ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR ARSENIC

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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ADDENDUM for ARSENIC
Supplement to the 2007 Toxicological Profile for Arsenic

Background Statement

This addendum to the Toxicological Profile for Arsenic supplements the profile that was released in 2007.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances. CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2007.

Chapter numbers in this addendum coincide with the Toxicological Profile for Arsenic (ATSDR 2007). This document should be used in conjunction with the profile. It does not replace it.

3. HEALTH EFFECTS

3.1 INTRODUCTION

A large number of studies on the toxicity of arsenic have been published since the most recent update of the ATSDR Toxicological Profile for Arsenic (Agency for Toxic Substances and Disease Registry 2007). The scope of this addendum is focused on new data in humans and on information that advances the understanding of arsenic-induced toxicity. Toxicity studies in humans primarily were selected from a recent EPA draft development document that identified studies with a low risk of bias and provided measures of arsenic exposure (EPA 2014a). All toxicity outcomes were considered for inclusion in this addendum, except for studies on well-established effects of arsenic exposure (skin lesions, hematological effects, and acute arsenicosis). Where multiple epidemiology studies were available on the same end point, the discussion focuses mainly on the strongest study designs (e.g., prospective cohort studies, case-control studies, large cross-sectional cohort studies). As it is widely accepted that arsenic is carcinogenic, studies confirming the carcinogenesis of arsenic in humans are identified, but are not reviewed in detail; however, studies on the transplacental carcinogenesis potential of arsenic are reviewed in detail. Animal studies are limited to those that focus on toxicity outcomes that are difficult to assess or have not been assessed in humans (e.g., developmental effects, transplacental carcinogenesis, toxicokinetics) and toxicity of organic arsenicals, which has a very limited database. For most toxicological end points, studies details are provided in tables, with summaries of results described in the text.

Since publication of the 2007 ATSDR Toxicological Profile for Arsenic (Agency for Toxic Substances and Disease Registry, 2007), numerous epidemiological studies have examined associations between exposure to arsenic in drinking water and various health outcomes. These have included large-scale longitudinal cohort studies, case-control studies, and cross-sectional studies. The newer studies strengthen the evidence that exposure to arsenic in drinking water can produce a wide array of health effects. Increasing levels of arsenic in drinking water and/or urinary arsenic levels have been associated with increasing risks for the following outcomes:

- death and pulmonary disease in adults and increased risk of respiratory disease in children following *in utero* and early life exposure;
- cardiovascular outcomes including arrhythmia (e.g., QTc interval prolongation), increased blood pressure and hypertension, atherosclerosis, and death from various forms of cardiovascular disease, including ischemic heart disease and stroke;
- diarrhea in children and lesions of the gums and tongue in adults;

- diabetes in children and adults;
- ocular effects, including conjunctivitis, cataract/ocular opacity, and pterygium;
- disturbances in immune responses including delayed hypersensitivity response in adults and risk of infection in infants;
- impairment of neurological function in adults including decreased peripheral nerve conduction velocity, peripheral neuropathy, and altered sensory function;
- developmental effects ranging from fetal and infant deaths, congenital heart anomalies, delays in growth and neurological development, and increased susceptibility to infections; and
- cancer of the bladder and urothelium, gastrointestinal tract, kidney, liver, lung, pancreas, and skin; with associations between *in utero* exposure and cancers of the bladder and kidney.

Recent studies also provide additional evidence for the role of genetic polymorphisms in contributing to population variability in pharmacokinetics and sensitivity to the adverse effects of exposure to arsenic. Polymorphisms that have been examined include AS3MT, cystathione-β-synthase, glutathione S-transferase π1, glutathione S-transferase ω1, methylenetetrahydrofolate reductase, and N-6 adenine-specific DNA methyltransferase 1. Individuals with polymorphisms associated with a higher monomethylarsonic acid (MMA):dimethylarsinic acid (DMA) ratio in urine may be more susceptible to arsenic-induced toxicity.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

3.2.1.3 Immunological and Lymphoreticular Effects

***Inorganic Arsenicals*.** Humoral immunity was suppressed in male C57B1/6N mice following inhalation exposure (nose-only) to arsenic trioxide (mean measured concentrations: 0, 0.064, or 1.0 mg/m^3) for 14 days (3 hours/day). The primary T cell-dependent antibody response to sheep red blood cell challenge was suppressed by >70% (data presented graphically; $p<0.05$) in both arsenic trioxide exposure groups. No effects on immune response were observed following stimulation of B cells to lipopolysaccharide or of T cells to Concavalin A. No cytotoxicity was observed in spleen cells and no effects were observed for spleen cell surface markers expression for B cells, T cells, natural killer cells, or macrophages (Burchiel et al. 2009).

3.2.2 Oral Exposure

3.2.2.1 Death

***Inorganic Arsenicals*.** Several epidemiological studies have evaluated the association between exposure to arsenic in drinking water with deaths due to respiratory disease, cardiovascular disease, and cancer. These studies are discussed in Sections 3.2.2.2 (Systemic Effects: Respiratory and Cardiovascular) and 3.2.2.7 (Cancer).

3.2.2.2 Systemic Effects

Respiratory Effects.

***Inorganic Arsenicals*.** Several epidemiological studies have examined associations between exposure to inorganic arsenic in drinking water and mortality from nonmalignant respiratory disease and morbidity, as measured by pulmonary function and respiratory symptoms (Dauphine et al. 2011; Ghosh et al. 2007; Majumdar et al. 2009; Nafeess et al. 2011; Parvez et al. 2010, 2013; Paul et al. 2013b; Pesola et al. 2012; Smith et al. 2013). Details of the individual study designs and outcomes are provided in Table 3-1. These studies have found increased risks of death and pulmonary disease in adults and increased risk of respiratory disease in children following *in utero* and early life exposure.

The risk of death due to nonmalignant respiratory disease in humans exposed to arsenic in drinking water was examined in a large prospective study of 26,043 adults in Bangladesh (Argos et al. 2014). Increased risk of mortality due to nonmalignant respiratory disease occurred, with an adjusted hazard ratios of 1.75 (95% confidence interval [CI]: 1.15, 2.66) for urine arsenic concentrations ≥332.0 µg/g creatinine, respectively. A positive trend for increasing risk with increasing urinary arsenic level (p=0.008) was observed.

The risk of nonfatal respiratory disease in humans exposed to arsenic in drinking water has been examined in prospective cohort studies in adults (Parvez et al. 2010, 2013) and children (Smith et al. 2013). The risk of clinical symptoms of respiratory disease, including cough and breathing problems, was increased in a cohort of 10,833 adults in Bangladesh exposed to arsenic in drinking water (Parvez et al. 2010). Adjusted hazard ratios for cough were increased at drinking water concentration ranges of 90–178 µg/L (adjusted hazard ratio: 1.52; 95% CI: 1.23, 1.88) and >178 µg/L (adjusted hazard ratio: 1.51; 95% CI: 1.21, 1.87). Adjusted hazard ratios for breathing problems were increased at a drinking water concentration range of 7–40 µg/L (adjusted hazard ratio: 1.44; 95% CI: 1.20, 1.74), with slightly higher risk estimates for arsenic concentration ranges of 90–178 and >178 µg/L. Similar results were observed

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Death due to lung disease				
Argos et al. 2014	Study design: prospective cohort Location: Bangladesh Population: 26,043 adults Data collection period: initial enrollment 2000–2002, with an average 8.5-year follow-up	Exposure measures: arsenic concentration in urine, adjusted for creatinine As concentration: Tertiles: - T1: <132.5 µg/g - T2: 132.5–331.9 µg/g - T3: ≥332.0	Variables assessed: death due to nonmalignant lung disease Adjustments: age, sex, BMI, education, smoking Analysis: Cox proportional hazards regression	The risk of mortality due to nonmalignant lung disease was increased in T2 and T3, compared to T2, with a positive test for trend (p=0.008). Adjusted hazard ratios (95% CI): - T2: 1.37 (0.90, 2.08) - T3: 1.75 (1.15, 2.66)
Respiratory symptoms and pulmonary function				
Dauphine et al. 2011	Study design: retrospective cohort Location: Chile Population: 32 exposed adults (mean age: 48 years; exposed to >800 µg/L before age 10); compared to 65 reference adults with high early-life exposure Data collection period: 2008	Exposure measures: arsenic concentration in drinking water calculated from municipal water sources As concentration: Tertiles: - T1: <50 µg/L - T2: 50–250 µg/L - T3: >800 µg/L	Variables assessed: any respiratory symptom, chronic cough, chronic phlegm, chronic bronchitis, trouble breathing, breathlessness upon walking fast/uphill, at group pace, at one pace, pulmonary functions tests (predicted FEV_1, predicted FVC, FEV_1 residual, FVC residual) Adjustments: age, sex, smoking, childhood secondhand smoke, use of wood, charcoal, or kerosene in childhood home, occupational air pollution, education Analysis: multivariate logistic regression	All pulmonary function tests were significantly decreased (p=0.02–0.03) in T3, but not T2, compared to T1. Trend tests across tertiles showed a statistically significant decreasing trend for all pulmonary function tests (p=0.005–0.008). In the exposed group, FEV_1 and FVC were decreased by 11.5% (p= 0.04) and 12.2% (p=0.04), respectively, compared to controls. The prevalence odd ratio was significant for breathlessness while walking at group pace (prevalence odd ratio: 5.94; 95% CI: 1.36, 26.0; p=0.009). No association was observed for other respiratory symptoms or variables.

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Ghosh et al. 2007	Study design: cross-sectional cohort Location: India Population: 725 exposed (373 with skin lesions, 352 without skin lesions), 389 controls; age range: 15–70 years Data collection period: 2003–2005	Exposure measures: arsenic concentration in drinking water in drinking water from individual participants As concentration: Range (all participants): - 0–1,188 µg/L Mean±SD: - control: 6.97±2.10 µg/L - cases (no skin lesions): 186.89±124.67 µg/L - cases (with skin lesions): 200.83±145.83 µg/L	Variables assessed: respiratory illness based on presence of history of cough, chest sounds in lungs, shortness of breath Adjustments: age, sex, smoking Analysis: logistic regression	Exposure to arsenic in drinking water was associated with a higher risk of respiratory illness compared to controls. Exposed participants with skin lesions had a higher risk of developing respiratory illness than those without skin lesions: Adjusted odds ratios (95% CI): - cases (no skin lesions): 3.21 (1.65, 6.26) - cases (with skin lesions): 13.54 (7.45, 24.62) A trend test for odds ratios was statistically significant (p<0.001).
Majumdar et al. 2009	Study design: cross-sectional cohort Location: India Population: exposed: 3,825; controls: 3,451; children and adults (age range specified as ≤9–≥60 years of age); no participants had arsenical skin lesions Data collection period: not reported	Exposure measures: drinking water from wells used by each participant. As concentration: Quintiles: - Q1: <50 µg/L - Q2: 50–199 µg/L - Q3: 200–499 µg/L - Q4: 500–799 µg/L - Q5: ≥800 µg/L	Variables assessed: chronic lung disease, diagnosed based on symptoms of cough and respiratory distress, as reported by participants to a physician, and “chest signs” (not specified) during physical examination Adjustments: none reported Analysis: Chi-square	The prevalence of chronic lung disease in female, but not male, participants in was significantly increased in Q5 compared to Q1. Prevalence odds ratios (95% CI): - males: 0.93 (0.65, 1.3) - females: 1.76 (1.1, 2.6)

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Nafeess et al. 2011	Study design: cross-sectional cohort Location: Pakistan Population: exposed: 100, controls: 100; ≥15 years of age Data collection period: 2009	Exposure measures: drinking water collected from each participant As concentration: Controls: ≤10 µg/L Exposed: - ≥100 µg/L - ≥250 µg/L	Variables assessed: respiratory symptoms (cough, phlegm, wheezing, breathlessness), pulmonary function tests (FEV_1, FVC, FEV_1/FVC) Adjustments: age, sex, height, smoking status Analysis: multivariate linear regression	For arsenic exposure to drinking water concentrations ≥100 µg/L, FVC was significantly (p=0.028) decreased by 221.9 mL, compared to controls. No statistically significant decreases in FEV_1 or FEV_1/FVC were observed. For arsenic exposure to drinking water concentrations ≥250 µg/L, FEV_1 and FVC were significantly decreased by 226.4 mL (p=0.030) and 354.8 mL (p=0.003), respectively. No statistically significant decrease in FEV_1/FVC was observed. No association was observed between arsenic exposure and symptoms of respiratory disease.
Parvez et al. 2010	Study design: prospective cohort Location: Bangladesh Population: 10,833 adults Data collection period: 2002–2006, with 4-year follow-up	Exposure measures: arsenic concentration in drinking water from primary well for each participant and urine (corrected for creatinine) As concentration: Drinking water quintiles: - Q1: ≤7 µg/L - Q2: 7–40 µg/L - Q3: 40–90 µg/L - Q4: 90–178 µg/L - Q5: >178 µg/L Urine quintiles: - Q1: ≤90 µg/g - Q2: 90–160 µg/g - Q3:160–246 µg/g	Variables assessed: chronic cough, breathing problems, and blood in sputum, evaluated by physicians Adjustments: age, sex, smoking BMI, education, skin lesion Analysis: hazard ratios determined by Cox proportional hazards models	Significant positive associations between exposure to arsenic (based on levels in drinking water and urine) and clinical symptoms of respiratory disease. For chronic cough based on arsenic concentration in drinking water, adjusted hazard ratios were significant in Q3–Q5, compared to Q1. Based on urine, adjusted hazard ratios were significant for Q4 and Q5, compared to Q1. Adjusted hazard ratios (95% CI) for cough (drinking water): - Q3: 1.40 (1.11, 1.75) - Q4: 1.57 (1.25, 1.97) - Q5: 1.60 (1.27, 2.01)

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
		- Q4: 246–406 µg/g - Q5: >406 µg/g		Adjusted hazard ratios (95% CI) for cough (urine): - Q4: 1.52 (1.23, 1.88) - Q5: 1.51 (1.21, 1.87) Adjusted hazard ratios for breathing problems were significant based on drinking water in Q2–Q5, compared to Q1, and based on urine in Q4 and Q5, compared to Q1. Adjusted hazard ratios (95% CI) for breathing problems (drinking water): - Q2: 1.44 (1.20, 1.74) - Q3: 1.52 (1.25, 1.84) - Q4: 1.42 (1.16, 1.73) - Q5: 1.41 (1.56, 1.72) Adjusted hazard ratios (95% CI) for breathing problems (urine): - Q4: 1.28 (1.06, 1.54) - Q5: 1.27 (1.05, 1.53) Hazard ratios for blood in sputum were significant drinking water for Q3 and Q4, but not Q5, compared to Q1. Hazard ratios based on urine were not significant.

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Parvez et al. 2013	Study design: prospective cohort Location: Bangladesh Population: 950 adults Data collection period: 2000–2002 with follow-up 2006–2007	Exposure measures: arsenic concentration in drinking water from primary well for each participant and urine (corrected for creatinine) As concentration: Drinking water tertiles: - T1: <19 µg/L - T2: >19–97 µg/L - T3: >97 µg/L Urine tertiles: - T1: <125 µg/g - T2: >125–285 µg/g - T3 >285 µg/g	Variables assessed: pulmonary function tests (FEV_1, FVC) Adjustments: age, sex, BMI, smoking, betel nut use, education, skin lesion Analysis: multivariate linear regression	Negative associations were observed between arsenic levels in drinking water and in urine and pulmonary function. Adjusted betas (95% CI) based on drinking water were significant for T3 for FEV_1 and FVC: - FEV_1 for T3: -80.6 (-181.4, -17.5); p=0.01 - FVC for T3: -97.3 (-181.8, -12.7); p=0.02 The adjusted betas (95% CI) based on urine was significant for T3 for FEV_1 - FEV_1 for T3: -90.5 (-173.6, -7.4); p=0.03 For each increase of 1 SD for arsenic concentration in water (118.1 µg/L), FEV_1 and FVC were decreased by 46.5 mL (p=0.01) and 53.1 mL (p=0.005), respectively. For each increase of 1 SD for arsenic concentration in urine (277.2 µg/g), FEV_1 and FVC were decreased by 48.3 mL (p=0.005) and 55.2 mL (p=0.02), respectively.
Paul et al. 2013b	Study design: cross-sectional Location: India Population: adult males and females; 189 exposed, 171 controls Data collection period: Data were collected from same participants for two time periods: 2005–	Exposure measures: drinking water from individual participants As concentration: mean±SD for 2005–2006: - controls: 4.13±3.18 - cases: 190.1±110.53 mean±SD for 2010–2011: - controls: 3.7±3.0 - cases: 37.94±27.08	Variables assessed: respiratory symptoms (persistent cough, thoracic sounds, throat irritation, shortness of breath, hoarseness) Adjustments: none Analysis: ratio of incidence in exposed to control groups	The risk of development of respiratory symptoms was significantly increased in cases compared to controls for both collection periods. Odds ratios (95% CI): 2005–2006: - 6.07 (2.47, 14.95) 2010–2011: - 11.45 (5.04, 25.97)

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
	2006 and 2010–2011			
Pesola et al. 2012	Study design: cross-sectional Location: United States (Arizona) Population: 7,568 adult nonsmokers Data collection period: not reported	Exposure measures: arsenic concentration in drinking water and urine As concentration: Drinking water quintiles: - Q1: <7 µg/L - Q2: 7–<39 µg/L - Q3: 39–<91 µg/L - Q4: 91–<179 µg/L - Q5: ≥179 µg/L Urine quintiles were not reported	Variables assessed: history of dyspnea, as determined by a physician Adjustments: age, sex, education, BMI, blood pressure Analysis: unconditional logistic regression for odds ratios; Chi-squared test for trend test	A significant positive association was observed between arsenic concentrations in drinking water and urine and dyspnea in nonsmokers for Q3–A5, compared to Q1. Positive trends (p<0.01) were observed for arsenic in drinking water and urine. Adjusted odds ratios (95% CI) for drinking water: - Q3: 1.96 (1.43, 2.70); p<0.001 - Q4: 2.14 (1.56, 2.92); p<0.001 - Q5: 1.80 (1.31, 2.49); p<0.001 Adjusted odds ratios (95% CI) for urine: - Q3: 1.92 (1.38, 2.65); p<0.001 - Q4: 1.94 (1.41, 2.68)' p<0.001 - Q5: 1.87 (1.36, 2.58); p<0.001
Smith et al. 2013	Study design: prospective cohort Location: Bangladesh Population: children with *in utero* exposure, assessed at 7–17 years of age; 491 exposed; 159 controls Data collection period: wells sampled 2002–2003; dates for data collection in children not specified	Exposure measures: arsenic concentration in drinking water *in utero* and early life (first 5 years of life) from tube wells for each participant As concentration: Tertiles: - T1 (control): <10 µg/L - T2: 10–499 µg/L - T3: ≥500 µg/L Quintiles: - Q1: <10 µg/L - Q2: 10–199 µg/L - Q3: 200–399 µg/L - Q4: 400–599 µg/L - Q5: ≥600 µg/L	Variables assessed: respiratory symptoms (cough, wheeze, shortness of breath), respiratory disease (asthma, pneumonia), pulmonary function tests (FEV_1, FVC) Adjustments: age and gender for respiratory symptoms: age, gender, height, mother's and father's education, father's smoking status, number of rooms in the house for pulmonary function Analysis: logistic regression	Analysis based on tertiles: Relative to controls, children exposed to arsenic were significantly more likely to have cough (when not having a cold), wheezing (all wheezing and wheezing when not having a cold), and shortness of breath (walking fast/uphill and walking on level ground). Significant adjusted odds ratios (95% CI): Cough: - T3: 2.53 (1.12, 5.69); p=0.01 Wheeze (all): - T2: 2.14 (1.36, 3.36); p<0.001 - T3: 2.17 (1.26, 3.75); p<0.01 Wheeze (when not having a cold): - T3: 8.41 (1.66, 42.6); p<0.01

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				Shortness of breath (walking fast/climbing): - T2:2.74 (1.18, 6.37); p<0.01 - T3: 3.19 (1.22, 8.32); p<0.01 Shortness of breath (walking on level ground): - 3.86 (1.08, 13.7); p=0.02 Asthma: - T2: 1.84 (1.04, 3.26); p=0.02 - T3: 2.33 (1.19, 4.57); p<0.01 Analysis based on quintiles: Compared to Q1, significant adjusted odds ratios were observed for all wheezing, wheezing when not having a cold, cough when not having a cold, shortness of breath when walking fast/climbing, shortness of breath when walking on level ground, and asthma. Adjusted odds ratios (95% CI): Wheezing (all): - Q2: 1.98 (1.03, 3.80) - Q3: 1.51 (0.83, 2.74) - Q4: 3.17 (1.78, 5.64) - Q5: 2.12 (1.19, 3.76) Wheezing when not having a cold: - Q4: 8.65 (1.64, 45.7) - Q5: 8.21 (1.56, 43.1) Cough without having a cold: - Q5: 2.47 (1.05, 5.79)

Table 3-1. Respiratory Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				Shortness of breath (walking fast/climbing): - Q3: 2.89 (1.06, 7.91) - Q4: 4.09 (1.56, 10.7) - Q5: 3.20 (1.18, 8.71) Shortness of breath (walking on level ground): - Q4: 4.50 (1.17, 17.3) Asthma: - Q4: 2.26 (1.13, 4.49) - Q5: 2.38 (1.17, 4.83) Statistically significant trends were observed for wheezing (p<0.001), asthma (<0.01), cough when not having a cold (p=0.03), shortness of breath when walking fast/climbing (p<0.01), shortness of breath when walking on level ground (p=0.01), and wheezing when not having a cold (p<0.01). No association was observed between arsenic exposure and pulmonary function.

As = arsenic; BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SD = standard deviation

for this cohort based on urine arsenic concentrations. Associations were observed between arsenic concentrations in drinking water and urine and decrements in pulmonary function, measured by forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), in a cohort of 950 adults in Bangladesh (Parvez et al. 2013). For each increase of 1 standard deviation (SD) for arsenic concentration in water (118.1 µg/L), FEV_1 and FVC were decreased by 46.5 mL (p=0.01) and 53.1 mL (p=0.005), respectively. For each increase of 1 SD for arsenic concentration in urine (277.2 µg/g creatinine), FEV_1 and FVC were decreased by 48.3 mL (p=0.005) and 55.2 mL (p=0.02), respectively. The risk of asthma and respiratory symptoms was increased in a cohort of 491 children (aged 7–17 years) exposed *in utero* and throughout childhood (Smith et al. 2013). Elevated risk of asthma was observed at drinking water concentration ranges of 400–599 µg/L (adjusted odds ratio: 2.26; 95% CI: 1.13, 4.49) and ≥600 µg/L (2.38; 95% CI: 1.17, 4.83). Similarly, adjusted hazard ratios for symptoms of respiratory disease (wheeze and shortness of breath) were increased at arsenic drinking water ranges of 200–399 µg/L and higher. Retrospective cohort and cross-sectional studies also show increased risks for decreased pulmonary function and symptoms of respiratory disease (Dauphin et al. 2011; Ghosh et al. 2007; Majumdar et al. 2009; Nafeess et al. 2011; Paul et al. 2013b; Pesola et al. 2012).

Cardiovascular Effects.

***Inorganic Arsenicals*.** Several epidemiological studies have examined effects of exposure to inorganic arsenic in drinking water and effects on the cardiovascular system, including death due to, and incidence or prevalence of, cardiovascular disease, cardiac arrhythmias, increased blood pressure, pulse pressure and hypertension, and atherosclerosis. Details of the individual study designs and outcomes are provided in Table 3-2. In general, these studies have found increased risk in association with exposures to arsenic in drinking water and/or urinary arsenic concentrations for the following cardiovascular outcomes: arrhythmia (e.g., QTc interval prolongation), increased blood pressure and hypertension, atherosclerosis, and death from various forms of cardiovascular disease, including ischemic heart disease and stroke.

Risk of death due to cardiovascular disease in humans exposed to arsenic in drinking water have been examined in several prospective cohort studies (Chen et al. 2011b; Liao et al. 2012; Moon et al. 2013; Rahman et al. 2014; Wade et al. 2009). Most of these studies found positive associations (Chen et al. 2011b; Moon et al. 2013; Rahman et al. 2014; Wade et al. 2009). Increased risk for cardiovascular-related deaths occurred in association with drinking water arsenic concentrations ranging from 50 to 900 µg/L. The largest prospective cohort studies were conducted in Bangladesh (Chen et al. 2011b; Rahmann et al. 2014). The Chen et al. (2011b) study (11,746 adults) found increased risk of mortality due to heart disease in association with drinking water concentrations ranging from 148.1 to 864.0 µg/L

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Death due to cardiovascular disease				
Chen et al. 20011b	Study design: prospective cohort Location: Bangladesh Population: 11,746 men and women Data collection period: initial assessment in 2000, with an average 6-year follow-up	Exposure measures: arsenic in 5,966 contiguous wells in the area As concentration range: Quartiles: - Q1: 0.1–12.0 µg/L - Q2: 12.1–62.0 µg/L - Q3: 62.1–148.0 µg/L - Q4: 148.1–864.0 µg/L	Variables assessed: death due to cardiovascular disease (circulatory disease, ischemic heart disease and other forms of heart disease, ischemic heart disease, cerebrovascular disease) Adjustments: sex, age, smoking, education, changes in urinary arsenic concentration (adjusted for creatinine) between visits Analysis: Cox proportional hazards	A dose-response relationship was observed for arsenic exposure in drinking water and mortality from ischemic heart disease and other heart disease (p=0.0019) and from ischemic heart disease (p=0.0294). Hazard ratios (95% CI) for ischemic heart disease and other heart disease: - Q1: 1 - Q2: 1.22 (0.65, 2.32) - Q3: 1.35 (0.71, 2.57) - Q4: 1.92 (1.07, 3.43) Hazard ratios (95% CI) for ischemic heart disease: - Q1: 1 - Q2: 1.22 (0.56, 2.65) - Q3: 1.49 (0.70, 3.19) - Q4: 1.94 (0.99, 3.84) No relationship was observed for exposure to arsenic in drinking water and death due to circulatory disease or cerebrovascular disease.
Liao et al. 2012	Study design: prospective cohort Location: Taiwan Population: 380 exposed; 303 controls Data collection period: 2002	Exposure measures: cumulative arsenic exposure, based on arsenic concentrations in artisan wells As concentration range: - <14.6 mg/L-year - >14.7 mg/L-year	Variables assessed: death due to cardiovascular disease Adjustments: age, gender, smoking, hypertension, diabetes Analysis: Cox proportional hazards	Compared to controls, no association was observed between cumulative arsenic exposure and death due to cardiovascular disease (hazard ratio: 1.89; 95% CI: 0.50, 7.10).

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Moon et al. 2013	Study design: prospective cohort Location: United States Population: 3,575 adult American Indian males (40%) and females (60%) Data collection period: baseline 1989–1991; follow-up through 2008	Exposure measures: arsenic concentration in urine, corrected for creatinine As concentration range: Quartiles: - Q1: <5.8 µg/g - Q2: 5.8–9.7 µg/g - Q3: 9.8–15.7 µg/g - Q4: >15.7 µg/g	Variables assessed: death due to cardiovascular disease, coronary heart disease, and stroke Adjustments: study center, age, sex, education, smoking, BMI, LDL cholesterol Analysis: Cox proportional hazards	For the highest exposure group, but not lower exposure groups, significant elevated risk of death due to cardiovascular disease, coronary artery disease, and stroke was observed. Adjusted hazard ratios (95% CI) for the Q4 group: - cardiovascular disease: 1.65 (1.20, 2.27 - coronary artery disease: 1.71 (1.19, 2.44) - stroke: 3.03 (1.08, 8.50) A positive trend was observed for mortality due to cardiovascular disease ($p<0.001$) and coronary artery disease ($p<0.001$), but not mortality due to stroke ($p=0.061$). Note that hypertension, diabetes, and kidney disease were identified as confounding factors.

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rahman et al. 2014	Study design: prospective cohort Location: Bangladesh Population: 61,074 adults; males: 42.5%; females: 57.5% Data collection period: 2003–2010	Exposure measures: arsenic concentration in drinking water As concentration: Tertiles - T1: <10 µg/L - T2: 10–49 µg/L - T3: ≥50 µg/L	Variables assessed: Adjustments: age, sex, education, socio-economic status Analysis: Cox proportional hazards	Exposure to arsenic in drinking water was associated with an increased risk of mortality due to stroke. The association was significant for combined males and females and for females, but not males, exposed to ≥50 µg/L. Significant trends were observed for combined males and females (p=0.00058) and for females (p=0.00004), but not males (p=0.45). Adjusted hazard ratios (95% CI): Males and females: - T1: 1 - T1: 1.20 (0.92, 1.57) - T3: 1.35 (1.04, 1.75) Females: - T1: 1 - T2: 1.31 (0.87, 1.98) - T3: 1.72 (1.15, 2.57)
Wade et al. 2009	Study design: retrospective cohort Location: China Population: 572 males (57%) and females (43%); children (<16 years: ~4%) and adults (~96%) Data collection period: 1997–2004	Exposure measures: arsenic concentration in drinking water from each household As concentration range: Quintiles: - Q1: 0–5 µg/L - Q2: 5.1–20 µg/L - Q3: 20.1–100 µg/L - Q3: 100.1–300 µg/L - Q4: >300 µg/L	Variables assessed: mortality due to heart disease and stroke Adjustments: age, sex, education, smoking, drinking, farm work Analysis: multivariate Poisson regression	A significant association was observed between arsenic concentration in drinking water and death due to heart disease at arsenic concentrations >300 µg/L (adjusted incidence ratio risk: 5.08; 95% CI: 1.45, 17.81; p=0.011). No association was observed at lower drinking water arsenic concentrations and mortality due to cardiovascular disease or for any drinking water arsenic concentration and mortality due to stroke.

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Incidence of cardiovascular disease				
Moon et al. 2013	Study design: prospective cohort Location: United States Population: 3,575 adult American Indian males (40%) and females (60%) Data collection period: baseline 1989–1991; follow-up through 2008	Exposure measures: arsenic concentration in urine, corrected for creatinine As concentration range: Quartiles: - Q1: <5.8 µg/g - Q2: 5.8–9.7 µg/g - Q3: 9.8–15.7 µg/g - Q4: >15.7 µg/g	Variables assessed: incidence of fatal and nonfatal cardiovascular disease, coronary heart disease, and stroke Adjustments: study center, age, sex, education, smoking, BMI, LDL cholesterol Analysis: Cox proportional hazards	For Q4, but not lower quartiles, significant elevated risk for incidence of cardiovascular disease and coronary artery disease was observed. Adjusted hazard ratios (95% CI) for the >15.7 µg/g group: - cardiovascular disease: 1.65 (1.20, 2.27) - coronary artery disease: 1.71 (1.19, 2.44) - stroke: 3.03 (1.08, 8.50) A positive trend was observed for cardiovascular disease (p<0.001), coronary artery disease (p<0.004) and stroke (p=0.061). Note that hypertension, diabetes, and kidney disease were identified as confounding factors.
Xia et al. 2009	Study design: cross-sectional Location: China Population: 12,309 male (50%) and female (50%) children (≤16 years: ~18%) and adults (≥17 years: ~82%) Data collection period: not reported	Exposure measures: arsenic concentration collected from individual households As concentration range: Mean: 37.94 µg/L Range: 0.05–637.7 µg/L	Variables assessed: cardiovascular disease (self-reported, doctor diagnosed Adjustments: gender, alcohol use, occupation, farm work, water source Analysis: logistic regression	A borderline association for cardiovascular disease with arsenic exposure was observed in males (odds ratio: 1.10, p=0.07), but not females (odds ratio: 0.99, p=0.80). The presence of arsenic-induced skin lesions was associated with cardiovascular disease (odds ratio: 1.62, p<0.01) but not associated with stroke (odds ratio 1.04, p=0.89).

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Cardiac arrhythmias				
Chen et al. 2013b	Study design: prospective cohort Location: Bangladesh Population: 1,715 male (61%) and female (39%) adults (HEALS participants); age range 20–77 years Data collection period: 2005–2010	Exposure measures: concentration of arsenic in well water (measured in 10,971 contiguous wells) and urine (adjusted for urinary creatinine) As concentration range: - well water: 0.1–790 µg/L - Urinary As: 7–4,306 µg/g creatinine	Variables assessed: PR interval, QRS duration and QTc interval (QT interval corrected for heart rate); QTc prolongation defined as ≥450 mseconds in men and ≥460 mseconds in women) Adjustments: sex, age, BMI, smoking status, education Analysis: linear regression using continuous dependent variable	Based on the adjusted odds ratio for a 1-SD increase in baseline well water (108.7 µg/L) and in urinary arsenic concentration (270.7 µg/g creatinine), a positive association was observed for QTc prolongation in women. Adjusted odds ratio (95% CI): - well water arsenic: 1.24 (1.05, 1.47) - urinary arsenic: 1.24 (1.01, 1.53) A positive trend for QTC prolongation in women was also observed for both well water (p=0.01) and urinary arsenic (p=0.04). No associations for QTc prolongation in men or PR or QRS prolongation in men or women were observed.
Morduhkovich et al. 2009	Study design: cross-sectional cohort Location: USA (Boston, Massachusetts area) Population: 226 males; mean age 73 Data collection period: 2000–2002 or 2006	Exposure measures: arsenic concentration in toenails As concentration range: mean 0.069 µg/g; range 0.052–0.11 µg/g	Variables assessed: QT and QTc interval Adjustments: age, body mass index, mean arterial pressure, fasting glucose, serum C-reactive protein, smoking, calcium channel blocker use, antioxidant use Analysis: multivariate linear regression	Positive association between toenail arsenic concentration and QT and QTc interval duration. - QT interval increase of 3.8 mseconds per interquartile range arsenic toenail concentration (corresponding to a 0.059 µg/g increment of toenail arsenic concentration); p<0.05 - QTc increase of 2.5 msec per interquartile range arsenic toenail concentration; p<0.05

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Wang et al. 2009b	Study design: cross-sectional cohort Location: Taiwan Population: 441 exposed (257 with 0.1–19.9 mg/L cumulative arsenic exposure and 184 with ≥20 mg/L cumulative arsenic exposure); 194 controls Data collection period: not reported	Exposure measures: arsenic measured in drinking water (measured in main wells from each village); lifetime cumulative exposure (arsenic concentration in drinking water x duration of exposure As cumulative exposure: - ~0 mg/L-year - 0.1–19.9 mg/L-year - ≥20 mg/L-year	Variables assessed: P wave duration, PR interval, QRS duration, QT and QTc interval (>460 mseconds) Adjustments: age, gender, hypertension, diabetes mellitus, serum total cholesterol and triglyceride levels, BMI, smoking, alcohol consumption Analysis: multiple logistic regression	Statistically significant (p<0.001) exposure-related trends were observed for increased duration of QT and QTc intervals. Significant associations were observed between QTc interval and ischemic heart disease and carotid intima-medium thickness and plaque. No apparent associations were observed between cumulative arsenic exposure and P wave duration, PR interval and QRS duration.
Hypertension/blood pressure				
Chen et al. 2012b	Study design: cross-sectional cohort Location: Taiwan Population: 240 adults; 95 males and 145 females (60 per quartile); lowest quartile treated as control Data collection period: not reported	Exposure measures: urine arsenic (adjusted for urinary creatinine) As concentration range: - Q1: <1.4 µg/g creatinine - Q2: 1.4–4.3 µg/g creatinine - Q3: 4.3–8.0 µg/g creatinine - Q4: >8.0 µg/g creatinine	Variables assessed: blood pressure (hypertension defined as average systolic blood pressure ≥130 mmHg, average diastolic blood pressure ≥85 mmHg, and/or history of hypertension that was regularly treated with antihypertensive drugs) Adjustments: not reported Analysis: unconditional logistic regression	A statistically significant trend (p=0.021) between urine arsenic concentration and risk of hypertension was observed. Odds ratio for development of hypertension was significant in Q2 (odds ratio: 2.1; 95% CI: 1.0–4.4; p<0.05) and Q4 (odds ratio: 3.0; 95% CI: 1.4–6.3; p<0.01)

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Guha-Mazumder et al. 2012	Study design: case-control (recruited from a cross-sectional study) Location: India (West Bengal) Population: 208 cases; 100 controls; age range 15–74 years Data collection period: not reported	Exposure measures: arsenic measured in wells of each participant; cumulative arsenic exposure (mg/L-year) and arsenic concentration in urine and hair As cumulative exposure: - 0–4.5 mg/L-year - >4.5 mg/L-year As concentration in hair: - 0–0.18 mg/kg - 0.19–2.0 mg/kg - >2.0 mg/kg	Variables assessed: blood pressure (hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) Adjustments: age, sex, BMI Analysis: multivariate logistic regression	A positive association between cumulative exposure to >4.5 mg/L-year and hypertension was observed. Adjusted odds ratio: 2.87 (95% CI: 1.26, 4.83). A dose-response relationship was observed between increasing cumulative arsenic exposure and arsenic level in hair and hypertension (p-values not reported).
Hawkesworth et al. 2013	Study design: prospective cohort Location: Bangladesh Population: 2,499 child-mother pairs Data collection period: 2000–2004 and 2007–2009	Exposure measures: maternal urine arsenic at weeks 8 and 30 of gestation; urine arsenic in children at 18 months Urine As concentration: - maternal (8 weeks): 80 µg/L (10^{th}, 90^{th} percentile: 24, 383 µg/L) - maternal (30 weeks): 83 µg/L (10^{th}, 90^{th}: 26, 415 µg/L) at week 30 - child (18 months): 34 µg/L (10^{th}, 90^{th} percentile: 12, 154 µg/L)	Variables assessed: diastolic and systolic blood pressure children at 4.5 years of age Adjustments: sex, age, parental wealth index, height at 4.5 years, season of birth, maternal early pregnancy blood pressure Analysis: log-transformed linear regression	*In utero* exposure to arsenic was associated with a minimal increase in blood pressure at 4.5 years of age. Each 1 mg/L increase in maternal urinary arsenic during pregnancy was associated with a 3.69 mmHg (95% CI: 0.74, 6.63; p=0.01) increase in child systolic and a 2.91 mmHg (95% CI: 0.41, 5.42; p=0.02) increase in child diastolic blood pressure. Adjusted beta (95% CI), based on combined 8- and 30-week maternal urine arsenic: - systolic: 3.69 (0.74, 6.63) - diastolic: 2.91 (0.41, 5.42) A 1 mg/L increase in child urinary arsenic 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. Adjusted beta (95% CI), based on child urine arsenic: - systolic: 8.25 (1.37, 15.1)

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				- diastolic: 2.75 (-3.09, 8.59)
Islam et al. 2012a	Study design: cross-sectional Location: Bangladesh Population: 1,004 adult males and females Data collection period: 2009	Exposure measures: arsenic concentration in drinking water (from wells of each participant) As concentration: Quartiles: - Q1: 10–22 µg/L - Q2: 23–32 µg/L - Q3: 33–261 µg/L - Q4: >262 µg/L	Variables assessed: systolic blood pressure ≥140 mmHg (systolic hypertension), diastolic blood pressure ≥90 mmHg (diastolic hypertension), elevated pulse pressure (≥55 mmHg). Adjustments: age, sex, education, marital status, religion, monthly income, BMI Analysis: multiple logistic regression; Cuzick's nonparametric test for trend	A dose-response relationship (p for trend <0.01) between arsenic concentration in drinking water and increased pulse pressure was observed, based on exposure quartiles. Adjusted odds ratios (95% CI): - Q1: 1 - Q2: 3.87(1.22, 12.20) - Q3: 4.32 (1.23, 15.11) - Q4: 7.32 (2.18, 24.60) No association was observed between arsenic concentration in drinking water and hypertension.
Jones et al. 2011	Study design: cross-sectional Location: United States (national; NHANES) Population: 4,167 adults, ≥20 years of age Data collection period: 2003–2008	Exposure measures: concentrations of total arsenic and DMA in urine As concentration: Total arsenic median: 8.3 µg/L Total DMA: 3.6 µg/L	Variables assessed: hypertension, defined as a mean systolic blood pressure ≥140 mmHg, a mean diastolic blood pressure ≥90 mmHg, a self-reported physician diagnosis, or use of antihypertensive medication. Adjustments: age, sex, race, ethnicity, education, BMI, serum cotinine, urine creatinine levels Analysis: logistic regression	No association was observed between urinary total arsenic or DMA concentration and systolic or diastolic blood pressure.

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Kunrath et al. 2013	Study design: cross-sectional Location: Romania Population: normotensive adult men; 19 exposed, 16 controls Data collection period: not reported	Exposure measures: arsenic concentration in drinking water (from main drinking water source for each participant) As concentration range (mean±SD): - controls: 1.0±0.2 µg/L - cases: 40.2±30.4 µg/L	Variables assessed: blood pressure (hyperreactivity defined as a combined stress-induced change in systolic pressure of >20 mmHg and diastolic pressure of >15 mmHg) under conditions of anticipatory stress (anticipation to cold exposure) and cold stress Adjustments: none reported Analysis: multivariate ANOVA and logistic regression	Compared to controls, cases had a higher percentage of individuals with blood pressure hyperreactivity to anticipatory stress (12.5 versus 47.4%, p=0.035) and cold stress (37.5 versus 73.7%; p=0.044). Logistic regression analysis showed that blood pressure hyperactivity was associated with arsenic concentration in drinking water. Odds ratios (95% CI): - anticipatory stress: 6.30 (1.11, 35.67); p=0.038 - cold stress: 4.67 (1.11–19.65); p=0.036
Li et al. 2013a	Study design: cross-sectional Location: China (Inner Mongolia) Population: 669 adult males and females; Data collection period: not reported	Exposure measures: arsenic concentration in drinking water (from main drinking water source for each participant), cumulative exposure for each participant As concentration: Range: 0–760 µg/L Tertiles: T1: <10 µg/L T2:10–50 µg/L T3: >50 µg/L	Variables assessed: blood pressure (hypertension defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or history of hypertension under regular treatment with antihypertensive agents) Adjustments: gender, age, smoking, alcohol consumption, BMI, cumulative arsenic exposure, diabetes Analysis: multiple logistic regression	The risk of hypertension for the highest tertile was 1.937 (95% CI: 1.018, 3.687) and was significantly increased (p<0.05) compared to the lowest tertile. The adjusted odds ratio for T2 was not significant compared to the lowest exposure group. A dose-response trend for prevalence of hypertension was observed (p-value not reported).

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Li et al. 2013b	Study design: cross-sectional Location: China (Shanyin county of Shanxi province) Population: 604 adult males (42%) and females (58%) Data collection period: not reported	Exposure measures: cumulative arsenic exposure (based on arsenic in main drinking water source for each participant and duration of residence); urine arsenic concentration (adjusted for creatinine) As cumulative exposure: Range: 0–0.65 mg/L-year Tertiles: - T1: <0.10 mg/L-year - T2: 0.10–0.35 mg/L-year - T3: >0.35mg/L-year Total urinary As: Tertiles: - T1: <93.77 µg/g - T2: 93.77–250.61 µg/g - T3: >250.61 µg/g	Variables assessed: blood pressure (hypertension defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or history of hypertension under regular treatment with antihypertensive agents) Adjustments: gender, age, smoking, alcohol consumption, BMI Analysis: multiple logistic regression	For the T3, a positive association was observed, based on arsenic cumulative exposure (adjusted odd ratio: 1.871; 95% CI: 1.022, 3.424). The adjusted odds ratio based on total urinary arsenic was 1.648 (95% CI: 0.999, 2.721). Significant trends were observed for increased risk of hypertension based on arsenic cumulative exposure (p=0.040) and on total urinary arsenic (p=0.046).

