

Arsenic and Inorganic Arsenic Compounds

CAS No. 7440-38-2 (Arsenic)

No separate CAS No. assigned for inorganic arsenic compounds

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as As

Carcinogenicity

Arsenic and inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans.

Cancer Studies in Humans

Epidemiological studies and case reports of humans exposed to arsenic or arsenic compounds for medical treatment, in drinking water, or occupationally have demonstrated that exposure to arsenic and inorganic arsenic compounds increases the risk of cancer. Cancer tissue sites include the skin, lung, digestive tract, liver, urinary bladder, kidney, and lymphatic and hematopoietic systems. Skin cancer has been reported in individuals exposed to arsenic for therapeutic reasons, sometimes in combination with cancer at other tissue sites, such as blood-vessel cancer (angiosarcoma) of the liver, intestinal and urinary-bladder cancer, and meningioma (tumors of the membranes covering the central nervous system). However, only skin cancer has been clearly associated with medical use of arsenic in epidemiological studies (IARC 1973, 1980).

Several studies have reported an association between skin cancer and exposure to arsenic in drinking water. Epidemiological studies conducted in Taiwan, in an area where blackfoot disease (a disorder of the peripheral blood vessels caused by arsenic) is endemic, found that exposure to drinking water containing arsenic at concentrations ranging from 0.35 to 1.14 mg/L increased the risks of urinary-bladder, kidney, skin, lung, liver, and colon cancer. Occupational exposure to inorganic arsenic compounds, especially in mining and copper smelting, consistently has been associated with increased risk of lung cancer (predominantly adenocarcinoma, with a slight excess of small-cell cancer); the risk of lung cancer increased with increasing cumulative exposure to arsenic. Exposure of smelter workers to arsenic also has been associated with increased risks of cancer of the kidney, digestive tract, and lymphatic and hematopoietic systems. Epidemiological studies and case reports of workers in other industries exposed to arsenic, such as glass workers, hat makers, and pesticide workers, also have reported excesses of cancer (mainly lung and skin cancer) (IARC 1973, 1980).

Since arsenic was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, numerous epidemiological studies have evaluated the carcinogenicity of arsenic in drinking water. Several studies have reported exposure-response relationships for several types of cancer, including urinary-bladder, kidney, lung, and skin cancer (Cantor 1997, Ferreccio *et al.* 2000). A few studies have suggested that exposure to arsenic in drinking water is associated with cancer at additional tissue sites, including prostate cancer in men and nasal cancer in both sexes (Cantor 1997). Some evidence suggests that arsenic exposure is more strongly associated with transitional-cell carcinoma of the urinary bladder than with other types of urinary-bladder cancer (Guo *et al.* 1997, Chiou *et al.* 2001). Most studies found associations with cancer of the lung, urinary bladder, or prostate at lower arsenic concentrations than those reported in the Taiwanese study cited above; however, the evidence for carcinogenic effects at very low concen-

trations of arsenic is inconclusive (Kurttio *et al.* 1999, Lewis *et al.* 1999, Ferreccio *et al.* 2000, Chiou *et al.* 2001, Steinmaus *et al.* 2003, Bates *et al.* 2004). In some studies of urinary-bladder cancer, an association with arsenic exposure was observed only when the analysis was limited to smokers and to arsenic exposures that had occurred at least 40 years previously (Steinmaus *et al.* 2003, Bates *et al.* 2004).

Cancer Studies in Experimental Animals

Metallic arsenic, arsenic trioxide, sodium arsenite, sodium arsenate, potassium arsenite, lead arsenate, calcium arsenate, and pesticide mixtures containing arsenic have been tested for carcinogenicity in experimental animals (IARC 1980, 1987). Mice and rats were exposed to various arsenic compounds by oral administration and subcutaneous injection. Mice were also exposed by dermal application, inhalation, and intravenous injection, and rats by intratracheal instillation and femoral intramedullary injection. In other studies, dogs were exposed orally, hamsters by intratracheal instillation, and rabbits by intramedullary injection. In rats, oral exposure to arsenic trioxide caused stomach cancer (adenocarcinoma), and intratracheal instillation of a pesticide mixture containing calcium arsenate compounds caused a high incidence of lung cancer (adenocarcinoma). Benign and malignant lung tumors (adenoma and carcinoma) were also observed at low incidences in hamsters following intratracheal instillation of arsenic trioxide, and benign lung tumors (adenoma) occurred in neonatal mice subcutaneously injected with arsenic trioxide following prenatal exposure via a single subcutaneous injection during gestation. Lymphocytic leukemia and lymphoma were observed in mice given weekly intravenous injections of an aqueous solution of sodium arsenate for 20 weeks and in female mice and their offspring following subcutaneous injections of sodium arsenate throughout pregnancy. In most of the other studies in experimental animals, no tumors were observed, or the results were inconclusive.

