Arsenic Compounds, Inorganic*

Known to be a human carcinogen
First Listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans. Epidemiological studies and case reports of humans exposed to arsenic compounds for medical treatment, in drinking water, or occupationally have demonstrated that exposure to inorganic arsenic compounds increases the risk of cancer. Cancer tissue sites include the skin, lung, digestive tract, liver, bladder, kidney, and lymphatic and hematopoietic systems (organs and tissues involved in production of blood). Skin cancer has been reported in individuals exposed to arsenic for therapeutic reasons, sometimes in combination with other cancers, such as angiosarcoma (blood-vessel tumors) of the liver, intestinal and 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. 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 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 was found to increase 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 other workers 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 the reviews for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer (IARC), numerous epidemiological studies have evaluated the carcinogenicity of arsenic in drinking water. Several studies have reported dose-response relationships for several types of cancer, including bladder, kidney, lung, and skin cancer (reviewed by Cantor 1997, Ferreccio *et al.* 2000). A few studies have suggested that arsenic exposure in drinking water is associated with cancer at additional tissue sites, including prostate cancer in males and nasal cancer in males and females (reviewed by Cantor 1997). Some evidence suggests that arsenic exposure is more strongly associated with transitional-cell carcinoma of the bladder than with other types of bladder cancer (Guo *et al.* 1997, Chiou *et al.* 2001). Most studies found associations with cancer of the lung, 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 concentrations 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 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).

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 were exposed to various arsenic compounds by oral administration, dermal application, inhalation, intravenous (i.v.) injection, and subcutaneous (s.c.) injection; rats were exposed by oral administration, intratracheal instillation, s.c. injection, and intramedullary injection (into the central cavity of the femur). In other studies, dogs were exposed by oral administration, hamsters by intratracheal instillation, and rabbits by intramedullary injection. Oral administration of arsenic trioxide caused stomach adenocarcinoma in rats. Intratracheal instillation of a pesticide mixture containing calcium arsenate compounds induced a high incidence of lung adenocarcinoma in rats, and intratracheal instillation of arsenic trioxide caused low incidences of lung adenoma and carcinoma in hamsters. Subcutaneous injection of neonatal mice with arsenic trioxide (following a single maternal s.c. injection during gestation) caused lung adenoma. In another study, s.c. injections of sodium arsenate throughout pregnancy caused lymphocytic leukemia and lymphoma in female mice and their offspring. Lymphocytic leukemia and lymphoma also were induced in mice given weekly i.v. injections of an aqueous solution of sodium arsenate for 20 weeks. In most of the other studies in experimental animals, including oral-exposure studies in mice, rats, and dogs, dermal-exposure studies in mice, inhalation-exposure studies in mice, s.c.-injection studies in mice and rats, and intramedullary-injection studies in rats and rabbits, no tumors were observed or the results were inconclusive. IARC (1987) concluded that there was limited evidence for the carcinogenicity of inorganic arsenic compounds in experimental animals.

Properties

Arsenic is a naturally occurring semimetallic element with an atomic weight of 74.92. Pure arsenic (which rarely is found in nature) exists in three allotropic forms: yellow (alpha), black (beta), and gray (gamma) (HSDB 2001). 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 more than 5. Arsenic trioxide, the most common arsenic compound in commerce, melts at 312°C and boils at 465°C (ATSDR 2000). 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 2003).

Use

The end-use distribution of inorganic arsenic compounds in the United States has varied over the years. 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. 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 (pesticides and fertilizers) declined to about 15% to 20% of total arsenic consumption by the early 1990s and since 1995 has remained

at about 4% (Edelstein 1994, Reese 1998, ATSDR 2000, Brooks 2002).

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. Other uses of arsenic from 1990 to 2002 included use in glass (3% to 4%) and nonferrous alloys (1% to 4%). By the 1990s, there also was a renewed interest in the use of arsenic for treatment of acute promyelocytic leukemia (ATSDR 2000). Wood preservatives are expected to remain the major domestic use for arsenic; 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 will reduce this use of arsenic. CCA will continue to be used in wood products for industrial use (ATSDR 2000, Brooks 2002).

Arsenic is 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 2000).

Production

The United States is the world's leading consumer of arsenic; however, arsenic has not been produced in the United States since 1985, when production of 2,200 metric tons (4.9 million pounds) was reported. All arsenic metal and compounds consumed in the United States now are imported. Before 1985, U.S. arsenic production varied widely, reaching a peak of 24,800 metric tons (54.7 million pounds) in 1944. Average annual production was 12,200 metric tons (26.9 million pounds) from 1935 to 1959 and 5,100 metric tons (11.2 million pounds) from 1960 to 1985. U.S. imports of arsenic and arsenic compounds increased as production decreased, with annual averages of about 8,300 metric tons (18.3 million pounds) from 1935 to 1959, 11,300 metric tons (24.9 million pounds) from 1960 to 1985, and 23,300 metric tons (51.4 million pounds) from 1986 to 2002. Annual exports reached a peak of 4,200 metric tons (9.3 million pounds) in 1941, but since 1985 have ranged from 36 to 1,350 metric tons (79,000 to 3 million pounds) (Buckingham and Reese 2002, USGS 2003). Arsenic imports are mainly in the form of arsenic trioxide; arsenic metal generally accounts for about 3% to 5% of imports (USGS 2003). U.S. consumption of arsenic and arsenic compounds is expected to decline as maintenance-free batteries replace lead-acid storage batteries and as CCA is eliminated from residential wood products. The three principal U.S. producers of arsenical wood preservatives have begun a voluntary transition from CCA to alternative wood preservatives (Brooks 2002).