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Wang et al. 2011	Study design: prospective cohort Location: Taiwan Population: 352 adult males (46%) and females (54%) Data collection period: 1990 to 2002–2003	Exposure measures: arsenic concentration in drinking water (main drinking water source for each participant);cumulative arsenic exposure; urine arsenic concentration (adjusted for creatinine) As in drinking water: Tertiles: - T1: <538 µg/L - T2: 538–700 µg/L - T3: >700 µg/L As cumulative exposure: Tertiles: - T1: <5.6 mg/L-year - T2: 5.6–15.6 mg/L-year - T3: >15.6 mg/L-year As(V) in urine: Tertiles: - T1: <1.20 µg/g - T2: 1.20–2.67 µg/g - T3: >2.67 µg/g	Variables assessed: blood pressure (hypertension defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or history of hypertension under regular treatment with antihypertensive agents) Adjustments: age Analysis: multivariate analysis	Compared to T1, an association was observed between urinary As(V) and hypertension (adjusted relative risk: 2.43; 95% CI%: 1.10, 5.86; p=0.047) for T3. No association was observed for T2. No association was observed between cumulative arsenic exposure or arsenic concentration in drinking water and hypertension. Diastolic blood pressure increased with increased cumulative arsenic exposure (beta=0.27; p<0.001).

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Atherosclerosis/carotid thickness/carotid plaque				
Chen et al. 2013a	Study design: cross-sectional cohort Location: Bangladesh Population: 959 adult males (40%) and females (60%) (HEALS participants) Data collection period: 2010–2011	Exposure measures: arsenic concentration in drinking water from 10,971 tube wells; arsenic concentration in urine (adjusted for creatinine) As in drinking water: - mean 81.1 µg/L - 10^{th}–90^{th} percentiles: 1–225 µg/L As in urine: - Mean: 259.5 µg/g - 10^{th}-90^{th} percentiles: 60.3–538.6 µg/g	Variables assessed: carotid intima-media thickness Adjustments: gender, age, BMI, smoking, systolic blood pressure, diabetes Analysis: multiple linear regression using continuous dependent variable	Every 1 SD increases in urinary arsenic concentration (357.9 µg/g creatinine) was associated with an increase of 11.7 µm in carotid intima-media thickness. - adjusted Beta: 11.7 µm/357.8 µg/creatinine (95% CI: 1.8, 21.6); p=0.020 Every 1 SD increase in well water concentration (102.0 µg/L) was associated with an increase of 5.1-µm in carotid intima-media thickness, although the association was not statistically significant (p=0.058). - adjusted Beta: 5.1 µm/102.5 µg/gL (95% CI: −0.2, 10.3)
Hsieh et al. 2008b	Study design: case control Location: Taiwan Population: adult males and females; 235 cases; 244 controls Data collection period: 1997–1998	Exposure measures: well water (individual homes); cumulative arsenic exposure As in drinking water: Tertiles: - T1: ≤10 µg/L - T2: 10.1–50.0 µg/L - T3: ≥50.1 µg/L Cumulative As exposure: Tertiles: - T1: ≤0.2 mg/L-year - T2: 0.3–1 mg/L-year - T3: ≥1.1 mg/L-year	Variables assessed: presence of carotid atherosclerosis based on ultrasound results for intima-media thickness (≥1.0 mm), plaque (occurrence in at least two locations) and presence of stenosis >50% in the left or right common carotid artery Adjustments: age, gender Analysis: multiple logistic regression	A significant trend was observed for the relationship between both arsenic concentration in well water (p=0.0049) and cumulative arsenic exposure (p=0.0047) and carotid atherosclerosis. A positive association was observed for T3 based on arsenic concentration in well water and for arsenic cumulative exposure and carotid atherosclerosis. Adjusted odds ratios (95% CI) for well water: - T1: 1.0 - T2: 1.5 (0.7, 2.1) - T3: 2.4 (1.2, 4.6); p<0.05

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				Adjusted odds ratios (95% CI) for cumulative arsenic exposure: - T1: 1.0 - T2: 1.1 (0.5, 2.1) - T3: 1.9 (1.1, 3.1); p<0.05
Li et al. 2009	Study design: cross-sectional cohort Location: southwestern Taiwan Population: adults males (41%) and females (59%); 145 exposed; 345 controls Data collection period: 2002–2004	Exposure measures: arsenic concentration in drinking water (obtained from previous surveys of village well water); cumulative arsenic exposure As in drinking water: Tertiles: - T1: <1 µg/L - T2: 1–700 µg/L - T3: >700 µg/L Cumulative As exposure: Tertiles: - T1: <0.1 mg/L-year - T2: 0.1–15.0 mg/L-year - T3: >15 mg/L-year	Variables assessed: carotid atherosclerosis (defined as carotid artery intima-media wall thickness of >1.0 mm) Adjustments: age, gender, BMI, smoking, cholesterol (LDL-HDL), hypertension, diabetes Analysis: multiple logistic regression	Prevalence of carotid atherosclerosis was increased in cases compared to controls Adjusted odds ratios (95% CI) for arsenic in drinking water: - T1: 1 - T2: 3.04 (1.48, 6.24); p<0.01 - T3: 1.99 (0.90, 4.37) Adjusted odds ratios (95% CI) for cumulative arsenic exposure: - T1: 1 - T2: 2.20 (0.95, 5.09) - T3: 2.74 (1.34, 5.60); p<0.01 A dose-response trend was positive for arsenic cumulative exposure and carotid atherosclerosis (p<0.003), but not for arsenic concentration in drinking water and carotid atherosclerosis.
Osorio-Yanze et al. 2013	Study design: cross-sectional cohort Location: Mexico Population: 199 male (54%) and female (46%) children 3–14 years of age Data collection period: not reported	Exposure measures: arsenic concentration in urine As concentration range: Tertiles: - T1: <35 µg/L (used to represent the permissible limit for occupational exposure) - T2: 35–70 µg/L - T3: >70 µg/L	Variables assessed: carotid intima-media thickness Adjustments: atherogenic index (total cholesterol/LDL), BMI, age, plasma asymmetric dimethylarginine (a predictor of cardiovascular disease) Analysis: multivariate linear regression	Compared to T1, T3 was associated with a 0.058 mm increase in carotid intima-media thickness (p=0.003). No association for carotid intima-media thickness was observed T2. Adjusted Betas (95% CI): - T1: 1 - T2: 0.035 mm per µg/L (-0.0028–0.072); p=0.070 - T3: 0.058 mm per µg/L (0.0198–0.095); p=0.003

Table 3-2. Cardiovascular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Wu et al. 2010	Study design: case control Location: Taiwan Population: adult males and females; Lanang cohort: low exposure (250 cases; 256 controls); LMN cohort: high exposure (117 cases; 164 controls) Data collection period: 1998–1999	Exposure measures: arsenic concentration in drinking water from each participants house As concentration range: Lanang cohort quintiles: - Q1: ≤10 µg/L - Q2: 10.1–50 µg/L - Q3: 50.1–100 µg/L - Q4: 100.1–300 µg/L - Q5: >300 µg/L LMN cohort tertiles: - T1: ≤300 µg/L - T2: 300–750 µg/L - T3: >750 µg/L	Variables assessed: carotid atherosclerosis (measured by extracranial carotid artery intima-media thickness and plaque) Adjustments: age, sex, hypertension history, diabetes history Analysis: logistic regression	The risk of atherosclerosis was associated with increased arsenic concentration in drinking water for both low and high exposure cohorts. A positive trend also was observed for high, but not low, exposure cohort ($p<0.05$). Adjusted odds ratios (95% CI) for Lanang cohort: - Q1:1 - Q2: 2.68 (0.70, 9.56) - Q3: 2.98 (1.21, 7.34); $p<0.05$ - Q4: 3.07 (1.23, 7.65); $p<0.05$ - Q5: 2.62 (1.04, 6.60); $p<0.05$ Adjusted odds ratios (95% CI) for LMN cohort: - T1: 1 - T2:1.93 (0.81–4.60) - T3: 2.78 (1.14–6.78); $p<0.05$

ANOVA = analysis of variance; As = arsenic; BMI = body mass index; CI = confidence interval; DMA = dimethylarsinic acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NHANES = National Health and Nutrition Examination Survey; SD = standard deviation

(adjusted hazard ratio: 1.92; 95% CI: 1.07, 3.43). The Rahman et al. (2014) study (61,074 adults) found increased risk of death due to stroke in females (but not males) in association with drinking water concentrations ≥50 µg/L (adjusted hazard ratio: 1.72; 95% CI: 1.15, 2.57). A retrospective cohort study conducted in China (572 adults) found increased risk of death due to heart disease associated with exposure to drinking water concentrations >300 µg/L (adjusted incidence ratio risk: 5.08; 95% CI 1.45, 17.81; Wade et al. 2009). Increased risk of cardiovascular death was also associated with urinary arsenic in a prospective cohort study conducted in the United States (3575 adults; Moon et al. 2013). The highest risk was for stroke (adjusted hazard ratio: 3.03; 95% CI: 1.08, 8.50), which occurred in association with urinary arsenic levels >15.7 µg/g creatinine.

Several studies have examined increased risk of nonfatal cardiovascular disease in humans exposed to arsenic in drinking water (Chen et al. 2012b, 2013a, 2013c; Guha-Mazumder et al. 2012; Hawkesworth et al. 2013; Hsieh et al. 2008b; Islam et al. 2012a; Jones et al. 2011; Li et al. 2009, 2013a, 2013b; Morduhkovich et al. 2009; Osorio-Yanze et al. 2013; Wang et al. 2009a, 2011; Wu et al.2010). Morbidity outcomes have included coronary artery disease, stroke, increased blood pressure, and cardiac arrhythmias. Increased risks occurred in association with drinking water arsenic concentrations and were also associated with increased urinary arsenic levels.

Case-control studies have found increased risk of coronary artery disease in association with exposure to arsenic in drinking water (Hsieh et al. 2008b; Wu et al. 2010). In the Hsieh et al. (2008b) study (235 cases, Taiwan), occurrence of carotid atherosclerosis was associated with increasing well water concentration and cumulative exposure. Risk was elevated in association with well water concentrations >50 µg/L (adjusted odds ratio: 2.4; 95% CI: 1.2, 4.6). In the Wu et al. (2010) study (250 cases, Taiwan), risk of carotid atherosclerosis was elevated in association with drinking water concentrations of 50–100 µg/L (adjusted odds ratio: 2.98 (95% CI: 1.21, 7.34). Elevated risk of carotid atherosclerosis was also found in several cross-sectional cohort studies (Chen et al. 2013a; Li et al. 2009; Osorio-Yanze et al. 2013). In the Li et al. (2009) study (adults; 145 exposed; 345 controls; Taiwan), the adjusted odds ratio for carotid atherosclerosis was 3.04 (95% CI: 1.48, 6.24) in association with drinking water arsenic levels of 1–700 µg/L. The Osorio-Yanze et al. (2013) study evaluated thickening of the carotid intima-media in children (199 children, Mexico) and found thickening to be significantly associated with urinary arsenic levels. The estimated strength of the effect was a 58 µm increase per µg As/L urine (95% CI: 19.8, 95) in subjects who had urinary arsenic levels >70 µg/L. Chen et al. (2013a) also found a significant association between carotid thickening and urinary arsenic levels (959 adults, Bangladesh). The effect size was 11.7 µm per 357.8 µg As/g creatinine (95% CI: 1.8, 21.6).

Associations between arsenic exposure in drinking water and cardiac arrhythmias have been studied in a prospective cohort study and in several cross-sectional cohort studies (Chen et al. 2013b; Morduhkovich et al. 2009; Wang et al. 2009a). The largest of the studies was a prospective cohort study conducted in Bangladesh (1,715 adults; Chen et al. 2013b). Risk of QTc interval prolongation was elevated in females (but not males). The adjusted odds ratio in females was 1.24 (95% CI: 1.05, 1.47) for a 108.6 µg/L increase in well water arsenic concentration and 1.24 (95% CI: 1.01, 1.53) for a 270.7 µg/g creatinine increase in urinary arsenic level. Prolongation of QTc interval was also observed in a cross-sectional cohort study (411 adults, Taiwan) in association with cumulative exposures to arsenic in drinking water over the range 0.1–>20 mg/L-year (Wang et al. 2009a).

Associations between arsenic in drinking water and blood pressure have been studied in cohort and case-control studies. Outcomes evaluated have included increased blood pressure, increased pulse pressure, and hypertension (Chen et al. 2012b; Guha-Mazumder et al. 2012; Hawkesworth et al. 2013; Islam et al. 2012a; Jones et al. 2011; Kunrath et al. 2013; Li et al. 2013a, 2013b; Wang et al. 2011). A case-control study conducted in India (280 cases) found a significant association between cumulative exposure to arsenic in well water and hypertension (Guha-Mazumber et al. 2012). The adjusted odds ratio for hypertension associated with cumulative exposure >4.5 mg/L-year was 2.87 (95% CI: 1.26, 4.83). In a prospective cohort study (352 adult subjects, Taiwan), risk of hypertension was elevated in association with urinary arsenic levels >2.67 µg/g creatinine (adjusted relative risk: 2.43; 95% CI: 1.10, 5.86; Wang et al. 2011). Several cross-sectional cohort studies have also found significant associations between arsenic exposure and hypertension (Chen et al. 2012b; Kunrath et al. 2013; Li et al. 2013a, 2013b). Chen et al. (2012b, 240 adults, Bangladesh) found elevated risk of hypertension in association with urinary arsenic levels >8.0 µg/g creatinine (adjusted odds ratio: 3.0; 95% CI: 1.4, 6.3). Li et al. (2013a, 2013b) examined associations between risk of hypertension and drinking water arsenic concentration in two populations in China (669 and 604 adults). In one population, risk of hypertension increased in association with drinking water arsenic concentrations >50 µg/L (adjusted odds ratio: 1.937; 95% CI: 1.018, 3.687; Li et al. 2013a). In another population, risk of hypertension increased in association with cumulative drinking water arsenic exposure >0.35 mg/L-year (adjusted odds ratio: 1.871; 95% CI: 1.022, 3.424; Li et al. 2013b).

A prospective cohort study examined blood pressure outcomes children (4.5 years of ages) born in areas with endemic contamination of well water (2,499 child-mother pairs, Bangladesh; Hawkesworth et al. 2013). Systemic and diastolic blood pressure in the children increased in association with both maternal

and child urinary arsenic levels. The estimated effect size was an increase of 3.69 mmHg systolic (95% CI: 0.74, 6.63) and 2.91 mmHg diastolic (95% CI: 0.41, 5.42) per mg/L increase in maternal urinary arsenic. In relation to child urinary arsenic levels, the effect size was 8.25 mmHg systolic (95% CI: 1.37, 15.1) and 2.75 mmHg diastolic (95% CI: -3.09, 8.59) per mg/L increase in urinary arsenic measured at age 18 months. A cross-sectional study (1,004 adults, Bangladesh) found increased risk of elevated pulse pressure (>55 mmHg) in association with drinking water arsenic concentrations of 23–32 µg/L (3.87; 95% CI: 1.22, 12.20; Islam et al. 2012a). Adjusted odds ratios were 7.32 (95% CI: 2.18, 24.6) for exposures to >262 µg/L.

Gastrointestinal Effects.

Inorganic Arsenicals. Epidemiological studies have examined effects of exposure to inorganic arsenic in drinking water on the gastrointestinal system (Majumdar et al. 2009; Syed et al. 2013). Details of the individual study designs and outcomes are provided in Table 3-3. The prevalence of diarrhea was increased in a cross-sectional study (3,451 children and adults, India) (Majumdar et al. 2009). Prevalence odds ratios for males and females were 4.97 (95% CI: 2.0, 12.0) and 5.49 (95% CI: 2.7, 10.9), respectively, for drinking water concentrations ≥800 µg/L. Results of a cross-sectional study in 11,454 adults (Bangladesh) showed an increased risk of lesions of the gums and tongue at urine arsenic concentrations of 134–286 µg/g creatinine, but not at urine arsenic concentrations >286–5,000 µg/g creatinine (Syed et al. 2013). Adjusted multinomial odds ratios for lesions of the gums and tongue were 2.90 (95% CI: 1.11, 7.54; $p<0.05$) and 2.79 (95% CI: 1.51, 5.15; $p<0.01$), respectively.

Musculoskeletal Effects.

Inorganic Arsenicals. Endochondrial ossification in rats was affected by exposure to inorganic arsenic in drinking water (Aybar Odstrcil et al. 2010). Male Wistar rats were exposed to drinking water with 0 or 10 mg/L sodium arsenite (equivalent to 0.21 mg/kg body weight/day, as reported by study authors) for 45 days. Microscopic examination of sections of the tibia showed significant increases ($p<0.05$) in the thickness of growth plate cartilage (124% of control) and the hypertrophic zone (113% of control) in arsenic-exposed rats, compared to controls. Bone volume and the number of circulating osteocytes were not affected by arsenic exposure.

Hepatic Effects.

Inorganic Arsenicals. The prevalence of hepatomegaly was investigated in a cross-sectional cohort study of 3,825 children and adults (age range ≤9–≥60 years) exposed to arsenic in drinking water in India (Majumdar et al. 2009). The study authors did not report any adjustments for confounding factors.

Table 3-3. Gastrointestinal Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Lesions of the oral cavity				
Syed et al. 2013	Study design: cross-sectional Location: Bangladesh Population: 11,454 adults, ages 17–75 years; male: 43%; female: 57% Data collection period: 2000–2002	Exposure measures: Urine arsenic concentration, corrected for creatinine As concentration: Mean: 101.6 µg/g Range: 0.1–854 µg/g Tertiles: - Q1: 7–134 µg/g - Q2: >134–286 µg/g - Q3: >286–5,000 µg/g	Variables assessed: lesions of the gums, lips, and tongue Adjustments: study authors state that adjustments to odds ratios were made, but do not indicate specify specific adjustments Analysis: multinomial multivariate regression	A significant association between urinary arsenic concentrations for Q2 participants, but not Q3 participants, for arsenical lesions of the gums, compared to participants in Q1. Adjusted multinomial odds ratio: 2.90; 95% CI: 1.11–7.54; $p<0.05$. A significant association between urinary arsenic concentrations for Q2 participants, but not Q3 participants, for arsenical lesions of the tongue, compared to participants in Q1. Adjusted multinomial odds ratio: 2.79; 95% CI: 1.51, 5.15; $p<0.01$. No statistically significant ($p>0.05$) association between urinary arsenic concentration and lesions of the lips were identified.

Table 3-3. Gastrointestinal Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Diarrhea				
Majumdar et al. 2009	Study design: cross-sectional Location: India Population: exposed: 3,825; controls: 3,451; children and adults (age range specified as ≤9–≥60 years); no participants had arsenical skin lesions Data collection period: not reported	Exposure measures: drinking water from wells used by each participant. As concentration: Quintiles: - Q1: <50 µg/L - Q2:59–199 µg/L - Q3: 200–499 µg/L - Q4: 500–799 µg/L - Q5: ≥800 µg/L	Variables assessed: diarrhea as reported to a physician Adjustments: none reported Analysis: Chi-square	The overall prevalence of diarrhea in male and female participants in Q5 was significantly increased compared to Q1. Prevalence: - males: 4; p=0.01 - females: 3.8; p=0.04 Prevalence odds ratios (95% CI): - males: 4.97 (2.0, 12.0) - females: 5.49 (2.7, 10.9)

AS = arsenic; CI = confidence interval

Prevalence odds ratios were increased for drinking water concentrations ≥500 µg/L in males (5.13; 95% CI: 3.4, 7.6) and females (4.34; 95% CI: 2.8, 6.5), compared to controls exposed to <50 µg/L.

Renal Effects.

Organic Arsenicals. Effects of subchronic exposure to methylated arsenic metabolites in drinking water on the bladder urothelium have been studied in F344 rats (Shen et al. 2006; Wang et al. 2009b). Shen et al. (2006) exposed male and female rats to drinking water containing 0, 187 mg/L monomethylarsonic acid [MMA(V)], 184 mg/L dimethylarsinic acid [DMA(V)], or 182 mg/L trimethylarsine oxide (TMAO) for 13 weeks. Examination of the urothelium by scanning electron microscopy showed that rats exposed to MMA(V) or TMAO were similar in appearance to controls. In rats exposed to DMA(V), the urothelium showed several pathological changes including leafy or ropy microridges, short uniform microvilli, and pleomorphic microvilli exfoliation, necrosis, and epithelial separation. In DMA(V)-exposed rats, the average urothelial lesion severity score in females was 83% higher than the score in males, indicating that females rats are more sensitive than rats to DMA(V)-induced bladder toxicity. Similar effects were observed in female rats exposed to 0, 1, 4, 40, or 100 mg/L DMA(V) for 13 weeks (Wang et al. 2009b). Examination of the urinary bladder by light microscopy showed vacuolization and nuclear hyperchromatin in the transitional epithelium for all exposure groups, with a dose-dependent increase in incidence. Electron microscopy of rats exposed to 100 mg/L revealed sites of necrotic and exfoliated cells of the transitional epithelium and round superficial transitional cells of variable size with polymorphic microvilli (an indication of regeneration and hyperplasia). Rats exposed to 1–40 mg/L were similar in appearance to controls.

Endocrine Effects.

Inorganic Arsenicals. Several case-control and cross-sectional cohort studies have examined associations between exposure to inorganic arsenic in drinking water and diabetes (Chen et al. 2010c, 2011a, 2012a; Coronado-Gonzolez et al. 2007; Del Razo et al. 2011; Gribble et al. 2012; Islam et al. 2012b; James et al. 2013; Kim and Lee 2011; Kim et al. 2013; Li et al. 2013a; Navas-Acien et al. 2008, 2009; Pan et al. 2013; Rhee et al. 2013; Steinmaus et al. 2009). A prospective cohort study evaluated the association between arsenic exposure and impaired glucose tolerance during pregnancy (Ettinger et al. 2009). Details of the individual study designs and outcomes are provided in Table 3-4. Most, but not all, studies found an increased risk of diabetes in association with exposures to arsenic in drinking water and/or urinary arsenic concentrations.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Diabetes				
Chen et al. 2010c	Study design: cross-sectional Location: Bangladesh Population: 11,319 participants in HEALS Data collection period: 2000–2002	Exposure measures: arsenic in drinking water from 5,966 area wells and arsenic concentration in urine As concentration range: - range in drinking water: 0.1–864 µg/L - range in urine: 1–205 µg/L	Variables assessed: self-reported physician diagnosis of diabetes, dipstick urinalysis for glucose Adjustments: age, BMI, smoking, education, urinary creatinine Analysis: unconditional logistic regression	No association or dose-response trends were observed between arsenic concentration in drinking water or urine and the prevalence of diabetes mellitus or glucosuria.
Chen et al. 2011a	Study design: cross-sectional Location: Taiwan Population: 910 exposed, 133 controls Data collection period: 2002–2005	Exposure measures: arsenic concentration in urine (corrected for creatinine) As concentrations: Quartiles: - Q1: ≤35 µg/g - Q2: >35–75 µg/g - Q3: >75–200 µg/g - Q4: >200 µg/g	Variables assessed: diabetes (fasting plasma glucose ≥126 mg/dL or treatment with diabetic therapy) Adjustments: age, location of residence, smoking, hypertension, urinary lead, cadmium, and nickel Analysis: multiple logistic regression	For subjects in Q3 and Q4, the risk for type 2 diabetes was increased approximately 2-fold compared to Q1. A dose-response relationship was observed ($p<0.05$). Adjusted odds ratios (95% CI): - Q3: 2.08 (1.05, 3.69) - Q4: 2.22 (1.21, 4.09)
Coronado-Gonzalez et al. 2007	Study design: case control Location: Mexico Population: adult males and females; 200 cases, 200 controls Data collection period: 2003	Exposure measures: arsenic concentration in urine, corrected for creatinine As concentration: Tertiles: - T1: <63.5 - T2: 63.5–104 µg/g - T3: >104 µg/g	Variables assessed: diagnosis of diabetes (fasting glucose values 126 mg/100 mL or a history of diabetes treated with insulin or oral hypoglycemic agents) Adjustments: age, sex, hypertension, family history of diabetes, obesity, serum lipids Analysis: multivariate analysis with unconditional logistic regression	Compared to T1, urine arsenic concentrations of arsenic for T2 and T3 were associated with an increased risk of diabetes. Adjusted odds ratios (95% CI): - T2: 2.16 (1.23, 3.79) - T3: 2.84 (1.64, 4.92)

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Del Razo et al. 2011	Study design: cross-sectional Location: Mexico Population: 258 male and female children (28% ≤18 years old) and adults (72% >18 years old) Data collection period: not reported	Exposure measures: arsenic concentration in main drinking water source for participant; arsenic concentration (total and metabolites) in urine As concentration range: Drinking water: - range: 3.1–215.2 µg/L - geometric mean (GSD): 24.4 (2.9) µg/L Urine: - range total arsenic: 2.3–233.7 ng/mL - geometric mean (GSD): 24.7 (2.8) ng/mL - range DMA: 0–64.8 ng/mL - geometric mean (GSD): 0.9 (3.2) ng/mL	Variables assessed: fasting blood glucose (FBG), fasting plasma insulin (FPI), oral glucose tolerance oral (OGTT), glycated hemoglobin (HbA1c), insulin resistance (IR) Adjustments: age, sex, hypertension, obesity Analysis: log-transformed linear regression	A positive association was observed between arsenic concentration in drinking water and urine levels of DMA (but not total arsenic) and the prevalence of diabetes. Adjusted odds ratios (95% CI): - drinking water: 1.13 (1.05, 1.22); p<0.01 - urine DMA: 1.24 (1.00, 1.55); p=0.05 Negative associations were observed for arsenic concentration in drinking water and for concentration of total arsenic in urine. Results indicate that different arsenic-induced diabetes has a different underlying mechanism that type 2 diabetes (characterized by insulin resistance). Adjusted beta (95% CI: - FPI (drinking water) =: -2.084 (-2.720, -1.448); p<0.01 - IR (drinking water): -1.641 (-2.358, -0.924); p<0.01 - FPI (total arsenic in urine: -5.313 (8.068, -2.559); p<0.01 - IR (total arsenic in urine): -4.538 (-7.514, -1.562); p<0.01

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Gribble et al. 2012	Study design: cross-sectional Location: United States (Arizona, North Dakota, Oklahoma, South Dakota) Population: 3,925 male (41%) and female (59%) adults from Native American communities Data collection period: 1989–1991	Exposure measures: arsenic (total) concentration in urine As concentration: Mean: 14.1 µg/L Quartiles: - Q1: <7.9 µg/L - Q2: 7.9–<14.0 µg/L - Q3: 14.1–<24.1 µg/L - Q4:≥24.2 µg/L	Variables assessed: diabetes (fasting plasma glucose ≥126 mg/dL, 2-hour glucose level ≥200 mg/dL, HbA1c ≥ 6.5%, or diabetes treatment) Adjustments: age, sex, education, alcohol consumption, smoking, BMI, urine creatinine Analysis: Poisson regression models	The prevalence of diabetes was associated with urine total arsenic concentration in Q2–Q4, although the association was restricted to participants with poorly controlled diabetes (i.e., HbA1c ≥8%. Adjusted prevalence ratios (95% CI): - Q2: 1.15 (1.04, 1.27) - Q3: 1.21 (1.08, 1.34) - Q4: 1.28 (1.14, 1.44)
Islam et al. 2012b	Study design: cross-sectional Location: Bangladesh Population: adult males and females; 89 exposed; 915 controls Data collection period: not reported	Exposure measures: arsenic concentration in residential drinking water As concentration: Mean±SD: 159±198.5 µg/L Quartiles: - Q1: 10–22 µg/L - Q2: 23–32 µg/L - Q3: 33–261 µg/L - Q4: ≥262 µg/L	Variables assessed: diagnosis of diabetes (fasting blood glucose >126 mg/dL or self-reported physician diagnosis of type 2 diabetes) Adjustments: age, sex, education, BMI, family history of type 2 diabetes Analysis: multivariate linear regression	For data stratified into two groups by arsenic concentration in drinking water (referents: <50 µg/L; exposed: ≥50 µg/L), exposure was associated with an increase in the risk of diabetes of 2.1-fold. Adjusted odds ratios: - <50 µg/L: 1 - >50 µg/L: 2.1 (95% CI: 1.3, 3.2) For data stratified into quartiles, an association for arsenic exposure and the risk of diabetes was observed Q4 compared to Q1 (adjusted OR: 1.9; 95% CI: 1.1–3.5), but not Q2 and Q3 compared to Q1. A positive trend (p<0.01) was observed across quartiles.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
James et al. 2013	Study design: case cohort Location: United States (Colorado) Population: adult males and females; 141 cases; 347 control cohort Data collection period: initial visit 1984–1988; follow-up visits 1988–1992 and 1997–1998	Exposure measures: arsenic concentration in drinking water in individual residences; TWA exposure As concentration in drinking water: Range: not detected–752 µg/L Mean: 39 µg/L TWA exposure: Quartiles: - Q1: 1–<4 µg/L-year - Q2: ≥4–<8 µg/L-year - Q3: ≥8–<20 µg/L-year - Q4: ≥20 µg/L-year	Variables assessed: diabetes (self-reported diagnosis with medical record verification, plasma glucose ≥140 mg/dL or 2-hour glucose level ≥200 mg/dL Adjustments: age, gender, ethnicity, BMI, physical activity level Analysis: Cox proportional hazards model	A significant association was observed between arsenic exposure and risk of diabetes. For each 15 µg/L increase in TWA arsenic exposure, the risk of diabetes increases by 27%. Adjusted hazard ratio: 1.27 (95% CI: 1.01, 1.59); p=0.04 For exposure based on quartiles, significant adjusted hazard ratios (95% CI) were observed Q4, but not Q2 or Q3 compared to Q1. Adjusted hazard ratio: 1.55 (1.00, 2.51); p=0.05 No trend was observed across TWA exposure quartiles (p=0.07).
Kim and Lee 2011	Study design: cross-sectional Location: South Korea Population: KNHANES 2008; 1,677 adult males (47%) and females (53%) Data collection period: 2007–2009	Exposure measures: arsenic concentration in urine, corrected for creatinine Mean As concentrations (95% CI): All participants: 121.1 µg/g (111.5, 131.6) Males: 103.3 µg/g (93.1, 114.7) Females: 137.8 µg/g (122.4, 155.1)	Variables assessed: diagnosis of diabetes (fasting serum glucose ≥126 mg/dL, self-reported physician diagnosis of diabetes, or self-reported use of insulin or oral hypoglycemic medication) Adjustments: age, sex, BMI, smoking, alcohol use, education, hypertension, regional area, residential area, seafood consumption Analysis: multiple regression analysis	Based on continuous exposure, total urinary arsenic was associated with diabetes in combined male and female and in female participants, but not in male participants. Adjusted odds ratio (95% CI): - combined: 1.312 (1.040, 1.655) - males: 1.126 (0.803, 1.577) - females: 1.502 (1.038, 2.171) Results indicate that a doubling of urinary arsenic (log-transformed) in females and in combined males and females is associated with an increased risk of diabetes of approximately1.5 and 1.3, respectively.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Kim et al. 2013	Study design: case control Location: United States (Arizona) Population: Native American adults (≥25 years); 150 exposed; 150 controls Data collection period: 1982–2007	Exposure measures: arsenic concentration in urine, adjusted for creatinine [Note: units as reported in the publication (µg/L) are not typical for urine concentrations that have been corrected for creatinine (µg/g)] As concentration range: - total arsenic: 6.6–123.1 µg/L - inorganic arsenic: 0.1–36.0 µg/L	Variables assessed: diagnosis of diabetes (2-hour post-load plasma glucose following a 75-g oral glucose tolerance test of ≥200 mg/dL) Adjustments: age, sex, BMI Analysis: logistic regression	Risk for diabetes was not significantly elevated for total arsenic or inorganic arsenic in urine. Adjusted odds ratio (95% CI): - Total arsenic: 1.11 (0.79, 1.57) - Inorganic arsenic: 1.16 (0.89, 1.53)

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Li et al. 2013a	Study design: cross-sectional Location: China (Inner Mongolia) Population: 669 adult men (43%) and women (57%) Data collection period: not reported	Exposure measures: drinking water in each well As concentration: Range: 0–760 µg/L Tertiles: - T1: <10 µg/L - T2: 10–50 µg/L - T3: >50 µg/L	Variables assessed: diabetes (diagnosis not specified) Adjustments: gender, age, smoking, alcohol, cumulative arsenic exposure Analysis: logistic regression	No significant association was observed between arsenic exposure and type 2 diabetes. Adjusted odds ratios (95'% CI): - T2: 1.362 (0.519, 3.571) - T3: 1.578 (0.584, 4.262)
Navas-Acien et al. 2008	Study design: cross-sectional Location: United States Population: 788 adults (≥20 years); males (49%) and females (51%) NHANES participants Data collection period: 2003–2004	Exposure measures: arsenic concentration in urine Total As concentration: median: 7.1 µg/L 20th percentile: 3.0 µg/L 80th percentile: 16.5 µg/L Tertiles: - T1: <4.8 µg/L - T2: 4.8–10.8 µg/L - T3: >10.8 µg/L	Variables assessed: diagnosis of diabetes (defined as fasting serum glucose level ≥126 mg/dL, self-reported physician diagnosis of diabetes, or self-reported use of insulin or oral hypoglycemic medication) Adjustments: sex, age, race/ethnicity, urine creatinine, education, BMI, hypertension medication use, urine markers of seafood intake Analysis: logistic regression	Total urine arsenic for the 80th percentile was associated with an increased prevalence of type 2 diabetes. Adjusted odds ratios (95 CI): - 20th percentile: 1.05 (0.57, 1.94) - 80th percentile: 3.58 (1.18, 10.83) A significant trend was observed for tertiles (p=0.03), although adjusted odds ratios were not significant based on intertertile comparison.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Navas-Acien et al. 2009	Study design: cross-sectional Location: US Population: 1,279 adult male and female NHANES participants (160 with diabetes; aged ≥20 years) Data collection period: 2003–2006	Exposure measures: arsenic concentration in urine As concentration: Median: 7.4 µg/L 20th percentile: 3.4 µg/L 80th percentile: 17.2 µg/L	Variables assessed: diagnosis of diabetes (defined as fasting serum glucose level ≥126 mg/dL, self-reported physician diagnosis of diabetes, or self-reported use of insulin or oral hypoglycemic medication) Adjustments: age, sex, race/ethnicity, urine creatinine, urine arsenobetaine, blood mercury Analysis: not reported	Total urine arsenic for the 80th percentile was associated with an increased prevalence of type 2 diabetes. Adjusted odd ratios (95% CI): - 20th percentile: 1 - 80th percentile: 2.86 (1.23, 6.63) For a subset of participants with undetectable arsenobetaine, an association was observed between arsenic in urine and the prevalence of diabetes. Adjusted odds ratios (95% CI) - 20th percentile: 1 - 80th percentile: 2.60 (1.12, 6.03)

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Pan et al. 2013	Study design: case control Location: Bangladesh Population: adult males and females; 84 cases, 849 controls Data collection period: 2001–2011	Exposure measures: arsenic concentration in drinking water and toenails for each participant Drinking water (µg/L): - mean±SD, controls: 142±278.1 - mean±SD, exposed: 202.4±277.2 Quartiles: - Q1: ≤1.7 µg/L - Q2: 1.8–15.5 µg/L - Q3: 15.6–170 µg/L - Q4: ≥170 µg/L Toenails (µg/g): - mean±SD, controls: 4.8±7.1 - mean±SD, exposed: 5.4±SD Quartiles: - Q1: ≤0.93 µg/g - Q2: 0.94–2.12 µg/g - Q3: 2.13–6.18 µg/g - Q4: ≥6.19 µg/g	Variables assessed: diagnosis of diabetes (based on hemoglobin A1c levels ≥6.5%) Adjustments: age, sex, BMI, smoking, skin lesions, arsenic in drinking water, arsenic in toenails Analysis: logistic regression	An association was observed between exposure to arsenic in drinking water (Q3 and Q4 compared to Q1) and in toenails (Q2–Q4 compared to Q1) and increased risk of diabetes. Drinking water adjusted odds ratios (95% CI): - Q3: 3.07 (1.38, 6.85) - Q4: 4.51 (2.01, 10.09) Toenail adjusted odds ratios (95% CI): - Q2: 3.34 (1.46, 7.64) - Q3: 3.40 (1.46, 7.89) - Q4: 6.22 (2.63, 14.69)

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rhee et al. 2013	Study design: cross-sectional Location: Korea (not specified) Population: 3,602 adults (aged ≥20 years); males (49%) and females (51%); NHANES participants; Data collection period: 2008–2009	Exposure measures: arsenic concentration in urine, corrected for creatinine As concentration range: 70.7–193.4 µg/g As quartiles: - Q1: <70.7 µg/g - Q2: 70.7–117.7 µg/g - Q3: 117.7–<193.4 µg/g - Q4: ≥193.4 µg/g	Variables assessed: diagnosis of diabetes (self-reported physician diagnosis or treatment with insulin or oral antidiabetic medication); glucose tolerance test, insulin resistance test, insulin secretion capacity Adjustments: age, sex, urban or rural residence, smoking, alcohol consumption, occupation, serum mercury level. Analysis: logistic regression (for risk of diabetes based on quartiles) and multiple linear regression (for continuous exposure)	Arsenic exposure is associated with increased risk of diabetes for Q4, but not Q2 or Q3, compared to Q1. A positive trend across quartiles was observed (p=0.009). Adjusted odd ratios (95% CI): - Q3: 1.42 (0.94, 2.13) - Q4: 1.56 (1.03, 2.36)
Steinmaus et al. 2009	Study design: cross-sectional Location: United States (national) Population: NHANES participants; 795 adult males (53%) and females (47%) Data collection period: 2003–2004	Exposure measures: arsenic concentration in urine Total urinary As: Mean±SD:16.7±39.7 µg/L Tertiles: - T1: ≤5.2 µg/L - T2: 5.3–11.8 µg/L - T3: >11.8 µg/L Urinary inorganic As: Mean±SD: 10.6±14.1 µg/L Tertiles: - T1: ≤2.7 µg/L - T2: 2.8–5.0 µg/L - T3: >5.0 µg/L	Variables assessed: diagnosis of diabetes (self-report physician diagnosed or use of insulin or other antidiabetic medications) Adjustments: sex, age, ethnicity, BMI, serum cotinine, current use of hypertensive medication Analysis: logistic regression	No evidence of increased risk of diabetes for T2 or T3 compared to T1 was observed using total urinary arsenic or inorganic arsenic.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Metabolic syndrome				
Chen et al. 2012a	Study design: case-control Location: Taiwan Population: adult males and females; exposed 111; controls 136 Data collection period: 2002–2003	Exposure measures: drinking water (measured in village wells) and cumulative exposure As concentration: Drinking water tertiles: - T1: <700 µg/L - T2: 700–767.65 µg/L - T3: >767.65 µg/L Cumulative exposure - T1: <12.60 µg/L-year - T2: 12.60–18.90 µg/L-year - T3: >18.9 µg/L-year	Variables assessed: metabolic syndrome (a strong predictor of type 2 diabetes); defined as the presence of three or more of the risk factors: fasting plasma glucose (≥110 mg/dL), triglycerides (≥150 mg/dL), HDL (≤40 mg dL for men and ≤50 mg dL for women),increased systolic (≥130 mm Hg) or diastolic (≥85 mm Hg) blood pressure, and waist girth (≥90 cm for men and ≥80 cm for women). Adjustments: age, betel nut chewing Analysis: multiple logistic regression	Adjusted odds ratios were not significant for an association between arsenic drinking water concentration or cumulative arsenic exposure and increased risk of metabolic syndrome.

Table 3-4. Endocrine Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Impaired glucose tolerance during pregnancy				
Ettinger et al. 2009	Study design: prospective cohort Location: United States (Oklahoma) Population: 532 pregnant women, examined during weeks 24 and 28 of gestation Data collection period: 2002–2008	Exposure measures: arsenic concentration in blood (collected at delivery) and hair Blood As: Range: 0.2–24.1 µg/L Mean±SD:1.7±1.5 Quartiles: - Q1: 0.23–0.92 µg/L - Q2: 0.93–1.39 µg/L - Q3: 1.40–2.08 - Q4: 2.09–24.07 Reporting discrepancy noted for maximum concentration and upper value for the highest quartile Hair As (range): 1.1–724.4 ng/g	Variables assessed: glucose tolerance test (impair glucose tolerance defined as blood glucose level of >140 mg/dL 1 hour after oral challenge with 50-g oral glucose Adjustments: age, Native American race, pre-pregnancy BMI, Medicaid use, marital status Analysis: multivariate logistic regression	Arsenic concentration in blood was associated with an increased risk of impaired glucose tolerance at 24–28 weeks of gestation for Q3 and Q4, compared to Q1. Adjusted odds ratios (95% CI): - Q3: 2.65 (1.12, 6.36) - Q4: 2.79 (1.13, 6.87) Arsenic concentration in blood was significantly correlated with 1-hour blood glucose levels (p=0.02). An interquartile increase in blood arsenic concentration of 1.2 µg/L was associated with 1.76 times higher odds of impaired glucose tolerance. No correlation was observed for arsenic concentration in hair (p=0.08) and 1-hour blood glucose levels. Blood and hair levels of arsenic were not significantly correlated (p=0.08) with each other.

As = arsenic; BMI = body mass index; CI = confidence interval; DMA = dimethylarsinic acid; GSD = geometric standard deviation; HEALS = Health Effects for Arsenic Longitudinal Study; KNHANES = Korea National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey SD = standard deviation; TWA = time-weighted average

A case-cohort study conducted in Colorado (141 adult cases) found a significant association between exposure to arsenic in drinking water and the risk of diabetes (James et al. 2013). For exposure based on time-weighted average drinking water concentrations ≥20 µg/L-year, the adjusted hazard ratio for diabetes was 1.55 (95% CI: 1.00, 2.51). In a case-control study conducted in Mexico (200 adult cases), adjusted odds ratios were 2.16 (95% CI: 1.23, 3.79) and 2.84 (95% CI: 1.64, 4.92) for urine arsenic concentrations of 63.5–104 and >104 µg/g creatinine, respectively (Coronado-Gonzales et al. 2007). Increased risk of diabetes was also observed in a case-control study conducted in Bangladesh (84 adult cases, Pan et al. 2013). Adjusted odds ratios of 3.07 (95% CI: 1.38, 6.85) and 4.51 (95% CI: 2.01, 10.09) were observed for drinking water arsenic concentrations of 15.6–170 and ≥170 µg/L, respectively. Several cross-sectional cohort studies also found significant associations between arsenic exposure and diabetes (Chen et al. 2011a; Del Razo et al. 2011; Gribble et al. 2012; Islam et al. 2012b; Kim and Lee 2011; Navas-Acien et al. 2008, 2009; Rhee et al. 2013). Risk estimates in these studies ranged from 1.13 (95% CI: 1.05, 1.22) based on drinking water concentration of arsenic (Del Razo et al. 2011) to 3.58 (95% CI: 1.18, 10.83) based on urine arsenic concentrations (Navas-Acien et al. 2008).

A prospective cohort study of 532 pregnant women from Oklahoma showed a significant association between arsenic concentration in blood and impaired glucose tolerance during weeks 24–28 of gestation (Ettinger et al. 2009). Adjusted odds ratios were 2.65 (95% CI: 1.12, 6.36) and 2.79 (95% CI: 1.13, 6.87) for blood arsenic concentrations of 1.40–2.08 and 2.09–24.07 µg/L, respectively. An interquartile increase in blood arsenic concentration of 1.2 µg/L was associated with 1.76 times higher odds of impaired glucose tolerance.

