# Arsenic Exposure, Assessment, Toxicity, Diagnosis, and Management

## *Guidance for Occupational and Environmental Physicians*

*Beth A. Baker, MD, MPH, Victoria A. Cassano, MD, MPH, and Carolyn Murray, MD, MPH, ACOEM Task Force on Arsenic Exposure*

Arsenic is ubiquitous in the environment and human exposure can occur from multiple possible routes including diet. Occupational medicine physicians asked to evaluate workers with elevated urine arsenic levels may be unaware that many sources of arsenic exposure are not work related. In this paper, we address arsenic exposure sources and pathways, adverse health effects of arsenic exposure and those subpopulations at increased risk, and the evaluation and treatment of those exposed to elevated arsenic levels.

Arsenic is ubiquitous in the environment, and human exposure can occur from myriad natural and anthropogenic sources. Inorganic arsenic is a metalloid compound with known cancerous and noncancerous health effects. Arsenic in food is an increasingly recognized exposure pathway. We discuss dietary sources of arsenic and approaches to mitigating exposure. Physicians need to understand that many sources of arsenic may be nonwork-related and recognize populations at particular risk of elevated exposures. Physicians need to identify potential routes of exposure and select appropriate biomarkers for exposure evaluations.

In this paper, the multiple possible routes of arsenic exposure are discussed, highlight changing trends in sources of arsenic, as well as applicable United States (US) arsenic regulations from the Occupational Safety and Health Administration (OSHA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA). We also review how to evaluate, counsel, and manage patients with potential arsenic exposure and assess for possible health effects. This includes how to differentiate between organic and inorganic arsenic sources and order and interpret urine speciation, when necessary.

From the ACOEM, Elk Grove Village, Illinois.

This position paper was developed by the ACOEM Task Force on Arsenic Exposure under the auspices of the Council of Scientific Advisors. It was reviewed by the Committee on Policy, Procedures, and Public Positions, and approved by the ACOEM Board of Directors on July 28, 2018. ACOEM requires all substantive contributors to its documents to disclose any potential competing interests, which are carefully considered. ACOEM emphasizes that the judgments expressed herein represent the best available evidence at the time of publication and shall be considered the position of ACOEM and not the individual opinions of contributing authors.

The authors declare no conflicts of interest.

Address correspondence to: Marianne Dreger, MA, ACOEM, 25 Northwest Point Blvd, Suite 700, Elk Grove Village, IL 60007 (mdreger@acoem.org).



DOI: 10.1097/JOM.0000000000001485

## EXPOSURE SOURCES AND PATHWAYS

Arsenic occurs naturally in geological formations and is abundant in the earth's crust.[1,2] Arsenic, primarily in its inorganic form (iAs), can be found in soil, air, and water. Human exposure can occur through many different pathways, through occupations, the environment, and in food. Some of the major potential arsenic exposure sources are listed in Tables 1 and 2. The widespread contamination of tube wells in Bangladesh is an example of an exposure pathway from naturally present iAs of geologic origin. Arsenic contamination of drinking water from geologic and manmade sources has been found globally as well as in regions of the US. The US EPA maximum contaminant level (MCL) for arsenic in drinking water is 10 μg/L or 10 ppb for public water supplies. Human activity, including mining, smelting, pesticide use, and coal ash disposal, has been linked to water and soil contamination. Use of arsenic contaminated water for agricultural irrigation extends the exposure pathway to soil and food crops. Other sources of soil contamination with arsenic include release of arsenates in pressure-treated lumber (eg, chromated copper arsenate) and localized industrial activities. The use of arsenical drugs in animal agriculture and the subsequent use of animal wastes and processed human biosolids as fertilizers are another potential soil and food crop contamination pathway.[3] Inhalation of arsenic has been a widely described occupational exposure pathway. Dermal exposure is considered a minor pathway in comparison to inhalation and ingestion and one that would not pose a significant health risk in most settings.[4]

Arsenic in the food supply is an increasingly recognized exposure pathway. Rice can absorb inorganic arsenic (iAs) from soil and water up to 10 times more efficiently than other food crops.[5] Rice flour is a common ingredient in processed foods, and brown rice syrup is used as a sweetener in many snack foods. As a natural occurring element, arsenic is incorporated into many other terrestrial and marine foods at low levels. Market-based studies have found varying concentrations of iAs in a wide range of food products.[6] Studies using National Health and Nutrition Education Survey (NHANES) data have calculated that arsenic exposure from food may exceed the quantity ingested from drinking water that meets the current EPA MCL.[7] Individuals who are not at risk of arsenic exposure from their drinking water or their occupation may still have significant exposure to iAs from food sources.[8]

## FEDERAL REGULATIONS

OSHA regulations regarding iAs are found in 29 Code of Federal Regulations (CFR) 1910.1018.[9] The permissible exposure level (PEL) for iAs is 10 $\mu g/m^3$ of air, averaged over an 8-hour period without regard to the use of a respirator. The action level is 5 $\mu g/m^3$ of air. A medical surveillance program must be established for all employees exposed at or above the action level, for at least 30 days per year without regard to the use of respirators. Areas where exposure is anticipated to be above the PEL must be designated and demarcated as a regulated area. All personnel entering a regulated area are required by OSHA to be supplied with the proper respiratory protection,[9] and employers must have a respiratory protection program in accordance with 29 CFR 1910.134.[10] In regulated areas, food, beverages, chewing tobacco, and gum are not permitted.

