkers; (b) regression coefficient—continuous, drinking water; (c) regression coefficient—categorical, biomarkers; (d) regression coefficient—categorical, drinking water (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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. They observed a statistically significant, inverse association between iAs and birth weight among women living in Antofagasta (high arsenic exposure) compared to women in Valparaiso (low arsenic exposure). The authors also found that the association between iAs and birth weight was nearly twice as large in preterm infants (average reduction in birth weight 107 g) compared to full-term infants (average reduction in birth weight 44 g), but the interaction was not statistically significant (Hopenhayn et al., 2003). Bloom et al. (2015) conducted a prospective cohort study using the LIFE cohort in the United States. They found no association between preconception maternal or paternal total urinary arsenic levels and birth outcome (birth length, birth weight) or gestational age at birth, except for a statistically significant, positive association between the highest tertile of paternal arsenic levels (≥20.15 µg/L) and birth weight. In a separate analysis, Bloom et al. (2016) conducted a preliminary cohort study using pregnant women (n=122) that participated as controls in their earlier study 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 and shorter birth length among smokers.

Other cohort studies observed associations with increased birth weight, though most of these effect estimates were not statistically significant (Shih et al., 2020; Goodrich et al., 2019; Mullin et al., 2019; Signes-Pastor et al., 2019a; 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 non-statistically significant positive association with birthweight (Goodrich et al., 2019).

Several cross-sectional studies that evaluated the association between arsenic and birth weight also were identified in the literature search (see Figure 3-31). Luo et al. (2017)measured As in whole blood samples 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. The decrease in birthweight associated with moderate arsenic exposure was greater in male infants and non-smoking mothers. 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, negative association between maternal blood arsenic levels and birth weight. 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 (Wang et al., 2022a; Xu et al., 2022). However, some cross-sectional studies reported mostly null results. For example, one study conducted in Bangladesh found no association between drinking water iAs levels and birth weight (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. 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). They observed a non-statistically significant association with reduced birth weight. 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). 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 to 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

Studies across diverse geographic regions utilizing a variety of exposure assessment methods provide generally consistent results indicating statistically significant and nonsignificant inverse associations between iAs and birth weight.

Fetal growth

Twenty-three *medium* or *high* confidence epidemiological studies were identified that measured indices of fetal growth in utero or at birth (see Figure 3-32). Approximately half of these studies used total urinary maternal arsenic levels to estimate exposure (Fano-Sizgorich et al., 2021; Kim et al., 2020; Muse et al., 2020; Shih et al., 2020; Wai et al., 2020; Goodrich et al., 2019; Sun et al., 2019; Liao et al., 2018; Liu et al., 2018; Almberg et al., 2017; Davis et al., 2015; Thomas et al., 2015; Kippler et al., 2012); use of this proxy for iAs concentration would be expected to increase the variability of the exposure estimates and result in bias to the null. Yet, these exposure assessment challenges were balanced by other study strengths that contributed to overall *medium* or *high* confidence ratings.

There were 17 cohort studies evaluating the association between arsenic and fetal growth measures. 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. They also observed a significant decrease in chest circumference in association with increased first and second trimester maternal urinary arsenic as

well a significant decrease in biparietal diameter in relation to urinary arsenic over all three trimesters. Liu et al. (2018) measured arsenic in maternal urine samples from 1390 women during each trimester of pregnancy. They observed decreases in birth length and increased risk for small for gestational age (SGA) associated with arsenic concentrations measured in maternal urine during the third trimester of pregnancy (median = 13.59 µg/L). In stratified analyses, these associations persisted for girls, but were attenuated for boys (see Figure 3-33). However, another study in China did not observe an effect of second trimester maternal urinary arsenic (geometric mean = 20.03 µg/L) on birth length or head circumference (Sun et al., 2019). There were also nine cohort 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 (Goodrich et al., 2019); head circumference (males only) (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 (Muse et al., 2020; Shih et al., 2020; Signes-Pastor et al., 2019a); head circumference (Shih et al., 2020). Four studies at a range of arsenic exposure levels (e.g., median maternal blood arsenic = 0.75 µg/L (Thomas et al., 2015); median maternal urinary arsenic = 18 µg/L (Kim et al., 2020)) documented no association with any measured fetal growth parameters (Rahman et al., 2021; Kim et al., 2020; Almberg et al., 2017; Thomas et al., 2015). Of the two studies conducted in Bangladesh (Malin Igra et al., 2021; Wai et al., 2020), only the study utilizing maternal urinary arsenic as a biomarker (geometric mean = 50.8 µg/L) identified an inverse association: head circumference (Wai 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 ug/L), placenta (median < 0.004 ng/g), or blood (geometric mean = 2.21 ug/L) (Daniali et al., 2023; Fano-Sizgorich et al., 2021; Freire et al., 2019).

Six cross-sectional studies were also identified. Four of these studies evaluated fetal growth endpoints at birth in relation to maternal or cord blood (Wang et al., 2022a; Xu et al., 2022; Lee et al., 2021; Claus Henn et al., 2016). Mixed findings were observed (see Figure 3-33). One study in China observed small statistically significant associations between cord blood arsenic (median (IQR)= 1.71 (2.03) µg/L) and birth length but no association with head circumference (Wang et al., 2022a), while another study in China observed inverse associations for both birth length and head circumference in relation to both maternal blood arsenic (median (range)= 5.45 (0.7-17.1) µg/L) and 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 (Claus Henn et al., 2016). The remaining two cross-sectional studies evaluated exposure via maternal urinary samples and evaluated fetal growth during gestation (Davis et al., 2015; Kippler et al., 2012). 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, negative association between maternal urinary arsenic levels and occipitofrontal diameter at GW 8. At GW 30, a statistically significant association was found between decreased femur length and maternal urinary arsenic levels at GW 30. No association was found between other fetal growth endpoints and maternal arsenic at either GW 14 or GW 30. Interestingly, 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. 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 (Davis et al., 2015).

Summary

Studies covering overlapping exposure levels and evaluating varying fetal growth outcomes provide conflicting results regarding the effect of arsenic on fetal growth. However, some of the strongest evidence is based on studies at the highest exposure levels.

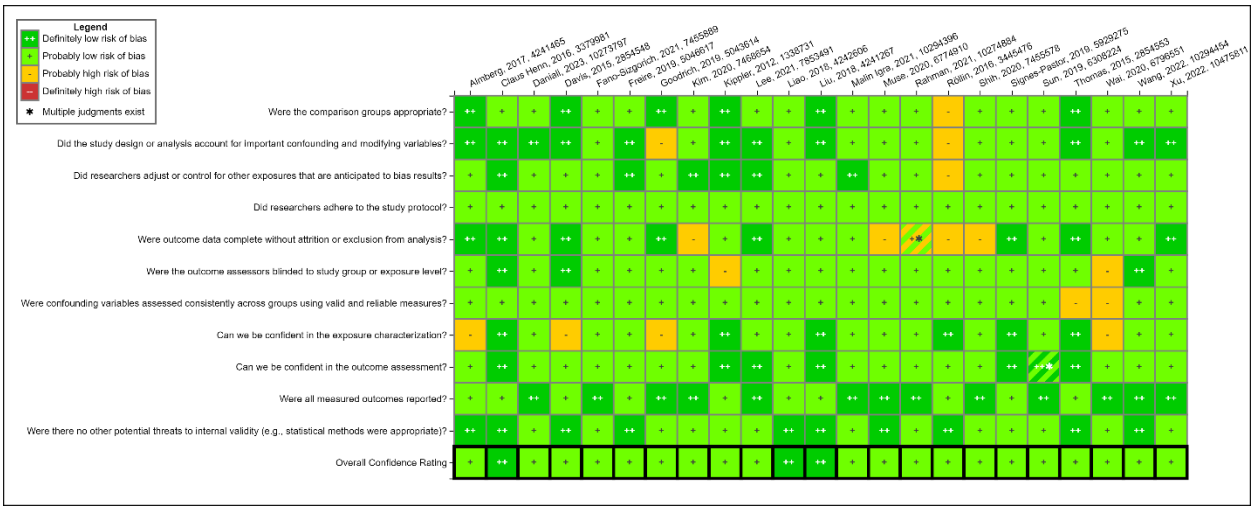
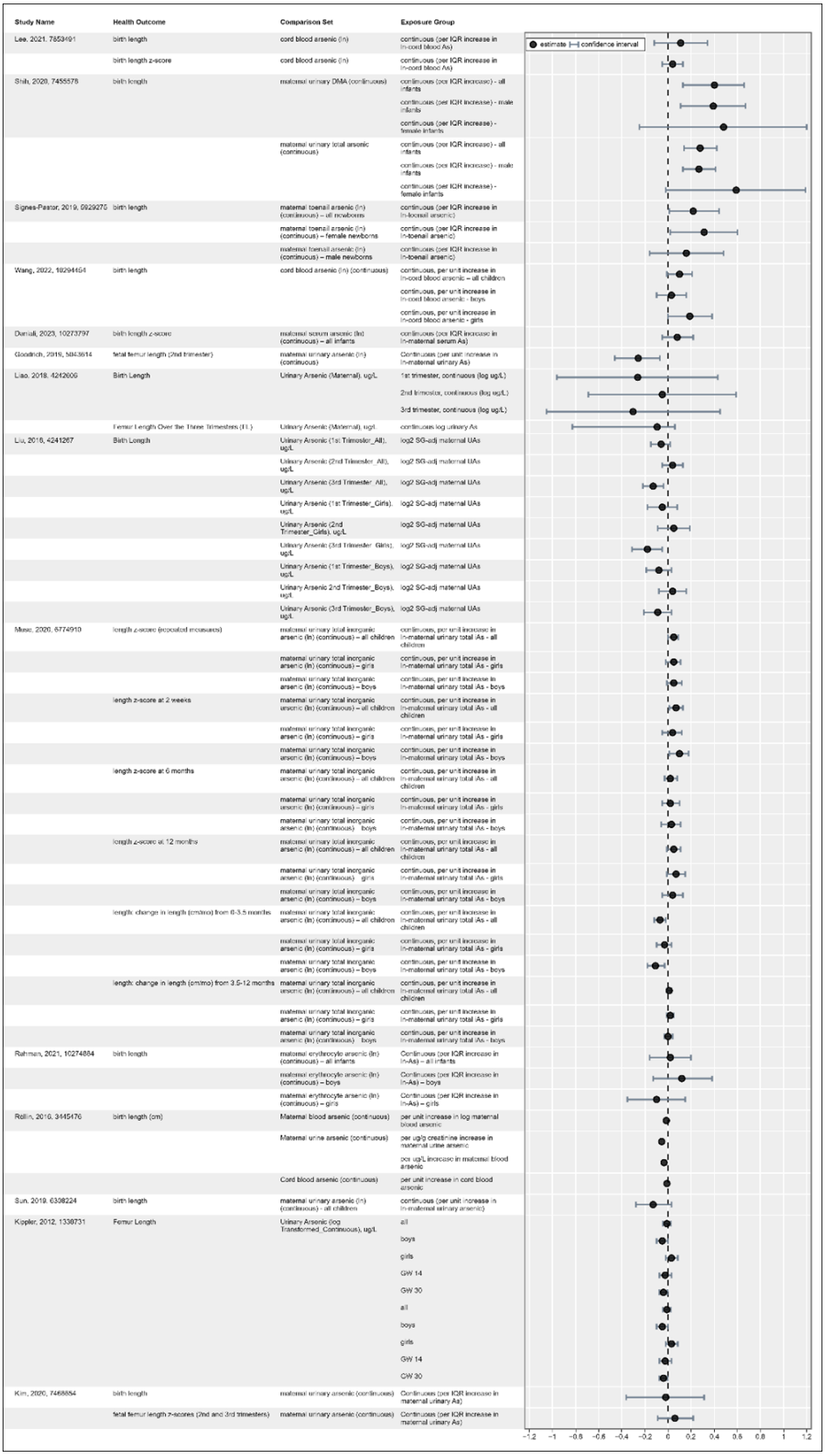
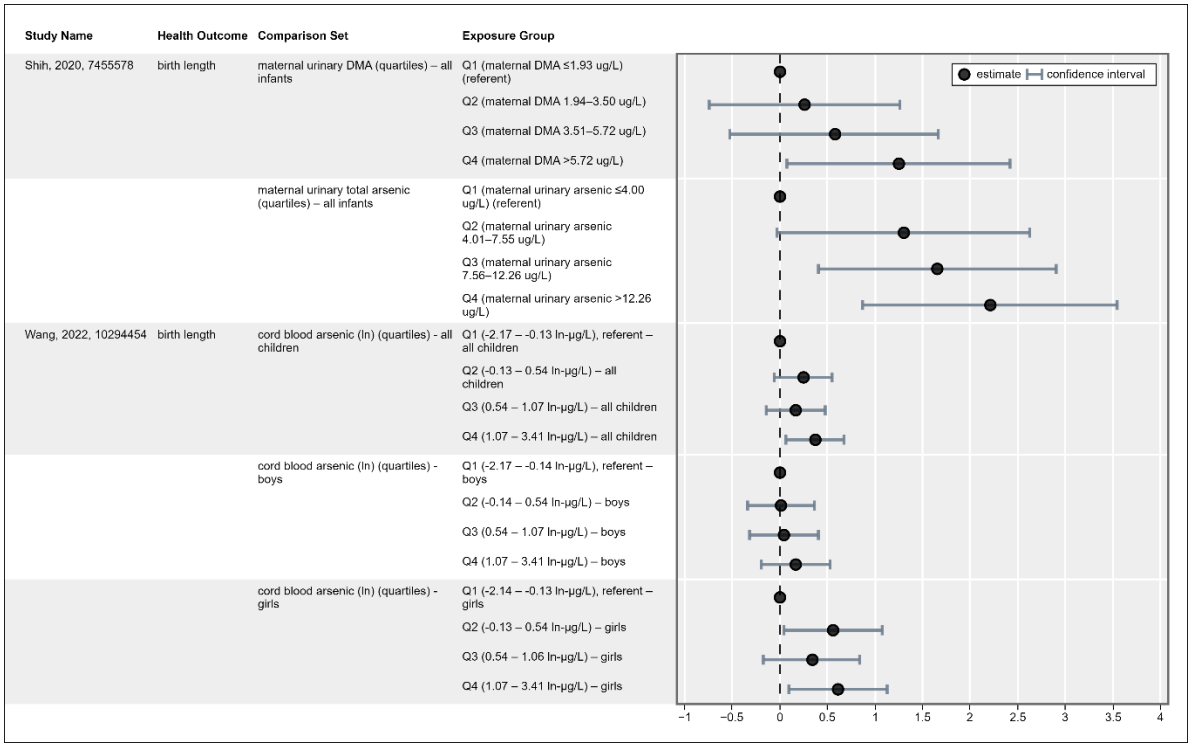


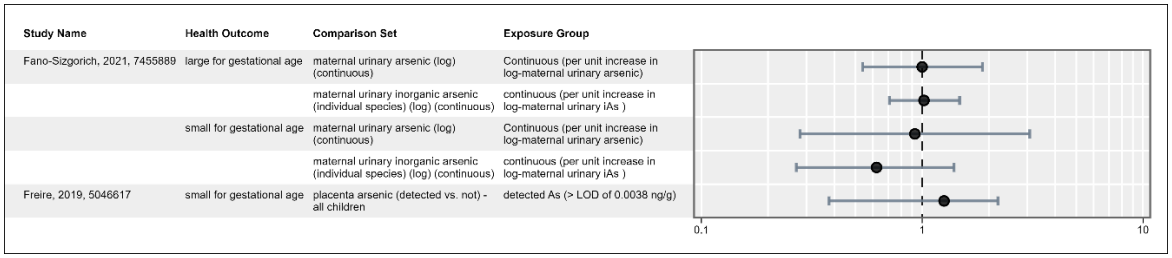
Figure 3-32. Study evaluation ratings for references evaluating fetal growth (see interactive version in HAWC).



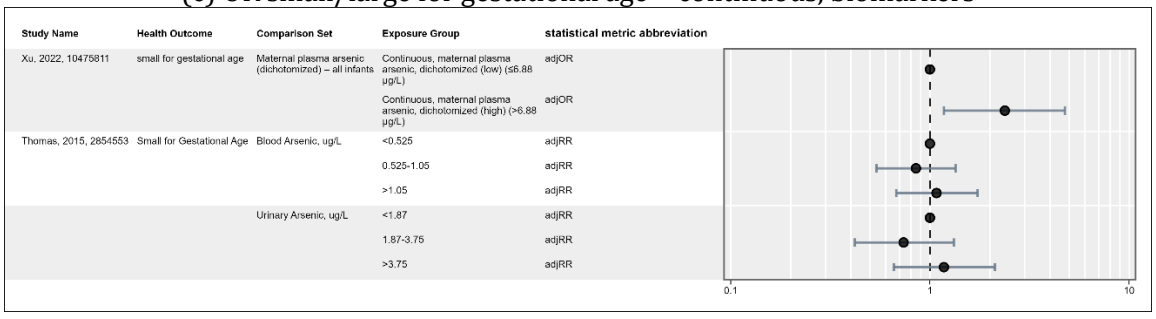
(a) coefficient for measures of length—continuous, biomarkers



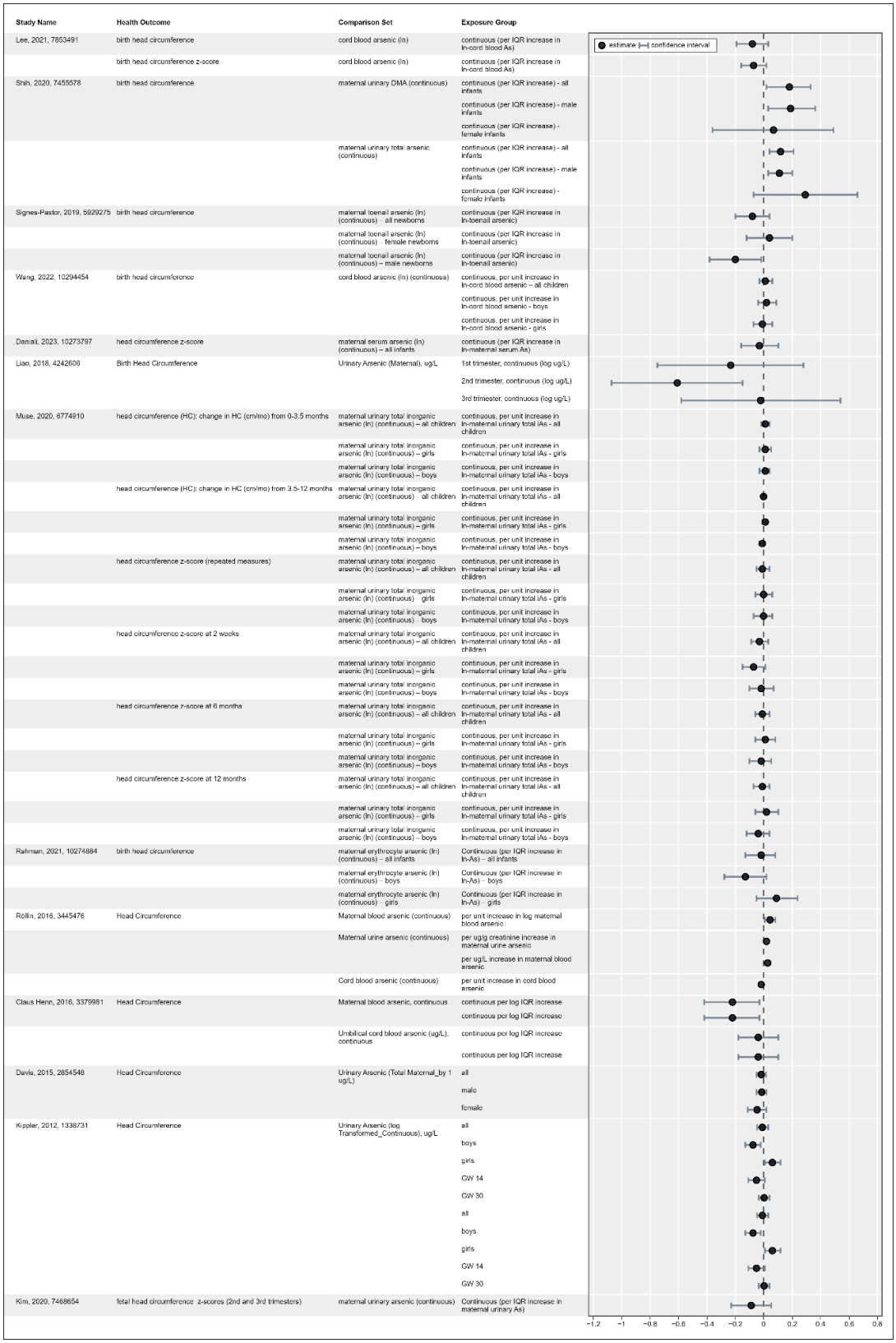
(b) coefficient for measures of length—categorical, biomarkers



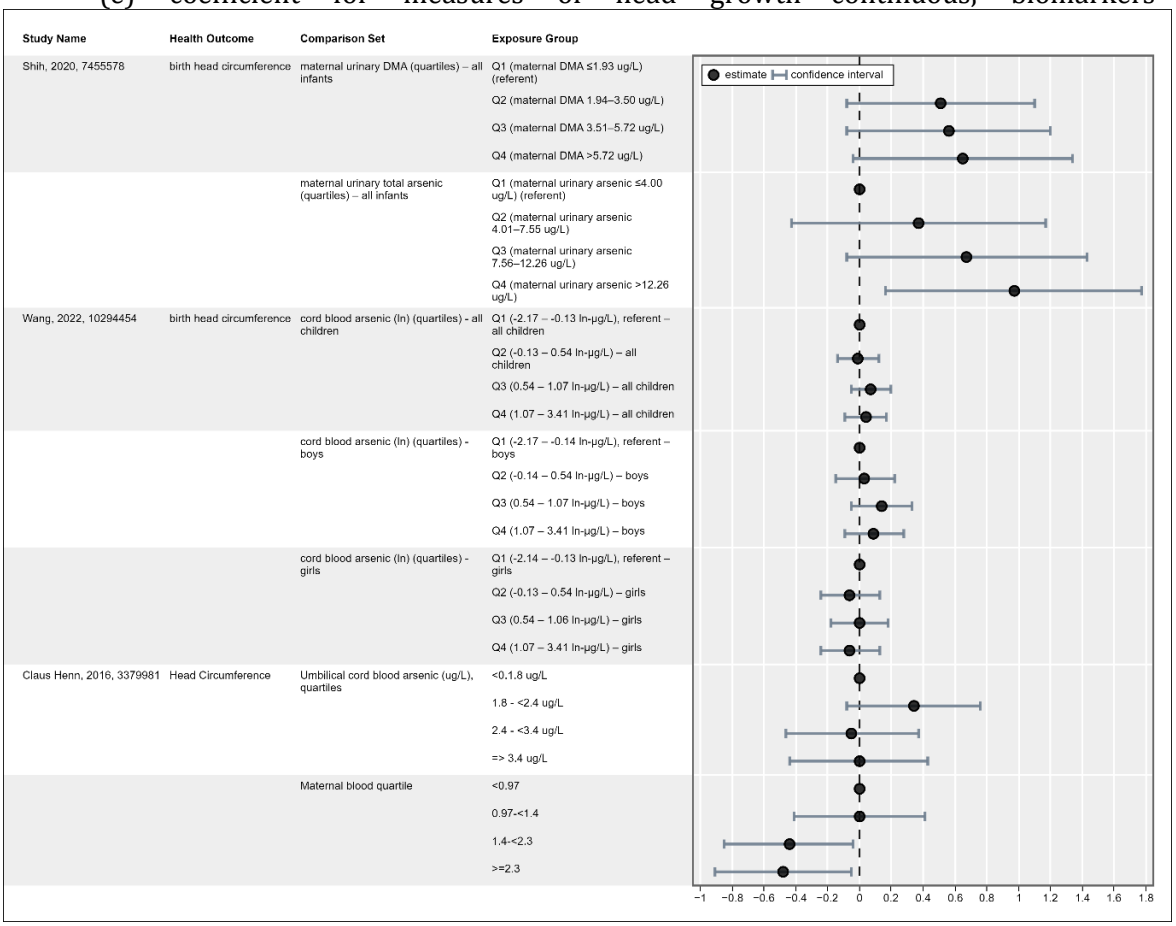
(c) OR small/large for gestational age—continuous, biomarkers



(d) OR/RR small for gestational age—categorical, biomarkers


Study Name
Health Outcome
Comparison Set
Exposure Group
estimate
confidence interval
Lee, 2021, 7863491
birth head circumference
cord blood arsenic (ln)
continuous (per IQR increase in ln-cord blood As)
birth head circumference z-score
cord blood arsenic (ln)
continuous (per IQR increase in ln-cord blood As)
Shih, 2020, 7455578
birth head circumference
maternal urinary DMA (continuous)
continuous (per IQR increase) - all infants
continuous (per IQR increase) - male infants
continuous (per IQR increase) - female infants
maternal urinary total arsenic (continuous)
continuous (per IQR increase) - all infants
continuous (per IQR increase) - male infants
continuous (per IQR increase) - female infants
Signes-Pastor, 2019, 5929275
birth head circumference
maternal toenail arsenic (ln) (continuous) - all newborns
continuous (per IQR increase in ln-toenail arsenic)
maternal toenail arsenic (ln) (continuous) - female newborns
continuous (per IQR increase in ln-toenail arsenic)
maternal toenail arsenic (ln) (continuous) – male newborns
continuous (per IQR increase in ln-toenail arsenic)
Wang, 2022, 10294454
birth head circumference
cord blood arsenic (ln) (continuous)
continuous, per unit increase in ln-cord blood arsenic – all children
continuous, per unit increase in ln-cord blood arsenic - boys
continuous, per unit increase in ln-cord blood arsenic - girls
Daniali, 2023, 10273797
head circumference z-score
maternal serum arsenic (ln) (continuous) – all infants
continuous (per IQR increase in ln-maternal serum As)
Liao, 2018, 4242606
Birth Head Circumference
Urinary Arsenic (Maternal), ug/L
1st trimester, continuous (log ug/L)
2nd trimester, continuous (log ug/L)
3rd trimester, continuous (log ug/L)
Muse, 2020, 6774910
head circumference (HC): change in HC (cm/mo) from 0-3.5 months
maternal urinary total inorganic arsenic (ln) (continuous) – all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) – girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) – boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
head circumference (HC): change in HC (cm/mo) from 3.5-12 months
maternal urinary total inorganic arsenic (ln) (continuous) - all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) – girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) – boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
head circumference z-score (repeated measures)
maternal urinary total inorganic arsenic (ln) (continuous) – all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) - girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) - boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
head circumference z-score at 2 weeks
maternal urinary total inorganic arsenic (ln) (continuous) – all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) – girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) – boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
head circumference z-score at 6 months
maternal urinary total inorganic arsenic (ln) (continuous) – all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) – girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) – boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
head circumference z-score at 12 months
maternal urinary total inorganic arsenic (ln) (continuous) – all children
continuous, per unit increase in ln-maternal urinary total iAs - all children
maternal urinary total inorganic arsenic (ln) (continuous) - girls
continuous, per unit increase in ln-maternal urinary total iAs - girls
maternal urinary total inorganic arsenic (ln) (continuous) - boys
continuous, per unit increase in ln-maternal urinary total iAs - boys
Rahman, 2021, 10274884
birth head circumference
maternal erythrocyte arsenic (ln) (continuous) – all infants
Continuous (per IQR increase in ln-As) – all infants
maternal erythrocyte arsenic (ln) (continuous) - boys
Continuous (per IQR increase in ln-As) - boys
maternal erythrocyte arsenic (ln) (continuous) - girls
Continuous (per IQR increase in ln-As) - girls
Rollin, 2016, 3445476
Head Circumference
Maternal blood arsenic (continuous)
per unit increase in log maternal blood arsenic
Maternal urine arsenic (continuous)
per ug/g creatinine increase in maternal urine arsenic
per ug/L increase in maternal blood arsenic
Cord blood arsenic (continuous)
per unit increase in cord blood arsenic
Claus Henn, 2016, 3379981
Head Circumference
Maternal blood arsenic, continuous
continuous per log IQR increase
continuous per log IQR increase
Umbilical cord blood arsenic (ug/L), continuous
continuous per log IQR increase
continuous per log IQR increase
Davis, 2015, 2854548
Head Circumference
Urinary Arsenic (Total Maternal_by 1 ug/L)
all
male
female
Kippler, 2012, 1338731
Head Circumference
Urinary Arsenic (log Transformed_Continuous), ug/L
all
boys
girls
GW 14
GW 30
all
boys
girls
GW 14
GW 30
Kim, 2020, 7468654
fetal head circumference z-scores (2nd and 3rd trimesters)
maternal urinary arsenic (continuous)
Continuous (per IQR increase in maternal urinary As)
−1.2
−1
−0.8
−0.6
−0.4
−0.2
0
0.2
0.4
0.6
0.8

(e) coefficient for measures of head growth—continuous, biomarkers



(f) coefficient for measures of head growth—categorical, biomarkers

Figure 3-33. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and fetal growth (a) coefficient for measures of length—continuous biomarkers; (b) coefficient for measures of length—categorical biomarkers; (c) Odds ratio small/large for gestational age—continuous biomarkers; (d) Odds ratio/relative risk small for gestational age—categorical biomarkers;l) coefficient for measures of head growth—continuous, biomarkers; (f) coefficient for measures of head growth—categorical, biomarkers (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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 3-34 and Figure 3-35). Most of these studies, from the United States, Mexico, Spain, China, Israel, Peru, and Myanmar, observed no association between arsenic and preterm birth (see Figure 3-35) (Bulka et al., 2022; Fano-Sizgorich et al., 2021; Karakis et al., 2021; Rahman et al., 2021; Howe et al., 2020; Shih et al., 2020; Freire et al., 2019; Yu et al., 2019; Wai et al., 2017; Bloom et al., 2015; Laine et al., 2015; Myers et al., 2010). 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 pre-pregnancy maternal total urinary arsenic levels (mean (SD)= 17.13 (28.76) µg/L) and gestational age at delivery. 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. Similarly, a cross-sectional study conducted in Mexico observed no association between drinking water iAs levels (mean = 24.6 µg/L) or urinary arsenic levels (35.5 µg/L) and gestational age at delivery (Laine et al., 2015).

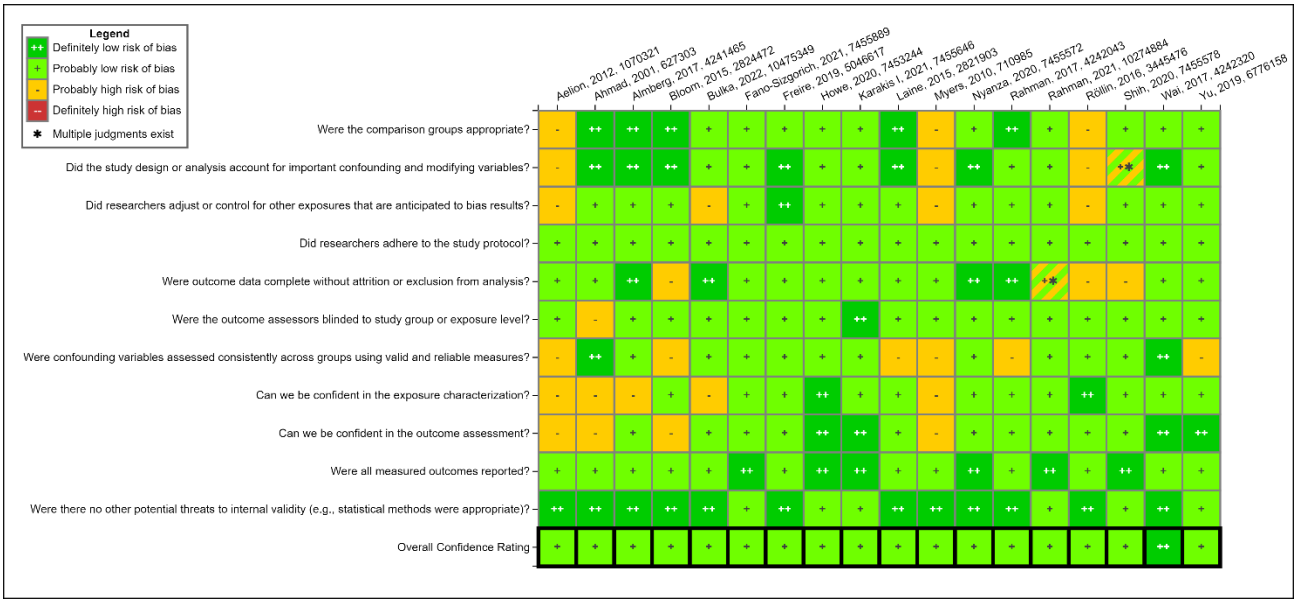


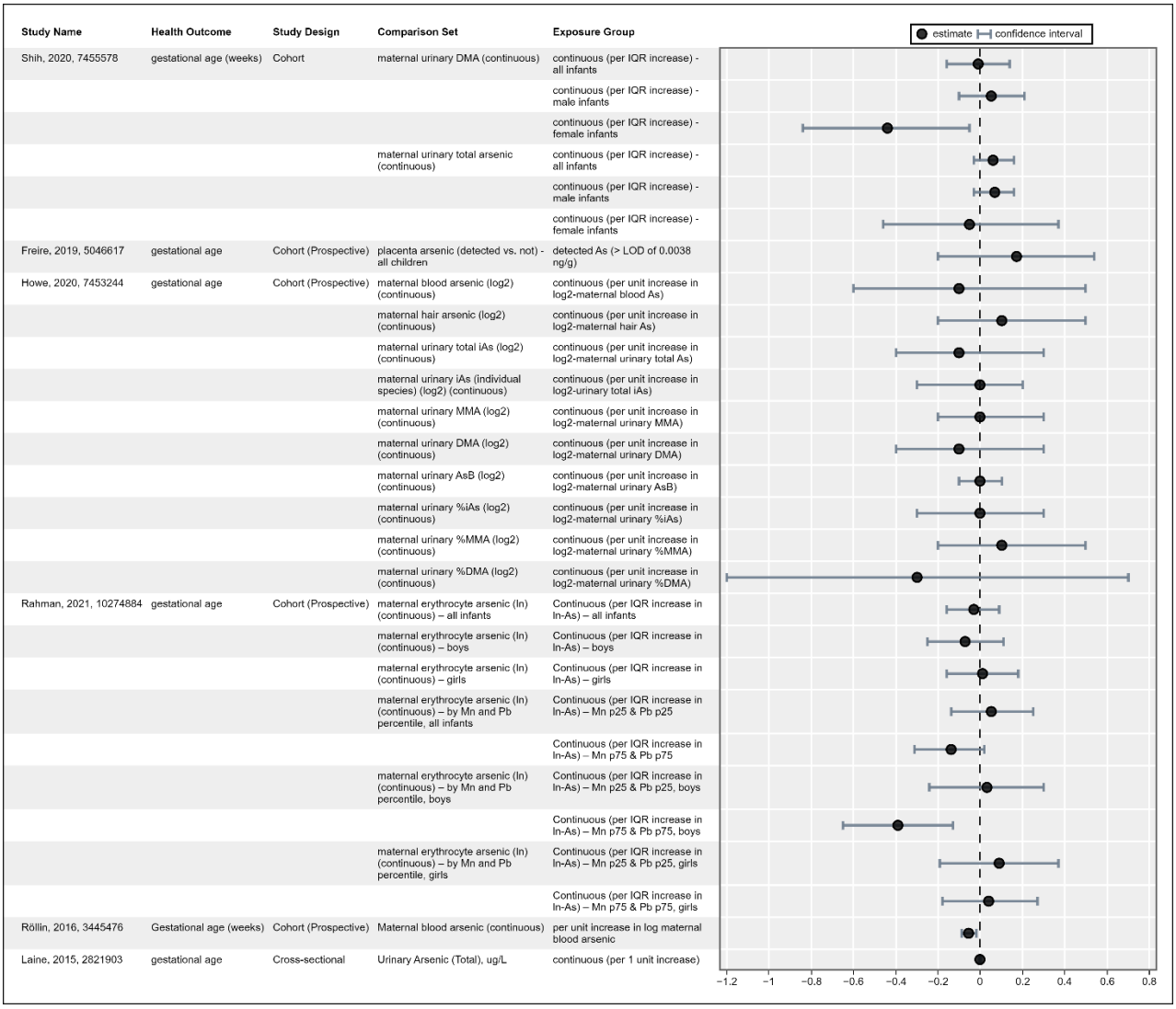
Figure 3-34. Study evaluation ratings for references evaluating prematurity (see interactive version in HAWC).

