ARSENIC COMPOUNDS, INORGANIC*

First Listed in the *First Annual Report on Carcinogens*

CARCINOGENICITY

Inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC 1987). Many cases of skin cancer have been reported among people exposed to arsenic through medical treatment with inorganic trivalent arsenic compounds. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma, intestinal and urinary bladder cancers, and meningioma. Epidemiological studies of cancer after medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained. No relation was found between prostatic cancer and treatment of syphilis with arsenicals. An association between environmental exposure to arsenic through drinking water and skin cancer has been observed and confirmed. Epidemiological studies in areas where drinking water contained 0.35 to 1.14 mg/L arsenic showed elevated risks for cancers of the bladder, kidney, skin, liver, lung, and colon in both men and women. Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer. An almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure. Other smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of approximately 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and hematolymphatic malignancies. The observation in a study of an increase in lung cancer risk among a population of smelter workers has been confirmed, with a risk of six-fold to eight-fold among roasters. With regard to the histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat cell cancers were observed among smelter workers (IARC 1973, 1980).

An IARC Working Group reported that there is limited evidence of carcinogenicity of inorganic arsenic compounds in experimental animals (IARC 1973, 1980, 1982, 1987). When injected subcutaneously during the first 3 days of life into mice whose mothers had been injected subcutaneously once during gestation, arsenic trioxide induced lung adenomas. When administered by intratracheal instillation, arsenic trioxide induced low incidences of carcinomas, adenomas, papillomas, and adenomatoid lesions of the respiratory tract in hamsters of both sexes. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats. A high incidence of lung carcinomas was induced in rats after a single intratracheal instillation of a pesticide mixture containing calcium arsenate. Intratracheal instillations of calcium arsenate into male hamsters resulted in a borderline increase in the incidence of lung adenomas, whereas no such effect was observed with arsenic trisulfide. When administered in the drinking water, sodium arsenite enhanced the incidence of renal tumors induced in male rats by intraperitoneal injection of *N*-nitrosodiethylamine (IARC 1973, 1980).

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* No separate CAS registry numbers are assigned for arsenic compounds, inorganic.

PROPERTIES

Arsenic occurs naturally in the earth's crust. It occurs most often as the sulfide in a number of complex minerals containing copper, lead, iron, nickel, cobalt, and other metals (ATSDR 2000). Arsenic and certain arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic is not soluble in water; calcium arsenate and calcium arsenites are sparingly soluble in water; the remaining arsenicals are soluble in water. Arsenic pentoxide, potassium arsenite, and the three 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 2001).

USE

The estimated end-use distribution of arsenic in the U.S. in 2000 was 88% in wood preservatives, 4% in agricultural chemicals (principally herbicides and desiccants), 4% in nonferrous alloys, 3% in glass, and 1% in other uses. More than 95% of the arsenic consumed was estimated to have been in compound form, primarily of arsenic trioxide. Production of chrome copper arsenate, a wood preservative, accounted for more than 90% of the domestic consumption of arsenic trioxide. Wood treated with chrome copper arsenate is referred to as "pressure treated wood" and in 1997, approximately 728 million cubic feet of wood product were pressure treated in the U.S. Chrome copper arsenate is widely used in protecting utility poles, building lumber, and foundations from decay and insect attack. Wood preservatives are expected to remain the major domestic use for arsenic. The demand for arsenic in the U.S. should continue to correlate closely with demand for new housing and growth in the renovation or replacement of existing structures using pressure-treated lumber (ATSDR 2000, USGS 2000).

Arsenic is also used in the production of lead alloys used in lead-acid batteries. Arsenic may be added to alloys used for bearing, type metal, lead ammunition, and automotive body solder. It may also be added to brass to improve resistance to corrosion. High purity arsenic is used in a variety of semiconductor applications, including solar cells, light-emitting diodes, lasers, and integrated circuits (ATSDR 2000).

Inorganic arsenic compounds were used in medicine until the 1970s, primarily for treatment of leukemia, psoriasis, and asthma. Currently, there has been a renewed interest in arsenic use for the treatment of acute promyelocytic leukemia (ATSDR 2000).

PRODUCTION

Arsenic has not been produced in the U.S. since 1985, and all arsenic metal and compounds consumed in the U.S. are imported. In 2000, more than 95% of the arsenic consumed was in compound form, principally as arsenic trioxide. Production of chrome copper arsenate accounted for more than 90% of the domestic consumption of arsenic trioxide. The value of arsenic metal and compounds consumed domestically in 2000 was estimated to be $20 million. In 2000, U.S. domestic imports of arsenic metal were 830 metric tons and for arsenic compounds, 23,600 metric tons. The U.S. exported 41 metric tons of arsenic metal in 2000. China was the largest supplier of arsenic to the U.S. in 2000, accounting for most imports of arsenic trioxide (ATSDR 2000, USGS 2000).