Dermal Effects.

Inorganic Arsenicals. Skin lesions are one of the most common and characteristic effects of arsenic ingestion in humans. Dermal effects include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. Recent epidemiological studies provide additional evidence of adverse dermal effects associated with exposure to arsenic-contaminated drinking water (Argos et al. 2011; Barati et al. 2010; Fatmi et al. 2009, 2013; Hashim et al. 2013; Li et al. 2013a; Lindberg et al. 2008; Melkonian et al. 2011; Pesola et al. 2012; Pierce et al. 2011; Xia et al. 2009).

Ocular Effects.

Inorganic Arsenicals. Ocular effects of exposure of humans to drinking water have been studied in cross-sectional and cross-sectional cohort studies (Ghosh et al. 2007; Lin et al. 2008; Paul et al. 2013b;

See et al. 2007). These studies have shown associations between exposure to arsenic in drinking water and increased risk ocular effects, including conjunctivitis, cataract/ocular opacity, and pterygium. Details of the individual study designs and outcomes are provided in Table 3-5.

Studies evaluating the risk of conjunctivitis show an increased risk at mean arsenic drinking water concentrations >39.94 µg/L, with risk estimates ranging from 4.66 (95% CI: 2.45, 8.85) for exposure to a mean arsenic concentration in drinking water of 186.89 µg/L to 37.22 (95% CI: 20.56, 67.36) for exposure to a mean arsenic concentration in drinking water of 200.83 µg/L (Ghosh et al. 2007; Paul et al. 2013b). Ghosh et al. (2007) reported a positive trend for increasing risk with increasing drinking water arsenic level ($p<0.001$). In a study conducted in Taiwan (349 adults), a dose-response relationship ($p<0.05$) between cumulative arsenic exposure and posterior subcapsular opacity was observed (See et al. 2007). Adjusted odds ratios for cumulative exposure to 12.1–20 and >20 mg/L-year were 4.78 (95% CI: 1.03, 22.18) and 5.70 (95% CI: 1.23, 26.32), respectively. A cross-sectional study in adults (223; Taiwan) showed that an increased cumulative exposure to arsenic in drinking water was associated with an increase in the prevalence of pterygium (Lin et al. 2008). Adjusted odds ratios for cumulative exposure to 0.1–15.0 and >15.1 mg/L-year were 2.04 (95% CI: 1.04, 3.99) and 2.88 (95% CI: 1.42, 5.83), respectively.

3.2.2.3 Immunological and Lymphoreticular Effects

***Inorganic Arsenicals*.** Effects of exposure to arsenic in drinking water on immunological function was investigated in a cross-sectional study in of 577 children (mean age 4.5 years) in Bangladesh (Ahmed et al. 2014). Following adjustments for age, gender, and socio-economic status, the delayed hypersensitivity response following intradermal challenge with purified protein derivative was negatively associated with urine arsenic concentrations of 126–1,228 µg/L, (adjusted risk ratio: 1.37; 95% CI: 1.07, 1.74) compared to the control group with urine arsenic concentrations of 12–34 µg/L. A statistically significant ($p=0.003$) trend across the urine concentration range of 35–1,228 µg/L was observed. Associations also were observed between the urine concentration range of 107–1,228 µg/L and decreasing plasma concentrations of cytokines IL-2 (adjusted beta: -1.57; 95% CI: -2.56, -0.57) and TNF-α (adjusted beta: -4.53; 95% CI: -8.62, -0.42). Results are consistent with effects on cell-mediated immunity. In addition, epidemiological studies have found associations between maternal exposure to arsenic in drinking water and susceptibility to infections and thymic function of infants; results of these studies are reviewed in Section 3.2.2.6 (Developmental Effects).

Table 3-5. Ocular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Conjunctivitis				
Ghosh et al. 2007	Study design: cross-sectional cohort Location: India Population: 725 cases (373 with skin lesions, 352 without skin lesions), 389 controls; age range: 15–70 years Data collection period: 2003–2005	Exposure measures: arsenic concentration in drinking water in drinking water from individual participants As concentration: Range (all participants): - 0–1,188 µg/L Mean±SD: - control: 6.97±2.10 µg/L - cases (no skin lesions): 186.89±124.67 µg/L - cases (with skin lesions): 200.83±145.83 µg/L	Variables assessed: self-reported history of conjunctivitis Adjustments: age, sex, smoking Analysis: logistic regression	Exposure to arsenic in drinking water was associated with a higher risk of conjunctivitis compared to controls. Exposed participants with skin lesions had a higher risk of developing conjunctivitis than those without skin lesions: Adjusted odds ratios (95% CI): - Controls: 1 - Cases (no skin lesions): 4.66 (2.45, 8.85) - Cases (with skin lesions): 37.22 (20.56, 67.36) A trend test for odds ratios was statistically significant (p<0.001).
Paul et al. 2013b	Study design: cross-sectional cohort Location: India Population: males and females; 189 cases, 171 controls Data collection period: Data were collected from same participants for two time periods: 2005–2006 and 2010–2011	Exposure measures: drinking water from individual participants As concentration: Mean±SD for 2005–2006 - controls: 4.13±3.18 µg/L - cases: 190.1±110.53 µg/L Mean±SD for 2010–2011 - controls: 3.7±3.0 µg/L - cases: 37.94±27.08 µg/L	Variables assessed: conjunctivitis (not caused by bacterial or viral infections or allergens), diagnosed by an ophthalmologist Adjustments: none Analysis: ratio of incidence in exposed to control groups	The risk of development of conjunctivitis was significantly increased in cases compared to controls for both collection periods. Odds ratios (95% CI): 2005–2006: - controls: 1 - cases: 11.15 (4.91, 25.32) 2010–2011: - controls: 1 - cases: 20.51 (9.84, 42.72)

Table 3-5. Ocular Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Cataracts/ocular opacity				
See et al. 2007	Study design: cross-sectional Location: Taiwan Population: 349 male and female adults (43% male; 57% female; ages 37–81) Data collection period: 1988–1996 for arsenic exposure; eye examinations conducted in 1996	Exposure measures: drinking water, expressed as cumulative arsenic exposure, based on well water concentration and time of residence As concentration: Quartiles: - Q1: 0 - Q1: 0.1–12 mg/L-year - Q3: 12.1–20 mg/L-year - Q4: >20 mg/L-year	Variables assessed: cortical opacity, nuclear opacity, overall cataracts, posterior subcapsular opacity, as diagnosed by an ophthalmologist Adjustments: age, sex, diabetes status, occupational exposure to sunlight Analysis: Chi-square test	A dose-response relationship ($p<0.05$) between cumulative arsenic exposure and posterior subcapsular opacity was observed. Adjusted odd ratios (95% CI): - Q1: 1 - Q1: 2.19 (0.40, 12.07) - Q3: 4.78 (1.03, 22.18); $p<0.05$ - Q4: 5.70 (1.23, 26.32); $p<0.05$ Adjusted odds ratios were not statistically significant for cortical opacity, nuclear opacity, or overall cataracts.
Pterygium				
Lin et al. 2008	Study design: cross-sectional Location: Taiwan Population: adult males and females, >40 years of age; 223 exposed, 160 controls Data collection period: not reported	Exposure measures: drinking water, expressed as cumulative arsenic exposure, based on well water concentration and time of residence As concentration: Controls: <0.1 mg/L-year Cases: - 0.1–15.0 mg/L-year - ≥15.1 mg/L-year	Variables assessed: ophthalmologist diagnosis of pterygium Adjustments: age, sex, exposure to sunlight and sandy environments Analysis: multiple logistic regression	Increased cumulative exposure to arsenic in drinking water was associated with a significant increase in the prevalence of pterygium. Adjusted odds ratios (95% CI): - <0.1 mg/L-year: 1 - 0.1–15.0 mg/L-year: 2.04 (1.04, 3.99), $p<0.05$ - ≥15.1 mg/L-year: 2.88 (1.42, 5.83); $p<0.05$

As = arsenic; CI = confidence interval

A study in animals provides evidence of immune effects following intermediate-duration exposure to oral arsenic (Ezeh et al. 2014). Exposure of male C57BL/6J mice to drinking water concentrations of 19, 75, or 300 µg As/L (as sodium arsenite) for 30 days suppressed humoral immunity. The T-dependent antibody response to sheep red blood cells was significantly ($p<0.05$) decreased by approximately 55 and 49% of control in the 75 and 300 µg/L groups, respectively. Lymphoid progenitor cells were more sensitive to effects of arsenic than myeloid progenitor cells.

3.2.2.4 Neurological Effects

***Inorganic Arsenicals*.** Several epidemiological studies have examined effects of exposure to inorganic arsenic in drinking water on the neurological system using cross-sectional or cross-sectional cohort study designs (Ali et al. 2010; Ghosh et al. 2007; Guo et al. 2007; Li et al. 2006; Paul et al. 2013b; Tseng et al. 2006). Details of the individual study designs and outcomes are provided in Table 3-6. These studies found increased risks in association with exposures to arsenic in drinking water and/or urinary arsenic concentrations for decreased plasma cholinesterase activity, decreased peripheral nerve conduction velocity, peripheral neuropathy, and altered sensory function. In addition, effects on neurological function and development have been observed in children exposed to arsenic *in utero* and early life; results of these studies are reviewed in Section 3.2.2.6 (Developmental Effects).

In a cross-sectional study conducted in Bangladesh (141 adults), a significant, negative correlation was observed between plasma cholinesterase activity and arsenic concentration in drinking water (Spearman correlation coefficient: 0.52; $p<0.001$) (Ali et al. 2010). A cross-sectional study of 130 adolescents in Taiwan showed an association between exposure to drinking water concentration >50 µg/L and decreased nerved conduction velocity (adjusted odds ratio: 7.8; 95% CI: 1.001, 69.5) (Tseng et al. 2006). Exposure to arsenic in drinking water was associated with increased risk of peripheral neuropathy in adults in India and China (Ghosh et al. 2007; Li et al. 2006; Paul et al. 2013b). Increased risk of peripheral neuropathy was observed at mean drinking water concentrations ranging from 37.94 to 200.83 µg/L (Ghosh et al. 2007; Paul et al. 2013b) and at a drinking water concentration range of 400–700 µg/L (Li et al. 2006). A cross-sectional cohort study conducted in China (680 exposed) showed significant increases in the incidence of hearing loss ($p=0.005$), loss of taste ($p=0.001$), and blurred vision ($p<0.001$) in participants exposed to an arsenic drinking water concentration >50 µg/L, compared to participants (189) exposed to ≤50 µg/L (Guo et al. 2007).

Table 3-6. Neurological Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Enzyme activity				
Ali et al. 2010	Study design: cross-sectional Location: Bangladesh Population: 141 participants; 89 male and 52 female; mean age: 37.7 years (range not reported) Data collection period: not reported	Exposure measures: arsenic concentration in water (tube wells for individual households or communities), hair, nails As concentration: Water (mean±SD): - 224.92±57.20 µg/L Hair (mean±SD): - 5.27±7.06 µg/g Nails (mean±SD): - 7.51±7.64 µg/g	Variables assessed: plasma cholinesterase activity (PChE) Adjustments: Analysis: Spearman correlation coefficient (r_s) test	A statistically significant, negative correlation was observed between PChE activity and arsenic concentration in water (r_s=-0.52; p<0.001), hair (r_s=-0.47; p<0.001) and nails (r_s=-0.35; p<0.001). PChE activity was significantly lower (23% decrease; p<0.001) for participants with exposure to arsenic water concentrations >50 µg/L compared to those with exposure to ≤50 µg/L. PChE activity was also significantly lower (20% decrease; p<0.001) in participants with arsenic-induced skin lesion compared to those without lesions.
Peripheral neuropathy/conduction velocity				
Ghosh et al. 2007	Study design: cross-sectional cohort Location: India Population: 725 exposed (373 with skin lesions, 352 without skin lesions), 389 controls; age range: 15–70 years Data collection period: 2003–2005	Exposure measures: arsenic concentration in drinking water in drinking water from individual participants As concentration: Range (all participants): - 0–1,188 µg/L Mean±SD: - Control: 6.97±2.10 µg/L - Cases (no skin lesions): 186.89±124.67 µg/L - Cases (with skin lesions): 200.83±145.83 µg/L	Variables assessed: peripheral neuropathy assessed by pain and paresthesia in stocking and glove distribution, numbness, weakness, muscle cramps, anesthesia, hypoesthesia, decreased reflects as assessed by a neurologist Adjustments: age, sex, smoking Analysis: logistic regression	Exposure to arsenic in drinking water was associated with a higher risk of peripheral neuropathy compared to controls. Exposed participants with skin lesions had a higher risk of developing peripheral neuropathy than those without skin lesions: Adjusted odds ratios (95% CI): - controls: 1 - cases (no skin lesions): 3.99 (1.95, 8.09) - cases (with skin lesions): 15.61 (8.2, 29.71) A positive trend for increasing risk of peripheral neuropathy with increased concentration of arsenic in drinking water was observed (p<0.001).

Table 3-6. Neurological Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Li et al. 2006	Study design: cross-sectional Location: China Population: 309 participants (mean age: 34.7 years) Data collection period: not reported	Exposure measures: arsenic concentration in drinking water from individual households As concentration: Tertiles: - T1: 0–20 µg/L - T2: 100–300 µg/L - T3: 400–700 µg/L	Variables assessed: self-reported neurological symptoms (amnesia, impaired autonomic nervous system [ANS], headache, hearing loss, impaired heat/cold sensation, numbness, pain, impaired sense of smell, impaired vibration sensation), pin prick response of arms and legs Adjustments: age, gender, smoking, alcohol consumption, education Analysis: multiple logistic regression	The incidence if self-reported neurological symptoms was significantly ($p<0.05$) elevated in the T3, relative to T1, for pain and impaired vibration sensation, but not for other self-reported symptoms. No statistically significant increases for self-reported neurological symptoms were observed for T2 compared to T1. The probability of an increased pin prick score for arms and legs was significantly increased ($p>0.005$) T3, but not T2, compared to T1.
Paul et al. 2013b	Study design: cross-sectional cohort Location: India Population: male and female adults (18–70 years); 189 exposed, 171 controls Data collection period: Data were collected from same participants for two time periods: 2005–2006 and 2010–2011	Exposure measures: drinking water from individual participants As concentration: Mean±SD for 2005–2006 - controls: 4.13±3.18 µg/L - exposed: 190.1±110.53 µg/L Mean±SD for 2010–2011 - controls: 3.7±3.0 µg/L - exposed: 37.94±27.08 µg/L	Variables assessed: neurological symptoms (muscle cramps, numbness, pain, paraesthesias of stocking and glove regions), assessed by a neurologist Adjustments: none Analysis: ratio of incidence in exposed to control groups	The risk of development of peripheral neuropathy was significantly increased in cases compared to controls for both collection periods. Odds ratios (95% CI): 2005–2006: - controls: 1 - exposed: 9.08 (3.48, 23.72) 2010–2011: - controls: 1 - exposed: 18.48 (7.75, 44.06)

Table 3-6. Neurological Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Tseng et al. 2006	Study design: cross-sectional Location: Taiwan Population: 130 adolescents, ages 12–14 years Data collection period: not reported	Exposure measures: arsenic concentration in drinking water; cumulative dose of arsenic As concentration: Drinking water tertiles: - T1: ≤10 µg/L - T2: 10–50 µg/L - T3: >50 µg/L Cumulative arsenic dose tertiles: - T1: ≤50.0 mg - T2: 50.1–100.0 mg - T3: >100.0 mg	Variables assessed: sural sensory action potential nerve conduction velocity Adjustments: gender, height Analysis: multiple logistic regression	A significant ($0.01 \leq p < 0.05$) association was observed between exposure to a cumulative arsenic dose for T3, but not T2, and decreased conduction velocity. Adjusted odds ratio: 2.9 (95% CI: 1.1, 7.5). For drinking water concentration, a significant ($0.01 \leq p < 0.05$) decrease in nerve conduction velocity was observed in T3, but not T2, compared to T1. Adjusted odds ratio: 7.8 (95% CI: 1.001, 69.5).
Sensory function				
Guo et al. 2007	Study design: Cross-sectional cohort Location: Population: exposed: 680, controls: 189 (age not reported) Data collection period: 1992–2004	Exposure measures: arsenic concentration in drinking water from primary drinking water source As concentration: Controls: ≤50 µg/L Exposed: >50 µg/L	Variables assessed: loss of hearing, loss of taste, blurred vision, and numbness of limbs, based on physical examination Adjustments: none reported Analysis: not reported	The incidence of hearing loss, loss of taste, blurred vision, and numbness of limbs was significantly increased in cases compared to controls. Incidence (%) for each endpoint in controls and cases: Loss of hearing - controls: 2 - exposed: 40 ($p=0.005$) Loss of taste - controls: 0 - exposed: 37 ($p=0.001$) Blurred vision - controls: 7 - exposed: 118 ($p<0.001$) Numbness of limbs - controls: 0 - exposed: 228 ($p<0.001$)

As = arsenic; CI = confidence interval

3.2.2.5 Reproductive Effects

***Inorganic Arsenicals*.** Human epidemiological studies have examined associations between exposure to inorganic arsenic in drinking water and semen quality or endometriosis (Pollack et al. 2013; Xu et al. 2012). Details of study designs and outcomes for these studies are provided in Table 3-7. The risk of decreased sperm concentration was associated with urine DMA concentrations in a cross-sectional study of 96 men in China (Xu et al. 2012). Urinary concentrations of DMA above the median value of 20.9 µg/g creatinine were associated with decreased sperm concentrations (adjusted odds ratio: 7.2; 95% CI: 1.4, 37.1). No significant associations were observed between urinary concentration of DMA and sperm motility or semen volume, or between urinary concentrations of inorganic arsenic MMA and sperm concentration, sperm motility, or semen volume. In a matched cohort study of 473 women in California and Utah, no association between urine arsenic concentrations ≥10.83 µg/L (upper range not reported) and endometriosis was observed (Pollack et al. 2013).

Several studies in animals have shown adverse effects of oral exposure to inorganic arsenic on male and female reproductive systems (Akram et al. 2010; Chatterjee and Chatterji 2010; Li et al. 2012; Pachnanda and Singh 2012; Reilly et al. 2013; Singh et al. 2011). Details of study designs and outcomes for these studies are provided in Table 3-8. In male mice and rats, oral exposure arsenic produced several adverse effects, including decreased testicular weight, decreased spermatogenesis and sperm motility, decreased fertility, and histopathological changes to testes and epididymes (Li et al. 2012; Pachnada and Singh 2012; Singh et al. 2011). Of these studies, the lowest exposure found to be associated with reproductive effects was a study in which male rats exposed to drinking water collected from wells in India (arsenic concentration 0.102 mg/L) for 1–3 weeks resulted in significant testicular toxicity (Singh et al. 2011). Findings included duration-dependent decreases in testicular weight (10–28%), sperm count (20–57%), and sperm motility (26–58%), compared to controls, and atrophic changes in testes due to degenerative changes in spermatogenic and Leydig cells. Exposure of female rats to drinking water containing 4.0–200 mg/L arsenic for 1–4 weeks days caused significant decreases in uterine weight and length, serum levels of hormones (estradiol, progesterone, follicle-stimulating hormone, luteinizing hormone), and histopathological changes to the uterus (Akram et al. 2010; Chatterjee and Chatterji 2010). In addition, the time to onset of puberty was significantly delayed by approximately 2 days and changes to mammary gland morphology were observed in immature female rats exposed (gavage) to 10 mg/kg/day as sodium arsenite (Reilly et al. 2013). Effects of pre- and postnatal exposure on the female reproductive system are reviewed in Section 3.2.2.6 (Developmental Effects).

Table 3-7. Reproductive Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Endometriosis				
Pollack et al. 2013	Study design: matched cohort Location: United States (Salt Lake City, Utah and San Francisco, California) Population: 473 women (ages 18–44) scheduled for laparoscopic surgery; matched cohort: 127 Data collection period: 2007–2009	Exposure measures: As concentration in urine As concentration: Mean: 8.37 µg/L (95% CI: 7.41, 9.46) Tertiles: - T1: <4.94 µg/L - T2: 4.94–10.83 µg/L - T3: >10.83 µg/L	Variables assessed: endometriosis defined as surgically visualized disease Adjustments: age, BMI, smoking, location, race, vitamin use Analysis: logistic regression	No association was observed between As concentration in urine and endometriosis, based on comparison of adjusted odds ratios for tertiles.
Semen quality				
Xu et al. 2012	Study design: cross-sectional Location: China Population: 96 men Data collection period: 2009–2010	Exposure measures: urine total inorganic As (As*i*) DMA and MMA, adjusted for creatinine As concentration (median): - As*i*: 4.03 µg/g - DMA: 20.9 µg/g - MMA: 2.77 µg/g	Variables assessed: semen volume, sperm concentration, sperm motility, compared to reference values Adjustments: age, BMI, abstinence time, smoking, alcohol consumption Analysis: assessments based on dichotomous urinary As concentration for each variable by binary logistic regression	Urinary concentrations of DMA above the median value were associated with decreased sperm concentrations (adjusted odds ratio: 7.2; 95% CI: 1.4–37.1; p=0.02). No significant associations were observed between urinary concentration of DMA and sperm motility or semen volume, or between urinary concentrations of As*i* or MMA and any variable.

AS = arsenic; BMI = body mass index; CI = confidence interval; DMA = dimethylarsinic acid; MMA = monomethylarsonic acid

Table 3-8. Reproductive Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
Effects on the male reproductive system				
Li et al. 2012	Male mice (strain and age at initiation of treatment not specified); 10 per group	Drinking water containing 0, 1, 2, or 4 mg/L arsenic trioxide for 60 days	Sperm activity and malformation, spermatogenesis, relative weight of testes and epididymes, histopathology of testis and epididymis	Sperm activity: Significantly ($p<0.05$) decreased by 15–17% in the 2 and 4 mg/L groups compared to controls. Percentage of sperm malformation: Significantly ($p<0.05$) increased 2.5-fold in the 4 mg/L group Spermatogenesis (numbers of developing sperm at different stages): - Spermatogonia: significantly ($p<0.05$) decreased by approximately 31 and 41% in the 2 and 4 mg/L groups, respectively, compared to control. - Spermatocytes: significantly ($p<0.05$) decreased by approximately 25 and 40% in the 2 and 4 mg/L groups, respectively, compared to control. - Spermatids: significantly ($p<0.05$) decreased by approximately 17% in the 4 mg/L group compared to control. - Mature spermatids: significantly ($p<0.05$) decreased by approximately 12% in the 4 mg/L group compared to control. Relative weight of testes and epididymes: - Testes: significantly decreased ($p<0.05$) by approximately 12–13% in the 2 and 4 mg/L groups compared to controls. - Epididymes: significantly decreased ($p<0.05$) by approximately 15–17% in the 2 and 4 mg/L groups compared to controls. Histopathology of testes: In the 2 and 4 mg/L groups, seminiferous tubules showed disruption of spermatogenesis, reduced layers of germs cell alignment, and decreased numbers of spermatozoa.

Table 3-8. Reproductive Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
				No effects observed in the 1 mg/L group. Histopathology of epididymis: In the 2 and 4 mg/L groups, microscopic examination of the epididymis showed marked decreases in lumen area and sperm and sparse stereocilia of principal cells.
Pachnanda and Singh 2012	Adult male Swiss albino rats; 10 rats per group	Gavage; 0, 1, 2, or 3 mg/kg body weight/day sodium arsenite for 30 days	Body and testicular weight, histopathological evaluation of testes, fertility	Body and testicular weight: No significant changes in body weight; significant ($p<0.05$), dose-related decreases in testicular weight, ranging from approximately 22% (1 mg/kg bw/day) to 54% (3 mg/kg body weight/day). Testicular histopathology: Pathological findings in treatment groups included shrunken seminiferous tubules with defective spermatogenesis and decreased layers of germ cells, changes to organization of spermatogonia and spermatocytes, spermatocytes with swollen nuclei, atrophied spermatocytes, sloughing of dead germ cells into the lumen, dissolution of the tubule membrane, and leakage of germ cells into the interstitial space. Severity of changes increased with dose. Spermatogenesis was markedly inhibited at the highest dose. Fertility: In matings with females, the percentage of infertile males was 80% in the 1 mg/kg/day group, compared to controls. Males in the 2 and 3 mg/kg/day groups were completely infertile.
Singh et al. 2011	Adult male albino rats; 5 per group	Drinking water collected from Agra, India containing 0.102 mg/L for 7, 14, or 21 days; control group treated with distilled water	Body weight, organ weight, sperm count, sperm motility, histopathological evaluation of testes	Body weight: Significant, but small, decreases in body weight (approximately 6–7%; $p<0.05$) for all treatment durations. Testicular weight: Significant ($p<0.05$) duration-dependent decreases of approximately 10, 20, 28% at 7, 14, and 21 days, respectively. Sperm count: Significant duration-dependent decreases of

Table 3-8. Reproductive Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
				approximately 20 ($p<0.05$), 43 ($p<0.001$), and 57% ($p<0.001$) at 7, 14, and 21 days, respectively. Sperm motility: Significant decreases of approximately 26 ($p<0.01$), 42 ($p<0.01$), and 58% ($p<0.001$) at 7, 14, and 21 days, respectively. Testicular histopathology: Atrophic changes in testis due to degenerative changes in spermatogenic and leydig cells; specific observations included: apical degeneration and obliterated lumen; irregular shape of seminiferous tubules, blood vessels, sertoli cells, spermatatids, myoid cells, and tunica albugenia; decreased number of spermatids; and reduced number of interstitial Leydig cells.
Effects on the female reproductive system				
Akram et al. 2010	Immature female Sprague-Dawley rats (28 days old); 8 rats per group	Drinking water containing 0, 50, 100, or 200 mg/L sodium arsenite for 28 days (to maturity of animals)	Uterine weight and height; histology of uterus; plasma hormone levels (estradiol, progesterone, FSH and LH)	Uterine weight: Over the dose range, significant ($p<0.001$) decreases in uterine weight ranged from 32% (50 mg/L) to 85% (200 mg/L) of control. Uterine length: Over the dose range, significant ($p<0.001$) decreases in uterine length ranged from 16 (50 mg/L) to 40% (200 mg/L) of control. Uterine histopathology: Dose-dependent alterations included cuboidal epithelial cells, decreased epithelial height, loss of basement membrane, loss of demarcation between epithelial and endometrial stroma, dense endometrial stroma with irregular cells, AND decreased thickness of endometrium and myometrium. Hormone levels: Significant ($p<0.001$) dose-dependent decreases compared to control: - estradiol: 49% (50 ppm) to 72% (200 mg/L) - progesterone: 16% (50 ppm) to 53% (200 mg/L) - FSH: 32% (50 ppm) to 60% (200 mg/L)

Table 3-8. Reproductive Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
				- LH: 24% (50 ppm) to 47% (200 mg/L)
Chatterjee and Chatterji 2010	Adult female Sprague-Dawley rats; adults; 3 rats per group for dose- and duration-ranging studies; 5 rats per group for main study	Drinking water; Dose-ranging study: 0, 0.4, 4.0, 40, or 80 mg/L sodium meta-arsenite for 28 days; Duration-ranging: 4.0 mg/L for 7, 14, 28, or 56 days; Main study: 0 or 4.0 mg/L for 28 days	Serum estradiol levels, serum hormone levels (FSH and LH), uterine weight, histopathology of uterus	Dose-ranging study: Significant ($p<0.05$) decreases in serum estradiol levels occurred at all arsenic groups, reaching a maximum decrease (approximately 85%) at ≥4 mg/L. Duration-ranging study: Significant ($p<0.05$) decreases in serum estradiol levels occurred at 14, 38 and 56 days, with a maximum decrease (approximately 88%) at 28 days. Main Study: - Hormone levels: FSH and LH significantly ($p<0.05$) decreased by 77 and 65%, respectively, compared to control. - Uterine weight: significantly ($p<0.01$) decreased by 29% compared to control. - Histopathology: significant findings include decreased luminal diameter, height of luminal epithelial cells, diameter of endometrial glands, and width of longitudinal muscle layer.
Reilly et al. 2013	Immature female Sprague-Dawley rat; age: postnatal day 12; 20 and 15 rats for control and treatment groups, respectively	Gavage exposure to 10 mg/kg arsenic, as sodium arsenite; dosing from postnatal day 12 to postnatal days 30 or to 35–43 (onset of puberty)	Onset of puberty (measured by time to vaginal opening and diestrus); mammary gland morphology; serum levels of puberty-related (insulin-like growth factor 1 [IGF-1], GH, FSH, LH, and estradiol)	Time to onset of puberty: Time to vaginal opening significantly ($p<0.05$) decreased by 1.8 days; time to diestrus significantly ($p<0.05$) decreased by 1.95 days. Mammary gland morphology: Compared to controls, the following were observed in arsenic-treated rats: higher mean number of terminal end buds, undifferentiated progenitor cells, increased presence of alveolar buds; fewer terminal ducts, absence of lobular type 1 structures. Hormone levels: IGF-1 levels in serum were significantly ($p<0.01$) decreased by 22% compared to controls; no significant changes in levels of GH, FSH, or LH, compared to controls

As = arsenic; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone

3.2.2.6 Developmental Effects

***Inorganic Arsenicals*.** Several case-control, prospective cohort, and cross-sectional cohort studies have examined associations between exposure to inorganic arsenic in drinking water and developmental outcomes (Ahmed et al. 2012; Farzan et al. 2013; Guan et al. 2012; Hamadini et al. 2010, 2011; Hsieh et al. 2014; Jin et al. 2013; Khan et al. 2012; Kippler et al. 2012; Nahar et al. 2014; Parvez et al. 2011; Rahman et al. 2007, 2009, 2010, 2011; Raqib et al. 2009; Roy et al. 2011; Rudnai et al. 2014; Saha et al. 2012; Vall et al. 2012; Wasserman et al. 2007, 2011, 2014; Wu et al. 2014). Outcomes investigated included fetal death, fetal malformations, fetal and neonatal growth, neurodevelopment, infection vulnerability and thymus function, and cancer (see Section 3.2.2.7 Cancer). Details of the individual study designs and outcomes are provided in Table 3-9. In general, these data provide evidence for associations between exposure to arsenic and developmental effects ranging from fetal and infant deaths, congenital heart anomalies, delays in growth and neurological development, and increased susceptibility to infections. Although exposures in most study populations were from drinking water, most studies evaluated internal exposure metrics such as urinary arsenic or blood arsenic levels, rather than drinking water exposure levels. Increased risk of fetal heart anomalies was observed in association with drinking water arsenic concentrations >10 µg/L (Rudnai et al. 2014). Increased risk of fetal or infant death was associated with exposures to drinking water arsenic levels >222–408 µg/L or maternal urinary arsenic concentrations >261 µg/L (Rahman et al. 2007, 2011). Increased risk of infant respiratory infections was associated with maternal urinary arsenic concentrations >39 µg/L (Rahman et al. 2011).

Prospective cohort studies have examined associations between exposure to arsenic in drinking water and fetal or infant death (Rahman et al. 2007, 2011). A large cohort study (29,134 pregnancies, Bangladesh) found increased risk of fetal death and infant death (occurring <12 months of age death) and postnatal death (occurring >28 days and <12 months of age) in association with drinking water arsenic concentrations in the range of 227–408 µg/L (Rahman et al. 2007). Relative risks were 1.14 (95% CI: 1.01, 1.30) for fetal death, 1.29 (95% CI: 1.08, 1.53) for infant death, and 1.55 (95% CI: 1.17, 2.05) for postnatal death. In a smaller prospective study (2,924 pregnancies, Bangladesh), risk of infant death was also elevated in association with urinary arsenic concentration >268 µg/L (adjusted hazard ratio: 5.01; 95% CI: 1.41, 17.84; Rahman et al. 2010). An ecological study of villages in Shanxi province of China found significant correlations between cropland soil arsenic concentrations and prevalence of birth defects (Wu et al. 2014).

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Fetal loss and infant death				
Rahman et al. 2007	Study design: prospective cohort Location: Bangladesh Population: 29,134 pregnant women Data collection period: 1991–2000	Exposure measures: arsenic concentration in water for each participant As concentration: Quintile ranges (mean) - Q1: <10 µg/L (<1) - Q2: 10–166 µg/L (77) - Q3: 167–276 µg/L (225) - Q4: 277–408 µg/L (340) - Q5: ≥409 µg/L (515)	Variables assessed: fetal loss (fetal death after week 28 of gestation), infant death (death <12 months after birth), neonatal death (death within 28 days of birth), postnatal death (death >28 days and <12 months after birth) Adjustments: none (no significant confounding factors were identified) Analysis: Cox proportional hazards and logistic regression	A significant increase in relative risk for fetal loss was observed for the 277–408 µg/L quintile (relative risk: 1.14; 95% CI: 1.01, 1.30), but not for other quintiles. Significant increases in relative risk were observed for infant death for the three highest quintiles. A significant (p=0.02) dose-response relationship for arsenic exposure and risk of infant death also was observed. Relative risk: - Q1: 1 - Q2: 1.13 (95% CI: 0.95, 1.35) - Q3: 1.19 (95% CI: 1.00, 1.42) - Q4: 1.29 (95% CI: 1.08, 1.53) - Q5: 1.19 (95% CI: 1.00, 1.41) The relative risk of neonatal death was not increased for any of the exposure quintiles. A significant increase in relative risk for postnatal death was observed for the 277–408 µg/L quintile (relative risk: 1.55; 95% CI: 1.17, 2.05), but not for other quintiles.

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rahman et al. 2010	Study design: prospective cohort Location: Bangladesh Population: 2,924 pregnant women Data collection period: 2002–2004	Exposure measures: arsenic concentration in urine, adjusted for specific gravity; collected at 8 and 30 weeks of gestation As concentration: Quintile ranges (median) for mean of 8- and 30-week urine - Q1: <38 µg/L (30) - Q2: 39–67 µg/L (50) - Q3: 68–133 µg/L (94) - Q4: 134–267 µg/L (189) - Q5: 268–2,019 µg/L (390)	Variables assessed: spontaneous abortion, stillbirth, infant mortality (birth to 365 days; excluding birth asphyxia and accidental death) Adjustments: none for spontaneous abortion; asset index, and gestational age for stillbirth and infant mortality, plus season and location of women's residence for infant mortality Analysis: logistic regression for spontaneous abortion and stillbirth; Cox proportional hazards for infant death	No association was observed between urine arsenic concentrations and spontaneous abortion (based on 8-week urine) or still birth (based on mean of 8- and 30-week urine). A significant ($p<0.005$) dose-related increased in infant mortality was observed with increasing arsenic exposure (based on mean of 8- and 30-week urine). Adjusted hazard ratios: - Q1: 1 - Q2: 1.78 (95% CI: 0.44, 7.16) - Q3: 1.83 (95% CI: 0.45–7.35) - Q4: 2.29 (95% CI: 0.58, 9.05 - Q5: 5.01 (95% CI: 1.41–17.84)
Fetal malformations				
Jin et al. 2013	Study design: case control Location: China Population: maternal-fetal pairs, with infants diagnosed with neural tube defects; cases 80; controls 50 Data collection period: started in 2003	Exposure measures: arsenic concentration in placenta As concentration: - ≤8.93 ng/g - >8.93 ng/g	Variables assessed: neural tube defects Adjustments: none Analysis: multivariate logistic regression	No association was observed between placental levels of arsenic at concentrations >8.93 ng/g and elevated risk of neural tube defects (odds ratio: 0.88; 95% CI: 0.43, 1.78).

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rudnai et al. 2014	Study design: case control Location: Hungary Population: mother-infant pairs; cases: 9,734; controls: 5,880 Data collection period: 1987–2003	Exposure measures: arsenic concentration in drinking water As concentration: Sextile ranges - S1: 0–10.0 µg/L - S2: 10.1–20.0 µg/L - S3: 20.1–30.0 µg/L - S4: 30.1–40.0 µg/L - S5: 40.1–50.0 µg/L - S6: >50.0 µg/L	Variables assessed: congenital heart anomalies (all, ventral septal defect, atrial septal defect, ductus Botalli persistens, anomalies of the pulmonary artery Adjustments: child's gender, age of mother Analysis: logistic regression	Statistically significant associations were observed between drinking water arsenic concentrations (10.1 through 40.0) and all congenital heart anomalies. Adjusted odds ratios (95% CI): - S1: 1 - S2: 1.51 (1.33, 1.71); p<0.001 - S3: 1.30 (1.04, 1.63); p=0.022 - S4: 1.42 (1.06, 1.91); p=0.019 Significant associations were observed between arsenic concentration >10 µg/L and atrial septal defect and ductus Botalli persistens. Adjusted odds ratios (95% CI): - atrial septal defect: 1.79 (1.59, 2.01); p<0.001 - ductus Botalli persistens: 1.81 (1.54, 2.11); p>0.001
Wu et al. 2014	Study design: cross-sectional cohort (ecological) Location: China Population: 6,415 infants Data collection period: 2002–2004	Exposure measures: arsenic concentration in cropland soil As concentration: - minimum: 7.86 µg/g - maximum: 91.59 µg/g - median: 17.12 µg/g - mean (SD): 20.29 (11.52) µg/L	Variables assessed: all birth defects, as diagnosed by a physician Adjustments: none reported Analysis: Pearson correlation	A statistically significant correlation was observed between cropland soil concentration of arsenic (log transformed) and risk of birth defects. Pearson correlation: 0.239; p=0.019

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Fetal size and early childhood growth rate				
Guan et al. 2012	Study design: cross-sectional cohort Location: China Population: 125 mother-infant pairs Data collection period: 2006–2007	Exposure measures: arsenic concentration in maternal and cord blood at birth As concentration: Mean maternal: 6.91 µg/L Mean cord: 3.71 µg/L	Variables assessed: birth height, birth weight, chest circumference, head circumference Adjustments: Analysis: multiple linear regression	A negative association was observed between maternal arsenic blood concentration and birth weight, birth height, and chest circumference, but not head circumference. Adjusted beta (CI not reported): - Weight: -0.19 (p=0.015) - Height: -0.20 (p=0.017) - Chest circumference: -0.31 (p=0.001) A negative association was observed between cord blood and head circumference. Adjusted beta (CI not reported): -0.19 (0=0.021).
Kippler et al. 2012	Study design: cross-sectional cohort Location: Bangladesh Population: 1,929 maternal-fetal pairs Data collection period: 2001–2003	Exposure measures: arsenic concentration in maternal urine at 8 and 30 weeks of gestation As concentration Mean±SD: - 8 weeks:152±180 µg/L - 30 weeks: 168±195 µg/L	Variables assessed: biparietal diameter, occipito-frontal diameter, head circumference, abdominal circumference, and femur length as assessed by ultrasound at 14 and 30 weeks of gestation. Adjustments: maternal BMI, socio-economic status, birth order, fetal sex Analysis: mixed effect linear regression	At 14 weeks of gestation, a negative association between maternal urine arsenic concentration (log_2 transformed) and fetal occipito-frontal diameter (in all fetuses) was observed (adjusted beta: -0.060; 95% CI: 0.11, -0.0079; p=0,024). However, no association was observed at 30 weeks of gestation (adjusted beta: -0.016; 95% CI: -0.048, 0.016; p=0.32). No associations were observed between maternal urine arsenic concentration (log_2 transformed) and other fetal size measures.

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rahman et al. 2009	Study design: prospective cohort Location: Bangladesh Population: 1,578 mother-infant pairs Data collection period: 2001–2003	Exposure measures: arsenic concentration in maternal urine collected at 8 and 30 weeks of gestation exposure values expressed as averages of the 8- and 30-week collections As concentration: Mean±SD:160±163 µg/L Median: 95 µg/L Range: 6–978 µg/L	Variables assessed: birth length, weight, chest circumference, head circumference Adjustments: BMI, socio-economic status Analysis: least-squared linear regression	Significant negative associations were observed between arsenic concentration in urine and birth weight, head circumference ($p=0.041$), and chest circumference ($p<0.001$). Adjusted beta coefficients: - Weight (g per g/L) -1.68; SE: 0.62; $p=0.007$ - Head (mm per g/L): -0.05; SE: 0.03; $p=0.041$ - Chest (mm per µg/L): -0.14; SE:0.03; $p<0.001$
Saha et al. 2012	Study design: prospective cohort Location: Bangladesh Population: 2,372 infants; 52% males; 48% females Data collection period: 2001–2003	Exposure measures: arsenic concentration in urine of mothers (collected at 8 and 30 weeks of gestation) and children (collected at 18 months) As concentration: Mother quintiles (8 weeks): - Q1: 1.2–33 µg/L - Q2: 33–57 µg/L - Q3: 57–115 µg/L - Q4: 116–245 µg/L - Q5: 246–1,611 µg/L Mother quintiles (30 weeks): - Q1: 1.8–36 µg/L - Q2: 36–63 µg/L - Q3: 63–120 µg/L - Q4: 121–272 µg/L - Q5: 273–1,632 µg/L Child quintiles: - Q1: 2.4–16 µg/L	Variables assessed: attained length and weight at 3, 6, 8, 12, 18, 21, and 24 months Adjustments: urinary arsenic, age, maternal BMI, socio-economic factors Analysis: multivariate linear regression	Based on maternal urine arsenic concentration at 30 weeks of gestation, a significant ($p<0.05$) linear trend was observed for decreasing weight at 3, 6, 9, 12, and 24 months and decreasing length at 3–9 months (combined males and females). No significant trends were observed for maternal urine arsenic concentration at 8 weeks of gestation and weight or length throughout the 24-month period. Inverse associations were observed between child urine arsenic concentration and weight of females at 18, 21, and 24 months. Effects were typically significant and most pronounced for the second and third quintiles. For example, adjusted betas (95% CI) at 24 months: - Q1: reference - Q2: -0.11 (-0.31, 0.094) - Q3: -0.35 (-0.56, -0.14)

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
		- Q2: 16–26 µg/L - Q3: 26–46 µg/L - Q4: 46–96 µg/L - Q5: 96–937 µg/L		- Q4: -0.22 (-0.42, -0.014) - Q5: -0.13 (-0.34, 0.074) Inverse associations were also observed between child urine arsenic concentration and length of females at 18, 21, and 24 months, with results showing a similar pattern of significance as weight. For example, adjusted betas (95% CI) at 24 months: - Q1: reference - Q2: -0.025 (-0.60, 0.55) - Q3: -0.71 (-1.30, -0.12) - Q4: -0.64 (-1.21, -0.058) - Q5: -0.39 (-0.97, 0.19) No associations were observed between child urine arsenic concentration and weight or length of males or combined males and females at 18, 21, or 24 months.
Vall et al. 2012	Study design: cross-sectional cohort Location: Spain (Tenerife Island) Population: 96 mother-infant pairs Data collection period: 2006–2007	Exposure measures: meconium As concentration: not reported; categorized as "As non-detected" (n=46) or "As detected" (n=37).	Variables assessed: infant mortality, prematurity, gestational age at birth, birth weight and length, cranial perimeter Adjustments: none Analysis: Chi-square test	Birth weight was significantly (p=0.043) increased for infants with arsenic in meconium compared to those without arsenic in meconium. Birth weight (SD): - No meconium: 3,235.5 (405.2) - Meconium: 3,459.3 (537.4) Based on comparison to infants with no arsenic detected in meconium, no statistically significant differences (p>0.05) were observed for infant mortality, prematurity, gestational age at birth, birth length, or cranial perimeter for infants with

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				arsenic detected in meconium.
Neurodevelopmental effects				
Hamadani et al. 2010	Study design: prospective cohort Location: Bangladesh Population: 1,745 mother-child pairs Data collection period: 2002–2003	Exposure measures: arsenic concentration in mothers (mean of urine collected at 8 and 30 weeks of gestation) and children (at 18 months) As concentration: Mean mothers: 96 µg/L Quartiles mothers: - 0–44 µg/L - 45–95 µg/L - 96–215 µg/L - >215 µg/L Mean children: 35 µg/L Quartiles children: - 0–18 µg/L - 19–35 µg/L - 36–80 µg/L - >80 µg/L	Variables assessed: mental development index, psychomotor development index, comprehension, and expression assessed at 18 months of age Adjustments: age, sex, social and economic factors Analysis: multiple linear regression	No effects on developmental parameters were observed based on mother or child urine arsenic concentration.
Hamadani et al. 2011	Study design: prospective cohort Location: Bangladesh Population: 2,260 mother-child pairs Data collection period: 2002–2008	Exposure measures: arsenic concentration in mothers (collected at 8 and 30 weeks of gestation) and children (collected at 1.5 and 5 years) As concentration range: Mean (8 and 30 weeks) mothers: 80 µg/L Quartiles mothers at 30 weeks (slightly higher concentrations relative to those at 8 weeks):	Variables assessed: performance IQ (PIQ), verbal IQ (BIQ), and full-scale IQ (FSIQ) at 5 years of age Adjustments: home stimulation, fathers education, mother's BMI and IQ, assets, number of children in household, gestational age, birth length, current height-for-age score Analysis: linear regression	Means of PIQ, VIQ, and FSIQ (combined males and females) by quartile of mother's and children's urinary arsenic showed significant negative trends (p≤0.008). Negative associations were observed between (log) urine arsenic and VIQ in females, but not for males or combined males and females. The association for girls was strongest for the 5-year urine arsenic. Adjusted betas (95% CI) for VIQ: - Mother (8 weeks): -1.2 (-2.4, -0.06); p=0.039

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
		- 0–40 µg/L - 41–82 µg/L - 83–228 µg/L - >228 µg/L Mean children at 1.5 years: 34 µg/L Mean children at 5 years: 51 µg/L Quartiles children (at 5 years; slightly higher concentrations relative to those at 1.5 years): - 0–29 µg/L - 30–50 µg/L - 51–80 µg/L - >120 µg/L		- Mother (30 weeks): -1.5 (-2.6, -0.4); p=0.007 - Child (1.5 years): -0.9 (-2.1, 0.4); p=0.164 - Child (5 years): -2.4 (-3.8, -1.1); p<0.001 A significant negative association was observed between (log) urine at 5 years and FSIQ in females, but not for females based on mother gestational urine arsenic or child 1.5 years urine arsenic or for males or combined males and females for any urine arsenic. - Child (5 years): -1.4 (-2.7, -01); p=0.029 Urine arsenic concentration of 100 µg/L at age 5 years was associated with a 2.6-point decrease in VIQ and 0.9-point decrease in FSIQ in females.
Hsieh et al. 2014	Study design: case-control Location: China Population: 63 cases, 35 controls (4–6 years of age) Data collection period: 2010–2012	Exposure measures: arsenic concentration in urine (corrected for creatinine) As concentration(µg/g creatinine): Mean: - 31.68 (cases) - 25.75 (controls Tertiles: - T1: ≤ 13.56 - T2: 13.57–24.71 - T3: >24.71	Variables assessed: clinical assessment of cognitive, speech and language, gross and fine motor, social/emotional delays Adjustments: age, sex, birth weight, ethnicity, gestation length, blood lead or mercury Analysis: logistic regression	Significant association between urinary arsenic concentration (µg/g creatinine) and risk of any single or multiple developmental delays. Adjusted odds ratio (95% CI): - T1: 1 - T2: 5.95 (0.64 55.57) - T3: 11.83 (1.52, 91.82) Based on a multivariate model which included blood lead, age, birth weight, length of gestation and ethnicity of mother, the odds ratio for (95% CI) for urinary arsenic was 3.03 (1.23–7.44).