Conversely, six studies (Nyanza et al., 2020; Almberg et al., 2017; Rahman et al., 2017a; Röllin et al., 2016; Aelion et al., 2012; Ahmad et al., 2001) observed associations with preterm birth using a variety of exposure assessment metrics and across a variety of geographic areas (see Figure 3-35). 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); these results were similar when arsenic measured in toenail samples (median = 1.2 µg/g) were 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.

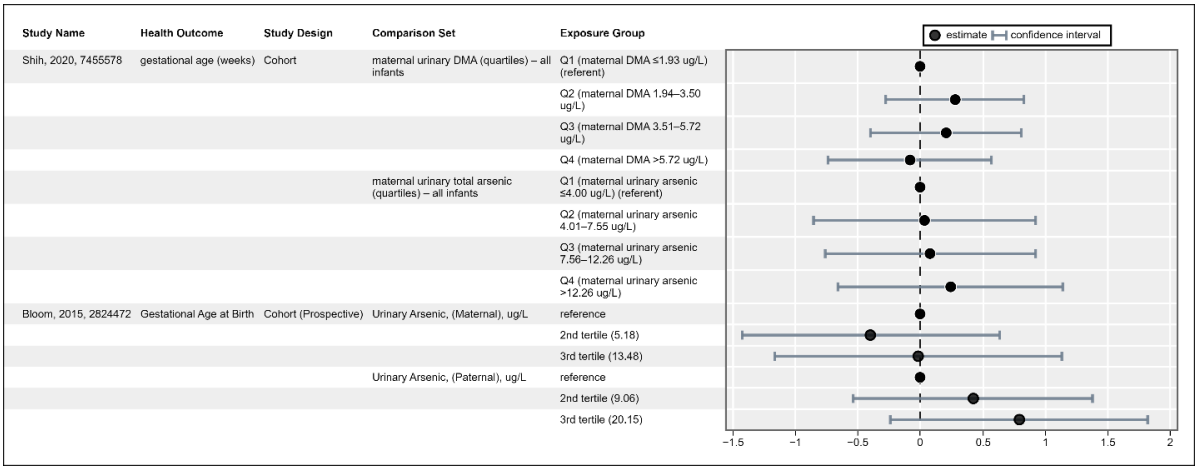
Summary

Most studies, covering varying geographic regions, reported no association between arsenic exposure and prematurity. However, six stud3-89epresentingting both high and low exposure scenarios reported significant positive associations between arsenic exposure and preterm birth.



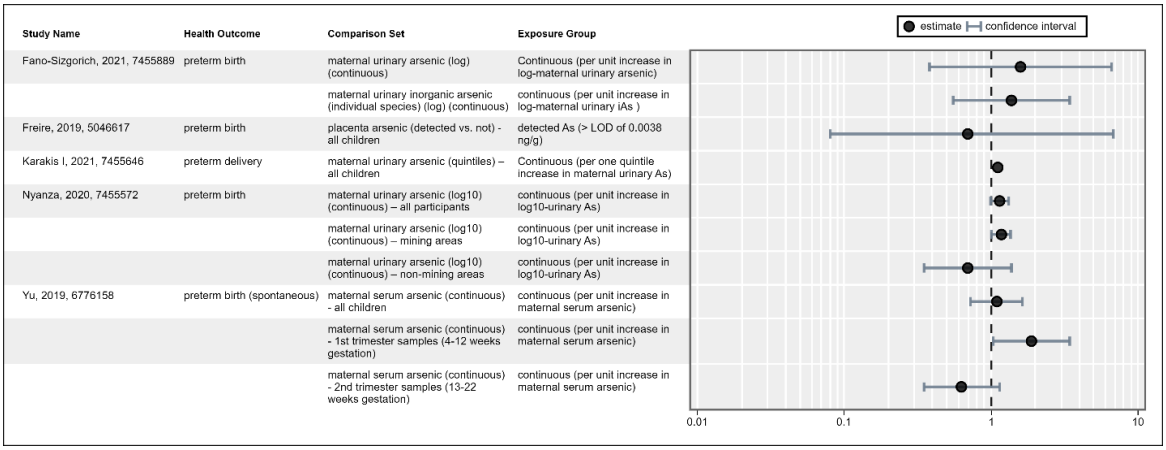
Study Name	Health Outcome	Study Design	Comparison Set	Exposure Group
Shih, 2020, 7455578	gestational age (weeks)	Cohort	maternal urinary DMA (continuous)	continuous (per IQR increase) - all infants
				continuous (per IQR increase) - male infants
				continuous (per IQR increase) - female infants
			maternal urinary total arsenic (continuous)	continuous (per IQR increase) - all infants
				continuous (per IQR increase) - male infants
				continuous (per IQR increase) - female infants
Freire, 2019, 5046617	gestational age	Cohort (Prospective)	placenta arsenic (detected vs. not) - all children	detected As (> LOD of 0.0038 ng/g)
Howe, 2020, 7453244	gestational age	Cohort (Prospective)	maternal blood arsenic (log2) (continuous)	continuous (per unit increase in log2-maternal blood As)
			maternal hair arsenic (log2) (continuous)	continuous (per unit increase in log2-maternal hair As)
			maternal urinary total iAs (log2) (continuous)	continuous (per unit increase in log2-maternal urinary total As)
			maternal urinary iAs (individual species) (log2) (continuous)	continuous (per unit increase in log2-urinary total iAs)
			maternal urinary MMA (log2) (continuous)	continuous (per unit increase in log2-maternal urinary MMA)
			maternal urinary DMA (log2) (continuous)	continuous (per unit increase in log2-maternal urinary DMA)
			maternal urinary AsB (log2) (continuous)	continuous (per unit increase in log2-maternal urinary AsB)
			maternal urinary %iAs (log2) (continuous)	continuous (per unit increase in log2-maternal urinary %iAs)
			maternal urinary %MMA (log2) (continuous)	continuous (per unit increase in log2-maternal urinary %MMA)
			maternal urinary %DMA (log2) (continuous)	continuous (per unit increase in log2-maternal urinary %DMA)
Rahman, 2021, 10274884	gestational age	Cohort (Prospective)	maternal erythrocyte arsenic (ln) (continuous) – all infants	Continuous (per IQR increase in ln-As) – all infants
			maternal erythrocyte arsenic (ln) (continuous) – boys	Continuous (per IQR increase in ln-As) – boys
			maternal erythrocyte arsenic (ln) (continuous) – girls	Continuous (per IQR increase in ln-As) – girls
			maternal erythrocyte arsenic (ln) (continuous) – by Mn and Pb percentile, all infants	Continuous (per IQR increase in ln-As) – Mn p25 & Pb p25
				Continuous (per IQR increase in ln-As) – Mn p75 & Pb p75
			maternal erythrocyte arsenic (ln) (continuous) – by Mn and Pb percentile, boys	Continuous (per IQR increase in ln-As) – Mn p25 & Pb p25, boys
				Continuous (per IQR increase in ln-As) – Mn p75 & Pb p75, boys
			maternal erythrocyte arsenic (ln) (continuous) – by Mn and Pb percentile, girls	Continuous (per IQR increase in ln-As) – Mn p25 & Pb p25, girls
				Continuous (per IQR increase in ln-As) – Mn p75 & Pb p75, girls
Röllin, 2016, 3445476	Gestational age (weeks)	Cohort (Prospective)	Maternal blood arsenic (continuous)	per unit increase in log maternal blood arsenic
Laine, 2015, 2821903	gestational age	Cross-sectional	Urinary Arsenic (Total), ug/L	continuous (per 1 unit increase)

(a) Regression coefficient—gestational age, continuous, biomarkers

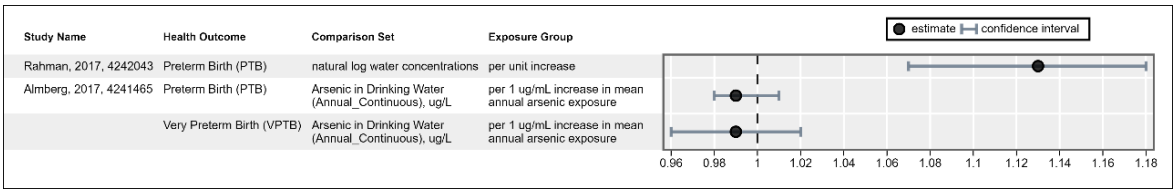


Study Name	Health Outcome	Study Design	Comparison Set	Exposure Group
Shih, 2020, 7455578	gestational age (weeks)	Cohort	maternal urinary DMA (quartiles) – all infants	Q1 (maternal DMA ≤1.93 ug/L) (referent)
				Q2 (maternal DMA 1.94–3.50 ug/L)
				Q3 (maternal DMA 3.51–5.72 ug/L)
				Q4 (maternal DMA >5.72 ug/L)
			maternal urinary total arsenic (quartiles) – all infants	Q1 (maternal urinary arsenic ≤4.00 ug/L) (referent)
				Q2 (maternal urinary arsenic 4.01–7.55 ug/L)
				Q3 (maternal urinary arsenic 7.56–12.26 ug/L)
				Q4 (maternal urinary arsenic >12.26 ug/L)
Bloom, 2015, 2824472	Gestational Age at Birth	Cohort (Prospective)	Urinary Arsenic, (Maternal), ug/L	reference
				2nd tertile (5.18)
				3rd tertile (13.48)
			Urinary Arsenic, (Paternal), ug/L	reference
				2nd tertile (9.06)
				3rd tertile (20.15)

(b) Regression coefficient—gestational age, categorical, biomarkers



(c) OR or RR—preterm birth, continuous, biomarkers



(d) OR or RR—preterm birth, continuous, drinking water arsenic

Figure 3-35. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and prematurity. (a) regression coefficient—gestational age, continuous, biomarkers; (b) regression coefficient—gestational age, categorical, biomarkers; (c) OR or RR—preterm birth, continuous, biomarkers; (d) OR or RR—preterm birth, continuous, drinking water arsenic (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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 3-36), four of which were conducted in Bangladesh (Malin Igra et al., 2021; Wai et al., 2020; Gardner et al., 2013; Saha et al., 2012). The other two studies were conducted in New Hampshire (Muse et al., 2020) and Israel (Karakis et al., 2021). Malin Igra et al. (2021) evaluated exposure using maternal blood samples during early pregnancy.

Two of these studies suggest that prenatal arsenic exposure at a range of concentrations can affect postnatal growth (see Figure 3-37). 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 at 1–6 months of age. By contrast, Muse et al. (2020) documented a positive association between maternal second trimester total urinary arsenic (median = 3.96 µg/L) and length World Health Organization (WHO) Z-score over the first year of life but an inverse association with length growth rate up to 3.5 months. 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 µ–/L - 80–84 µg/L) and childhood growth outcomes up to age 10 years (Karakis et al., 2021; Malin Igra et al., 2021; Gardner et al., 2013; Saha et al., 2012).

Summary

From a limited evidence base, 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.

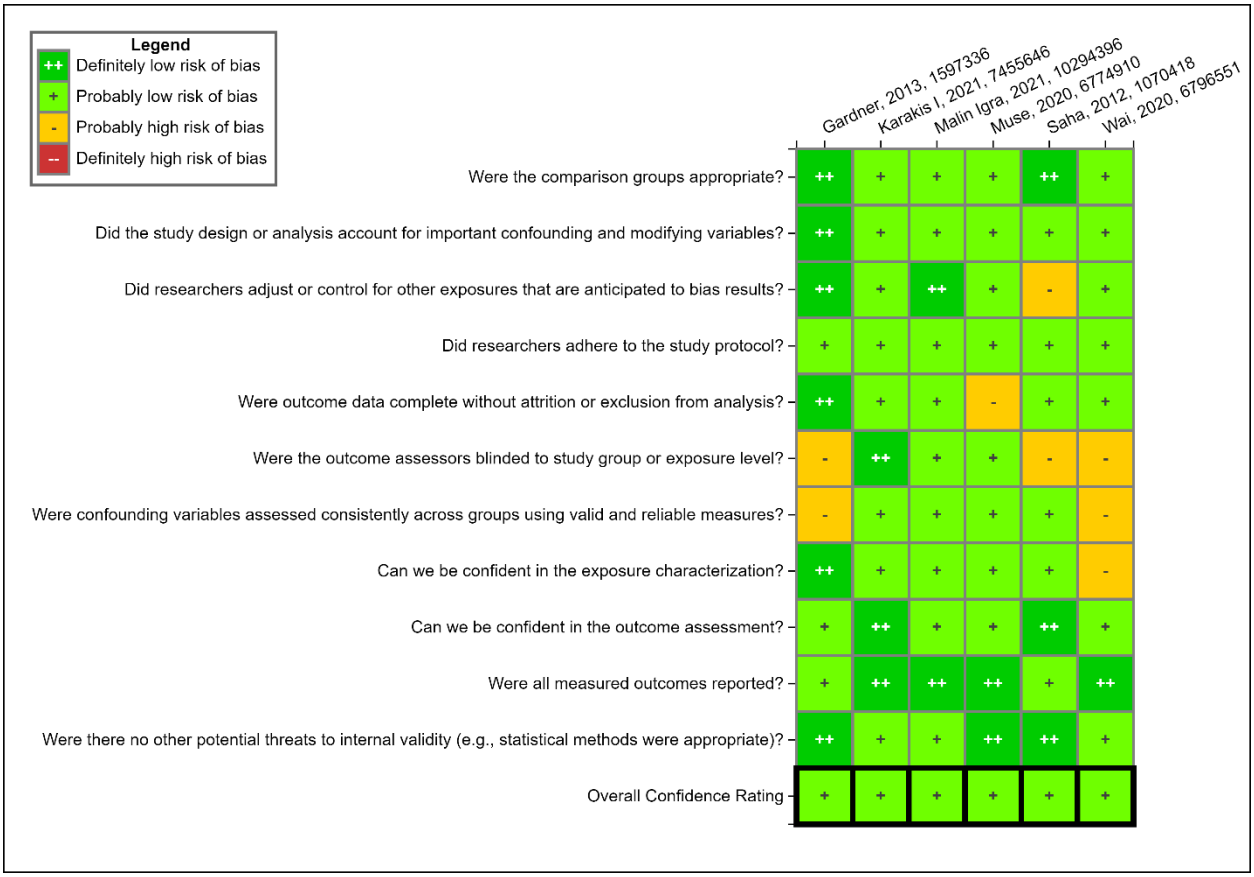
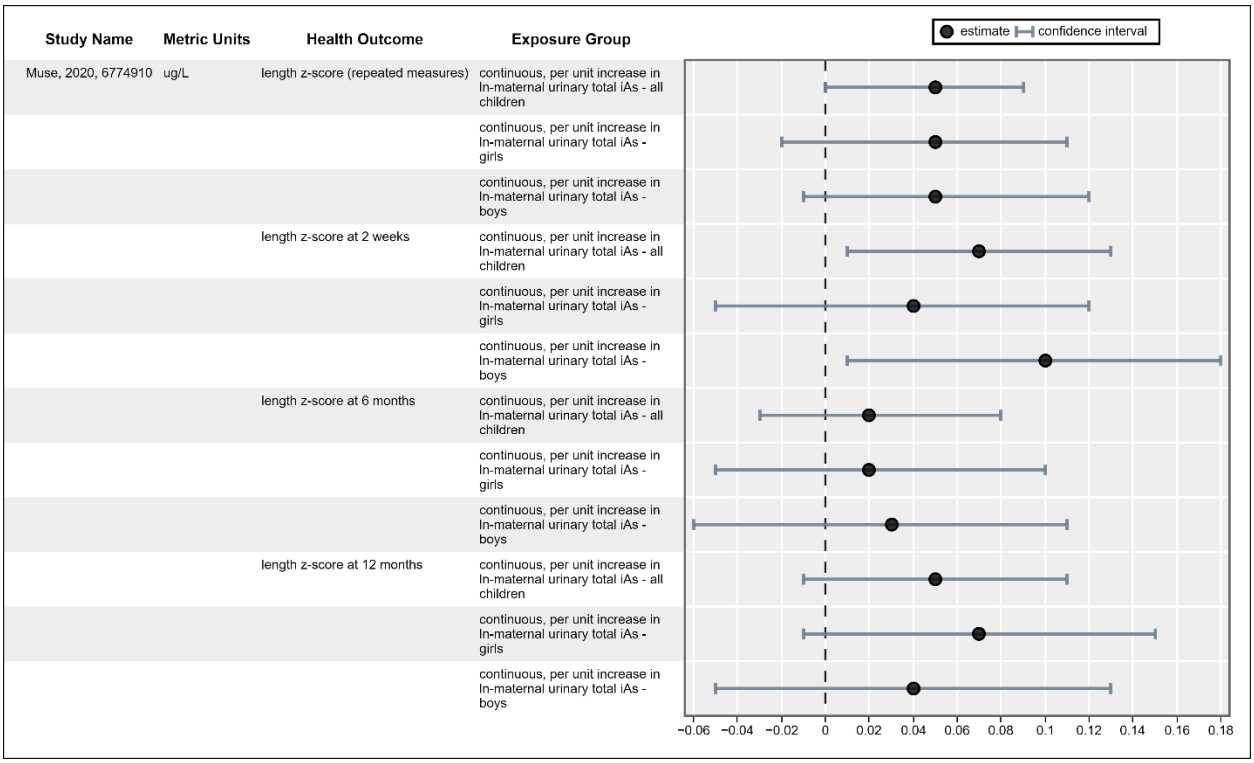
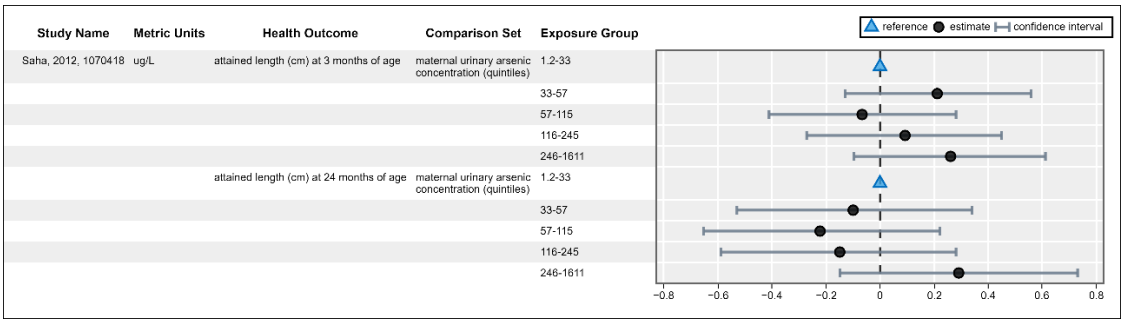


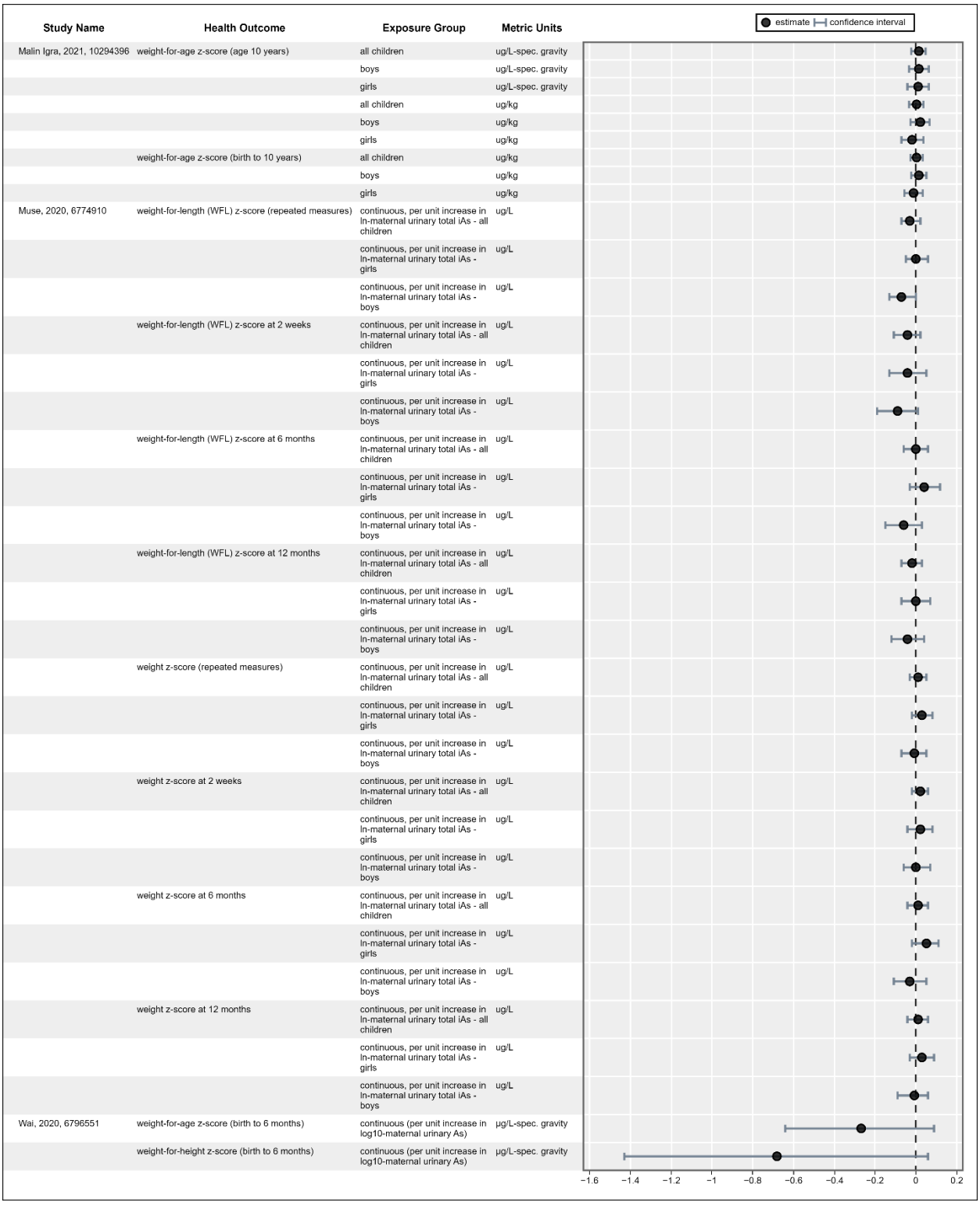
Figure 3-36. Study evaluation ratings for references evaluating postnatal growth (see interactive version in HAWC).



(a) Regression coefficient for length parameters—continuous, biomarkers

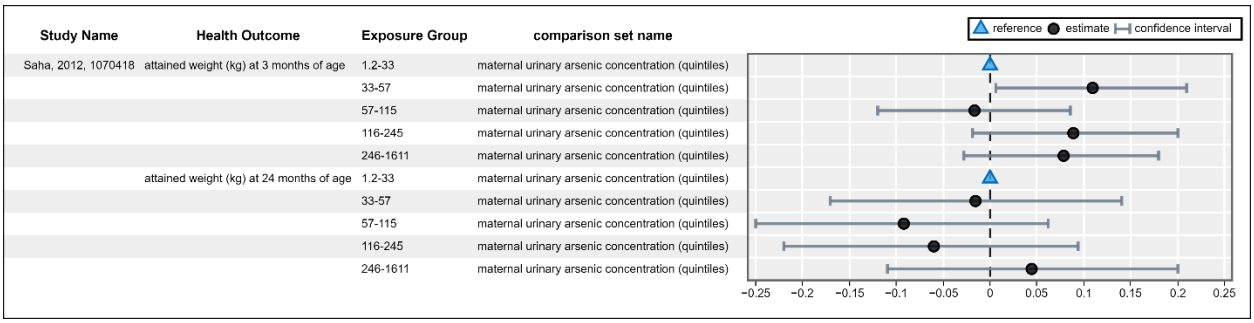


(b) Regression coefficient for length parameters—categorical, biomarkers



Study Name	Health Outcome	Exposure Group	Metric Units
Malin Igra, 2021, 10294396	weight-for-age z-score (age 10 years)	all children	ug/L-spec. gravity
		boys	ug/L-spec. gravity
		girls	ug/L-spec. gravity
		all children	ug/kg
		boys	ug/kg
		girls	ug/kg
	weight-for-age z-score (birth to 10 years)	all children	ug/kg
		boys	ug/kg
		girls	ug/kg
Muse, 2020, 6774910	weight-for-length (WFL) z-score (repeated measures)	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight-for-length (WFL) z-score at 2 weeks	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight-for-length (WFL) z-score at 6 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight-for-length (WFL) z-score at 12 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight z-score (repeated measures)	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight z-score at 2 weeks	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight z-score at 6 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
	weight z-score at 12 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L
Wai, 2020, 6796551	weight-for-age z-score (birth to 6 months)	continuous (per unit increase in log10-maternal urinary As)	µg/L-spec. gravity
	weight-for-height z-score (birth to 6 months)	continuous (per unit increase in log10-maternal urinary As)	µg/L-spec. gravity

(c) Regression coefficient for weight parameters, continuous, biomarkers



(d) Regression coefficient for weight parameters, categorical, biomarkers

Figure 3-37. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and postnatal growth. (a) regression coefficient for length parameters—continuous, biomarkers; (b) regression coefficient for length parameters—categorical, biomarkers; (c) regression coefficient for weight parameters, continuous, biomarkers; (d) regression coefficient for weight parameters, categorical, biomarkers (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Mechanistic Observations

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 but found no association between these effects and pregnancy and birth 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). 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 to 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). For more information see MOA appendix in protocol.

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search (see Section 3.11 of iAs Protocol), suggest the following as potential modifying factors that may affect the risk of arsenic-associated adverse pregnancy and birth outcomes (see Table 3-5):

- **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 (Signes-Pastor et al., 2019a; Luo et al., 2017; Kippler et al., 2012), while others suggest increased susceptibility among females (Signes-Pastor et al., 2019a; Liu et al., 2018).

Table 3-5. Risk modifiers for pregnancy and birth 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)

Evidence Judgment

The currently available **evidence indicates** that iAs exposure likely causes adverse pregnancy and birth outcomes in humans (see Table 3-6) given sufficient exposure conditions[19]. This conclusion is based on epidemiological studies at a range of exposure levels 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.

Overall, there is *moderate* evidence for an association between arsenic exposure and fetal and infant mortality, based on thirteen *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)). This evidence is bolstered by largely consistent results across study type and geographic region. A dose-response gradient was observed in some (e.g., (Kwok et al., 2006); (Rahman et al., 2010); (Milton et al., 2005)) but not all studies. Ecological studies also provide supporting evidence for the association between iAs exposure and fetal and infant mortality, including at lower levels of exposure (e.g.,

[19] The "sufficient exposure conditions" are more fully evaluated and defined for the identified health effects through dose-response analysis in Section 4.

<100 µg/L in drinking water) (Cherry et al., 2010); (Myers et al., 2010); (Cherry et al., 2008); (Hopenhayn-Rich et al., 2000).

There is also *moderate* evidence for an association between arsenic exposure and birth weight. Thirty-six *medium* or *high* confidence studies across diverse geographic regions utilizing a variety of exposure assessment methods provide mostly consistent results indicating inverse and suggestive inverse associations between iAs and birth weight (e.g., (Rahman et al., 2021; Liao et al., 2018; Kile et al., 2016; Rahman et al., 2009)). There is coherence with the evidence bases for fetal growth and postnatal.

There is *slight* evidence for an association between arsenic exposure and fetal growth, based on twenty-four *medium* or *high* confidence studies. Studies using a variety of exposure assessment methods and covering a range of overlapping exposure levels had *unexplained inconsistency* with positive (e.g., (Muse et al., 2020; Shih et al., 2020; Signes-Pastor et al., 2019a)), null (e.g., (Almberg et al., 2017; Thomas et al., 2015)), and inverse (e.g., (Goodrich et al., 2019; Liao et al., 2018; Liu et al., 2018)) associations with fetal growth parameters. A dose-response gradient is suggested, given the strongest evidence observed at higher exposure (Liao et al., 2018); (Liu et al., 2018); (Kippler et al., 2012). There is coherence with the evidence bases for birth weight and postnatal growth.

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 six studies representing both high and low exposure scenarios reported positive associations (Nyanza et al., 2020; Almberg et al., 2017; Rahman et al., 2017a; Röllin et al., 2016; Aelion et al., 2012; Ahmad et al., 2001). There in unexplained inconsistency in these studies covering overlapping arsenic exposure levels.

There is also *slight* evidence for the association between prenatal arsenic exposure and postnatal growth based on significant associations in two (Muse et al., 2020; Wai 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 bases for birth weight and fetal growth.

Evidence is inadequate for several potential modifying factors (polymorphisms, nutrition, methylation capacity, gender).

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

Table 3-6. Evidence profile table for epidemiological evidence on iAs and pregnancy and birth 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 cohort and cross-sectional studies conducted in Bangladesh and India, where iAs levels in drinking-water wells commonly exceed 200 µg/L. Some studies also provide evidence at lower levels of exposure (e.g., <100 µg/L)	• Most studies are *medium* or *high* confidence • *Consistency* - across geographic regions and study types • *Dose-response gradient* - in many but not all studies	• *No factors noted*	⊕⊕⊙ *Moderate*
Birth Weight 36 *medium* or *high* confidence studies	Studies across diverse geographic regions utilizing a variety of exposure assessment methods provide generally consistent results indicating statistically significant and nonsignificant inverse associations between iAs and birth weight.	• Most studies are *medium* or *high* confidence • *Consistency* - across geographic regions and study types • *Coherence* - with fetal and postnatal growth evidence	• *No factors noted*	⊕⊕⊙ *Moderate*
Fetal Growth 24 *medium* or *high* confidence studies	Studies covering overlapping arsenic exposure levels provide conflicting results. However, some of the strongest evidence is based on studies at the highest exposure levels.	• Most studies are *medium* or *high* confidence • *Dose-response gradient* - with strongest evidence at higher exposure levels • *Coherence* - with birth weight and postnatal growth evidence	• *Unexplained inconsistency* - between studies with overlapping exposure levels	⊕⊙⊙ *Slight*

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)**
Prematurity 18 *medium* or *high* confidence studies	Most studies reported no association, but six studies repesenting both high and low exposure scenarios reported significant positive associations.	• Most studies are *medium* or *high* confidence	• *Unexplained inconsistency* - between studies with overlapping exposure levels	⊕⊙⊙ *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.	• Most studies are *medium* or *high* confidence • *Coherence* - with birth weight and fetal growth evidence	• *Unexplained inconsistency* - between studies with overlapping exposure levels	⊕⊙⊙ *Slight*

1

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 (NASEM, 2019) the assessment focuses on the epidemiological evidence to highlight those studies in humans that best support dose-response analysis. Based on 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 72 studies that report on the association between arsenic exposures and neurodevelopmental effects (see Figure 3-38). The publications underwent study evaluation, and 52 of the studies were considered *medium* or *high* confidence. Of the remaining studies, 17 were considered low confidence or uninformative due to limitations as noted in HAWC (see HAWC), and 3 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). Due to 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.

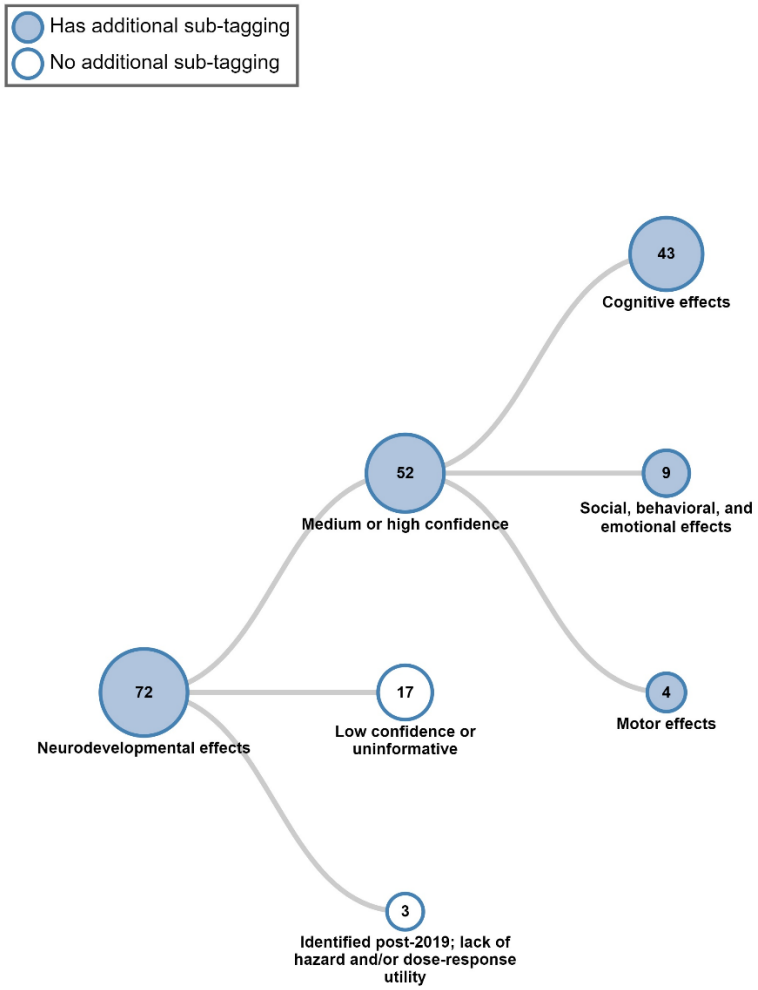


Figure 3-38. Literature tree for epidemiological studies assessing neurodevelopmental effects (see interactive version in HAWC).

Evidence from Epidemiological Studies

This section summarizes the epidemiological studies that evaluated an association between iAs exposure and neurodevelopmental outcomes. Many of the cross-sectional studies evaluated populations that had experienced chronic or lifelong exposure to arsenic, and thus the concurrent exposure measurements are expected to be a reasonable proxy for exposure during an etiologically relevant period. In the context of lifetime exposure, however, cohort studies are generally a more reliable observational study design that reduce uncertainties related to chance, bias, and confounding when assessing neurodevelopmental effects associated with *in utero* and early childhood arsenic exposure. While many studies examined drinking water exposure to arsenic, others reported arsenic levels in biomarkers of exposure such as urine, hair, and toenail. The

information below is organized by type of neurodevelopmental effect: (1) cognitive effects; (2) social, behavioral, and emotional effects; and (3) motor effects.

Cognitive effects

Forty-three epidemiological studies assessed an association between arsenic and cognitive function in children and classified as *medium* or *high* confidence (see Figure 3-39). 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.

