CASARETT & DOULL'S TOXICOLOGY 5th EDITION

by a variety of toxic effects including hypotension, skin rashes, and, possibly, cataract formation. It seems to be more effective in hemosiderosis due to blood transfusion but is less effective in treatment of hemochromatosis.

Dithiocarbamate (DTC)

Dithiocarb (diethyldithiocarbanate), or DDC, has been recommended as the drug of choice in the treatment of acute nickel carbonyl poisoning. The drug may be administered orally for mild toxicity and parenterally for acute or severe poisoning (Sunderman, 1979). It has also been used experimentally for removal of cadmium bound to metallothionein (Kojima et al., 1990). A number of DTC compounds with various substitutions of nonpolar, nonionizing groups have been synthesized by Jones and Cherian (1990). Sodium, *N*-(4-methoxybenzyl)-D-glucamine dithiocarbamate (MeOBGDTC) is one of the most effective in removal of cadmium from tissues. The Cd–MeOBGDTC complex is excreted in the bile rather than in the kidney, avoiding the nephrotoxicity characteristic of cadmium chelates. To date the use of this compound has been limited to experimental studies in rodents.

MAJOR TOXIC METALS WITH MULTIPLE EFFECTS

Arsenic

Arsenic is particularly difficult to characterize as a single element because its chemistry is so complex and there are many different arsenic compounds. It may be trivalent or pentavalent and is widely distributed in nature. The most common inorganic trivalent arsenic compounds are arsenic trioxide, sodium arsenite, and arsenic trichloride. Pentavalent inorganic compounds are arsenic pentoxide, arsenic acid, and arsenates, such as lead arsenate and calcium arsenate. Organic compounds may also be trivalent or pentavalent, such as arsanilic acid, or may even occur in methylated forms as a consequence of biomethylation by organisms in soil, fresh water, and seawater. A summary of environmental sources of arsenic as well as their potential health effects is contained in the U.S. EPA document on arsenic (EPA, 1987b).

Inorganic arsenic is released into the environment from a number of anthropogenic sources which include primary copper, zinc, and lead smelters, glass manufacturers that add arsenic to raw materials, and chemical manufacturers. The National Air Sampling Network tests conducted by the U.S. EPA indicate that in areas not influenced by copper smelters, maximum 24-h concentrations do not exceed 0.1 $\mu g/m^3$. In near point emissions (copper smelters), concentrations may exceed 1 $\mu g/m^3$. Drinking water usually contains a few micrograms per liter or less. Most major U.S. drinking water supplies contain levels lower than 5 μg per liter. It has been estimated that about 350,000 people might drink water containing more than 50 μg per liter (Smith et al., 1992). Levels exceeding 50 μg per liter have been found in Nova Scotia where the arsenic content of bedrock is high. Even higher concentrations, exceeding the 50 μg per liter standard have also been reported from various mineral springs (e.g., in Japan, 1.7 mg As/liter; in Cordoba, Argentina, 3.4 mg per liter; in Taiwan, from artesian well water, 1.8 mg per liter). Most foods (meat and vegetables) contain some level of arsenic, but the daily diet in the United States generally contains below 0.04 mg; however, it may contain 0.2 mg per day if the diet contains seafood. Dietary arsenic notwithstanding, the total daily intake of arsenic by humans without industrial exposure is usually less than 0.3 mg per day.

The major source of occupational exposure to arsenic in the United States is in the manufacture of pesticides, herbicides, and other agricultural products. High exposure to arsenic fumes and dust may occur in the smelting industries; the highest concentrations most likely occur among roaster workers.

Toxicokinetics. Airborne arsenic is largely trivalent arsenic oxide, but deposition in airways and absorption from lungs is dependent on particle size and chemical form. Six to nine percent of orally administered ^{74}As-labeled trivalent or pentavalent arsenic is eliminated in the feces of mice, indicating almost complete absorption from the gastrointestinal tract. Limited data also suggest nearly complete absorption of soluble forms of trivalent and pentavalent arsenic. Excretion of absorbed arsenic is mainly via urine. The biological half-life of ingested inorganic arsenic is about 10 h and 50 to 80 percent is excreted in about 3 days. The biological half-life of methylated arsenic is about 30 h.

Arsenic has a predilection for skin and is excreted by desquamation of skin and in sweat, particularly during periods of profuse sweating. It also concentrates in nails and hair. Arsenic in nails produces Mee's lines (transverse white bands across fingernails), which appear about 6 weeks after the onset of symptoms of toxicity. The time of exposure may be estimated from measuring the distance of the line from the base of the nail and the rate of nail growth, which is about 0.3 cm per month or 0.1 mm per day. Arsenic in hair may also reflect past exposure, but intrinsic or systematically absorbed arsenic in hair must be distinguished from arsenic that is deposited from external sources. Human milk contains about 3 μg per liter of arsenic.

