



IRIS Toxicological Review of Inorganic Arsenic

CASRN 7440-38-2

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Integrated Risk Information System
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EXECUTIVE SUMMARY

ES.1 SUMMARY OF OCCURRENCE AND HEALTH EFFECTS

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

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

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

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

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

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

ES.2 TOXICITY VALUES FOR NONCANCER AND CANCER EFFECTS

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

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

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

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

Health outcome	Hazard descriptor	BMDL ₀₅ (µg/kg-d)	UF _C	RfD (µg/kg-d)	Confidence in RfD
Diabetes	Evidence demonstrates	0.174 ^a	3	0.058	<i>High</i>
IHD		0.171 ^a	3	0.057	<i>Medium-high</i>
Fetal, newborn, and infant health outcomes	Evidence indicates (likely)	0.237 ^b	3	0.079	<i>Medium</i>
Developmental neurocognitive		0.315 ^b	3	0.105	<i>Medium</i>
Overall RfD	—	—	—	0.06	<i>Medium-High</i>

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

^bThe fetal, newborn, and infant health outcome and developmental neurocognitive PODs are BMDLs calculated as described in Sections 4.4 and 4.5.

Mean lifetime extra risks of 7.9 and 10.1 were estimated for bladder cancer and lung cancer, respectively, for a hypothetical U.S. cohort of 10,000 individuals¹ exposed for a lifetime at the U.S. drinking water standard of 10 µg/L. The cancer slope factors (CSF) provided for bladder cancer and lung cancer in Table ES-2 represent the slope of the linear trendline between the estimated 95% upper bound on lifetime extra risk and dose, from zero dose to 0.2 µg/L. These CSF values can be multiplied by other estimates of lifetime µg/kg-day dose to estimate the 95% upper bound on lifetime extra risk for the endpoint in question. As noted in Table ES-2 (footnote b), these cancer slope factors are estimated from the risk estimates in the low-dose region (corresponding to <0.2 µg/kg-day for bladder and lung cancer), which displays an approximately linear dose-response relationship. Above that dose level, the relationship becomes increasingly nonlinear and risk estimates should not be obtained using the CSF. Instead, at higher doses, the polynomial equations

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

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

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

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

^aEstimate of the 95% upper-bound lifetime extra risk per $\mu\text{g}/\text{kg} \cdot \text{day}$ oral dose above an estimate of risk at zero dose, assuming U.S. background risks are associated with a U.S. background dose of 0.0365 $\mu\text{g}/\text{kg}$, which includes 0.02 $\mu\text{g}/\text{kg} \cdot \text{day}$ from diet, 0.0165 $\mu\text{g}/\text{kg} \cdot \text{day}$ from water and 0 $\mu\text{g}/\text{kg} \cdot \text{day}$ from air (see Section 4.3.4).

^bEPA estimates of lifetime extra risk per $\mu\text{g}/\text{kg}\cdot\text{day}$ dose above background is increasingly nonlinear above 0.2 $\mu\text{g}/\text{kg}\cdot\text{day}$ for bladder (see Section 4.3.5) and lung (see Section 4.3.6) cancer. For these health outcomes, risk estimates in the nonlinear region should not be obtained from the CSF, but from the nonlinear polynomial equations provided in those sections.

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

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

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

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

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

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