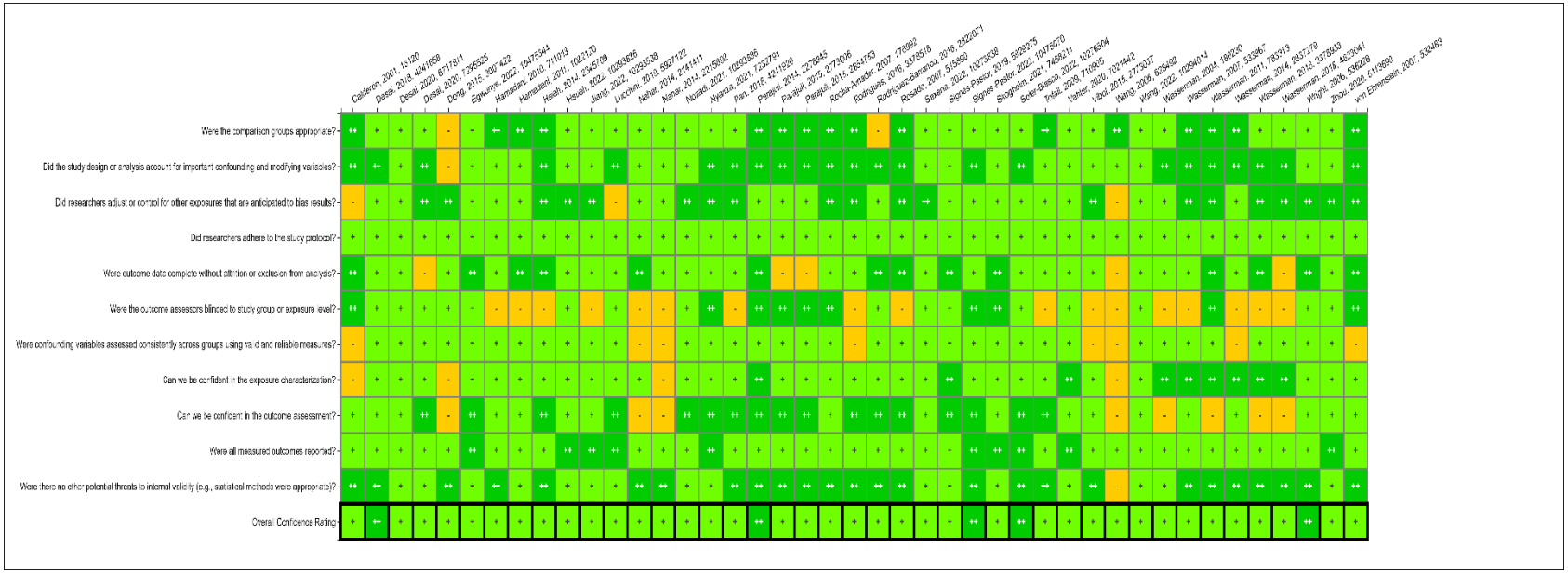
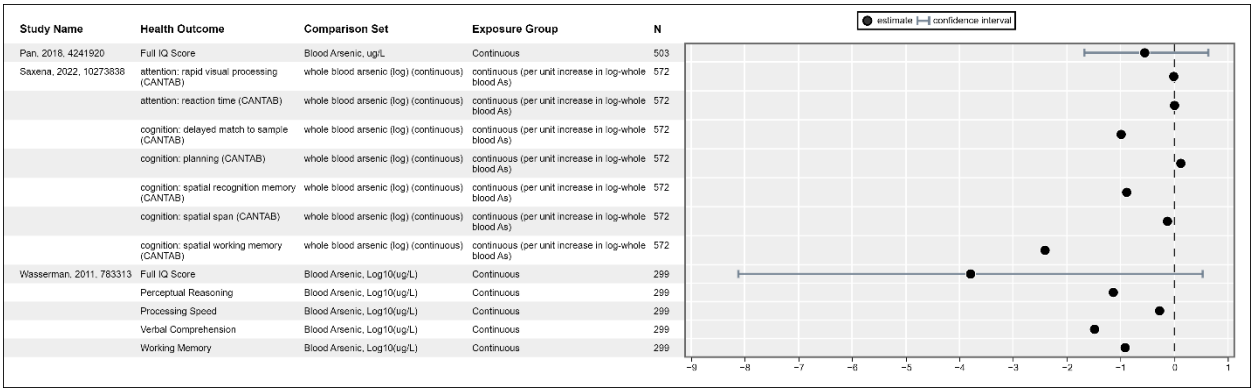


Figure 3-39. Study evaluation ratings for references evaluating cognitive effects (see interactive version in HAWC).

Cross-sectional studies

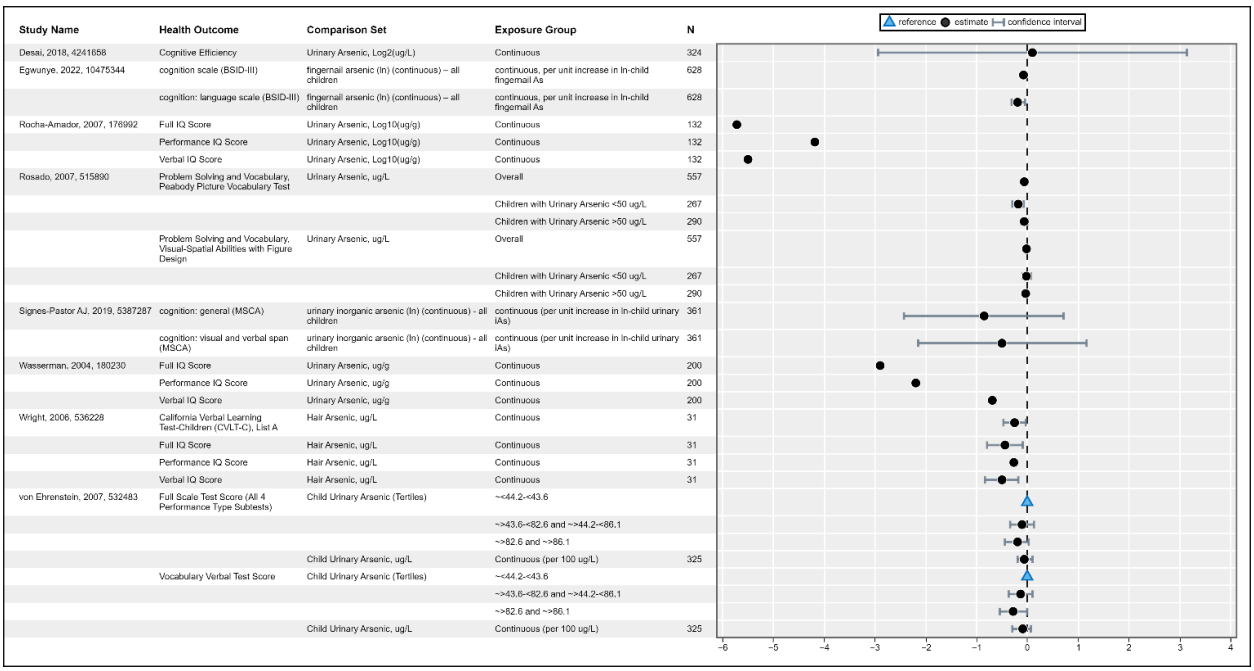
Some of the most consistent evidence for an association between arsenic exposure and cognitive deficits comes from 23 cross-sectional studies conducted in the United States (Wasserman et al., 2014); (Wright et al., 2006); Mexico (Calderón et al., 2001); (Rocha-Amador et al., 2007); (Rosado et al., 2007); 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); China (Wang et al., 2006); India (von Ehrenstein et al., 2007); Cambodia (Vibol et al., 2015); Uruguay (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 3-40). The majority of these cross-sectional studies evaluated populations that had experienced chronic or lifelong exposure to arsenic, reducing concern about temporality normally present for this study design. Some of the data presentation figures below include studies that use different exposure assessment techniques as described in the column labeled "Exposure metric" and/or have different reference groups. Thus, quantitative comparisons of the magnitude of the associations between studies is not appropriate. The intent of the figures is to facilitate analyses of patterns of associations across studies.

In studies from the United States Wright et al. (2006); Wasserman et al. (2014), arsenic exposure and intellectual function was examined among school-aged children (see Figure 3-40). 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 to children exposed to <5 μg/L arsenic in drinking water, those exposed to arsenic levels 5–10 μg/L had statistically significantly lower full-scale IQ scores and lower scores in perceptual reasoning, working memory, and verbal comprehension. No association was observed with 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 scores and word recall (see Figure 3-40).



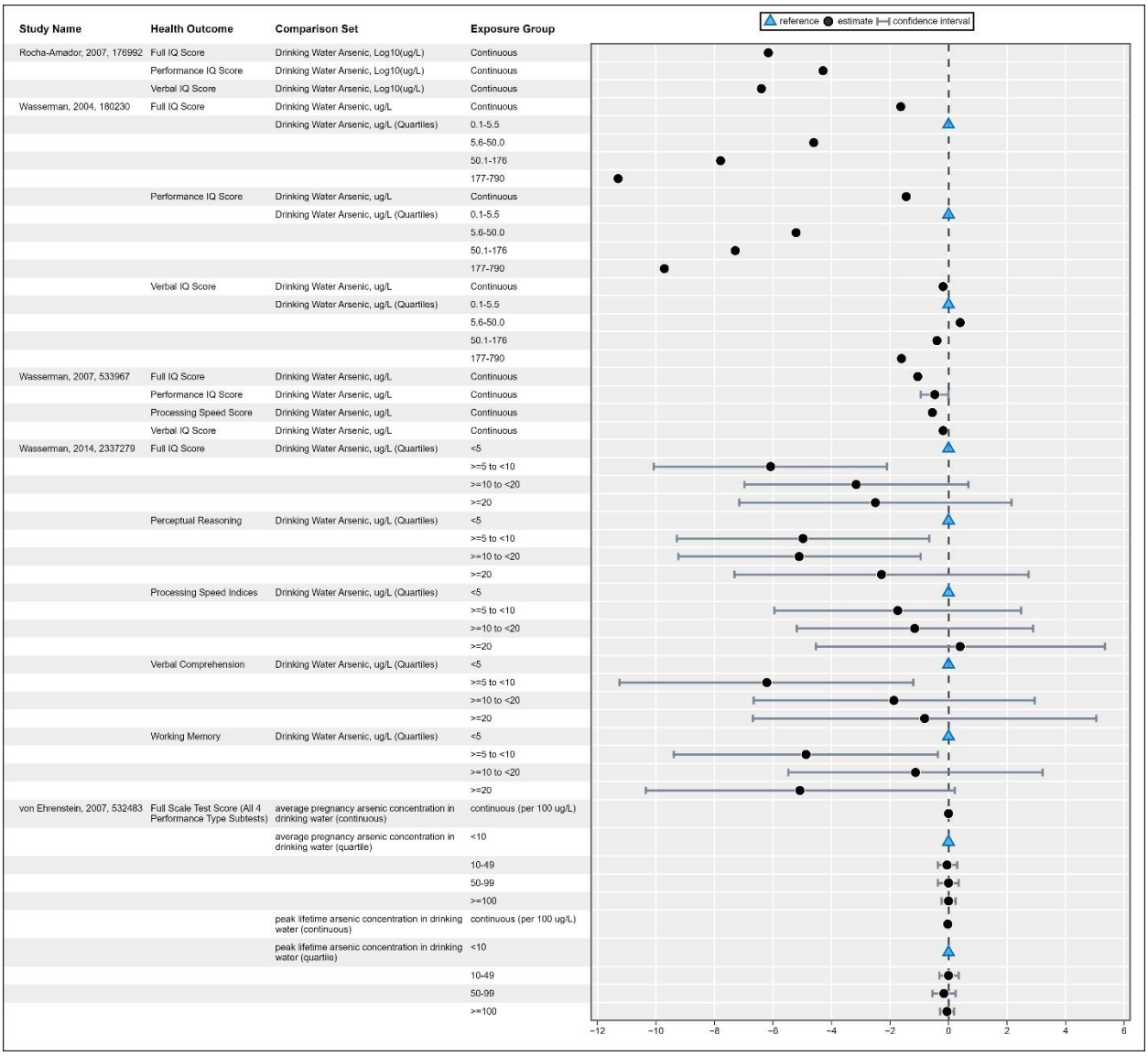
Study Name	Health Outcome	Comparison Set	Exposure Group	N
Pan, 2018, 4241920	Full IQ Score	Blood Arsenic, ug/L	Continuous	503
Saxena, 2022, 10273838	attention: rapid visual processing (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572
	attention: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

(a) Regression coefficient—blood biomarkers



Study Name	Health Outcome	Comparison Set	Exposure Group	N
Desai, 2018, 4241658	Cognitive Efficiency	Urinary Arsenic, Log2(ug/L)	Continuous	324
Egwunye, 2022, 10475344	cognition scale (BSID-III)	fingernail arsenic (ln) (continuous) – all children	continuous, per unit increase in ln-child fingernail As	628
	cognition: language scale (BSID-III)	fingernail arsenic (ln) (continuous) – all children	continuous, per unit increase in ln-child fingernail As	628
Rocha-Amador, 2007, 176992	Full IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132
	Performance IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132
	Verbal IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132
Rosado, 2007, 515890	Problem Solving and Vocabulary, Peabody Picture Vocabulary Test	Urinary Arsenic, ug/L	Overall	557
			Children with Urinary Arsenic <50 ug/L	267
			Children with Urinary Arsenic >50 ug/L	290
	Problem Solving and Vocabulary, Visual-Spatial Abilities with Figure Design	Urinary Arsenic, ug/L	Overall	557
			Children with Urinary Arsenic <50 ug/L	267
			Children with Urinary Arsenic >50 ug/L	290
Signes-Pastor AJ, 2019, 5387287	cognition: general (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-child urinary iAs)	361
	cognition: visual and verbal span (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-child urinary iAs)	361
Wasserman, 2004, 180230	Full IQ Score	Urinary Arsenic, ug/g	Continuous	200
	Performance IQ Score	Urinary Arsenic, ug/g	Continuous	200
	Verbal IQ Score	Urinary Arsenic, ug/g	Continuous	200
Wright, 2006, 536228	California Verbal Learning Test-Children (CVLT-C), List A	Hair Arsenic, ug/L	Continuous	31
	Full IQ Score	Hair Arsenic, ug/L	Continuous	31
	Performance IQ Score	Hair Arsenic, ug/L	Continuous	31
	Verbal IQ Score	Hair Arsenic, ug/L	Continuous	31
von Ehrenstein, 2007, 532483	Full Scale Test Score (All 4 Performance Type Subtests)	Child Urinary Arsenic (Tertiles)	~<44.2-<43.6	
			~>43.6-<82.6 and ~>44.2-<86.1	
			~>82.6 and ~>86.1	
		Child Urinary Arsenic, ug/L	Continuous (per 100 ug/L)	325
	Vocabulary Verbal Test Score	Child Urinary Arsenic (Tertiles)	~<44.2-<43.6	
			~>43.6-<82.6 and ~>44.2-<86.1	
			~>82.6 and ~>86.1	
		Child Urinary Arsenic, ug/L	Continuous (per 100 ug/L)	325

(b) Regression coefficient—biomarkers (urine, hair, nail)



(c) Regression coefficient—drinking water

Figure 3-40. Thumbnail schematic of cross-sectional studies addressing the association between iAs exposure and neurodevelopmental effects. (a) regression coefficient—blood biomarkers—continuous; (b) regression coefficient—biomarkers (urine, hair, nail); (c) regression coefficient—drinking water; (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

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 (see online HAWC forest plot). 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 and nonsignificant associations with performance and verbal IQ scores (see Figure 3-40). The authors also reported statistically significant associations between arsenic levels in drinking water and outcomes. Calderón et al. (2001) studied children (mean age= 7.5 years) in two Mexican communities (Martinez and Morales: mean urinary arsenic concentration 40.2 µg/g and 62.9 µg/g creatinine, respectively). The authors reported significantly lower full-scale and verbal IQ scores in Martinez (higher arsenic exposure) compared to Morales (lower arsenic exposure). (see Figure 3-40). They also used the data from the IQ test to calculate an additional subset of scores into four areas (concepts, knowledge, sequential, and spatial) and found statistically significantly lower scores in all four tests in Martinez compared to Morales.

Several cross-sectional studies identified in the literature review were conducted in India (von Ehrenstein et al., 2007) 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). von Ehrenstein et al. (2007) used validated tests to assess neurodevelopmental effects in children 5–15 years of age in India (see Figure 3-40). The authors reported a statistically significant inverse association between child urinary arsenic levels (mean= 78 µg/L) and performance on vocabulary, object assembly, and picture completion tests. In Bangladesh, Nahar et al. (2014a) assessed the association between arsenic and IQ using urinary arsenic levels in children aged 4–5 years (mean= 126 µg/L) and 9–10 years (mean= 181.9 µg/L). Among the 4- to 5-year-old children, there was an inverse association between urinary arsenic and IQ (non-verbal) in the three exposure groups (low= 137 µg/L; medium: 137 < 400 µg/L; and high: >400 µg/L respectively) which resulted in decreased mean IQ percentiles, only statistically significant in the high exposure group. Among the 9- to 10-year-old children, there was an inverse association between both arsenic and IQ at urinary arsenic levels >137 µg/L which decreased mean IQ percentiles. Nahar et al. (2014b) used the same tests as Nahar et al. (2014a) to evaluate the association between arsenic exposure (mean drinking water arsenic levels = 71.7 µg/L; mean urinary arsenic levels= 205.3 µg/L) and cognitive function in adolescents (14–15 years of age) in Bangladesh. They found a significant association between IQ and drinking water arsenic levels ≥11 µg/L. In Bangladesh, 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. 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 Wasserman et al. (2011) found a statistically significant inverse association between blood arsenic levels (mean= 4.81 µg/L) and full-scale IQ, verbal comprehension, and working memory in 8-11 year olds. 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 verbal comprehension, processing speed, working memory, and perceptual reasoning (urinary arsenic only). 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 3-40). (Saxena et al., 2022) examined adolescents in Bangladesh and observed a statistically significant negative association between spatial working memory and blood arsenic.

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 saw fingernail arsenic concentrations (median(IQR): 0.4 (0.3–0.5) µg/g) to be significantly associated with reduced language scores (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 a statistically significant, negative association 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 to the control group (2 µg/L) (see Figure 3-40). The IQ scores were 10 and 4 points lower, respectively, in the high and medium arsenic exposure groups compared to students in the control group. Pan et al. (2018) similarly studied children aged 9–11 years and examined the association between IQ score and arsenic concentrations in blood and urine in southern China and observed no significant associations.

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, increased latency in the selective attention and simple reaction time tests. Another study from Spain examining neuropsychological development observed negative associations with the scores in the quantitative index and working memory function only in boys, using a spot urine sample at age 4 (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. In (Desai et al., 2020a), no significant associations between urinary arsenic and academic achievement measures were seen. However, in (Desai et al., 2020b), urinary arsenic was inversely associated with visual attention measures, including the number of stages completed and pre-executive shift errors of the visual attention task, and span length of the spatial-memory task.

Cohort and case-control studies

Additional evidence supporting an association is observed in 19 *medium* or *high* confidence cohort and case-control studies examining cognitive effects in young children and adolescents (see Figure 3-41).

Hamadani et al. (2011) followed up with the same MINIM children 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 maternal and child urinary arsenic levels was found at GW 8 and 1.5 years of age, respectively. 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.

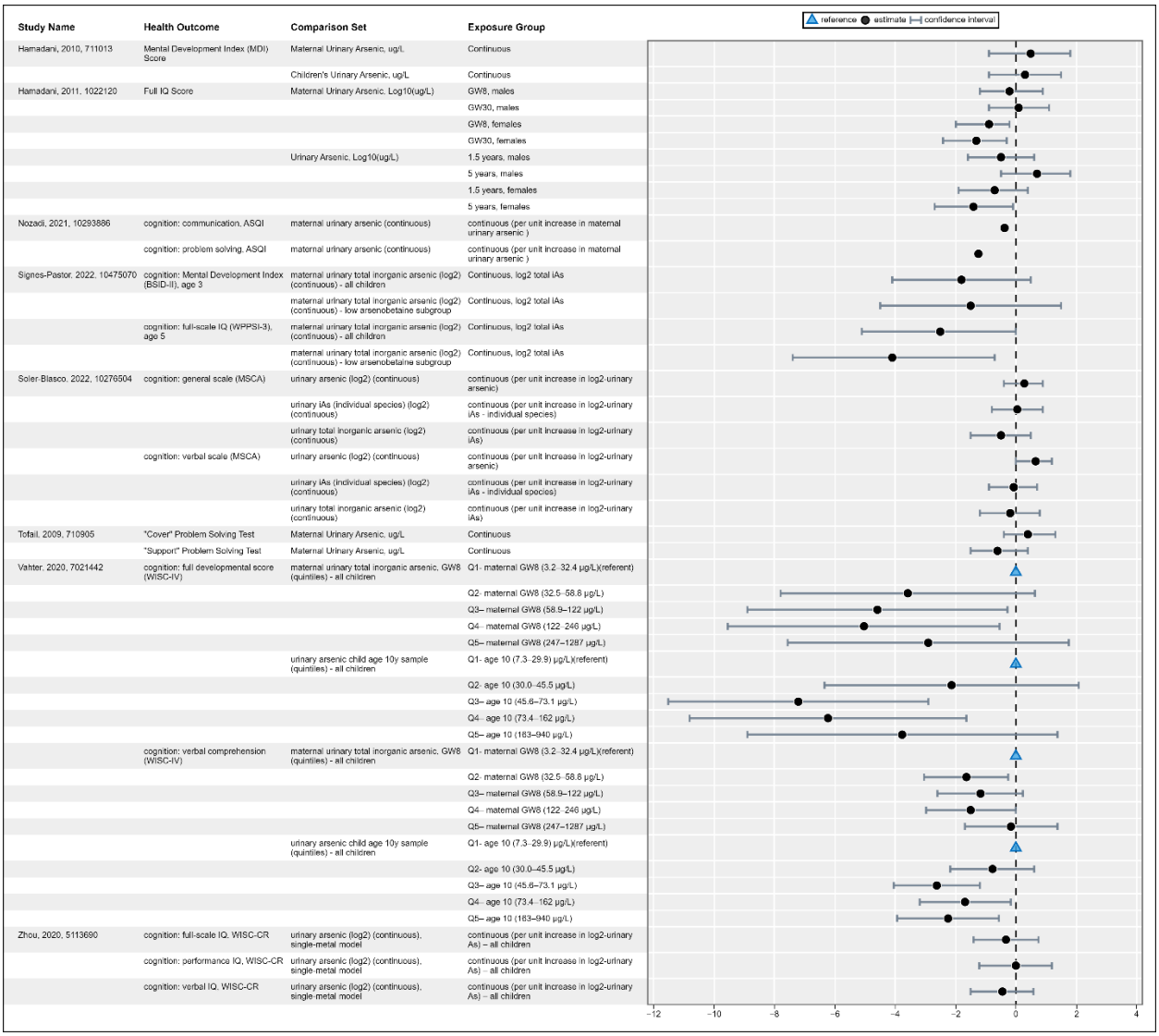
Three prospective cohort studies evaluated the association between arsenic and neurodevelopment using a cohort of maternal-infant pairs in Nepal (Parajuli et al., 2014);(Parajuli et al., 2015a);(Parajuli et al., 2015b). These studies estimated *in utero* exposure using arsenic levels in cord blood (mean 1.33 µg/L) and assessed neurodevelopmental indicators 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 and mental development or psychomotor development at any time point (6, 24, or 36 months of age). In Bangladesh, three studies evaluated high-level arsenic exposure and neurodevelopment 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 3-41a). Tofail et al. (2009) assessed psychomotor development and 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). The authors found no associations with psychomotor development or problem solving. A follow-up study by Hamadani et al. (2010) assessed the psychomotor and 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 or infant urinary arsenic levels (median 34.6 µg/L) and impaired neurodevelopment.

Consistent findings are observed in a body of more recent cohort studies, across different exposure markers, including fingernail, urine, hair, and cord blood, and different countries, including China, Taiwan, United States, Spain, and Bangladesh (Jiang et al., 2022); (Signes-Pastor et al., 2022); (Soler-Blasco et al., 2022); (Vahter et al., 2020), (Wang et al., 2022b); (Zhou et al., 2020); (Nozadi et al., 2021). For children in a study from Bangladesh, compared to the first urinary arsenic quintile at 10 years (<30 µg/L), the third and fourth quintiles (30–45 and 46–73 µg/L, respectively) had statistically significant lower full developmental scores (Vahter et al., 2020). Maternal urinary

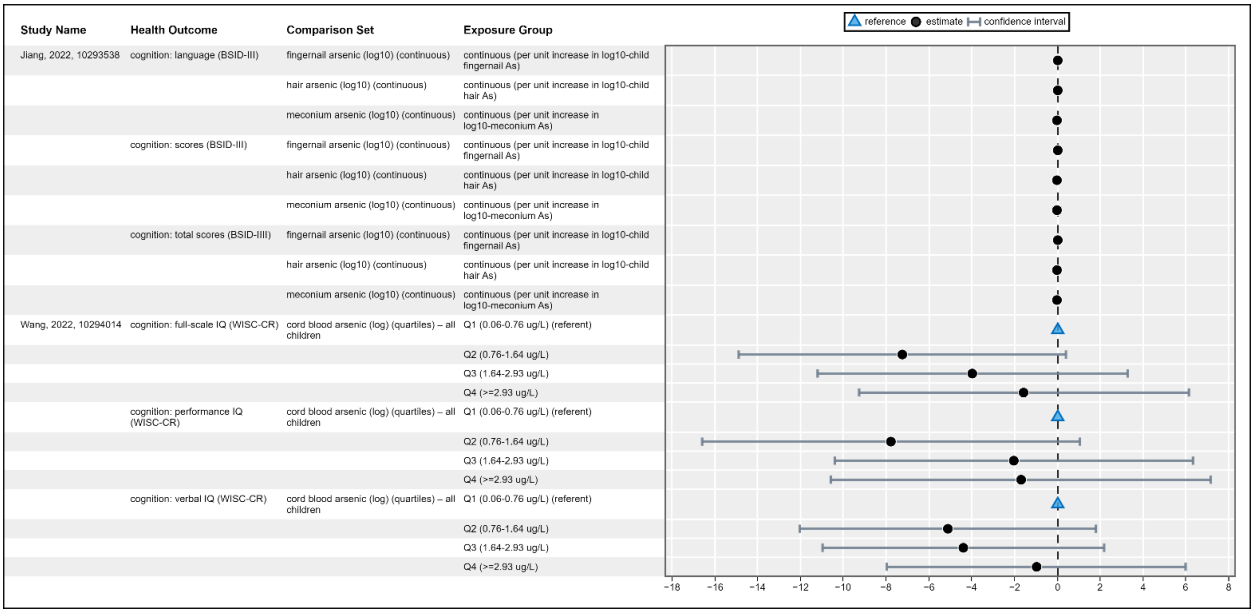
arsenic in early pregnancy, but not late pregnancy, showed inverse associations with full developmental scores and with verbal comprehension. Additionally, analyses using children's hair arsenic concentrations showed similar results (Vahter et al., 2020). In Taiwan, 3-year-old children and meconium arsenic levels were seen to be negatively associated with cognitive and language scores, but the results were not statistically significant (Jiang et al., 2022).

In a birth cohort in Spain, authors saw monomethylarsonic acid (MMA) concentrations measured in the first trimester of pregnancy to be inversely associated with the scores for the general, verbal, quantitative, memory, executive function and working memory scales of children aged 4-5 years (Soler-Blasco et al., 2022). Similar results of a decrease in mental development index as well as IQ were seen in a U.S. cohort (n = 260) of children (at ages 3 and 5 years old) with maternal urinary arsenic measurements from 26 weeks pregnancy (median(IQR): 3.63 (2.40-5.86) µg/L) (Signes-Pastor et al., 2022). Also in the U.S., the Navajo Birth Cohort Study (n = 327) found arsenic, measured in maternal urine at the time of delivery (geometric mean: 6.13 µg/L), had a negative linear effect on problem-solving scores in infants at ages 10 to 13 months (Nozadi et al., 2021). In a cohort from China (n=148), authors examined intelligence in school-aged children originally part of a birth cohort. Using cord blood arsenic concentrations (median(IQR): 1.64 (0.76–2.93) µg/L), the authors saw statistically significant impacts on children's verbal intelligence quotient (Wang et al., 2022b). However, a different cohort study from China, using the same well-established testing scale for children's intelligence, observed no associations between arsenic concentration from children's urine samples (median(IQR): 26.05 (12.88–43.80) µg/L) and IQ (Zhou et al., 2020).

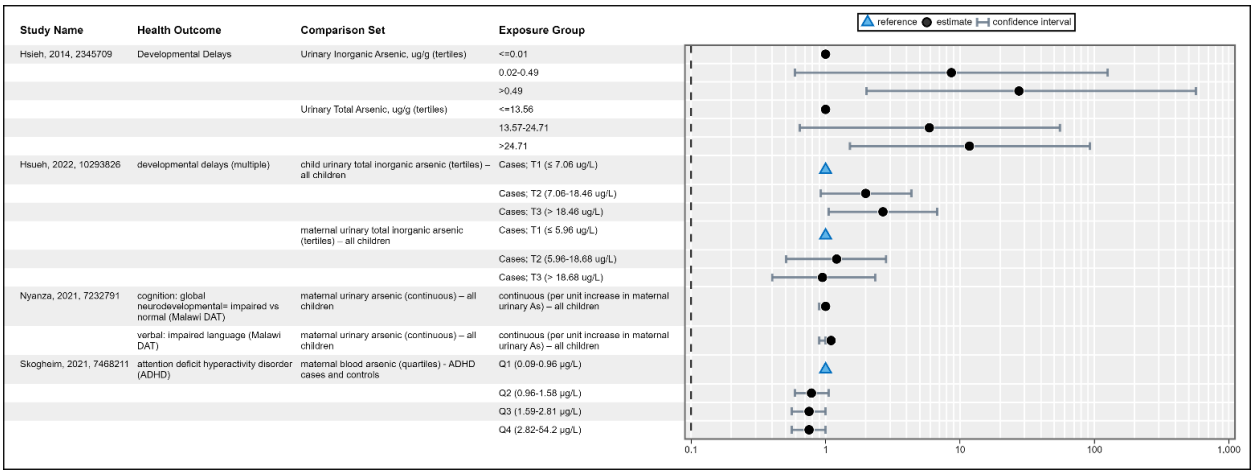
In a case-control study from Taiwan, Hsieh et al. (2014) compared mean total urinary arsenic levels in children aged 4–6 years with (19.7 µg/L) and without (10.2 µg/L) developmental delays. A statistically significant association between urinary total arsenic levels >24.7 µg/g creatinine and increased odds of 'developmental delay' was reported.



(a) Regression coefficient—urine biomarkers



(b) Regression coefficient—non-urinary biomarkers (blood, hair, nail, meconium)



(c) Odds ratios, prevalence ratios—biomarkers

Figure 3-41. Thumbnail schematic of cohort and case-control studies addressing the association between inorganic arsenic exposure and cognitive effects (a) regression coefficient—urine biomarkers; (b) regression coefficient—non-urinary biomarkers (blood, hair, nail, meconium);(c) odds ratios, prevalence ratios—biomarkers (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Social, behavioral, and emotional effects

The systematic literature review identified 9 *medium* or *high* confidence epidemiological studies (see Figure 3-42) 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, anxiety and depression, and personal social development (see Figure 3-43).

Four of these studies examined the association between arsenic and autism spectrum disorder (ASD), all case-control design: (Nabgha-e-Amen et al., 2020); (Rahbar et al., 2021); (Adams et al., 2013); and (Skogheim et al., 2021). In the Norwegian Mother, Father and Child Cohort, a statistically significant association between autism spectrum disorder and GW 17 maternal blood sample (2nd quartile of exposure (OR = 1.77 (CI: 1.26–2.49)), with decreasing non-statistically significant trend in Q3 and Q4) was observed (Skogheim 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. Similarly, another case-control study observed no statistically significant difference in adjusted geometric mean arsenic blood concentration for controls (1.29 µg/L) compared to autism cases (1.47 µg/L) in Pakistan (Rahbar et al., 2021). However, a separate case-control study from Pakistan observed a large statistically significant association of arsenic in hair (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) with ASD risk in children (Nabgha-e-Amen et al., 2020).

Several studies across different countries that examined emotional effects in children. In a cross-sectional study in Spain, authors observed urinary arsenic to be associated with internalizing problems in children, including anxiety, and somatic and thought problems (Rodríguez-Carrillo et al., 2022). In a cross-sectional study in Italy, urinary arsenic was statistically significantly associated with increased neurobehavioral problems, including anxious depressed, somatic complaints, attention problems, and rule breaking behavior (Renzetti et al., 2021). A cohort study from Israel found no association between maternal urine sample collected prior to delivery and child behavioral disorders (Karakis et al., 2021). In Mexico, Roy et al. (2011) reported modest associations between 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) received statistically significant higher scores on the oppositional behavior rating. However, the 3rd and 4th quartile findings were null; there was no trend seen over quartiles. 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 and cord serum arsenic levels were measured (Liang et al., 2020). Compared with the low arsenic reference group (<1.27 ug/L), medium (1.27–2.89 ug/L) and high (>2.89 ug/L) arsenic groups were

significantly associated with increased risks of a 'significant development delay' in the personal-social domain among infants.

