The toxicity and carcinogenicity of arsenic are well known, but vexing questions remain. The current controversy over the appropriate Federal limit for arsenic in drinking water highlights some of the difficult scientific, ethical, economic, and political issues that complicate standard-setting in occupational and environmental health. These include limitations in the scientific evidence concerning the risk at low doses, uncertainty about the appropriate mathematical models for estimating the risk at low-level exposures based on data from higher-level exposures, and controversies concerning the appropriate safety margin, level of evidence required for standard-setting, and costs of remediation.

**CHEMICAL FORMS OF ARSENIC**

Arsenic is a naturally occurring element widely present in the environment. While occasionally found in its pure form as a metal, arsenic more typically occurs as a component of inorganic compounds (e.g., with oxygen, iron, chlorine and/or sulfur) or in organic compounds.\(^1\)\(^2\) In addition, lead and copper ores are commonly contaminated with small concentrations of arsenic.

As is true for many metals, the toxicity of arsenic depends upon its chemical form. Most exposure in industry and from building products (treated wood) is to trivalent compounds such as arsenic trioxide, sodium arsenite, and arsenic trichloride. These are more toxic than pentavalent compounds such as arsenic pentoxide, arsenic acid, and lead and calcium arsenates. Both trivalent and pentavalent forms of arsenic are found in arsenic-contaminated water. The trivalent and pentavalent forms may interconvert once they are absorbed.\(^3\)

Organic arsenic compounds found in fish and shellfish may account for significant dietary intake of arsenic. These compounds are much less toxic than inorganic arsenic.\(^1\) Organic forms of arsenic have not been associated with cancer.

Although arsenic is infamous as a poison, the many arsenic compounds have a wide variety of uses. The major current use is in wood preservatives. Arsenic is also used in insecticides and herbicides (although its use in agriculture in the
United States ended in 1993), as a preservative in animal hides, as an additive to lead and copper for hardening, in glass manufacturing to eliminate the natural green color, and in some medicines, mostly for veterinary use.\(^4\) Arsine gas is used as a “doping agent” to enhance electrical junctions in semiconductors. In the 1800s and early 1900s, inorganic arsenic was widely used in pesticides (e.g., rat poison) and in treating some human diseases, such as syphilis. A widely used arsenic compound, Fowler’s solution (potassium arsenite), was prescribed for chronic infections, anemia, and skin diseases. Pentavalent arsenic is still used to treat advanced trypanosomiasis, and arsenic trioxide has recently been introduced as a treatment for promyelocytic leukemia.\(^5\,^6\)

### OCCUPATIONAL AND GENERAL EXPOSURES

People may be exposed to arsenic in many ways. Very high acute exposures by ingestion occur with homicide or suicide attempts (Table 1). Quite high exposures over longer periods of time may occur in some occupational settings through inhalation and ingestion of dust. Such exposures are now rare in the United States. People who live near current or past industrial or agricultural sources of arsenic may sustain fairly high exposures through inhaling fumes and/or ingesting contaminated food. People who live in areas where arsenic is naturally high in drinking water may ingest high levels of arsenic over the course of a lifetime. Finally, low chronic exposures may occur through diet, especially among people who eat much seafood.

Arsenic has not been produced in the United States since 1985. In the past, workers in smelters and in plants that manufactured, packaged, or distributed arsenical pesticides had high exposures to arsenic fumes and dust, predominantly through inhalation. Workplace exposure to arsenic may still occur in the wood preservative industry. Workers in semiconductor manufacturing may be exposed to arsine gas.\(^4\)

Community exposure to arsenic may occur near past or current industrial sources. Facilities

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**TABLE 1**

| Setting                        | Route and Time Frame of Exposure | Amount                |
|-------------------------------|----------------------------------|-----------------------|
| **Ingestion of Food and/or Water** |                                  |                       |
| Arsenic poisoning             | Poison ingestion, acute          | 100 mg                |
| Taiwan high arsenic areas, well water | Well water, chronic (lifetime) | 0.35 - 1.14 mg/L (0.5 - 1.7 mg/day) |
| US. high-arsenic areas, well water | Well water, chronic (lifetime) | 0.05-0.1 mg/L (0.075 - 0.15 mg/day) |
| Typical U.S. adult diet (mostly organic arsenic) | Food, chronic (lifetime) | Up to 0.05 mg/day |
| **Inhalation**                 |                                  |                       |
| Copper smelter workers        | Breathing workplace air, (chronic working years) | 0.05 - 0.5 mg/m3 (up to 10 mg/day) |
| Before 1970                   |                                  |                       |
| OSHA limit                    |                                  | 0.01 mg/m3 (0.2 mg/day) |
such as wood preservative and glass factories may contaminate nearby air and soil. Communities near former smelters, or near fields or orchards where arsenic pesticides were used, may have residual contamination of soil.\(^7\)