Thirteen suppliers of arsenic, 35 suppliers of arsenic trioxide, 16 suppliers of arsenic pentoxide, 13 suppliers of sodium arsenate, three suppliers of lead arsenate, 12 suppliers of calcium arsenate, two suppliers of potassium arsenite, and two suppliers of calcium arsenite were identified in the U.S. in 2001 (Chem Sources 2001). Thirteen manufacturers of arsenic, nine manufacturers of arsenic trioxide, ten manufacturers of arsenic pentoxide, two manufacturers of sodium arsenate, one manufacturer of calcium arsenate, one manufacturer of potassium arsenate, and one manufacturer of calcium arsenite were identified in 2001 (HSDB 2001). There were three principle producers of arsenical wood preservatives in the U.S. in 2000. One of these producers also produces arsenic acid used in the glass industry (USGS 2000).

EXPOSURE

Population exposure to arsenic and arsenic compounds may occur through consumption of foods. Food provides an average intake of about 40 µg of arsenic per person per day. The highest levels 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 and feed additives. Potential consumer exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or improperly disposed arsenical chemicals (ATSDR 2000).

Additionally, the general population is potentially exposed to arsenic compounds through air emissions from pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette tobacco, burning of fossil fuels, and other sources (ATSDR 2000). Arsenic used as color pigments in paints can also be ingested by contamination of hands, fingernails, food, cups, cigarettes, and by holding paint brushes in the mouth (HSDB 2001). EPA's Toxic Chemical Release Inventory (TRI) listed 78 industrial facilities that released arsenic and 518 facilities that released arsenic compounds in 1999 (TRI99 2001). These facilities reported releases of arsenic to the environment of 199,990 lb of arsenic and 11.9 million lb of arsenic compounds.

Since arsenic production no longer occurs in the U.S. and many uses for arsenical pesticides have been banned, the number of workers exposed to arsenic has likely drastically decreased since the early 1980s. NIOSH estimated that 1.5 million industrial workers were potentially exposed to arsenic and its compounds during manufacturing and processing operations. The National Occupational Exposure Survey (1981-1983) indicated that 36,194 total workers, including 4,007 women, were potentially occupationally exposed to arsenic, arsenic pentoxide, arsenic trioxide, or sodium arsenite (NIOSH 1984).

REGULATIONS

The U.S. Consumer Products Safety Commission (CPSC) regulates arsenic sulfide, arsenates, and arsenites by prohibiting the presence of any of the chemicals in fireworks devices.

EPA regulates arsenic and certain arsenic compounds under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Reportable quantities (RQs) have been established under CERCLA and CWA for arsenic (1 lb) and certain

arsenic compounds (arsenic pentoxide, arsenic trioxide, and lead arsenate, 5,000 lb; calcium arsenate, calcium arsenite, potassium arsenite, sodium arsenate, and sodium arsenite, 1,000 lb). The CERCLA RQs for all of these arsenic compounds are 1 pound. Under RCRA, EPA regulates arsenic as a hazardous constituent of waste. EPA limits arsenic in drinking water to a maximum level of 0.05 mg/L (effective in 2006 the maximum level will be lowered to 0.010 mg/L). Under SARA, EPA has established threshold planning quantities (TPQs) for some arsenic compounds and subjects arsenic and arsenic compounds to reporting requirements.

FDA enforces tolerances set by EPA under the FD&CA for residues of pesticides containing arsenic in fruits and vegetables, field crops, and livestock. FDA has also set tolerance limits for the residue of arsenic compounds when used as veterinary drugs and in the feed and drinking water of animals, as well as food, color additives, and bottled water.

Based on evidence of carcinogenicity in humans, NIOSH recommends a ceiling limit of 2 $\mu g/m^3$ (15 min) as a recommended expsosure limit (REL) for arsenic and inorganic compounds, as arsenic. OSHA regulates arsenic and arsenic compounds under the Hazard Communication Standard and as chemical hazards in laboratories. OSHA has promulgated a standard of 10 $\mu g/m^3$ for occupational exposure to inorganic arsenic compounds. Additionally, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls. Regulations are summarized in Volume II, Table 15.

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