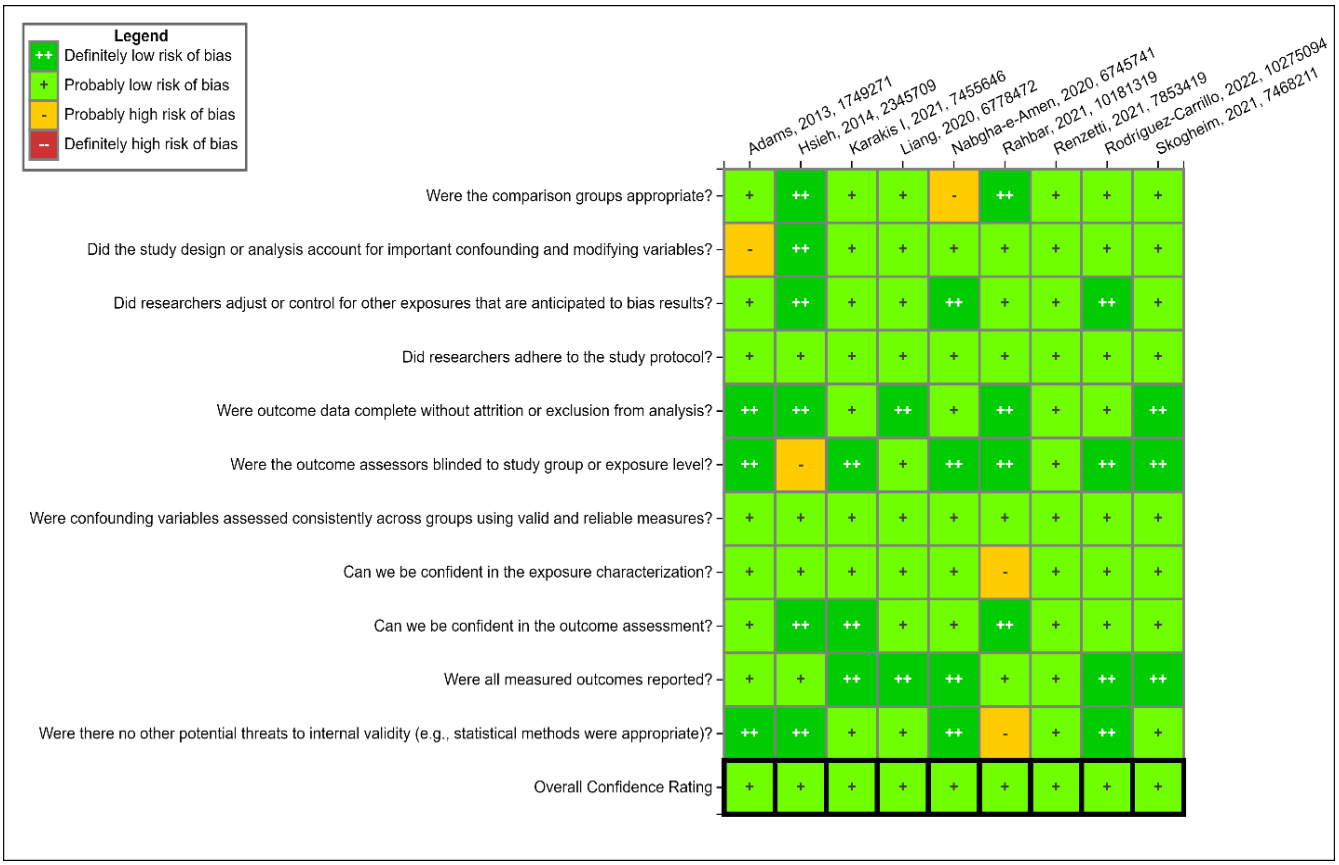
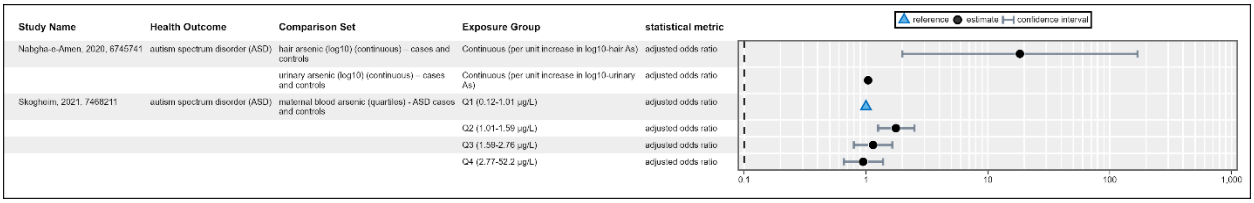
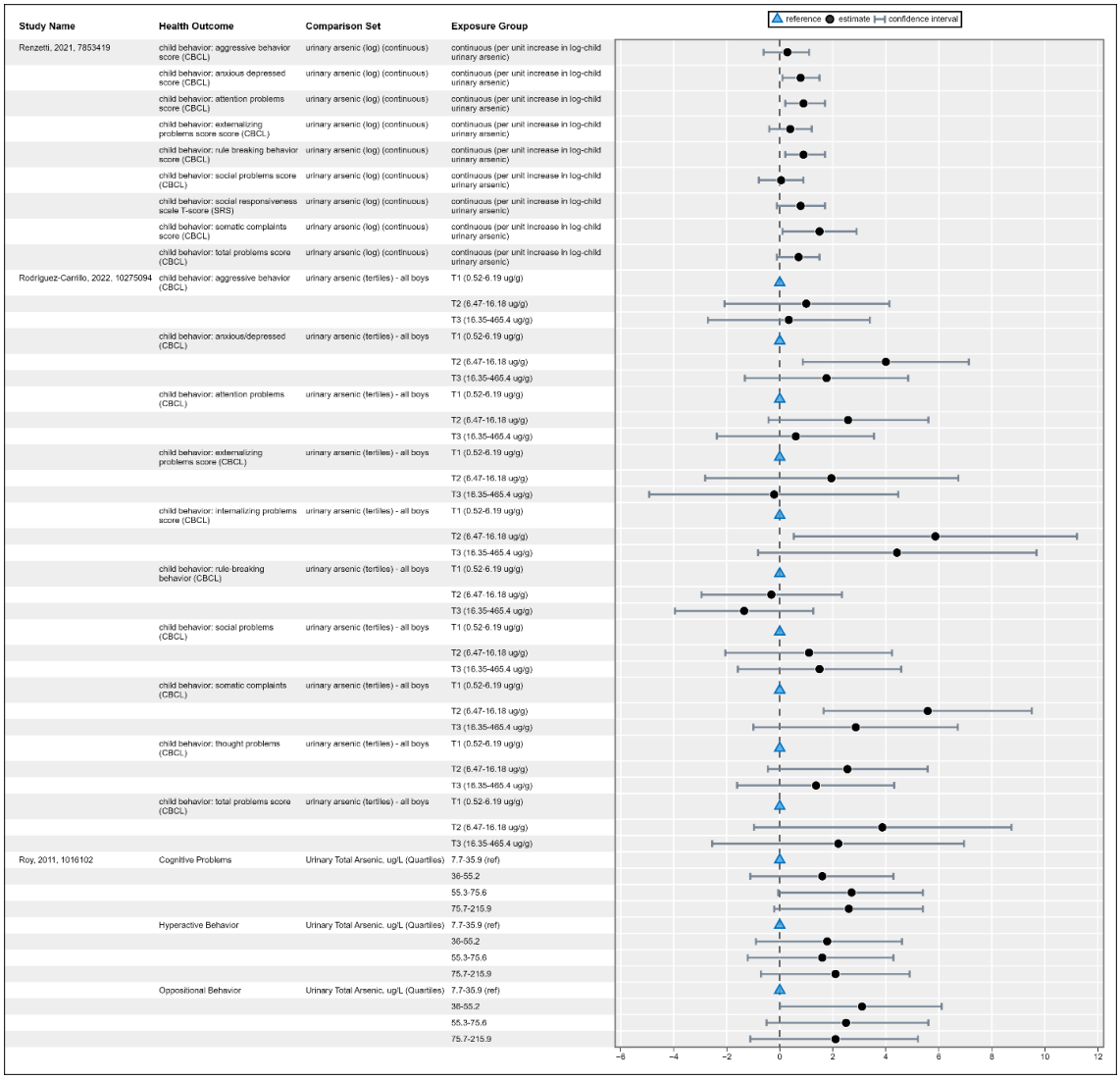


Figure 3-42. Study evaluation ratings for references evaluating social, behavioral, and emotional effects (see interactive version in HAWC).



(a) Odds ratio for autism spectrum disorder—urine biomarkers



(b) Regression coefficient—urine biomarkers

Figure 3-43. Thumbnail schematic of studies addressing the association between inorganic arsenic exposure and social, behavioral, and emotional effects (a) Odds ratio for autism spectrum disorder—urine biomarkers; (b) regression coefficient—urine biomarkers (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Motor effects

Four studies, using four different exposure measures, examined motor functions and skills in Bangladesh, Vietnam, Spain, and Taiwan (Egwunye et al., 2022); (Parvez et al., 2011); (Signes-Pastor et al., 2019b); and (Jiang et al., 2022) (see Figure 3-44 and Figure 3-45). A cross-sectional study that investigated an association between arsenic and motor coordination in children aged 8–11 years in Bangladesh assessed various endpoints including body coordination, manual coordination, fine manual control, and strength and agility Parvez et al. (2011). The authors observed a statistically significant negative association between total motor composite and body coordination scores and mean arsenic levels in drinking water (43.3 μg/L), blood (4.8 μg/L), toenails (5.9 μg/g), and urine (246.5 g creatinine/L) (Parvez et al., 2011). From Spain, a cross-sectional study examining neuropsychological development found statistically significant inverse associations between gross motor and fine motor scores and urine sample in 4-year-olds (Signes-Pastor et al., 2019b). In Vietnam, no significant association was observed between fingernail arsenic (median(IQR)=0.4 (0.3–0.5) μg/g) and motor skills, cross-sectionally (Egwunye et al., 2022). Finally, a small cohort (n = 53) study of 3-year-olds from Taiwan observed hair arsenic level to be statistically significantly associated with gross motor development (Jiang et al., 2022).

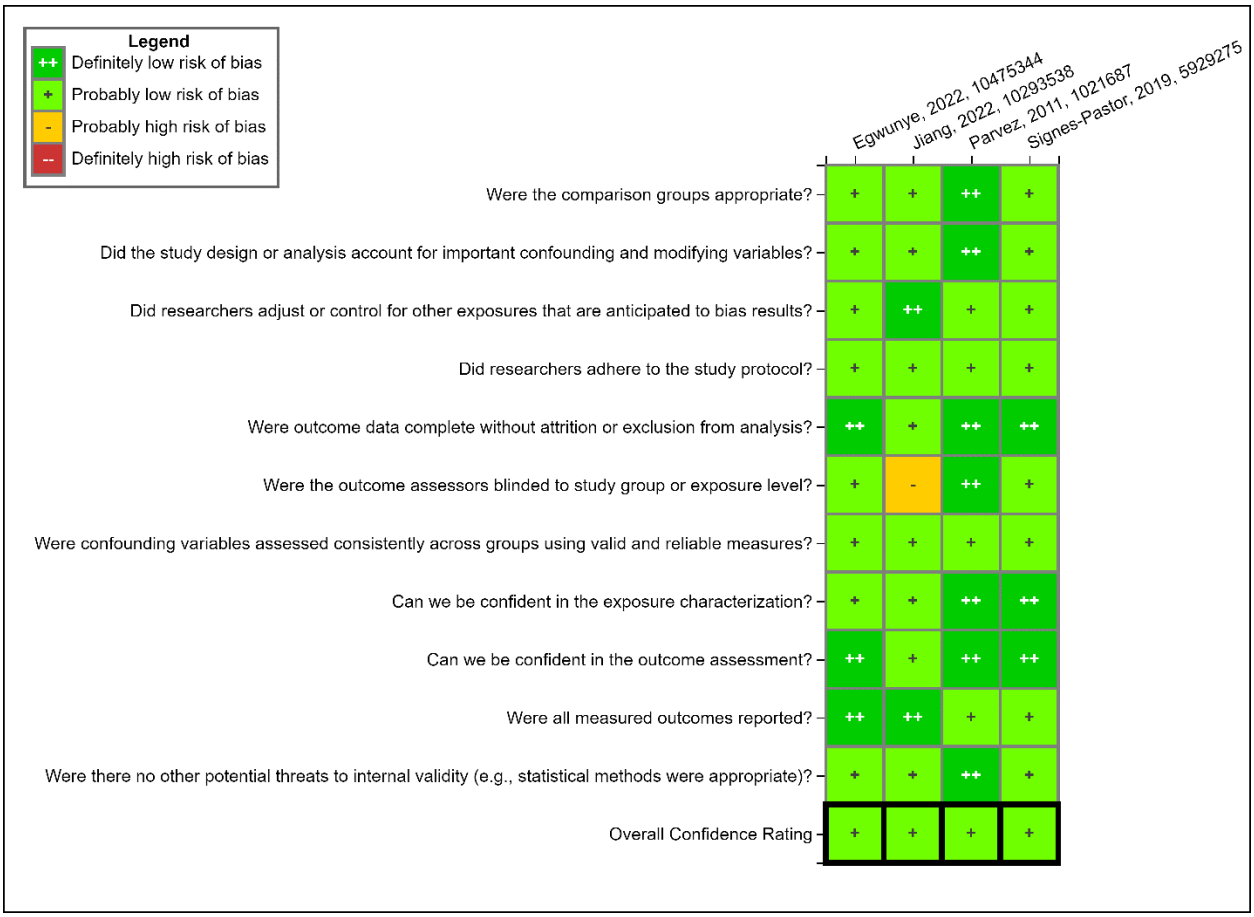
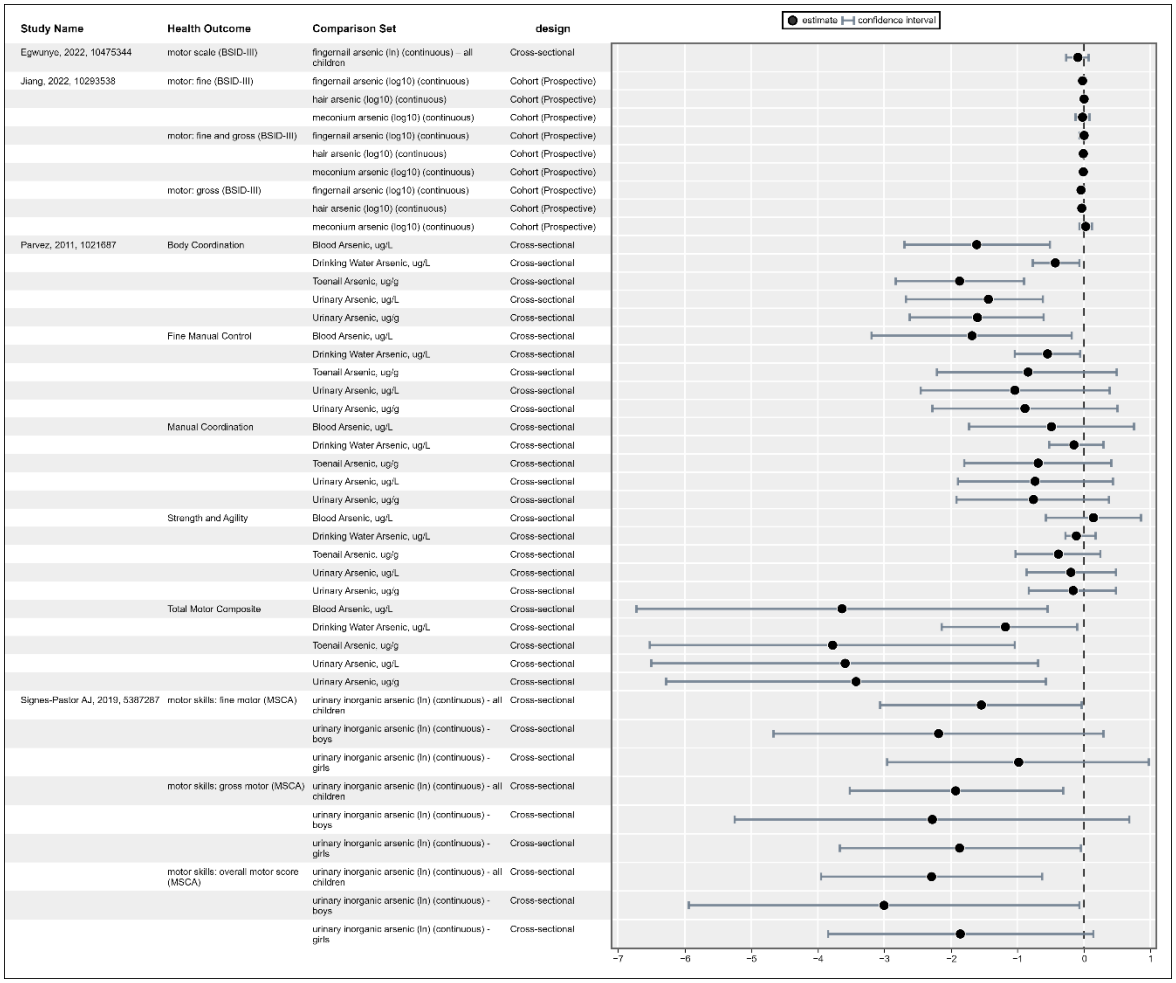


Figure 3-44. Study evaluation ratings for references evaluating motor effects (see interactive version in HAWC).



Study Name	Health Outcome	Comparison Set	design
Egwuniye, 2022, 10475344	motor scale (BSID-III)	fingernail arsenic (ln) (continuous) - all children	Cross-sectional
Jiang, 2022, 10293538	motor: fine (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)
		hair arsenic (log10) (continuous)	Cohort (Prospective)
		meconium arsenic (log10) (continuous)	Cohort (Prospective)
	motor: fine and gross (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)
		hair arsenic (log10) (continuous)	Cohort (Prospective)
		meconium arsenic (log10) (continuous)	Cohort (Prospective)
	motor: gross (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)
		hair arsenic (log10) (continuous)	Cohort (Prospective)
		meconium arsenic (log10) (continuous)	Cohort (Prospective)
Parvez, 2011, 1021687	Body Coordination	Blood Arsenic, ug/L	Cross-sectional
		Drinking Water Arsenic, ug/L	Cross-sectional
		Toenail Arsenic, ug/g	Cross-sectional
		Urinary Arsenic, ug/L	Cross-sectional
		Urinary Arsenic, ug/g	Cross-sectional
	Fine Manual Control	Blood Arsenic, ug/L	Cross-sectional
		Drinking Water Arsenic, ug/L	Cross-sectional
		Toenail Arsenic, ug/g	Cross-sectional
		Urinary Arsenic, ug/L	Cross-sectional
		Urinary Arsenic, ug/g	Cross-sectional
	Manual Coordination	Blood Arsenic, ug/L	Cross-sectional
		Drinking Water Arsenic, ug/L	Cross-sectional
		Toenail Arsenic, ug/g	Cross-sectional
		Urinary Arsenic, ug/L	Cross-sectional
		Urinary Arsenic, ug/g	Cross-sectional
	Strength and Agility	Blood Arsenic, ug/L	Cross-sectional
		Drinking Water Arsenic, ug/L	Cross-sectional
		Toenail Arsenic, ug/g	Cross-sectional
		Urinary Arsenic, ug/L	Cross-sectional
		Urinary Arsenic, ug/g	Cross-sectional
	Total Motor Composite	Blood Arsenic, ug/L	Cross-sectional
		Drinking Water Arsenic, ug/L	Cross-sectional
		Toenail Arsenic, ug/g	Cross-sectional
		Urinary Arsenic, ug/L	Cross-sectional
		Urinary Arsenic, ug/g	Cross-sectional
Signes-Pastor AJ, 2019, 5387287	motor skills: fine motor (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional
	motor skills: gross motor (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional
	motor skills: overall motor score (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional

Figure 3-45. Thumbnail schematic of studies addressing the association between inorganic arsenic exposure and motor effects—regression coefficient—biomarkers—continuous exposure (see interactive data graphic). Note: plots may include studies with both transformed and untransformed expressions of the independent variable. Comparison between plots may not be appropriate as both logarithmic and arithmetic scales are used.

Mechanistic Observations

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 gluta—thione 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.

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search (see Section 3.11 of iAs Protocol) on modifying factors identified in Table 3-7, 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.

- **Lifestage:** The evidence summarized above is suggestive that early-life exposure to arsenic results in an increased risk of cognitive effects in children.

- **Sex:** Information is inadequate to determine if one sex is more susceptible than the other is to neurodevelopmental effects from arsenic exposure. Only two studies (Hamadani et al., 2011); (Rosado et al., 2007) evaluated sex differences and the results were conflicting.

Table 3-7. 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)
Lifestage	Summarized above	Summarized above	Summarized above
Sex	Hamadani et al. (2011);	Decrease in full-scale and verbal IQ in 5-year-old girls; low and non-statistically significant associations in 5-year-old boys	Bangladesh: 51 µg/L (median, urine)
	Rosado et al. (2007)	Different associations between urinary arsenic and results on cognitive tests for 6- to 8-year-old boys compared to girls	Mexico: 58.1 µg/L (mean, 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 3-8) given sufficient exposure conditions[20]. This conclusion is based on studies of humans that assessed exposure levels of <100µg/L primarily showing cognitive effects and, to a lesser extent, social, behavioral, and emotional effects, and motor effects.

There is *moderate* evidence supporting an association between arsenic and cognitive effects that comes from *medium* or *high* confidence cross-sectional and cohort epidemiological studies. A number of these studies found evidence of associations between generally low concentrations of arsenic (e.g., <100 µg/L arsenic in drinking water) . Largely consistent, inverse associations between arsenic exposure and childhood IQ and other cognitive measures were observed across diverse geographic locations and arsenic exposure metrics in the cross-sectional and cohort

[20] The "sufficient exposure conditions" are more fully evaluated and defined for the identified health effects through dose-response analysis in Section 4.

studies. A dose-response gradient was observed in some studies (e.g., (Wasserman et al., 2004); (Wang et al., 2006); (Wasserman et al., 2018); (von Ehrenstein et al., 2007)). Some inconsistencies across the cross-sectional and cohort studies may be due in part to different measurements of arsenic exposure (e.g., drinking water, urine, blood), the heterogeneity in the outcomes that were assessed, the use of neuropsychological assessments that might not have been normalized for non-U.S. populations, and variations in the age of assessment. In addition, the cross-sectional study design could have failed to capture the critical window of exposure, deficit onset, or both.

There is *slight* evidence for an association between arsenic exposure and social, behavioral, and emotional effects. Nine *medium* or *high* confidence studies across diverse geographic regions, using different types of exposure biomarkers, measured autism or behavioral-related endpoints. Four case-control studies examined autism, with unexplained inconsistency of findings across these studies. While varied study designs across different populations examined emotional effects, some inconsistencies were seen across results, with associations observed between iAs and anxiety, thought problems, and rule breaking behavior, but not with behavioral disorders. There is coherence with the evidence bases for cognitive effects and motor effects.

There is *slight* evidence for an association between arsenic exposure and motor effects, as only four *medium* or *high* confidence studies evaluated this outcome. Studies examined populations in different countries using varied exposure assessment methods; three studies observed significant adverse, and one study observed null effects on motor skills and scores. There is coherence with the evidence bases for cognitive effects and social, behavioral, and emotional effects. 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.

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 <100µg/L primarily showing cognitive effects, and, to a lesser degree, social, behavioral, and emotional effects and motor effects. Neurodevelopmental effects are considered a direct result of iAs exposure, and therefore, measures of these effects (e.g., change in IQ scores) are considered for dose-response analysis (see Section 4.5).

Table 3-8. 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)**
Cognitive and behavioral deficits 43 *medium or high* confidence studies	Large cross-sectional and cohort studies evaluating populations chronically exposed to arsenic report generally consistent evidence of cognitive and behavioral deficits across diverse populations and with a variety exposure and outcome assessment methods.	• Most studies are medium or high confidence - reporting an effect • Consistency - across multiple geographic regions • Dose-response gradient - observed in some but not all analyses • Coherence - with evidence of effects on social, behavioral, and emotional effects, and motor effects		⊕⊕⊙ *Moderate*
Social, behavioral, and emotional effects 9 *medium* or *high* confidence studies	Two case-control studies identified an association with autism. Varied study designs across different populations examined emotional effects, with associations observed between iAs and anxiety, thought problems, rule breaking behavior, while other studies found null results for behavioral disorders.	• Most studies are medium or high confidence - reporting an effect • Coherence - with cognitive effects and motor effects	• Unexplained inconsistency - between studies in the evidence base	⊕⊙⊙ *Slight*
Motor effects 4 *medium* or *high* confidence studies	Three cross-sectional studies identified an association between arsenic and adverse effects on motor skills and scores.	• Coherence - with cognitive effects, social, behavioral, and emotional effects	• Unexplained inconsistency - between studies in the evidence base	⊕⊙⊙ *Slight*

1

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 meta-regression 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 meta-regression approach. Diabetes, pregnancy and birth 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 focuse on six adverse health outcomes for hazard identification and dose-response analysis in this assessment. Table 3-9 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[21] and were prioritized for dose-response analysis.

Table 3-9. 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 diabetes type 2 diabetes

[21] 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 other 4 outcomes EPA continued to prioritize these endpoints for further dose-response analysis.

Health outcome category	NRC Tier	Evidence Judgments	Measures Considered in Different Studies
Diseases of the circulatory system	**1 & 3**	**Evidence demonstrates**	cerebrovascular disease mortality stroke mortality CHD & other heart disease mortality CHD mortality coronary atherosclerosis mortality myocardial infarction mortality CVD mortality peripheral artery disease mortality cerebrovascular disease stroke CHD CVD hypertension QTc prolongation carotid atherosclerosis
Neurodevelopmental effects	**2**	**Evidence indicates**	intellectual function short and long term memory verbal comprehension perceptual reasoning processing speed impulsivity motor control selective and focused attention reaction time problem-solving
Pregnancy and birth outcomes	**2 & 3**	**Evidence indicates**	spontaneous abortion infant mortality stillbirths birth weight

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 high quality are available, meta-regerssion analyses can increase the precision of the estimated POD (U.S. EPA, 2022). Section 4.3 focuses on meta-regression analyses of bladder cancer, lung cancer, diseases of the circulatory system (DCS) and diabetes. These meta-regression analyses allowed for a more precise estimate of risks above and below the RfD, as well as CSF estimates that are based on more than one POD. Dose-response analyses for pregnancy and birth outcomes and neurodevelopmental effects are featured Sections 4.4 and 4.5. For several of the outcomes in Table 3-5, 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 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. 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).

4. DOSE-RESPONSE ANALYSIS

4.1. INTRODUCTION

For this assessment, EPA evaluated multiple dose-response methods, including applying individual models to facilitate prioritization for more complex analyses and applying multiple traditional and Bayesian methods to more fully utilize a wider array of studies for derivation of toxicity values. EPA's approach to the dose-response assessment for iAs presented in this report addresses NAS (NASEM, 2019) and NRC recommendations for (1) advancing dose-response by presenting quantitative representations of uncertainty in lieu of EPA's traditional uncertainty factors (NRC, 1994);(NRC, 2009);(NRC, 2013);(NASEM, 2019); (2) identifying susceptible populations and background exposures (NRC, 2009);(NRC, 2013);(NASEM, 2019); (3) taking a more consistent, unified approach for cancer and noncancer endpoints (NRC, 2009); (NRC, 2013); and (4) expanding the use of Bayesian methods (NRC, 2014); (NASEM, 2019).

The Bayesian analyses of bladder and lung cancer, DCS, and diabetes derive model-based predictions of lifetime extra risk (with confidence intervals) associated with μg/kg-day exposure above background, across ranges of doses relevant to the U.S. population. When applicable, statistical meta-analyses (U.S. EPA, 2022), such as the (Allen et al., 2020b; Allen et al., 2020a) meta-regression methods are used to quantitatively combine results within a set of studies. To the extent possible, the meta-analyses performed in this assessment quantitatively assess model uncertainty, exposure uncertainty, biological considerations, and individual and study population variability. Population-specific factors that influence the estimation of iAs intake (dose) from reported exposure metrics (e.g., water concentrations) and an iAs PBPK model validated for estimating intake (dose) from reported urinary levels were used to estimate a common dose measure (average lifetime daily μg/kg) to increase the number of studies that could be combined. The meta-regression modeling approach used enables variability in the dose-response slope estimates to be quantified across study populations.

To take advantage of the large iAs epidemiological evidence base, meta-regression methods are used to convert different reported exposure metrics to a common μg/kg-day dose metric (see Section 4.3.2) and reported incidence data to "effective counts" that match the reported adjusted relative risk estimates (see Section 4.3.3). Deriving a common dose metric enables studies using differing exposure metrics to be combined and deriving "effective counts" allows case-control and cohort studies to be analyzed in the same meta-analysis. The Bayesian meta-regression modeling uses relatively broad prior assumptions based in part on the causality conclusions of the hazard identification (see Section 4.3.4 for details). The hierarchical structure of the Bayesian meta-regression model, which estimates separate α^* (intercept) parameters for each data set, provides

insight into dose-response heterogeneity and improves the quantification of overall uncertainty and variability.

This chapter 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 meta-regression analyses for four prioritized health outcomes: bladder cancer,[22] lung cancer, diseases of the circulatory system (DCS), and diabetes (see Section 4.3), and (3) dose-response analysis for two other prioritized health outcomes with data sets not suitable for Bayesian meta-regression: pregnancy and birth outcomes (see Section 4.4) and neurodevelopmental cognitive effects (see Section 4.5). The approaches used to conduct dose-response were informed by prior feedback from NRC (NRC, 2014); (NRC, 2013); (NRC, 2011); (NRC, 2009); (NRC, 2001). The dose-response methods utilized by EPA were described in the iAs protocol (see Appendix A) and reviewed and supported by the (NASEM, 2019). 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). For DCS, diabetes, pregnancy and birth outcomes, and neurodevelopmental cognitive effects, reference doses (RfDs) are derived (see Section 4.6) and polynomial equations relating extra risk and dose above background are provided, when possible.

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 US background exposures), identify those that allow for multiple-study meta-regression 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 (see the iAs Protocol [link provided in Appendix A, Section 2.3.1]). 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 neurodevelopmental health outcomes. No appropriate dose-response data sets were identified for immune system health outcomes. The neurodevelopmental 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 dividing the exposure estimated to result in a 20% increase in relative risk (RRE_{20}) by a background exposure estimate (Hobbie et al., 2020). Separate RRBs were derived for each data set using an estimate of the U.S. (Hobbie et al., 2020) population background exposure (RRB-US) and the mean background exposure for the study population reference group (RRB-SP).

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). The results of the RRB analysis, considering both the number of adequate supporting studies and the relatively high percentage of low RRB-US values[23] 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) and diabetes (see Section 4.3.8). The RRB results 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. Higher-level dose-response analyses were also performed for pregnancy and birth outcomes (see Section 4.4) and neurodevelopmental 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.

[23] 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 a 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.

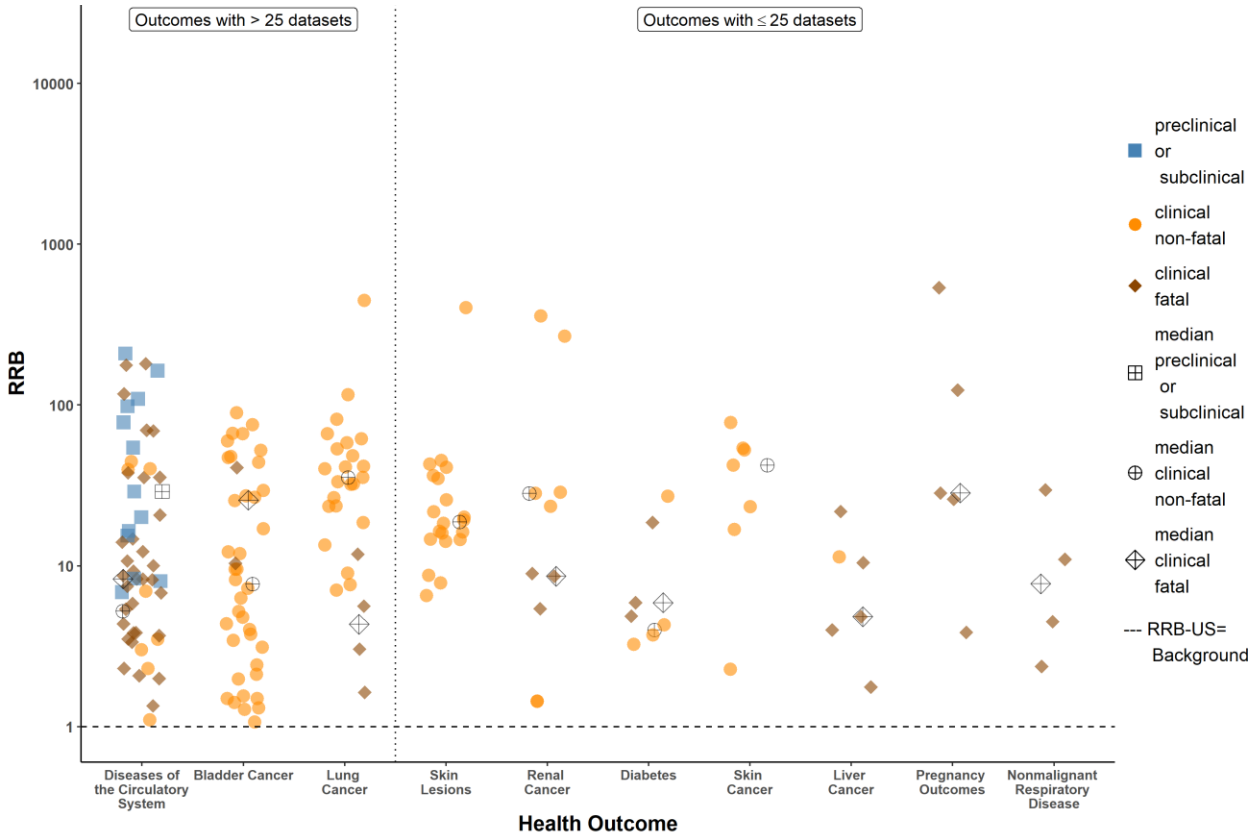


Figure 4-1. Individual data set (solid symbols) and median (crosshatch symbols) relative risk increase over the U.S. background exposure (RRB-US) estimates for health outcomes with >25 and ≤25 data sets.[24]

4.3. BAYESIAN META-REGRESSION ANALYSES

4.3.1. Identification of Studies and Data for Bladder Cancer, Lung Cancer, Diseases of the Circulatory System, and Diabetes Meta-Regressions

The procedures used to select studies and data sets for inclusion in the Bayesian meta-regression dose-response assessments for bladder cancer, lung cancer, DCS, and diabetes are described in the iAs Protocol (link provided in Appendix A). First, for each of these health outcomes, the original set of studies was analyzed to identify data sets most appropriate for meta-regression dose-response. For this step, the dose-response screening-level criteria described by Hobbie et al. (2020) and summarized in the iAs Protocol (link provided in Appendix A), Section 5.1, were applied to medium and high confidence studies.

[24]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).

Second, criteria of particular importance for EPA's meta-regression approach [see the iAs Protocol (link provided in Appendix A), Section 5.2.2] were considered to identify the study data sets for use in the meta-regression analyses. The criteria considered particularly important for EPA's meta-regression approach include study design (i.e., case-control or cohort); exposure metric (i.e., use of exposure metric that is or can be converted to an oral ingestion rate); risk metric (i.e., RR, OR, HR); reporting of numeric exposure-groups characterization; incidence reporting (cases and controls, or cases and cohort size); length of follow-up (i.e., ability to obtain or estimate person-years); number of exposure groups (two plus the reference group required); number of cases/dose group; and endpoint (incidence or mortality of a relevant health outcome). Although EPA's PBPK model allows for the conversion of urine biomarker data to oral doses, studies using other biomarkers (e.g., toenail and hair concentrations) were excluded from the meta-regressions due to uncertainties in converting those metrics to oral doses.

To promote consistency and to document the meta-regression data set selection, at least 2 reviewers evaluated studies according to the above considerations and provided qualitative ratings for each element and provided an overall rating (good/criteria met, fair, poor/criteria not met) for each criterion, with a brief description of the basis for the choice. Reviewers then discussed the ratings and resolved differences or refined concerns. To help focus the discussions, the number of study limitations for each study were tabulated, and studies with the most markdowns were further examined for suitability.

The final selection of data sets also considered issues related to the potential utility for extrapolation to the U.S. population. EPA prioritized including suitable low-exposure studies in meta-analyses, recognizing a large proportion of available studies evaluated populations with exposures much higher than commonly experienced in the United States. Primarily for this reason, this analysis does not include studies of populations within Southwest Taiwan, where diseases associated with historically high arsenic exposures have been "endemic" for centuries. In addition to extremely high exposures and high incidences of arsenic-associated diseases such as Blackfoot Disease, Southwest Taiwan populations suffer from poor nutrition relative to U.S. populations. Nevertheless, some studies that could be considered moderate exposure were included to ensure susceptible subpopulations would be represented among the meta-regression data sets. This helps address concerns related to the potential presence of genetic polymorphisms, inadequate nutrition, or other differences that can influence dose-response sensitivity. As discussed below, the data sets selected include both moderately exposed and low-exposure populations. Selecting diverse studies facilitates the investigation of heterogeneity in arsenic-related dose-response.

Identification of Studies for Bladder Cancer Dose-Response Analysis

Forty-two 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 on the basis of criteria outlined above for the final bladder cancer meta-regression dose-response analysis (see Figure 4-2).

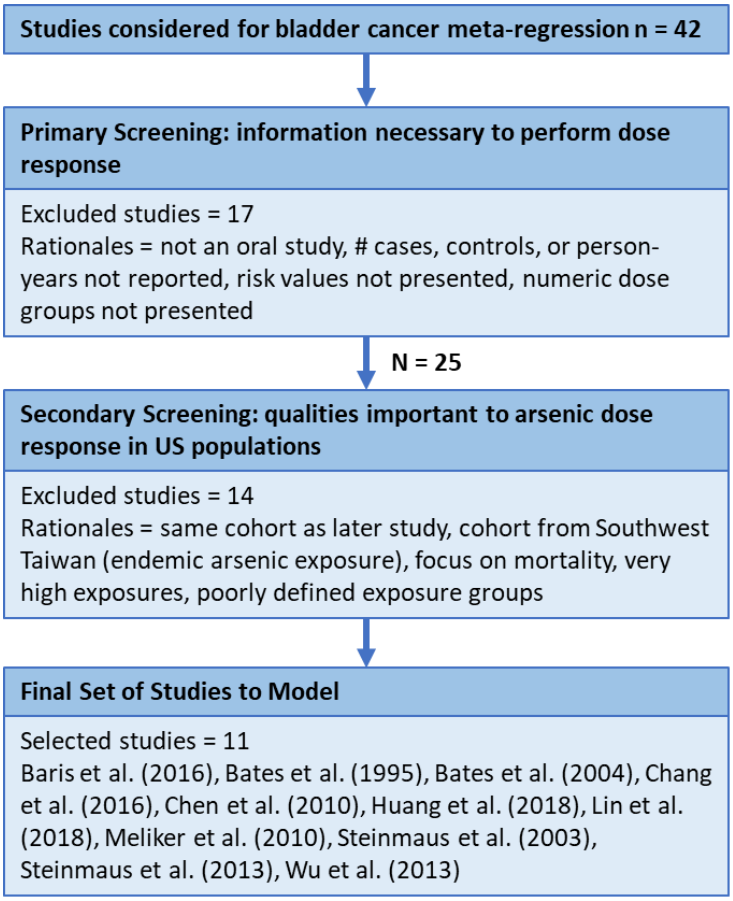


Figure 4-2. Study selection flow for identification of studies for bladder cancer Bayesian meta-regression.