Properties

Arsenic is a naturally occurring semimetallic element with an atomic weight of 74.9. Pure arsenic (which rarely is found in nature) exists in three allotropic forms: yellow (alpha), black (beta), and gray (gamma) (HSDB 2009). Many inorganic arsenic compounds are found in the environment, frequently occurring as the sulfide form in complex minerals containing copper, lead, iron, nickel, cobalt, and other metals. Arsenic compounds occur in trivalent and pentavalent forms; common trivalent forms are arsenic trioxide and sodium arsenite, and common pentavalent forms are arsenic pentoxide and the various arsenates. Arsenic and arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic has a specific gravity of 5.73, sublimes at 613°C, and has a very low vapor pressure of 1 mm Hg at 373°C. Many of the inorganic arsenic compounds occur as white, odorless solids with specific gravities ranging from about 1.9 to over 5. Arsenic trioxide, the most common arsenic compound in commerce, melts at 312°C and boils at 465°C (ATSDR 2007). In water, elemental arsenic is insoluble, calcium arsenate and arsenites are sparingly soluble, and arsenic trioxide, arsenic pentoxide, and other arsenicals are soluble. Arsenic pentoxide, potassium arsenite, and the sodium salts are soluble in ethanol. Arsenic, arsenic pentoxide, arsenic trioxide, the calcium arsenites, lead arsenate, and potassium arsenate are soluble in various acids. When heated to decomposition, arsenic compounds emit toxic arsenic fumes (HSDB 2009).

Use

Inorganic arsenic compounds were widely used as pesticides from the mid 1800s to the mid 1900s and were used in medicine until the 1970s, primarily for treatment of leukemia, psoriasis, and asthma. The use

of arsenic for treatment of acute promyelocytic leukemia resumed in the 1990s. By the mid 1970s, arsenic use was shifting from pesticides to wood preservatives, and by 1980, wood preservatives were the primary use. Total agricultural-chemical use (in pesticides and fertilizers) declined to about 15% to 20% of total arsenic consumption by the early 1990s and has remained at about 4% since 1995 (Edelstein 1994, Reese 1998, ATSDR 2007, Brooks 2009).

Since the mid 1990s, arsenic trioxide used in wood preservation has accounted for 86% to 90% of total U.S. arsenic consumption. Wood treated with chromated copper arsenate (CCA), known as “pressure-treated wood,” has been used widely to protect utility poles, building lumber, and foundations from decay and insect attack. However, a voluntary phase-out of CCA for certain residential uses (e.g., in wood for decks, play structures, fencing, and boardwalks) that went into effect December 31, 2003, has reduced this use of arsenic. CCA continues to be used in wood products for industrial use. Other uses of arsenic in the 1990s included use in glass (3% to 4%) and nonferrous alloys (1% to 4%) (ATSDR 2007, Brooks 2009).

By the 1990s, there was renewed interest in the use of arsenic for treatment of acute promyelocytic leukemia (ATSDR 2007). Arsenic trioxide is approved by the U.S. Food and Drug Administration for treating this type of leukemia when other chemotherapy treatments have failed (MedlinePlus 2009). Arsenic is also used in the production of lead alloys used in lead-acid batteries. It may be added to alloys used for bearings, type metals, lead ammunition, and automotive body solder, and it may be added to brass to improve corrosion resistance. High-purity arsenic is used in a variety of semiconductor applications, including solar cells, light-emitting diodes, lasers, and integrated circuits (ATSDR 2007).