**TABLE 1.** Potential Sources of Environmental or Nonoccupational Exposure to Arsenic[2,8,18,24,57–59]

| |
|---|
| Environmental Contamination from Natural Sources |
| Rock and soil: |
| Dissolution of arsenic into groundwater |
| Dust |
| Volcanic activity |
| Environmental Contamination from Human Activity |
| Coal powered power plants |
| Incinerators |
| Mining, smelting, fossil fuel (coal) combustion |
| Pesticide residue in soil and groundwater |
| CCA-treated lumber |
| Application of soil amendments (fertilizer; poultry litter) and human biosolids |
| Irrigation water (contamination from natural and/or human activity) |
| Groundwater (contamination from natural and/or human activity) |
| Food contaminated with arsenic |
| Rice products – rice milk, rice cereal, rice flour, brown rice sweetener |
| Apple juice, grape juice |
| Wine, beer |
| Seafood |
| Bivalves—clams, mussels, oysters, scallops |
| Crustaceans—crab, lobster |
| Algae |
| Seaweed, kelp |
| Fish—cold water and bottom feeding fish-cod, herring, mackerel |
| Medications |
| Melarsoprol—treatment for parasitic infections |
| Arsenic trioxide—treatment for promyelocyctic leukemia and other cancers |
| Folk or Ayurvedic medicine—primarily Chinese, Indian origin |
| Seaweed supplements-kelp |
| Homeopathic remedies |
| Thiacetarsamide (heartworm treatment for dogs) |
| Intentional poisoning |

**TABLE 2.** Potential Sources of Occupational Exposure to Arsenic[2,8,18]

| |
|---|
| Agriculture and Gardening |
| Pesticides |
| Currently used in US |
| Monosodium methyl arsenate (MSMA) |
| Use banned by EPA in US, but maybe used in other countries |
| Inorganic arsenics, lead arsenate |
| Organic arsenics |
| Disodium methyl arsenate (DSMA) |
| Cacodylic acid |
| Lumber preservatives |
| Ammoniacal copper zinc arsenate (ACZA) |
| Chromated copper arsensate (CCA)—nonresidential applications only in US |
| Manufacturing |
| Ammunition |
| Glass and ceramics—arsenic trioxide, inorganic arsenic |
| Lead acid batteries—elemental or inorganic arsenic |
| Metal alloys (eg, lead, brass, bronze) —elemental or inorganic arsenic |
| Optical industries—light emitting or laser diodes, fiber optic crystals |
| Coal burning power plants—byproduct, exposure depends on level of arsenic in coal |
| Electronics/aerospace/telecom industries |
| Gallium Arsenide microchips and circuit board, arsine gas, tributylarsine |
| Fireworks (manufactured outside of US) |
| Hide preserving and leatherwork-leather preservative |
| Metallurgy |
| Mining—elemental or inorganic arsenic, arsine gas |
| Pigments and paint—primarily historical use in US |
| Smelting of copper, lead, zinc, sulfide mineral |
| Byproduct or contaminant—inorganic arsenic, arsenic trioxide |

## EPA REGULATIONS REGARDING ARSENIC

The US EPA regulates arsenic and compounds containing arsenic under numerous different statutes including the Clean Water Act; Clean Air Act; Safe Drinking Water Act; Resource Conservation and Recovery Act (RCRA); Comprehensive Environmental Response, Compensation and Liability Act (CERCLA); Superfund Amendments and Reauthorization ACT (SARA); and Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The new EPA Worker Protection Standard for Agricultural Workers also contains regulations regarding arsenic containing herbicides and pesticides.

## ADVERSE HEALTH EFFECTS AND SUBPOPULATIONS WITH AN INCREASED RISK OF HEALTH EFFECT

Arsenic is relatively unique compared with other hazardous chemicals in that the majority of evidence of adverse health effects is derived from studies of human populations rather than animal studies. Widespread exposure from contaminated drinking water has generated a significant body of epidemiological literature linking chronic ingestion of iAs to both cancer and noncancer health effects. Arsenic is well established as a cause of cancer of the lung, bladder, and skin.[11] There is less evidence of an association with other cancers, such as prostate, kidney, and liver. Noncancer health effects of arsenic exposure have been described for numerous organ systems, including the respiratory, cardiovascular, hematological, gastrointestinal, immune, dermal, reproductive, and endocrine systems as well as the central and peripheral nervous system.[2,12–16]