Data Sets Selected for Urinary/Bladder Cancer Meta-Regression

Of the 11 selected studies, 10 were case-control studies and 1 was a cohort study. Four data sets were from U.S. populations, five from Northeast Taiwan, and one each from Argentina and northern Chile. 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), and urinary arsenic excretion (µg/gm creatinine). To support the meta-regression, 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, Table C-16. Although these epidemiological studies were considered suitable for dose-response, the exposure measurement for most have some degree of uncertainty. For example, water arsenic exposure or intake often is estimated from one or a few measurements of arsenic concentrations, and historical exposures are inferred to be similar to those taken in the recent past. Section 4.3.2 describes EPA's approach to addressing these uncertainties and estimating arsenic daily intake.

Urine biomarker metrics of iAs dose were evaluated against bladder cancer incidence in four hospital-based data sets, three consisting of subjects recruited from the National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital in Northeast Taiwan (Wu et al., 2013);(Huang et al., 2018);(Lin et al., 2018) and one consisting of subjects recruited from the China Medical University Hospital located in Midwest Taiwan in the city of Taichung. EPA has estimated daily arsenic intake using a 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).[25] The estimated iAs intake for this cohort (0.215–1.2 μg/kg-day) is lower than in most of the other selected data sets and within or near the range of intakes observed in the United States. Because the Wu et al. (2013) data set exhibits a much steeper dose-response curve than the other three urine studies, EPA has conducted a detailed review of data related to this cohort and its impact on the meta-regression (see Appendix C, Sections C.1.2 Bladder Cancer; Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses and C.1.2 Bladder Cancer; Bladder cancer sensitivity analyses). An important consideration is this Northeast Taiwan cohort has been the subject of multiple additional epidemiological investigations (Pu et al., 2007); (Huang et al., 2008); (Chung et al., 2011);(Wu et al., 2012a);(Chung et al., 2013);(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. EPA also conducted sensitivity analyses on this and the other urine studies (see *Sensitivity Analyses,* Appendix C, Section C.1.2 Bladder Cancer; Bladder cancer sensitivity analyses).

EPA found considerable overlap between the studies included in the current meta-regression and those identified in 5 earlier meta-analyses (see Appendix C, Table C-17). Of the eleven studies chosen by EPA, a core group of five studies were chosen for all (Bates et al., 2004); (Meliker et al., 2010); (Baris et al., 2016) or for all but one (Chen et al., 2010b); (Steinmaus et al., 2013) of the meta-analyses published after them. Studies selected for the earlier meta-analysis that were not used in the EPA meta-regression analysis tended to be either (1) superseded by later analyses of the same cohorts, or (2) based on a dose metric that EPA determined was not sufficiently reliable (e.g., toenail arsenic.) EPA also excluded studies when exposure measurements were judged to be too uncertain from a quantitative perspective and/or the range of exposures too narrow. Due in part to the availability of EPA's iAs PBPK model, four recent urine biomarker studies (Chang et al., 2016); (Huang et al., 2018); (Lin et al., 2018); (Wu et al., 2013) were included in EPA's

[25]According to EPA's 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).

meta-analysis that were not included in any of the previous meta-analysis. These studies were not available at the time most of these authors began their literature reviews and were explicitly excluded from the (Saint-Jacques et al., 2014), (Lynch et al., 2017b) and (Shao et al., 2021) meta-analyses.

Identification of Studies for Lung Cancer Dose-Response Analysis

Forty-four medium or high confidence studies with exposure- or dose-response data were considered for dose-response, from which 8 studies (10 data sets) were selected to analyze lung cancer meta-regression dose-response (see Figure 4-3).

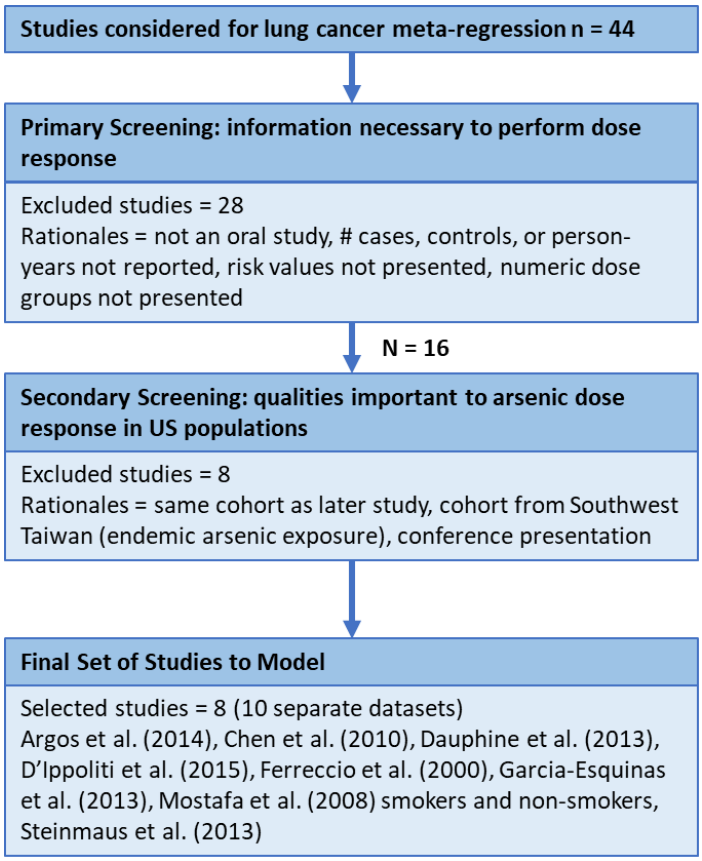


Figure 4-3. Study selection flow for identification of studies for lung cancer Bayesian meta-regression.

Data Sets Selected for Lung Cancer Meta-Regression

Eight studies (10 data sets) were selected for inclusion in the Bayesian meta-regression for lung cancer. Several studies that passed the initial screening step (i.e., contained information necessary for dose-response modeling) were excluded after further consideration of study characteristics. These studies investigated the effect of iAs on lung cancer in subsets of older studies: (Ferreccio et al., 2013);(Steinmaus et al., 2014);(Steinmaus et al., 2015) earlier investigations (earlier studies on the same cohort were excluded because later studies had

increased follow-up time and greater person-years): (Chiou et al., 1995);(Chen et al., 2004);(Ferreccio et al., 1998) or fewer dose groups compared to an earlier study in same cohort: (Yang et al., 2013). Ultimately, 8 studies (10 data sets) were included in the meta-regression analysis: 4 cohort studies (Argos et al., 2014); (Chen et al., 2010a);(García-Esquinas et al., 2013);(D'Ippoliti et al., 2015) and 4 case-control studies (Dauphiné et al., 2013);(Ferreccio et al., 2000);(Steinmaus et al., 2013);(Mostafa et al., 2008).The Mostafa et al. (2008) study reported results for smokers and nonsmokers separately, and the D'Ippoliti et al. (2015) study reported results for males and females separately; these 4 data sets were included in the meta-regression separately, resulting in the modeling of 10 total data sets.

Appendix C, Table C-27 lists the eight studies selected for inclusion in the Bayesian meta-regression for lung cancer. One study was from Northeast Taiwan, one from Italy (two data sets), and two each from U.S. populations, Bangladesh (three data sets), and northern Chile. 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), and urinary arsenic excretion (μg/g creatinine). 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 empirical and PBPK models of the relationships between arsenic intake and urinary excretion. The As intakes estimated in the Argos et al. (2014) study (2.1−21.2 μg/kg-day) are generally in line with those estimated for other selected non-U.S. data sets. Although the estimated intakes for (García-Esquinas et al., 2013) (0.14−0.59 μg/kg-day) are lower, they are comparable to the other U.S. data set [i.e., Dauphiné et al. (2013): 0.11−3.1], 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 meta-regression database.

EPA found considerable overlap between the studies included in the EPA meta-regression analysis and those identified in earlier meta-analysis (see Appendix C, Table C-27). Of the eight studies chosen by EPA, a core group of five studies were chosen for all (Chen et al., 2010a); (Dauphiné et al., 2013); (Steinmaus et al., 2013) or for all but one (Mostafa et al., 2008); (D'Ippoliti et al., 2015) of the meta-analyses published after them. The four studies selected for the earlier meta-analyses not used in the current meta-regression were determined unsuitable because they were conducted in the Southwest Taiwan "endemic" region (Chiou et al., 1995);(Chen et al., 2004), on the basis of data reported in (Ferreccio et al., 2000);(Smith et al., 2009), used toenail arsenic as the exposure metric (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 DCS Dose-Response Analysis

DCS[26] is a broad term used in this assessment to encompass ischemic heart disease (IHD),[27] 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 combined cases of IHD and stroke—often referred to as cardiovascular disease (CVD) in epidemiological literature—and cases of clinically diagnosed IHD alone, however, have reported similar 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 meta-regression analyses for dose-response described in this section focuses on studies that involving clinical diagnoses of four DCS outcome categories: CVD incidence,[28], IHD incidence, CVD fatality, and IHD fatality.

Fifty-eight medium-to-high confidence studies with exposure- or dose-response data were considered for dose-response, from which eight studies (15 data sets) were selected for the final DCS meta-regression dose-response analyses (see Figure 4-4).

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

[27]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.

[28]The terms used most often by study authors are "nonfatal and fatal CVD" or "nonfatal and fatal IHD," but to avoid confusion these outcomes are referred to as "CVD incidence" and "IHD incidence" in this section.

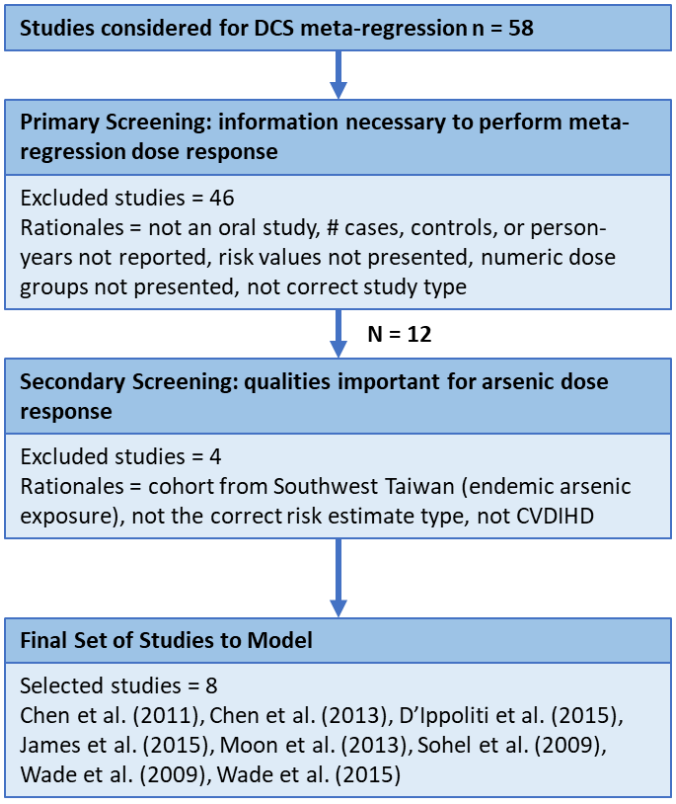


Figure 4-4. Study selection flow for identification of studies for DCS Bayesian meta-regression.

Data sets selected for DCS meta-regressions

Appendix C, Table C-43 summarizes the 8 studies (15 data sets), 7 cohort studies, and 1 case-control study selected for inclusion in the Bayesian meta-regression analyses of CVD incidence (2 data sets), IHD incidence (4 data sets), CVD fatality (5 data sets), or IHD fatality (4 data sets) after dose-response study quality considerations. These considerations were particularly important for EPA's meta-regression approach [see the iAs Protocol (link provided in Appendix A), Sections 5.1 and 5.2.2]. All the cohort studies were deemed to have involved adequate follow-up durations for DCS health outcomes to occur.[29] The third column of Table C-43 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 meta-regression, all exposure, intake, and excretion metrics were converted to estimates of lifetime daily arsenic intake. EPA's approach to addressing exposure uncertainties in these studies and estimating arsenic daily intake are described in Section 4.3.2.

[29]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).

For three DCS studies (D'Ippoliti et al., 2015); (James et al., 2015);(Moon et al., 2013), 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). The results from the (Moon et al., 2017b; 2013) urinary arsenic study are considered relevant for assessing the relationship between the relatively low levels of arsenic intake most U.S. populations experience and DCS outcomes. The other five studies included in one or more of the DCS health outcome meta-regression analyses involved populations exposed to much higher iAs levels, ranging from 0.7 to 22 µg/kg-day estimated daily doses associated with approximately 46 to 1,568 µg/L drinking water exposures. Three of these studies were of Bangladeshi populations with estimated daily intakes of 1.5 to 22 µg iAs/kg (Sohel et al., 2009), 2 to 15.1 µg iAs/kg (Chen et al., 2011b), and 1.8 to 2.8 µg iAs/kg (Chen et al., 2013b). The other two high exposure studies used in the meta-regression were studies in Inner Mongolia. Estimated daily iAs intake ranged from 0.8 to 2.9 µg/kg-day (Wade et al., 2015) and 0.7 to 12.7 µg/kg-day (Wade et al., 2009) associated with approximate drinking water exposure ranges of 54 to 204 µg/L, and 46 to 904 µg/L, respectively.

Appendix C, Section C.1.2 Diseases of the Circulatory System; Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses also contains a review of the overlap between studies included in the current meta-regression analysis and those identified in other published meta-analyses (see Table C-44). 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 only CVD or IHD studies selected by Moon et al. (2017b) excluded from the EPA meta-regression analysis are (Farzan et al., 2015a) and (Chen et al., 1996). Farzan et al. (2015a) was not included due to the high level of uncertainty in converting doses from toenail concentrations to oral doses. Chen et al. (1996) is a study of townships in Southwest Taiwan with endemic arseniasis that has experienced extreme iAs exposures not relevant to U.S. populations.

Identification of Outcomes and Studies for Diabetes Dose-Response Analysis

Twenty-five medium or high confidence studies with exposure- or dose-response data were considered for dose-response, from which 4 studies (4 data sets) were selected for the final diabetes meta-regression dose-response analysis (see Figure 4-5).

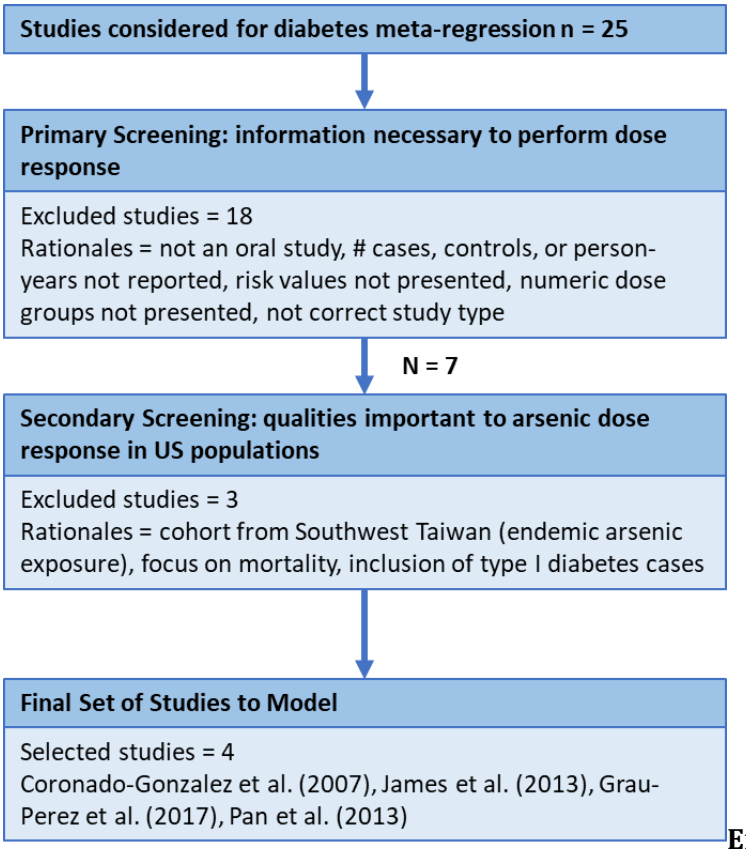


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Figure 4-5. Study selection flow for identification of studies for diabetes Bayesian meta-regression.

Data Sets Selected for Diabetes Meta-Regression

Appendix C, Table C-36 lists the four data sets selected for inclusion in the Bayesian meta-regression 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), daily average intake from water, cumulative exposure (μg/L-years in water), and urinary arsenic excretion (μg/g creatinine). To support the meta-regression, all exposure, intake, and excretion metrics were converted to estimates of lifetime daily arsenic intake. EPA's approach to addressing exposure uncertainties and estimating arsenic daily intake are described in Section 4.3.2. Only studies of Type II diabetes were considered for dose-response.

As noted above, EPA estimated daily arsenic intake for two data sets [(Coronado-González et al., 2007)and (Grau-Perez et al., 2017)], on the basis of empirical and PBPK models of the relationships between arsenic intake and urinary excretion. The estimated As intakes for (Coronado-González et al., 2007) (1.3–4.56 μg/kg-day) is generally in line with the estimated intakes for other selected non-U.S. data sets. The estimated intake for (Grau-Perez et al., 2017) (0.07–0.27 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, (2013): 0.11–3.1 μg/kg-day],

especially at the low end of the exposure range. The James et al. (2013) cumulative exposure study is also associated with relatively low iAs intake values: 0.109–0.133 µg/kg-day. This makes the Grau-Perez et al. (2017) and James et al. (2013) data sets the most sensitive studies in the diabetes meta-regression database.

(Wang et al., 2014) performed the only meta-analyses comparable to the EPA meta-regression approach in that it involved meta-regression modeling of multiple studies of the relation between type II 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 which, as previously discussed, were excluded from the EPA analysis due to their high degree of uncertainty and questionable relevance. Of the four diabetes studies used in the EPA analysis, two were included in the (Wang et al., 2014) analysis (James et al., 2013); (Coronado-González et al., 2007), but the two later publications (Pan et al., 2013b); (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 Meta-Regressions

The conversion of study-specific exposure metrics to a common dose metric is an essential aspect of the iAs meta-regression approach as it allows multiple studies to be combined, which increases the precision of the dose-response modeling results. Hobbie et al. (2020) describes methods for performing these dose conversions, and they are also summarized in the updated iAs Protocol, Section 5.3 (see Appendix A). Appendix C, Section C.1.1 Treatment of Dose Uncertainty provides additional details on the methods for treating dose uncertainty. Of particular note is that by calculating a common dose metric, the present analysis can include studies that used urinary biomonitoring as the exposure assessment method and studies that assessed exposure on the basis of drinking water intake. Application of a PBPK model 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 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 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 in (Allen et al., 2020a) and in Appendix C, Section 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.[30] 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 daily μg/kg intake doses (Allen et al., 2020a). Appendix C.1.2 provides the three selected sets of dose values (in average daily μg iAs/kg body weight) used in the analyses of bladder cancer, lung cancer, diabetes, and DCS. Appendix C, Section 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 Meta-Regressions

To further expand the number of studies that could be included in the iAs meta-regression 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 meta-regression 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, Section C.1.1 Adjusting for Covariates, were applied to the bladder cancer, lung cancer, DCS, and diabetes data sets. The resulting effective counts for these four data sets are presented in Appendix C, Section C.1.2.

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

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

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

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 implementing such an analysis are described by (Allen et al., 2020b) and in Appendix C, Section

[30]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 lognormal 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 lognormal fitting.

C.1.1. X is scalar (having the value of iAs dose in μg/kg) and s(x) = x, so β (i.e., the slope) is also a scalar.

As Allen et al. (2020b) describes the hierarchical structure for the meta-regression assumes the α* parameter was separate and independent for each data set. 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. Prior probability distributions were assigned to the model parameters as shown in Table 4-1.

Table 4-1. Prior parameter values for meta-regressions

Parameter	Prior distribution
β(i)[a]	Normal (β_mean, β_sigma)
β_mean	Gamma (a = 0.52, b = 1.12)
β_sigma	Half-Cauchy (scale = 5)

[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, Section C.1.1 Sensitivity Analysis of Possible Non-monotonic 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 diffuse, uninformative prior 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 ($p < 0.01$) and equally unlikely to be less than 1.0001 at that dose.[31] 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 Appendix C, Section C.1.2). A prior for α*(i) is not needed; it is a function of β(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, Section C.1.1 Bayesian Meta-Regression Methods, defines those relationships and specifies the priors for those other parameters.

[31]1 μg/kg is 27 times greater than the estimated U.S. background (median) iAs dose of 0.0365 μg/kg.

The key output of the meta-regressions—the posterior distribution for the "pooled" (average) value of the logistic slope—is used in lifetable calculations to estimate the U.S. population lifetime[32] probability of observing a health outcome as a function of iAs dose (average daily μg/kg). The overall methodology is described by (Allen et al., 2020a); (Allen et al., 2020b). 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 risks of 1.9% for bladder cancer (see Appendix C.1.2.1.6), 5.7% for lung cancer (see Appendix C.1.2.2.6), 15.5% for fatal CVD and 7.7% for fatal IHD (see Appendix C.1.2.4.6) were obtained from CDC lifetables. U.S. lifetime risk of 70% (Leening et al., 2014),[33] 40% for IHD incidence (Lloyd-Jones et al., 1999),[34] and 40% for diabetes (Gregg et al., 2014) 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 estimates obtained from the meta-regression 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.[35] EPA's iAs PBPK model indicates this level of U.S. background 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.

4.3.5. Bayesian Meta-Regression 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, Section C.1). As discussed in Section 4.3.2, meta-regression analyses were performed with estimates of low, maximum likelihood, and high doses to investigate dose conversion uncertainties. This section presents the results for meta-regressions using the MLE doses. The meta-regressions for bladder cancer included both case-control and cohort studies; the selected studies, converted doses (low, MLE, high) and effective

[32]For computational purposes, 85 years was used to define the upper limit for lifetime risk calculations.
[33]Leening et al. (2014) reported similar lifetime risk of CVD at an index age of 55 years for men (67.1%) and women (66.4%) living in Rotterdam, the Netherlands.
[34]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.
[35] 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").

counts used in the bladder cancer meta-regressions are presented in Appendix C, Section C.1.2 Bladder Cancer.

A summary of the results of the bladder cancer meta-regression 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 0.58, and its 5th percentile is 0.32 (see Table 4-2). The mean coefficient of variation (CV), β_sigma/β_mean, is 1.9, 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, Section C.1.2 Bladder 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 bladder cancer studies (see Appendix C, Section C.1.2 Bladder Cancer; Summary of bladder cancer meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Bladder Cancer; 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%	25%	50%	75%	95%
β_mean	0.3138	0.1956	0.0161	0.1654	0.3056	0.4407	0.6508
β_sigma	0.5804	0.2118	0.3193	0.4355	0.5397	0.6831	0.9656
β Chen et al. (2010c)	0.0753	0.0199	0.0412	0.0623	0.0762	0.0888	0.1069
β Steinmaus et al. (2013)	0.5149	0.1174	0.3239	0.4367	0.514	0.5942	0.7092
β Wu et al. (2013)	1.0394	0.1535	0.7902	0.9359	1.0375	1.1438	1.2964
β Bates et al. (1995)	0.3279	0.6562	-0.7237	-0.0629	0.3189	0.7091	1.4004
β Steinmaus et al. (2003)	-0.0765	0.4408	-0.8266	-0.3634	-0.054	0.2205	0.6050
β Bates et al. (2004)	-0.1753	0.0878	-0.3272	-0.2327	-0.1707	-0.1145	-0.0400
β Meliker et al. (2010)	0.2050	0.4542	-0.5513	-0.0886	0.2135	0.5054	0.9208

Parameter	Mean	Standard deviation	5%	25%	50%	75%	95%
β Baris et al. (2016)	0.6510	0.4718	-0.0838	0.3365	0.6275	0.9399	1.4547
β Chang et al. (2016)	0.1151	0.0508	0.0296	0.0815	0.115	0.1502	0.1982
β Huang et al. (2018)	0.5908	0.1957	0.2789	0.4572	0.5856	0.7208	0.9172
β Lin et al. (2018)	0.9097	0.3925	0.2928	0.6354	0.8945	1.1689	1.5888

[a]Inference for Stan model: MR hier all — gamma v7; 4 chains, each with iter = 25,000; warmup = 21,250; thin = 2; post-warmup draws per chain = 1,875, total post-warmup draws = 7,500.

Extrapolation of Bladder Cancer Risk to Target Population

β_mean [the posterior distribution for the "pooled" (average) value of the logistic slope parameter] was 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 daily μg/kg). Allen et al. (2020a); Allen et al. (2020b) describes the methodology. 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, Section C.1.2 Bladder Cancer; 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 values derived from the bladder cancer meta-regression 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 and Figure 4-6 represent 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, 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. Figure 4-6 is a forest plot showing the extra risk predictions for the individual data sets and for the 8×10^{-4} pooled estimate of extra risk at a lifetime iAs dose of 0.13 μg/kg-day.

Table 4-3. Pooled meta-regression 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 daily inorganic arsenic dose (µg/kg-day)[b]								
	0	**0.02**	**0.0365[b]**	**0.075**	**0.13**	**0.185**	**0.24**	**0.57**	**1.12**
5th percentile	0	0.06	0.11	0.23	0.40	0.57	0.74	1.76	3.47
Mean	0	1.19	2.17	4.49	7.85	11.27	14.75	36.87	79.04
95th percentile	0	2.44	4.48	9.32	16.44	23.81	31.44	83.24	197.26

[a]Extra lifetime risks are presented as mean risk/10,000 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, 0.02 µg/kg from diet, 0.0165 µg/kg from water and 0 µg/kg from air (see Section 4.3.4).

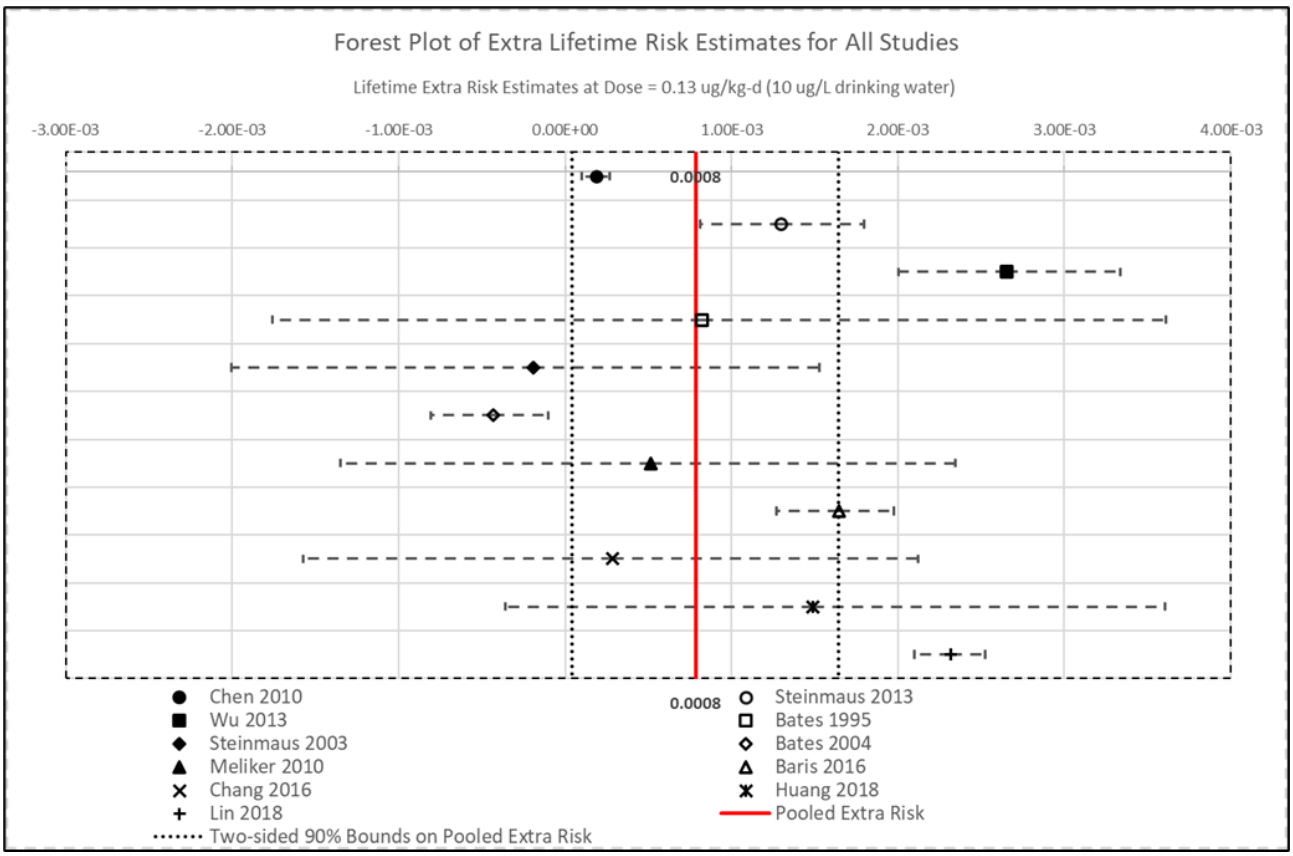

Figure 4-6. Bladder cancer extra lifetime risk for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake for a U.S. population). Based on meta-regression of all bladder cancer studies using maximum likelihood estimates for dose.

Polynomial and linear (slope factor) 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 4-3. The slope of the upper confidence limit (UCL) on the extra risk associated with dose above background through this approach is analogous to the traditional EPA cancer slope factor (CSF)[36]. Although EPA's modeling approach in this assessment does not assume linearity, the model slope at low doses is sufficiently linear (after visual inspection) for the derivation of a CSF, thus the CSF for bladder cancer due to iAs exposure is 1.27×10^{-2} per µg/kg-day. To generate estimates other than those illustrated in Table 4-3, meta-regression models and lifetable spreadsheets available in the EPA HERO database can be applied in accordance with methods (Allen et al., 2020b; Allen et al., 2020a) describes.

[36] 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.

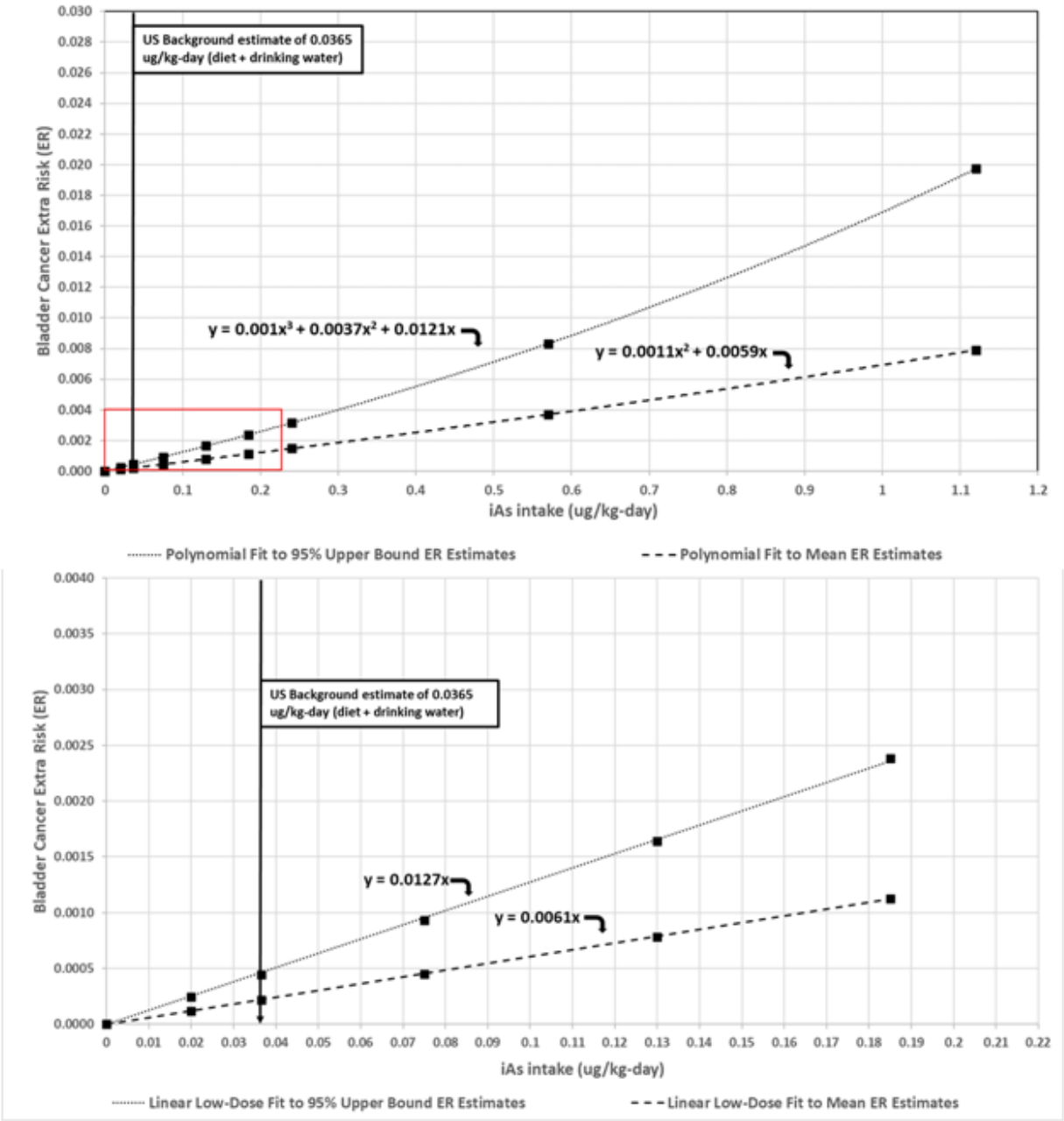

Figure 4-7. U.S. bladder cancer lifetime extra risk versus µg/kg-d iAs doses for all doses (top plot) and low doses (bottom plot). The polynomial equations can be used to approximate high dose extra risk. The linear equations can be used to approximate low dose (< 0.22 µg/kg-day) extra risk. The linear slope of 1.27×10^{-2} for the 95% upper bound is analogous to an EPA cancer slope factor (CSF). See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

Summary of Meta-Regression of Bladder Cancer Studies

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). Uncertainties in average exposures for the exposure groups and in the conversion to average µg/kg 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, Sections C.1.1 Treatment of Dose Uncertainty and C.1.1 Adjusting for Covariates for details.

Following those adjustments, the meta-regression 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 considered adequate for all but two datasets. The high dose was dropped to obtain adequate fit for the Lin et al. (2018) and Steinmaus et al. (2013) datasets because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the meta-regression modeling results (see Appendix C, Section C.1.2 Bladder Cancer; Summary of bladder cancer meta-regression 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 meta-regression. The mean of the posterior distribution for β_mean (using the MLE dose estimates) was 0.31 (90% credible interval[37], 0.016 to 0.65) per µg/kg.

The β_mean posterior was used to derive 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 the Extrapolation of Bladder Cancer Risk to Targe Population section and in (Allen et al., 2020b; 2020a). As shown in Table 4-3, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming intake levels of 0.02–1.12 µg/kg-day, approximately equivalent to U.S. water iAs exposures of 1.5–100 µg/ L). At 0.02 µg/kg-day, the mean of the extra lifetime risk distribution was 1.2 per 10,000 (90% credible interval, 0.06 to 2.4 per 10,000). At 1.12 µg/kg-day, the mean extra lifetime risk was 79 per 10,000 (90% credible interval, 3.5 to 197 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 daily µg/kg (see Appendix C, Section C.1.2 Bladder Cancer; Bladder cancer sensitivity analyses). The effect was minimal overall: The mean lifetime extra risk estimate at 0.13 µg/kg-day changed from 7.85 per 10,000 to 9.1 (using systematically lower dose values consistent with the level of uncertainty) or 6.2 (using systematically higher dose values consistent with the level of uncertainty). The low-end and high-end dose values resulting from a combination of

[37]A credible interval is the Bayesian analog to a confidence interval in frequentist statistics.

various factors indicate the results are not sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels. Similar findings were observed for extra risk estimates at the assumed dietary (no drinking water contribution) background dose of 0.02 μg/kg-day (MLE = 1.2/10,000, low = 3.6/10,000, and high = 0.9/10,000) and high 1.12 μg/kg-day dose (MLE = 79/10,000, low = 94.0/10,000, and high = 60.2/10,000).