Production

Before 1985, U.S. arsenic production varied widely, peaking at 54.7 million pounds in 1944. Although the United States is the world's leading consumer of arsenic, arsenic has not been produced domestically since 1985, when production of 4.9 million pounds was reported (Brooks 2009, USGS 2009). U.S. apparent consumption of arsenic was estimated at 16.2 million pounds in 2006, declining steadily to 7.9 million pounds in 2009 (USGS 2010). All arsenic metal and compounds consumed in the United States now are imported (USITC 2018). From the 1930s to the 2000s, U.S. imports of arsenic metal and compounds exceeded 10 million pounds, but imports in 2017 were much lower (2.1 million pounds) (USITC 2018). U.S. exports of arsenic metal and compounds also approached 10 million pounds in the 1940s (Brooks 2010). Exports decreased to a low of less than 100,000 lb in 1996, but had increased to 1.5 million pounds by 2017 (USITC 2018). Exports classified as arsenic metal may include arsenic-containing e-waste, such as computers and other electronics destined for reclamation and recycling in other countries.

Exposure

Evidence for the exposure of the U.S. general population to arsenic comes from the 2009–2010 National Health and Nutrition Examination Survey, which reported that the geometric mean concentration of total arsenic in urine was 9.28 µg/L, based on a sample of 2,860 individuals of all ages, both genders, and all race and ethnicity groups (CDC 2018).

The general population is exposed to arsenic and arsenic compounds primarily through consumption of foods. The estimated daily dietary intake of inorganic arsenic ranges from about 1 to 20 µg; however, the average daily dietary intake of arsenic in all forms is about 40 µg. The highest levels of arsenic (in all forms) are detected in seafood, rice, rice cereal, mushrooms, and poultry. Inorganic arsenic was

reported in the tissue of livestock that had been administered arsenic drugs or feed additives (ATSDR 2007), and U.S. Department of Agriculture researchers reported that consumption of meat from chickens fed an organic arsenic compound (4-hydroxy-3-nitrophenylarsonic acid) could result in ingestion of 21.1 to 30.6 µg of inorganic arsenic per day for people in the 99th percentile of consumption level (Lasky *et al.* 2004). This organic arsenic compound, which is used as an antimicrobial in animal and poultry feeds, is found mostly unchanged in poultry litter; however, under anaerobic conditions, *Clostridium* bacteria can transform it to release arsenate (Stolz *et al.* 2007). The release of inorganic arsenic from large quantities of poultry litter could have a detrimental effect on soil and water quality (Jackson *et al.* 2003). Arsenic used as pigments in paints can be ingested through contamination of hands, fingernails, food, cups, or cigarettes or through the practice of holding paint brushes in the mouth (HSDB 2009).

Potential exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or arsenical chemicals that were disposed of improperly (ATSDR 2007). Natural soil concentrations of arsenic (in all forms) typically range from 0.1 to 40 mg/kg, averaging 5 to 6 mg/kg. Through natural processes, arsenic in soil can be released to groundwater or surface water. In the United States, mean arsenic concentrations generally are higher in groundwater systems (wells) than in surface-water systems. Arsenic concentrations in groundwater and surface water are lowest in the mid-Atlantic and southeastern regions, intermediate in New England, the Midwest, and the south-central and north-central regions, and highest in the West (EPA 2000). U.S. drinking water contains arsenic at an average concentration of 2 µg/L; however, 12% of groundwater systems in the West and 12% of surface-water systems in the north-central region contain arsenic at levels exceeding 20 µg/L (ATSDR 2007). In addition, several states have groundwater systems with maximum levels of arsenic exceeding 50 µg/L, including California (99 µg/L), Nevada (150 µg/L), and Texas (86 µg/L) (EPA 2000). Reported arsenic concentrations in groundwater in Fairbanks, Alaska, ranged up to 1,670 µg/L (USGS 2001).

The general population may also be exposed to arsenic compounds emitted to the air by pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette smoking, burning of fossil fuels, and other sources (ATSDR 2007). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of arsenic between 1988 and 2007 ranged from 77,000 lb to over 77 million pounds, while releases of arsenic compounds ranged from 3.4 million to 568 million pounds. Releases showed no clear trends over this period. In 2007, 51 facilities released arsenic, and 245 facilities released arsenic compounds (TRI 2009).