An important and potentially controllable source of arsenic exposure is through drinking water. In fact, drinking water accounts for the majority of human arsenic exposure worldwide. In parts of Taiwan and Japan, the Ganges River delta (especially in Bangladesh), and parts of western South America (in northern Chile, southwestern Bolivia, southern Peru, and Argentina), arsenic occurs naturally in drinking water at levels from several hundred to several thousand parts per billion (ppb). Water in some areas of the United States, especially in the West, also contains arsenic, with the highest areas in the 50 ppb to 100 ppb range (see figure 1). Most US sites of high arsenic in drinking water are rural communities. Albuquerque, NM, is the only urban area in the US with substantial arsenic concentrations in drinking water.

Other potential exposures to arsenic are generally less intense and briefer in duration than occurred from past occupational exposures or from highly contaminated drinking water. Since wood preservatives represent a major use of arsenic, breathing sawdust from cutting arsenic-preserved wood, or breathing the smoke from burning this wood, may result in arsenic exposure. Hazardous waste sites are another potential source of arsenic exposure.\(^1\)

The Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental
Protection Agency (EPA) have rated arsenic as a top priority hazardous waste based on three factors: It is found at a high proportion of hazardous waste sites; there is a high potential for human exposure at these sites; and it poses a significant threat to health. Other potential environmental sources include emissions from facilities such as pesticide manufacturing plants, smelters, and glass factories. The burning of cigarette tobacco and fossil fuels are other sources of air emissions of arsenic.

Finally, a low level of arsenic exposure is common in the diet. Most meat and vegetables contain low levels of arsenic, and the average US diet provides about 50 micrograms of arsenic (mostly organic) per day. Diets high in seafood can contain several times that amount. As noted above, this is primarily the safer organic forms of arsenic.

Carcinogenicity of Arsenic

Arsenic is unusual in that the evidence of carcinogenicity comes from human data; an animal model of arsenic carcinogenicity has been elusive. The first evidence linking arsenic with cancer emerged from case reports of skin cancer after exposure to inorganic arsenic in medical treatments, drinking water or pesticides. Subsequently, epidemiological studies systematically examined the association between arsenic and cancer. These studies fall into two broad categories: Studies of lung cancer in highly exposed workers, and studies of the lung, skin, and urinary tract cancers in communities with contaminated water.

Inhalation Exposure

Numerous occupational epidemiological studies have examined cancer occurrence among workers who manufactured arsenical pesticides and worked in mines and copper smelters. Exposures were often extraordinarily high; the air concentrations of arsenic in smelters prior to the 1970s were commonly 50 to 100 times higher than the current occupational limit of 0.01 mg/m³. Studies in the United States, Sweden and Japan together provide a solid body of evidence; many have followed cohorts of several thousand workers for as long as four or five decades (e.g., Enterline et al., 1995; Lubin et al., 2000). Together, these studies consistently show up to a 10-fold increase in lung cancer risk with higher and more prolonged exposures. Other cancers have not consistently been associated with inhaled arsenic exposure.

Ingestion of Contaminated Drinking Water

Epidemiological studies of populations in Taiwan, Bangladesh, and Argentina with high levels of arsenic in drinking water have shown elevated risks of cancers of the urinary tract, lung, and skin, and, less consistently, cancers of the colon and liver. Some of these studies report an increased risk of transitional cell bladder cancer at levels of arsenic below the current US standard of 50 ppb.