Occupational physicians should recognize unique subpopulations that may be at an increased risk for elevated arsenic exposure and increased susceptibility to adverse health effects. Underlying genetic or metabolic factors, life stages where vulnerability may be increased, and dietary exposures influenced by individual preferences, cultural practices, age, and dietary restrictions (eg, gluten free) all may result in increased arsenic exposure. For example, children may have three times the exposure to arsenic of adults, partly due to their higher consumption per kilogram body weight and because of the presence of rice and rice products in foods marketed for children.[8] Individuals on gluten-free diets also ingest more rice flour and rice-based products. NHANES participants who were on gluten-free diets had elevated urine arsenic levels compared with nongluten-free

 

diet controls.[17] Genetic polymorphism for several of the enzymes involved in arsenic metabolism may be in part responsible for the individual variation in sensitivity to arsenic health effects.[18]

## EXPOSURE EVALUATION

### Environmental Exposures

Well-water contamination with iAs from natural geologic sources and/or industrial processes is present throughout the US populations in these regions who use private wells may be exposed to iAs at levels exceeding the recommended EPA MCL.[19,20] Drinking and cooking with iAs contaminated water and the use of contaminated water to irrigate crops that can mobilize arsenic, such as rice, presents multiple pathways for human exposure. Table 1 lists potential environmental or nonoccupational exposures to arsenic.

Dietary exposure to organic arsenic is of less concern than iAs exposure. Fish, seafood, seaweed, and aquatic sediment may contain organic arsenic, commonly in the form of arsenobetaine and to a lesser extent, as arsenocholine and arsenosugars.[21] Some seafood such as fin fish or crustaceans contain high levels of arsenobetaine, an organic arsenic that is relatively nontoxic and excreted intact in urine.[13,22] Seaweed and marine algae contain arsenosugars. These may also be present in bivalves such clams, mussels, oysters, and scallops and other marine food, which feed on the algae and seaweed.[23] These arsenosugars may be metabolized to dimethylarsinic acid ($DMA^V$) and thio-dimethylarsinic acid (thio-$DMA^V$), which have been associated with cellular toxicity and genotoxicity, although their impact on human health is unclear.[23]

Ingestion of food contaminated with iAs poses a greater health concern. Children tend to eat or drink a smaller variety of foods so ingestion of contaminated apple juice, infant formula, or rice cereal may represent a significant source of exposure during a period of heightened vulnerability to adverse effects. FDA has promulgated action levels for iAs in apple juice and infant rice cereal due to this concern. As previously noted, individuals who consume a gluten-free diet tend to eat more rice-based foods and thus have a higher potential for increased iAs exposure.[17] Arsenic toxicity may also occur after use of some traditional remedies or ayurvedic medication from several Asian countries.

### Occupational Exposures

Occupational exposure is typically due to inhalation exposure and may occur through the semiconductor manufacturing industry or mining or smelting of ores such as lead or copper and other nonferrous metals. Monosodium methanearsonate (MSMA) may still be used as a pesticide in the US. Arsenic exposure can occur from coal-fired power plants or incinerators from coal or other products that contact arsenic from the ash or environmental release.[24] Arsenic is also used in metal alloys, battery grids, bearing, ammunition, and some types of glass manufacturing.[25] Arsenic is also used in the manufacture of semiconductor chips (particularly gallium arsenide chips) and circuit boards used in the electronics, aerospace, and telecommunications industry.[25] Table 2 lists potential occupational exposures to arsenic.

### Signs and Symptoms of Toxicity

Signs or symptoms of arsenic toxicity depend on the type of arsenic, route of exposure, and whether the exposure is acute, subacute, or chronic. Inorganic arsenic (iAs) and trivalent arsenite ($As^{+3}$) are generally more acutely toxic than pentavalent arsenate ($As^{+5}$), which is usually more acutely toxic then organic arsenic. Cellular membranes are more permeable to trivalent arsenic ($As^{+3}$) then pentavalent arsenic ($As^{+5}$).[18] In vivo interconversion of $As^{+5}$ and $As^{+3}$ occur, and chronic exposure to both forms has resulted in a similar pattern of toxicity. Arsine gas is highly toxic, causing hemolysis. Exposure may occur in the semiconductor and electronics industry.

### Signs and Symptoms of Chronic Exposure

Chronic arsenic poisoning is most likely due to environmental or occupational exposure and has a more insidious onset. The most specific overt sign of chronic inorganic arsenic ingestion is skin or dermal effects.[2,13,22] Gastrointestinal effects may occur but are less common than with acute toxicity. Hyperpigmentation is the most common dermal effect, but hypopigmentation or alternating hyperpigmentation and hypopigmentation (raindrops on a dusty road) may occur. Hyperkeratosis with bilateral thickening of the palms and soles may also occur.[2] Focal hyperkeratotic lesions or corns may occur on the feet, palms, face, or other parts of the body. Skin lesions may progress to nonmelanoma skin cancers such as squamous cell carcinoma, basal cell carcinoma, and Bowen disease.[13,14]

