Arsenic (As) is a metalloid with physicochemical properties of both metals and nonmetals. It occurs in -3, 0, +3 and +5 valence states; however, most toxicity in humans is associated with exposure to arsenic in the +3 or +5 valence states.\textsuperscript{1,2} The environmental cycling of arsenic involves a series of redox reactions as well as volatilization and precipitation of arsenic-containing species.\textsuperscript{3} Human activities, such as burning of fossil fuels, manufacturing processes, and smelting of ores, may disperse arsenic in the environment.\textsuperscript{4} Important commercial uses of arsenic include as a metal alloy, a wood preservative, and a pesticide. Arsenic is also used in semiconductors.\textsuperscript{4}
Organoaarsenicals have a long history of pharmaceutical use. Melarsoprol, an organoaarsenical, is the only drug available to treat advanced cases of trypanosomiasis, and inorganic arsenic (as the trioxide) is used to treat refractory cases of acute promyelocytic leukemia.

Food, drinking water, soil, and air are the major potential sources of exposure to arsenic. In the United States, airborne arsenic typically is a minor source of exposure. Occupational exposure through smelting, pesticide production, and semiconductor production, as well as the burning of coal with a high arsenic concentration, can increase respiratory exposure to arsenic. The low permeability of skin for inorganic arsenic limits dermal absorption of arsenic from soil. However, soil arsenic may be an important source of exposure in young children who exhibit significant hand-to-mouth activity.

The average level of arsenic in the earth’s crust is 2 mg/kg (ppm), but background concentrations range from 1 to 40 mg/kg, with an average of 5 mg/kg. Anthropomorphic activities such as mining, smelting, and agricultural pesticide use and manufacture can increase the levels of arsenic in soils markedly. In the United States, arsenic pesticides were often used on cotton and in fruit orchards. Other potential sources of arsenic exposure may not be obvious. For example, construction of playground equipment and decks with wood treated with chromated copper arsenate as preservative likely accounts for some exposure of children to inorganic arsenic.

In the majority of the United States, drinking water is not an important source of arsenic exposure. A large survey of water supply systems found that less than 1% had arsenic concentrations above 10 μg/L (equivalent to ppb). In some areas, primarily the southwestern and western parts, drinking water supplies can exceed 50 ppb of inorganic arsenic. Dietary arsenic is an important source of exposure to this metalloid, with the median US dietary intake about 12 μg per day for adults, assuming 1.5 kg of solid food daily. The 90th percentile for population intake is about 24 μg.

Dietary arsenic includes both inorganic and organic forms. Most arsenic in US diets is derived from seafood and consists primarily of two organoaarsenicals, arsenobetaine and arsenocholine. These organoaarsenicals are relatively nontoxic and contribute little, if any, to the overall risk associated with exposure to arsenic. The inorganic arsenic in marine fish is generally less than 4% of total arsenic exposure. Freshwater fish may be a source of greater exposure to inorganic arsenic, although this issue has not been thoroughly examined.

Among foods, the highest levels of inorganic arsenic have been found in processed poultry, rice, cereals, mushrooms, powdered beverages, flour, grape juice, and spinach. Preparing foods in arsenic-containing water increases the arsenic content by 10% to 30% for most foods but by a factor of 2 to 2.5 for foods such as beans or rice, which absorb cooking water. The average dietary intake of inorganic arsenic in the United States has been estimated at 8 to 15 μg per day.

Exposure to arsenic from environmental sources is thought to have
declined markedly during the past 30 years. Occupational exposures to arsenic are better regulated, and many smelting operations that released inorganic arsenic into the environment have been discontinued. Wood treated with chromated copper arsenate will become a less important source of inorganic arsenic exposure because it has been voluntarily phased out from deck and playground equipment use. However, important issues remain concerning the consequences of acute and chronic exposure to arsenic.