Placental transfer of arsenic has been shown in hamsters injected intravenously with high doses (20 mg/kg body weight) of sodium arsenate, and studies of tissue levels of arsenic in fetuses and newborn babies in Japan show that the total amount of arsenic in the fetus tends to increase during gestation, indicating placental transfer. A study of pregnant women in the United States found cord blood levels of arsenic to be similar to maternal blood levels (Kagey et al., 1977).

Biotransformation of Arsenic In Vivo. The metabolism and potential for toxicity of arsenic is further complicated by in vivo transformation of inorganic forms by methylation to monomethyl and dimethyl arsenic. Current knowledge of this process has been summarized by Styblo and colleagues (1995). Dimethyl arsenic is the principal transformation product. This is presumed to be a process of detoxification of the more toxic inorganic forms, and dimethyl arsenic appears to be a terminal metabolite which is rapidly formed and rapidly excreted. However, exposure to inorganic arsenic may exceed the rate of its transformation, resulting in toxicity from the inorganic form, so that consideration of toxic dose–responses to inorganic arsenic must be assessed in the light of what is known about metabolic transformation. Ingestion of arsenic-containing seafood does not result in the increased excretion of inorganic arsenic and methylarsinic and dimethylarsinic

acid, but rather it results in large increases in excretion of cacodylic acid (Buchet et al., 1980).

Oxidation and Reduction Reactions of Inorganic Arsenic. A number of experiments in animals suggest that reduction of pentavalent arsenic to arsenic trioxide occurs in vivo. The biochemical mechanism for in vivo methylation of inorganic arsenic is a reductive process, and it is presently presumed that reduction of arsenic in vivo is related to biomethylation. Lerman and coworkers (1983) found, using in vitro techniques, that in the rat isolated hepatocytes readily methylate trivalent arsenic while there is virtually no methylation of pentavalent arsenic. These studies suggest that pentavalent arsenic must first be converted to arsenite prior to methylation. Trivalent inorganic arsenic undergoes extensive oxidation in aerated water. The pH of aqueous solutions appears to be a major factor in the relative stability of either valency form. Trivalent arsenic in alkaline solutions is more rapidly oxidized than at acidic pH. Pentavalent inorganic arsenic is, by contrast, relatively stable at neutral or alkaline pH but undergoes reduction with decreasing pH.

Cellular Effects. It has been known for some years that trivalent compounds of arsenic are the principal toxic forms, and pentavalent arsenic compounds have little effect on enzyme activity. A number of sulfhydryl-containing proteins and enzyme systems have been found to be altered by exposure to arsenic. Some of these can be reversed by addition of an excess of a monothiol such as glutathione. Effects on enzymes containing two thiol groups can be reversed by dithiols such as 2,3-dimercaptopropanol (BAL) but not by monothiols.

Arsenic affects mitochondrial enzymes and impairs tissue respiration (Brown et al., 1976), which seems to be related to the cellular toxicity of arsenic. Mitochondria accumulate arsenic, and respiration mediated by NAD-linked substrates is particularly sensitive to arsenic and is thought to result from a reaction between the arsenite ion and the dihydrolipoic acid cofactor, which is necessary for oxidation of the substrate (Fluharty and Sanadi, 1961). Arsenite also inhibits succinic dehydrogenase activity and uncouples oxidative phosphorylation, which results in stimulation of mitochondrial ATPase activity. Mitchell et al. (1971) proposed that arsenic inhibits energy-linked functions of mitochondria in two ways: competition with phosphate during oxidative phosphorylation and inhibition of energy-linked reduction of NAD.

Arsenic compounds are inducers of metallothionein in vivo. Potency is dependent on the chemical form of arsenic. As(III) is most potent, followed by As(V), monomethylarsenate, and dimethylarsenate (Kreppel et al., 1993).

Information from experimental studies with rats, chicks, minipigs and goats have shown that arsenic in its inorganic form may be an essential nutrient, but the nutritional essentiality for humans has not been established (EPA, 1987b).

Toxicology. Ingestion of large doses (70 to 180 mg) of arsenic may be fatal. Symptoms of acute illness, possibly leading to death, consist of fever, anorexia, hepatomegaly, melanosis, and cardiac arrhythmia with changes in electrocardiograph results that may be the prodroma of eventual cardiovascular failure. Other features include upper-respiratory-tract symptoms, peripheral neuropathy, and gastrointestinal, cardiovascular, and hematopoietic effects. Acute ingestion may be suspected from damage to mucous membranes such as irritation, vesicle formation, and even sloughing. Sensory loss in the peripheral nervous system is the most common neurological effect, appearing 1 or 2 weeks after large exposures and consisting of Wallerian degeneration of axons, a condition that is reversible if exposure is stopped. Anemia and leukopenia, particularly granulocytopenia, occur a few days following exposure and are reversible.