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Khan et al. 2012	Study design: cross-sectional cohort Location: Bangladesh Population: 840 children (8–11 years of age) Data collection period: not reported	Exposure measures: arsenic concentration in urine (corrected for creatinine) and in drinking water collected from each child's home As concentration: Water mean±SD: 119.5±147.5 µg/L Water range: 0.1–1,263.2 µg/L Urine mean±SD: 368.0±307.9 µg/L Urine range: 47.4–2,589.7 mg/g	Variables assessed: Bangla language score, English language score, math score Adjustments: grade in school, maternal education, paternal education, head circumference, within-teacher correlations for rating the children Analysis: spline regression model	No association was observed between drinking water or urine arsenic concentration and scores for Bangla language, English language, or math.
Nahar et al. 2014	Study design: cross-sectional cohort Location: Bangladesh Population: 312 adolescents; 14–15 years of age; 44% males, 56% females Data collection period: not reported	Exposure measures: arsenic concentration in drinking water (for each participant) and urine As concentration: Water mean: 71.7 µg/L Water range: 0.8–621.9 µg/L Water arsenic quartiles: - Q1: 0.8–10 µg/L - Q2: 11–50 µg/L - Q3: 51–100 µg/L - Q4: >100 µg/L Urine mean: 205.3 µg/L Urine range: 6–2,794 µg/L Urine arsenic tertiles: - T1: 1-≤137 µg/L - T2: >137–≤400 µg/L - T3: >400–1,312 µg/L	Variables assessed: IQ, social competence (SQ) Adjustments: socio-economic status Analysis: one-way analysis of variance and one-way analysis of covariance	IQ percentiles were significantly decreased by 17, 16, and 22% in quartiles 2, 3, and 4, respectively. SC percentiles were decreased by approximately 6 and 7% in quartiles 3 and 4, respectively. Based on urine arsenic concentration, IQ and SC scores were significantly lower in the 2nd and 3rd tertiles compared to the 1st tertile. In the 2nd and 3rd tertiles, IQ percentiles were decreased by approximately 20% and SC percentile was decreased by approximately 10%, compared to the 1st tertile.

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Parvez et al. 2011	Study design: cross-sectional cohort Location: Bangladesh Population: 304 children, 8–11 years of age. Data collection period: 2008	Exposure measures: arsenic concentration in drinking water, blood, urine, and toenails As concentration (mean±SD): Drinking water: 43.3±73.6 µg/L Blood: 4.8±3.2 µg/L Urine: 78.0±72.1 µg/L Urine (corrected for creatinine): 246.5±183.9 µg/g Toenails: 5.9±6.3 µg/g	Variables assessed: motor function assessed by fine motor function (FMF), manual coordination (MC), body coordination (BC), strength and agility, total motor composite (TMC) score Adjustments: sex, school attendance, head circumference, mother's intelligence, plasma ferritin, blood levels of manganese, lead, and selenium Analysis: log transformed linear regression	Inverse associations were observed for arsenic concentrations in drinking water, blood, urine and toenail and BC, FMC (blood and urine only) and TMC. Statistically significant associations are shown below. Adjusted Betas (95% CI): Drinking water: - BC: -0.43 (-0.77, -0.06); p<0.05 - FMC: -0.54 (-1.03. -0.05); p<0.05 - TMC: -1.18 (-2.13, -0.10); p<0.05 Blood: - BC: -1.61 (-2.70, 0.51); p<0.01 - FMC: -1.68 (-3.18, -0.18); p<0.05 - TMC: -3.63 (-6.72, -0.54); p<0.05 Urine: - BC: -1.43 (-2.67, -0.61); p<0.05 - TMC: -3.59 (-6.50, -0.68); p<0.01 Urine (corrected for creatinine): - BC: -1.60 (-2.61, -0.60); p<0.01 - TMC: -3.42 (-6.27, -0.57); p<0.05 Toenails: - BC: -1.86 (-2.83, -0.89); p<0.01 - TMC: -3.77 (-6.52, -1.03); p<0.01
Roy et al. 2011	Study design: cross-sectional cohort Location: Mexico Population: 526 children, 6–7 years of age (first graders) Data collection period: 2001	Exposure measures: urine As concentration: Median: 55.2 µg/L Range: 7.7–215.9 µg/L Quartiles: - Q1: 7.7–35.9 µg/L - Q2: 36–55.2 µg/L - Q3: 55.3–75.6 µg/L - Q4: 75.7–215.9 µg/L	Variables assessed: neurobehavioral outcomes rated by parents and teachers (ADHD index, cognitive problems, hyperactive behavior, oppositional behavior, mean behavior scores) Adjustments: age, sex, mothers education, crowding at home socio-economic status, ownership of home, child's	No significant association was observed between urinary arsenic concentration and any behavioral outcome as rated by parents, or for the overall mean behavior score as rated by either parents or teachers. For behavioral outcomes rated by teachers, significant odds ratios were observed for ADHD index in Q3 (adjusted OR: 2.4; 95% CI: 1.1, 4.9) and oppositional behavior in Q4 (Adjusted OR: 2; 95%CI: 1.0, 4.3).

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
			hemoglobin and lead Analysis: logistic regression for odds ratios; linear regression for betas.	However, no significant effects were observed for other behavioral variables and no dose-response relationships were observed for any variable.
Tofail et al. 2009	Study design: prospective cohort Location: Bangladesh Population: 1,799 infants, 7 months of age Data collection period: 2003–2004	Exposure measures: maternal urinary arsenic concentration (mean of values obtained at 8 and 30 weeks of gestation) As concentration: Median: 82.5 µg/L	Variables assessed: problem solving ability (two problem-solving tests), motor development, behavioral ratings Adjustments: socioeconomic background, age, sex Analysis: multiple linear regression	No significant effects of gestational arsenic exposure on infants' problem solving abilities, motor ability, or behavior were observed.
Wasserman et al. 2007	Study design: cross-sectional cohort Location: Bangladesh Population: 301 children, 6 years of age Data collection period: 2004–2005	Exposure measures: drinking water from tube wells at each home and children's urine arsenic concentration (adjusted for creatinine) As concentration: Drinking water (mean±SD): - 120.1±134.4 µg/L Drinking water quartiles: - Q1: 0.1–20.9 µg/L - Q2: 21–77.9 µg/L - Q3: 78–184.9 µg/L - Q4: 185–864 µg/L Urine (mean±SD): - 347.7±352.7 µg/g	Variables assessed: children's intellectual function based on Wechsler Preschool and Primary Scale of Intelligence (performance, verbal, processing speed, general ability) Adjustments: parent's education and occupation, manganese concentration in drinking water Analysis: linear regression	Water arsenic concentration was negatively associated with performance score and processing speed score, although no association was observed between water arsenic and verbal score or general ability score. Adjusted betas (SE): - Performance: -0.48 (0.24); p≤0.05 - Processing: -0.54 (0.28); p≤0.05 Based on comparisons between quartiles, a significant negative dose-response relationship was observed for performance score (p=0.05), but not for other variables (data were not presented). No significant associations were observed between urinary arsenic concentration and intellectual function variables.

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Wasserman et al. 2011	Study design: cross-sectional cohort Location: Bangladesh Population: 303 children, ages 8–11; males 49.8%, females 50.2% Data collection period: 2008	Exposure measures: arsenic concentration in blood As concentration: Blood arsenic mean (SD): - 4.81 (3.2) µg/L Water arsenic mean (SD): - 43.32 (73.65) µg/L	Variables assessed: children's intellectual function based on Wechsler Intelligence Scale for Children; measured by general ability, verbal comprehension, working memory, perceptual reasoning, processing speed Adjustments: blood manganese, maternal intelligence, maternal age, school months, head circumference, plasma ferritin Analysis: linear regression	A significant negative association was observed between concentration of arsenic in blood and verbal comprehension (adjusted beta: -1.49; SE: 0.71; $p<0.05$). No associations were observed between blood arsenic and other variables.
Wasserman et al. 2014	Study design: cross-sectional cohort Location: Maine Population: 272 children in grades 3–5; males 53.3%, females 46.7% Data collection period: 2008	Exposure measures: arsenic concentration in drinking water, measured in homes of each participant As concentration: Mean±SD: - 9.88±15.06 µg/L Quartiles: - Q1: <5 µg/L - Q2: ≥5-<10 µg/L - Q3: ≥10-<20 µg/L - Q4: ≥20 µg/L	Variables assessed: children's intellectual function based on Wechsler Intelligence Scale for Children; measured by full scale IQ (FSIQ), working memory (WM), perceptual reasoning (PE), verbal comprehension (VC), processing speed (PS) Adjustments: number of children in the home, maternal IQ, maternal education, school district, home environment Analysis: linear regression	Compared to Q1, significant negative associations were observed between water arsenic and full scale IQ, working memory, perceptual reasoning, and verbal comprehension in Q2, and between for perceptual reasoning in Q3. Scores were reduced by approximately 5–6 points. No significant associations were observed between water arsenic and any variable for Q4. Adjusted beta±SE: Q2: - FSIQ: -6.09±1.98; $p<0.01$ - WM: -4.88±2.24; $p<0.05$ - PR: -4.97±2.14; $p<0.05$ - VC: -6.22±2.49: $p<0.05$ Q3: - PR: -5.10±2.06; $p<0.05$

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Thymic function/immunological effects				
Ahmed et al. 2012	Study design: prospective cohort Location: Bangladesh Population: 130 maternal-fetal pairs Data collection period: 2001–2003	Exposure measures: arsenic concentration in maternal blood collected at 14 weeks of gestation and maternal urine collected at 8 or 14 and 30 weeks of gestation As concentration: Blood: 4.7 µg/L µg/kg Urine (8 or 14 wk): 69 µg/L Urine (30 wk): 85 µg/L	Variables assessed: thymic function measured by signal-joint T-cell receptor-arrangement excision circles (sjTRECs) mononuclear cells in cord blood Adjustments: season of birth, socio-economic status, number of days mother had fever during pregnancy Analysis: linear regression	Gestational exposure to arsenic was associated with decreased sjTRECs in cord blood, indicating impaired production of naïve T cells. Adjusted betas (95% CI): Urine (8 or 14 weeks) - -0.25 (-0.48, -0.01); p=0.03 Urine (30 weeks) - <5 µg/L: -0.53 (-0.93, -0.13); p=0.009 - ≥5 µg/L: 0.15 (-0.55, 0.85); p=0.67 Blood (14 weeks) - <1.8 µg/kg: -1.27 (-1.89, -0.66); p<0.001 - ≥ 1.8 µg/kg: 0.70 (-0.01, 1.41): 0.06
Farzan et al. 2013	Study design: prospective cohort Location: United States (New Hampshire) Population: 214 mother-infant pairs; infants 4 months of age Data collection period: 2009	Exposure measures: arsenic concentration in maternal urine and in drinking water from each home tap As concentration: Urine: - mean±SD: 6.0±7.5 µg/L - median: 3.7 µg/L Water: - mean: 5.2 µg/L - range: 0.01–67.5 µg/L	Variables assessed: Respiratory tract infections and related prescription medication and physician visits Adjustments: sex, maternal age, gestational age, birth weight, breast feeding, day care attendance, parity Analysis: Logistic and Poisson regression	Significant dose-response relationship was observed for maternal urinary arsenic concentration and infant respiratory tract infections (RTII; upper, URTI; lower LRTI). Relative risk (95% CI) for respiratory tract outcome per one-fold increase in urinary arsenic (ln-transformed): - RTI symptoms: 4.0 (1.0, 15.9) - LRTI treated with prescription medication: 3.3 (1.2, 9.0) - URTI: 1.6 (1.0, 2.5) - Cold symptoms treated with prescription medication: 2.3 (1.0, 5.2) Relative risk (95% CI) for cumulative number of infections per one-fold increase in urinary arsenic (ln-transformed): - URTI treated with prescription medication: 1.6 (1.1, 2.4) - URTI with physician visit: 1.5 (1.0, 2.1)

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Rahman et al. 2011	Study design: prospective cohort Location: Bangladesh Population: 1,552 mother-fetal pairs Data collection period: 2002–2004	Exposure measures: maternal urine, mean of collections at 8 and 30 weeks of gestation As concentration: Mean±SD: 152±175 µg/L Median: 79 µg/L Range: 1–1,211 µg/L Quintiles: - Q1: <39 µg/L - Q2: 39–64 µg/L - Q3: 65–132 µg/L - Q4: 133–261 µg/L - Q5: >261 µg/L	Variables assessed: incidence and severity of lower respiratory tract infection (LRTI) and diarrhea in infants during the first 12 months of life, as reported by mothers Adjustments: mother's education, asset index, BMI, gestational age, infant sex Analysis: Poisson regression	Based on maternal urinary arsenic concentrations, the risk of LRTI, severe LRTI, and diarrhea was significantly increased in infants during the first year of life. A positive trend ($p<0.05$) across quintiles was also observed for LRTI and severe LRTI. Adjusted relative risk (95% CI): All LRTI: - Q1: 1 - Q2: 1.28 (1.02, 1.61) - Q3: 1.33 (1.07, 1.67 - Q4: 1.57 (1.27, 1.96) - Q5: 1.69 (1.36, 2.09) Severe LRTI: - Q1: 1 - Q2: 1.33 (1.03, 1.71) - Q3: 1.31 (1.02, 1.69) - Q4: 1.54 (1.21, 1.97) - Q5: 1.54 (1.21, 1.97) Diarrhea: - Q1: 1 - Q2: 0.99 (0.83, 1.19) - Q3: 0.96 (0.80, 1.15) - Q4: 1.25 (1.05, 1.48) - Q5: 1.20 (1.01, 1.43)

Table 3-9. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Humans

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Raqib et al. 2009	Study design: prospective cohort Location: Bangladesh Population: 140 mother-infant pairs Data collection period: not reported	Exposure measures: arsenic concentration in maternal urine obtained at 30 weeks of gestation As concentration: Median (90% CI): 68.5 (23.7, 365.8) µg/L Mean±SD: 152.4±233.9 µg/L Range: 1–2,020 µg/L	Variables assessed: thymic index (thymus size) assessed at 2, 6, and 12 months of age by ultrasound Adjustments: gender, BMI-for-age in infants, maternal BMI, socio-economic factors Analysis: multiple linear regression	A significant, negative association was observed between maternal urine arsenic concentration at 30 weeks of gestation and thymic index of infants at ages 2–12 months. Adjusted betas (95% CI): - 2 months: -0.01 (-0.02, -0.001); p=0.03 - 6 months: -0.015 (-0.02, -0.005); p=0.004 - 12 months: -0.012 (-0.02, -0.002); p=0.01

ADHD = attention deficit hyperactivity disorder; As = arsenic; BMI = body mass index; CI = confidence interval; SD = standard deviation; SE = standard error

Associations between exposure to arsenic in drinking water and risk of fetal malformation have been examined in case-control and cross-sectional cohort studies (Jin et al. 2013; Rudnai et al. 2014; Wu et al. 2014). A large case-control study (9,734 cases, Hungary) found increased risk of congenital heart anomalies in association with drinking water arsenic levels >10.1 µg/L (adjusted odds ratio: 1.51, 95% CI 1.33, 1.71; Rudnai et al. 2014). In a smaller case-control study (80 cases, China), exposure to arsenic in drinking water was not associated with risk of neural tube defects (Jin et al. 2013).

Several prospective and cross-sectional studies have examined associations between exposure to arsenic in drinking water and various metrics of fetal and postnatal growth (Guan et al. 2012; Kippler et al. 2012; Rahman et al. 2009; Saha et al. 2012; Vall et al. 2012). Prospective studies conducted found significant associations between exposure to arsenic and fetal and postnatal growth (Rahman et al. 2009; Saha et al. 2012). In the Rahman et al. (2009) study (1,578 mother-infant pairs, Bangladesh), an increase in maternal urinary arsenic was associated with significant reductions of body weight, head circumference, and chest circumference at birth. The Saha et al. (2012) study (2,372 infants, Bangladesh) found significant associations between increasing urinary arsenic concentrations measured at age 18 months and decreasing postnatal body weight and length, measured at ages 18–24 months. Cross-sectional cohort studies also found significant associations between increasing fetal exposure (maternal urine or cord blood) and decreasing birth weight and size (Guan et al. 2012; Kippler et al. 2012).

Several studies have examined associations between exposure to arsenic in drinking water and various metrics of neurodevelopment (Hamadini et al. 2010, 2011; Hsieh et al. 2014; Khan et al. 2012; Nahar et al. 2014; Parvez et al. 2011; Roy et al. 2011; Wasserman et al. 2007, 2011, 2014). Prospective studies conducted on the same mother-infant cohort (1,745–2,260 mother-infant pairs, Bangladesh) did not find significant associations between fetal exposure to arsenic and mental development index or psychomotor index when assessed at age ≤18 months (Hamdini et al. 2010; Tofail et al. 2009); however, significant associations were found between increasing maternal or child urinary arsenic levels and decreasing IQ assessed at age 5 years (Hamadini et al. 2011). At age 5 years, in females, a urinary arsenic concentration of 100 µg/L was associated with 2.6-point decrease in verbal IQ and a 0.9-point decrease in full-scale IQ. Several cross-sectional studies have also found associations between exposure to arsenic and IQ (Nahar et al. 2014; Wasserman et al. 2007, 2011, 2014). A cross-sectional cohort study of children (304 children ages 8–11 years, Bangladesh) found significant associations between increasing exposure to arsenic in drinking water or arsenic concentrations in blood or urine and decrements in motor function (Parvez et al. 2011). A small case-control study (63 cases, 35 controls, age 4–6 years) found a significant association between risk of developmental delays (any cognitive, speech, motor or social/emotional delay) and

urinary arsenic levels (Hsieh et al. 2014). The adjusted odds ratio for any delay was 11.83 (95% CI: 1.52, 91.82) in association with urinary arsenic levels >24.71 µg/g creatinine.

Several prospective cohort studies have examined associations between maternal exposure to arsenic in drinking water and susceptibility to infections and thymic function of infants (Ahmed et al. 2012; Farzan et al. 2013; Rahman et al. 2011; Raqib et al. 2009). Prospective studies have found increased risk of respiratory tract infection in infants in association with maternal exposure to arsenic in drinking water (Farzan et al. 2013; Rahman et al. 2011). In the Rahman et al. (2011) study (1,552 mother-infant pairs, Bangladesh), risk of infection during the first postnatal 12 months increased in association with increasing maternal urinary arsenic levels >39 µg/L. The adjusted relative risks associated with maternal urinary arsenic concentrations 39–64 µg/L were 1.28 (95% CI: 1.02, 1.61) for all respiratory tract infections and 1.33 (95% CI: 1.03, 1.71) for severe lower respiratory tract infections. Risk of infantile diarrhea was also elevated in association with maternal urinary arsenic concentrations of 133–261 µg/L (adjusted relative risk: 1.25; 95% CI: 1.05, 1.48). In the Farzan et al. (2013) study (214 mother-infant pairs, United States), adjusted relative risks at age 4 months associated with doubling maternal urinary arsenic concentration were 4.0 (95% CI: 1.0, 15.9) for respiratory tract infection, 3.3 (95% CI: 1.2, 9.0) for lower respiratory tract infection, and 1.6 (95% CI: 1.0, 2.5) for upper respiratory tract infection. Prospective studies of the same cohort (130 or 140 mother-infant pairs, Bangladesh) found significant associations between maternal urinary arsenic levels and infant thymic index, and cord blood naïve T-cells (indicative of thymic suppression; Ahmend et al. 2012; Raqib et al. 2009).

Studies in animals also show adverse developmental effects, including neural tube defects, skeletal anomalies and decrements in pulmonary function, following *in utero* and lactational exposure to inorganic arsenic (Hill et al. 2008; Lantz et al. 2008; Ramsey et al. 2013a, 2013b). Details of the individual study designs and outcomes are provided in Table 3-10. Dose-related increases in the incidence of neural tube defects (exencephaly) were observed in mouse pups born to dams administered (gavage) 4.8–14.4 mg/kg on gestational days 7.5–8.5 (Hill et al. 2008). Dose-related skeletal anomalies also were observed, including sternebral, rib, vertebral, and, calvarial abnormalities. Gestational and early life exposure to arsenic in drinking water altered pulmonary function and morphology in mice. Lantz et al. (2008) reported increased airway reactivity following gestational exposure to drinking water concentrations of 50–100 µg/L. An increase in smooth muscle and collagen surrounding airways was also observed in mice exposed to 100 µg/L. In mice exposed to 100 µg/L sodium arsenite in drinking water during gestation, several changes in pulmonary function and morphology were observed in pups including decreased thoracic volume, and decreased number of alveoli and alveolar surface area (Ramsey et al. 2013a, 2013b).

Table 3-10. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
Skeletal anomalies				
Hill et al. 2008	Pregnant LM/Bc/Fnn mice; 20 per group	Gavage on gestational days 7.5–8.5 to 0, 4.8, 9.6, or 14.4 mg/kg sodium arsenite	Implantations, resorptions, fetal weight, neural tube defect, skeletal anomalies	Implantations and resorptions: No significant differences between control and exposure groups. Fetal weight: Significantly ($p<0.05$) decreased by approximately 11–21; decreases were not dose-related. Neural tube defect: Dose-related significant increases in exencephaly were observed. Numbers of litter with exencephaly were 0, 1, 5, and 9 in the 0, 4.8, 9.6, and 14.4 mg/kg groups, respectively Skeletal anomalies: Significantly ($p<0.05$) dose-related increases in the incidence of the following effects were observed, relative to controls: - 4.8 mg/kg: calvarial abnormalities - 9.6 mg/kg: sternebral, rib, vertebral, and calvarial abnormalities - 14.4 mg/kg: sternebral, vertebral, and calvarial abnormalities
Pulmonary effects				
Lantz et al. 2009	C57B1/6 mice; 3–5 per group	Dams and pups exposed throughout gestation through postnatal day 28 to drinking water containing 0, 5, 10, 50, or 100 µg/L sodium arsenite	Pulmonary function in response to methacholine challenge; lung morphology	Methacholine challenge: At postnatal day 25, airway reactivity was significantly increased in mice in the 50 or 100 µg/L groups, compared to control. Lung morphology: In the 100 µg/L group significant increases were observed in smooth muscle and collagen surrounding airways.

Table 3-10. Developmental Effects of Oral Exposure to Inorganic Arsenicals in Animals

Reference	Species	Exposure	Variables assessed	Outcomes
Ramsey et al. 2013a	Pregnant BALB/c, C57Bl/6 and C3H/HeARC mice; 24–29 pups per group	Dams exposed from gestational day 8 through pup age of 2 weeks to 0 or 100 µg/L sodium arsenite	Lung volume, number of alveoli in the lung, alverolar surface area, alveolar volume and airway resistance, tissue damping and elastance, airway histopathology	Effects observed in C57Bl/6 strain, but not BALB/c or C3H/HeARC strains. Lung volume: Significantly decreased ($p<0.001$) by approximately 30% compared to control. Number of alveoli in lung: Significantly decreased ($p<0.05$) by approximately 50% compared to control. Alveolar surface area: Significantly decreased ($p<0.001$) by approximately 35% compared to control. Alveolar volume and airway resistance: No change compared to control. Tissue damping and elastance: Significantly ($p<0.05$) decreased compared to control. Airway histopathology: Mucous cell metaplasia.
Ramsey et al. 2013b	Pregnant C57Bl/6 mice; 24–25 control pups; 13–23 treated pups per group	Dams exposed to drinking water containing 0, 10, or 100 µg/L sodium arsenite from gestational day 8 to birth	Examinations at pup age of 2 weeks: thoracic gas volume, airway resistance, tissue damping, tissue elastance, pressure volume curves	Thoracic gas volume: Significantly ($p=0.02$) decreased in males in the 100 µg/L group, but not in females. Airway resistance: Significantly decreased in males in the 10 µg/L group, but not the 100 µg/L group, compared to controls. No significant effect in females. Tissue damping: significantly decreased ($p<0.001$) in both treatment groups compared to control. Tissue elastance: No significant decreases.

Gestational exposure of dams to 10 µg/L resulted in significantly increased airway resistance in male pups, but not female pups (Ramsey et al. 2013b). Mucous cell metaplasia also was observed in pups born to dams exposed to 100 µg/L sodium arsenite in drinking water (Ramsey et al. 2013a).

Organic Arsenicals. Taylor et al. (2013) investigated the effects of arsenobetaine exposure during gestation and lactation on developmental outcomes in rats. Dams were administered 0, 0.1, 1, or 10 mg/kg/day arsenobetaine by gavage from gestational day 8 through lactation, and offspring were evaluated at birth, postnatal day 13, and postnatal day 90. For pups examined at birth and postnatal day 13, no effects were observed on litter size, birth weight or length, sex ratio, behavior, posture, gross malformations, or tissue weights (major organs and reproductive organs). Clinical chemistry and hematology parameters were not evaluated. Pups examined on postnatal day 90 were normal in appearance, posture, and behavior and no adverse changes in clinical chemistry parameters were observed. Statistically ($p<0.05$) and clinically (change >5% compared to control) significant changes in hematology parameters, compared to controls, were observed for males and females. In males, decreased hematocrit (10 mg/kg/day: 20% decrease), percentage of monocytes (1 and 10 mg/kg/day: 50% decrease), and number of eosinophils (10 mg/kg/day: 40% decrease) were observed. In females, the percentage of monocytes was decreased (10 mg/kg/day: 23% decrease) and the number of platelets was increased (1 mg/kg/day: 6% increase; 10 mg/kg/day: 16% increase). In offspring followed for 90 days, the onset of puberty was delayed in males and females. In males, prepubital separation was decreased by 1 day in the 0.1 and 1 mg/kg groups compared to controls. In females, vaginal opening was delayed in the 0.1 and 10 mg/kg/day groups by 7 and 4 days, respectively, compared to controls, although no treatment-related change was observed for the length of time between vaginal opening and the onset of estrus.

3.2.2.7 Cancer

Inorganic Arsenicals. Inorganic arsenic is recognized by the International Agency for Cancer (IARC 2012) and the National Toxicology Program (NTP 2014) as a carcinogen based on evidence in humans. Recent epidemiology studies of populations exposed to arsenic in drinking water provide additional evidence of that arsenic is a carcinogen in humans. These studies show associations between exposure to inorganic arsenic in drinking water and cancer of the bladder and urothelium (Chen et al. 2010b; Chung et al. 2011, 2013a, 2013b; Feki-Tounsi et al. 2013; Ferreccio et al. 2013; Hsu et al. 2013a; Huang et al. 2008a, 2008b; Smith et al. 2006, 2012; Steinmaus et al. 2013; Wu et al. 2012a, 2013), gastrointestinal tract (Hsu et al. 2013b), kidney (Huang et al. 2011, 2012; Mostafa and Cherry 2013; Yuan et al. 2010), liver (Hsu et al. 2013b), lung (Argos et al. 2014; Chen et al. 2010c; Garcia-Esquinas et al. 2013; Heck et

al. 2009; Khlifi et al. 2014; Sawada et al. 2013; Steinmaus et al. 2013), pancreas (Garcia-Esquinas et al. 2013; Hsu et al. 2013b), and skin (Gilbert-Diamond et al. 2013; Leonardi et al. 2012).

Results of studies in humans (Smith et al. 2006, 2012; Yuan et al. 2010) exposed to arsenic in drinking water suggest that exposure to oral arsenic *in utero* and/or early life is carcinogenic. Details of the individual study designs and outcomes are provided in Table 3-11. Smith et al. (2006) conducted a retrospective study on two birth cohorts in Chile exposed to high concentrations of arsenic in drinking water (approximately 870 µg/L) during1958–1970 to examine the relationship between high exposure *in utero* and early childhood and cancer deaths in adults aged 30–49 years. For the period before and after the high exposure period, arsenic concentrations in drinking water were approximately 40–100 µg/L. The cohort born during the period before the high exposure (1950–1957) was exposed during early childhood and the cohort born during the high exposure period was exposed *in utero* with possible childhood exposure. Standard mortality ratios (SMRs) were based on national data for Chile. For mortality due to lung cancer, SMRs (combined men and women) for the 1950–1957 and 1958–1970 birth cohorts were 7.0 (95% CI: 5.4, 8.9) and 6.1 (95% CI: 3.5, 9.9), respectively (Smith et al. 2006). For the same population, Smith et al. (2012) examined cohorts born 1940–1957 (pre-high exposure period) and 1958–1970 (high exposure period). For combined birth cohorts (1940–1970), SMRs were significantly increased for mortality due to bladder cancer (18.1; 95% CI: 11.3, 27.4), laryngeal cancer (8.1; 95% CI: 3.5, 16.0), lung cancer (7.0; 95% CI: 5.9, 8.2), kidney cancer (3.5; 95% CI: 2.1, 5.4), liver cancer (2.5; 95% CI: 1.6, 3.7), and other cancer (1.2; 95% CI: 1.1, 1.3). In the same Chilean population, early life exposure was associated with increased mortality due to kidney cancer (Yuan et al. 2010). For a birth cohort born just before or during the high exposure period (1950–1970), the SMR for men and women (combined) aged 30–39 was 7.08 (95% CI: 3.05, 14.0). Finding of these studies suggest that exposure to high concentration of arsenic in drinking water *in utero* and/or early childhood is associated with increased mortality due to several types of cancer.

A study conducted at the NTP Laboratory showed that lifetime exposure of CD1 mice to arsenic in drinking water at concentrations that are relevant to human exposures increased the incidence of lung cancer (Waalkes et al. 2014). Mice were exposed to 0, 50, 500, or 5,000 µg/L arsenic (as sodium arsenite) from gestation to up to 2 years. In male mice exposed to 50 and 500 µg/L (but not 5,000 µg/L), the incidence of bronchiolo-alveolar tumor (adenoma or carcinoma) was significantly increased to 51% ($p<0.05$) and 54% ($p<0.01$), compared to control (22%). In female mice exposed to 50 µg/L, but not higher concentrations, a significant increase ($p<0.05$) in the incidence of bronciolo-alveolar adenoma was observed, compared to control (50 µg/L: 25%; control: 11%).

Table 3-11. Cancer in Humans Following *In Utero* and/or Early Life Exposure to Arsenic in Drinking Water

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Smith et al. 2006	Study design: retrospective cohort Location: Cities of Antofagastra and Mejillones, Chile; this location had a defined period (1958–1970) of exposure to high concentrations of arsenic in drinking water Population: Approximately 60,000 children (as reported in Smith et al. 2012) exposed during the high exposure period. Two birth cohorts: (1) born prior to high exposure period (1950–1957), with probable in childhood exposure; (2) born during high exposure period (1958–1970) with probable *in utero* (and possible childhood) exposure. Standard group: national data for Chile, excluding the high exposure area. Data collection period: 1989–2000	Exposure measures: drinking water As concentrations (approximate): - 1950–1957: 90 µg/L - 1958–1970: 870 µg/L - 1971–1980: 100 µg/L - 1981–1990: 70 µg/L - 1991–2000: 40 µg/L	Variables assessed: mortality due to lung cancer in the age group 30–49 during 1989–2000; data collected from death certificates Adjustments: none Analysis: standard mortality ratios with Chile as the reference, Poisson regression	Mortality due to lung cancer was increased in persons with probable *in utero* and childhood exposure to high arsenic concentrations in drinking water. Standard mortality ratios (95% CI): Born 1950–1957: - 30–39 years (male):12.8 (7.1–21.1); p<0.001 - 30–39 years (female): 4.2 (0.5–15.1); p=0.084 - 30–39 years (combined):10.3 (6.0, 16.5); p<0.001 - 40–49 years (male): 7.2 (5.1, 9.9); p<0.001 - 40–49 years (female): 4.8 (2.6, 8.1); p<0.001 - 40–49 years (combined): 6.3 (4.7, 8.3) p<0.001 - 30–49 years (male): 8.2 (6.2, 10.8); p<0.001 - 30–49 years (female): 4.7 (2.7, 7.7); p<0.001 - 30–49 years (combined): 7.0 (5.4, 8.9); p<0.001 Born 1958–1970: - 30–39 years (male): 9.2 (4.8, 16.1); p<0.001 - 30–39 years (female): 3.6 (0.7, 10.5); p=0.052 - 30–39 years (combined): 7.0 (3.9, 11.6); p<0.001

Table 3-11. Cancer in Humans Following *In Utero* and/or Early Life Exposure to Arsenic in Drinking Water

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				- 40–49 years (male): 3.4 (0.01, 18.9); p=0.255 - 40–49 years (female): 0 - 40–49 years (combined): 2.0 (0.01, 11.2); p=0.391 - 30–49 years (male): 8.1 (4.3, 13.9); p<0.001 - 30–49 years (female): 2.9 (0.6, 8.5); p=0.087 - 30–49 years (combined): 6.1 (3.5, 9.9); p<0.001
Smith et al. 2012	Study design: retrospective cohort Location: Cities of Antofagastra and Mejillones, Chile; this location had a defined period (1958–1970) of exposure to high concentrations of arsenic in drinking water Population: Approximately 60,000 children exposed during the high exposure period. Two birth cohorts: (1) born prior to high exposure period (1940–1957), with probable in childhood exposure; (2) born during high exposure period (1958–1970) with probable *in utero* and possible childhood exposure. Standard group: national data for Chile, excluding the high exposure area. Data collection period: 1989–2000	Exposure measures: drinking water As concentrations (approximate, as reported in Smith et al. 2006: - 1940–1947: not reported - 1950–1957: 90 µg/L - 1958–1970: 870 µg/L - 1971–1980: 100 µg/L - 1981–1990: 70 µg/L - 1991–2000: 40 µg/L	Variables assessed: mortality due to cancer in the age group 30–49 during 1989–2000; data collected from death certificates Adjustments: none Analysis: standard mortality ratios with Chile as the reference, Poisson regression	Exposure to drinking water with high concentrations of arsenic (1958–1970) increased risk of mortality due to all cancer, bladder cancer, laryngeal cancer, and liver cancer. Standard mortality ratios (95% CI): 1940–1957 cohort: - all cancer males: 2.1 (1.9, 2.4); p<0.001 - all cancer females: 1.4 (1.2, 1.6); p<0.001 - bladder cancer males: 13.7 (6.8, 24.5); p<0.001 - bladder cancer females: 7.9 (1.0, 28.6); p=0.03 - laryngeal cancer males: 8.9 (3.6, 18.3); p<-0.001 - laryngeal cancer females: none observed - liver cancer males: 2.4 (1.2, 4.4); p=0.01 - liver cancer females: 1.5 (0.5, 3.2); p=0.23 - all other cancers males: 1.0 (0.8, 1.2); p=0.64 - all other cancers females: 1.2 (1.0, 1.4);

Table 3-11. Cancer in Humans Following *In Utero* and/or Early Life Exposure to Arsenic in Drinking Water

Reference	Study design and population	Exposure	Variables assessed	Outcomes
				p<0.01 1958–1970 cohort: - all cancer males: 2.2 (1.7, 2.8); p<0.001 - all cancer females: 1.4 (1.1, 1.8); p<0.01 - bladder cancer males: 65.7 (24.1, 143); p<0.001 - bladder cancer females: 43.0 (8.9, 126); p<0.001 - laryngeal cancer males: 27.4 (0.7, 153); p=0.04 - laryngeal cancer females: none observed - liver cancer males: 5.9 (1.9, 13.7); p<0.01 - liver cancer females: 4.7 (1.3, 12.0); p=0.01 - all other cancers males: 1.5 (1.1, 2.0); p=0.01 - all other cancers females: 1.2 (0.9, 1.6); p=0.09 Combined cohorts (1940–1970): - bladder cancer: 18.1 (11.3, 27.4); p≤0.001 laryngeal cancer: 8.1 (3.5, 16.0); p≤0.001 - lung cancer: 7.0 (5.9, 8.2); p≤0.001 - kidney cancer: 3.5 (2.1, 5.4); p≤0.001 - liver cancer: 2.5 (1.6, 3.7); p≤0.001 - other cancer: 1.2 (1.1, 1.3); p=0.002

Table 3-11. Cancer in Humans Following *In Utero* and/or Early Life Exposure to Arsenic in Drinking Water

Reference	Study design and population	Exposure	Variables assessed	Outcomes
Yuan et al. 2010	Study design: retrospective cohort Location: Cities of Antofagastra and Mejillones, Chile; this location had a defined period (1958–1970) of exposure to high concentrations of arsenic in drinking water Population: Approximately 60,000 children exposed during the high exposure period. Two birth cohorts: (1) born prior to high exposure period (before 1950), with no early life exposure; (2) born before or during high exposure period (1950–1970) with probable *in utero* and childhood exposure. Standard group: national data for Chile, excluding the high exposure area. Data collection period: 1971–2000	Exposure measures: drinking water As concentrations - 1950–1954: 90 µg/L - 1955–1959: 870 µg/L - 1960–1969: 870 µg/L - 1970–1974: 260 µg/L - 1975–1979: 110 µg/L - 1980–1984: 80 µg/L - 1985–1990: 60 µg/L - 1990–1994: 40 µg/L	Variables assessed: mortality due to kidney cancer in the age group 30–49 born during 1950–1970 and for the age group 40+, born before 1950; data collected from death certificates Adjustments: none Analysis: standard mortality ratios with Chile as the reference, Poisson regression	Early life exposure was associated with increased mortality due to kidney cancer. For the cohort born just before or during the high exposure period (1950–1970), the standard mortality ratio for men and women (combined) aged 30–39 was 7.08 (95% CI: 3.05–14.0; p<0.001). Standard mortality ratios (95% CI): 1950–1970 birth cohort (death at 30–39 years of age): - men: 5.63 (1.52, 14.4) - women: 9.52 (2.56, 24.4) - combined: 7.08 (3.05, 14.0) Before 1950 birth cohort (death at 40+ years of age): - men: 2.68 (2.19, 3.26) - women: 3.91 (3.12, 4.84) - combined: 3.12 (2.69, 3.61)

As = arsenic; CI = confidence interval

Organic Arsenicals. Studies in animals have evaluated carcinogenic effects of the arsenic metabolites methylarseonous acid [MMA(III)] and dimethylarsenic acid [DMA(III)] (Tokar et al. 2012a, 2012b). Gestational exposure of CD1 mice to MMA(III) produced cancer in offspring (Tokar et al. 2012a). Pregnant mice were exposed to 0, 12.5, or 25 mg/L MMA(III) in drinking water on days 8–18 of gestation. Offspring were assessed for tumors for up to 2 years. In male offspring, the incidences of hepatocellular carcinoma in the 25 mg/L group (control: 0%; 12.5 mg/L: 12%; 25 mg/L: 22%), adrenalademona in both treatment groups (control: 0%; 12.5 mg/L: 28%; 25 mg/L: 17%), and lung adenocarcinoma 12.5 mg/L group only (control: 17%; 12.5 mg/L: 44%) were significantly ($p<0.05$) increased. For hepatocellular carcinoma, a significant dose-related trend was observed ($p=0.018$). In female offspring, the incidences of adrenal cortical adenoma at 25 mg/L (control: 0%; 25 mg/L: 26%) and total epithelial uterine tumors in both treatment groups (control: 0%; 12.5 mg/L: 26%; 25 mg/L: 30%) were significantly ($p>0.05$) increased. The carcinogenic potential of DMA(III) was examined in offspring of CD1 mice exposed to 0 or 85 mg/L sodium arsenite (As[III]) in drinking water on gestational days 8–18, followed by life-time exposure (post-lactation) to DMA(III) (0 or 200 mg/L) in drinking water (Tokar et al. 2012b). Exposure to As(III) plus DMA(III) significantly ($p<0.05$) increased the incidence of renal cellular carcinoma (control: 0; As(III): 2%; DMA(III): 0; As(III) plus DMA(III): 13%) compared to control. The incidence of hepatocellular carcinoma was significantly ($p<0.05$) increased for As(III) alone and As(III) plus DMA(III) compared to control (control: 6%; As(III): 20%; DMA(III): 8%; As(III) plus DMA: 43%) and for As(III) plus DMA(III) compared to As(III) alone. Significant increases ($p<0.05$, compared to control) in the incidences of adenocarcinoma of the lung and adenoma of the adrenal cortex were observed, but there were no statistically significant differences between treatment groups. Results indicate that exposure of adults mice to DMA(III) alone induced tumors of the kidney, lung and adrenal cortex and promoted development of hepatocellular carcinoma induced by prenatal exposure to As(III).