An Indian study found the most common symptoms in a group of 4865 subjects with elevated arsenic in their drinking water were diffuse hyperpigmentation, rain drop pigmentation, hypopigmentation, and palmar and plantar keratosis and less commonly asthmatic bronchitis and hepatomegaly.[26] A review of the Health Effects of Arsenic Longitudinal Study (HEALS) data on 20,000 subjects in Bangladesh with elevated well water arsenic exposure found evidence for increased pre-malignant skin lesions, high blood pressure, neurological dysfunction, and all-cause mortality.[27] Other effects of chronic arsenic exposure include peripheral neuropathy, gastrointestinal symptoms, diabetes, renal system effects, enlarged liver, non-cirrhotic portal hypertension, peripheral neuropathy, anemia, hypertension, and cardiovascular disease (CVD).[2,13] Exposure to low to moderate levels of arsenic in drinking water ($<100\,\mu g/L$) have been associated with elevated cardiovascular risks in several studies.[15,16] For example, a 2017 meta-analysis of 12 studies showed a pooled statistically significant increased risk of several CVD outcomes such as coronary vascular disease incidence and mortality and coronary heart disease and mortality (relative risks of 1.07 to 1.16) with chronic exposure to $20\,\mu g/L$ water arsenic compared with $10\,\mu g/L$ water arsenic.[16]

Blackfoot disease is an obliterative peripheral vascular disease seen in populations exposed to inorganic arsenic in drinking water from wells in southwestern Taiwan.[13,28] Vasospastic or Raynaud disease have been reported in smelter workers, German vineyard workers, and in populations with elevated exposure to arsenic in drinking water.[13] Chronic arsenic exposure may result in pulmonary fibrosis, hepatic fibrosis, and bone marrow suppression (leukopenia and anemia).[13,24]

The International Agency for Research on Cancer (IARC) and the US EPA have classified arsenic in drinking water as a human carcinogen leading to cancers of the skin, bladder, and lung based largely on epidemiological studies of large highly exposed populations in Taiwan, Argentina, Chile, Bangladesh, and West Bengal (India).[11,29] Arsenic is also classified as a human carcinogen by the National Academy of Sciences and the National Toxicology Program (NTP). Arsenic ingestion has been associated with squamous cell skin carcinoma, basal cell skin carcinoma, lung cancer, and bladder cancer. Arsenic-related cancer usually takes more than 10 years to develop.[2] Lung cancer has also been associated with inhalation exposure to smelter workers and pesticide workers with chronic arsenic exposure.[13] More limited evidence has associated arsenic exposure in drinking water with other cancers, including cancer of the kidney, angiosarcoma of the liver, and other liver cancers.[30,31] Both monomethylarsonic acid (MMA) and DMA are also classified as possible human carcinogens (IARC Group 2B).[2]

A 2015 systematic review and meta-analysis of adverse pregnancy outcomes following exposure to high levels of arsenic in water (arsenic levels 50 μg/L or greater) showed an increased risk of spontaneous abortion and stillbirth and a moderate increased risk of neonatal and infant mortality.[2,32] Children exposed early in life to inorganic arsenic (in utero or postnatally) had an increased risk of bronchiectasis and lung cancer.[2,33,34] Adults with exposure to elevated levels of arsenic in utero had elevated bladder and lung cancer rates as adults despite their arsenic exposure ending as much as 40 years earlier.[35] In general, exposure to iAs in drinking water has been associated with fetal deaths, congenital heart abnormalities, delay in growth and neurological development, and increased susceptibility to respiratory infection.[18] A New Hampshire study showed a 10% increase in risk of gestational diabetes mellitus with each 5 μg/L increase in well water arsenic concentration.[36]

## Laboratory Analysis

Diagnosis of arsenic toxicity should be based on the integration of exposure history, clinical findings, and if possible laboratory confirmation of exposure. Traditionally, a 24-hour urinary arsenic was considered the most definitive diagnostic laboratory test.[13,37–39] However, a spot urine arsenic is much easier to collect and is now more commonly used to assess individual patients and in large populations studies. Two studies have shown that spot urine arsenic levels did correlate well with 24-hour urine arsenic levels and that random spot urine arsenic levels were stable throughout the day.[40,41] Another study showed that spot random urine arsenic levels correlated well with first morning void urine arsenic levels.[42] Blood arsenic does not appear to be a reliable biomarker of arsenic exposure because arsenic is rapidly cleared from the blood,[22,38] and may have a low correlation with recent exposure.