**ACUTE ARSENIC POISONING**

A discussion of the toxicity of arsenic should be prefaced with a brief description of its metabolism in humans. Like other metalloids (eg, selenium), inorganic arsenic is metabolically transformed into methylated species. Hence, a person exposed to inorganic arsenic excretes inorganic arsenic, methyl arsenic, and dimethyl arsenic in urine. Although it has been commonly assumed that the methylation of inorganic arsenic is a detoxification process, recent evidence suggests some of the intermediates formed in the methylation process may be more toxic than inorganic arsenic. Future research should identify the roles of the metabolites of inorganic arsenic in its action as an acute or chronic toxin and as a carcinogen in humans.

**Sources of Exposure**

Acute inorganic arsenic poisoning has been associated with ingestion of pesticides containing inorganic arsenic, use of folk remedies containing substantial amounts of inorganic arsenic, and ingestion of fireworks containing inorganic arsenic. Inorganic arsenic occasionally has been used as a poison with suicidal or homicidal intent. In the latter case, tasteless, colorless, and odorless inorganic arsenic is typically added surreptitiously to food. Because ant traps containing arsenic trioxide are an attractive menace to young children who ingest these sugar-laden devices, children account for a relatively high percentage cases of accidental inorganic-arsenic poisoning.

Two methylarsenicals are used as pesticides in the United States. Monosodium methylarsonate and disodium methylarsonate are postemergent weed killers, and cacodylic acid (dimethylarsinic acid) is used as a defoliant and dessicant. Cases of accidental and inadvertent occupational exposure to these pesticides have been reported, and these compounds have been used with suicidal intent.

**Signs and Symptoms**

Criteria for diagnosis of acute arsenic exposure include a documented history of exposure or a urinary arsenic concentration exceeding 175 μg per 24 hours or an arsenic concentration of arsenic in nails or pubic hair exceeding 150 μg/100 g. Arsenic in a 24-hour urine sample is considered the most reliable measure of arsenic exposure. Care should be taken to assure that an elevated concentration of arsenic in urine is not attributable to recent ingestion of seafood that contains high concentrations of relatively innocuous organoarsenicals (ie, arsenocholine, arsenobetaine).

Among the wide range of signs and symptoms that have been associated with acute arsenic poisoning are nausea, vomiting, diarrhea, hypotension, acute renal failure, cyanosis, tachycardia, ventricular fibrillation, malaise, delirium, seizure, and coma. A garlic odor on the breath, possibly due to expiration of volatile arsines, also has been associated with inorganic arsenic poisoning.
Treatment

Supportive therapy and treatment with chelating agents generally are recommended. The value of gastrointestinal decontamination is uncertain, but gastric lavage and treatment with activated charcoal have been used.\textsuperscript{23} Although 2,3-dimercaptopropanol — dimercaprol — has been the chelating agent of choice for many years, water-soluble dithiol-containing chelators have been shown to be effective in the treatment of acute poisoning with either inorganic arsenic\textsuperscript{30} or an organoarsenical pesticide.\textsuperscript{26} These agents, 2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-sulfonic acid (DMPS), can be given orally.

Combined therapy with dimercaprol and one of the dithiol-containing chelators has also been described. Stephanopoulos and colleagues\textsuperscript{23} treated a child with acute inorganic arsenic poisoning with intramuscular dimercaprol (5 mg/kg per dose every 6 hours for 3 days) followed by oral DMSA (10 mg/kg per dose every 8 hours for 5 days). The oral DMSA dosage was then reduced to 10 mg/kg every 12 hours until the concentration of arsenic in a spot urine was less than 50 µg/L. Given the low rates of adverse reactions to DMPS and DMSA, it is possible these drugs may replace dimercaprol as the drugs of choice for treatment of acute arsenic poisoning.\textsuperscript{31}

**Historically, chronic exposure to inorganic arsenic in occupational and environmental settings has been associated with increased prevalence of skin cancer and internal cancers. Hence, inorganic arsenic has been classified as a class 1 carcinogen in humans.**