3.3 GENOTOXICITY

Inorganic Arsenicals. Recent studies in humans chronically exposed to arsenic by environmental or occupational exposure show that exposure to arsenic is associated with non-specific and oxidative DNA damage (Basu et al. 2005; Mendez-Gomez et al. 2008; Pei et al. 2013; Vuyyuri et al. 2006), chromosome damage (Paiva et al. 2006), increase micronuclei frequency (Banergee et al. 2013; Bartolotta et al. 2011; Gamino-Gutierrez et al. 2013; Martinez et al. 2005; Paiva et al. 2008; Paul et al. 2013a; Vuyyuri et al. 2006), and decrease DNA repair (Mendez-Gomez et al. 2008). Details of these studies are summarized in Table 3-12.

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
DNA damage				
Basu et al. 2005	Location: India Population: adults; 30 exposed; 30 controls	As concentrations (µg/L): Drinking water (mean±SE): - control: 7.69±0.49 - exposed: 247.12±19.93 Urine (mean±SE): - control: 12.49±1.35 - exposed: 259.75±33.89	Cell type: peripheral blood lymphocytes Assessment: nonspecific DNA damage (comet assay); oxidative DNA (comet assay combined with formamido-pyrimidine-DNA glocosylase enyzme digestion	Exposure to arsenic in drinking water significantly increased non-specific and oxidative DNA damage, compared to controls. Comet assay (comet length; mean±SE) - control: 22.193±0.908 - exposed: 86.296±1.846 (p<0.01) Comet assay plus enzyme digestion (comet length; mean±SE): - control: 25.879±1.266 - exposed: 111.075±2.385 (p<0.01)
Mendez-Gomez et al. 2008	Location: Mexico Population: 3 groups of elementary school children based on location to a smelter: Group A (distant): n=21; Group B (intermediate); n=19; Group C (near): n=21.	As concentrations: Drinking water (µg/L): - Group A: 26.05 - Group B (control): 6.8 - Group C: 13.16 Urine (µg/L): - Group A: 143 - Group B (control): 100 - Group C: 115	Cell type: peripheral blood lymphocytes Assessment: nonspecific DNA damage (comet assay)	For Group C, but not Group A, comet assay results show a significant increase in comet tail length (13% increase compared to control; p<0.05) and the percentage of cells with tail length >20 µm (26% increase compared to control; p<0.05).

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Pei et al. 2013	Location: China Population: exposed: 75 adult males with arsenicosis (severity of mild, moderate, and severe based on degree of skin lesions); controls: 12 males without skin lesions	As concentrations: Drinking water (µg/L) (no statistical differences between groups): - control: 27.20 - mild: 29.00 - moderate: 27.87 - severe: 35.57 Urine (µg/g creatinine): - control: 10.88 - mild: 14.87 - moderate: 16.54 - severe: 19.05 ($p<0.05$ compared to control)	Cell type: peripheral blood polymorphonuclear leukocytes (PNMs) Assessment: oxidative DNA damage (8-OHdG immunochemical staining of leukocytes)	In PMNs, but not monocytes, positive 8-OHdG reactions were observed, indicating oxidative damage to DNA.
Vuyyuri et al. 2006	Location: India Population: controls: 165; exposed: 200 glass workers; mean years of exposure: 12.3; 72% male; 28% female	As concentrations: Blood (µg/L; mean±SE): - control: 11.74±0.51 - exposed: 56.76±0.48 ($p<0.05$ compared to control)	Cell type: peripheral blood leukocytes Assessment: DNA damage (comet assay: tail length)	Compared to control, a statistically significant ($p<0.05$) increase in basal DNA damage was observed in exposed workers. Comet tail length (µm; mean±SE): - control: 8.29±0.71 - exposed: 14.95±0.48 No differences were observed between males and females.

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Chromosome aberrations/sister chromatid exchange				
Paiva et al. 2006	Location: Chili Population: smelting plant workers: (1) arsenic-exposed workers (n=105); (2) internal control: office workers at the smelting plant (n=53); (3) external control: reference smelter workers with no arsenic exposure (n=48)	As concentrations: Total arsenic in urine (µg/L; mean±SE): - exposed: 136.01±10.18* - Ref 1: 64.60±5.05** - Ref 2: 21.34±2.64 *Significantly different (p<0.001) Ref 1 and Ref 2. **Significantly (p<0.001) difference from Exposed and Ref 2.	Cell type: peripheral blood lymphocytes Assessment: SCE and percentage of HFCs, defined as cells that displayed SCE values above the 95th percentile of the SCE/cell distribution for the study population.	Sister chromatid exchanges (SCEs) and high frequency cells (HFCs) were significantly increased in the exposed group compared to the reference groups. SCE/cell (mean±SE): - exposed: 6.28±0.09 (p<0.01 versus external control) - Ref 1: 6.21±0.23 - Ref 2: 5.84±0.14 HFC (%) (mean±SE): - exposed: 2.21±0.20 (p<0.01 versus external and internal controls) - Ref 1: 1.30±0.24 - Ref 2: 1.20±0.23
Micronuclei formation				
Banerjee et al. 2013	Location: India Population: 6 groups based on arsenic range in rice; Group 1 (n=113); Group 2 (n=118); Group 3 (n=84); Group 4 (n=35); Group 5 (n=30); Group 6 (n=37	Total As concentrations: Cooked rice (µg/kg): - Group 1: ≤100 - Group 2: >100–≤150 - Group 3: >150–≤200 - Group 4: >200–≤250 - Group 5: >250–≤300 - Group 6: >300 Urine (µg/L; mean±SD): - Group 1: 32±37 - Group 2: 38±40 - Group 3: 48±51 - Group 4: 76±74 - Group 5: 87±64 - Group 6: 96±81	Cell type: urothelial cells Assessment: micronuclei formation	Micronuclei frequency was significantly higher (p<0.001) for groups with cooked rice arsenic concentrations >200 µg/kg, compare to the group with the lowest arsenic concentrations ≤100 µg/kg.

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Bartolotta et al. 2011	Location: Argentina Population: exposed rural (4 male and 4 adults: control rural (5 males and 5 females); exposed urban (8 males and 11 females); control urban (10 males and 12 females)	As concentrations: Drinking water (µg/L; approximate concentrations; data presented graphically): - exposed rural: 45–400 - control rural: <30 - exposed urban: <10 - control urban: 80 *Total arsenic contained approximately 88% inorganic arsenic	Cell type: exfoliated buccal cells Assessment: micronuclei formation	Micronuclei formation was significantly increased in exposed rural and urban groups, compared to respective controls. No differences between males and females were observed for either population. Percentage of micronuclei (mean±SE): Rural population: - exposed: 2.15±0.13 (p=0.0005) - control: 0.94±0.06 Urban population: - exposed: 0.27±0.01 (p=0.002) - control: 0.15±0.02
Gamino-Gutierrez et al. 2013	Location: Villa de la Paz, Mexico (historical mining site) Population: exposed: 98 children (ages 4–10 years) residing in Villa de la Paz for at least 2 years; control: 42 unexposed children from a different location	As concentrations: Soil arsenic concentration (mg/kg soil): - range: 212–16,595 - mean 1,062 Urine arsenic (µg/g creatinine): Exposed: - range 5.4–283.4 - mean: 40.3 Control: - range: 1.4–43.6 - control: 16.3	Cell type: exfoliated epithelial cells Assessment: micronuclei frequency	Micronuclei formation in exposed children was associated with urine arsenic levels. - correlation coefficient: 0.49 - p<0.001

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Martinez et al. 2005	Location: Antofagasta region of Chile Population: 102 controls; 105 exposed	As concentrations: Drinking water range (µg/L): - controls: 0.2 - exposed: 0.3–1.0870 Fingernails (µg/g): - control: 3.57 - exposed: 10.15	Cell type: buccal cells Assessment: frequency of micronuclei	No increase in micronuclei formation was observed in control vs exposed groups. Micronuclei frequency (mean±SE): - control: 2.74±0.26 - exposed: 3.14±0.32
Paiva et al. 2008	Location: Chili Population: smelting plant workers: (1) arsenic-exposed workers (n=105); (2) internal control: office workers at the smelting plant (n=52); (3) external control: reference smelter workers with no arsenic exposure (n=50)	As concentrations: Total arsenic in urine (µg/L; mean±SE): - exposed: 136.01±10.18* - Ref 1: 63.30±4.97** - Ref 2: 23.65±3.45 *Significantly different (p<0.001) Ref 1 and Ref 2. **Significantly (p<0.001) difference from exposed and Ref 2.	Cell type: peripheral blood leukocytes Assessment: analysis of variance test	No differences in micronuclei frequencies were observed between the three groups.

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Paul et al. 2013a	Location: India Population: 3 cohorts studied in 2004–2005 and 2010–2011. Cohort 1: exposed with no skin lesions (n=61 for follow-up study); Cohort 2: exposed with skin lesions (n=67 for follow-up study; Cohort 3: control (n=54 for follow-up study)	As concentrations: 2004–2005 assessment: Drinking water (µg/L): - Cohort 1: 348.23 - Cohort 2: 327.56 - Cohort 3: not detected Urine (µg/L): - Cohort 1: 642.31 - Cohort 2: 598.64 - Cohort 3: 11.62 2010–2011 assessment: Drinking water (µg/L): - Cohort 1: 5.60 - Cohort 2: 8.53 - Cohort 3: not detected Urine (µg/L): - Cohort 1: 21.99 - Cohort 2: 26.14 - Cohort 3: 15.34	Cell type: urothelial cells Assessment: micronuclei formation; to determine if micronuclei formation decreased following implementation of measure to decreased arsenic concentration in drinking water	Reduction in Arsenic concentration in drinking water was associated with a decreased in micronuclei formation. In exposed cohorts, significant reductions in micronuclei formation were observed in the assessment conducted 2010–2011 compared to the assessment conducted in 2004–2005. Micronuclei frequency (mean±SD): Cohort 1: - 2004–2005: 5.15±1.73 - 2010–2011: 1.84±0.38 (p<0.001) Cohort 2: - 2004–2005: 4.51±1.27 - 2010–2011: 1.62±0.77 (p<0.001) Cohort 3: - 2004–2005: 1.21±0.25 - 2010–2011: 1.24±0.33
Vuyyuri et al. 2006	Location: India Population: controls: 165; exposed: 200 glass workers; mean years of exposure: 12.3; 72% male; 28% female	As concentrations: Blood (µg/L; mean±SE): - control: 11.74±0.51 - exposed: 56.76±0.48 (p<0.05 compared to control)	Cell type: Buccal cells Assessment: micronucleus frequency	Compared to control, a statistically significant (p<0.05) increase in micronuclei formation was observed in exposed workers. Percent micronuclei formation (mean±SE): - control: 0.21±0.36 - exposed: 1.52±0.41 No differences were observed between males and females.

Table 3-12. Genotoxicity in Humans Exposed to Oral Arsenic

Reference	Study population	Exposure	Cell type and variables assessed	Outcomes
Decreased DNA repair				
Mendez-Gomez et al. 2008	Location: Mexico Population: 3 groups of elementary school children based on location to a smelter: Group A (distant): n=21; Group B (intermediate); n=19; Group C (near): n=21	As concentrations: Drinking water (µg/L): - Group A: 26.05 - Group B (control): 6.8 - Group C: 13.16 Urine (µg/L): - Group A: 143 - Group B (control): 100 - Group C: 115	Cell type: peripheral blood lymphocytes Assessment: DNA repair capacity (analysis of breaks following treatment of cells with H_2O_2	DNA repair was significantly reduced in Groups A (48% decrease; p=0.01) and C (74% decrease; p=0.001) compared to Group B

As = arsenic; DNA = deoxyribonucleic acid; HFC = high frequency cell; SD = standard deviation; SCE = sister chromatid exchange; SE = standard error

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.2 Oral Exposure

Absorption of Water Soluble Inorganic and Organic Arsenic. Absorption of inorganic and organic arsenic has been studied in a juvenile swine model (Juhasz et al. 2006). Arsenic bioavailability (fraction of dose absorbed into blood) was lower for MMA(V) and DMA(V) compared to inorganic arsenite (As(III)) or arsenate (As(V)). Following a gavage dose of 80 or 100 µg As/kg, bioavailability was 103.9% (±25.8 SD) for As(III), 92.5% (±22.3 SD) for As(V), 16.7% (+5.0 SD) MMA(V) and 33.3% (+1.7 SD) for DMA(V).

Absorption of Inorganic Arsenic in Food. A mass balance approach was used to estimate absorption of arsenic from ingested food in a small group of human subjects (n=13 adults including 7 females; Stanek et al. 2010). The study consisted of two phases conducted approximately 2–3 years apart, with partial overlap of subjects in both phases. The subjects consumed self-prepared meals of their choosing and refrained from consuming foods that may have had high arsenic levels such as seafood, sea vegetables, rice, mushrooms, spinach, and grape juice. The subjects collected duplicate diet samples for all foods and beverages consumed during the study. Arsenic absorption was estimated from measurements of daily arsenic intakes (based on the duplicate diet samples) and excretion (fecal and urine) over a period of 7 days. The estimated average absorption of arsenic from food was 87.5% (95% CI: 81.2, 93.8) in the first phase of the study and 89.7% (95% CI: 83.4, 96.0) in the second phase of the study.

Absorption of arsenic from grains and vegetables has been studied in a juvenile swine model (Juhasz et al. 2006, 2008). Arsenic in rice was identified as a mixture of organic and inorganic compounds and the relative amounts of each varied with rice variety. Arsenic in market-purchased Basmati white rice cooked in water containing 1,000 µg/L As(V) was identified as 100% inorganic arsenic. Bioavailability (fraction of dose absorbed into blood) of arsenic from the cooked white rice was 89% ±9 (SD). Arsenic in greenhouse grown Quest rice was identified as 86% organic arsenic (primarily DMA; valence not specified). Bioavailability from the greenhouse grown Quest rice was 33.1% ±3.2 (SD). Lower bioavailability of arsenic from Quest rice was consistent with lower bioavailability of MMA and (16.7% ±5.0 SD) and DMA (33.3% ±1.7 SD) compared to As(III) (103.9% ±25.8 SD) or As(V) (92.5% ±22.3 SD) when administered by gavage. In swine, bioavailability of arsenic in rinsed edible portions of vegetables was estimated to be 52% ±18 (SD) for chard, 50% ±13 (SD) for lettuce, 77% ±20 (SD) for

radish and 98% ±23 (SD) for mung bean (Juhasz et al. 2008). All of the arsenic in the vegetables was identified as either inorganic As(III) or As(V).

Absorption of Inorganic Arsenic in Soil. Absorption of arsenic from soil was estimated in a mass balance study (Stanek et al. 2010). Arsenic absorption was estimated from measurements of daily arsenic intakes and excretion over a period of 7 days in a group of 11 adults. Soil was ingested daily in a capsule containing approximately 0.6 g soil and 112 µg arsenic. Characteristics of the soil were not reported, other than one soil sample having been collected at a cattle dip site where, presumably, arsenate pesticides had been used. The estimated average absorption of arsenic from soil was 48.7% (95% CI: 36.2, 61.3) compared to 89.7% (95% CI: 83.4, 96.0) from food. This study suggests that absorption of arsenic from soil was approximately 46% lower than absorption from food (soil/food ratio=54%).

Studies conducted in animals show that bioavailability of arsenic in soil tends to be lower than that of arsenic that is dissolved in water. An analysis of animal bioassay data on relative bioavailability (RBA) of soil arsenic (i.e., absorption from ingested soil relative to absorption of ingested sodium arsenate) included 103 RBA estimates on 88 soils collected from sites contaminated as a result of mining and/or smelting operations, pesticide or herbicide application, and/or manufacture (EPA 2012a). Estimates of RBA included in the analysis were derived from bioassays conducted in juvenile swine, mice, or monkeys (Bradham et al. 2011; Brattin and Casteel 2013; Juhasz et al. 2007a, 2014a; Roberts et al. 2002, 2007; Rodriguez et al. 1999). The average RBA for the 88 soils was 30%, the median was 28% and the 5th and 95th percentiles were 4.1 and 56%, respectively. The highest RBA observed was 78%. A major portion of the observed variability in RBA for different soils can be explained by variations in bioaccessibility of arsenic (solubility of arsenic in the gastrointestinal tract). Bioaccessibility, measured with *in vitro* extraction assays, has been shown to strongly correlate with RBA measured in animals (Basta et al. 2007; Bradham et al. 2011; Brattin et al. 2013; Bruce et al. 2007; Denys et al. 2012; Juhasz et al. 2007a, 2007b, 2009, 2011, 2014a, 2014b; Makris et al. 2008; Roberts et al. 2007; Rodriquez et al. 1999; Ruby et al. 1996; Wragg et al. 2011). This suggests that physical and chemical factors that influence the dissolution of arsenic from arsenic-bearing particles in the gastrointestinal tract are important determinants of absorption of soil arsenic. These may include particle morphology, including the degree to which arsenic is surficial or occluded within particles, and arsenic mineralogy, which may affect solubility within the gastrointestinal tract (Bradham et al. 2011; Brattin et al. 2013).

3.4.1.3 Dermal Exposure

Dermal absorption of arsenate and arsenic in soil has been studied in Rhesus monkeys (Lowney et al. 2007). Soil or a sodium arsenate solution was applied to the shaved abdomen of monkeys (n=3) for a period of 8 hours and urinary arsenic excretion was measured for a period of 7 days during and following dosing. The sodium arsenate dose was 1.3 or 1.4 mg arsenic. Soils were dried and sieved to <150 µm particle size and applied at a dose of 4 mg soil/cm^2 to achieve a monolayer on the skin surface. Soils were applied dry or wet. The dosing area (100 cm^2) was covered to prevent removal of the soil from the skin (e.g., ingestion). Absorption was estimated as the ratio of the cumulative urinary excretion of arsenic 0–96 hours following the dermal dose to the cumulative urinary excretion following an intravenous dose of sodium arsenate. Soil samples from Colorado (1,230 mg As/kg soil) and New York (1,400 mg As/kg soil) were studied. Arsenic in the Colorado soil was identified as being primarily iron-arsenic oxide (95%). Arsenic in the New York soil was primarily arsenic oxide (87%) and lead arsenate (10%). In two dosing trials, absorption following dermal application of sodium arsenate ranged from 0.3 to 4.3% (mean 2.5% ±2.3 SD) in the first trial and from 1.9 to 16% (mean 6.7% ±7.8 SD) in the second trial. Arsenic was not detectable above background following dermal dosing with either soil. Estimated absorption from soil doses ranged from 0.19 to 0.33% when applied dry (mean 0.24% ±0.08 SD) and from 0 to 0.85% when applied wet (mean 0.50% ±0.44 SD).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Distribution of arsenic following inhalation exposure has been studied in mice (Burchiel et al. 2009, 2010). Mice (male C57B1/6N) were exposed (nose-only) to aerosols of arsenic trioxide at concentrations of 50 or 1,000 µg As/m^3 for 3 hours/day for 14 days. The mass median diameters of the two exposures were 2.5 µm (±1.7 geometric standard deviation [GSD]) and 2.3 µm (±2.3 GSD). Immediately following exposure, dose-related increases in absorbed arsenic were observed in bladder, blood, brain, kidney, liver, lung, and spleen. The highest concentrations were observed in liver, followed by bladder and kidney.

3.4.3 Metabolism

Two metabolic pathways for inorganic arsenic, an enzymic arsenic reduction/methylation pathway and an alternative pathway involving nonenzymatic formation of arsenic-glutathione complexes, are described in Agency for Toxic Substances Disease Registry (2007). A third metabolic pathway recently has been proposed (Bhattacharjee et al. 2013a; Rehman and Naranmandura 2012). This novel pathway involves initial binding of inorganic arsenic to sulfhydryl groups of cysteinyl moieties on proteins, followed by

reductive methylation catalyzed by arsenic(III) methyltransferase (AS3MT) and using the methyl group donor S-adenosylmethionine (SAM) to form MMA(V) and DMA(V). The products of this proposed pathway are the same as for the reduction/methylation and alternative pathways.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

3.4.5.1 Summary of PBPK Models

***El-Masri and Kenyon (2008) Model*.** El-Masri and Kenyon (2008) developed a human PBPK model for simulating ingested inorganic arsenate [As(V)], arsenite As(III), MMA(V), and DMA(V). The model consists of four interconnected submodels representing each of the above arsenic species. Each submodel includes compartments representing blood, brain, heart, kidney, liver, lung, skin and gastrointestinal tract. Exchanges of arsenic between blood and tissues are simulated as flow-limited clearances governed by tissue blood flow. First-order absorption from the gastrointestinal tract is assumed for all four arsenic species. Arsenic metabolism activity is assigned to kidney, liver, and lung, with lung being a lumped compartment representing the contribution from all other tissues other than kidney and liver. Oxidation and reduction of As(V) and As(III) is assumed to be first order and governed by rate constants for each species. Reduction of MMA(V) and DMA(V) is also assumed to be first order. Methylation of As(III) and MMA(III) is assumed to be capacity-limited with the rates governed by K_m and V_{max} and K_i, where K_i is the noncompetitive inhibition constant for As(III) or MMA(III). All of the simulated arsenic species are excreted in urine. Excretion of As(III), As(V), MMA(V), or DMA(V) is simulated as first-order transfer from kidney to urine. Urinary excretion of MMA(III) or DMA(III) formed from reduction of MMA(V) or DMA(V), respectively, is simulated as a direct first-order transfer of the reduced metabolite to the urine (without entering the circulation). This non-physiologic simplification eliminates the need to parameterize the blood and tissue kinetics of MMA(III) and DMA(III).

Absorption rate constants were optimized from data on blood arsenic concentration kinetics in mice that received oral doses of As(V), As(III), MMA(V), or DMA(V) (Hughes et al. 2005; Kenyon et al. 2005a, 2005b). Rate constants for urinary excretion were optimized from data on urinary excretion in adults who were administered a single oral dose of arsenic (500 μg) as As(III), MMA(V), or DMA(V) (Buchet et al. 1981a). Values for K_m and K_i for methylation were derived from *in vitro* studies of the purified methyltransferases (Wildfang et al. 1998; Zakharyan et al. 1999). Values for methylation V_{max} and all other metabolism rate constants were optimized from data on urinary excretion humans dosed with As(III), MMA(V), or DMA(V) (Buchet et al. 1981a). Values for tissue/blood partition coefficients were

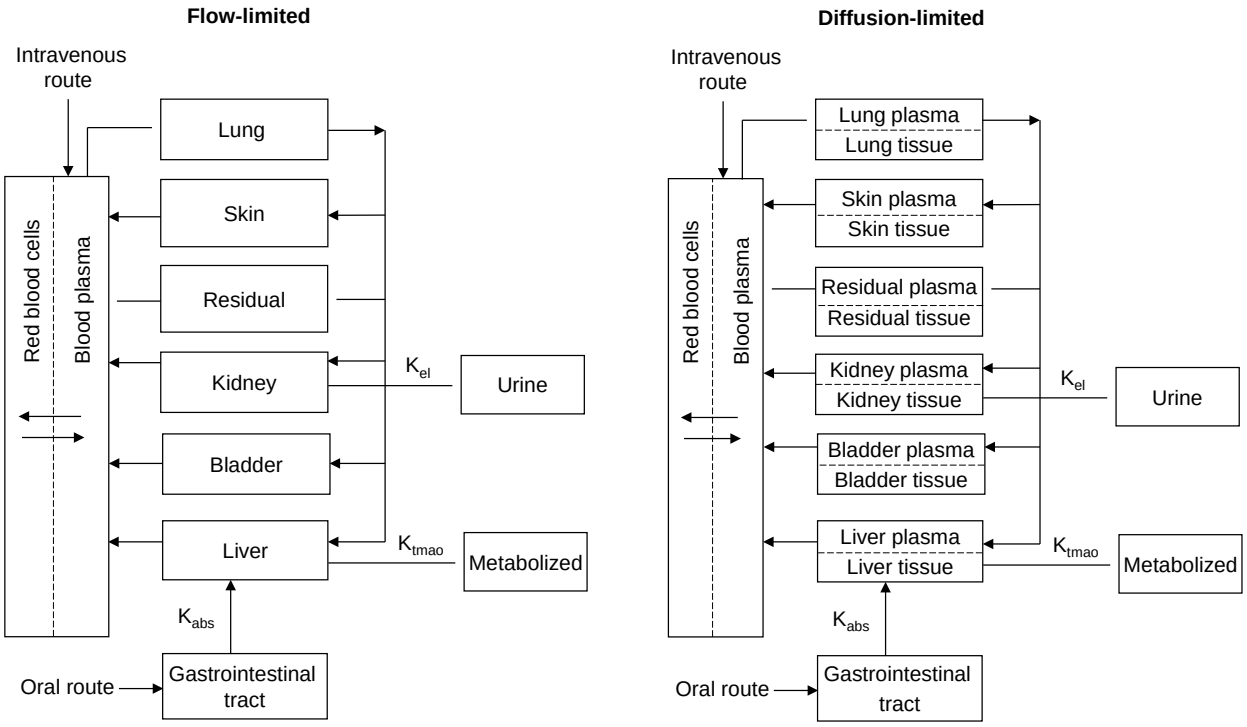
derived from tissue/blood arsenic ratios measured in autopsy samples from poisoning cases (Yu 1999a); however, alternative values based on studies conducted in rodents were also evaluated.

The model was evaluated by comparing predictions with observation made in humans of urinary excretion of total arsenic, inorganic arsenic, DMA, and MMA from studies not used in model calibration (Aposhian et al. 2000; Mandal et al. 2001; Mann et al. 1996b; Valenzuela et al. 2005). Sensitivity analyses showed that urinary predictions were sensitive to values assigned to rate constants for urinary excretion, reduction, and V_{max} for methylation. Metrics used to evaluate agreement between predictions and observations included median performance error and PBPK index (El-Masri and Kenyon 2008; Krishnan et al. 1995). The model performed better at predicting excretion of inorganic arsenic (error <10%) than methylated arsenic. At arsenic doses up to 500 µg, median percent error was <60% for methylated arsenic; however, error was larger at higher arsenic doses. The model overpredicted DMA excretion following a 1,000 µg arsenic dose (percent error >300%), which may reflect a dose-dependence of methylation not simulated in the model (Buchet et al. 1981b).

***Evans et al. (2008) Model*.** Evans et al. (2008) developed a mouse PBPK model for simulating injected and ingested DMA(V) (see Figure 3-1). The model includes compartments representing blood, plasma, red blood cells, kidney, liver, lung, skin, urinary bladder, and gastrointestinal tract. Exchanges of arsenic between blood and tissues are simulated as either flow-limited or diffusion-limited clearances. Absorption from the gastrointestinal tract and excretion of DMA(V) from kidney to urine were assumed to be first order. The blood compartment included subcompartments representing red blood cells and plasma, with exchanges between the two governed by binding constants or DMA(V) in both subcompartments. Metabolism of DMA(V) (to TMAO) was assigned to the liver and was assumed to be first order.

Partition coefficients were optimized from data on tissue DMA(V) concentration in mice that received singe intravenous injections of DMA(V) (1.11 or 111 mg DMA(V)/kg; Hughes and Kenyon 1998). Urinary excretion data from the intravenous studies were used to estimate the urinary excretion rate constant (Hughes and Kenyon 1998). The metabolism rate constant was calculated from urinary excretion kinetics of TMAO in mice that received and oral dose of DMA(V) (Marafante et al. 1987). Parameters were first optimized for the flow-limited model, with diffusion permeability constants set to zero. Parameters, including permeability coefficients, were re-optimized for the diffusion limited model, keeping values of the metabolism and urinary excretion rate constants the same in both models. The partition coefficients for the two models were similar. The absorption rate constant was optimized from

Figure 3-1. Flow- and Diffusion-Limited DMA(V) PBPK Model



C_a = arterial blood; DMA = dimethylarsinic acid; K_{abs} = absorption from stomach; K_{el} = kidney clearance; K_{tmao} = metabolism; PBPK = physiologically based pharmacokinetic

Source: Evans et al. 2008; reproduced by permission of Oxford University Press in the format reuse in government report via Copyright Clearance Center.

data on tissue DMA concentrations following a single gavage dose (1.11 or 111 mg DMA(V)/kg; Hughes et al. 2008).

Model performance was evaluated using the PBPK index statistic for comparing predictions and observations (Krishnan et al. 1995). For most tissues (plasma, kidney, liver, red blood cells), the diffusion-limited model yielded PBPK indices that were approximately 30% lower than the flow-limited model, for both the intravenous calibration data and the oral data (only the absorption rate constant was optimized to the oral data). Lower PBPK indices indicate that the diffusion-limited model provided a better fit to the observations than the flow-limited model. Sensitivity analyses showed that sensitivity apparent soon after dosing (e.g., <5 hours) was not always evident at later time periods. Urinary predictions were sensitive to values assigned to rate constants for urinary excretion, reduction, and V_{max} for methylation. With the exception of kidney, standardized coefficients for diffusion permeability coefficients were zero for predictions of all other tissues, suggesting that the diffusion-limited model had its largest impact on kidney kinetics. This is consistent with improved PBPK indices for the kidney in the diffusion-limited model (0.03–0.07) compared to the flow-limited model (0.13–0.25).

3.4.5.2 Arsenic PBPK Model Comparison

The El-Masri and Kenyon (2008) and Evans et al. (2008) models supplement two other models, the Mann model (Gentry et al. 2004; Mann et al. 1996a, 1996b) and the Yu model (Yu 1998a, 1998b, 1999a, 1999b) that are described in the ATSDR Toxicological Profile for Arsenic (Agency for Toxic Substances and Disease Registry 2007). Major features of the four models are compared in Table 3-13.

Table 3-13. Comparison of Major Features of PBPK Models for Arsenic

Model	Species[a]	Absorption pathways[b]	Tissues[c]	Metabolic pathways	Excretion pathways[d]	Comment
El-Masri and Kenyon (El-Masri and Kenyon 2008)	HUM	OR	BL, BR, GI, HE, KI, LI, LU, SK	$As^{III} \leftrightarrow As^{V}$ $As^{III} \rightarrow MMA^{V}$ $MMA^{V} \rightarrow DMA^{V}$ $DMA^{V} \leftrightarrow DMA^{III}$ $MMA^{V} \leftrightarrow MMA^{III}$	UR	Simulates kinetics following dosing with As^{III}, As^{V}, MMA^{V}, or DMA^{V}. Metabolism in kidney, liver, and lung (representing all other tissues). Tissue-plasma exchanges flow-limited.
Evans (Evans et al. 2008)	MOU	IV, OR	BL, BLAD, GI, KI, LI, LU, OT, PL, RBC, SK	$DMA^{V} \rightarrow TMAO$	UR	Simulates kinetics following dosing with DMA^{V}. Metabolism assigned to liver. Tissue-plasma exchanges diffusion-

Table 3-13. Comparison of Major Features of PBPK Models for Arsenic

Model	Species[a]	Absorption pathways[b]	Tissues[c]	Metabolic pathways	Excretion pathways[d]	Comment
						limited.
Mann (Gentry et al. 2004; Mann et al. 1996a, 1996b)	HAM, HUM, MOU, RAB	IT, INH, IV, OR	BL, GI, KI, LI, LU, OT, PL, RBC, SK	$As^{III} \leftrightarrow As^{V}$ $As^{III} \rightarrow MMA$ $MMA \rightarrow DMA$	FE, UR	Simulates kinetics following dosing with As^{III}, As^{V}, or DMA. Methylation assigned to liver; oxidation and reduction of arsenic is assigned to plasma. Tissue-plasma exchanges diffusion-limited.
Yu (Yu 1998a, 1998b, 1999a, 1999b)	HUM, MOU, RAT	OR	FA, KI, LINT, LI, LU, MU, SINT, SK, ST, VRG	$As^{III} \leftrightarrow As^{V}$ $As^{III} \rightarrow MMA$ $MMA \rightarrow DMA$	BI, FE, UR	Simulates kinetics following dosing with As^{III}, As^{V}, MMA, or DMA. Metabolism is assigned to kidney and liver. Tissue-plasma exchanges flow-limited.

[a]Species: HUM = human; HAM = hamster; MOU = mouse; RAB = rabbit; RAT = rat.
[b]Absorption pathways: INH = inhalation; IT, intratracheal; IV = intravenous; OR = oral.
[c]Tissues: BL = blood; BLAD = bladder; BR = brain; KI = kidney; LI = liver; LINT = large intestine; MU = muscle; OT = other; PL = plasma; RBA = red blood cell; SINT = small intestine; SK = skin; ST = stomach; VRG = vessel rich group.
[d]Excretion pathways: BI = biliary; FE = fecal; UR = urine.

AS = arsenic; DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

3.4.5.3 Discussion of Models

Risk assessment applications of the El-Masri and Kenyon (2008) and Evans et al. (2008) models have not been reported. The Evans et al. (2008) model simulates DMA(V) absorption and kinetics in the mouse and applications would be limited to dosimetry predictions in mice dosed with DMA(V). The El-Masri and Kenyon (2008) model simulated absorption and kinetics of As(III), As(V), MMA(V), or DMA(V) and simulates all of the major metabolic pathways for these species. The model was used to predict urinary MMA(III) and DMA(III) excretion in populations exposed to inorganic arsenic in drinking water (Aposhian et al. 2000; Mandal et al. 2001). When average drinking water concentrations and typical drinking water intakes (1.5–2.0 L/day) were assumed in these simulations, predictions agreed well with population means for metabolite excretion.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Cellular Uptake. Cellular uptake of arsenic depends upon the arsenic oxidation state and cell type. Arsenic can cross cell membranes by passive diffusion or carrier protein mediated transport. For passive diffusion, cell membranes are more permeable to As(III) than As(V). For carrier-mediate transport, aquaglycoprotein channels and phosphate transporters have been proposed as mechanisms for carrier-mediated transport of arsenite and arsenate, respectively (Bustaffa et al. 2014; Druwe and Vaillancourt 2010; Kumagai and Sumi 2007).

Genetic Polymorphisms of Arsenic-metabolizing Enzymes. As reviewed by Agency for Toxic Substances Disease Registry (2007), As(III) is more toxic than As(V) and, similarly, methylated forms of arsenite appear to be more toxic than methylated forms of arsenate. Therefore, alterations in arsenic metabolism that result in increased formation or decreased oxidation of As(III) compounds to As(V) compounds may increase arsenic-induced toxicity. As noted in several reviews, genetic polymorphisms for several enzymes involved in arsenic metabolism have been associated with increased As(III) metabolites in urine. Alterations in arsenic metabolism may, in part, provide a basis for interindividual sensitivity to arsenic (Bailey and Fry 2014a, 2014b; Bhattacharjee et al. 2013a; Bustaffa et al. 2014; Faita et al. 2013; Naujokas et al. 2013; Sumi and Himeno 2012; Smith and Steinmaus 2009). Recent studies have examined the relationship between polymorphisms of arsenic metabolizing enzymes and urine profiles of metabolites and/or risk of arsenic-induced effects in human populations. Polymorphisms examined include AS3MT (Agusa et al. 2009; Engstrom et al. 2009, 2011; Porter et al. 2010; Rodrigues et al. 2012; Tellez-Plaza et al. 2013), cystathione-β-synthase (Porter et al. 2010), glutathione S-transferase π1 (Agusa et al. 2012; Antonelli et al. 2014; Marcos et al. 2006), glutathione S-transferase ω1 (Ahsan et al. 2007; Antonelli et al. 2014; Marcos et al. 2006; Porter et al. 2010; Rodrigues et al. 2012), methylenetetrahydrofolate reductase (Ahsan et al. 2007; Chung et al. 2010; Porter et al. 2010), and N-6-adenine-specific DNA methyltransferase 1 (Harari et al. 2013). In general, results show that genetic polymorphisms of arsenic-metabolizing enzymes in humans are associated with differences in the MMA:DMA ratio in urine.

3.5.2 Mechanisms of Toxicity

The toxicity of arsenic, including cancer, is most likely due to multiple mechanisms, with some mechanisms acting sequentially or synergistically. Two general types of mechanisms appear to be involved in arsenic-induced toxicity: (1) formation of reactive oxygen species (ROS) and subsequent

damage to cellular macromolecules and oxidative stress and (2) interaction of reactive arsenic or arsenic metabolite species with cellular macromolecules. In addition, recent advances in mechanisms of arsenic-induced toxicity have focused on epigenetic changes.

ROS. Results of mechanistic studies of arsenic toxicity suggest a role of ROS in the toxicity of inorganic arsenic (Bailey and Fry 2014b; Bhattacharjee et al. 2013a, 2013b; Bustaffa et al. 2014; Druwe and Vaillancourt 2010; Faita et al. 2013; Kumagai and Sumi 2007; Martinez et al. 2011; Salinkow and Zhitkovich 2008). Superoxide anion and subsequent formation of hydrogen peroxide and hydroxyl radical have been proposed as the primary ROS associated with arsenic-induced oxidative stress. Oxidative stress is considered to be one of the initial biological effects in arsenic-induced toxicity, including carcinogenesis.

Arsenic-induced ROS generation has been associated with numerous effects on cellular targets, which can directly damage cellular targets or lead to a cascade of effects in response to oxidative stress. The following effects have been associated with arsenic-induced ROS: reduced steady-state levels of nitric oxide; alterations in intracellular oxidation/reduction reactions, which can alter intracellular redox status; decreased glutathione levels; lipid peroxidation; damage to proteins; inhibition of pyruvate dehydrogenase; disruption of the mitochondrial membrane and inhibition of mitochondrial enzymes; altered protein phosphorylation and subsequent disruption of various signal-transduction pathway; increased expression of stress-response transcription factors, and genomic instability through damage to DNA (single and double strand breaks, DNA adducts, base-pair mutations, rearrangement of deletions insertions, and sequence amplifications), irreversible inhibition of DNA repair, telomere dysfunction, and mitotic arrest.

Interactions of Arsenic and Arsenic Metabolites with Cellular Targets. Interaction of reactive arsenic or arsenic metabolite species with cellular macromolecules are associated with alterations in cell function (Bhattacharjee et al. 2013a; Bustaffa et al. 2014; Druwe and Vaillancourt 2010; Salinkow and Zhitkovich 2008; Wantanabe and Hirano 2013). Due to the reactivity of arsenic and metabolites, several cellular targets for arsenic-induced effects have been identified, with most having numerous cascading effects. Arsenate, arsenite, MMA, and DMA directly interact with thiol groups of macromolecules (e.g., cysteine and glutathione). As a result, arsenic can inhibit the activity of thiol-rich enzymes, including pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase, and tyrosine phosphatases, and interact with zinc finger proteins. Arsenic also has been shown to interfere with oxidative phosphorylation through the formation an unstable arsenate ester. Arsenic species participate in several biochemical reactions including covalent

interactions, methylation and demethylation reactions, acid-base reactions, and oxidation-reduction reactions. Arsenic alters proteins in the insulin signaling pathway, leading to a disruption of glucose homeostasis. Other cellular effects attributed to arsenic include stimulation of the sphingosine-1-phosphate receptor (a G protein-coupled receptor), mitotic arrest, and interactions with tubulin (leading to mitotic arrest).

Epigenetic Changes. The epigenome refers to chemical compounds that function as gene regulators without altering DNA sequences. Recent research has shown the importance of the epigenome in maintaining development, growth, and cellular homeostasis. Epigenetic changes can lead to changes in gene expression and cause genetic instability. Changes to the epigenome have been proposed as important mechanisms in arsenic-induced toxicity, developmental effects, and carcinogenesis (Arita and Costa 2009; Bailey and Fry 2014b; Bhattacharjee et al. 2013a, 2013b; Bustaffa et al. 2014; Martinez et al. 2011; Salinkow and Zhitkovich 2008). However, specific biological consequences and causal relationships of epigenetic changes have not been established and are likely to vary with cell types and arsenic dose and exposure duration.

Arsenic has been shown to affect the epigenome by alterations in DNA methylation, histones, and microRNAs (miRNAs). DNA methylation is the addition of a methyl group to a cytosine or adenine nucleotide in DNA; methylation is an important mechanism for regulating gene expression. Results of *in vitro* and animal studies and studies of human population, have shown that arsenic induces both hypo- and hypermethylation of DNA. Alterations in DNA methylation have been associated with development of arsenic-induced diseases, including carcinogenesis and developmental effects. It has been proposed that hypomethylation upregulates oncogenes and that hypermethylation downregulates tumor suppressor genes. Histones, the main protein component of chromatin, are involved in regulation of gene expression. DNA wraps around histones, forming nucleosomes. Recent studies show that arsenic can produce post-translational modifications to histones through methylation, acetylation, phosphorylation, and ubiquination of specific amino acids within the histone, and thereby affect gene transcription. miRNAs are small noncoding RNAs that are involved in post-transcriptional regulation of gene expression. Arsenic has been shown to alter expression of miRNAs and it has been proposed that miRNAs are involved in the development and progression of cancer.

3.7 CHILDREN'S SUSCEPTIBILITY

As discussed in Section 3.2.2.6, developmental and neurodevelopmental effects have been observed in infants and children following prenatal and early life exposure to arsenic in drinking water (Ahmed et al.

2012; Farzan et al. 2013; Guan et al. 2012; Hamadini et al. 2010, 2011; Hsieh et al. 2014; Jin et al. 2013; Khan et al. 2012; Kippler et al. 2012; Nahar et al. 2014; Parvez et al. 2011; Rahman et al. 2007, 2009, 2010, 2011; Raqib et al. 2009; Roy et al. 2011; Rudnai et al. 2014; Saha et al. 2012; Vall et al. 2012; Wasserman et al. 2007, 2011, 2014; Wu et al. 2014). In addition, prenatal exposure of humans and animals to arsenic is associated with the development of cancer in offspring later in life (see Section 3.2.2.7; Smith et al. 2006, 2012; Tokar et al. 2012a, 2012b; Yuan et al. 2010).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Genetic polymorphisms of enzymes involved in the metabolism of arsenic, including AS3MT and glutathione transferases (Bailey and Fry 2014a, 2014b; Bhattacharjee et al. 2013a; Bustaffa et al. 2014; Faita et al. 2013; Naujokas et al. 2013; Sumi and Himeno 2012; Smith and Steinmaus 2009) are associated with differences in the MMA:DMA ratio in urine. Individuals with polymorphisms associated with a higher MMA:DMA ratio in urine may be more susceptible to arsenic-induced toxicity.

4. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

U.S. production of metallic arsenic and arsenic trioxide ceased in 1985; limited quantities of metallic arsenic, however, may be recovered from gallium arsenide semiconductor scrap (USGS 2014).

5.2 IMPORT/EXPORT

China was the major import source for elemental arsenic during the years 2009–2012, supplying 87%, followed by Japan (12%) and others (1%). Morocco was the major import source for arsenic trioxide during the years 2009–2012, supplying 67%, followed by China (20%), Belgium (12%), and others (1%) (USGS 2014).

U.S. exports of elemental arsenic were 354 metric tons in 2009, 481 metric tons in 2010, 705 metric tons in 2011, and 439 metric tons in 2012, and are estimated to be 1,750 metric tons in 2013 (USGS 2014).