Total urine arsenic is the most commonly used biomarker of arsenic exposure.[22,43] After it is absorbed, inorganic arsenic is methylated in the body to MMA and DMA.[22,43,44] The sum of inorganic arsenic (such as $As^{+3}$, $As^{+5}$, MMA, and DMA) and organic arsenic (such as arsenobetaine) in the urine are often combined by the laboratory and reported as the total arsenic level. A study of total urine arsenic and speciated arsenic from 2557 NHANES participants found MMA, DMA, and arsenobetaine were the major contributors to the total urine arsenic level.[21] At these background exposure levels, the upper 95th percentile for total urinary arsenic was 65.4 μg/L or 50.2 μg/g creatinine.[21]

Normal total urine arsenic levels may vary from laboratory to laboratory but may be defined by the laboratory as a urine arsenic greater than 50 μg/L, 100 μg/g creatinine, or 100 μg total arsenic.[22,24,38] With acutely symptomatic arsenic toxicity, total urine arsenic is typically greater than 1000 μg/L.[25] The American Conference of Governmental Industrial Hygienist's (ACGIH) Biological Exposure Index for arsenic is 35 μg/L urine arsenic (inorganic arsenic and methylated metabolites) at the end of the workweek.[45,46] Laboratory reports of minimally elevated urine arsenic levels cannot be interpreted by just comparing results to a ''normal range'' to determine whether arsenic toxicity is present, particularly chronic toxicity. It is important to look for signs of actual arsenic toxicity and compare urine levels to a known or calculated toxicity threshold from the literature or a suitable reference work.[47]

Other considerations that arise when testing for urine arsenic include whether to adjust for urinary concentration (by adjusting for creatinine) and whether to request speciation of the urine arsenic.[22] Adjusting the urine arsenic by the creatinine concentration may theoretically account for dilution or concentration of the spot urine (μg/g creatinine). Many laboratories report the 24-hour urine arsenic level as both μg/L (not corrected for creatinine) and μg/g Cr (corrected for creatinine). Adjusting arsenic concentration for creatinine concentration is less important in 24-hour urine specimens, as urine concentration is typically a 24-hour average and not as variable as may occur with a spot specimen. Adjusting the arsenic concentration for creatinine concentration is recommended by some authors for spot urine arsenic samples to correct for variable urine concentration at the time of a spot urine specimen collection and may be most helpful when comparing serial spot urine arsenic levels over time in a single individual patient.[21]

Many population studies of drinking water arsenic exposure use spot urine arsenic levels, which are not adjusted for creatinine.[21,43,48,49] However, a study of US NHANES data stressed the need to report levels as both unadjusted and adjusted for creatinine and to assess whether a creatinine adjusted value was ''abnormal'' by considering the body weight, gender, and age of the subjects.[50] This approach would be most important if the arsenic value adjusted for creatinine is significantly different from the unadjusted arsenic value or if there is only an adjusted arsenic value to review. Because urine creatinine concentration is significantly associated with age, sex, race/ethnicity, and body mass index, between individual variations in urine arsenic levels reported as μg/g creatinine may reflect changes to these demographic factors that affect the creatinine denominator and not actual differences in arsenic exposure.[37,50] Creatinine adjustment of urinary arsenic in children or malnourished individuals may yield a value that seems inordinately high compared with values in similarly exposed well-nourished adults because children and malnourished individuals excrete relatively less creatinine.[37]

Ingestion of shellfish, fish, or seaweed, which contains primarily nontoxic organic arsenicals, can cause elevated total urine arsenic and confound the estimation of iAs exposure.[22,25] Speciation of urine arsenic levels allows the quantification of inorganic arsenic and its methylated metabolites (MMA and DMA) in the urine and nontoxic forms of organic arsenic such as arsenobetaine or arsenocholine [22,44] However, it is important to keep in mind that some seafood and fish contain DMA and organosugars in seafood and algae are also metabolized to DMA, underscoring the importance of a thorough dietary history.[51] Alternatively, a spot urine arsenic could be collected again after 1 to 2 weeks abstinence from seafood or fish consumption.

Urine should be collected in metal-free polyethylene containers but not acid-rinsed containers, as the acid may alter the arsenic species.[38] If urine arsenic is normal and arsenic toxicity is still suspected, hair or nail testing may help identify arsenic exposure. Arsenic accumulates in hair and nail with iAs as the predominant form.[22] The potential for external contamination must also be considered, as it could result in a false-positive hair or nail assay. In population studies, hair and nail testing have been used to identify arsenic exposure. If individuals ingest and bathe in arsenic contaminated water, have contact with arsenic in soil, or encounter airborne arsenic or arsenic containing dust in the workplace, the arsenic levels in hair or nails probably reflect both internal consumption and external exposure.[22]

## Treatment Options

Significant acute arsenic toxicity, though rare, can be life-threatening and may require hospitalization, as maintaining appropriate fluid and electrolyte balance and EKG monitoring are crucial. It is important to identify the source of arsenic exposure and remove the patient from exposure as much as possible. In the US, private wells or very small community water systems are a more likely source of arsenic exposure than are large community water supplies regulated by EPA. If drinking water is considered a possible source of exposure, then the physician needs to determine the source of a patient's drinking water. Patients who are suspected to have

 

drinking water exposure to arsenic should have their well water tested. They should use bottled water until their well has been shown to not be a source of arsenic exposure or until an appropriate filtration system can be put in place to remove the arsenic.