Exposure

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. Trace levels of arsenic have been reported in the tissue of livestock that were administered arsenic drugs or feed additives. 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 2000). 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 2003).

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 ground water or surface water. In the United States, mean arsenic concentrations generally are higher in ground-water systems (wells) than in surface-water systems. Arsenic concentrations in ground water 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 ground-water systems in the West and 12% of surface-water systems in the north-central region contain arsenic at levels exceeding 20 µg/L (ATSDR 2000). In addition, several states have ground-water 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 ground water in Fairbanks, Alaska, range up to 1,670 µg/L (USGS 2001). The general population also may 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 2000).

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 2000). No recent occupational exposure surveys were located; however, according to the National Occupational Exposure Survey (1981–1983), more than 57,000 workers, including more than 11,000 women, potentially were exposed to arsenic, arsenic pentoxide, arsenic trioxide, arsenic acid, arsenic oxide, arsenic sulfide, or arsenic trichloride (NIOSH 1984).

EPA's Toxics Release Inventory listed 67 industrial facilities that released arsenic and 524 facilities that released arsenic compounds in 2001 (TRI01 2003). Between 1988 and 2001, reported annual releases of arsenic ranged from about 90,000 lb (40,000 kg) to more than 2.3 million pounds (1.0 million kilograms). Releases of arsenic compounds during this period ranged from 3.4 million pounds (1.5 million kilograms) to 19.5 million pounds (8.8 million kilograms). Reported releases fluctuated from year to year, with no clear trends.

Regulations

CPSC

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

EPA

Clean Air Act

- Mobile Source Air Toxics: Arsenic Compounds listed as a Mobile Source Air Toxic for which regulations are to be developed
- NESHAP: Listed as a Hazardous Air Pollutant (HAP)
- Prevention of Accidental Release: Threshold Quantity (TQ) = 15,000 lb (arsenous trichloride); 1,000 lb (arsine)
- Urban Air Toxics Strategy: Arsenic Compounds identified as one of 33 HAPs that present the greatest threat to public health in urban areas

Clean Water Act

- Biosolids Rule: Ceiling concentration of total arsenic for land application = 75 mg/kg
- Effluent Guidelines: Listed as a Toxic Pollutant (arsenic and compounds)
- Water Quality Criteria: Based on fish/shellfish and water consumption = 0.018 µg/L (arsenic); based on fish/shellfish consumption only = 0.14 µg/L

Comprehensive Environmental Response, Compensation, and Liability Act

- Reportable Quantity (RQ) = 1 lb (arsenic, arsenic acid, arsenic disulfide, arsenic

pentoxide, arsenic trioxide, arsenic trisulfide, arsenous oxide, arsenous 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

Federal Insecticide, Fungicide, and Rodenticide Act

The tolerance for residues of arsanilic acid (a plant regulator) on grapefruit = 2 ppm (0.7 ppm total arsenic)

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

Registrations for most non-wood preservative uses of inorganic arsenicals have been cancelled and almost all registrations for chromated copper arsenate products for residential uses have been voluntarily cancelled

Resource Conservation and Recovery Act

Characteristic Toxic Hazardous: TCLP Threshold = 5.0 mg/L

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - P010, P011, P012, F032, F034, F035, K031, K060, K084, K101, K102, K161, K171, K172

Listed as a Hazardous Constituent of Waste (arsenic and arsenic compounds)

Safe Drinking Water Act

Maximum Contaminant Level (MCL) = 0.050 mg/L (0.010 mg/L effective 1/23/06)

FDA

Maximum permissible level in bottled water = 0.05 mg/L

Specified color additives may contain maximum arsenic levels that range from 1-5 ppm

Specified straight color additives may contain maximum arsenic levels that range from 0.00014-0.0002%

Specified food additives may contain maximum arsenic levels that range from 0.1-3 ppm

All drug products containing potassium arsenite are withdrawn from the market

A label must be put on drugs containing arsenic stating that prolonged use could cause serious injury

Tolerances for residues of arsenic in swine and chicken meat and by-products and chicken eggs range from 0.5-2 ppm

Maximum levels allowed in feed and drinking water for animals range from 3-75 ppm

Toasted partially defatted cooked cottonseed flour may not contain added arsenic compound and therefore may not exceed a maximum natural background level of 0.2 ppm (total arsenic, calculated as As)

OSHA

Permissible Exposure Limit (PEL) = 0.010 mg/m^3

"Comprehensive Standards" for occupational exposure to inorganic arsenic have been developed

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 0.01 mg/m^3 (inorganic compounds); 0.05 ppm (arsine)

NIOSH

Immediately Dangerous to Life and Health (IDLH) = 5 mg/m^3

Ceiling Recommended Exposure Limit = 0.002 mg/m^3 (15-minute)

Listed as a potential occupational carcinogen

*No separate CAS registry number is assigned to arsenic compounds, inorganic.

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