5.3 USE

According to the National Pesticide Information Retrieval System (NPIRS), arsenic acid, arsenic pentoxide, and sodium methanearsonate are currently registered as pesticides in the United States; there are no active registrants listed for arsenic trioxide, calcium arsenate, lead arsenate, sodium arsenite, arsanilic acid, dimethylarsinic acid, disodium methanearsonate, methanearsonic acid, or sodium dimethylarsinate (NPIRS 2015).

The EPA issued a reregistration eligibility decision (RED) for wood preservatives containing chromated arsenicals, including chromated copper arsenate (CCA) and ammoniacal copper arsenate (ACA) (EPA 2008). Based on the results of the RED, the EPA concluded that current registered uses of chromated arsenicals are eligible for reregistration upon meeting specific risk mitigation procedures, proper end-use, and labeling. Active ingredients containing arsenic evaluated in the assessment include arsenic acid and arsenic oxide.

Gallium-arsenide (GaAs) is used in third- and fourth-generation “smartphones” (USGS 2014).

5.4 DISPOSAL

As of February 2014, both metallic arsenic from gallium arsenide semiconductor manufacturing and arsenic contained in the process water of wood treatment plants using CCA were recycled (USGS 2014). However, metallic arsenic was not recovered during metal recycling of electronic circuit boards, relays, and switches, which may contain arsenic, nor was metallic arsenic recovered from arsenic-containing residues or dust generated at nonferrous smelters in the United States (USGS 2014).

Wastes generated from the treatment of wood are regulated under the Resource Conservation and Recovery Act (RCRA). Waste water generated from wood preservation is listed as Hazardous Waste number F035 (EPA 2008).

CCA-treated wood is commonly disposed of in construction or demolition landfills, municipal solid waste landfills, or industrial nonhazardous waste landfills. Existing federal hazardous waste regulations require testing procedures to evaluate if a representative sample of the waste leaches arsenic above a certain threshold concentration. This value determines whether wastes containing arsenic are defined as hazardous waste. Some CCA-treated wood may meet this definition; however, because of an existing exemption by the federal register (40 CFR 261.4(b)(9)), CCA-treated wood is generally not defined as a

hazardous waste (EPA 2008). Disposal may occur with household trash, where the disposal would be defined by state and local waste management authorities (EPA 2008).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Arsenic has been identified in at least 860 of the 1,754 proposed (47), final (1,322), and deleted (385) hazardous waste sites listed on the EPA Superfund National Priorities List (NPL) (EPA 2013a; NLM 2014). However, the number of sites evaluated for arsenic is not known.

Exposure to the general population occurs through contaminated groundwater and can also occur from the ingestion of foods containing arsenic compounds. Exposure from drinking water, water used for food preparation, or water used in crop (especially rice) irrigation, is a source of concern, as elevated concentrations have been reported.

6.2 RELEASES TO THE ENVIRONMENT

Of the 20,853 Toxics Release Inventory (TRI) facilities reporting nationwide, elemental arsenic has been reported in 40 on site-releases and inorganic arsenic compounds have been reported in no on-site releases, for the reporting year 2012 (NLM 2014).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Ambient air and precipitation samples were collected at a site in Washington, DC (Melaku et al. 2008). The ambient air samples collected every 6 days over 7 months had total arsenic concentrations ranging of from 0.800 to 15.7 ng/m^3. Wet deposition samples collected every 6 days for 1 year resulted in total arsenic concentrations ranging from 0.20 to 1.3 µg/L.

6.4.2 Water

A Washington State Environmental Biomonitoring Survey was conducted with tap water samples from 82 households in South Whidbey from July to September 2011. Results indicated that 54% of the water samples exceeded the EPA drinking water standard (maximum contaminant level [MCL]=10 µg/L) (WA DOH 2015).

Wasserman et al. (2014) measured kitchen tap water in Maine households; the average value found was 9.88 μg/L. Close to one-third of the water samples exceeded the EPA drinking water standard (MCL=10 μg/L). The highest level found was 115.3 μg/L.

In September and October 2005, samples from eight sites located in Lake Mohawk, a man-made body of water in New Jersey, were assessed for arsenic concentrations (Barringer et al. 2011). Shallow and deep lake water and sediment samples were collected. Lakes depths ranged from 1 to 7 m. The source water for the lake is predominantly groundwater. The lake is surrounded by approximately 2,200 homes and a golf course located on the western shore. It was reported that in the mid-20th century, an estimated 300,000 kg of arsenical pesticides were applied to the lake. Concentrations of arsenic in sediment cores ranged from 91 to 460 mg/kg (91–460 μg/g). Concentrations in filtered (27.5–31.5 μg/L) and unfiltered (23–26 μg/L) water samples appeared to be evenly distributed in the lake.

In 2006, arsenic concentrations were measured in samples of runoff water, from two detention basins in Raccoon Creek, New Jersey (USGS 2011a). Arsenic concentrations in water samples collected in September, 2006 upstream of the outfall of basin one, at the basin, and at the outfall reported for detention basin one were 0.663, 2.56, and 2.44 μg/L, respectively, for filtered samples and 2.28, 2.68, and 2.45 μg/L, respectively, for unfiltered samples. Arsenic concentrations in water samples collected in May, 2006 upstream of the outfall of basin two, at the basin, and at the outfall reported for detention basin two were 0.872, 1.54, and 2.10 μg/L, respectively, for filtered samples and 1.39, 1.63, and 2.21 μg/L, respectively, for unfiltered samples. Arsenic concentrations in water samples collected in September, 2006 upstream of the outfall of basin two, at the basin, and at the outfall reported for detention basin two were 1.00, 4.35, and 3.11 μg/L, respectively, for filtered samples and 3.10, 4.35, and 3.71 μg/L, respectively, for unfiltered samples.

In Sutherlin, Oakland, and Yoncalla, Oregon, naturally occurring arsenic in groundwater was studied by the Environmental Health Assessment Program (EHAP), a part of the Oregon Department of Human Services (DHS) Office of Environmental Public Health (Agency for Toxic Substances and Disease Registry 2009). Well water analysis was performed for 124 samples collected from 114 private wells between June 9 and June 18, 2008. Arsenic was detected in 29 of the wells at concentrations ranging from 1 to 460 ppb (0.001–0.460 μg/L). Water samples that exceeded the EPA drinking water standard (MCL=10 μg/L) occurred in 13 of the wells located in areas east of Sutherlin, 11 of which were intended for domestic use.

Arsenic in groundwater has been correlated to the geology of the region, including aquifer characteristics, pH, redox conditions, and concentrations of inorganic minerals (Jones and Pilcher 2007; Meliker et al. 2009; Root et al. 2010; USGS 2011b). Aquifer recharge and aquifer storage and recovery (ASR) are processes employed in storing available water in aquifers and using the water when it is needed. Arsenic mobilization was investigated in Southwest Central Florida (Jones and Pilcher 2007) and southeastern Michigan groundwater (Meliker et al. 2009). From 300 core samples of 19 wells, a mean concentration of 3.5 µg/L arsenic was found in the Limestone of wells, in Southwest Central Florida region, used in groundwater recharge. Study results confirmed that arsenic is released from minerals containing arsenic, such as pyrite. Pyrite becomes unstable and dissolves when redox conditions shift towards a more oxidizing environment, increasing the potential of leaching arsenic into the stored water. Conditions in the Suwannee Limestone were reducing; therefore, low levels of arsenic were found. Arsenic concentrations in well water from 13 of the 19 wells were <0.02 µg/L; 6 of the 19 samples had levels ranging from 0.022 to 0.036 µg/L (Jones and Pilcher 2007). The spatial relationships in groundwater recharge wells, well characteristics, and dissolved arsenic in unconsolidated and bedrock aquifers of southeastern Michigan were studied (Meliker et al. 2009). Total arsenic concentrations in water from 641 bedrock wells in the Southeastern Michigan region ranged from not detectable to 161 µg/L; the mean total arsenic concentration was 4 µg/L and the median was 3 µg/L (Meliker et al. 2009). Total arsenic concentrations in water from 71 unconsolidated wells in the Southeastern Michigan region ranged from not detectable to 46 µg/L; the mean total arsenic concentration was 11 µg/L and the median was 17 µg/L.

During the spring and summer of 2009 in east-central Massachusetts, 478 private bedrock wells were sampled for analysis of arsenic concentrations by the U.S. Geological Survey (USGS 2011b). In 24% of the samples, arsenic concentrations were below the method detection limit of 0.2 µg/L. Concentrations up to 1,540 µg/L were reported. Concentrations >10 µg/L were found in 13–15% of samples. Correlations with bedrock units were made in order to calculate the probability of elevated arsenic in area wells. It was estimated that 5,741 wells in the State of Massachusetts may contain arsenic concentrations >10 µg/L.

Arsenic concentrations in mine groundwater and sediment from the Judge Tunnel, a water treatment facility in Park City, Utah, were measured. Total arsenic concentrations of 0.009–0.010 mg/L (9–10 µg/L) and <5 µg/L were reported in unfiltered and filtered water samples, respectively. The total arsenic concentrations in sediments collected from water storage tanks was 320 mg/kg (320 µg/g) (Pawlak et al. 2008). In one area of the Park City distribution system, hydrant-flushed water had elevated arsenic concentrations of 21.2–151 µg/L.

Arsenopyrite and pyrite, present in gold-bearing quartz veins of the Lucky Shot Gold Mine in Alaska, were attributed to the elevated arsenic concentrations in mine tailings and drainage water (Torrance et al. 2012). The mine was in operation from 1920 to 1942, producing 252,000 ounces of gold. Water samples were collected in August 2010 and September 2011 from 17 established monitoring wells. Total arsenic concentrations ranged from <1.0 µg/L found downstream to 752.5 µg/L found in water seeping from mine tailings. The main source of arsenic was found to be discharge from the mine adits. Less than half of the monitoring wells (five total) had total arsenic concentrations >10 µg/L. Arsenite accounted for close to 100% of the total arsenic present in the majority of the wells. A <2% difference in arsenic concentrations from filtered versus unfiltered samples indicated that the majority of arsenic present was in aqueous form.

In 2008, speciation of arsenic was performed in groundwater samples of a former ammunition depot and filling station in Germany operating in the 1940s (Daus et al. 2010). Remediation of the site was performed in 2005 by soil excavation. In June 2008, samples were taken at the source 2.0–15 m below the surface. Total arsenic reported in this study includes the summation of arsenite, arsenate, phenylarsonic acid, phenylarsine oxide, and diphenylarsinic acid. The highest concentration of total arsenic in source samples of groundwater was reported as 16 mg/L (16,000 µg/L), detected 4.4–5.4 m below the surface. Concentrations >1 mg/L (1,000 µg/L) were typically confined to depths ≤10 m. In November 2008, groundwater samples were taken 1 km from the source in the flow direction of the groundwater, at depths ranging from 4.8 to 25.0 m below the surface. Total arsenic concentrations were <400 µg/L. The species found here included arsenite, arsenate, phenylarsonic acid, phenylarsine oxide, and diphenylarsinic acid. Proportions of the species changed with the sampling depth.

Ayotte et al. (2015) analyzed five datasets containing arsenic concentrations in wells in the United States. Data were compiled for 1,245 public and private drinking water wells. The two most recent samples available for each well were used for this analysis. Data from filtered samples of 312 public and private wells collected from 1993 to 2008 at aquifers across the United States were obtained from the USGS National Water-Quality Assessment (NAWQA) Program dataset. Samples in New England were obtained from 607 public bedrock wells sampled from 1995 to 2008. A dataset for the Lamprey River basin was compiled from unfiltered water samples from 148 domestic wells across the basin in 2004 and 2005. The Lamprey River basin samples were analyzed at the New Hampshire Department of Environmental Services (NHDES) Laboratory, an EPA contract laboratory, and the EPA National Air and Radiation Environmental Laboratory. Unfiltered samples from 35 private bedrock wells near the Mottolo

Superfund site sampled from 2009 to 2010 and analyzed at the NHDES laboratory and 143 domestic bedrock wells sampled from 2002 to 2012 by homeowners and analyzed by EPA laboratory were also included. Concentrations of arsenic in a specific well did not vary greatly over time: <±4 µg/L variability in 87% of the wells considered in this analysis. Variability in arsenic concentrations occurred more often in public water supplies compared to private wells. Variability was dependent upon multiple factors including geochemical parameters. Data indicated a weak correlation to seasonal variability in the New England area but not in California; concentrations in New England during the first half of the year were lower than arsenic concentrations in the second half of the year. Variability in California wells appeared to be a result of geochemical processes as well as aquifer storage and recovery practices, including groundwater recharge methods.

Speciation tests were performed in 65 wells from 59 sites across the United States with naturally occurring arsenic (Sorg et al. 2014). The sites chosen for the study were either part of the EPA Arsenic Demonstration Program (ADP) (n=50), proposed sites for the ADP program (n=5), or EPA research project sites (n=4). Analysis was conducted monthly for up to 3 years in select wells. Arsenate was found as the dominant species in 31 wells, arsenite was the dominant species in 29 wells, and almost equal amounts of the two species were found in 5 wells. Overall concentrations of arsenic species in a specific well did not vary greatly over time. The average iron content was 29, 1,544, 30, and 129 µg/L for the wells located in the East, Midwest, West, and Farwest regions, respectively. The average oxidation/reduction potentials were 244, -17, 179, and 213 mV for the wells located in the East, Midwest, West, and Farwest regions, respectively. The average pH of the wells in this assessment ranged from 7.4 to 7.9 in all four regions. On average, 92–100% of arsenic in the samples was in soluble form, and arsenate occurred as the dominant species in the East, West, and Farwest wells. Sites in the East region included wells in Maine, New Hampshire, Vermont, Rhode Island, Connecticut, Delaware, Maryland, New York, and Pennsylvania. In the East region, the average concentration of total arsenic found was 27.6 µg/L, the average particulate concentration was 0.3 µg/L, the average soluble arsenic concentration was 27.8 µg/L, and the average concentrations of arsenate and arsenite were 19.8 and 8.0 µg/L, respectively. Sites in the West region included wells in Texas, South Dakota, Nebraska, New Mexico, Arizona, and Montana. In the West region, the average concentration of total arsenic found was 36.3 µg/L, the average particulate concentration was 1.5 µg/L, the average soluble arsenic concentration was 35.0 µg/L, and the average concentrations of arsenate and arsenite were 30.4 and 5.2 µg/L, respectively. Sites in the Farwest region included wells in California, Oregon, Washington, Idaho, Nevada, and Utah. The average concentration of total arsenic found was 34.1 µg/L, the average particulate concentration was 1.3 µg/L, the average soluble arsenic concentration was 33.1 µg/L, and the

average concentrations of arsenate and arsenite were 28.2 and 4.8 µg/L, respectively. Arsenite occurred as the dominant species in anoxic Midwest wells with elevated iron concentrations. Sites in the Midwest region included wells in Ohio, Michigan, Indiana, Illinois, Wisconsin, Minnesota, and Louisiana. The average concentration of total arsenic found was 28.6 µg/L, the average particulate concentration was 2.6 µg/L, the average soluble arsenic concentration was 26.1 µg/L, and the average concentrations of arsenate and arsenite were 2.3 and 24.1 µg/L, respectively.

Erikson and Barnes (2005) evaluated arsenic concentrations in public water systems located inside (1,764 wells) and outside (2,182 wells) an area where glacial sediment had been deposited, known as the northwest provenance Wisconsin-aged drift. Bedrock and glacial drift wells in North Dakota, South Dakota, Minnesota, and Iowa were also investigated. The study found that inside the drift, 12.0% of public water systems exceed 10 µg/L, while only 2.4% of public water systems exceed 10 µg/L outside the area. Of the wells located inside the drift, 1.5% exceeded 10 µg/L arsenic bedrock with well depths ranging from 800 to 186 m (n=132), 3.8% exceeded 10 µg/L arsenic with well depths ranging from 185 to 92 m (n=263), and 22.1% exceeded 10 µg/L arsenic with well depths ranging from 91 to 4 m (n=131). Of the wells located inside the drift, 8.5% exceeded 10 µg/L with well depths ranging from 157 to 65 m (n=120), 27.0% exceeded 10 µg/L arsenic with well depths ranging from 64 to 28 m (n=236), and 7.4% exceeded 10 µg/L arsenic depths ranging from 28 to 7 m (n=118).

Pichler et al. (2008) investigated arsenic concentrations and seasonal variations in 28 golf course lakes at four golf courses in Hillsborough County, Florida. Each of the four sites studied used private wells as their water source and applied monosodium methanearsonate as an herbicide. Surface water samples were collected monthly from February 2001 through January 2002. Total arsenic concentrations detected in lake samples ranged from 0 to 124 µg/L and an annual mean of 10.9 µg/L was reported for all lakes. The most recently renovated course had the lowest levels of total arsenic.

Hudak et al. (2008) compiled data on arsenic concentrations in 64 wells supplied by the Seymour Aquifer. Data were obtained from the Ground Water Database of the Texas Water Development Board sampled during 2001 and 2004. The median concentrations of arsenic in water were 3.5, 2.7, and <2.0 µg/L in irrigation wells, domestic wells, and public wells, respectively. Well depths ranged from 7.3 to 55.5 m, with a median value of 16.8 m. No statistically significant correlation was found between arsenic concentrations and well depths.

6.4.3 Sediment and Soil

Background concentrations of total arsenic in farming soils collected from Poland ranged from 4.98 to 17.40 mg/kg (4.98–17.40 μg/g) soil, with an average arsenic concentration of 8.83 mg/kg (8.83 μg/g) soil (Loska et al. 2005). Xu et al. (2008) evaluated growing practices (aerobic and flooded) and their effects on soil arsenic concentrations using soil from the upper layer (0–20 cm) of a field on the Rothamsted farm, Southeast England. The initial total arsenic concentration of the soil was reported as 15.1 mg/kg (15.1 μg/g). It was shown that flooding practices result in soil solutions with higher overall arsenic concentrations, arsenite was the predominant species. In samples collected between 12 and 97 days after flooding treatments, arsenite accounted for 81–95% of the total arsenic. In aerobic practices arsenate was the predominant species, accounting for >88% of the total arsenic. In soils under flooded conditions, the concentration of total arsenic (mainly arsenite) increased from 4 to 16.9 μg/L from day 3 to 97, while in soils under aerobic treatment, total arsenic levels decreased from 3.3 to 1.0 μg/L. In two soil samples in which 10 mg/kg (10 μg/g) arsenic was added to the soil, total arsenic concentrations remained at an elevated level (between 35 and 60 μg/L) from day 3 to 97 during the flooded treatment, but decreased during the aerobic treatment from 23–27 to 4 μg/L. Soil samples from 10 sites in Serbia, where high levels of arsenic had been found in suspended particles in the air, were analyzed with inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and atomic absorption spectroscopy (AAS) to evaluate airborne heavy metal contamination (Serbula et al. 2012). Arsenic levels ranged from 16.8 to 95.5 mg/kg soil. The highest concentrations of arsenic were located in the urban industrial sampling zone and the lowest concentrations were located in the rural sampling zone. The control sample from Sumrakovac, Serbia had an arsenic concentration of 9 mg/kg soil.

Presley et al. (2010) reported measured concentrations of arsenic in New Orleans, Louisiana soils before Hurricane Katrina (June 2005) and after Hurricane Rita (January 2006). A total of 39 sites were sampled, 37 of which were schoolyards. Total arsenic concentration ranged from 1.20 to 11.30 mg/kg (1.20–11.30 μg/g) in four soil samples collected before Hurricane Katrina. Total arsenic concentration ranged from below reliable detection limits up to 24.30 mg/kg (24.30 μg/g) in 18 soil samples collected after Hurricane Rita. The 17 soil samples collected both before and after Hurricane Katrina had a geometric mean arsenic concentration of 4.73 μg/g before and 6.99 μg/g after. Warren et al. (2012) reported measured concentrations of arsenic in surface estuarine and marine sediments from 10 sites along the Mississippi Gulf Coast in New Orleans, Louisiana after Hurricane Katrina, from September 2005 to 2006. ICP-mass spectrometry (MS) was used to detect concentrations of arsenic ranging from 0.37 to 7.43 μg/g for the <2 mm particle size fractions and 2.50–17.1 μg/g for the <63 μm particle size fractions.

At an arsenic contaminated site in Kidsgrove, Staffordshire, soil sampled at 0–30, 30–70, and 70–100 cm depth had arsenic detected at concentrations of 280, 200, and 96 mg/kg soil, respectively, when the soil samples were microwave digested in concentrated 14 M nitric acid (Beesley et al. 2010). Arsenic-contaminated soil samples from a former nonferrous metal refinery plant and an abandoned mine tailing site in Korea were collected from 0- to 30-cm depths (Kim et al. 2014). A mean arsenic concentration of 61.2 mg/kg soil was detected from the smelter location samples and 82,300 mg/kg soil from the mine location samples. X-ray photoelectron spectroscopy was used to determine that As(V)-O was the major chemical form of arsenic at both sites investigated.

In 2006, arsenic concentrations were measured in soils, sediments, clay, and grab samples of runoff water, from two detention basins in Raccoon Creek, New Jersey (USGS 2011a). Soil and sediment samples collected in October at basin one had total arsenic concentrations ranging from 3.0 to 16.1 mg/kg (3.0–16.1 µg/g). Soil and sediment samples collected in June and July at basin two had total arsenic concentrations ranging from 12.0 to 45.4 mg/kg (12.0–45.4 µg/g). Total arsenic concentrations in soil from Victoria, Australia, collected in areas with a history of gold mining activity, ranged from 3.3 to 130 µg/g; the geometric mean was 11.5 µg/g (Pearce et al. 2010). Tsuji et al. (2005) analyzed total arsenic and arsenic species in urine, toenails, and soil of Middleport, New York residents. The range of total arsenic detected in urine was 2.1–773 µg/L in all participants. The arsenic concentration levels in soil and dust averaged 18.8 and 10.6 mg/kg (18.8 and 10.6 µg/g), respectively.

6.4.4 Other Environmental Media

Total arsenic levels in rice have shown notable variations with geographical region, cultivation methods, rice strain, and degree of polishing/milling practices. In addition, arsenic speciation can vary in different rice strains (Gilbert-Diamond 2011; Lei et al. 2013; Sommella 2013; Zavala et al. 2008). In a field study conducted in Chenzhou City Hunan, China, 34 rice genotypes grown in arsenic-contaminated fields had arsenic concentrations ranging from 9.07 to 25.26 g/dry weight plant (Lei et al. 2013). Rice grown and cultivated using flooded conditions contained 10–15-fold higher levels of arsenic species, specifically in the form of DMA, compared to rice grown under aerobic (i.e., non-flooded, well drained) conditions (Xu et al. 2008). Grain samples from flooded treatments had total arsenic concentrations ranging from 1 to 2.5 mg/kg (1–2.5 µg/g). Narukawa et al. (2014) evaluated 10 brown rice samples from six regions in Japan. The study found that the species of arsenic in the samples was directly related to the degree of polishing and milling; the concentrations of DMA in milled rice tended to be lower than polished rice. The concentration of inorganic arsenic decreased with increased milling and the concentration of inorganic arsenic in milled rice was higher than that in polished rice.

Rice grown in the south-central region of the United States tends to contain a higher average concentration of total arsenic (0.30 µg/g) compared to rice grown in California (0.17 µg/g) (Gilbert-Diamond 2011). Sommella et al. (2013) performed a survey of commercial rice purchased in Italian stores. Based on analysis of eight varieties from four different regions, it was confirmed that arsenic concentrations are not homogeneous. The highest mean concentration of total arsenic was 0.28 mg/kg found in Emilia, while the lowest mean concentration was 0.11 mg/kg (0.11 µg/g) found in Calabria. A study and review of rice crops in the United States, Australia, China, Asia, and Europe showed that the percentage of total arsenic in rice is dominated by either DMA or inorganic arsenic. Rice in the United States, Italy, and China was found to be dominated by the DMA species. Speciation of arsenic was assessed in U.S. commercially produced rice (Zavala et al. 2008). Of the 24 samples evaluated, 2 brown rice samples contained the highest concentrations of 0.45 and 0.71 mg/kg (0.45–0.71 µg/g). White rice samples had total arsenic concentrations of 0.162–0.383 mg/kg (0.162–0.383 µg/g) and brown rice samples had total arsenic concentrations of 0.201–0.71 mg/kg (0.201–0.71 µg/g). In general, brown rice had overall higher levels of As(III); As(III) concentrations ranged from 0.097 to 0.168 mg/kg (0.097–0.168 µg/g). White rice samples had As(III) concentrations of 0.049–0.122 mg/kg (0.049–0.122 µg/g). The total arsenic concentrations reported for 3 types of rice grain cultivated in Arkansas ranged from 0.253 to 0.356 mg/kg (0.253-0.356 µg/g), for 5 types of rice grain cultivated in California ranged from 0.162 to 0.345 mg/kg (0.160–0.710 µg/g) and for 16 types of rice grain cultivated in Texas ranged from 0.190 to 0.710 mg/kg (0.190–0.710 µg/g) (Zavala et al. 2008). Table 6-1 provides the concentrations of arsenic speciation in the U.S. commercial rice samples from the study.

Food products purchased both over the internet and from stores in the Hanover, New Hampshire area were evaluated for arsenic concentrations. Organic brown rice syrup (OBRS) and products containing OBRS, such as toddler formula, cereal and energy bars, were included. Total arsenic in three rice syrups tested ranged from 78 to 406 ng/g (0.08–0.4 µg/g). Inorganic arsenic accounted for 80–90% of the total arsenic in two of the syrups and 50% in the third. The third, however, had the highest concentration of arsenic overall at 406 ng/g. Fifteen of the 17 baby formulas evaluated did not have OBRS as an ingredient and contained levels of arsenic ranging from 2 to 12 ng/g (0.002–0.012 µg/g). OBRS was listed as an ingredient in 2 of the 17 baby formulas. Levels of inorganic arsenic in these two reconstituted formulas were 8–9 µg/L for dairy-based formulas and approximately 15–25 µg/L for soy-based formulas.

Table 6-1. Speciation of Arsenic in U.S. Commercial Rice

Rice color/state of production	Total arsenic (HNO_3/H_2O_2)	Species (TFA extraction) (µg/g)				Species recovery percent total arsenic[a]
		DMA	As(III)	As(V)	Sum	
Brown						
Arkansas	0.253	0.068	0.133	0.012	0.212	84
California	0.201±0.005	0.036	0.115	0.013	0.164	81
California	0.236	0.067	0.145	0.009	0.221	94
California	0.354	0.186	0.097	0.006	0.289	82
California	0.273	0.171	0.102	<0.005	0.273	100
Texas[b]	0.710±0.028	0.572	0.168	<0.005	0.769	108
Texas	0.450±0.021	0.320	0.116	<0.005	0.437	97
Texas	0.241±0.003	0.068	0.157	0.011	0.236	98
Texas	0.258	0.069	0.142	0.008	0.218	85
White						
Arkansas	0.287	0.142	0.081	0.008	0.231	80
Arkansas	0.356±0.008	0.190	0.066	<0.005	0.256	72
California	0.162±0.006	0.040	0.112	0.017	0.169	104
Texas	0.242	0.171	0.049	0.023	0.242	100
Texas[c]	0.253±0.002	0.138	0.076	0.095	0.312	123
Texas[d]	0.383±0.003	0.302	0.071	0.003	0.382	100
Texas	0.369±0.008	0.221	0.069	0.013	0.302	82
Texas	0.190±0.002	0.061	0.122	0.008	0.192	101
Texas	0.203±0.005	0.095	0.094	0.013	0.201	99
Texas	0.195±0.017	0.106	0.086	0.014	0.207	106
Texas	0.270±0.020	0.179	0.098	0.008	0.285	106
Texas	0.256	0.128	0.118	0.014	0.259	101
Texas	0.351	0.239	0.078	0.007	0.323	92
Texas	0.240±0.014	0.171	0.081	0.013	0.265	111
Texas	0.222	0.143	0.084	0.003	0.230	104

[a]Values >100% represent experimental error between two different analytical methods.
[b]Contained MMA at 0.013 and an unidentified arsenic species at 0.017 µg/g.
[c]Contained MMA at 0.003 µg/g.
[d]Contained MMA at 0.006 µg/g.

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; TFA = trifluoroacectic acid

Source: Zavala et al. 2008

Total arsenic concentrations in 100 cereal and energy bars tested ranged from 8 to 128 ng/g (0.08–0.128 µg/g). Analysis of 12 of the bars containing rice had an average of 70% inorganic arsenic (Jackson et al. 2012).

Jackson et al. (2012) analyzed 15 infant formulas and 41 first foods for arsenic concentrations and found that rice-containing products had elevated levels of total arsenic. Of the formulas that were speciated, inorganic arsenic accounted for 100% of the total arsenic present. The highest concentrations of total arsenic reported for rice-based formula and first food puree in pears/raspberries were 11.89±0.64 ng/g (0.01189 µg/g) and 20.20 ng/g (0.02020 µg/g), respectively. Tables 6-2 and 6-3 summarize the results.

Table 6-2. Total Arsenic Concentrations for Main Brand Infant Formulas

Total arsenic (µg/g)	Dairy	Rice	Percent inorganic arsenic
0.00536 ±0.00021	Yes	No	Not speciated
0.01127±0.00035	No	No	100%
0.00929±0.00043	No	No	100%
0.01189±0.00064	No	Yes	100%
0.00576±0.0004	Yes	No	Not speciated
0.00695±0.00043	No	No	100%
0.01143±0.00109	No	No	100%
0.00602±0.00026	Yes	Yes	Not speciated
0.00819±0.00063	Yes	Yes	100%
0.00814±0.00077	Yes	No	100%
0.00938±0.00031	Yes	No	100%
0.00292±0.00033	Yes	No	Not speciated
0.00962±0.00135	No	No	100%
0.00342±0.0002	Yes	No	Not speciated
0.0026±0.00044	Yes	No	Not speciated

Source: Jackson et al. 2012

Table 6-3. Total Arsenic Concentration in First-Food Purees

Ingredients	Total arsenic (µg/g)
Apples	0.00069–0.00674
Apples and apricots	0.00148
Apples and blueberries	0.00093
Apples and plums	0.00097
Apple and strawberries	0.0012
Applesauce	0.00065
Bananas	0.00032–0.00399
Carrots	0.00168–0.00175
Corn and butternut squash	0.00048
First prunes	0.00125
Green beans	0.0009–0.00321
Peaches	0.00334
Pears	0.00317–0.01752
Pears and mango	0.01501
Pears and raspberries	0.02020
Pears and wild blueberries	0.00100
Peas	0.00314
Prunes	0.00201
Prunes and oatmeal	0.00174
Select prunes	0.00163
Select sweet potatoes	0.00781
Squash	0.00048–0.00190
Sweet carrots	0.00207
Sweet peas	0.00074–0.00106
Sweet potatoes	0.00145–0.00503
Winter squash	0.00068

Source: Jackson et al. 2012

A review done by the World Health Organization (WHO 2011a) reported that washing rice with water can eliminate up to 23% of arsenic, with As(III) being the species with the highest elimination potential. In addition, cooking methods such as boiling and baking may remove arsenic from foods such as vegetables, cereals, and seafood. The majority of studies conducted have been on rice boiling, and results indicate that large volumes of water are required to remove total arsenic (up to 35%) and inorganic arsenic (up to 45%) (WHO 2011a). Cooking with arsenic-contaminated water, however, has been shown to increase arsenic concentrations.

Arsenic speciation in 31 infant rice cereals sold in U.S. stores was performed via ICP-MS-high performance liquid chromatography (HPLC) (Juskelis et al. 2013). Mixed grain, single grain, whole grain, organic, white, and brown rice cereals were assessed. Cereals were purchased in Illinois, Texas, California, and North Dakota. The average concentrations of total arsenic and inorganic arsenic found were 174.4–101.4 µg/kg (0.1744–0.1014 µg/g). Total inorganic arsenic concentrations ranged from 55.5 to 158.0 µg/kg (0.0555–0.1580 µg/g). The major organic arsenic species detected was DMA; MMA was not typically detected unless at trace amounts. There were no notable differences in the inorganic arsenic concentrations of organic cereals versus conventional rice cereals. The lowest concentrations of inorganic arsenic were found in mixed-grain cereals. The levels of inorganic arsenic per serving ranged from 0.8 (mixed grain cereal) to 2.4 µg (organic whole grain cereal).

Arsenic concentrations were analyzed for 32 gluten-free food products purchased in Spain (Munera-Picazo et al. 2014a). The gluten-free foods products evaluated in this study, such as baking flour, breadcrumbs, pasta, breads, pastries, beer, and rice milk, had a rice content of 5–100%. The pastas contained the highest levels of total arsenic (0.109–0.120 µg/g) and inorganic arsenic (0.0730–0.0842 µg/g).

Dust samples were analyzed near a former wood treatment facility in southern Alabama (Hensley et al. 2007). Attic dust samples from 11 buildings located in a 1-mile radius of the facility had an average total arsenic concentration of 29.8 mg/kg (29.8 µg/g). The range was from 2.0 to 261.0 µg/g.

Speciation of arsenic in several mid-Atlantic fish and shellfish samples was achieved via ICP-MS (Green and Crecelius 2006). Summer flounder, Atlantic croaker, and Hard clam samples were collected from Delaware Inland Bays in 2002. Striped bass samples were collected from the Delaware Estuary and lower to mid Delaware Bay. Total arsenic concentrations in all 27 samples ranged from 0.36 to 3.33 µg/g (limit of detection [LOD] of 0.04 µg/g). Inorganic arsenic concentrations were reported as detected above

the blank but less than the detection limit in 5 samples and not detected in 22 samples (LOD=0.03 µg/g). MMA concentrations were not detected in 10 samples and reported as detected above the blank but less than the detection limit in 17 samples (LOD=0.01 µg/g). DMA was reported as detected above the blank but less than the detection limit in 20 samples, below the LOD in 1 sample, and in concentrations ranging from 0.0412 to 0.528 in 6 samples(LOD=0.04 µg/g).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The Updated Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention (CDC 2015), reported 2003–2012 data from the National Health and Nutrition Examination Survey (NHANES). These data are summarized in Tables 6-4 through 6-19. Total arsenic levels in the urine (see Table 6-4) and urine, creatinine corrected (see Table 6-5) were evaluated for various ages and ethnicities. In addition values were reported of concentrations in urine for arsenic(V) acid, arsenobetaine, arsenocholine, arsenous (III) acid, DMA(V), monomethylarsonic acid (MMA(V)), and TMAO. Mean values of total arsenic (creatinine corrected) in the urine were 8.24 and 9.15 µg/g for 2,557 members of the general U.S. population sampled during 2003–2004 and 2,576 members of the general U.S. population sampled during 2005–2006, respectively. Mean values of total arsenic (creatinine corrected) in the urine were 8.46 and 9.90 µg/g for 2,605 members of the general U.S. population sampled during 2007–2008 and 2,860 members of the general U.S. population sampled during 2009–2010, respectively. The mean value for toal arsenic (creatinine corrected) in the urine for 2,502 members of the general U.S. population sampled during was 7.77 µg/g. The two highest geometric means (creatinine corrected) during 2009–2010 of 10.8 and 10.6 µg/g resulted from 2,028 samples from participants ≥20 years old and 1,459 samples from female participants, respectively. Throughout all survey years, females had a higher geometric mean of total arsenic (creatinine corrected) than males and the age group of ≥20 years had higher means than the 6–11-year-old group, which had higher means than ages 12–19 years (CDC 2015). Concentrations of arsenic(V) acid (corrected for creatinine) throughout all NHANES survey years were below the detection limits of the analytical methods (1.0 µg/L). Concentrations of arsenous (III) acid (corrected for creatinine) were below the dectection limits of the analytical methods (1.2 µg/L) for reporting years 2003–2010, but were at detectable levels for the reporting years 2011–2012 (Table 6-13).

Table 6-4. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	8.30 (7.19–9.57)	7.70 (6.90–8.90)	16.0 (14.1–18.7)	37.4 (31.6–43.5)	65.4 (48.7–83.3)	2,557
	2005–2006	9.29 (8.05–10.7)	8.65 (7.48–9.99)	17.1 (14.9–20.6)	41.1 (33.3–49.7)	66.7 (53.7–87.0)	2,576
	2007–2008	8.10 (7.44–8.83)	7.49 (6.90–8.12)	14.9 (13.2–17.0)	33.3 (29.8–38.7)	50.8 (42.3–65.1)	2,605
	2009–2010	9.28 (8.47–10.2)	8.15 (7.20–8.98)	18.0 (15.3–20.8)	44.6 (39.0–55.1)	85.6 (64.7–114)	2,860
	2011–2012	6.85 (5.85–8.02)	6.09 (5.22–7.12)	13.0 (10.9–16.6)	32.0 (25.9–39.0)	52.5 (41.9–66.2)	2,504
Age group							
6–11 years	2003–2004	7.08 (5.66–8.84)	6.80 (5.90–7.70)	10.9 (8.90–14.2)	24.6 (13.8–61.8)	46.9 (17.5–178)	290
	2005–2006	7.19 (5.81–8.90)	6.96 (5.32–8.88)	11.5 (9.19–16.0)	19.6 (13.1–51.5)	34.1 (19.6–58.5)	355
	2007–2008	6.85 (5.98–7.83)	6.40 (5.74–7.23)	10.8 (9.75–12.3)	22.5 (16.9–34.7)	41.0 (21.1–52.8)	390
	2009–2010	6.63 (5.74–7.66)	5.94 (5.14–7.19)	10.8 (9.37–12.5)	26.0 (18.2–33.4)	37.7 (27.8–65.6)	378
	2011–2012	6.02 (5.03-7.19)	5.50 (4.58–6.56)	10.5 (7.93–14.1)	30.1 (16.7–46.5)	53.0 (37.5–70.3)	399
12–19 years	2003–2004	8.55 (7.34–9.97)	8.10 (6.80–9.40)	15.2 (12.2–17.8)	30.5 (23.1–40.4)	46.1 (32.9–62.5)	725
	2005–2006	8.19 (6.87–9.77)	7.92 (6.37–9.50)	14.0 (11.6–18.1)	28.2 (22.9–32.9)	41.9 (32.7–48.0)	701
	2007–2008	7.09 (6.17–8.14)	6.87 (5.88–7.86)	11.4 (9.41–13.7)	20.4 (16.1–26.6)	38.2 (21.6–53.3)	373
	2009–2010	6.45 (5.58–7.47)	6.11 (5.26–6.89)	10.8 (8.59–13.7)	25.9 (16.2–32.9)	38.8 (27.8–55.1)	454
	2011–2012	6.01 (4.45–8.11)	5.26 (3.95–7.47)	10.9 (7.74–16.9)	25.9 (16.6–44.0)	44.0 (25.9–153)	390
≥20 years	2003–2004	8.41 (7.25–9.77)	7.90 (7.00–9.10)	17.0 (15.0–19.7)	40.5 (34.9–46.2)	66.2 (51.2–93.1)	1,542
	2005–2006	9.76 (8.43–11.3)	9.12 (7.85–10.4)	18.9 (15.8–22.9)	44.2 (35.2–56.1)	71.4 (57.7–98.3)	1,520
	2007–2008	8.43 (7.70–9.22)	7.94 (7.09–8.67)	16.2 (14.5–18.6)	35.2 (30.4–42.3)	59.0 (44.2–75.6)	1,842
	2009–2010	10.2 (9.14–11.3)	8.75 (7.95–9.81)	20.4 (17.2–24.1)	52.1 (42.4–66.1)	93.1 (74.2–127)	2,028
	2011–2012	7.09 (6.03–8.33)	6.31 (5.32–7.45)	13.6 (11.3–18.3)	33.2 (26.7–39.5)	52.5 (41.9–77.3)	1,715

Table 6-4. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	9.50 (8.34–10.8)	8.90 (7.70–9.80)	17.6 (15.2–20.1)	41.6 (32.5–52.8)	65.8 (48.7–95.4)	1,281
	2005–2006	10.1 (8.61–11.8)	8.95 (8.05–10.0)	18.3 (15.5–22.9)	40.8 (31.0–52.6)	63.7 (46.4–78.7)	1,271
	2007–2008	9.25 (8.28–10.3)	8.50 (7.37–9.53)	17.0 (14.6–19.4)	36.0 (32.1–44.2)	62.5 (44.3–84.6)	1,318
	2009–2010	10.1 (9.06–11.3)	8.80 (7.80–9.75)	20.4 (16.1–23.9)	47.4 (42.1–64.1)	89.1 (71.6–114)	1,401
	2011–2012	7.69 (6.35–9.31)	6.84 (5.33–8.59)	15.4 (11.7–19.7)	33.5 (27.7–41.9)	56.5 (42.2–78.0)	1,262
Females	2003–2004	7.30 (6.02–8.84)	6.90 (5.90–8.30)	15.0 (11.3–19.5)	33.4 (26.5–41.7)	60.5 (40.8–77.1)	1,276
	2005–2006	8.60 (7.38–10.0)	8.18 (6.64–9.97)	15.9 (13.7–19.9)	41.5 (32.2–53.7)	72.6 (54.8–122)	1,305
	2007–2008	7.14 (6.51–7.82)	6.54 (6.09–7.14)	12.7 (11.6–14.4)	30.1 (26.0–34.0)	49.1 (40.1–57.5)	1,287
	2009–2010	8.55 (7.44–9.83)	7.63 (6.45–8.62)	15.8 (13.1–19.9)	41.5 (31.7–55.5)	81.5 (54.3–132)	1,459
	2011–2012	6.14 (5.22–7.22)	5.42 (4.79–6.25)	11.6 (9.85–13.7)	29.0 (22.5–38.2)	50.6 (37.5–79.8)	1,242
Race/ethnicity							
Mexican Americans	2003–2004	9.29 (8.12–10.6)	9.20 (8.10–10.3)	16.2 (13.5–19.9)	34.4 (24.0–60.5)	68.2 (41.3–111)	618
	2005–2006	9.55 (8.54–10.7)	9.11 (7.99–10.3)	15.6 (14.0–17.1)	29.2 (21.4–56.8)	67.6 (41.7–81.4)	652
	2007–2008	8.98 (8.13–9.92)	8.84 (7.80–9.48)	15.4 (12.3–19.7)	35.2 (25.0–46.0)	53.0 (44.2–77.4)	510
	2009–2010	8.47 (7.30–9.84)	7.96 (6.87–9.08)	13.9 (11.3–17.7)	34.7 (25.0–53.2)	60.9 (49.3–78.7)	613
	2011–2012	7.12 (5.73–8.84)	6.94 (5.34–8.70)	12.2 (9.84–16.5)	24.2 (18.4–35.7)	44.0 (23.8–70.3) 317	317
Non-Hispanic blacks	2003–2004	11.6 (9.50–14.1)	10.4 (7.90–11.8)	21.5 (14.9–34.4)	43.5 (36.2–61.8)	78.0 (43.6–141)	722
	2005–2006	11.0 (8.60–14.0)	9.55 (6.99–13.3)	21.9 (14.9–28.9)	44.9 (31.1–71.4)	82.3 (49.2–164)	692
	2007–2008	10.5 (9.40–11.7)	9.21 (8.22–10.4)	18.4 (16.1–21.5)	42.4 (32.9–52.8)	65.6 (45.5–112)	585
	2009–2010	10.9 (9.46–12.5)	9.26 (7.70–11.4)	21.7 (17.6–24.2)	49.1 (32.2–81.7)	84.8 (51.3–174)	546
	2011–2012	9.31 (7.19–12.0)	8.18 (6.16–10.8)	17.9 (13.1–25.3)	46.8 (28.8–76.5)	82.1 (53.1–107)	669