Chelation therapy is typically reserved for patients with severe acute toxicity and is most effective when initiated within minutes to hours, as efficacy declines or disappears as the time interval between exposure and onset of chelation increases.[24,52] In the 1940s, dimercaprol, aka British antilewisite (BAL) was developed,[53] and it is still used occasionally for severe arsenic toxicity.[54] Dimercaprol and 2,3-Dimercaptosuccinic acid (DMSA) are the two most common chelators available in the US. DMPS (2,3 Dimercaptopropanesulfonate) may be the chelating agent of choice for arsenic according to several studies but has not been approved by the US FDA. An FDA advisory committee has recommended that intravenous DMPS be available for compounding in hospital settings for the treatment of severe acute poisoning by arsenic.[55]

DMPS and DMSA have a higher therapeutic index than BAL and offer therapeutic advantages, as they do not redistribute arsenic to the brain.[52] Chelation therapy is rarely indicated with less severe acute toxicity or with chronic toxicity. Removal from further arsenic exposures, if possible, is important. Arsenic has a relatively short half-life of about 4 hours in the urine. Although chelation following chronic exposure may accelerate metal excretion, potential therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished for chronic arsenic intoxication.[52]

Arsine gas poisoning treatment should focus on maintaining fluid balance with intravenous hydration. Osmotic diuresis with mannitol may be helpful to maintain urine output and decrease the risk of renal failure.[25] Other treatments that have been attempted if the plasma or serum hemoglobin are 1.5 g/dL or higher or there are signs of renal insufficiency include exchange transfusion or hemodialysis if renal failure develops.[25]

## ADVICE TO PATIENTS ON MINIMIZING ARSENIC EXPOSURE

Individuals working in industries utilizing or producing arsenicals should be aware of the OSHA regulations and use personal protective equipment as supplied by their employer. Patients using CCA-treated lumber in nonresidential applications should follow the warning to use personal protective equipment such as gloves, eye goggles, and respiratory protection.[24] Other recommendations to reduce the elevated risk of cancer in subjects with ongoing arsenic exposure is to advise them to stop smoking cigarettes and to limit sun exposure and use sunscreen.

There is currently no FDA standard for iAs in rice, aside from the current guidance document for infant rice cereal. The amount of iAs in rice varies widely with the highest levels seen in rice grown in the southern regions of the US, largely on former cotton fields where arsenical pesticide residues remain in the soil. As arsenic is deposited in the rice hull, brown rice tends to have higher iAs content than white rice of the same type. According to extensive testing done by The Consumers Union, white basmati rice from California, India, and Pakistan, and sushi rice from the US have on average half the level of iAs than all other rice types. Rinsing rice well before use and cooking rice such as pasta, in a larger amount of water, can reduce iAs content. Alternating rice with other grains such as millet and quinoa that do not take up arsenic from the soil is a good option for patients concerned with dietary arsenic exposure.[56]

## CONCLUSION

Occupational and environmental medicine (OEM) physicians need to be aware that multiple exposure pathways for arsenic exist beyond occupational exposure. They also must be able to differentiate between organic and inorganic arsenic and be able to assess arsenic exposure. They need to select appropriate biomarkers for exposure and appropriate treatment and provide counseling for those with arsenic exposure. With both the US EPA and FDA having active policy reviews underway pertaining to arsenic in drinking water and food, OEM physicians will need to stay up-to-date on the evolving science and regulatory agency recommendations.