For example, a recent study from Taiwan compared the incidence of this cancer in communities with specified levels of arsenic in their drinking water to the incidence in referent communities with a level of 10 ppb or lower. The relative risk was 1.9, 8.2, and 15.3, in communities with arsenic levels of 10 ppb to 50 ppb, 50.1 ppb to 100 ppb, and greater than 100 ppb, respectively. A series of studies in Córdoba, Argentina divided that state’s 26 departamentos into three categories: High-exposure, medium-exposure, and low-exposure. In the high-exposure area, elevated arsenic levels in drinking water averaged 178 ppb. There was a dose-related increase in bladder cancer, lung cancer, and kidney cancer among both men and women. The highest exposures were associated with relative risks in the range of two.

A recent cohort study examined a population in Utah exposed to median arsenic concentrations in drinking water that ranged as
high as 166 ppb.\textsuperscript{16} Investigators compared the mortality of the exposed people to the mortality of the state of Utah, using standardized mortality ratios (SMRs). There was no increase in cancers of the urinary tract, lung, or skin, as might have been expected. The only significant cancer excess was of prostate cancer in men, a cancer not previously associated with arsenic in drinking water; the significance of this finding is unclear. However, the study was relatively small, with 2,203 deaths, of which fewer than 600 were in people classified as highly exposed, so the power to detect increases in cancer was limited. Moreover, this was a unique population of Mormons, with little or no exposure to alcohol, tobacco, and caffeine, so the ability to generalize these results may be limited.

What Do the Animal and Laboratory Evidence Suggest?

Animal studies do not provide evidence of arsenic carcinogenicity.\textsuperscript{4,10,17} In fact, arsenic is highly unusual in that as a human carcinogen, animal carcinogenicity has not been established.\textsuperscript{9} Evidence that arsenic compounds cause mutations in bacteria is inconclusive. However, arsenic compounds have induced chromosomal aberrations in mammalian cells.\textsuperscript{10,18} Chromosomal aberrations were also observed in the peripheral lymphocytes of smelter workers occupationally exposed to arsenic and in patients treated with arsenical compounds.\textsuperscript{10}

What Do the Expert Agencies Say?

The National Toxicology Program evaluates exposures that may be carcinogenic. Exposures that are thought to be carcinogenic are included in the Reports on Carcinogens, which are published every two years. Each exposure is assigned to one of two categories: “Known to be human carcinogens,” or “Reasonably anticipated to be human carcinogens.” The first category includes substances for which human studies (epidemiology studies and/or experimental studies) provide “sufficient evidence” of carcinogenicity in humans. The second category includes substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. Using this scheme, the National Toxicology Program classifies arsenic compounds as a known human carcinogen.\textsuperscript{4}

The International Agency for Research on Cancer (IARC) also evaluates exposures that may be carcinogenic. IARC classifies exposures into one of four categories: Group 1 exposures are those “known to be carcinogenic to humans,” usually based on “sufficient” human evidence, but sometimes based on “sufficient” evidence in experimental animals and “strong” human evidence. Group 2 exposures are divided into two categories. Group 2A (“probably carcinogenic to humans”) has stronger evidence, and Group 2B (“possibly carcinogenic to humans”) has weaker evidence. Group 3 exposures are not considered classifiable, because available evidence in limited or inadequate. Finally, Group 4 exposures are “probably not carcinogenic to humans” based on evidence suggesting lack of carcinogenicity in humans and in experimental animals. IARC rates arsenic and arsenic compounds as carcinogenic to humans (Group 1). IARC notes that this evaluation applies to the group of chemicals as a whole and not necessarily to all the individual chemicals in the group.\textsuperscript{19}

The Environmental Protection Agency (EPA), through its Integrated Risk Information System, uses a classification scheme very similar to that of IARC. It classifies exposures into one of five categories: (A) Human carcinogen, (B) Probable human carcinogen, (C) Possible human carcinogen, (D) Not classifiable as to human carcinogenicity, and (E) Evidence of noncarcinogenicity for humans. EPA classifies arsenic as a human carcinogen (Group A).\textsuperscript{17}
**Does Arsenic Cause Any Other Health Problems?**

Arsenic is an acute and a chronic toxin. An acute inhalation exposure may cause sore throat and irritated lungs. Acute exposure, by either inhalation or ingestion, can also damage many tissues including nerves, gastrointestinal tract, and skin. An intense acute exposure can be fatal.