**CHRONIC ARSENIC TOXICITY**

Historically, chronic exposure to inorganic arsenic in occupational and environmental settings has been associated with increased prevalence of skin cancer and internal cancers. Hence, inorganic arsenic has been classified as a class 1 carcinogen in humans.\textsuperscript{32} In recent years, chronic exposure to inorganic arsenic in drinking water has been linked to increased risks of vascular disease and diabetes.\textsuperscript{33} These effects are commonly seen only in individuals with long-term use of drinking water supplies that contain inorganic arsenic levels greater than 300 ppb. There is much debate in the scientific community about the risk associated with chronic use of drinking water that contains relatively low concentrations of inorganic arsenic,\textsuperscript{34} especially the degree to which data concerning the health effects of long-term exposure to high concentrations of inorganic arsenic may be applied to assessing risk of exposure to lower concentrations of inorganic arsenic. The new maximum contaminant level of 10 µg/L for inorganic arsenic in drinking water reflects concern over the adverse health effects.
associated with chronic exposure to this element.\textsuperscript{35}

A study in a US population chronically exposed to inorganic arsenic in drinking water found a statistically significant correlation between the concentration of inorganic arsenic in drinking water and the concentration of arsenic in urine.\textsuperscript{36} This study, in which about half of the participants were between ages 6 and 18, found no significant difference between adults and children in the urinary output of arsenic. However, children may be less efficient than adults in converting inorganic arsenic into its methylated metabolites.\textsuperscript{37}

There are few data on arsenic exposure in utero or in early postnatal life. The concentration of arsenic in cord blood approximates that found in maternal blood, suggesting that arsenic crosses the placenta.\textsuperscript{38} However, low concentrations of arsenic in breast milk may limit exposure in nursing infants.\textsuperscript{39,40}

From a public health perspective, it is of particular concern to determine whether chronic exposure to arsenic during childhood will affect growing and developing organ systems. Children in India exposed to high levels of inorganic arsenic in drinking water show typical arsenic-induced skin lesions (Figure 1, see page 463).\textsuperscript{41} These skin lesions may be linked to the subsequent appearance of skin cancer and internal cancers. Recent studies found neurobehavioral deficits in Taiwanese adolescents chronically exposed to greater than 300 ppb of inorganic arsenic in drinking water.\textsuperscript{42}

If children are particularly vulnerable to adverse effects of chronic arsenic exposure, what can be said about the risk associated with exposure at relatively low levels? The answer to this question enhances understanding of the dose-response relations for various adverse effects of arsenic and of the molecular processes that underlie the toxic and carcinogenic actions of arsenic. Chronic exposure to inorganic arsenic from drinking water will be reflected by an increased arsenic concentration in urine. As noted above, it is important to ensure that an elevated concentration of arsenic in urine is not attributable to recent ingestion of seafood that contains high concentrations of innocuous organoarsenicals. An exposure-assessment model may be useful in estimating aggregate exposure of children to inorganic arsenic from various environmental sources.\textsuperscript{43} This procedure may help identify environmental sources of arsenic exposure that may require removal or abatement.

**SUMMARY**

Arsenic is a toxic chemical and may cause adverse health effects in children and adults. It is known to affect the nervous, gastrointestinal, and hematological systems and cause skin and internal cancers in people exposed to levels greater than 300 ppb in their drinking water. For most people, the major exposure to arsenic comes from food (8 to 14 μg inorganic arsenic per day), but when the arsenic level in water is elevated, drinking water becomes the predominant source of exposure. Because it is very difficult to limit arsenic exposure from food, it would be wise to limit arsenic exposure from those more controllable sources. Pediatricians should ascertain the levels of arsenic in drinking water of patients with high arsenic levels, using the supplier or, in the case of private wells, a professional water-testing laboratory assay. The Safe Drinking Water Act does not cover private wells or those water systems with less than 15 hook-ups or those that serve less than 25 people.\textsuperscript{44} Pediatricians should instruct parents to use prepared baby formulas or prepare them using water with the arsenic removed and to curtail playing time for younger children in places that have sand containing large amounts of arsenic. Such procedures will limit arsenic exposure to a minimum.

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