Other sensitivity analyses performed for the bladder cancer meta-regression 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 alternative exposure metrics or lagged analyses within studies and omitting individual data sets from the analysis (see Appendix C, Section C.1.2 Bladder Cancer; Bladder cancer sensitivity analyses). The sensitivity analysis examining the impact of different gamma prior distributions for β_mean did not result in large differences 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 meta-regression. Incorporation of estimates of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk.

When all four urine studies are excluded, the mean logistic slope decreased by 57%. Conversely, when only urine studies are used in the meta-regression, the mean logistic slope increased by 71%. These results indicate that the urinary biomarker studies are important drivers of the overall estimated association between iAs exposure and bladder cancer in this meta-regression.

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. Appendix C, Table C-25 shows consideration of these alternative data sets in the meta-regression did not substantially influence the final modeling; the greatest difference was a 30% decrease in the estimated logistic slope when the 40-year lagged mg exposure metric was used from the Baris study.

Finally, the influence of the individual studies on the meta-regression result (see Appendix C, Table C-23) 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. But even in this case, the removal of that study reduced the mean and upper bound β_mean slope estimates by 30% or less.

In summary, inclusion of a background inhalation exposure had the least (≤ 0.3%) and the exclusion (57%) or exclusive use (71%) 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 study selection (≤ 35%), the (Baris et al., 2016) study metric selected (≤ 30%), variability/uncertainties in the exposure factors (≤ 16%), and alternative gamma prior distributions (≤ 8%).

4.3.6. Bayesian Meta-Regression 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). As discussed in Section 4.3.2, meta-regression analyses were performed with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for meta-regressions using the MLE doses. The meta-regressions for lung cancer included both case-control and cohort studies; the selected studies, converted doses (low, MLE, high) and effective counts used in the lung cancer meta-regressions are presented in Appendix C, Section C.1.2 Oral Lung Cancer.

In this section, a summary of the results of the lung cancer meta-regression 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 0.715, and its 5th percentile is 0.24 (see Table 4-4). This is associated with a mean coefficient of variation (CV), β_sigma/β_mean, of about 2.3, 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, Section 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, Section C.1.2 Oral Lung Cancer; Summary of lung cancer meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Oral Lung Cancer; Lung cancer sensitivity analyses).

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

Parameter	Mean	Standard deviation	5%	25%	50%	75%	95%
β_mean	0.3153	0.2434	0.0135	0.1288	0.2724	0.4453	0.7697
β_sigma	0.715	0.3765	0.2380	0.4634	0.6518	0.887	1.3935
β Argos et al. (2014)	0.0193	0.0121	-0.0009	0.0112	0.0194	0.0276	0.0389
β García-Esquinas et al. (2013)	0.763	0.5319	-0.0177	0.3775	0.7257	1.1112	1.6860
β Chen et al. (2010a)	0.0318	0.009	0.0167	0.0259	0.0322	0.0379	0.0460
β D'Ippoliti et al. (2015) – M	1.5689	0.6368	0.4725	1.127	1.5975	2.0187	2.5919
β D'Ippoliti et al. (2015) – F	0.9071	0.9924	-0.2553	0.2448	0.6998	1.3479	2.7566
β Dauphiné et al. (2013)	0.0812	0.1235	-0.1222	-0.0005	0.0795	0.1659	0.2883

Parameter	Mean	Standard deviation	5%	25%	50%	75%	95%
β Ferreccio et al. (2000)	0.6939	0.1862	0.3852	0.5711	0.6964	0.8191	0.9924
β Steinmaus et al. (2013)	0.1312	0.0229	0.0933	0.1158	0.1311	0.1469	0.1685
β Mostafa et al. (2008) – NS	0.0011	0.0182	-0.0291	-0.0111	0.0014	0.0134	0.0304
β Mostafa et al. (2008)– S	0.0418	0.0122	0.0216	0.0336	0.0417	0.05	0.0619

Extrapolation of Lung Cancer Risk to Target Population

The posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, was 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 daily μg/kg including background levels of U.S. exposure). The methodology is presented in (Allen et al., 2020b; 2020a). 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.1.2.2.6. Application of the methods described in Section 4.3.4, using the pooled β_mean values derived from the lung cancer meta-regression 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 4-9. Table 4-5 and illustrate 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. Figure 4-8 is a forest plot that shows the predictions for the individual data sets and for the 2.4×10^{-3} pooled estimate of extra risk at a lifetime iAs dose of 0.13 μg/kg.

Table 4-5. Pooled meta-regression estimates of extra lifetime lung 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 daily inorganic arsenic dose (μg/kg-day)[b]								
	0	0.02	0.0365[b]	0.075	0.13	0.185	0.24	0.57	1.12
5th percentile	0	0.16	0.29	0.59	1.03	1.46	1.90	4.52	8.90
Mean	0	3.65	6.67	13.79	24.10	34.57	45.21	112.72	240.40
95th percentile	0	8.80	16.15	33.65	59.49	86.35	114.27	306.17	737.83

[a]Extra lifetime risks are presented as mean risk/10,000 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, 0.02 μg/kg from diet, 0.0165 μg/kg from water and 0 μg/kg from air (see Section 4.3.4).

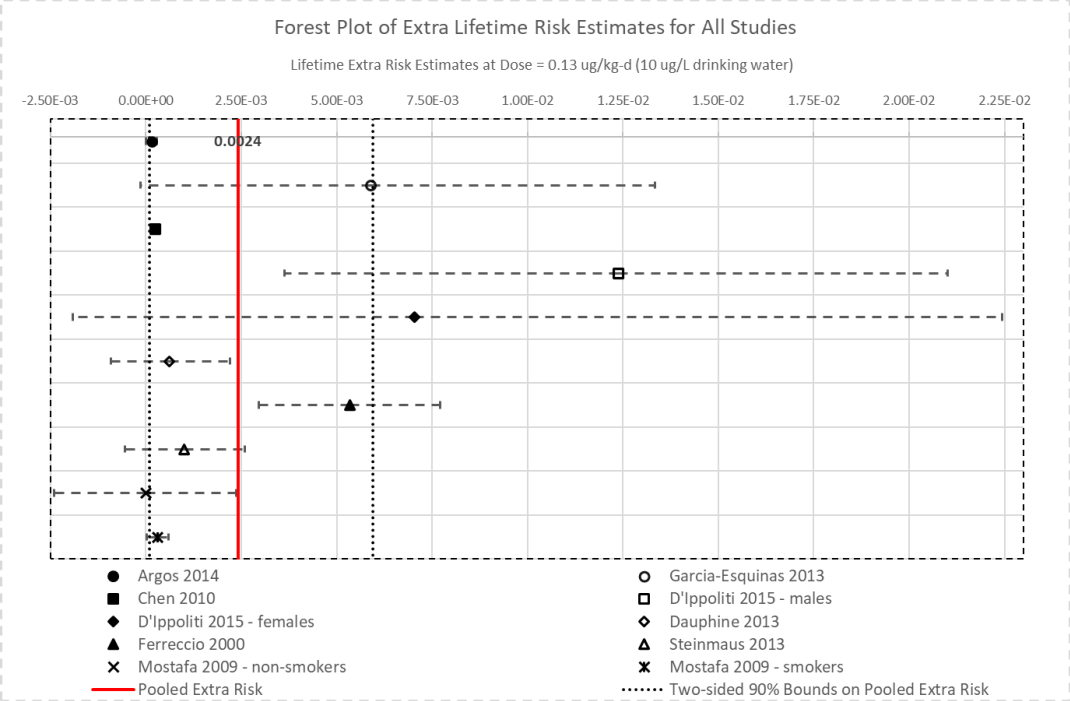

Figure 4-8. Lung cancer extra lifetime risk for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake). Based on meta-regression of all lung cancer studies using MLE doses.

Polynomial and linear (slope factor) formulas given in Figure 4-9 are provided for convenience in approximating lifetime extra risk at doses and exposures other than those presented in Table 4-5. The linear slope of the upper confidence limit (UCL) on the extra risk associated with dose above background can be used in a manner analogous to an EPA cancer slope factor (CSF). Although EPA's modeling approach does not assume linearity, the model slope at low doses is sufficiently linear (after visual inspection)for the derivation of such a CSF, thus the CSF for lung cancer due to iAs exposure is 4.62×10^{-2} per µg/kg-day. To generate estimates other than those illustrated in Table 4-5, meta-regression models and lifetable spreadsheets available in the EPA HERO database can be applied in accordance with methods (Allen et al., 2020b; Allen et al., 2020a) describes.

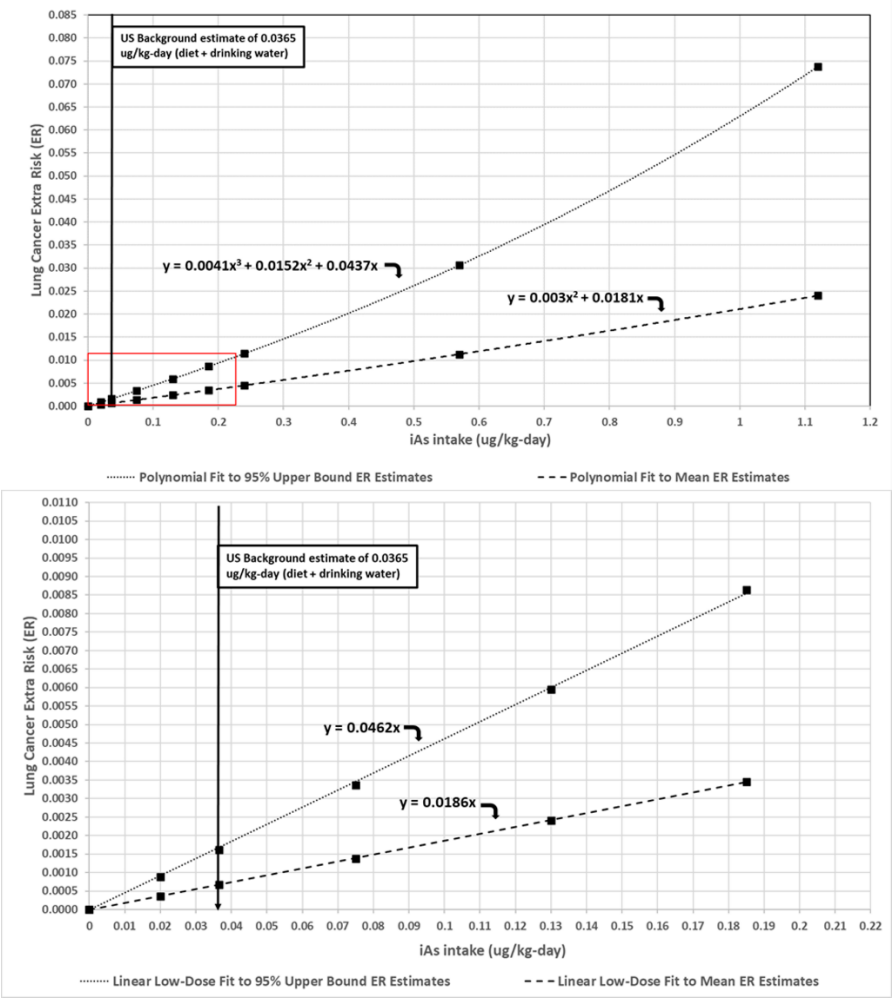

Figure 4-9. U.S. lung cancer lifetime extra risk versus µg/kg-d iAs doses for all doses (top plot) and low doses (bottom plot). The polynomial equations can be used to approximate high dose extra risk. The linear equations can be used to approximate low dose (< 0.22 µg/kg-day) extra risk. The linear slope of 4.62×10^{-2} for the 95% upper bound is analogous to an EPA cancer slope factor (CSF). See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

Summary of Meta-Regression 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). Uncertainties in average exposures for the exposure groups and in the conversion to average µg/kg 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) also were adjusted to account for the effect of covariates.

Given those adjustments, the meta-regression approach described in Section 4.3.4 was applied to 10 data sets (8 separate studies, with 1 cohort study reporting effects individually for

males and females and 1 case-control study reporting effects individually for smokers and nonsmokers). On the basis of visual inspection, the model fit was considered adequate for all but two datasets. The high dose was dropped to obtain adequate fit for the Ferreccio et al. (2000) and female results from D'Ippoliti et al. (2015) datasets because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the meta-regression modeling results (see Appendix C, Section C.1.2 Oral Lung Cancer; Summary of lung cancer meta-regression 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 meta-regression. The mean of the posterior distribution for β_mean (using the MLE doses) was 0.32 (90% credible interval, 0.14 to 0.77) per μg/kg.

The β_mean posterior (using the MLE doses) was used to derive a 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 the *Extrapolation of Lung Cancer Risk to Target Population* section. These U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios incorporating background iAs exposure (assuming intake levels of 0.02–1.12 μg/kg-day, approximately equivalent to U.S. water iAs exposures of 1.5–100 μg/L). At 0.02 μg/kg-day, the mean of that extra lifetime risk distribution was 3.65 per 10,000 (90% credible interval, 0.16 to 8.8 per 10,000). At 1.12 μg/kg-day (10 μg/L), the mean extra lifetime risk was 240 per 10,000 (95% credible interval, 8.9 to 738 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 daily μg/kg (see Appendix C.1.2.2.6). The effect was minimal overall: The mean lifetime extra risk estimate at 0.13 μg/kg-day changed from 24.1 per 10,000 to 28.6 (using lower dose values consistent with the level of uncertainty) to 21.4 (using 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 meta-regression 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, Section C.1.2 Oral Lung Cancer; Extrapolation of lung cancer extra risk to target U.S. population). 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 (see Appendix C, Table C-34). Incorporation of estimates of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk.

Excluding the two urine studies increased the mean logistic slope by 6%. The two studies influence the analysis in opposite directions, with the exclusion of Argos et al. (2014) increasing the

slope by 21% and the exclusion of García-Esquinas et al. (2013) decreasing the slope by 16%. 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 meta-regression.

Finally, the influence of the individual studies on the meta-regression result (see Appendix C, Section C.1.2 Oral Lung Cancer; Extrapolation of lung cancer extra risk to target U.S. population) were tested. Across most included studies, the effect of removing single studies from the analysis was minimal, with changes to the β_mean logistic slope not exceeding 25%. The largest two data sets had the largest impact when removed. 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 and the male dataset from D'Ippoliti. In these cases, the removal of the study reduced the mean of the β parameter by 66% and 68%, respectively.

In summary, inclusion of a background inhalation exposure had the least (≤ 0.3%) and study selection has the potential to have the greatest (≤ 68%) 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 (≤ 18%), alternative gamma prior distributions (≤ 10%), and the use of urine biomarker studies (≤ 6%).

4.3.7. Bayesian Meta-Regression Dose-Response Results for DCS (CVD and IHD)

Bayesian dose-response analyses for DCS (CVD and IHD) incidence and fatal health outcomes were conducted as previously described (see Sections 4.3.1 to 4.3.4 and Appendix C, Section C.1). As discussed in Section 4.3.2, EPA performed meta-regression analyses with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for meta-regressions using the MLE doses. The meta-regressions for DCS health outcomes included both case-control and cohort studies. Appendix C, Section C.1.2 Diseases of the Circulatory System describes the selected studies, converted doses (low, MLE, high), and effective counts used in the DCS meta-regressions, detailed modeling results using MLE doses, and sensitivity analyses.

As Appendix C, Table C-43 shows, studies of the DCS health outcomes outside the United States and Italy involved high iAs daily doses that were all at or well above the highest average daily dose levels estimated for studies of U.S. (Moon et al., 2013);(James et al., 2015)or Italian populations (D'Ippoliti et al., 2015). EPA's preliminary analyses and the results of the Moon et al. (2017b) meta-analysis indicate, although dose-dependent increases were apparent in both groups of studies, the association appeared to increase much more steeply in the low-dose studies. Steep dose-responses for low exposed populations relative to high exposed populations has been reported for other chemicals and noncancer endpoints such as lead and IQ (U.S. EPA, 2013). To investigate the extent to which this may be occurring for DCS health outcomes, DCS studies of populations exposed predominantly below and DCS studies of populations exposed predominantly above the range of doses observed in the United States (average daily dose estimates <1 μg/kg-day; drinking water levels <100 μg/L) were analyzed together and in separate meta-regression analyses.

CVD Incidence Meta-regression Analysis for MLE Doses

Table 4-6 presents summary results for the CVD incidence analyses for all studies, low-dose studies, and high-dose studies 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 on the meta-regression for CVD incidence using all studies is 0.8872, and its 5th percentile is 0.096 (see Table 4-6). The mean coefficient of variation (CV), β_sigma/β_mean, is about 3.85, indicating 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, Section C.1.2 Diseases of the Circulatory System 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, Section C.1.2 Diseases of the Circulatory System; Summary of DCS meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Diseases of the Circulatory System).

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

	All studies				High-dose studies[a]				Low-dose studies[a]			
Parameter[b]	mean	5%	50%	95%	mean	5%	50%	95%	mean	5%	50%	95%
β_mean	0.2305	0.0022	0.1396	0.7797	--	--	--	--	--	--	--	--
β_sigma or SD[c]	0.8872	0.0962	0.5227	2.8879	0.02	--	--	--	0.19	--	--	--
β Chen et al. (2013b)	0.0370	0.0103	0.0374	0.0629	0.04	0.01	0.04	0.06	--	--	--	--
β Moon et al. (2013)	0.4593	0.0985	0.4617	0.7920	--	--	--	--	0.54	0.23	0.54	0.85

[a]Studies were categorized as "low dose" if daily dose estimated for exposure groups were predominantly below 1 μg/kg and "high dose" if they were not.
[b]Model fits for all parameters were reasonable, with Rhat values close to 1 (within 3 decimal places).
[c]The SD on individual study b estimates are reported for the low and high-dose study analyses because they were not meta-regressions.

IHD Incidence Meta-regression Analysis for MLE Doses

Table 4-7 presents summary results for the IHD incidence analyses for all studies, low-dose studies and high-dose studies 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 means for β_mean ranged from 0.2 (β_sigma mean = 0.71) for the high

dose studies to 0.52 (β_sigma mean = 2.0) for the low dose studies (see Table 4-7). The mean coefficient of variation (CV), β_sigma/β_mean, for the meta-regressions of all studies, high-dose studies, and low-dose studies were 2.1, 3.6, and 3.8, respectively, indicating moderate to 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, Section C.1.2 Diseases of the Circulatory System 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, Section C.1.2 Diseases of the Circulatory System; Summary of DCS meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses).

Table 4-7. Summary of Bayesian analysis output for IHD incidence, focusing on key parameters for risk estimation in the target population using MLE doses

Parameter[b]	All studies				High-dose studies[a]				Low-dose studies[a]			
	mean	5%	50%	95%	mean	5%	50%	95%	mean	5%	50%	95%
β_mean	0.3442	0.0068	0.286	0.8998	0.1968	0.0005	0.1016	0.9211	0.5221	0.0013	0.3733	1.8577
β_sigma	0.7295	0.1675	0.581	1.7908	0.7134	0.0137	0.3889	3.4958	2.0074	0.1113	1.4137	7.3252
β Chen et al. (2013b)	0.0401	0.0103	0.040	0.069	0.0393	0.0039	0.0393	0.0741	--	--	--	--
β James et al. (2015)	1.0088	0.1415	0.967	2.036	--	--	--	--	1.6456	0.2745	1.6422	3.0947
β Moon et al. (2013)	0.4644	0.1127	0.465	0.818	--	--	--	--	0.5092	0.0758	0.5123	0.9405
β Wade et al. (2015)	0.4568	0.1000	0.444	0.844	0.3555	-0.011	0.3351	0.8847	--	--	--	--

[a]Studies were categorized as "low dose" if daily dose estimated for exposure groups were predominantly below 1 µg/kg and "high dose" if they were not.
[b]Model fits for all parameters were reasonable, with Rhat values close to 1 (within three decimal places).

Fatal CVD Meta-regression Analysis for MLE Doses

Table 4-8 presents summary for the fatal CVD analyses for all studies, low-dose studies, and high-dose studies 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 means for β_mean ranged from 0.024 (β_sigma mean = 0.042) for the high-dose studies to 0.69 (β_sigma mean = 1.6) for the low dose studies (see Table 4-8). The mean coefficient of variation (CV), β_sigma/β_mean, for the meta-regressions of all studies, high-dose studies, and low-dose studies were 2.7, 1.7, and 2.4, respectively, indicating moderate to 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, Section C.1.2 Diseases of the Circulatory System 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, Section C.1.2 Diseases of the Circulatory System; Summary of DCS meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses).

Table 4-8. Summary of Bayesian analysis output for fatal CVD, focusing on key parameters for risk estimation in the target population using MLE doses

Parameter [b]	All studies				High-dose studies[a]				Low-dose studies[a]			
	mean	5%	50%	95%	mean	5%	50%	95%	mean	5%	50%	95%
β_mean	0.2408	0.0034	0.178	0.7105	0.0243	0.0002	0.0185	0.0897	0.6889	0.0032	0.613	1.8907
β_sigma	0.6417	0.0180	0.5815	1.4696	0.0417	0.0008	0.0204	0.2473	1.6353	0.0494	1.1237	6.3815
β Chen et al. (2011b)	0.0335	0.0103	0.034	0.0564	0.0278	0.0045	0.0266	0.0554	--	--	--	--
β D'Ippoliti et al. (2015)	0.8740	0.0179	0.905	1.7051	--	--	--	--	1.451	0.5276	1.427	2.4955
β Wade et al. (2009)	0.0158	-0.0800	0.019	0.0965	0.0185	-0.049	0.0188	0.0793	--	--	--	--
β Moon et al. (2013)	0.7484	0.0196	0.796	1.3527	--	--	--	--	1.0325	0.4253	1.0382	1.6206
β Sohel et al. (2009)	0.0158	0.0078	0.016	0.0239	0.0159	0.0063	0.0159	0.0256	--	--	--	--

[a]Studies were categorized as "low dose" if daily dose estimated for exposure groups were predominantly below 1 µg/kg and "high dose" if they were not.
[b]Model fits for all parameters were reasonable, with Rhat values close to 1 (within 3 decimal places).

Fatal IHD Meta-regression Analysis for MLE Doses

Table 4-9 presents summary results for the fatal IHD analyses for all studies, low-dose studies, and high-dose studies 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 means for β_mean ranged from 0.0007 (β_sigma mean = 0.0014) for the high-dose studies to 0.74 (β_sigma mean = 2.3) for the low dose studies (see Table 4-9). The mean coefficient of variation (CV), β_sigma/β_mean, for the meta-regressions of all studies, high-dose studies, and low-dose studies were 2.8, 2.6, and 3.1, respectively, indicating moderate to 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, Section C.1.2 Diseases of the Circulatory System 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, Section C.1.2 Diseases of the Circulatory System; Summary of DCS meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses).

Table 4-9. Summary of Bayesian analysis output for fatal IHD, focusing on key parameters for risk estimation in the target population using MLE doses

Parameter[b]	All studies				High-dose studies[a]				Low-dose studies[a]			
	mean	5%	50%	95%	mean	5%	50%	95%	mean	5%	50%	95%
β_mean	0.4228	0.00533	0.332	1.1607	0.1011	0.0004	0.0528	0.6475	0.7427	0.0012	0.5709	2.2986
β_sigma	1.195	0.4196	1.022	2.5622	0.2594	0.0030	0.0821	1.6127	2.2771	0.133	1.6801	7.9695
β Chen et al. (2011b)	0.0453	0.0007	0.0455	0.087	-0.1315	-1.5435	-0.0755	1.3112	--	--	--	--
β D'Ippoliti et al. (2015)	1.5969	0.6771	1.838	2.482	--	--	--	--	2.0895	0.9138	2.0865	3.3332
β Wade et al. (2009)	0.0793	0.0046	0.0798	0.147	0.1055	-1.2622	0.0609	1.6981	--	--	--	--
β Moon et al. (2013)	1.0611	0.4644	1.0804	1.645	--	--	--	--	1.1687	0.5023	1.1699	1.8302

[a]Studies were categorized as "low dose" if daily dose estimated for exposure groups were predominantly below 1 µg/kg and "high dose" if they were not.
[b]Model fits for all parameters were reasonable, with Rhat values close to 1 (within 3 decimal places).

Model Fit/Convergence for DCS Meta-regressions

The meta-regression results shown above for each of the four DCS health outcomes indicate different β_mean estimates for analyses using all studies, only low-dose studies, and only high-dose studies. Overall, the Stan® software used to perform the meta-regression modeling indicates model fit/convergence (when including all studies and in the sub analyses) was not as good for the DCS outcomes relative to the bladder cancer, lung cancer, and diabetes meta-regressions (see Appendix C, C.1.2.2.5). Meta-regression fits using only high-dose studies were inadequate, but EPA was able to obtain adequate model fits for meta-regressions using all studies and only low-dose studies. The low-dose study analyses relied on just two studies or just one study in the case of CVD incidence, however, and the use of only low-dose studies did not significantly improve the fit/convergence when compared to the use of all studies. Further, the use of all studies increases confidence in and precision of the meta-regression results, making accurate reflections of the true U.S. population variability more likely. For these reasons, the full set of studies was used to estimate lifetime extra risks for each DCS health outcome (see next section).

Extrapolation of DCS Risk to Target U.S. Population

As discussed in the previous section, meta-regressions using all of the studies listed in Table 4-9 are used in this section to estimate risk to the target U.S. population. Appendix C, Section C.1.2 Diseases of the Circulatory System; Extrapolation to target U.S. population provides details of the lifetable approach used to extrapolate the risk of CVD and IHD mortality and the approximate lifetable approach used to extrapolate the risk of CVD and IHD incidence to the target U.S. population. In summary, for fatal CVD and IHD, the posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, was used with U.S. all-cause mortality and CVD and IHD mortality rates as input to a lifetable calculation of the lifetime probability of fatality from these health outcomes as a function of iAs dose (average daily μg/kg). Because information on CVD and IHD incidence rates across age groups is not available to populate a lifetable, the logistic slope parameter, β_mean, was used with a summary value for the U.S. lifetime probability of developing CVD and IHD to estimate the lifetime probability developing these CVD and IHD incidence as a function of iAs dose (average daily μg/kg, including estimated background iAs intake). The methodology is described in (Allen et al., 2020b; 2020a). The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant (i.e., daily) iAs dose.

The age-specific lifetable rates used in the fatal CVD and fatal IHD analyses are provided in Appendix C, Section C.1.2 Diseases of the Circulatory System; Extrapolation to target U.S. population. The CVD and IHD incidence background lifetime probabilities used in the analyses are estimated to be 70% (Leening et al., 2014) for CVD incidence[38] and 40% for IHD incidence (Lloyd-Jones et al., 1999).[39]

Using the β_mean values derived for the MLE set of dose estimates from the studies selected for the meta-regressions results in extra lifetime CVD incidence, IHD incidence, fatal CVD, and fatal IHD risks as a function of iAs dose (μg/kg-day), summarized in Figure 4-10 to Figure 4-13.[40] Figure 4-14 to Figure 4-17 are forest plots that show the predictions for the individual data sets and for the pooled estimate of extra risk at a daily dose of 0.13 μg/kg (roughly equal to a lifetime exposure to the current 10 μg iAs/L U.S. drinking water standard). Table 4-11 summarizes the calculated extra lifetime CVD incidence, IHD incidence, fatal CVD, and fatal IHD risks across a wide range of daily iAs doses in μg/kg-day for the MLE dose. These figures and tables reflect 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. As discussed in Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses, similar to the diabetes and lung and

[38]Leening et al. (2014) reported similar lifetime risk of CVD at an index age of 55 years for men (67.1%) and women (66.4%) living in Rotterdam, the Netherlands.
[39]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.
[40]The figures include polynomial equations that allow for the estimation of upper bound and MLE estimates of extra risk at doses that do not appear in Table 4-11. For noncancer endpoints, their primary purpose is for the estimation of risk at doses above the RfDs for the noncancer health outcomes.

bladder cancer analyses, risk predictions were not sensitive to uncertainties associated with low, MLE and high dose characterizations.

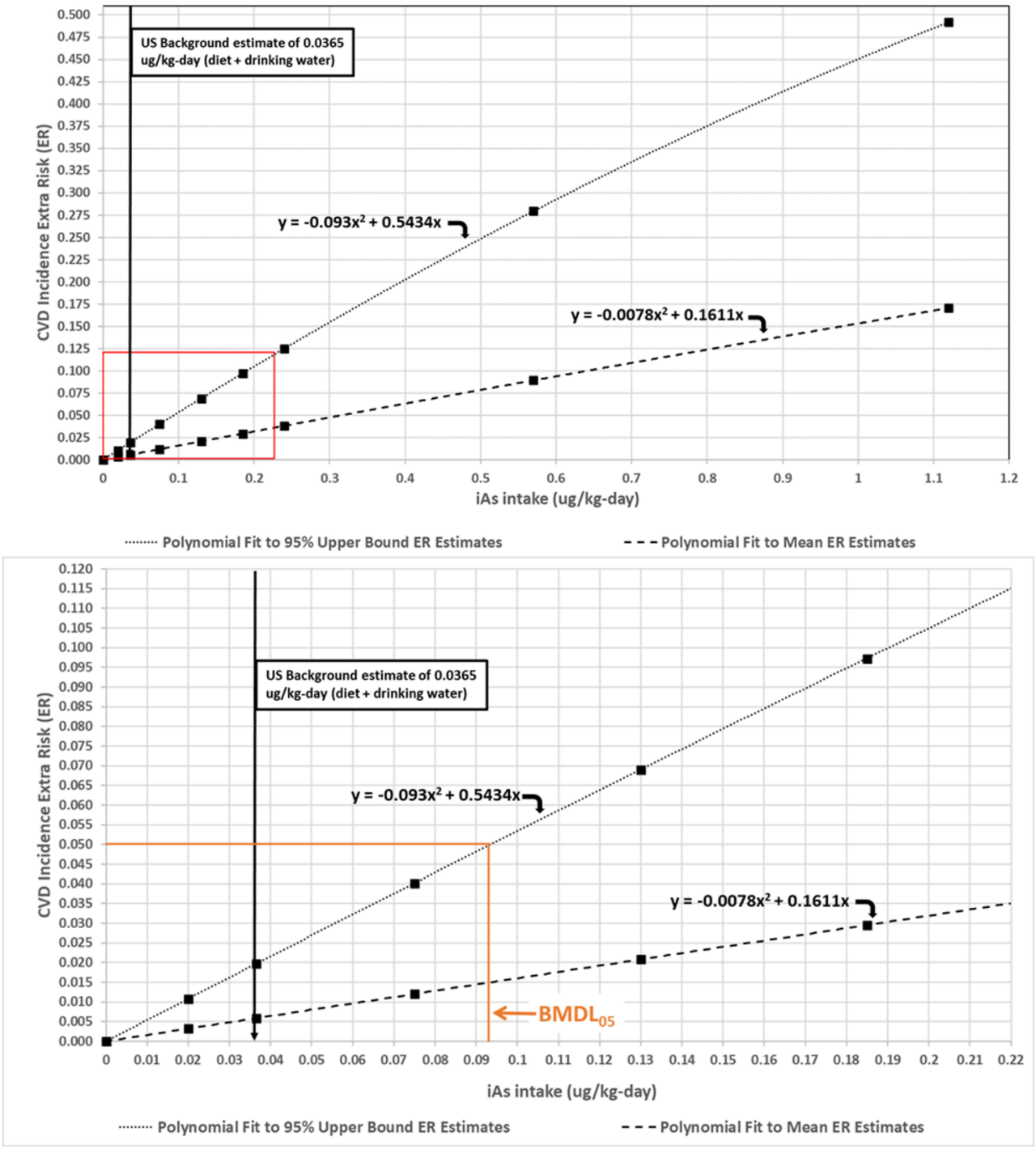

Figure 4-10. U.S. CVD incidence (all studies) lifetime extra risk versus µg/kg-d MLE doses for all doses (top plot) and low doses (bottom plot). See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

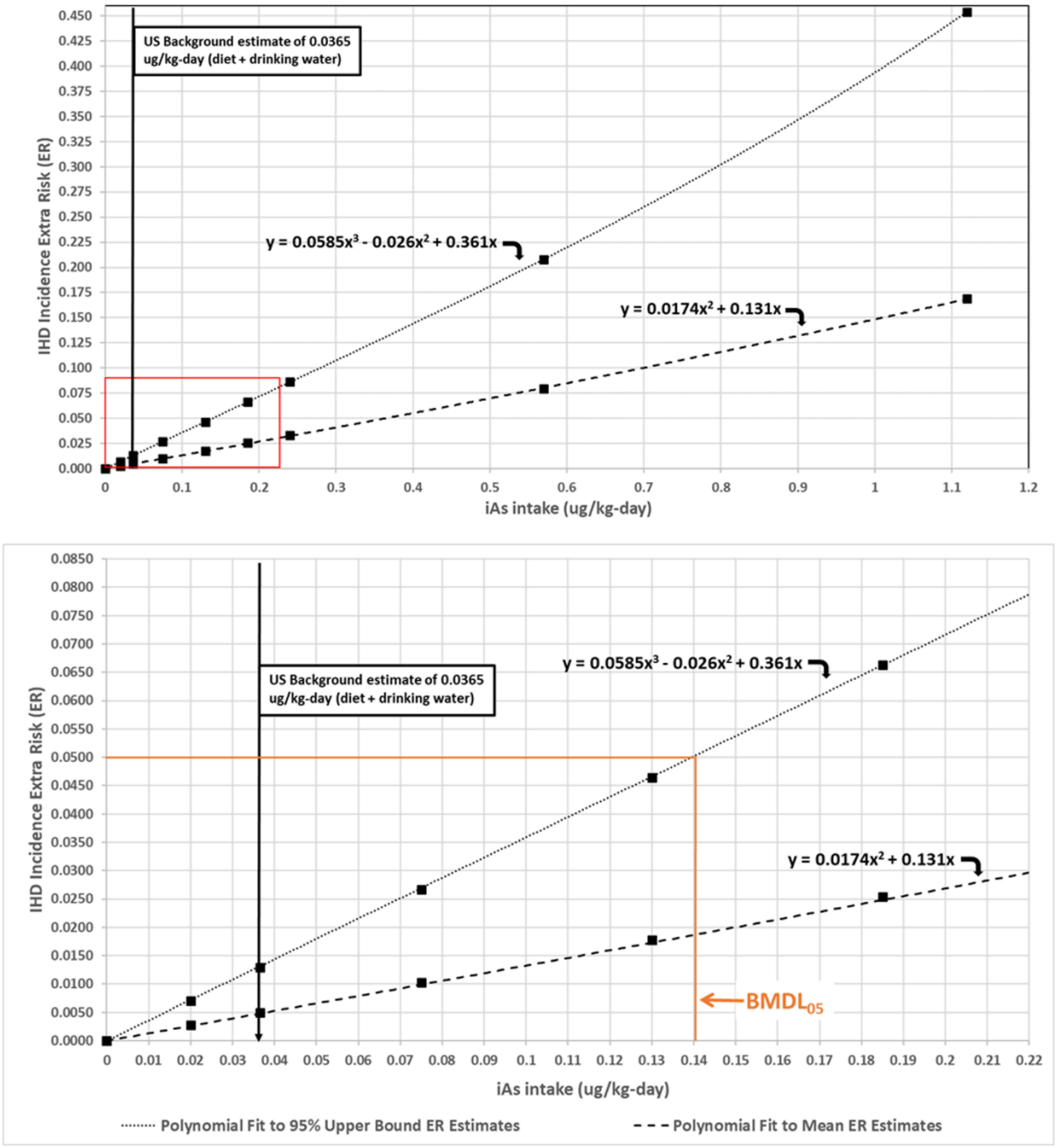

Figure 4-11. U.S. IHD incidence (all studies) lifetime extra risk versus µg/kg-d MLE doses for all doses (top plot) and low doses (bottom plot). See Section 4.3.4 for discussion of 0.0365 ug/kg-day U.S. background dose estimate.