Chronic exposure to lower levels of arsenic can also cause adverse health effects, including vascular disease, peripheral neuropathy, exacerbation of the complications of diabetes, cardiac arrhythmias, liver and kidney toxicity, anemia and leukopenia. Long-term exposure to inorganic arsenic is also commonly associated with a darkening of the skin and the appearance of keratoses, usually on the palms and soles. There is some evidence that arsenic is associated with ischemic heart disease. Finally, recent evidence suggests that arsenic may interfere with the function of some hormones.

**ARSENIC IN DRINKING WATER: A CURRENT POLICY CHALLENGE**

There is currently an active debate regarding the regulation of arsenic in drinking water. The Safe Drinking Water Act requires the US EPA to set standards for arsenic levels in drinking water to protect human health. EPA set the current standard of 50 ppb in 1975 based on a Public Health Service standard originally established in 1942. There is considerable scientific consensus that EPA’s standard is not sufficiently protective. This consensus is based on two kinds of evidence. First, investigators have extrapolated high-dose data, primarily from Taiwan, to the United States, and predicted a large number of excess cancers. Based on this approach, for example, one study concluded that arsenic levels of 50 ppb in drinking water would result in an increased risk of dying from liver, lung, kidney or bladder cancer by up to 13 deaths per 1000, a level comparable with that from environmental tobacco smoke and radon. This approach has been questioned since data from high-dose exposures may not be informative about consequences of lower-dose exposures, and since other factors such as dietary differences may make the Taiwanese data inapplicable to the United States. A second kind of evidence comes from epidemiologic studies of relatively lower-level exposures, such as one of the Taiwanese studies discussed above. Case-control results from Finland and Chile also suggest increased risk of bladder cancer and lung cancer, respectively, at water levels well below 50 ppb. A 1999 report by the National Research Council concluded that the 50 ppb standard does not protect public health and recommended lowering the standard, without specifying the level of that standard.

At the center of the policy challenge is the dose–response issue. In general, higher exposures to a hazardous chemical confer higher risk. The clearest data, in both epidemiological and animal studies, come from high-dose observations, because biological effects are more likely to occur following high-dose exposure. For regulators, the data provide a clear mandate to control very high-dose exposures to arsenic (and other toxins). However, most human exposures, even such exposures as drinking water in western states, occur at lower levels, where epidemiological data are less informative. This requires extrapolation of high-dose data to settings with much lower exposures, an effort fraught with uncertainty.

In January 2001, the EPA announced a new standard of 10 ppb. The new standard would apply to over 50,000 community water systems in the United States. Of these, the EPA estimated that about 3,000, serving 11 million people, would have to take corrective action to lower the levels of arsenic in their drinking water. Interestingly, a recent study of 793 wells in New Hampshire, which is not
considered a high-arsenic area, showed that more than 10% had arsenic levels above 10 ppb, and 2.5% had levels above 50 ppb.  

However, in March 2001, the new Administration announced a delay in implementing the revised arsenic standard, pending further review. The EPA requested the NRC to study a range of standards, from 3 ppb to 20 ppb. Until a new standard is announced, the old standard of 50 ppb continues to apply.

Underlying the debate about the standard are two challenges. First, compliance with strict standards will entail considerable costs for some water systems, since the technology that removes arsenic from water is expensive. Many of the contaminated water systems supply small communities that lack the financial resources to undertake such remediation. Currently, there are no Federal programs for assisting such communities, as exist for some hazardous waste sites. Second, the magnitude of the benefit—the amount of cancer avoided by lowering arsenic levels in water—is unclear. Both the 1999 NRC report and a more recent risk assessment pointed out that estimates of cancer avoided depend heavily on the choice of mathematical models used. For example, the drinking water arsenic dose associated with a 1% excess lifetime cancer risk (ED$_{0.01}$), combining bladder, lung, and liver cancer, ranged from less than 1 ppb to over 500 ppb, depending upon the model used. As a result, although there is general agreement that 50 ppb permits an unacceptable number of excess cancers, the available science does not point to a specific lower standard. Regulators will need to choose an approach to modeling before promulgating final standards. This process is currently underway; the EPA has contracted with the NRC to perform further risk assessments in an attempt to set a new standard.