## REFERENCES


1. Valberg P, Beck B, Bowers T, Keating J, Bergstrom P, Boardman P. Issues in setting health-based cleanup levels for arsenic in soil. *Regul Toxicol Pharmacol*. 1997;26:219–229.
2. World Health Organization. *Exposure to Arsenic: A Major Public Health Concern.* Geneva, Switzerland: WHO; 2010.
3. Nachman KE, Mihalic JN, Burke TA, Geyh AS. Comparison of arsenic content in pelletized poultry house waste and biosolids fertilizer. *Chemosphere*. 2008;71:500–506.
4. National Academy of Sciences. *Critical Aspects of the EPA's IRIS Assessment of Inorganic Arsenic: Interim Report.* Washington, DC: National Academies Press; 2013.
5. Williams PN, Villada A, Deacon C, et al. Greatly enhanced arsenic shoot assimilation in rice leads to elevated grain levels compared to wheat and barley. *Environ Sci Technol*. 2007;41:6854–6859.
6. Jackson BP, Taylor VF, Karagas MR, et al. Arsenic, organic foods, and brown rice syrup. *Enviorn Health Perspect*. 2012;120:623–626.
7. Xue J, Zartarian V, Wang SW, Liu SV, et al. Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003-2004 NHANES data. *Environ Health Perspect*. 2010;118:345–350.
8. European Food Safety Authority. EFSA Panel on Contaminants in the Food Chain: scientific opinion on arsenic in food. *EFSA J*. 2009;7:60–71.
9. US Occupational Safety and Health Administration. 29 CFR 1910.1018. OSHA Standard for Inorganic Arsenic. Available at: www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10023. Accessed August 8, 2018.
10. US Occupational Safety and Health Administration. 29 CFR 1910.134 OSHA Standard for Personal Protective Equipment. Available at: https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=12716. Accessed August 8, 2018.
11. International Agency for Research on Cancer. *A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts.* Lyon: World Health Organization Press; 2012.
12. Naujokas MF, Anderson B, Ahsan H, et al. The broad scope of health effects from chronic arsenic exposure: update on workwide public health problem. *Environ Health Perspect*. 2013;121:295–302.
13. US Agency for Toxic Substances and Disease Registry. *Arsenic Toxicity Case Study.* Public Health Services: US Department of Health and Human Services; 2009.
14. Melkonian S, Argos M, Chen Y, et al. Intake of several nutrients are associated with incidence of arsenic-related keratotic skin lesions in Bangladesh. *J Nutrition*. 2012;142:2128–2134.
15. James KA, Byers T, Hokanson JE, et al. Association with lifetime exposure to inorganic arsenic in drinking water and coronary heart disease in Colorado Residents. *Environ Health Perspect*. 2015;123:128–134.
16. Moon KA, Oberoi S, Barchowsky A, et al. A dose response meta-analysis of chronic arsenic exposure and incident cardiovascular disease. *Int J Epidemiol*. 2017;46:1924–1939.
17. Bulka CM, Davis MA, Karagas MR, et al. The unintended consequences of gluten-free diets. *Epidemiol*. 2017;28:e24–e25.
18. US Agency for Toxic Substances and Disease Registry. *Addendum to Toxicological Profile for Arsenic.* Washington, DC: US Department of Health and Human Services; 2016.
19. Ayotte JD, Gronberg JM, Apodaca LE. Trace Elements and Radon in Groundwater Across the United States, 1992-2003. Scientific Investigations Report 2011-5059. US Geological Survey: Reston, Va. 2011. Available at: https://pubs.usgs.gov/sir/2011/5059/pdf/sir2011-5059_report-covers_508.pdf. Accessed August 5, 2017.
20. National Research Council. *Arsenic in Drinking Water.* Washington, DC: National Academy Press; 1999.
21. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh K. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003–2004. *J Exposure Sci Environ Epidemiol*. 2009;19:59–68.


 