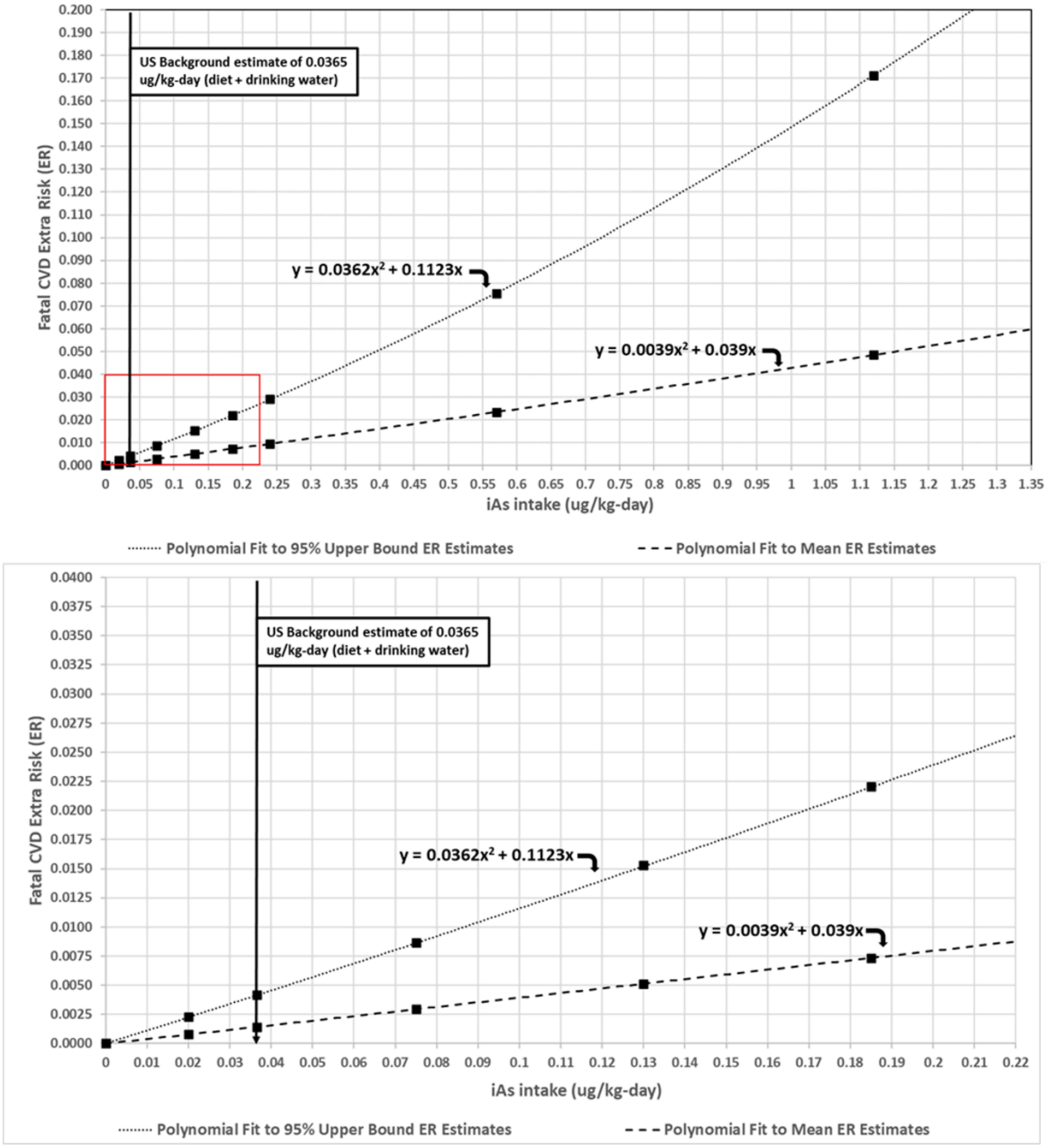

Figure 4-12. U.S. fatal CVD (all studies) lifetime extra risk versus µg/kg-d MLE doses for all doses (top plot) and low doses (bottom plot). See Section 4.3.4 for discussion of 0.0365 ug/kg-day U.S. background dose estimate.

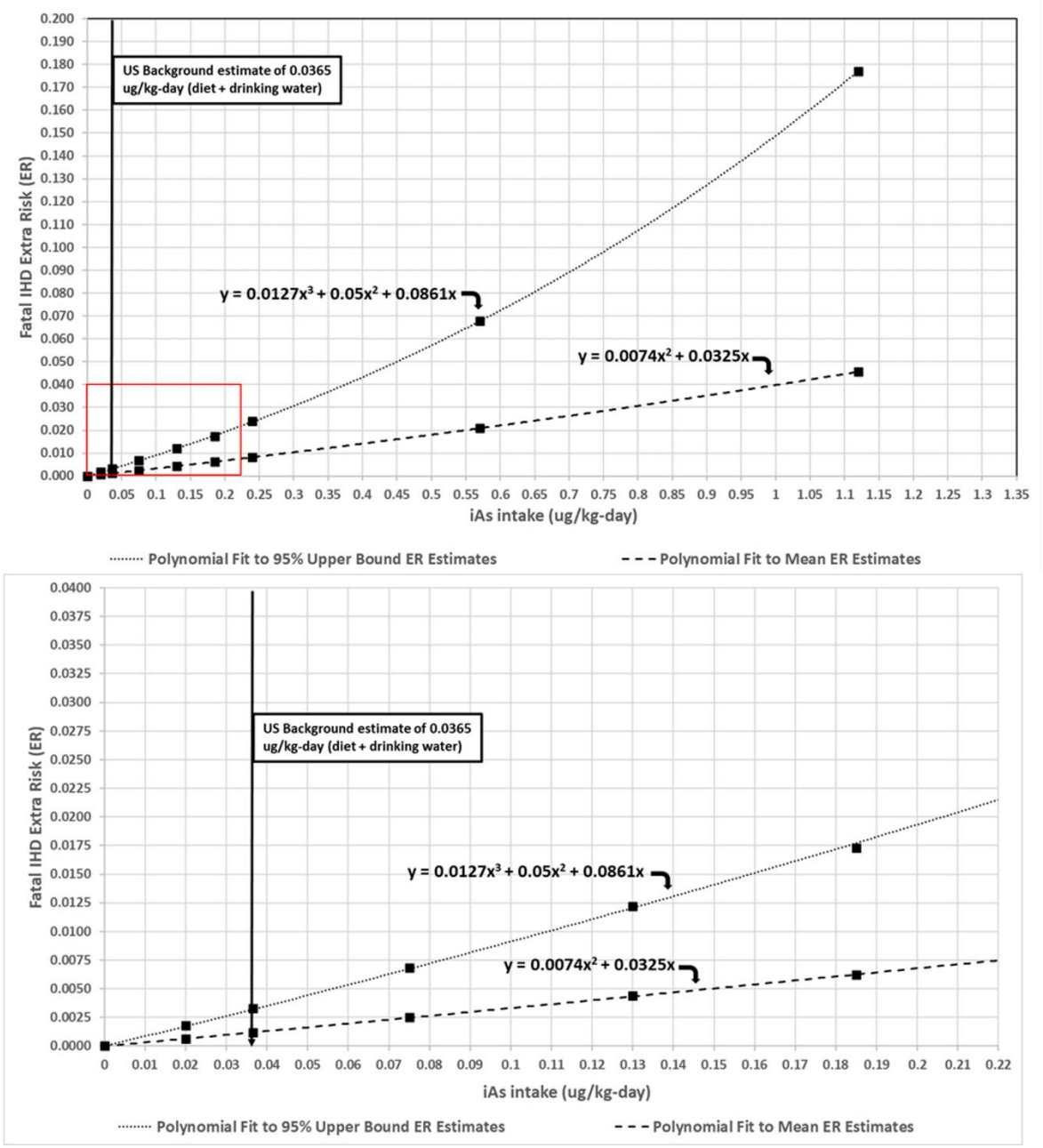

Figure 4-13. U.S. fatal IHD (all studies) lifetime extra risk versus µg/kg-d MLE doses for all doses (top plot) and low doses (bottom plot).

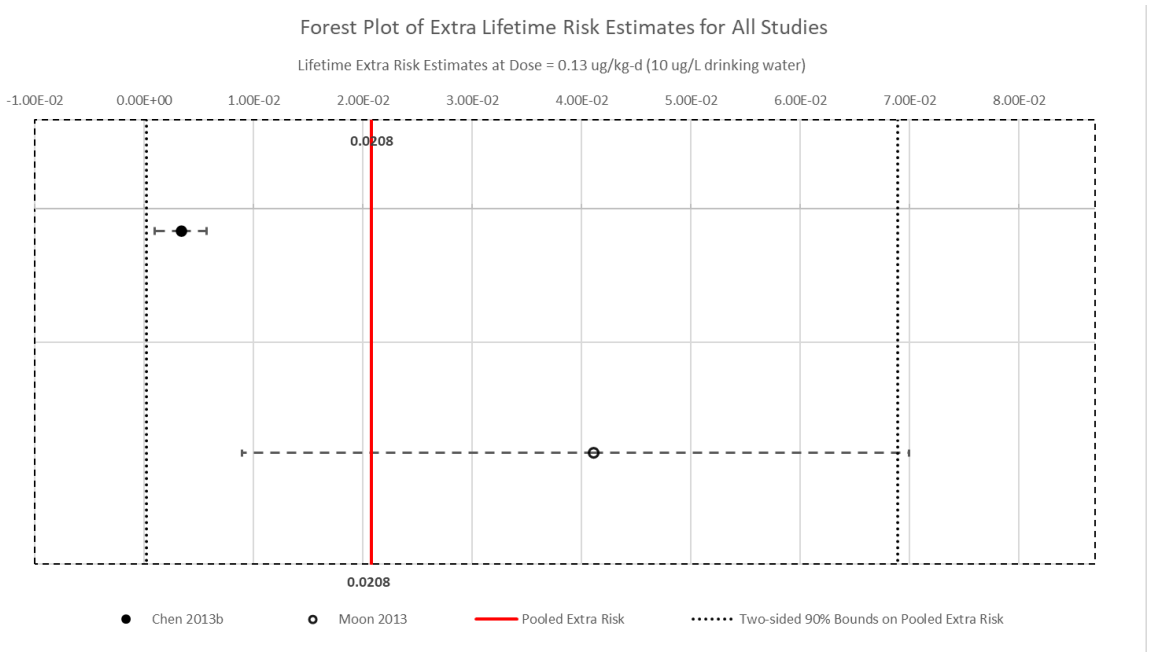

Figure 4-14. Forest plot of Bayesian model estimates of lifetime extra risk of CVD incidence for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake). Based on meta-regression of all CVD incidence studies using MLE doses.

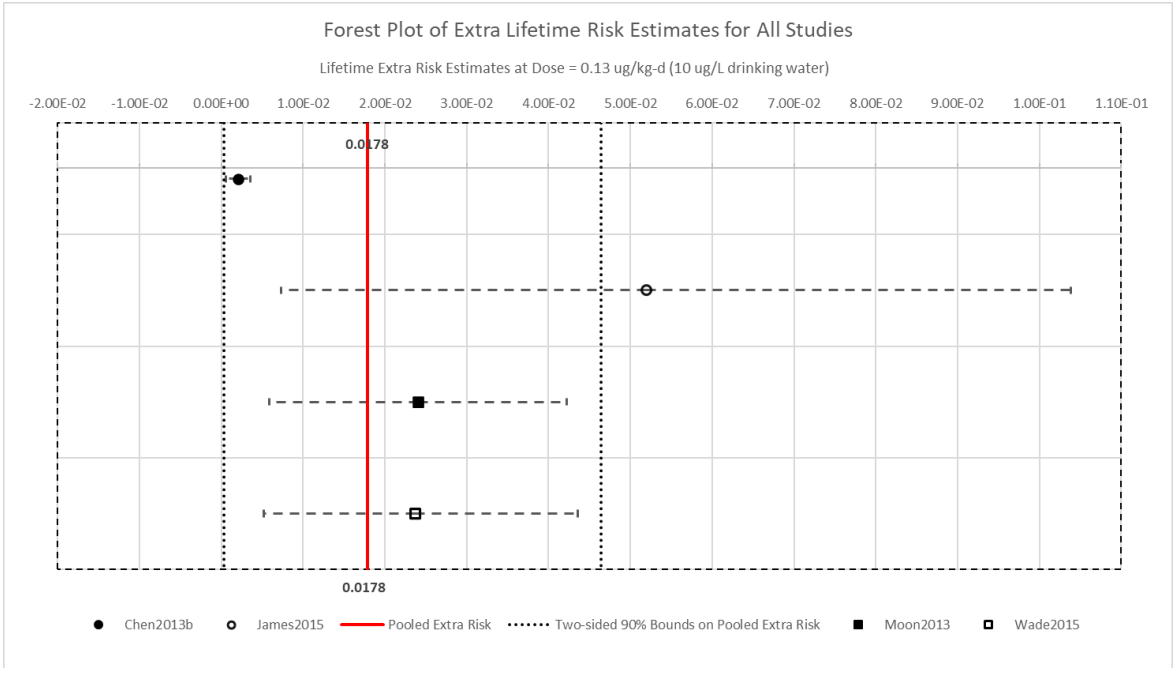

Figure 4-15. Forest plot of Bayesian model estimates of lifetime extra risk for IHD incidence for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake). Based on meta-regression of all IHD incidence studies using MLE doses.

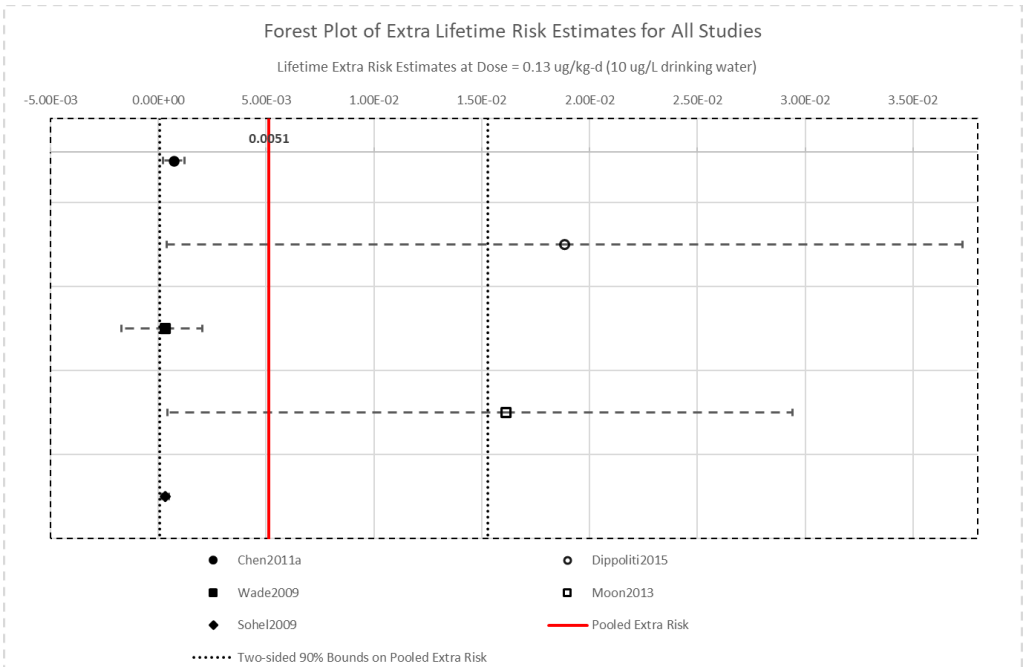

Figure 4-16. Forest plot of Bayesian model estimates of lifetime extra risk for fatal CVD for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake). Based on meta-regression of all CVD mortality studies using MLE doses.

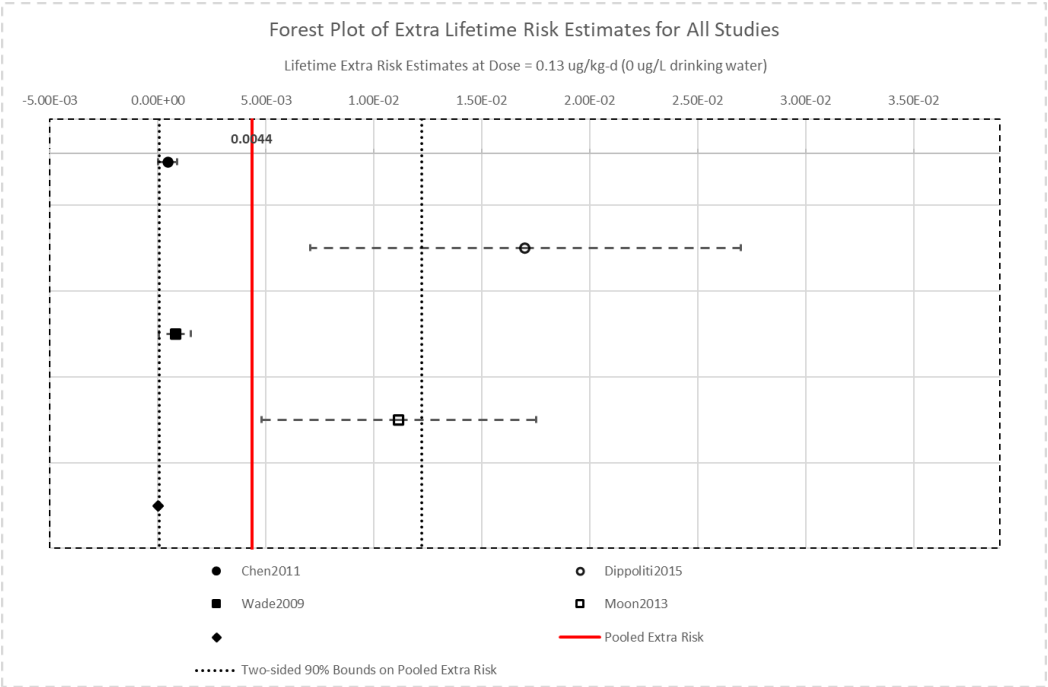

Figure 4-17. Forest plot of Bayesian model estimates of lifetime extra risk for fatal IHD (for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake). Based on meta-regression of all IHD mortality studies using MLE doses.

Table 4-10. Pooled meta-regression estimates of extra lifetime incidence risk (per 10,000) for DCS outcomes at various average daily iAs doses and estimated U.S. equivalent drinking water exposures above median U.S. doses and exposures using MLE doses [a, b]

Health outcome	Extra lifetime risk (per 10,000)	Average daily inorganic arsenic dose (µg/kg-d)[c]								
		0	0.02	0.0365[c]	0.075	0.13	0.185	0.24	0.57	1.12
CVD incidence	5%	0.00	0.31	0.57	1.18	2.04	2.90	3.77	8.95	17.58
	mean	0.00	32.16	58.65	120.31	208.00	295.24	382.03	892.96	1706.02
	95%	0.00	107.90	196.41	401.18	689.32	972.20	1249.70	2797.36	4918.66
IHD incidence	5%	0.00	0.55	1.00	2.05	3.55	5.05	6.55	15.55	38.39
	mean	0.00	27.34	49.93	102.74	178.41	254.34	330.53	792.25	1687.70
	95%	0.00	70.71	129.24	266.49	464.05	663.18	863.64	2081.04	4539.95
Fatal CVD	5%	0.00	0.11	0.20	0.42	0.72	1.03	1.34	3.17	6.24
	mean	0.00	7.83	14.31	29.50	51.41	73.54	95.89	234.91	485.77
	95%	0.00	22.81	41.82	86.85	152.87	220.89	290.97	756.19	1712.15
Fatal IHD	5%	0.00	0.08	0.15	0.32	0.55	0.78	1.01	2.40	4.72
	mean	0.00	6.59	12.07	24.99	43.76	62.16	82.50	208.70	455.88
	95%	0.00	17.75	32.68	68.51	122.23	173.16	239.15	676.91	1770.18

[a]Extra lifetime risks are presented as mean risk/10,000 with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Polynomial formulae given in Figure 4-10 to Figure 4-13 are provided for convenience in approximating lifetime extra risk at doses other than those in the table. To generate estimates other than those illustrated in Table 4-10, meta-regression models and lifetable spreadsheets available in the EPA HERO database can be applied in accordance with methods (Allen et al., 2020b; Allen et al., 2020a) describes.

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

Summary of Meta-Regression of DCS Studies

General limitations and uncertainties associated with the studies used in the DCS meta-regressions were discussed in Section 4.3.1. As for the bladder cancer and lung cancer meta-regression analyses, the exposure information from studies used in the meta-regression analyses were converted to estimates of lifetime daily doses of total iAs in units of average daily µg iAs per kg body weight (µg/kg). Uncertainties in average lifetime daily doses for the exposure groups and in the conversion to µg/kg 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, Sections C.1.1 Treatment of Dose Uncertainty and C.1.1 Adjusting for Covariates for details).

The visual fit of the model was adequate for all data sets within all DCS health outcomes, with moderate improvement to the meta-regression model fits when low-dose studies were analyzed separately versus combined with high-dose studies (see Appendix C.1.2 Diseases of the Circulatory System; Summary of DCS meta-regression results for MLE dose estimates). The β_mean posteriors obtained from meta-regression analyses were used to derive U.S.-specific lifetime extra-risk estimates for CVD incidence, IHD incidence, fatal CVD, and fatal IHD. As shown in Table 4 10, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming intake levels of 0.02 to 1.12 μg/kg-day, approximately equivalent to U.S. water iAs exposures of 5 to 100 μg/ L). At the assumed dietary (no drinking water contribution) background dose of 0.02 μg/kg-day, the means of the extra lifetime risk distribution for CVD incidence, IHD incidence, fatal CVD, and fatal IHD were 32, 27, 7.8, and 6.6, respectively, per 10,000 (the corresponding 95% credible intervals were 0.3 to 108, 0.55 to 71, 0.11 to 23, and 0.08 to 18 per 10,000). At high 1.12 μg/kg-day dose, the means of the extra lifetime risk distribution for CVD incidence, IHD incidence, fatal CVD, and fatal IHD were 1,706, 1,688, 486, and 456, respectively, per 10,000 (the corresponding 95% credible intervals were 18 to 4,919; 38 to 4,540; 6.2 to 1,712; and 4.7 to 1,770 per 10,000).

The estimates were derived using Bayesian meta-regressions of studies using the study selection approach described above. The meta-regressions were performed using the MLE daily doses estimated for study participants. To assess the uncertainty in the MLE doses, sensitivity analyses were performed that examined the influence of uncertainty on the means for the reported exposure-defined groups and on the conversions necessary to obtain a common metric, average daily μg/kg (see Appendix C, Section C.1.2 Summary of DCS meta-regression results for MLE dose estimates). The effect was minimal overall, with low-end and high-end estimate doses generally ranging 5-20% from MLE doses. This finding indicates that the results are not overly sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels. As summarized in this section (above) and in Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses, the choice of study population, specifically the exclusion of studies for which all exposure group daily dose estimates are outside the range of U.S. doses (>1 μg/kg-day) had a greater influence on the meta-regression results.

Other sensitivity analyses performed for the DCS meta-regressions 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.1.2.2.6). 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 (see Appendix C, Tables C-65 through C-68). Incorporation of estimates of inhalation exposures in the background estimate of total exposure decreased extra risk estimates by less than 1%.

Two urine biomarkers studies of DCS outcomes are Chen et al. (2011b), which reported only on fatal CVD and fatal IHD outcomes, and Moon et al. (2013), which reported on all four DCS health outcomes. As described in Appendix C, Section C.1.2 Diseases of the Circulatory System; DCS sensitivity analyses, removal of either or both of these studies had a moderate impact on the meta-regression β _mean estimates, except when either was removed individually from the CVD incidence or the fatal CVD meta-regressions. Only two studies were used in the CVD incidence meta-regression, and the β_mean logistic slope estimate decreased by 83% from 0.23 to 0.04 when the Moon et al. (2013) urine study was removed. This is because the β _mean estimate of 0.04 for the Chen et al. (2013b) drinking water study was 93% lower than the 0.54 β _mean estimated for Moon et al. (2013) urine study. For fatal CVD, removal of the Wade et al. (2009) study increased β_mean by 50%, and removal of the Moon et al. (2013) study decreased the β _mean by 86% (see Appendix C, Table C-63). This pattern is expected as Moon et al. (2013) is a low-dose study and Chen et al. (2011b) is a high-dose study (see Appendix C, Table C-45).

In summary, inclusion of a background inhalation exposure had the least (≤ 0.5%) and the exclusive use of the Moon et al. urine biomarker study from the CVD incidence (83%) and fatal CVD (86%) meta-regressions would have the greatest impact on the β_mean logistic slope estimates for DCS endpoints. The DCS β_mean logistic slope estimates were moderately impacted by variability/uncertainties in the exposure factors (≤ 20%) and alternative gamma prior distributions (≤ 24%).

The accuracy of these meta-regression results depends on the quality of available published studies. The analyses included only medium and high confidence studies, and most studies adjusted for appropriate covariates, including age, sex, smoking, and education or socioeconomic status. Compared to older studies, the more recent studies, including the three low exposure studies, have more comprehensive adjustment for potential confounders. Studies such as Moon et al. (2013) that assess individual-level data for biomarkers of internal dose that can be reliably converted (e.g., via a PBPK model) to estimates of intake are valuable indicators of total dose, particularly at the low levels of arsenic in U.S. drinking water.[41]

4.3.8. Bayesian Meta-Regression 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 meta-regression analyses with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for meta-regressions using the MLE doses. The meta-regressions for diabetes included both case-control and cohort studies; the selected studies, converted doses

[41]Although arsenic is excreted within days to weeks, urine arsenic is often used as a biomarker of chronic exposure because arsenic concentrations in drinking water are generally stable over time (Steinmaus et al., 2005). Nevertheless, EPA's assessment of dose extrapolation uncertainty approximates the impact of temporal variability using data for 10-yr variability in urine levels of 386 Moon et al. (2013) subjects (see Appendix C, Section C.1.2.4.3).

(low, MLE, high), and effective counts used in the diabetes meta-regressions are presented in Appendix C, Section C.1.2 Diabetes.

A summary of the results of the analyses using the MLE doses is presented in Table 4 12. Plots in Appendix C, Sections C.1.2 Diabetes; Summary of diabetes meta-regression 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 0.3365, and its 5th percentile is 0. 019 (see Table 4-12). The mean coefficient of variation (CV), β_sigma/β_mean, is about 1.7, 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, Section 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, Section C.1.2 Diabetes; Summary of diabetes meta-regression results for MLE dose estimates) and sensitivity analyses (see Appendix C, Section C.1.2 Diabetes; Diabetes sensitivity analyses).

Table 4-11. Summary of diabetes Bayesian analysis output using MLE dose estimates

Parameter	Mean	Standard error of the mean	Standard deviation	5%	25%	50%	75%	95%
β_mean	0.346	0.004	0.2784	0.0215	0.1786	0.2918	0.4252	0.8987
β_sigma	0.591	0.0152	0.7786	0.0188	0.1101	0.3088	0.7773	2.0549
β Grau-Perez et al. (2017)	0.0099	0.0171	0.9268	0.0099	0.2587	0.4502	1.1173	2.8047
β James et al. (2013)	0.0755	0.0058	0.3614	0.0755	0.2698	0.4324	0.7444	1.2243
β Coronado-González et al. (2007)	0.1466	0.0009	0.0775	0.1466	0.222	0.273	0.3253	0.4018
β Pan et al. (2013b)	0.1157	0.0011	0.0996	0.1157	0.2126	0.2775	0.3435	0.4414

Extrapolation of Diabetes Risk to Target Population

The posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, was used with a summary value of 40% for the U.S. lifetime probability of developing type

II diabetes (Gregg et al., 2014)[42] as the input to a lifetable calculation of the lifetime probability of diabetes as a function of iAs dose (average daily μg/kg). The methodology is presented in (Allen et al., 2020b; 2020a). 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 doses from each study results in extra lifetime diabetes risks as a function of iAs dose (μg/kg-day) summarized in Figure 4-18.[43] Figure 4-19 is a forest plot that shows the predictions for the individual data sets and the pooled estimate of extra risk at an iAs dose of 0.13 μg/kg-day. Table 4-13 summarizes the calculated extra risks across a wide range of iAs μg/kg-day MLE doses. These figures and tables reflect 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.

[42]For diabetes, age-stratified morbidity and mortality values were not available; therefore, a summary estimate of the lifetime probability of developing type II diabetes was used instead.

[43]The figures include polynomial equations that allow for the estimation of upper bound and MLE estimates of extra risk at doses that do not appear in Table 4-12. For noncancer endpoints, their primary purpose is for the estimation of risk at doses above the noncancer health outcome RfDs.

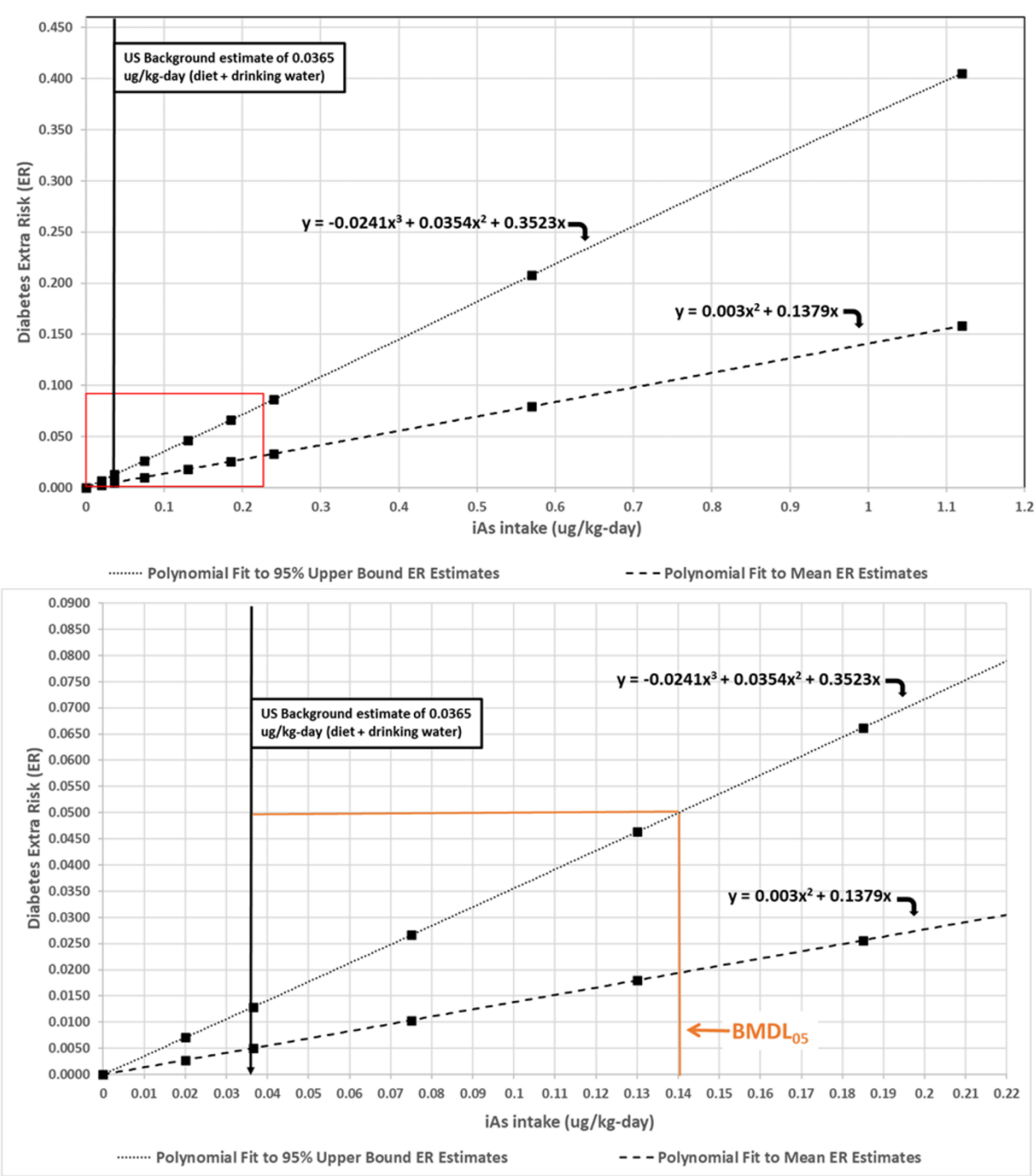

Figure 4-18. U.S. diabetes (all studies) lifetime extra risk versus µg/kg-d MLE doses for all doses (top plot) and low doses (bottom plot). See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

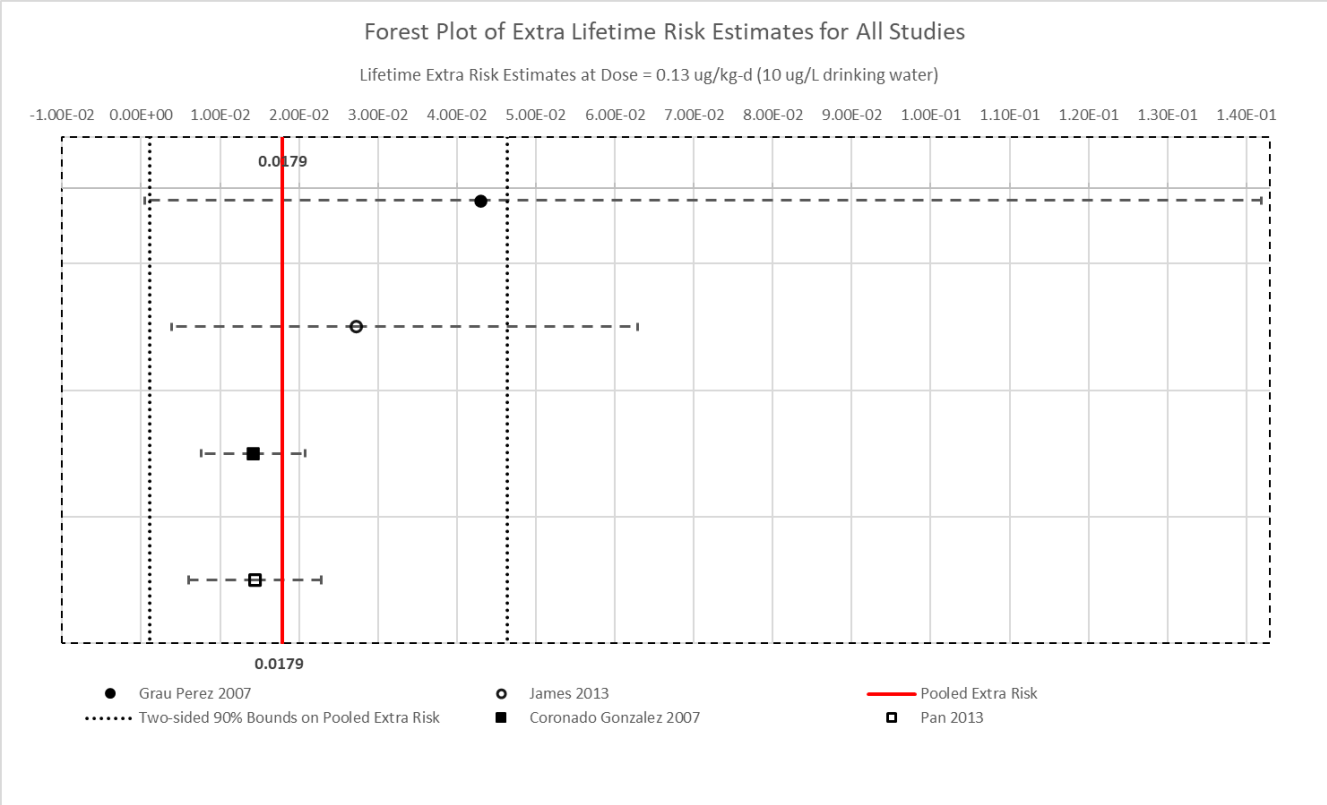

Figure 4-19. Forest plot of the pooled estimate of diabetes extra risk (solid line) and 95% confidence bounds on pooled extra risk (dotted lines). Extra risk calculated for 0.13 µg iAs/kg-day scenario (roughly equal to 10-µg iAs/L water exposure + background dietary intake for a U.S. population). Based on meta-regression of all diabetes studies using MLE estimates for dose.