### FOR MORE INFORMATION

General information on arsenic - Agency for Toxic Substances and Disease Registry (ATSDR)  
www.atsdr.cdc.gov/tfacts2.html

Arsenic in US ground water - US Geologic Survey (includes many useful links)  
http://webserver.cr.usgs.gov/trace/arsenic/

List and formulas of common arsenic compounds - Arsenic and Arsenic Compounds (Group 1) IARC  
http://193.51.164.11/htdocs/monographs/Suppl7/Arsenic.html

General information on arsenic, including current regulatory issues – EPA  
http://www.epa.gov/safewater/arsenic.html

Local drinking water information – EPA  
http://www.epa.gov/safewater/dwinfo.htm

Association of Occupational and Environmental Health Clinics  
http://www.aoec.org

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HOW SHOULD HEALTH PROFESSIONALS ADVISE PATIENTS WHO HAVE BEEN EXPOSED TO ARSENIC?

There are several laboratory methods for assessing arsenic exposure. Assays of hair and fingernails can detect relatively high-level arsenic exposures during the previous 6 to 12 months. However, these tests are difficult to standardize. Blood tests for arsenic reflect
only very recent exposures since arsenic is cleared from blood within a few hours; blood tests are therefore not suitable as an indicator of long-term exposure. Urine tests are the most reliable method for identifying low levels of arsenic exposure, but these too reflect recent exposures; most absorbed arsenic is excreted in urine within days. Physicians should be aware that a substantial fraction of arsenic in urine might be organic arsenic from fish consumption.

Since arsenic exposure increases the risk of cancer, especially skin, bladder, kidney, and lung cancer, exposed individuals should be informed of other risk factors and prevention strategies for these cancers. Although providers should counsel all patients against tobacco use and excessive sun exposure, this advice may be especially relevant to people who have been exposed to arsenic. Such patients should be instructed to notify their physicians of any signs and symptoms of these diseases (new skin lesions or changes in old lesions, hematuria, dysuria, persistent and/or blood-tinged sputum production, etc.). An appropriate schedule of skin examinations by a health care professional and monthly skin self-exams should be recommended. Based on the presence of other risk factors and the intensity and duration of arsenic exposure, other early detection testing (e.g., urine cytology) may be considered, although available evidence does not support firm recommendations on such testing.

Patients concerned about the level of arsenic in their drinking water should be advised that information on arsenic levels is available. Those on public water systems can check the Consumer Confidence Reports issued annually and/or seek information on-line at the EPA’s Office of Water (http://www.epa.gov/safewater/dwinfo.htm) or at their state Environment Department. Those who depend on private wells may contract to have their water tested by private firms. If the level is unacceptably high, patients may be counseled to consider obtaining drinking water from another source and advised that household water filters do not effectively remove arsenic.

For people currently employed in an industry where arsenic exposure is a concern, there are numerous ways to reduce or prevent exposures. Engineering changes, such as substituting safer materials for more hazardous materials, enclosing a process that may expose workers to hazards, or ventilating a work area, are important. Good work practices, such as changing clothes after work, washing work clothes regularly, and keeping food out of the work area, are also essential. Finally, personal protective equipment such as gloves and respirators may be an important part of a workplace protective program. For more information on preventing or reducing occupational exposures, workers should consult their company’s safety and health manager.

Many, but not all, “pressure-treated” lumber products contain inorganic arsenic compounds that protect the wood against termites and fungi. Because relatively little arsenic escapes from the wood, these products are generally quite safe. However, people may be exposed to dangerous levels by inhaling sawdust during construction. Acidic solutions promote release of the arsenic compounds from the wood, and are therefore not recommended for washing decks and other structures made with such products. Burning arsenic-treated lumber in stoves or open fires releases dangerous levels of arsenic in smoke and ashes, and should be avoided.

Patients concerned about exposures at work, from drinking water, from treated wood, or from other sources may be referred to specialists in environmental and occupational medicine, who can assess exposure levels, evaluate current health problems that may be related to the exposures, and provide information concerning future risks and how to minimize them. Providers or patients can locate such qualified professionals and facilities by check-
ing with the Association of Occupational and Environmental Clinics (http://www.aoec.org).

WHAT’S THE BOTTOM LINE?

There is strong epidemiological evidence that arsenic is a human carcinogen. Inhaling arsenic increases the risk of lung cancer, and ingesting arsenic increases the risk of skin, urinary tract, and lung cancer. Based on this evidence, expert agencies have classified arsenic as a human carcinogen. Because of the cancer risk and other health hazards associated with arsenic, exposures to arsenic should be minimized.

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