Table 6-4. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	7.12 (6.13–8.27)	7.00 (6.10–7.90)	13.7 (11.3–15.8)	29.0 (22.6–35.9)	53.1 (38.4–65.6)	1,074
	2005–2006	8.66 (7.20–10.4)	8.05 (6.52–9.66)	16.3 (13.4–20.6)	40.8 (29.4–50.2)	58.5 (46.0–88.0)	1,041
	2007–2008	6.98 (6.31–7.71)	6.46 (5.93–7.29)	12.4 (11.3–14.3)	28.3 (21.6–32.6)	42.1 (32.3–50.0)	1,088
	2009–2010	8.18 (7.46–8.96)	7.24 (6.46–8.21)	14.8 (12.7–17.4)	38.9 (31.7–44.4)	66.3 (49.3–88.7)	1,224
	2011–2012	5.89 (4.92–7.06)	5.08 (4.56–6.06)	10.8 (8.48–15.5)	26.3 (20.3–34.9)	43.2 (34.9–56.0)	820

CI = confidence interval

Source: CDC 2015

Table 6-5. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	8.24 (7.07–9.59)	7.04 (5.93–8.51)	14.1 (11.6–17.2)	30.4 (26.0–38.7)	50.4 (40.3–64.5)	2,557
	2005–2006	9.15 (7.93–10.6)	7.70 (6.55–8.98)	15.2 (11.7–19.4)	35.1 (26.5–44.7)	62.8 (44.7–85.0)	2,576
	2007–2008	8.46 (7.78–9.21)	7.06 (6.56–7.74)	13.8 (12.5–15.2)	28.9 (24.2–36.7)	49.0 (38.8–70.5)	2,605
	2009–2010	9.90 (9.06–10.8)	7.90 (6.98–8.97)	17.6 (15.4–20.2)	45.2 (36.6–53.3)	80.8 (60.5–94.4)	2,860
	2011–2012	7.77 (6.85–8.81)	6.39 (5.57–7.24)	13.7 (11.5–16.5)	30.8 (24.6–38.6)	50.4 (38.2–70.1)	2,502
Age group							
6–11 years	2003–2004	8.25 (6.58–10.3)	7.18 (5.93–9.45)	11.7 (9.10–16.3)	22.2 (12.0–69.5)	40.1 (14.7–188)	290
	2005–2006	8.88 (7.05–11.2)	7.87 (6.19–9.42)	11.8 (9.32–18.9)	24.5 (13.0–62.8)	45.4 (22.9–80.9)	355
	2007–2008	8.87 (8.06–9.77)	7.53 (6.73–7.88)	13.4 (10.2–16.0)	26.7 (19.9–34.0)	37.2 (28.6–71.4)	390
	2009–2010	8.97 (7.93–10.2)	7.42 (6.70–8.32)	11.0 (9.90–14.0)	33.5 (17.0–54.6)	60.8 (36.6–84.9)	378
	2011–2012	8.63 (7.26–10.3)	6.87 (5.84–8.00)	12.3 (9.58–15.5)	27.7 (17.7–57.7)	91.2 (26.2–129)	398
12–19 years	2003–2004	6.11 (5.23–7.13)	5.06 (4.47–6.04)	9.66 (7.44–11.2)	17.8 (12.0–26.0)	27.8 (20.7–35.9)	725
	2005–2006	6.30 (5.56–7.14)	5.19 (4.80–6.19)	9.62 (8.12–11.1)	19.4 (13.9–25.8)	28.0 (21.9–33.2)	701
	2007–2008	5.50 (4.91–6.16)	4.96 (4.25–5.40)	7.69 (6.09–9.31)	16.8 (10.8–21.1)	22.5 (16.8–29.1)	373
	2009–2010	6.06 (5.34–6.87)	4.95 (4.39–5.81)	9.18 (7.00–11.0)	19.2 (14.5–21.3)	28.4 (20.8–35.7)	454
	2011–2012	5.75 (4.49–7.36)	4.69 (3.70–5.73)	8.73 (6.26–13.3)	22.1 (11.5–52.6)	34.9 (21.1–159)	390
≥20 years	2003–2004	8.64 (7.38–10.1)	7.47 (6.20–9.01)	15.4 (12.7–18.8)	33.8 (27.3–41.2)	53.9 (45.4–64.5)	1,542
	2005–2006	9.75 (8.46–11.2)	8.22 (6.98–9.75)	17.0 (12.8–21.3)	41.0 (29.6–52.5)	68.4 (52.8–89.7)	1,520
	2007–2008	9.00 (8.20–9.88)	7.55 (6.79–8.53)	14.9 (13.1–17.1)	32.5 (25.8–41.0)	59.4 (41.0–86.2)	1,842
	2009–2010	10.8 (9.71–12.0)	8.73 (7.69–9.71)	20.1 (16.5–24.2)	50.8 (40.5–59.7)	87.3 (70.0–105)	2,028
	2011–2012	8.04 (7.07–9.14)	6.52 (5.88–7.69)	14.8 (12.1–18.8)	32.4 (25.2–39.8)	49.7 (38.2–70.1)	1,714

Table 6-5. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	8.00 (6.81–9.40)	6.75 (5.66–8.35)	13.7 (11.0–18.0)	28.7 (25.1–36.4)	45.6 (35.3–62.1)	1,281
	2005–2006	8.26 (7.09–9.63)	7.16 (5.87–8.54)	12.9 (10.2–18.0)	28.8 (22.9–36.3)	46.1 (35.1–66.5)	1,271
	2007–2008	8.30 (7.49–9.18)	6.79 (6.39–7.61)	13.2 (11.8–15.2)	28.9 (23.5–38.5)	47.7 (35.7–68.1)	1,318
	2009–2010	9.21 (8.55–9.93)	7.22 (6.43–8.67)	17.0 (14.9–18.6)	41.8 (35.4–47.9)	66.9 (52.0–81.5)	1,401
	2011–2012	7.20 (6.15–8.43)	6.13 (5.18–7.23)	12.5 (10.5–15.2)	28.3 (20.2–34.9)	50.4 (33.3–69.6)	1,261
Females	2003–2004	8.47 (7.12–10.1)	7.33 (6.10–8.75)	14.4 (11.7–17.7)	32.3 (24.2–46.6)	58.4 (42.8–75.0)	1,276
	2005–2006	10.1 (8.72–11.7)	8.29 (7.23–9.87)	17.4 (13.0–21.4)	43.8 (29.2–61.5)	74.1 (55.0–96.2)	1,305
	2007–2008	8.63 (7.91–9.41)	7.13 (6.53–8.33)	14.1 (12.3–16.9)	27.9 (24.1–37.0)	51.4 (39.7–83.3)	1,287
	2009–2010	10.6 (9.36–12.0)	8.38 (7.40–9.41)	18.6 (14.9–23.9)	50.8 (35.1–72.9)	87.8 (66.8–109)	1,459
	2011–2012	8.35 (7.40–9.42)	6.64 (6.12–7.37)	15.0 (12.2–19.1)	33.1 (26.1–41.4)	50.7 (39.8–79.0)	1,241
Race/ethnicity							
Mexican Americans	2003–2004	8.61 (7.33–10.1)	7.76 (6.30–9.44)	12.6 (10.2–15.9)	24.0 (17.7–34.8)	42.4 (24.8–62.4)	618
	2005–2006	8.98 (7.89–10.2)	7.48 (6.72–8.87)	12.8 (11.0–16.3)	28.1 (21.1–35.5)	49.1 (31.0–108)	652
	2007–2008	8.88 (7.71–10.2)	7.38 (6.51–8.63)	14.1 (10.6–17.8)	28.6 (22.5–35.3)	48.2 (31.1–75.7)	510
	2009–2010	8.88 (7.87–10.0)	7.62 (6.69–8.45)	13.2 (10.7–17.2)	31.4 (23.7–38.5)	49.8 (37.5–68.9)	613
Non-Hispanic blacks	2003–2004	8.31 (6.99–9.88)	6.88 (5.66–8.41)	13.8 (11.5–17.0)	27.6 (17.9–56.0)	54.3 (27.5–120)	722
	2005–2006	7.96 (6.40–9.92)	6.48 (5.21–8.30)	13.4 (10.0–18.6)	32.5 (18.7–66.5)	71.4 (35.6–98.8)	692
	2007–2008	7.72 (6.98–8.54)	6.60 (6.01–7.56)	13.4 (11.5–15.4)	25.7 (22.1–30.0)	42.7 (31.4–60.3)	585
	2009–2010	8.67 (7.54–9.98)	7.26 (5.96–9.02)	15.6 (12.4–21.3)	38.7 (31.5–48.7)	63.9 (43.1–102)	546
	2011–2012	8.00 (6.85–9.36)	6.91 (6.07–7.98)	11.9 (9.05–14.6)	26.1 (16.7–39.4)	40.8 (24.0–70.1)	317

Table 6-5. Geometric Mean and Selected Percentiles of Urinary Total Arsenic (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	7.50 (6.25–9.01)	6.32 (5.28–7.96)	12.5 (9.86–17.1)	26.8 (21.8–32.0)	40.0 (31.3–53.9)	1,074
	2005–2006	9.01 (7.57–10.7)	7.68 (6.18–9.56)	14.3 (11.1–20.8)	31.9 (24.1–46.1)	59.4 (37.9–96.2)	1,041
	2007–2008	7.82 (7.05–8.68)	6.72 (6.00–7.54)	12.5 (11.1–13.9)	24.6 (19.6–32.3)	43.1 (29.1–64.0)	1,088
	2009–2010	9.14 (8.35–10.0)	7.10 (6.43–8.06)	15.8 (13.7–18.4)	40.9 (30.4–50.8)	66.4 (50.9–90.0)	1,224
	2011–2012	7.24 (5.51–9.51)	5.83 (4.65–7.96)	13.5 (9.02–19.0)	28.8 (21.5–46.3)	55.4 (31.6–87.1)	669

CI = confidence interval

Source: CDC 2015

Table 6-6. Geometric Mean and Selected Percentiles of Urinary Arsenic(V) Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.50)	2,568
	2005–2006	*	<LOD	<LOD	<LOD	1.06 (<LOD–1.43)	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,852
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,517
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.30)	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	379
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.60)	728
	2005–2006	*	<LOD	<LOD	<LOD	1.00 (<LOD–1.30)	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	453
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.50)	1,548
	2005–2006	*	<LOD	<LOD	<LOD	1.09 (<LOD–1.71)	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,020
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,724

Table 6-6. Geometric Mean and Selected Percentiles of Urinary Arsenic(V) Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.50)	1,284
	2005–2006	*	<LOD	<LOD	<LOD	1.14 (<LOD–1.71)	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,396
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,264
Females	2003–2004	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.30)	1,284
	2005–2006	*	<LOD	<LOD	<LOD	1.01 (<LOD–1.22)	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.60)	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.80)	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	543
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.50)	1,078
	2005–2006	*	<LOD	<LOD	<LOD	1.10 (<LOD–1.74)	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,210
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-7. Geometric Mean and Selected Percentiles of Urinary Arsenic(V) Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	3.04 (<LOD–3.50)	2,568
	2005–2006	*	<LOD	<LOD	<LOD	3.23 (<LOD–3.55)	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,851
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,516
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	2.80 (<LOD–4.00)	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	378
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	1.75 (<LOD–2.41)	728
	2005–2006	*	<LOD	<LOD	<LOD	1.69 (<LOD–2.73)	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	453
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	3.18 (<LOD–3.70)	1,548
	2005–2006	*	<LOD	<LOD	<LOD	3.38 (<LOD–3.94)	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,020
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,723
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	2.61 (<LOD–3.18)	1,284
	2005–2006	*	<LOD	<LOD	<LOD	2.14 (<LOD–2.73)	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,395
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,263
Females	2003–2004	*	<LOD	<LOD	<LOD	3.33 (<LOD–3.89)	1,284
	2005–2006	*	<LOD	<LOD	<LOD	3.55 (<LOD–4.44)	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	2.69 (<LOD–3.50)	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	1.75 (<LOD–2.19)	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	542
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672

Table 6-7. Geometric Mean and Selected Percentiles of Urinary Arsenic(V) Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	3.33 (<LOD–3.95)	1,078
	2005–2006	*	<LOD	<LOD	<LOD	3.38 (<LOD–3.80)	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,210
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	824

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	1.55 (1.31–1.83)	1.00 (0.800–1.40)	5.20 (4.00–6.50)	16.8 (12.7–22.3)	35.0 (27.6–44.6)	2,568
	2005–2006	1.86 (1.43–2.41)	1.53 (0.980–2.26)	6.73 (4.80–8.91)	22.6 (16.5–30.3)	40.6 (30.7–59.4)	2,588
	2007–2008	*	0.670 (0.510–0.910)	4.26 (3.53–4.88)	16.6 (12.5–20.2)	29.5 (22.8–37.1)	2,576
	2009–2010	1.59 (1.38–1.83)	0.940 (0.720–1.26)	6.18 (4.67–7.87)	23.5 (19.8–30.1)	50.4 (35.7–63.2)	2,870
	2011–2012	*	<LOD	4.62 (3.25–6.25)	18.0 (13.7–23.2)	.5 (25.7–51.9)	2,517
Age group							
6–11 years	2003–2004	*	<LOD	1.80 (0.800–	8.80 (3.90–29.9)	29.9 (6.20–190)	292
	2005–2006	*	<LOD	4.00) 2.22	7.14 (2.34–29.9)	18.9 (5.46–45.0)	354
	2007–2008	*	<LOD	(0.620–5.35)	6.71 (3.37–8.38)	13.0 (7.22–25.2)	390
	2009–2010	*	<LOD	1.24 (0.780–2.42) 1.20 (0.590–3.12)	7.98 (5.20–15.7)	19.4 (9.25–47.9)	380
	2011–2012	*	<LOD	1.58	15.2 (6.60–)	49.6	401

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
				(<LOD–4.12)	35.6	(20.0–60.1)	
12–19 years	2003–2004	*	0.600 (0.400–0.800)	3.20 (2.00–4.70)	13.9 (7.20–25.1)	31.8 (17.2–35.8)	728
	2005–2006	*	0.550 (<LOD–1.14)	3.76 (1.95–7.16)	12.4 (9.15–20.4)	25.6 (16.4–32.4)	703
	2007–2008	*	<LOD	1.72 (0.780–2.62)	4.88 (3.49–9.17)	10.4 (6.81–23.6)	366
	2009–2010	*	<LOD	2.07 (1.26–3.60)	11.0 (5.35–16.7)	17.8 (12.8–24.0)	455
	2011–2012	*	<LOD	1.82 (<LOD–8.46)	17.6 (6.92–26.5)	32.6 (15.3–100)	392
≥20 years	2003–2004	1.74 (1.48–2.05)	1.30 (1.00–1.60)	6.10 (4.90–7.10)	18.5 (14.0–23.5)	35.5 (26.8–50.5)	1,548
	2005–2006	2.20 (1.71–2.84)	1.89 (1.41–2.64)	8.14 (5.86–10.4)	27.6 (18.7–35.7)	43.9 (36.0–67.9)	1,531
	2007–2008	1.46 (1.28–1.67)	0.960 (0.750–1.22)	5.08 (4.30–6.20)	19.1 (14.3–23.7)	31.7 (23.9–46.1)	1,820
	2009–2010	1.92 (1.63–2.26)	1.33 (0.960–1.91)	7.60 (6.06–9.90)	28.2 (21.9–34.9)	59.5 (45.7–76.7)	2,035
	2011–2012	*	<LOD	5.26 (4.07–6.58)	18.1 (13.4–24.0)	36.5 (24.4–53.4)	1,724
Gender							
Males	2003–2004	1.66 (1.43–1.93)	1.20 (0.900–1.50)	5.80 (4.40–7.10)	18.6 (13.9–23.7)	35.0 (26.8–40.5)	1,284
	2005–2006	1.83 (1.40–2.40)	1.44 (0.920–2.04)	6.63 (5.06–8.66)	23.2 (12.8–33.4)	37.1 (28.5–51.3)	1,276
	2007–2008	*	0.910 (0.660–1.26)	5.07 (4.01–6.81)	19.1 (13.8–22.6)	30.3 (22.8–46.1)	1,289
	2009–2010	1.71 (1.48–1.97)	0.990 (0.780–1.33)	7.14 (5.38–9.86)	26.8 (21.5–31.8)	57.4 (36.4–64.6)	1,402
	2011–2012	*	<LOD	5.22 (3.38–7.16)	18.4 (13.7–25.9)	41.7 (26.4–60.3)	1,264
Females	2003–2004	1.45 (1.17–1.80)	0.900 (0.700–1.40)	4.70 (3.40–6.20)	15.6 (11.1–25.3)	32.7 (21.1–51.3)	1,284
	2005–2006	1.88 (1.42–2.50)	1.64 (0.950–2.51)	6.81 (4.03–9.88)	21.8 (17.3–30.1)	43.3 (33.8–67.9)	1,312
	2007–2008	*	0.530 (0.410–0.650)	3.52 (2.94–4.35)	14.0 (10.9–17.5)	29.5 (19.4–34.0)	1,287
	2009–2010	1.49 (1.20–1.84)	0.890 (0.590–1.35)	5.54 (3.56–7.74)	21.2 (14.7–32.7)	47.1 (32.5–76.4)	1,468
	2011–2012	*	<LOD	4.18 (2.84–6.11)	17.0 (10.6–22.7)	33.5 (22.1–53.1)	1,253

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	2003–2004	1.19 (0.871–1.62)	0.800 (0.500–1.30)	3.20 (1.80–5.20)	10.2 (6.70–21.4)	31.4 (16.3–39.1)	621
	2005–2006	1.44 (1.23–1.69)	1.04 (0.770–1.35)	3.90 (3.03–5.06)	16.8 (11.1–32.0)	41.4 (23.4–57.9)	651
	2007–2008	*	0.560 (<LOD–0.910)	3.27 (2.00–5.65)	16.9 (9.73–20.8)	29.6 (19.3–40.5)	513
	2009–2010	*	0.640 (0.440–0.800)	3.58 (1.80–5.89)	15.5 (7.83–24.6)	31.9 (18.7–44.7)	617
	2011–2012	*	<LOD	3.78 (1.93–5.84)	12.5 (6.11–17.6)	19.3 (12.9–34.7)	317
Non-Hispanic blacks	2003–2004	2.29 (1.60–3.28)	2.00 (1.20–3.50)	7.70 (5.00–12.0)	23.7 (13.2–38.7)	45.6 (25.1–94.0)	725
	2005–2006	2.55 (1.64–3.99)	2.42 (1.15–4.58)	8.74 (6.01–14.4)	23.8 (15.9–48.9)	59.6 (30.5–121)	695
	2007–2008	1.58 (1.31–1.90)	1.11 (0.750–1.60)	5.88 (4.12–8.13)	21.9 (16.4–24.9)	35.9 (25.4–47.7)	586
	2009–2010	1.99 (1.60–2.47)	1.79 (1.05–2.41)	7.61 (5.34–10.0)	25.5 (15.4–37.6)	51.2 (31.0–90.9)	546
	2011–2012	*	1.19 (<LOD–2.91)	7.09 (3.79–13.4)	30.2 (17.2–51.9)	57.9 (36.1–81.5)	672
Non-Hispanic whites	2003–2004	1.37 (1.11–1.68)	0.800 (0.700–1.20)	4.30 (2.50–6.30)	13.3 (9.70–21.4)	29.3 (21.4–35.5)	1,078
	2005–2006	1.74 (1.27–2.40)	1.41 (0.750–2.27)	6.40 (3.93–9.04)	22.4 (14.1–30.1)	38.4 (27.8–66.8)	1,050
	2007–2008	*	0.530 (<LOD–0.780)	3.63 (3.06–4.38)	12.6 (9.08–17.1)	24.3 (17.6–30.3)	1,063
	2009–2010	1.43 (1.24–1.65)	0.800 (0.610–1.18)	5.40 (3.77–7.27)	20.6 (17.7–24.5)	41.3 (30.6–59.5)	1,226
	2011–2012	*	<LOD	4.07 (2.39–6.12)	16.7 (9.30–22.5)	30.0 (23.2–47.0)	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-9. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	1.54 (1.30–1.82)	1.16 (0.959–1.43)	5.00 (3.62–6.91)	16.2 (12.5–20.3)	29.4 (24.0–36.4)	2,568
	2005–2006	1.82 (1.40–2.37)	1.64 (1.10–2.41)	6.64 (4.48–8.79)	20.3 (14.5–28.1)	37.0 (27.5–58.3)	2,588
	2007–2008	*	1.00 (0.850–1.18)	4.07 (3.36–4.98)	14.7 (11.1–17.8)	27.7 (18.9–45.4)	2,576
	2009–2010	1.69 (1.45–1.97)	1.23 (0.980–1.47)	6.48 (4.90–8.00)	23.6 (18.5–30.7)	49.6 (36.6–61.3)	2,869
	2011–2012	*	<LOD	5.63 (4.42–7.22)	18.0 (13.8–26.1)	36.9 (26.9–45.6)	2,516
Age group							
6–11 years	2003–2004	*	<LOD	2.00 (1.15–4.83)	12.2 (4.13–39.7)	29.6 (6.80–153)	292
	2005–2006	*	<LOD	2.88 (1.04–6.25)	8.77 (2.88–40.5)	23.6 (6.86–74.8)	354
	2007–2008	*	<LOD	2.11 (1.27–3.79)	8.98 (4.76–14.8)	16.4 (8.98–23.8)	390
	2009–2010	*	<LOD	1.70 (1.21–3.02)	9.52 (5.08–20.7)	24.9 (9.81–50.7)	379
	2011–2012	*	<LOD	4.35 (<LOD–6.46)	16.0 (8.00–39.5)	69.0 (16.0–102)	401
12–19 years	2003–2004	*	.531 (0.400–.638)	2.14 (1.39–3.51)	9.29 (4.29–14.7)	17.3 (10.4–28.7)	728
	2005–2006	*	.620 (<LOD–.800)	2.82 (1.58–4.77)	10.5 (7.03–13.7)	15.4 (11.8–22.3)	703
	2007–2008	*	<LOD	1.28 (0.650–1.72)	5.17 (2.31–6.53)	9.88 (5.72–16.0)	366
	2009–2010	*	<LOD	2.25 (1.17–3.76)	8.69 (5.03–12.8)	14.0 (9.82–15.5)	455
	2011–2012	*	<LOD	3.36 (<LOD–8.94)	14.4 (5.56–23.8)	25.9 (13.6–104)	392
≥20 years	2003–2004	1.79 (1.51–2.12)	1.47 (1.15–1.88)	5.91 (4.32–7.72)	17.2 (13.4–21.8)	30.1 (26.1–36.4)	1,548
	2005–2006	2.19 (1.70–2.82)	2.13 (1.40–2.83)	7.79 (5.38–10.2)	24.4 (16.6–32.9)	43.1 (30.5–71.4)	1,531
	2007–2008	1.55 (1.36–1.78)	1.29 (1.13–1.52)	5.27 (3.91–6.40)	16.6 (12.2–21.6)	33.4 (21.0–55.9)	1,820
	2009–2010	2.03 (1.70–2.42)	1.52 (1.18–2.16)	7.65 (6.04–10.4)	27.7 (22.1–35.9)	57.0 (39.7–71.9)	2,035
	2011–2012	*	<LOD	6.25 (4.78–8.46)	19.3 (14.0–28.4)	35.8 (26.8–44.1)	1,723

Table 6-9. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	1.40 (1.18–1.67)	1.11 (0.909–1.28)	4.78 (3.61–6.70)	14.4 (11.1–18.5)	26.5 (18.6–29.9)	1,284
	2005–2006	1.50 (1.15–1.96)	1.25 (0.800–1.93)	5.11 (3.41–7.54)	15.3 (11.2–20.8)	30.5 (19.6–44.0)	1,276
	2007–2008	*	1.04 (0.870–1.25)	4.11 (3.16–5.30)	14.9 (10.1–17.9)	27.0 (17.8–49.2)	1,289
	2009–2010	1.56 (1.35–1.80)	1.04 (0.880–1.34)	6.20 (4.34–7.79)	23.4 (18.7–27.6)	39.2 (32.0–54.8)	1,401
	2011–2012	*	<LOD	4.94 (3.50–6.67)	16.7 (12.6–25.7)	35.7 (23.4–52.8)	1,263
Females	2003–2004	1.68 (1.37–2.05)	1.25 (0.938–1.67)	5.58 (3.50–7.43)	17.2 (12.3–24.5)	32.9 (25.6–46.3)	1,284
	2005–2006	2.20 (1.65–2.93)	2.04 (1.30–2.92)	7.86 (5.38–10.8)	26.4 (16.6–35.6)	46.2 (30.3–74.3)	1,312
	2007–2008	*	0.980 (0.800–1.18)	4.06 (3.35–5.29)	14.6 (11.1–17.8)	29.6 (18.2–50.0)	1,287
	2009–2010	1.83 (1.48–2.26)	1.36 (1.04–1.75)	6.65 (4.68–9.21)	24.1 (16.5–37.3)	57.0 (36.3–71.3)	1,468
	2011–2012	*	<LOD	6.48 (4.79–8.60)	18.8 (15.4–28.1)	37.0 (26.2–46.8)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	1.10 (0.786–1.55)	0.877 (0.612–1.40)	2.93 (1.78–5.21)	8.88 (5.50–15.4)	19.0 (9.64–29.4)	621
	2005–2006	1.35 (1.13–1.62)	0.970 (0.810–1.19)	4.21 (2.79–5.68)	16.6 (10.5–21.3)	36.9 (18.4–69.5)	651
	2007–2008	*	0.780 (<LOD–1.21)	3.04 (1.99–5.09)	13.7 (9.09–16.7)	28.9 (16.2–46.7)	513
	2009–2010	*	0.790 (0.670–0.940)	3.64 (2.28–4.41)	13.5 (7.78–19.1)	26.8 (16.5–42.0)	617
	2011–2012	*	<LOD	3.87 (2.80–5.76)	12.6 (8.36–22.6)	25.9 (13.4–40.3)	317
Non-Hispanic blacks	2003–2004	1.65 (1.19–2.30)	1.53 (0.901–2.45)	5.81 (4.25–7.82)	13.6 (9.76–27.9)	32.9 (13.4–82.1)	725
	2005–2006	1.84 (1.20–2.83)	1.71 (0.910–2.95)	6.07 (3.83–9.25)	19.4 (10.4–45.2)	47.5 (25.3–62.0)	695
	2007–2008	1.16 (0.955–1.41)	0.830 (0.620–1.12)	4.44 (3.23–6.58)	14.9 (10.5–17.6)	25.1 (17.4–40.0)	586
	2009–2010	1.59 (1.29–1.96)	1.30 (0.850–2.04)	5.92 (4.20–8.40)	19.5 (13.5–27.1)	37.9 (26.1–51.7)	545
	2011–2012	*	1.50 (<LOD–2.18)	6.00 (2.63–12.4)	20.3 (12.8–30.0)	38.7 (22.6–78.2)	672

Table 6-9. Geometric Mean and Selected Percentiles of Urinary Arsenobetaine (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	1.44 (1.15–1.80)	1.05 (0.833–1.36)	4.47 (2.73–6.83)	14.3 (10.9–18.6)	26.5 (18.6–32.0)	1,078
	2005–2006	1.81 (1.32–2.47)	1.65 (0.970–2.55)	6.65 (3.95–9.34)	19.7 (12.6–30.5)	36.6 (25.1–71.4)	1,050
	2007–2008	*	0.970 (<LOD–1.18)	3.56 (2.93–4.53)	11.6 (8.98–16.6)	23.8 (15.5–41.7)	1,063
	2009–2010	1.60 (1.36–1.87)	1.15 (0.900–1.43)	5.85 (4.33–7.65)	22.8 (15.6–29.4)	38.5 (32.0–57.0)	1,226
	2011–2012	*	<LOD	5.00 (4.06–7.55)	16.8 (12.7–28.7)	35.7 (21.0–45.6)	824

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-10. Geometric Mean and Selected Percentiles of Urinary Arsenocholine (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,871
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,517
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	380
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	728
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820

Table 6-10. Geometric Mean and Selected Percentiles of Urinary Arsenocholine (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,724
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,403
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,264
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,264
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	<LOD	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	<LOD	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	546
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-11. Geometric Mean and Selected Percentiles of Urinary Arsenocholine (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,870
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,516
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	379
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	728
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,723
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,403
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,263
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	<LOD	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	<LOD	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	545
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672

Table 6-11. Geometric Mean and Selected Percentiles of Urinary Arsenocholine (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	824

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-12. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,871
	2011–2012	*	<LOD	0.520 (<LOD–0.600)	0.840 (0.760–0.960)	1.11 (0.980–1.27)	2,517
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	380
	2011–2012	*	<LOD	0.540 (<LOD–0.660)	0.870 (0.710–1.00)	1.03 (0.820–1.22)	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	1.40 (<LOD–1.70)	728
	2005–2006	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.40)	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	0.610 (0.480–.720)	0 .920 (0.810–1.14)	1.18 (0.980–1.43)	392

Table 6-12. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	0.500 (<LOD–0.570)	0.830 (0.750–0.940)	1.11 (0.980–1.27)	1,724
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	1.26 (<LOD–1.73)	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	1.24 (<LOD–1.50)	1,403
	2011–2012	*	<LOD	0.600 (0.520–0.680)	0.980 (0.840–1.13)	1.31 (1.11–1.59)	1,264
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	>LOD	0.760 (0.600–0.840)	0.940 (0.810–1.07)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	2.00 (<LOD–3.00)	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.76)	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	0.570 (0.490–0.660)	0 .830 (0.770–1.03)	1.14 (0.880–1.37)	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	1.20 (<LOD–1.80)	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	546
	2011–2012	*	<LOD	**0.520** (<LOD–0.680)	0**.880** (0.700–1.10)	**1.21** (0.980–1.57)	672

Table 6-12. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	<LOD	0.800 (0.640–0.900)	1.03 (0.830–1.18)	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-13. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (Creatinine Corrected) (in µg As/g of creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,870
	2011–2012	*	<LOD	0.791 (<LOD–0.850)	1.35 (1.21–1.42)	1.79 (1.55–1.89)	2,516
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	379
	2011–2012	*	<LOD	1.03 (<LOD–1.13)	1.54 (1.26–1.79)	2.00 (1.55–2.62)	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	1.95 (<LOD–2.76)	728
	2005–2006	*	<LOD	<LOD	<LOD	2.02 (<LOD–3.04)	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	0.709 (0.607–0.850)	1.11 (0.971–1.31)	1.36 (1.03–2.50)	392

Table 6-13. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (Creatinine Corrected) (in µg As/g of creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	0.773 (<LOD–0.850)	1.36 (1.19–1.48)	1.79 (1.55–1.95)	1,723
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	2.43 (<LOD–3.15)	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	2.93 (<LOD–3.54)	1,402
	2011–2012	*	<LOD				
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	0.708 (0.645–0.756)	1.12 (0.981–1.25)	1.48 (1.28–1.70)	1,263
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	3.08 (<LOD–4.44)	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	3.54 (<LOD–4.72)	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	1.42 (1.36–1.62)	1.89 (1.70–2.27)	1,253
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	2.00 (<LOD–2.29)	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	545
	2011–2012	*	<LOD	0.723 (0.630–0.850)	1.13 (0.919–1.42)	1.55 (1.13–2.20)	317

Table 6-13. Geometric Mean and Selected Percentiles of Urinary Arsenous (III) Acid (Creatinine Corrected) (in µg As/g of creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	0.514 (<LOD–0.586)	0.919 (0.739–1.06)	1.22 (0.971–1.64)	672

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-14. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	3.71 (3.33–4.14)	3.90 (3.00–4.00)	6.00 (5.00–7.00)	11.0 (9.20–12.0)	16.0 (13.0–17.8)	2,568
	2005–2006	3.95 (3.59–4.35)	3.90 (3.46–4.31)	6.17 (5.53–7.04)	10.3 (9.00–12.2)	15.0 (12.2–17.8)	2,588
	2007–2008	3.67 (3.44–3.91)	3.58 (3.44–3.84)	5.96 (5.44–6.57)	9.78 (8.72–11.2)	13.3 (11.8–15.3)	2,576
	2009–2010	3.67 (3.43–3.93)	3.50 (3.25–3.76)	6.16 (5.59–6.73)	11.5 (9.35–13.7)	17.4 (14.0–21.0)	2,871
	2011–2012	3.47 (3.18–3.78)	3.37 (3.06–3.66)	5.81 (5.14–6.59)	9.55 (8.43–11.2)	14.0 (11.4–16.5)	2,517
Age group							
6–11 years	2003–2004	3.73 (3.12–4.45)	4.00 (3.00–4.00)	6.00 (5.00–7.00)	9.00 (7.00–12.0)	12.0 (8.00–22.0)	292
	2005–2006	3.96 (3.49–4.49)	3.94 (3.20–4.71)	5.94 (5.01–7.10)	10.5 (7.10–12.1)	13.0 (10.7–15.3)	354
	2007–2008	3.86 (3.45–4.32)	3.76 (3.47–4.01)	6.10 (5.29–6.99)	10.4 (7.57–13.9)	15.2 (9.32–39.2)	390
	2009–2010	3.53 (3.17–3.92)	3.27 (2.81–3.87)	5.76 (5.07–6.53)	10.7 (7.84–11.9)	12.8 (11.0–14.4)	380
	2011–2012	3.43 (3.06–3.85)	3.53 (2.81–4.05)	5.81 (5.21–6.38)	8.60 (7.55–9.73)	11.4 (9.35–13.7)	401

Table 6-14. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
12–19 years	2003–2004	3.85 (3.34–4.42)	4.00 (3.00–4.00)	6.00 (5.00–7.10)	9.30 (7.70–12.0)	13.0 (10.0–16.0)	728
	2005–2006	3.97 (3.46–4.55)	3.97 (3.31–4.64)	5.74 (5.11–7.10)	9.43 (7.63–11.6)	12.0 (10.7–13.9)	703
	2007–2008	3.60 (3.16–4.09)	3.66 (3.24–4.26)	5.53 (4.75–6.72)	8.90 (7.33–9.95)	10.7 (9.08–13.3)	366
	2009–2010	3.08 (2.77–3.43)	2.89 (2.64–3.29)	5.05 (4.44–5.77)	7.89 (6.87–10.1)	11.3 (8.75–13.8)	456
	2011–2012	3.27 (2.71–3.94)	3.33 (2.49–4.20)	5.02 (4.33–6.05)	8.53 (6.29–11.1)	11.6 (8.74–17.9)	392
≥20 years	2003–2004	3.69 (3.31–4.11)	3.70 (3.00–4.00)	6.00 (5.00–7.00)	11.0 (10.0–12.0)	16.0 (13.0–19.0)	1,548
	2005–2006	3.95 (3.58–4.36)	3.87 (3.46–4.32)	6.30 (5.59–7.28)	10.3 (9.25–13.3)	16.2 (12.5–19.4)	1,531
	2007–2008	3.66 (3.43–3.91)	3.56 (3.41–3.80)	5.97 (5.44–6.63)	9.89 (8.72–11.4)	13.8 (11.8–15.5)	1,820
	2009–2010	3.79 (3.51–4.09)	3.60 (3.33–3.87)	6.40 (5.71–7.03)	12.1 (9.52–16.0)	18.2 (15.8–23.6)	2,035
	2011–2012	3.51 (3.22–3.82)	3.37 (3.05–3.67)	5.91 (5.20–6.83)	9.94 (8.57–11.5)	14.1 (12.2–16.4)	1,724

Table 6-14. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	4.12 (3.60–4.71)	4.00 (3.70–4.30)	6.00 (5.60–7.70)	11.0 (9.00–15.0)	17.0 (12.1–22.0)	1,284
	2005–2006	4.17 (3.79–4.59)	4.04 (3.68–4.43)	6.32 (5.41–7.61)	10.5 (8.68–13.3)	14.8 (11.8–19.2)	1,276
	2007–2008	4.05 (3.73–4.40)	3.96 (3.63–4.27)	6.53 (5.77–7.15)	10.3 (9.31–12.0)	14.6 (11.6–20.2)	1,289
	2009–2010	3.89 (3.50–4.32)	3.71 (3.35–4.11)	6.33 (5.80–7.02)	11.6 (8.80–17.3)	19.2 (13.0–24.7)	1,403
	2011–2012	3.79 (3.40–4.239)	3.71 (3.33–4.29)	6.27 (5.36–7.61)	10.3 (8.75–12.5)	15.3 (12.5–16.7)	1,264
Females	2003–2004	3.37 (3.00–3.78)	3.00 (3.00–4.00)	5.50 (4.80–6.20)	10.0 (8.00–11.0)	14.0 (11.0–17.7)	1,284
	2005–2006	3.75 (3.37–4.18)	3.70 (3.28–4.21)	6.03 (5.46–6.99)	9.95 (8.81–12.2)	15.5 (11.6–19.0)	1,312
	2007–2008	3.34 (3.13–3.57)	3.37 (3.15–3.53)	5.48 (5.00–6.05)	8.99 (7.97–10.4)	11.9 (10.7–13.9)	1,287
	2009–2010	3.48 (3.22–3.76)	3.28 (2.95–3.63)	5.85 (5.21–6.69)	11.5 (9.42–13.3)	16.1 (13.8–17.7)	1,468
	2011–2012	3.19 (2.92–3.48)	3.01 (2.73–3.30)	5.30 (4.61–5.96)	8.96 (7.72–10.5)	12.2 (9.56–17.8)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	4.72 (4.27–5.22)	4.80 (4.00–5.00)	7.00 (6.00–9.00)	12.0 (10.0–16.0)	17.0 (12.0–25.0)	621
	2005–2006	4.43 (4.15–4.72)	4.66 (4.26–5.13)	6.93 (6.38–7.58)	9.51 (8.70–11.1)	13.1 (10.3–15.1)	651
	2007–2008	4.36 (4.05–4.69)	4.62 (4.07–5.07)	7.14 (6.23–7.76)	9.67 (8.39–10.8)	11.7 (9.96–17.6)	513
	2009–2010	3.90 (3.45–4.40)	3.98 (3.18–4.63)	6.53 (5.61–7.15)	10.7 (8.95–13.2)	16.2 (13.1–19.2)	618
	2011–2012	3.67 (3.33–4.04)	3.58 (3.27–4.18)	5.82 (5.24–6.47)	9.05 (7.91–10.0)	12.1 (9.61–17.4)	317
Non-Hispanic blacks	2003–2004	4.27 (3.71–4.92)	4.00 (3.50–5.00)	7.00 (6.00–8.00)	11.6 (9.00–15.0)	16.0 (14.0–18.7)	725
	2005–2006	4.28 (3.68–4.98)	4.02 (3.37–4.82)	6.42 (5.31–7.36)	10.9 (8.22–13.1)	15.2 (11.5–27.1)	695
	2007–2008	4.19 (3.92–4.49)	3.98 (3.63–4.27)	6.69 (5.80–7.43)	11.2 (10.1–12.5)	14.7 (12.1–19.2)	586
	2009–2010	4.09 (3.63–4.61)	3.93 (3.31–4.36)	7.13 (5.99–8.63)	12.3 (10.1–17.0)	18.2 (13.7–27.8)	546
	2011–2012	4.05 (3.46–4.74)	4.05 (3.35–4.65)	6.78 (5.46–8.21)	12.0 (10.0–14.2)	17.4 (14.2–19.8)	672

Table 6-14. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	3.27 (2.95–3.62)	3.00 (3.00–3.80)	5.00 (4.60–6.00)	9.00 (7.00–10.0)	12.0 (9.50–15.0)	1,078
	2005–2006	3.69 (3.28–4.15)	3.60 (3.19–4.08)	5.66 (5.10–6.70)	9.62 (8.11–11.8)	13.9 (10.6–17.8)	1,050
	2007–2008	3.23 (3.01–3.48)	3.34 (3.04–3.53)	5.14 (4.77–5.59)	8.27 (7.48–9.07)	10.5 (9.25–13.2)	1,063
	2009–2010	3.21 (3.07–3.37)	3.12 (2.91–3.29)	5.32 (5.00–5.66)	8.65 (7.23–10.1)	12.0 (10.1–14.4)	1,226
	2011–2012	3.06 (2.82–3.33)	2.97 (2.72–3.29)	4.95 (4.39–5.77)	7.98 (6.92–9.02)	10.5 (8.71–13.0)	825

CI = confidence interval

Source: CDC 2015

Table 6-15. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	3.69 (3.24–4.19)	3.37 (2.94–3.91)	5.71 (4.69–6.74)	9.09 (7.61–11.5)	13.0 (10.7–16.0)	2,568
	2005–2006	3.88 (3.57–4.22)	3.66 (3.39–3.93)	5.71 (5.10–6.43)	9.57 (7.95–10.9)	12.3 (10.6–15.0)	2,588
	2007–2008	3.83 (3.60–4.07)	3.62 (3.37–3.93)	5.80 (5.33–6.32)	9.01 (8.00–9.97)	11.6 (9.97–14.4)	2,576
	2009–2010	3.90 (3.64–4.18)	3.53 (3.30–3.80)	6.03 (5.36–6.62)	10.2 (9.15–11.8)	14.9 (12.3–19.2)	2,870
	2011–2012	3.92 (3.69–4.16)	3.65 (3.47–3.91)	5.92 (5.40–6.49)	9.86 (8.68–11.3)	13.1 (11.5–15.2)	2,516
Age group							
6–11 years	2003–2004	4.34 (3.57–5.28)	4.03 (3.20–4.80)	6.32 (4.65–8.33)	10.3 (7.00–13.9)	13.9 (7.86–21.8)	292
	2005–2006	4.89 (4.22–5.65)	4.31 (3.64–5.69)	6.85 (5.71–7.69)	10.0 (7.54–14.7)	14.7 (10.0–18.8)	354
	2007–2008	5.07 (4.56–5.64)	4.54 (4.08–4.82)	6.90 (6.14–7.76)	12.0 (8.39–17.1)	20.9 (12.0–40.8)	390
	2009–2010	4.77 (4.34–5.23)	4.48 (4.12–4.85)	6.41 (5.66–6.82)	10.0 (7.63–15.3)	16.5 (9.33–27.0)	379
	2011–2012	4.86 (4.54–5.21)	4.44 (4.10–4.70)	6.82 (6.15–7.69)	9.77 (8.65–11.5)	13.8 (10.3–15.0)	401

Table 6-15. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
12–19 years	2003–2004	2.74 (2.39–3.14)	2.55 (2.27–2.94)	3.77 (3.17–4.44)	5.88 (4.65–6.67)	7.18 (6.16–11.7)	728
	2005–2006	3.05 (2.78–3.34)	2.92 (2.55–3.29)	4.25 (3.87–4.84)	6.68 (5.49–8.06)	9.08 (7.11–10.6)	703
	2007–2008	2.80 (2.54–3.09)	2.69 (2.37–2.93)	3.91 (3.46–4.56)	6.27 (4.72–8.21)	8.21 (5.77–10.1)	366
	2009–2010	2.89 (2.61–3.20)	2.60 (2.36–2.86)	4.08 (3.43–4.80)	6.67 (5.71–8.57)	10.0 (7.61–12.6)	456
	2011–2012	3.13 (2.68–3.64)	3.02 (2.48–3.34)	4.51 (3.49–5.62)	7.03 (5.08–10.8)	10.8 (6.13–18.1)	392
≥20 years	2003–2004	3.79 (3.34–4.31)	3.48 (3.00–4.00)	5.95 (4.86–7.05)	9.45 (8.00–12.0)	13.5 (11.1–18.6)	1,548
	2005–2006	3.93 (3.62–4.27)	3.71 (3.42–4.02)	5.82 (5.22–6.47)	9.74 (8.00–11.2)	12.6 (10.9–15.8)	1,531
	2007–2008	3.89 (3.64–4.16)	3.69 (3.44–4.02)	5.96 (5.47–6.58)	9.10 (8.00–10.0)	11.6 (9.74–14.5)	1,820
	2009–2010	4.00 (3.70–4.32)	3.61 (3.33–3.90)	6.25 (5.57–6.88)	10.8 (9.23–12.9)	16.1 (12.6–22.2)	2,035
	2011–2012	3.96 (3.75–4.19)	3.73 (3.52–3.94)	6.05 (5.45–6.68)	10.1 (8.97–11.3)	13.1 (11.5–15.5)	1,723