22. Hughes MF. Biomarkers of exposure: a case study with inorganic arsenic. *Environ Health Perspect*. 2006;114:1790–1796.
23. Leffers L, Ebert F, Taleshi MS, et al. In vitro toxicological characterization of two arsenosugars and their metabolites. *Moi Nutr Food Res*. 2013;57:1270–1282.
24. Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Arsenic.* Washington, DC: US Department of Health and Human Services; 2007.
25. Lewis R, Kosnett MJ. Metals. In: Ladou J, Harrison R, editors. *Occupational and Environmental Medicine*. 5th ed., New York: McGraw-Hill Education; 2014. p. 463–485.
26. Saha KC. Diagnosis of arsenicosis. *J Environ Sci Health A Tox Hazard Subst Environ Eng*. 2003;38:255–272.
27. Chen Y, Parvez F, Gamble M, et al. Arsenic exposure at low-to moderate levels and skin lesions, arsenic metabolism, neurological function and biomarkers for respiratory and cardiovascular disease: review of recent findings from the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh. *Toxicol Applied Pharmacol*. 2009;239:184–192.
28. Rossman TG. Arsenic. In: Rom WN, Markowitz SB, editors. *Environmental and Occupational Medicine*. 4th ed., Philadelphia, PA: Lippincott Williams & Wilkins; 2007. p. 1006–1020.
29. National Center for Environmental Assessment, Environmental Protection Agency. US EPA Reference Arsenic, inorganic; CASRN 7440-38-2 EPA Integrated Risk Information System (IRIS) Chemical Assessment Summary. 1990. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary.pdf. Accessed October 5, 2018.
30. Ferreccio C, Smith AH, Durán V, et al. Control study of arsenic in drinking water and kidney cancer in uniquely exposed Northern Chile. *Am J Epidemiol*. 2013;178:813–818.
31. Liaw J, Marshall G, Yuan Y, Ferreccio C, Steinmaus C, Smith AH. Increased childhood liver cancer mortality and arsenic in drinking water in Northern Chile. *Cancer Epidemiol Biomarkers Prev.* 2008;17:1982–1987.
32. Quansah R, Armah FA, Essumang DK, et al. Association of arsenic with adverse pregnancy outcomes/infant mortality: a systematic review and meta-analysis. *Environ Health Perspect*. 2015;123:412–420.
33. Smith AH, Marshall G, Yuan Y, et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *Environ Health Perspect*. 2006;114:1293–1296.
34. Smith AH, Steinmaus CM. Health effects of arsenic and chromium in drinking water: recent human findings. *Annu Rev Pub Health*. 2009;30:107–122.
35. Steinmaus CM, Ferreccio C, Romo JA, et al. Drinking water arsenic in northern Chile: high cancer risks 40 years after exposure cessation. *Cancer Epidemiol Biomarkers Prev*. 2013;22:623–630.
36. Farzan SF, Gossai A, Chen Y, et al. Maternal arsenic exposure and gestational diabetes and glucose intolerance in the New Hampshire birth cohort study. *Environ Health*. 2016;15:106.
37. Nermell B, Lindberg AL, Rahman M, et al. Urinary arsenic concentration adjustment factors and malnutrition. *Environ Res*. 2008;106:212–218.
38. Munday SW. Arsenic. Goldfrank's Toxicologic Emergencies, 10th ed. New York: McGraw Hill Education; 2015: 1168–1183.
39. Gochfeld M, Laumbach R. Chemical hazards. In: Levy BS, Wegman DH, Baron SL, et al., editors. *Occupational and Environmental Health: Recognizing and Preventing Injury.* 6th ed., London, England: Oxford University Press; 2011. p. 210–211.
40. Calderon RL, Hudgens E, Le XC, Schreinemachers D, Thomas DJ. Excretion of arsenic in urine as a function of exposure to arsenic in drinking water. *Environ Health Perspect*. 1999;107:663–667.
41. Hewitt DJ, Millner GC, Nye AC, Simmons HF. Investigation of Arsenic exposure from soil at the Superfund Site. *Environ Res*. 1995;68:73–81.
42. Rivera-Nunez Z, Meliker JR, Linder AM, Nriagu JO. Reliability of spot urine samples to assessing arsenic exposure. *Int J Hyg Environ Health*. 2010;218:259–264.
43. Normandin L, Ayotte P, Levallois P, et al. Biomarkers of arsenic exposure and effects in a Canadian rural population exposed through groundwater contamination. *J Exposure Sci Environ Epidemiol*. 2014;24:127–134.
44. Mandal BK, Ogra Y, Anzai K, Suzuki KT. Speciation of arsenic in biological samples. *Toxicol Appl Pharmacol*. 2004;198:307–318.
45. American Conference of Industrial Hygienists. *Arsenic and Its Inorganic Compounds: TLV(R) Chemical Substances 7th Edition Documentation.* Cincinnati, OH: ACGIH; 2001.
46. American Conference of Industrial Hygienists. *TLVs and BEIs: Based on Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.* Cincinnati, OH: Signature Publications; 2017.
47. Guidotti TL, McNamara J, Moses MS. The interpretation of trace elements analysis in body fluids. *Indian J Med Res*. 2008;128:524–532.
48. Rivera-Numez Z, Meliker JR, Meeker JD, et al. Urine arsenic species, toenail arsenic and arsenic intake estimates in a Michigan population with low levels of arsenic in drinking water. *J Exposure Sci Environ Epidemiol*. 2012;22:182–190.
49. Melak D, Ferreccio C, Kalman D, et al. Arsenic methylation and lung and bladder cancer in a case-control study in Northern Chile. *Toxicol Appl Pharmacol*. 2014;274:225–231.
50. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham L, Pirkle JL. Urinary creatinine concentrations in the US population: implications for urinary biologic monitoring measurements. *Env Health Perspectives*. 2005;113:192–200.
51. Heinrich-Ramm R, Mindt-Prufert S, Szadkowski D. Arsenic species excretion after controlled seafood consumption. *J Chromatography B*. 2002;778:263–273.
52. Kosnett MJ. The role of chelation in the treatment of arsenic and mercury poisoning. *J Med Toxicol*. 2013;9:347–354.
53. Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: a historical perspective. *Toxicol Sci*. 2011;123:305–332.
54. Vilensky JA, Redman K. British anti-Lewisite (dimercaprol): an amazing history. *Ann Emerg Med*. 2003;41:378–383.
55. US Food and Drug Administration. Pharmacy Compounding Advisory Committee Meeting. 2016.
56. How Much Arsenic in in Your Rice. Consumer Reports. November 2014. Available at: https://www.consumerreports.org/cro/magazine/2015/01/how-much-arsenic-is-in-your-rice/index.htm. Accessed August 18, 2018.
57. Nachman KE, Ginsberg GL, Miller MD, Murray CJ, Nigra AE, Pendergrast CB. Mitigating dietary arsenic exposure: current status in the United States and recommendations for an improved path forward. *Sci Total Environ*. 2017;581–2:221–236.
58. US Environmental Protection Agency. Monosodium Methanearsonate (MSMA), an Organic Arsenical. EPA Web site. Available at: https://www.epa.gov/ingredients-used-pesticide-products/monosodium-methanearsonate-msma-organic-arsenical. Accessed February 19, 2018.
59. US Environmental Protection Agency. Arsenic Compounds. EPA Web site. Available at: https://www.epa.gov/sites/production/files/2016-09/documents/arsenic- compounds.pdf. Accessed February 19, 2018.


 