Table 4-12. Pooled meta-regression 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)	Average daily inorganic arsenic dose (µg/kg-d)[c]								
	0	**0.02**	**0.0365**	**0.075**	**0.13**	**0.185**	**0.24**	**0.57**	**1.12**
5th percentile	0	1.72	3.14	6.45	11.18	15.91	20.64	49.06	96.51
Mean	0	27.49	50.20	103.30	179.38	255.73	332.34	796.62	1581.96
95th percentile	0	70.62	129.08	266.14	463.45	662.31	862.51	2078.32	4050.39

[a]Extra lifetime risks are presented as mean risk/10,000 with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Polynomial formulae given in Figure 4-18 are provided for convenience in approximating lifetime extra risk at doses other than those in the table, particularly doses above the diabetes RfD. Meta-regression models and lifetable spreadsheets used to derive the values in the table (available from EPA HERO) should (Allen et al., 2020a);(Allen et al., 2020b).

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

Summary of Meta-Regression of Diabetes Studies

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). Uncertainties in average exposures for the exposure groups and in the conversion to average µg/kg daily doses were accounted for, as described in Section 4.3.2. Moreover, 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, Sections C.1.1 Treatment of Dose Uncertainty and C.1.1 Adjusting for Covariates for details).

Given those adjustments, the meta-regression approach described in Section 4.3.4 was applied to the set of four studies previously discussed. The high dose was dropped to obtain adequate model fit for the Pan et al. (2013b) because confidence bounds for one dose group was outside of the 90% confidence bounds for the meta-regression modeling results. The visual fit of the model was adequate for the other data sets. The choice of a hierarchical meta-regression model structure was supported by the moderately large variation (with mean estimated CV of about 1.9) estimated by the meta-regression. The mean of the posterior distribution for β_mean (using the MLE doses) was 0.35 (90% credible interval, 0.022 to 0.9) per µg/kg-day.

The β_mean posterior (using the MLE dose estimates) was used to derive a distribution of U.S.-specific lifetime extra-risk estimates via a lifetable analysis using the U.S. lifetime probability of developing type II diabetes, as summarized in the Extrapolation of Diabetes Risk to Target Population section. These U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming intake levels of 0.02 to 1.12 µg/kg-day, approximately equivalent to U.S. water iAs exposures of 1.5 to 100 µg/L). At 0.02 µg/kg-day, the mean of that extra lifetime risk

distribution was 50 per 10,000 (90% credible interval, 3.14 to 129 per 10,000). At 1.12 μg/kg-day, the mean extra lifetime risk was 1,582 per 10,000 (90% credible interval, 97 to 4,050 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 daily μg/kg) (see Appendix C.1.2.3.5). The mean lifetime extra risk estimate at 0.13 μg/kg-day increased approximately 19% when using the "low" dose estimates (213 vs. 179 per 10,000). Correspondingly, the lifetime extra risk at 0.13 μg/kg-day decreased approximately 18% when using the "high" dose estimates (146 vs. 179 per 10,000). Because the low-end and high-end dose values resulted from a combination of factors, the interval from 146 to 213 per 10,000 (for the 0.13 μg/kg-day intake level) should not be associated with a specific confidence or credible interval level; they do, however, 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 meta-regression 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.1.2.3.5). 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 (see Appendix C, Table C-42). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk.

Excluding the two urine studies decreased the mean logistic slope by 6%. The two studies influence the analysis in opposite directions, with the exclusion of Grau-Perez et al. (2017) decreasing the slope by 22% and the exclusion of (Coronado-González et al., 2007) increasing the slope by 34%. 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 meta-regression.

Finally, the influence of the individual studies on the meta-regression 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 (Pan et al., 2013b) data set. In that case, the removal of the study increased the mean of the β parameter by 36%.

In summary, inclusion of a background inhalation exposure had the least (≤ 0.2%) and study selection has the potential to have the greatest (≤ 36%) 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 (≤ 19%), alternative gamma prior distributions (≤ 11%), and the use of urine biomarker studies (≤ 6%).

4.4. PREGNANCY AND BIRTH OUTCOMES

Based on literature searches up to August 2022 (see Section 2.1), 102 pregnancy and birth outcome studies were identified, of which 68 were medium or high confidence and were advanced for consideration for dose-response[44]. 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 reported metrics based on blood, urine, or drinking water (expressed as µg/day). These studies were excluded from analysis because no PBPK models for converting biomarker metrics have been validated for pregnant women. Lack of validation in this population of interest lends considerable uncertainty to the extrapolation of urine and blood levels to drinking water. Therefore, to derive PODs, only the regression betas reported in a single high confidence study, Kile et al. (2016), were used.

4.4.1. Kile et al. (2016)

Kile et al. (2016) conducted a prospective cohort study of birthweight (g) versus maternal drinking water arsenic concentrations[45] (µg/L) in 1,153 pregnant women in Bangladesh (Kile et al., 2016). This results from this study were selected for dose-response modeling because it is a high confidence study that reported regression coefficients appropriate for dose-response.

Weight at birth was measured on a pediatric scale calibrated before each measurement and rounded to the nearest 10 g. The average birthweight was 2,836 g (SD: 415 g, range: 800–4,800 g). The authors used multivariate linear regression and structural equation modeling (SEM) to evaluate direct, indirect, total mediated, and total effects of drinking water arsenic concentrations on birthweight. The authors found a significant indirect effect mediated through gestational age at birth and, to a lesser extent, maternal weight gain throughout pregnancy. Kile et al. (2016) measured the association between drinking water iAs (µg/L) on birthweight (g), reporting a beta coefficient of −19.2 g per ln(µg/L) (95% CI: −24.6, −13.7) based on linear regression.

To calculate PODs from Kile et al. (2016) the reported β coefficients were first re-expressed in terms of per µg/L according to Dzierlenga et al. (2020). The re-expressed β and lower limit on the confidence interval then were used to estimate BMD and BMDL values using the general equation $y = mx + b$, substituting the re-expressed β value from this study for m and the mean birth weight for all U.S. births for b.

Kile et al. (2016) reported a β coefficient of −19.2 g (95% CI: −24.6, −13.7) per ln (µg/L) increase for the association between birth weight and iAs concentrations in drinking water in a Bangladesh cohort, based on their multiple linear regression analysis. Given the reported study-

[44]No studies identified in the literature search update were deemed informative for dose-response analysis.
[45]Toenail measurements were also taken, but at a lower rate than drinking water arsenic measurements (N~600). Also, toenail PBPK models are not verified for pregnant women. Furthermore, toenail exposure was strongly correlated with drinking water exposure (sigma_spearman = 0.49). So it is reasonable to believe that focusing on results of the drinking water exposure sufficiently captures the effect of inorganic arsenic exposure on birthweight, as reported by (Kile et al., 2016).

specific median (2.3 μg/L) and interquartile range (IQR) (0.9–36 μg/L) of the exposure from Kile et al. (2016), the distribution of exposure was estimated by assuming the exposure follows a log-normal distribution with mean and standard deviation:

$$\mu = ln(q_{50}) = ln(2.3) = 0.83 \quad (1)$$

$$\sigma = ln(q_{75}/q_{25})/1.349 = ln(0.9/36)/1.349 = 2.73 \quad (2)$$

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 −4.3 g (95% CI: −5.5, −3.1) per μg/L.

Typically, for continuous data, the preferred definition of the benchmark response (BMR) includes a basis for 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. The CDC Wonder site (https://wonder.cdc.gov/natality.html) provides vital statistics for babies born in the United States. In 2018, 3,791,712 live births occurred in the United States, according to final natality data. The mean and standard deviation were 3,261.6 ± 590.7 g (7.19 ± 1.30 lb), with 8.27% of live births falling below the public health definition of low birth weight (i.e., 2,500 g, or 5.5 lb). The full natality data for birth weight in the U.S. data were used as they are more relevant for deriving RfDs for the U.S. public than the birth weight data for the study-specific population (in Bangladesh), where approximately 21% of birth weights were below the 2,500 g adversity cutoff (Kile et al., 2016). Also, the CDC Wonder database can be queried so the exact percentage of the population falling below the cut-off value for clinical adversity can be determined. Thus, what constitutes an adverse response has a clinical measure: babies born weighing less than 2,500 g are considered low birth weight, and, further, 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). Given this clinical cut-off for adversity (i.e., birth weight below 2,500 g) and 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 continuous benchmark response. The hybrid approach harmonizes the definition of the BMR for continuous data with that for dichotomous data, and therefore is an advantageous approach.[46] 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. In the

[46]While the explicit application of the hybrid approach has not been not 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%.

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 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:

$$Extra\ Risk(ER) = (P(d) - P(0)) \ / \ (1 - P(0))$$

$$P(d) = ER(1 - P(0)) + P(0) = 0.05(1 - 0.0827) + 0.0827 = 0.1286$$

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.

The BMD was calculated by rearranging the equation $y = mx + b$ and solving for x, using 3261.6 g for the b term and −4.3 for the m term. Doing so results in a value of 21.4 ng/L:

$$x = (y - b)/m = (3169.2\ g - 3261.6\ g)/(-4.3\ g(\frac{ng}{mL})^{-1}) = 21.4\ ng/mL$$

To calculate the BMDL, the method is similar, except the lower limit on the β coefficient (−5.5 g per µg/L) is used for the m term. Kile et al. (2016) however, reported a two-sided 95% confidence interval for the β coefficient, 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. First, the standard error of the β coefficient can be calculated as:

$$SE = \frac{Upper\ Limit - Lower\ Limit}{3.92} = \frac{-3.1\ g(\frac{ug}{L})^{-1}}{3.92} = 0.63\ g(\frac{\mu g}{L})^{-1}$$

Then the corresponding 95% one-sided lower bound on the β coefficient can be calculated as:

$$95\%\ one\ sided\ LL = \beta - 1.645(SE(\beta)) = -4.3\ g(\frac{\mu g}{L})^{-1} - 1.645\left(0.63\ g(\frac{g}{L})^{-1}\right) = -5.35 g(\frac{\mu g}{L})^{-1}$$

Using this value for the m term results in a BMDL value of 17.3 µg/L maternal serum concentration. This was converted to a total dose of 0.23 µg/kg-day by multiplying 17.3 µg/L by

0.012 L/kg-day mean U.S. water consumption rate for pregnant women (U.S. EPA (2019), Table 3-1, "All Ages") and adding a 0.02 µg/kg-day median U.S. dietary background dose (Xue et al., 2010).

4.5. NEURODEVELOPMENTAL EFFECTS

The basis for study selection for screening analyses of exposure-response for the neurodevelopmental effects are described in (Hobbie et al., 2020), Section 4.2, and Appendix C, Section C.2.1. For neurodevelopmental effects, the screening level analyses indicated the Bayesian meta-regression approach described in this assessment would not be feasible due to the lack of dichotomous, relative risk studies for this endpoint. Criteria used to assess suitability for dose-response analysis differed for continuous neurodevelopmental endpoints versus dichotomous endpoints (see Appendix C, Section C.2.1). Of the 52 medium or high confidence neurodevelopmental studies considered, only 2 were identified as appropriate for further dose-response analyses. EPA received data sets of subject-specific exposure and response measurements and covariates from the authors of two studies (Wasserman et al., 2004); (Wasserman et al., 2014). Both studies examined the relationship between arsenic exposure and IQ as measured by a U.S.-based scoring method. The (Wasserman et al., 2004) study was conducted on a Bangladeshi population, however, and the study authors note a limitation of the study is the application of tests standardized to U.S. populations to assess IQ in a Bangladeshi population. Given this concern for generalizability, this study was excluded from further consideration for dose-response. The (Wasserman et al., 2014) study applies the U.S.-based IQ metric to a population of Maine school children, and so is more appropriate for a U.S. population. Thus, EPA performed dose-response evaluations using the full data set from (Wasserman et al., 2014). Use of these data allows for replication of the original study findings and additional investigation of the effects of covariates and limited numbers of different model specifications.

4.5.1. Wasserman et al. (2014)

Wasserman et al. (2014) conducted a cross-sectional study of IQ versus water arsenic concentrations in Maine school children. EPA evaluated (see Appendix C, Section C.2.2) and selected this study for dose-response modeling for the following reasons: The study was a high confidence study considered suitable for dose-response as it was conducted in the United States, and had complete data, including appropriate covariates, available from the study authors.

The authors recruited 272 elementary students in 3rd–5th grade, ages 8–12 years (average 9.67) from three school districts near Augusta, ME in 2006–2007. The data that the authors provided included arsenic concentration data measured at the point of use, school district of residence (three districts), with a range of household and individual covariates. Most children were white, the area was characterized as generally "mid-range" in economic status, and 71% and 86% of fathers and mothers, respectively, reported having "some college" or more education. The overall average water arsenic concentration was 9.88 ± 15.06 µg/L (10% of measurements were below the

detection limit of 0.1 µg/L.) The distribution was skewed, with a median of 4.6 µg/L, geometric mean of 2.6 µg/L, 5th and 95th percentile measurements of "ND" and 40.7 µg/L, respectively.

Experienced testers assessed children's IQ using WISC-IV. Raw test results were normalized to the U.S. population, and results are presented as Full Scale, Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed IQ scores. IQ scores were reported for four exposure strata (see Table 4-13). Table 4-13 shows most subjects (about 52%) were in the lowest exposure stratum.

Table 4-13. Water arsenic concentrations in referent and exposed subjects

Water arsenic concentration range	Number of subjects	Water arsenic (mean ± std. dev.)
<5	141	1.24 ± 1.37
>5–10	46	7.37 ± 1.34
>10–20	52	14.80 ± 3.06
>20	33	42.55 ± 20.43

As in their Bangladeshi study, (Wasserman et al., 2014) used a multiple linear regression analysis to evaluate the effect of arsenic exposure and other covariates on the various IQ metrics. Covariates included in the "core" regression were maternal intelligence and education levels, HOME score (a widely used assessment that combines interview and direct observation), the number of children living in the household, and school district. Table 4-14 summarizes the regression model results.

Table 4-14. Adjusted IQ changes in exposed groups relative to referents Wasserman et al. (2014)

Arsenic exposure µg/L, range (mean ± SD)	Subjects per exposure group (n)	Full Scale IQ	Working Memory	Perceptual Reasoning	Verbal Comprehension	Processing Speed
>5–10 (7.37 ± 1.34)	46	−6.09 ± 1.98**	−4.88 ± 2.24*	−4.97 ± 2.14*	−6.22 ± 2.49*	−1.74 ± 2.09
>10–20 (14.8 ± 3.06)	52	−3.15 ± 1.91	−1.13 ± 2.16	−5.10 ± 2.06*	−1.86 ± 2.39	−1.15 ± 2.01
>20 (42.55 ± 20.43)	33	−2.51 ± 2.29	−5.07 ± 2.59#	−2.29 ± 2.47	−0.82 ± 2.88	0.40 ± 2.42

Note: ** indicates differences from referent significant at $p < 0.01$, * = $p < 0.05$, # = $p < 0.10$.
Mean exposure level in referent population (n = 141) was 1.24 ± 1.37 µg/L.

Except for Processing Speed, the general pattern is one of relatively large differences between the mean IQ scores in the second stratum (5–10 µg/L) and those in the referent group (<5 µg/L) across the four metrics: Full IQ, Working Memory, Perceptual Reasoning, and Verbal Comprehension. The reductions in mean IQ from the referent group range from 4.88 to 6.22 points,

and all differences are significant at $p < 0.05$. The pattern of IQ scores was nonmonotonic with respect to the magnitude of effect at higher doses. Although the changes relative to the referent group are negative, most are smaller than those for the 5–10 μg/L group. Changes in average Full Scale IQ and Verbal Comprehension in the two highest exposure groups were not significant relative to referents. The reduction in average Working Memory score in the highest exposure group (–5.07) was highly significant, but the change in the 5–10 μg/L group (–1.13) was not. For Perceptual Reasoning, the IQ reduction in 5–10 μg/L group was highly significant, but the change relative to referents was not significant in the highest exposure group. Changes in average Processing Speed scores were not significant for any exposure group. EPA reproduced all modeling results from the original data.

The authors do not report the results of regression models when arsenic water concentration is included as a continuous variable. Thus, regressions were fit using the "core" model covariates and log-transformed individual water arsenic concentrations (see details in Appendix C, Section C.2.2). The coefficient for Working Memory was marginally statistically significant but the coefficients for the effect of log (water arsenic) on the other IQ metrics were not significant (see Table 4-15). All coefficients were negative. This pattern is consistent with the pattern of findings presented in Table 4-14, which indicated substantial nonlinearity in the relationship between water arsenic concentration and average IQ scores. Given the nonlinearity of the relationships, EPA concluded that applying the (log) linear model to estimating reductions in IQ scores would not be appropriate. Other important limitations of this study include:

- While the study is based on a U.S. population, limitations related to ethnic and socioeconomic differences still exist when attempting to estimate risk for the general population of U.S. children.

- The study is based on a population with relatively low arsenic exposures possibly limiting the study's ability to detect effects across the entire range of the dose-response curve.

- Dosimetric uncertainties, particularly related to dietary arsenic intake, exist in the study population. However, these uncertainties are smaller than for the Bangladeshi study (the only other neurodevelopmental study identified as appropriate for further consideration for dose-response analyses).

- The nonlinearity of the exposure-response relationship and relatively small numbers of subjects in the highest exposure groups introduce uncertainty into the risk characterization. Analysis of the data set as a whole indicates a high degree of confidence in statistically significant changes in four of the five endpoints above approximately 5 μg/L water arsenic. That analysis, however, considered dose as a categorical variable. When iAs was considered as a continuous variable, associations were not statistically significant.

The authors did not measure nor control for lead exposures, which are also known to be associated with reductions in children's IQ scores of the same general magnitude as observed in

this study. For these reasons, EPA has determined the Wasserman et al. (2014) study does not provide adequate support for the derivation of an RfD.

Table 4-15. Adjusted regression coefficients for (continuous) log water arsenic in (Wasserman et al., 2014) regression model

IQ metric	Adjusted beta	Std. error	*p*-Value
Full IQ	−1.43	0.803	0.076
Working Memory	−1.75	0.890	0.050
Perceptual Reasoning	−1.11	0.859	0.197
Verbal Comprehension	−0.97	1.015	0.341
Processing Speed	−0.69	0.829	0.410

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 except for neurodevelopmental effects. Table 4-16 presents a summary of studies, outcomes, and rationales considered for POD derivation.

Table 4-16. Endpoints considered for derivation of points of departure

Outcome	Reference	Exposure duration	POD derived?	Rationale
CVD incidence	Chen et al. (2013b);(Moon et al., 2013)	Chronic	Yes	Evidence judgment conclusion of evidence demonstrates; two high confidence studies met study screening criteria for meta-regression as described in iAs Protocol (see Section 5.2.2)
IHD incidence	Chen et al. (2013b); Moon et al. (2013); James et al. (2015); Wade et al. (2015)	Chronic	Yes	Evidence judgment conclusion of evidence demonstrates; multiple high confidence studies met study screening criteria for meta-regression as described in iAs Protocol (see Section 5.2.2)
Fatal CVD	Chen et al. (2011b); D'Ippoliti et al. (2015); Wade et al. (2009); Moon et al. (2013); Sohel et al. (2009)	Chronic	No	According to EPA's A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002b), studies investigating mortality endpoints are not preferred for reference value derivation
Fatal IHD	Chen et al. (2011b); D'Ippoliti et al. (2015); Wade et al. (2009); Moon et al. (2013)	Chronic	No	According to EPA's A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002b), studies investigating mortality endpoints are not preferred for reference value derivation
Diabetes	García-Esquinas et al. (2013); 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 as described in iAs Protocol (see Section 5.2.2)
Birth weight	(Kile et al., 2016)	Gestational	Yes	Evidence judgment conclusion of evidence indicates (likely); one high confidence study showing effects at relevant exposure levels in an US-relevant population
Neurodevelop-mental effects	Wasserman et al. (2018);	Developmental/ postnatal	No	Nonmonotonic dose-response shape; non-statistically significant response when iAs dose treated as a continuous variable in a regression analysis

The data for neurodevelopmental effects were deemed insufficient for POD derivation for several reasons, most notably the uncertainty surrounding the shape of the dose-response curve. In the original study, the authors categorized iAs exposure into three bins (>5–10 μg/L, >10–20 μg/L, >20 μg/L) and, while decrements of total IQ were observed in every exposure category, the strength of the association was statistically significantly decreased relative to control only in the lowest exposure group. When EPA obtained the raw data from the study authors and reran the regression treating iAs exposure as a continuous variable (see Section 4.5), the shape of the dose-response curve for full-scale IQ score confirmed the overall findings of the categorial exposure analysis (i.e., steepest slope in the low-dose region; see Appendix C, Figures C-45 and C-46). Although the adjusted regression coefficients for log(water iAs) were negative (indicating a downward trend with increasing water iAs concentration), the overall association between exposure and decreased full IQ failed to reach statistical significance at the $p < 0.05$ level (see Section 4.5, Table 4 17, Appendix C, Section C.2.2). Therefore, given the nonmonotonicity of the iAs dose-response curve and other uncertainties, this endpoint was not considered further for POD derivation.

4.6.2. Estimation of Points of Departure for RfD Derivation

The modeling approach used for diabetes and DCS is discussed in Appendix C, Section C.3. Briefly, after applying the meta-regression approach (described in Section 4.3), BMDs and BMDLs were estimated for diabetes and the two non-fatal DCS (CVD incidence and IHD incidence) health outcomes (see Table 4-17) as:

$$BMD = \frac{\ln\left(odds\ at\ P(d) \Big/ odds\ at\ P(0)\right)}{\beta\ mean}$$

and

$$BMDL = \frac{\ln\left(odds\ at\ P(d) \Big/ odds\ at\ P(0)\right)}{95^{th} upper\ bound\ on\ \beta\ mean}$$

where P(d) and P(0) are the probabilities associated with 5% and 0% extra risk, respectively, and β_mean_{95} is the 95% (one-sided) upper bound on the mean(β_mean) estimated in the meta-regressions for the Logistic model slope. 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 II diabetes, CVD or IHD, which have a high, 40%, 70% and 40% probability of occurrence, respectively, within the U.S. population (see Section 4.3.4), are not frank effects and do not warrant

a lower BMR on the basis of severity. Thus, proximity to the range of data becomes the more important consideration. According to EPA benchmark dose BMD guidance (U.S. EPA, 2012), "[t]ypically, a BMR near the low end of the observable range is selected as the basis for obtaining BMDs and BMDLs to serve as potential PODs for deriving quantitative estimates below the range of observation and to use for comparisons of effective doses corresponding to a common response level across chemicals, studies, or endpoints." EPA lifetime dose estimates for the low end of the available CVD incidence, IHD incidence and diabetes studies are 0.23 μg/kg-day, 0.23 μg/kg-day and 0.13 μg/kg-day, respectively (see Appendix C, Sections C.1.2 Diabetes; Diabetes study-specific dose conversions and C.1.2 Diseases of the Circulatory System; Study-specific dose conversions). EPA meta-regression BMD_{01} estimates of 0.06 μg/kg-day, 0.07 μg/kg-day and 0.07 μg/kg-day for CVD incidence, IHD incidence and diabetes, respectively, are well below the low end of observable dose range, whereas BMD_{05} estimates of 0.32 μg/kg-day, 0.36 μg/kg-day and 0.36 μg/kg-day are well within, but still close to the low end of the observable range (See Appendix C, Section C.3). Therefore, for all meta-regression endpoints, a BMR of 0.05 is used to estimate BMDL ($BMDL_{05}$) values that will serve as the points of departure for candidate toxicity values.

For pregnancy and birth outcomes, the modeling approach taken was to apply the hybrid benchmark response approach using the study-reported beta coefficients for the association of iAs exposure to decreased fetal weight in a single epidemiological study (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.

Table 4-17. 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)
CVD incidence	Meta-regression of 2 studies	$BMDL_{05}$	0.094[a]
IHD incidence	Meta-regression of 4 studies	$BMDL_{05}$	0.128[a]
Diabetes	Meta-regression of 4 studies	$BMDL_{05}$	0.127[a]
Birth weight	(Kile et al., 2016)	$BMDL_{05}$[b]	0.23

[a] $BMDL = \frac{\ln\left(odds\ at\ P(d) / odds\ at\ P(0)\right)}{95^{th} upper\ bound\ on\ mean(\beta\ mean)}$, where P(d) and P(0) are the probabilities associated with 5% and 0% extra risk, respectively, see details and modeling results in Appendix C, Section C.3.

[b] A BMDL05 of 17.3 μg iAs/L in drinking water 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 iAs/L exposure that results in 5% of the exposed population having a birth weight below the defined adversity threshold of 2,500 g. This was then converted to 0.24 μg/kg-day total dose by multiplying by 0.012 L/kg-day (mean water consumption rate for pregnant women) and adding a 0.02 μg/kg-day median U.S. dietary background dose (Xue et al., 2010) and assuming 0 μg/kg from air (see Section 4.3.4).

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 4-18 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 4-18. 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 DCS and diabetes endpoints because the meta-regressions investigated a heterogeneous mix of multiple study populations, each of which included and adjusted for many sensitive subpopulations including smokers, sex, nutritional status, lifestage, genetic variability, and methylation capacity. In particular, for CVD incidence and diabetes, the studies that had the largest impact on the pooled slope (and hence the pooled POD) were conducted in an American Indian population, which is a sensitive subpopulation with respect to both CVD and diabetes. For CVD incidence, American Indians are approximately 30-50% more likely to suffer from heart disease than other populations in the United States (CDC table ref). For diabetes, American Indians are twice as likely to suffer from diabetes than African Americans, and three times as likely as White Americans. For IHD incidence, the study that influenced the pooled slope to the greatest degree had a study population with a much higher water consumption rate than the average US population (0.017 L/kg-day vs. 0.011 L/kg-day) and thus represents a sensitive subpopulation with respect to degree of exposure. In all the meta-regression analyses, the final pooled slope is within an approximate range of 3-fold with respect to the most sensitive individual study in the analysis, indicating a larger UF_H is not necessary. A higher UF_H is not necessary for pregnancy and birth outcomes because the Bangladeshi population that formed the basis of the 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). Overall, a 3-fold UF is warranted to account for potential interindividual differences in pharmacokinetics and toxicodynamics within these sensitive subpopulations studied 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 to 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 meta-regression 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 years. 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_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 meta-regressions. 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 pregnancy and birth outcome of birth weight was 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 meta-regression.
UF_C	See Table 4-19	Composite uncertainty factor = $UF_A \times UF_H \times UF_S \times UF_L \times UF_D$.

Table 4-19 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 4-19. 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)
CVD Incidence	0.094	1	3	1	1	1	3	0.031
IHD Incidence	0.128	1	3	1	1	1	3	0.043
Diabetes	0.127	1	3	1	1	1	3	0.042
Birth weight	0.23	1	3	1	1	1	3	0.077

4.6.4. Selection of Lifetime RfD(s)

From among the candidate toxicity values presented in Table 4-19, organ/system-specific RfD values are selected for DCS, diabetes, and pregnancy and birth outcomes. The confidence decisions about the study, evidence base, POD quantification, and overall RfD for these organ/system-specific values are fully described in Table 4-20, 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 DCS is *high,* and the overall confidence in the organ-specific RfD for pregnancy and birth outcomes is *medium-low*.

Table 4-20. Organ/System-specific oral RfDs and confidence for iAs

Confidence categories	Designation	Discussion
Diabetes RfD = 0.042 µg/kg-d		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the studies used in the hierarchical Bayesian meta-regression 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 3.2.4).

Confidence categories	Designation	Discussion
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 meta-regression 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 = 0.031 µg/kg-d, based on CVD incidence[b, c]		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the studies used in the hierarchical Bayesian meta-regression analysis of CVD incidence 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 *medium*.
Confidence in evidence base supporting this hazard	High	Confidence in the evidence base for DCS 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 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 meta-regression 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 the confidence in individual components of the overall confidence determination is also *high*.
Birth weight RfD = 0.077 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 (pregnancy and birth outcomes) is *medium* as the hazard conclusion for this endpoint was that the *moderate* evidence indicates that iAs likely causes pregnancy and birth outcomes in humansbased primarily on high and medium confidence epidemiological studies of populations with high arsenic exposure levels.
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.

Confidence categories	Designation	Discussion
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.

[a]All study evaluation details can be found on HAWC.

[b]Although CVD incidence meta-regression is only based on two studies, they are high confidence studies and the results of that meta-regression are consistent with the results for the other three DCS health outcomes, which were based on meta-regressions of four or more studies.

[c] The lowest of the two candidate toxicity values for DCS endpoints was selected as the representative value for DCS health outcome.

Table 4-21 summarizes organ/system-specific RfDs for iAs selected in the previous section.

Table 4-21. Organ/System-specific oral RfDs for iAs

System	Basis	POD (μg/kg-day)	UF_C	RfD iAs (μg/kg-day)	Confidence
DCS	CVD incidence	0.094	3	0.031	High
Diabetes	Type II diabetes mellitus	0.127	3	0.042	High
Pregnancy and birth outcomes	Birth weight	0.24	3	0.077	Medium-low

From the identified human health effects of iAs and the derived organ/system-specific RfDs for DCS effects, diabetes, and pregnancy and birth outcomes (see Table 4-21), an RfD of 0.031 μg/kg-day based on increased CVD incidence in humans was selected as the overall RfD.[47] The 0.031 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 CVD incidence (over the estimated risk at zero dose) during a lifetime. As described in Table 4-20, confidence in the RfD is *high*, based on *high* confidence in the DCS organ/system-specific RfD. The DCS organ/system-specific RfD is based on the lowest POD_{HED} using a meta-regression approach that included *high* and *medium* confidence studies. The DCS organ/system-specific RfD is expected to be protective against all noncancer adverse health effects associated with iAs and across all life stages. The decision to select the DCS organ/system-specific RfD was based on all available organ-specific RfDs in addition to overall confidence and composite uncertainty for those RfDs.

4.7. SUMMARY OF DOSE-RESPONSE MODELING 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

[47]As a reminder, the estimated background dose of 0.0365 μg/kg-day is assumed to be associated with the estimated background risk of CVD incidence.

are presented in Tables 4-3 and 4-5 for bladder cancer and lung cancer, respectively, for a range of arsenic intakes, roughly corresponding to a range of drinking water arsenic concentrations up to 100 µg/L. 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: 4.0×10^{-5} – 1.6×10^{-3}) and 2.4×10^{-3} (90% CI: 1.0×10^{-4} – 6.0×10^{-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 daily µg/kg dose are presented in the dose-response plots provided in Sections 4.3.5 and 4.3.6.[48, 49] Although a nonlinear logistic model was used in the meta-regression analyses, the resulting dose-response relationships were sufficiently linear (after visual inspection), particularly below a 0.22 µg iAs/kg-day dose, to allow for the approximation of an EPA cancer slope factor (CSF) for the cancer endpoints. . For this assessment, the CSF is defined as an estimate of the 95% upper bound lifetime extra risk (above an estimate of the U.S. risk at zero iAs dose) associated with a 1 µg iAs/kg-day dose. Defined in this way, the approximate cancer-specific slope factors for bladder cancer and lung cancer are 1.3×10^{-2} $(\mu g/kg\text{-}d)^{-1}$ and 4.6×10^{-2} $(\mu g/kg\text{-}d)^{-1}$, respectively. These CSFs can be multiplied by an estimate of a lifetime daily oral µg/kg-day dose to approximate a 95% upper bound lifetime extra risk for the endpoint in question. A combined slope factor of ***5.3×10^{-2} $(\mu g/kg\text{-}d)^{-1}$, representing the risk of developing either tumor,*** was derived assuming that individual tumor risks are normally distributed.[50]

Sections 4.3.7, 4.3.8, 4.4, and 4.5 present the full details for the dose-response modeling of diseases of the circulatory system (DCS; as represented by cardiovascular disease [CVD] incidence and mortality and fatal ischemic heart disease [IHD]), diabetes, pregnancy and birth outcomes, and and 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.

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[48]To derive the most accurate values, meta-regression models and lifetable spreadsheets should be applied in accordance with methods described by (Allen et al., 2020a); (Allen et al., 2020b).

[49]These extra risk estimates assume a constant level of 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 (Steinmaus et al., 2013); (Yuan et al., 2007);(Farzan et al., 2013a).

[50] Calculated assuming a normal distribution for the individual risk estimates and deriving the variance of the risk estimate for each tumor site from the 95% UCL and MLE linear slope estimates shown in Figure 4-7 (bladder cancer) and Figure 4-9 (lung cancer). The combined CSF is the sum of MLE slopes + 1.645*composite SD. The composite SD is the square root of the sum of the SD2 values (SQRT (((0.0127-0.0061)/1.645))^2+((0.0462-0.0186)/1.645))^2) = 0.01725. Thus, the combined CSF is (0.0186+0.0061) + 1.645*0.01725 = 5.31E-2.

For all ingestion pathway endpoints, lifetime extra risk estimates, calculated using the Bayesian meta-regression approach, are presented in relationship to mean U.S. background rates for CVD incidence, IHD incidence, fatal CVD, fatal IHD, and diabetes outcomes of 70%, 40%, 15.5%, 7.7%, and 40%, 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 risks and 5th and 95th percentile estimates from the dose-response models are presented for a range of arsenic intakes, roughly corresponding to a range of drinking water arsenic concentrations up to 100 µg/L. 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 CVD incidence, IHD incidence, and diabetes are 2.1 $\times 10^{-2}$ (90% CI: 2.0 $\times 10^{-4}$ – 6.9 $\times 10^{-2}$), 1.8 $\times 10^{-2}$ (90% CI: 3.6 $\times 10^{-4}$ – 4.6 $\times 10^{-2}$), and 1.8 $\times 10^{-2}$ (90% CI: 1.1 $\times 10^{-3}$ – 4.6 $\times 10^{-2}$), respectively.

An RfD of **0.031 µg/kg-day based on increased CVD incidence in humans** was derived in this assessment (as described in Section 4.6). This value represents the total iAs dose that would not be expected to cause an appreciable increase in risk above the U.S. background risk of developing a noncancer health effect over a lifetime of iAs exposure, including in sensitive subgroups. As described in Section 4.6, confidence in this RfD is *high*, and it is expected to be protective across all life stages and all noncancer adverse health outcomes associated with iAs. Table 4-22 summarizes the dose-response modeling results for non-cancer endpoints associated with iAs exposure.

Table 4-22. Risk metrics for non-cancer health outcomes associated with inorganic arsenic exposure

Health outcome	Meta-regression $BMDL_{05}$[a] (µg/kg-day)	Single study $BMDL_{05}$[b] (µg/kg-d)	UFs	RfDs[c] (µg/kg-d)
CVD incidence	0.094	--	3	0.031
IHD incidence	0.140	--	3	0.047
Diabetes	0.140	--	3	0.047
Pregnancy and birth outcomes	--	0.210	3	0.077
Overall RfD	--	--	--	0.031

[a]A meta-regression dose-response slope estimate that accounts for model uncertainty (see Section 4.3.4 was used with U.S. lifetables to estimate the lower bound µg/kg-day total dose ($BMDL_{05}$) associated with a 5% lifetime extra risk.

[b]The pregnancy and birth outcome POD is a BMDL (the 17.3 µg/L $BMDL_{05}$ reported in Section 4.4 was converted to a µg/kg-day total dose by multiplying by 0.011 L/kg-day and adding a 0.02 µg/kg-day dietary background dose).

[c]RfD estimates of the total chronic dose (including background iAs dose) to U.S. populations, including sensitive subpopulations, likely to be without an appreciable adverse health effects.

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