Table 6-15. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	3.48 (2.95–4.10)	3.16 (2.70–3.82)	5.46 (4.17–6.90)	8.59 (6.92–12.0)	12.3 (8.84–18.9)	1,284
	2005–2006	3.43 (3.13–3.75)	3.24 (2.91–3.63)	5.11 (4.25–6.08)	7.90 (6.65–9.77)	11.0 (9.29–13.0)	1,276
	2007–2008	3.63 (3.41–3.85)	3.44 (3.22–3.68)	5.33 (5.00–5.82)	8.31 (7.21–10.1)	12.1 (9.73–14.9)	1,289
	2009–2010	3.54 (3.29–3.80)	3.20 (3.04–3.38)	5.31 (4.80–5.99)	9.24 (7.80–10.8)	13.3 (10.3–16.5)	1,402
	2011–2012	3.55 (3.27–3.86)	3.34 (3.11–3.69)	5.32 (4.75–6.06)	8.47 (7.35–9.73)	11.0 (9.45–14.1)	1,263
Females	2003–2004	3.89 (3.49–4.34)	3.57 (3.13–4.06)	5.78 (4.95–6.67)	9.32 (8.00–11.5)	13.7 (10.6–18.6)	1,284
	2005–2006	4.37 (4.03–4.75)	4.03 (3.72–4.51)	6.26 (5.71–6.84)	10.0 (8.50–12.6)	14.4 (11.2–19.3)	1,312
	2007–2008	4.02 (3.75–4.32)	3.80 (3.46–4.26)	6.15 (5.58–7.06)	9.23 (8.11–10.1)	10.9 (9.52–14.9)	1,287
	2009–2010	4.28 (3.96–4.63)	4.00 (3.62–4.32)	6.55 (5.98–7.14)	11.0 (9.64–13.2)	17.2 (13.2–24.4)	1,468
	2011–2012	4.30 (4.06–4.56)	4.10 (3.85–4.35)	6.68 (5.93–7.36)	10.8 (9.77–12.4)	14.9 (12.4–17.0)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	4.38 (3.80–5.05)	4.11 (3.29–4.90)	6.25 (4.84–8.15)	10.3 (8.00–11.8)	12.9 (11.1–15.2)	621
	2005–2006	4.16 (3.83–4.52)	4.00 (3.65–4.36)	5.94 (5.40–6.49)	8.69 (7.23–9.65)	10.2 (9.52–13.2)	651
	2007–2008	4.34 (3.87–4.88)	4.19 (3.66–4.83)	6.23 (5.31–7.44)	9.14 (8.00–11.0)	12.1 (10.1–15.1)	513
	2009–2010	4.06 (3.63–4.54)	3.95 (3.33–4.44)	6.32 (5.36–7.10)	9.23 (8.10–10.6)	11.7 (10.2–14.8)	618
	2011–2012	4.12 (3.83–4.44)	4.10 (3.43–4.59)	5.77 (5.29–6.37)	8.06 (7.49–9.54)	10.5 (8.70–14.8)	317
Non-Hispanic blacks	2003–2004	3.08 (2.69–3.52)	2.86 (2.60–3.24)	4.34 (3.82–5.05)	7.81 (5.82–9.45)	10.4 (7.61–16.9)	725
	2005–2006	3.08 (2.70–3.52)	2.91 (2.52–3.32)	4.21 (3.75–4.91)	7.33 (5.40–10.7)	11.6 (7.66–17.9)	695
	2007–2008	3.08 (2.87–3.31)	2.77 (2.56–3.13)	4.74 (4.31–5.22)	7.29 (6.58–8.26)	9.67 (8.26–11.0)	586
	2009–2010	3.26 (2.90–3.66)	2.86 (2.47–3.34)	5.10 (4.43–6.06)	10.0 (7.39–11.7)	13.1 (11.1–15.2)	545
	2011–2012	3.16 (2.66–3.74)	3.05 (2.41–3.67)	4.98 (4.01–6.08)	8.27 (6.68–9.70)	11.3 (8.87–13.7)	672

Table 6-15. Geometric Mean and Selected Percentiles of Urinary Dimethylarsinic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	3.44 (2.97–3.98)	3.17 (2.80–3.73)	5.16 (4.03–6.49)	8.00 (6.32–10.9)	11.1 (8.00–15.4)	1,078
	2005–2006	3.82 (3.47–4.21)	3.64 (3.30–3.93)	5.71 (4.90–6.51)	9.23 (7.26–10.6)	11.6 (9.93–13.9)	1,050
	2007–2008	3.62 (3.38–3.87)	3.48 (3.20–3.76)	5.38 (4.95–5.80)	8.00 (7.28–8.86)	10.0 (8.96–11.1)	1,063
	2009–2010	3.58 (3.36–3.81)	3.31 (3.09–3.49)	5.30 (4.87–5.75)	8.12 (7.06–9.21)	11.5 (9.43–14.3)	1,226
	2011–2012	3.68 (3.44–3.93)	3.47 (3.31–3.63)	5.32 (5.04–5.93)	9.07 (7.47–10.3)	11.5 (9.87–13.1)	824

CI = confidence interval

Source: CDC 2014

Table 6-16. Geometric Mean and Selected Percentiles of Urinary Monomethyl-arsonic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	1.20 (1.00–1.30)	1.90 (1.60–2.10)	2.40 (2.00–2.80)	2,567
	2005–2006	*	<LOD	1.19 (1.05–1.34)	1.72 (1.51–1.94)	2.12 (1.79–2.70)	2,588
	2007–2008	*	<LOD	1.11 (1.00–1.20)	1.61 (1.51–1.69)	2.09 (1.91–2.26)	2,576
	2009–2010	*	<LOD	1.02 (.920–1.10)	1.64 (1.41–1.83)	2.01 (1.82–2.28)	2,871
	2011–2012	*	<LOD	<LOD	1.36 (1.17–1.55)	1.83 (1.57–2.07)	2,517
Age group							
6–11 years	2003–2004	*	<LOD	1.00 (<LOD–1.40)	1.80 (1.30–2.60)	2.30 (1.70–2.90)	292
	2005–2006	*	<LOD	1.03 (<LOD–1.37)	1.54 (1.37–2.12)	2.12 (1.51–2.73)	354
	2007–2008	*	<LOD	1.05 (<LOD–1.28)	1.60 (1.32–1.83)	2.04 (1.64–2.86)	390
	2009–2010	*	<LOD	<LOD	1.38 (1.00–1.84)	1.81 (1.26–2.13)	380
	2011–2012	*	<LOD	<LOD	1.21 (0.970–1.40)	1.42 (1.24–1.54)	401

Table 6-16. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
12–19 years	2003–2004	*	<LOD	1.50 (1.10–1.80)	2.20 (1.70–3.00)	2.90 (2.20–3.60)	728
	2005–2006	*	<LOD	1.31 (1.09–1.46)	1.99 (1.62–2.23)	2.41 (2.04–2.89)	703
	2007–2008	*	<LOD	1.26 (1.11–1.35)	1.83 (1.54–2.22)	2.31 (1.87–2.90)	366
	2009–2010	*	<LOD	1.10 (0.910–1.25)	1.62 (1.33–1.92)	2.03 (1.74–2.30)	456
≥20 years	2003–2004	*	<LOD	1.20 (1.00–1.30)	1.80 (1.50–2.10)	2.30 (2.00–2.60)	1,547
	2005–2006	*	<LOD	1.20 (1.05–1.33)	1.70 (1.48–1.90)	2.06 (1.74–2.75)	1,531
	2007–2008	*	<LOD	1.08 (0.970–1.17)	1.58 (1.44–1.71)	1.98 (1.82–2.21)	1,820
	2009–2010	*	<LOD	1.02 (0.930–1.11)	1.65 (1.42–1.86)	2.03 (1.81–2.35)	2,035
	2011–2012	*	<LOD	<LOD	1.41 (1.15–1.67)	1.88 (1.58–2.08)	1,724

Table 6-16. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	*	<LOD	1.30 (1.10–1.60)	2.00 (1.80–2.40)	2.60 (2.10–3.00)	1,283
	2005–2006	*	<LOD	1.31 (1.12–1.49)	1.79 (1.57–2.09)	2.23 (1.85–2.86)	1,276
	2007–2008	*	<LOD	1.24 (1.13–1.35)	1.78 (1.63–1.94)	2.33 (1.97–2.71)	1,289
	2009–2010	*	<LOD	1.07 (0.970–1.23)	1.77 (1.47–2.01)	2.19 (1.83–2.68)	1,403
	2011–2012	*	<LOD	0.900 (<LOD–1.09)	1.28 (1.09–1.57)	1.59 (1.26–3.30)	392
Females	2003–2004	*	<LOD	1.00 (<LOD–1.20)	1.60 (1.30–1.90)	2.10 (1.70–2.60)	1,284
	2005–2006	*	<LOD	1.08 (0.920–1.24)	1.57 (1.36–1.90)	2.04 (1.67–2.50)	1,312
	2007–2008	*	<LOD	0.970 (<LOD–1.06)	1.42 (1.30–1.57)	1.81 (1.68–1.90)	1,287
	2009–2010	*	<LOD	0.950 (<LOD–1.06)	1.52 (1.27–1.74)	1.89 (1.66–2.12)	1,468
	2011–2012	*	<LOD	<LOD	1.15 (1.02–1.40)	1.57 (1.41–1.79)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	1.50 (1.20–1.90)	2.20 (1.70–2.80)	2.80 (2.00–4.40)	621
	2005–2006	*	<LOD	1.19 (1.10–1.32)	1.73 (1.51–1.97)	2.04 (1.67–2.51)	651
	2007–2008	*	<LOD	1.22 (1.02–1.35)	1.69 (1.43–2.12)	2.32 (1.75–2.85)	513
	2009–2010	*	<LOD	1.02 (<LOD–1.37)	1.65 (1.38–1.90)	2.02 (1.65–2.33)	618
	2011–2012	*	<LOD	>LOD	1.25 (1.04–1.65)	1.85 (1.25–3.26)	317
Non–Hispanic blacks	2003–2004	*	<LOD	1.10 (<LOD–1.30)	1.80 (1.40–2.00)	2.20 (1.70–2.70)	725
	2005–2006	*	<LOD	1.02 (.950–1.07)	1.35 (1.29–1.44)	1.70 (1.50–1.88)	695
	2007–2008	*	<LOD	1.21 (1.09–1.33)	1.79 (1.61–2.05)	2.32 (2.15–2.63)	586
	2009–2010	*	<LOD	1.02 (<LOD–1.18)	1.51 (1.36–1.84)	1.88 (1.73–2.24)	546
	2011–2012	*	<LOD	<LOD	1.26 (1.01–1.55)	1.65 (1.34–2.02)	672

Table 6-16. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non–Hispanic whites	2003–2004	*	<LOD	1.10 (.900–1.30)	1.80 (1.40–2.00)	2.10 (1.80–2.50)	1,077
	2005–2006	*	<LOD	1.22 (1.02–1.39)	1.75 (1.42–2.12)	2.14 (1.72–2.93)	1,050
	2007–2008	*	<LOD	1.04 (.930–1.15)	1.50 (1.37–1.63)	1.91 (1.69–2.09)	1,063
	2009–2010	*	<LOD	0.940 (<LOD–1.04)	1.45 (1.24–1.76)	1.90 (1.65–2.12)	1,226
	2011–2012	*	<LOD	<LOD	1.24 (1.03–1.49)	1.71 (1.34–2.04)	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2014

Table 6-17. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	1.33 (1.18–1.54)	2.22 (1.82–2.57)	2.86 (2.40–3.53)	2,567
	2005–2006	*	<LOD	1.28 (1.14–1.52)	2.37 (1.94–2.78)	3.13 (2.67–3.76)	2,588
	2007–2008	*	<LOD	1.31 (1.23–1.42)	2.24 (2.00–2.56)	3.19 (2.78–3.58)	2,576
	2009–2010	*	<LOD	1.36 (1.25–1.45)	2.16 (2.00–2.29)	2.91 (2.67–3.15)	2,870
	2011–2012	*	<LOD	<LOD	2.21 (2.03–2.42)	2.86 (2.63–3.32)	2,516
Age group							
6–11 years	2003–2004	*	<LOD	1.63 (<LOD–1.81)	2.31 (1.88–2.50)	2.52 (2.31–3.07)	292
	2005–2006	*	<LOD	1.44 (<LOD–1.83)	2.37 (1.65–3.20)	3.13 (2.29–4.92)	354
	2007–2008	*	<LOD	1.69 (<LOD–2.06)	2.46 (2.09–2.91)	3.20 (2.56–4.32)	390

Table 6-17. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
	2009–2010	*	<LOD	<LOD	2.37 (2.07–2.78)	3.16 (2.55–3.76)	379
	2011–2012	*	<LOD	<LOD	2.55 (2.17–3.15)	3.32 (2.52–4.50)	401
12–19 years	2003–2004	*	<LOD	1.10 (0.853–1.23)	1.53 (1.30–1.85)	2.07 (1.71–2.22)	728
	2005–2006	*	<LOD	1.05 (0.930–1.14)	1.56 (1.49–1.73)	1.97 (1.78–2.13)	703
	2007–2008	*	<LOD	0.970 (.880–1.07)	1.45 (1.19–1.73)	1.97 (1.49–2.34)	366
	2009–2010	*	<LOD	1.21 (1.02–1.45)	1.98 (1.60–2.56)	2.56 (1.94–4.57)	456
	2011–2012	*	<LOD	1.07 (<LOD–1.24)	1.75 (1.30–2.42)	2.52 (1.62–7.00)	392
≥20 years	2003–2004	*	<LOD	1.36 (1.18–1.58)	2.28 (1.82–2.79)	3.00 (2.43–3.53)	1,547
	2005–2006	*	<LOD	1.31 (1.13–1.58)	2.46 (2.00–2.91)	3.20 (2.78–3.81)	1,531
	2007–2008	*	<LOD	1.32 (1.23–1.45)	2.35 (2.02–2.67)	3.38 (2.78–3.83)	1,820
	2009–2010	*	<LOD	1.36 (1.25–1.45)	2.18 (2.00–2.29)	2.91 (2.78–3.20)	2,035
	2011–2012	*	<LOD	<LOD	2.25 (2.00–2.42)	2.74 (2.52–3.32)	1,723

Table 6-17. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2003–2004	*	<LOD	1.20 (1.05–1.36)	1.88 (1.53–2.34)	2.50 (2.07–3.45)	1,283
	2005–2006	*	<LOD	1.11 (.950–1.28)	1.78 (1.47–2.29)	2.46 (1.88–3.32)	1,276
	2007–2008	*	<LOD	1.18 (1.07–1.26)	2.06 (1.85–2.34)	2.71 (2.46–3.37)	1,289
	2009–2010	*	<LOD	1.16 (1.07–1.25)	1.79 (1.64–1.99)	2.29 (2.08–2.78)	1,402
	2011–2012	*	<LOD	1.13 (<LOD–1.24)	1.72 (1.58–1.85)	2.31 (1.92–2.67)	1,263
Females	2003–2004	*	<LOD	1.50 (<LOD–1.77)	2.40 (1.96–2.86)	3.00 (2.61–3.53)	1,284
	2005–2006	*	<LOD	1.58 (1.36–1.76)	2.78 (2.29–3.20)	3.56 (3.05–4.35)	1,312
	2007–2008	*	<LOD	1.45 (<LOD–1.60)	2.41 (1.94–2.91)	3.56 (2.78–4.27)	1,287
	2009–2010	*	<LOD	1.56 (<LOD–1.73)	2.46 (2.29–2.62)	3.37 (2.91–3.56)	1,468
	2011–2012	*	<LOD	<LOD	2.52 (2.27–2.74)	3.32 (2.74–3.94)	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	1.46 (1.11–1.93)	2.30 (1.84–3.00)	3.16 (2.40–3.85)	621
	2005–2006	*	<LOD	1.19 (1.08–1.35)	1.92 (1.60–2.13)	2.53 (2.06–2.91)	651
	2007–2008	*	<LOD	1.28 (1.10–1.60)	2.27 (1.64–2.71)	3.05 (2.35–3.76)	513
	2009–2010	*	<LOD	1.31 (<LOD–1.49)	2.00 (1.73–2.56)	3.05 (2.29–3.56)	618
	2011–2012	*	<LOD	<LOD	1.95 (1.54–2.25)	2.63 (1.85–3.32)	317
Non-Hispanic blacks	2003–2004	*	<LOD	0.816 (<LOD–0.985)	1.37 (1.14–1.61)	1.88 (1.46–2.17)	725
	2005–2006	*	<LOD	0.790 (0.720–0.880)	1.11 (0.980–1.34)	1.57 (1.23–1.98)	695
	2007–2008	*	<LOD	0.920 (0.840–1.06)	1.45 (1.33–1.73)	2.09 (1.73–2.56)	586
	2009–2010	*	<LOD	0.970 (<LOD–1.08)	1.73 (1.39–1.94)	2.29 (1.83–2.91)	545
	2011–2012	*	<LOD	<LOD	1.38 (1.21–1.62)	1.97 (1.75–2.33)	672

Table 6-17. Geometric Mean and Selected Percentiles of Urinary Monomethylarsonic Acid (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	1.33 (1.15–1.62)	2.28 (1.73–2.86)	2.86 (2.35–3.75)	1,077
	2005–2006	*	<LOD	1.35 (1.16–1.64)	2.50 (2.00–3.05)	3.20 (2.78–3.81)	1,050
	2007–2008	*	<LOD	1.35 (1.23–1.52)	2.37 (2.04–2.78)	3.37 (2.78–4.00)	1,063
	2009–2010	*	<LOD	1.36 (<LOD–1.52)	2.21 (1.99–2.37)	2.91 (2.67–3.20)	1,226
	2011–2012	*	<LOD	>LOD	2.33 (2.03–2.52)	2.86 (2.52–3.50)	824

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2014

Table 6-18. Geometric Mean and Selected Percentiles of Urinary Trimethylarsine Oxide (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,871
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,517
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	380
	2011–2012	*	<LOD	<LOD	<LOD	0.300 (<LOD–0.960	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	728
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392

Table 6-18. Geometric Mean and Selected Percentiles of Urinary Trimethylarsine Oxide (in µg As/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,724
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,403
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,264
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	<LOD	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	<LOD	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	546
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	825

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2014

Table 6-19. Geometric Mean and Selected Percentiles of Urinary Trimethylarsine Oxide (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	*	<LOD	<LOD	<LOD	<LOD	2,568
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	2,588
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	2,576
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,870
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	2,516
Age group							
6–11 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	292
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	354
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	390
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	379
	2011–2012	*	<LOD	<LOD	<LOD	1.06 (<LOD-1.39	401
12–19 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	728
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	703
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	366
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	456
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	392
≥20 years	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,548
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,531
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,820
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	2,035
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,723
Gender							
Males	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,276
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,289
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,403
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,263
Females	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,284
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,312
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,287
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,468
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	1,253
Race/ethnicity							
Mexican Americans	2003–2004	*	<LOD	<LOD	<LOD	<LOD	621
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	651
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	513
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	618
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	317
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	<LOD	<LOD	725
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	695
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	586
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	545
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	672

Table 6-19. Geometric Mean and Selected Percentiles of Urinary Trimethylarsine Oxide (Creatinine Corrected) (in µg As/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	<LOD	<LOD	1,078
	2005–2006	*	<LOD	<LOD	<LOD	<LOD	1,050
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,063
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,226
	2011–2012	*	<LOD	<LOD	<LOD	<LOD	824

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2014

MMA and DMA are excreted methylated metabolites commonly assessed to aid in evaluation of exposure (WHO 2011a). Concentrations of MMA throughout all NHANES survey years reported in the updated Fourth National report were below the detection limits of the methods (0.9 µg/L) (CDC 2014). The two highest geometric means (creatinine corrected) of DMA reported during 2009–2010 of 4.77 and 4.28 µg/g resulted from 379 samples from 6–11 year olds and 1,468 samples from female participants, respectively. Throughout all survey years, females had a higher geometric mean of DMA (creatinine corrected) than males. The age group 6–11 years had the highest mean of DMA (creatinine corrected) each period compared to 12–19- and 20-year-old groups. Mean values ranged from 4.34 to 5.07 µg/g for the 6–11-year-old age group (CDC 2014).

The NHANES data from 2003 to 2006 were analyzed to evaluate the correlation between rice consumption and concentrations of total urinary arsenic and urinary DMA in 3,027 and 2,653 U.S. adult participants, respectively, 20–85 years of age (Wei et al. 2014). The study took into consideration factors such as demographic variables, fish consumption, and drinking water. The study found a distinct relationship of increased total urinary arsenic and urinary DMA concentrations (both creatinine corrected) of participants who consumed rice more than twice per week compared to a reference group. Participants who consumed rice and grain less than twice per week had mean levels of 2.21 (total arsenic) µg/g creatinine and 1.32 (DMA) µg/g creatinine. Participants who consumed rice and grain at least twice per week had mean total arsenic levels of 2.42 µg/g creatinine and 1.58 (DMA) µg/g creatinine.

A Washington State Environmental Biomonitoring Survey was conducted with 172 participants and tap water samples from 82 households in South Whidbey from July to September 2011. Results indicated that the average urine levels (28.4 µg/g creatinine corrected) for total arsenic of the participants were higher than statewide and national levels. Urine arsenic levels were above the CDC's reporting level (50 µg/L) among 28% of the participants and 54% of the water samples were above the EPA's drinking water standard (MCL=10 µg/L) (WA DOH 2015).

In an ongoing study by the Maternal and Infant Environmental Exposure Project measures chemical exposures in pregnant women at the San Francisco General Hospital, a geometric mean of 7.71 µg/L arsenic was reported for 89 urine samples from pregnant women collected from 2010 to 2011 (LOD=0.158 µg/L) (OEHHA 2015).

In 2009, 229 pregnant women were evaluated for urinary arsenic excretion and recent rice consumption in an area of the United States with known elevated levels of arsenic in well waters (Gilbert-Diamond et al.

2011). A multiple regression model accounting for age, urinary creatinine, rice consumption, and water exposure was employed. Of the 229 pregnant women, 73 consumed rice and 156 did not consume rice. A range of total urinary arsenic levels from 2.86 to 8.72 µg/L (median=5.27 µg/L) was detected for the rice-consuming women, while 1.64–5.39 µg/L (median=3.38 µg/L) was detected for women who did not eat rice. The women who ate rice had a range of inorganic arsenic between 0.13 and 0.51 µg/L (median=0.28 µg/L), while the non-rice eaters had a range of inorganic arsenic between 0.13 and 0.36 µg/L (median=0.21 µg/L).

Occupational exposure to arsenic in the semiconductor manufacturing industry was reviewed (Park et al. 2010). A statistical analysis of air and wipe samples was used to classify fabrication workers with respect to observed arsenic levels in their surroundings. The study review concluded that people involved with maintenance work have higher potential for exposure than people in charge of routine production work. Maintenance processes result in arsenic-containing compounds being deposited on surrounding surfaces. These particles may become airborne or may accumulate on surfaces increasing the potential for exposure. Afridi et al. (2011) collected whole blood, urine, and hair samples from 42 steel mill production workers and 33 steel mill quality control workers aged 25–55 years who were affected by paralysis, and 62 non-paralyzed steel mill workers. A control group of 75 non-paralyzed male subjects was also included. Mean arsenic concentrations in hair samples from the control group, non-paralyzed steel mill workers, paralyzed quality control workers, and paralyzed production workers were 1.06±0.09, 1.67±0.17, 2.89±0.3, and 3.99±0.5 µg/g, respectively. Mean arsenic concentrations in whole blood samples from the control group, non-paralyzed steel mill workers, paralyzed quality control workers, and paralyzed production workers were 1.7±0.4, 2.56±0.3, 4.07±0.38, and 5.48±0.39 µg/L, respectively. Mean arsenic concentrations in urine samples from the control group, non-paralyzed steel mill workers, paralyzed quality control workers, and paralyzed production workers were 4.4±1.5, 5.3±0.84, 8.7±01.7, and 11.5±1.3 µg/L, respectively.

6.6 EXPOSURES OF CHILDREN

The NHANES data from 2003 to 2008 were analyzed to evaluate the correlation between rice consumption and dietary arsenic exposure in 2,323 participants under 18 years of age (Davis et al. 2012). The study took into consideration factors such as fish consumption and metabolic rates according to age. Results indicated that total urinary arsenic and urinary DMA concentrations were higher among the participants who had reported consumption of ≥0.25 cups of rice within 24 hours of the sampling time. The total urinary arsenic concentration of children who had consumed rice was 8.9 µg/L, while the

concentration was 5.5 µg/L among children who had not (Davis et al. 2012). The evaluation suggests that rice consumption has the potential to increase exposure to arsenic for U.S. children.

Munera-Picazo et al. (2014b) investigated Spanish gluten-free food products intended for young children and found levels of arsenic as high as 256 µg/kg. Rice-based pasta samples had the highest concentration of inorganic arsenic. Control samples for each food group had levels reported as not detected or below the limit of quantification for the method (6 µg/kg). Foods with a higher percentage of rice content typically contained higher levels of total arsenic and inorganic arsenic. A daily intake of inorganic arsenic for children ≤5 years old was found to range between 0.61 and 0.78 µg/kg body weight.

Wasserman et al. (2014) investigated arsenic exposure and intelligence in 272 children residing in Maine with an average age of 9.67 years. In 248 of the children, a notable correlation of nail arsenic concentrations and arsenic concentrations in household tap water was found. However, it was added that nail concentrations may be less accurate for children due to rapid growth of other systems. Measured household kitchen tap water had an average value of 9.88 µg/L, almost a third of samples exceeded the EPA MCL (10 µg/L). The studied concluded that children residing in homes with arsenic water concentration ≥5 µg/L demonstrated reduced Full Scale IQ scores compared to households with concentrations <5 µg/L.

A maximum amount of 4 µg arsenic was detected in hand washing samples for 66 children from eight playgrounds. Children's hands were rinsed immediately after playing on playground equipment constructed with CCA-treated wood in Edmonton, Alberta (Hamula et al. 2006).

Exposure to arsenic via contaminated soils has been investigated. Pearce et al. (2010) analyzed the concentration of arsenic in children's toenail clippings and household soils from areas with a history of gold mining activity in Victoria, Australia. The arsenic concentrations in children's toenails ranged from 0.15 to 2.1 µg/g; the geometric mean was 0.49 µg/g. The arsenic concentrations in soil ranged from 3.3 to 130 µg/g; the geometric mean was 11.5 µg/g. The distribution of arsenic in the nail clippings suggested periodic exposure patterns and a positive correlation between the nail concentrations, and soil concentrations indicated that contaminated soils can contribute to arsenic uptake by children.

Tsuji et al. (2005) analyzed total arsenic and arsenic species in urine from 77 children <7 years old, in urine from 362 subjects >7 years old, and in toenails from 67 subjects >7 years old living in Middleport, New York. The overall range of total arsenic detected in urine was 2.1–773 µg/L. The arsenic

concentrations in toenail samples were <1 mg/kg. Household soil and dust arsenic levels were also measured; the arsenic concentration levels averaged 18.8 and 10.6 mg/kg, respectively.

Children may be exposed to arsenic via consumption of apple juices. Exposure of children to arsenic from apple juice consumption was investigated (FDA 2013a). Based on data from NHANES, children aged 0–6 years consume an estimated 4.1 g/kg/day of apple juice. Monitoring data from the Toxic Elements Program (TEP) and an apple juice survey (AJS) were evaluated. Total arsenic concentrations are reported noting that levels of organic arsenic species were below the level of quantification, suggesting that inorganic arsenic accounts for the arsenic present in the samples. For TEP survey years 2008–2011, there were 153 samples ranging in concentrations ranging from not detected up to 45 ppb (0.045 µg/g) with an average concentration of 4.7 ppb (0.0047 µg/g). The average total arsenic concentrations reported for 2008, 2009, 2010, and 2011 were 8.8, 7.8, 6.6, and 2.7 ppb, respectively (0.0088, 0.0078, 0.0066, and 0.0027 µg/g). For AJS survey year 2011, there were 94 samples ranging in concentrations from not detected up to 36 ppb (0.036 µg/g), with an average concentration of 4.4 ppb (0.0044 µg/g).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

An ongoing study by the Firefighter Occupational Exposures Project measures chemical exposures in firefighters in Southern California. A geometric mean of 10.8 µg/L arsenic was reported for 101 urine samples collected from 2010 to 2011; the detection frequency was 100% (LOD=0.158 µg/L) (OEHHA 2015).

Medicinal use of arsenite results in direct exposure of arsenic for patients who are administered this type of therapy. A study by Nicolis et al. (2009) analyzed the hair of two patients receiving arsenic trioxide treatments. High arsenic levels in the patient's hair directly corresponded to treatment and decreased accordingly when treatment ceased.

Children and adults with celiac disease who consume a gluten-free diet tend to eat more rice-based foods; additionally, people who reside with children or adults with celiac disease may consume a similar diet. Food manufactured for people with celiac disease often contains rice and elevated levels of inorganic arsenic (Munera-Picazo et al. 2014a, 2014b).

Urine samples from 322 residents of an area in France with naturally high arsenic levels in soil were analyzed for arsenic (Fillol et al. 2010). The residents included adults and children >7 years of age.

Urinary arsenic concentrations ranged from below the limit of quantification to 28.2 µg/g creatinine and a geometric mean arsenic concentration of 4.4 µg/g creatinine. Two urine samples contained arsenate, half of the samples contained arsenite, MMA was in 19% of the samples, and DMA was the only arsenic species detected in all samples containing arsenic.

6.8 ADEQUACY OF THE DATA BASE

6.8.1 Identification of Data Needs

Children are exposed to arsenic by the same exposure routes as adults (e.g., ingestion of food and water) as well as possible exposure *in utero*. Data from the NHANES survey discussed in Section 6.5 indicated that higher urinary levels of DMA, a metabolite of arsenic exposure, were typically observed in children 6–11 years old as compared to adults. Continued monitoring of levels in children is needed.

Continued species-specific monitoring of rice, soil, and water sources would add value to exposure assessments.

6.8.2 Ongoing Studies

Biomonitoring programs in United States include the Minnesota Biomonitoring Program (http://www.health.state.mn.us/biomonitoring), Rocky Mountain Biomonitoring Consortium (https://www.colorado.gov/pacific/cdphe/rocky-mountain-biomonitoring-consortium), California Environmental Contaminant Biomonitoring Program (http://www.biomonitoring.ca.gov/), and Washington Environmental Biomonitoring Survey (http://www.doh.wa.gov/DataandStatisticalReports/EnvironmentalHealth/Biomonitoring).

7. ANALYTICAL METHODS

7.1 BIOLOGICAL SAMPLES

Inorganic arsenic and organic arsenic exhibit distinctly different toxic health effects. Speciation of arsenic in tissues and body fluids improves the evaluation of arsenic exposure. Seven arsenic compounds are able to be determined in urine using one method (Verdon et al. 2009). HPLC-ICP-MS with dynamic reaction cell (DRC) has been used to separate and quantify arsenobetaine, arsenocholine, TMAO, As(V), As(III), monomethylarsonate, and dimethylarsinate. Interconversion of arsenic species is minimized by freezing samples until analysis, followed by treatment with a slightly acidified buffer solution. Samples

are prepared with 0.1 M ammonium acetate (pH 5) and centrifuged at 4°C. The clarified supernatant is placed in a capped auto-sampler vial for analysis. Post column addition of arsenic internal standard improves the distinction of monoisotopic elements. The DCR mode minimizes interferences from the carrier gas. Detection limits for the selected species are As(V)=1.0, As(III)=1.2, DMA=1.7, MMA=0.9, arsenobetaine=0.4, arsenocholine=0.6, and TMAO=1.0, reported in μg As/L.

Development of the hydride-generation cryotrapping-AAS (HG-CT-AAS) technique for the analysis of major arsenic human metabolites, including dimethylmonothioarsinic acid, in biological samples was made to improve performance and lower detection limits (see Table 7-1; Hernandez-Zavala et al. 2008). Sample preparation involves generation of arsines from As(III) using a buffered mixture of tris-HCl and sodium borohydride, along with generation of arsines from both As(III) and As(V) by reduction using L-cysteine. The detection limits range from 9 to 20 pg arsenic for trivalent species and from 8 to 20 pg arsenic for pentavalent species.

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human, rat, mouse tissues	Reduction to arsines; cryotrapping	Atomic absorption spectrometry	8–20 pg arsenic [16–40 pg/mL (0.5-mL sample)]	73–117	Hernandez-Zavala et al. 2008

Analysis of hair is used in arsenic biomonitoring studies. Synchrotron radiation-based X-ray fluorescence (XRF) spectroscopy is used to quantify arsenic exposure in relation to time (Nicolis et al. 2009). In addition, micro-XRF cartography and micro- fluorescence-X-ray absorption near-edge spectroscopy (XANES) spectra was used to show the location and species of arsenic in hair samples. Exogenous absorption from external arsenic exposure would complicate hair biomonitoring results.

7.2 ENVIRONMENTAL SAMPLES

Dietary exposure to inorganic arsenic is of greater concern compared with exposure to organic arsenic compounds. Analytical methods for the speciation of arsenic in foods evaluate specific arsenic compounds rather than total arsenic (see Table 7-2).

Table 7-2. Analytical Methods for Determining Arsenic

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Reduction to arsine in acid solution; reaction with SDDC	EPA Method 206.4; SDDC colorimetric spectrophotometry at 535 nm	10 µg/L	100	EPA 1983
Water, biota, sediment, and soil digestates	SPE	HPLC-ICP-MS USGS method I-2020-05	0.06 µg/L	NR	USGS 2006
Wheat and rice	Seal between polyimide films	Fluorescence-XANES	NR	NR	Kopittke et al. 2014
Rice	Extraction with 2% v/v nitric acid	HPLC-ICP-MS	0.003 µg/g	94(±8)–11(±19)%	Maher et al. 2013
Rice	SPE	HG-AAS	0.02 mg/kg (0.02 µg/g)	101–106	Rasmussen et al. 2013

HG-AAS = hydride-generation atomic absorption; spectrometry; HPLC-ICP-MS = high-performance liquid chromatography = inductively coupled plasma-mass spectrometry; NR = not reported; SDDC = silver diethyldithiocarbamate; SPE = solid phase extractions; USGS = U.S. Geological Survey; XANES = X-ray absorption near-edge spectroscopy

The USGS National Water Quality laboratories have updated analytical methods for the determination of elements in environmental media, including arsenic (USGS 2006). A new ICP-MS method using collision/reaction cell technology was developed to improve accuracy in the analysis of aqueous matrices. The method is valid for both speciated and unspeciated arsenic evaluation.

Nitric acid extraction is a common technique employed for the successful separation of inorganic arsenic in rice samples (Baba et al. 2014; Maher et al. 2013; Rasmussen et al. 2013). Baba et al. (2014) and Maher et al. (2013) have validated the measurement and speciation of arsenic in rice using HPLC-ICP-MS. Baba et al. (2014) optimized a rapid speciation analysis of arsenic in rice using HPLC-ICP-MS. Arsenous acid, arsenic acid, methylarsonic acid, and dimethylarsinic acid were determined with the use of silica-based pentafluorophenyl (PFP) HPLC columns with an isocratic mobile phase of formic acid and methanol in 5 minutes. Arsenic species are extracted from finely ground rice samples using 0.15 M nitric acid. The LOD is reported as 0.002 mg arsenic/kg (0.002 µg/g).

Chen and Chen (2014) reported a LOD of 1.3 ng/g using solid phase extraction (SPE). Arsenic is extracted from rice samples via microwave assisted digestion with nitric acid-hydrogen peroxide. As(III) is oxidized to As(V) during digestion. Silica-based anion exchange cartridges separate As(V) form

organic arsenic compounds and quantification is achieved with hydride-generation atomic fluorescence spectrometry (HG-AFS).

XANES has been employed for arsenic speciation in rice. Kopittke et al. (2014) developed a method to illustrate the accumulation and transformation of arsenic within root tissues. Roots are sealed between two 8-µm thick polyimide films and analyzed continuously using X-ray fluorescence microscopy.

Visible and near-infrared diffuse reflectance spectroscopy (VNIRS) has been used for rapid monitoring of arsenic contamination in soils. Using the reflectance spectra of rice plants, arsenic concentrations in soils can be calculated using regression analysis methods (Shi et al. 2014). The method and techniques require optimization and validation.

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification Arsenic and inorganic arsenic compounds	 Group 1[a]	IARC 2014
WHO	Air quality guidelines Arsenic	 1.5x10^{-3} unit risk[b]	WHO 2000
	Drinking water quality guidelines Arsenic	 0.01 mg/L[c]	WHO 2011b
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA Arsenic and inorganic compounds	 0.01 mg/m^3	ACGIH 2014
AIHA	ERPGs	No data	AIHA 2014
NIOSH	REL (15-minute ceiling limit) Arsenic (inorganic compounds, as As)[d]	 0.002 mg/m^3	NIOSH 2010

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
DOE	PACs[e]		DOE 2012
	Arsenic		
	PAC-1	0.03 mg/m^3	
	PAC-2	0.58 mg/m^3	
	PAC-3	100 mg/m^3	
	Arsenic acid		
	PAC-1	0.057 mg/m^3	
	PAC-2	0.54 mg/m^3	
	PAC-3	190 mg/m^3	
	Arsenic pentoxide		
	PAC-1	0.73 mg/m^3	
	PAC-2	8 mg/m^3	
	PAC-3	150 mg/m^3	
	Arsenic trioxide		
	PAC-1	0.27 mg/m^3	
	PAC-2	3.0 mg/m^3	
	PAC-3	9.1 mg/m^3	
	Calcium arsenate		
	PAC-1	0.91 mg/m^3	
	PAC-2	10 mg/m^3	
	PAC-3	270 mg/m^3	
	Sodium arsenite		
	PAC-1	0.91 mg/m^3	
	PAC-2	10 mg/m^3	
	PAC-3	170 mg/m^3	
	Dimethylarsinic acid		
	PAC-1	0.5 mg/m^3	
	PAC-2	0.5 mg/m^3	
	PAC-3	130 mg/m^3	
	Sodium dimethylarsinate		
	PAC-1	1.1mg/m^3	
	PAC-2	4 mg/m^3	
	PAC-3	510 mg/m^3	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
EPA	AEGLs		EPA 2014d
	Arsenic pentoxide	Holding status[f]	
	Arsenic trioxide		
	AEGL 1	Not recommended[g]	
	AEGL 2		
	10- and 30-minute	3.7 mg/m^3	
	60-minute	3.0 mg/m^3	
	4-hour	1.9 mg/m^3	
	8-hour	1.2 mg/m^3	
	AEGL 3		
	10- and 30-minute	11 mg/m^3	
	60-minute	9.1 mg/m^3	
	4-hour	5.7 mg/m^3	
	8-hour	3.7 mg/m^3	
	Hazardous Air Pollutants	Yes	EPA 2014b
	Arsenic and inorganic compounds, including arsine		
OSHA	PEL (8-hour TWA) for general industry		OSHA 2013a
	Arsenic, organic compounds (as As)	0.5 mg/m^3	29 CFR 1910.1000, Table Z-1
	Inorganic arsenic	10 µg/m^3	OSHA 2013b29 CFR 1910.1018
	PEL (8-hour TWA) for construction		OSHA 2013c
	Arsenic, organic compounds (as As)	0.5 mg/m^3	29 CFR 1926.55 Appendix A
	Inorganic arsenic	10 µg/m^3	OSHA 2013d 29 CFR 1926.1118
	PEL (8-hour TWA) for shipyards		OSHA 2013e
	Arsenic, organic compounds (as As)	0.5 mg/m^3	29 CFR 1915.1000 Table Z
	Inorganic arsenic	10 µg/m^3	OSHA 2013f 29 CFR 1915.1018
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2013f 40 CFR 116.4
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, and sodium arsenite		
	Drinking water standards and health advisories for arsenic		EPA 2012
	DWEL	0.01 mg/L	
	RfD	0.0003 mg/kg/day	
	National primary drinking water regulations for arsenic		EPA 2009
	MCL	0.01 mg/L	
	MCLG	Zero	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
EPA	National recommended water quality criteria for inorganic arsenic		EPA 2014c
	Water + organism	0.018 µg/L[h]	
	Organism only	0.14 µg/L[h]	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2013b
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, sodium arsenite	1 pound	
c. Food			
FDA	Allowable levels for contaminants in bottled water for arsenic; proposed action level for inorganic arsenic in apple juice	0.010 mg/L	FDA 2013b 21 CFR 165.110
USDA	Nonsynthetic substances prohibited for use in organic crop production	Arsenic	USDA 2013 7 CFR 205.602
d. Other			
ACGIH	Carcinogenicity classification		
	Arsenic and inorganic compounds	A1[i]	ACGIH 2014
	BEI for inorganic arsenic plus methylated metabolites in urine at the end of the work week	35 µg As/L	
EPA	Carcinogenicity classification		IRIS 2003
	Inorganic arsenic	Group A[j]	
	Oral slope factor	1.5 per mg/kg/day	
	Inhalation unit risk	4.3×10^{-3} µg/m^3	
	RfD	3×10^{-4} mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity		EPA 2013c 40 CFR 302.4
	Arsenic, arsenic acid, arsenic pentoxide, arsenic trioxide, dimethyl arsenic acid, calcium arsenate, sodium arsenate, and sodium arsenite		
	Final RQ pounds	1	
	Effective date of toxic chemical release reporting		EPA 2013d 40 CFR 372.65
	Arsenic	1/1/87	

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
	Extremely hazardous substances and its threshold planning quantity (pounds)		EPA 2013e 40 CFR 355, Appendix A
	Arsenic pentoxide, arsenous oxide, sodium cacodylate	100/10,000	
	Calcium arsenate, sodium arsenite	500/10,000	
	Sodium arsenate	1,000/10,000	
NATIONAL (*cont.*)			
DHHS	Carcinogenicity classification		NTP 2014
	Arsenic and inorganic arsenic compounds	Known to be human carcinogens	

[a]Group 1: Carcinogenic to humans.
[b]Cancer risk estimates for lifetime exposure to a concentration of 1 μg/m^3.
[c]Provisional guideline value: as there is evidence of a hazard, but the available information on health effects is limited.
[d]NIOSH potential occupational carcinogen.
[e]Based on applicable 60-minute AEGLs, ERPGs, or TEELs.
[f]Holding status AEGLs have been reviewed by the NAC/AEGL Committee and are under further review.
[g]Due to insufficient data.
[h]This criterion is based on carcinogenicity of 10^{-6} risk.
[i]A1: Confirmed human carcinogen.
[j]Group A: Human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure indices; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = Drinking water equivalent level; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NAAQS = National Ambient Air Quality Standards; NAC = National Advisory Committee; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; RQ = reportable quantity; TEEl = temporary emergency exposure limit; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; WHO = World Health Organization

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