Inhalation and dermal contact are the primary routes of occupational exposure to arsenic. Because arsenic is no longer produced in the United States and many uses of arsenical pesticides have been banned, the number of workers exposed to arsenic likely has decreased since the early 1980s. Nevertheless, occupational exposure to arsenic (including forms other than inorganic compounds) is likely in several industries, including nonferrous smelting, wood preservation, glass manufacturing, electronics, and production and use of agricultural chemicals (ATSDR 2007). No recent occupational exposure surveys were found; however, the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 57,000 workers, including over 11,000 women, potentially were exposed to arsenic, arsenic pentoxide, arsenic trioxide, arsenic acid, arsenic oxide, arsenic sulfide, or arsenic trichloride (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Fireworks devices shall not contain arsenic sulfide, arsenates, or arsenites.

Department of Transportation (DOT)

Inorganic arsenic compounds are considered hazardous materials, and orthoarsenic acid is considered a marine pollutant; special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Arsenic compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Arsenic compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb for arsenous trichloride; = 1,000 lb for arsine.

Urban Air Toxics Strategy: Arsenic compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Limits have been established for arsenic in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Liquid hazardous wastes containing arsenic and/or compounds at levels ≥ 500 mg/L (as As) are prohibited from underground injection.

Effluent Guidelines: Arsenic and arsenic compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.018 $\mu\text{g/L}$ for arsenic; based on fish or shellfish consumption only = 0.14 $\mu\text{g/L}$ for arsenic.

Numerous inorganic arsenic compounds are designated hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for arsenic, arsenic acid, arsenic disulfide, arsenic pentoxide, arsenic trioxide, arsenic trisulfide, arsenic oxide, arsenic trichloride, sodium arsenate, lead arsenate, calcium arsenate, potassium arsenate, sodium arsenite, potassium arsenite, calcium arsenite.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Arsenic and arsenic compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for arsenic pentoxide, arsenic disulfide, arsenic trisulfide, arsenous oxide, sodium arsenate, calcium arsenate, arsenous trichloride, sodium arsenite, potassium arsenite; = 100 lb for arsine.

Threshold planning quantity (TPQ) = 100 lb for arsine; = 500 lb for arsenous trichloride; = 100 lb/10,000 lb for arsenic pentoxide, arsenic trioxide, arsenous oxide (solids in powder form with particle size $< 100 \mu\text{m}$ or in solution or molten form/all other forms); = 500 lb/10,000 lb for calcium arsenate, sodium arsenite, potassium arsenite; = 1,000 lb/10,000 lb for sodium arsenate.

Federal Insecticide, Fungicide, and Rodenticide Act

The label of each pesticide must state whether it contains arsenic in any form and the percentage of total and water-soluble arsenic.

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate (CCA).

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of arsenic or its compounds = P010, P011, P012, F032, F034, F035, K031, K060, K084, K101, K102, K161, K171, K172, K176.

Arsenic and arsenic compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.01 mg/L for arsenic.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level of arsenic in bottled water = 0.01 mg/L.

Specified color additives may be used in food, drugs, and cosmetics subject to limitations on arsenic levels as prescribed in 21 CFR 73 and 74.

Maximum arsenic levels in various specified food additives range from 0.1 to 3 ppm.

All drug products containing potassium arsenite are withdrawn from the market.

Labels must be put on drugs containing arsenic stating that prolonged use could cause serious injury and to keep out of the reach of children.

Maximum levels allowed in food additives permitted in feed and drinking water for animals range from 1 to 75 ppm.

Arsenic trioxide is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.010 mg/m³.

Comprehensive standards for occupational exposure to arsenic have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 mg/m³ for inorganic arsenic compounds; = 0.005 ppm for arsine.

Biological exposure index (BEI) (end of workweek) = 35 $\mu\text{g/L}$ for inorganic arsenic plus methylated metabolites in urine (elemental arsenic and soluble inorganic compounds, except gallium arsenide and arsine).

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 5 mg/m³ for inorganic compounds (as As).

Ceiling recommended exposure limit = 0.002 mg/m³ (15 min) for inorganic compounds (as As).

Inorganic arsenic compounds are listed as potential occupational carcinogens.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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