Chronic exposure to inorganic arsenic compounds may lead to neurotoxicity of both the peripheral and central nervous systems. Neurotoxicity usually begins with sensory changes, paresthesia, and muscle tenderness followed by weakness, progressing from proximal to distal muscle groups. Peripheral neuropathy may be progressive involving both sensory and motor neurones leading to demyelination of long axon nerve fibers, but effects are dose related. Acute exposure to a single high dose can produce the onset of paresthesia and motor dysfunction within 10 days. More chronic occupational exposures producing more gradual, insidious effects may occur over a period of years, and it has been difficult to establish dose–response relationships.

Liver injury, characteristic of longer-term or chronic exposure, manifests itself initially in jaundice and may progress to cirrhosis and ascites. Toxic effects on hepatic parenchymal cells result in the elevation of liver enzymes in the blood, and studies in experimental animals show granules and alterations in the ultrastructure of mitochondria, nonspecific manifestations of cell injury including loss of glycogen.

Peripheral vascular disease has been observed in persons with chronic exposure to arsenic in drinking water in Taiwan and Chile; it is manifested by acrocyanosis and Raynaud's phenomenon and may progress to endarteritis obliterans and gangrene of the lower extremities (blackfoot disease). This specific effect seems to be related to the cumulative dose of arsenic, but the prevalence is uncertain because of difficulties in separating arsenic-induced peripheral vascular disease from other causes of gangrene. Recently, Engel and Smith (1994) found an increase in mortality from vascular disease for U.S. counties where arsenic in drinking water exceeded 20 μg/dl but the authors recognize that the relationship may be spurious.

Carcinogenicity. The EPA (1987b) and IARC (1987) classify arsenic as a carcinogen for which there is sufficient evidence from epidemiological studies to support a causal association between exposure and skin cancer. In humans, chronic exposure to arsenic induces a series of characteristic changes in skin epithelium, proceeding from hyperpigmentation to hyperkeratosis. The hyperkeratosis has been described histologically as showing hematin proliferation of a verrucose nature with derangement of the squamous portions of the epithelium or squamous cell carcinoma in some cases. There may actually be two cell types of arsenic-induced skin cancer, basal cell carcinomas and squamous cell carcinomas arising in keratotic areas. The basal cell cancers are usually only locally invasive but squamous cell carcinomas may have distant metastases. The skin cancers related to arsenic differ from ultraviolet-light–induced tumors in that they generally occur on areas of the body not exposed to sunlight (e.g., on palms and soles) and they occur as multiple lesions.

Occupational exposure to airborne arsenic may also be associated with lung cancer, usually a poorly differentiated form of epidermoid bronchogenic carcinoma. The time period between initiation of exposure and occurrence of arsenic-associated lung cancer has been found to be in the order of 35 to 45 years. Enterline and Marsh (1980) report a latency period of 20 years in their study of copper smelter workers in Tacoma, Washington.

Other visceral tumors that have been associated with arsenic exposure include hemangiosarcoma of the liver. Other cancers noted in arsenic-exposed subjects include lymphomas, leukemia, and nasopharyngeal, kidney and bladder cancers. Smith et al. (1992) estimate that the lifetime risk of dying from cancers of the liver, lung, kidney or bladder could be as high as 13 per 1000 for persons drinking 1 liter per day of water containing more than 50 μg of arsenic per liter.

In contrast to most other human carcinogens, it has been difficult to confirm the carcinogenicity of arsenic in experimental animals. Intratracheal instillations of arsenic trioxide produced an increased incidence of pulmonary adenomas, papillomas, and adenomatoid lesions, suggesting that arsenic trioxide can induce lung carcinomas (Pershagan et al., 1984), but other studies testing As(III) and As(V) compounds by oral administration or skin application have not shown potential for either promotion or initiation of carcinogenicity. Similarly, experimental studies for carcinogenicity of organic arsenic compounds have been negative.

Studies on mutagenic effects of arsenic have been generally negative. Arsenic does not induce gene mutations in bacteria and was found to be inactive in inducing reverse mutation and mitotic gene conversion in yeast. Arsenate was found not to increase forward mutations at the thymidine kinase locus in mouse L51784 cells whereas other known or suggested mutagenic metals (cadmium, nickel, and trans-platinum) showed such activity.

Several studies suggest that both As(III) and As(V) compounds are capable of producing chromosome breaks and chromosome aberrations in human peripheral lymphocyte and human skin cultures. The majority of studies indicate, however, that people with workplace or pharmaceutical exposure to arsenic have increased levels of chromosomal aberrations and sister chromosome exchanges in peripheral lymphocytes, although the scientific rigidity of some of these studies has been questioned (EPA, 1987).

Reproductive Effects and Teratogenicity. High doses of inorganic arsenic compounds given to pregnant experimental animals produced various malformations in fetuses and offspring that were somewhat dependent on time and route of administration. However, no such effects have been noted in humans with excessive occupational exposures to arsenic compounds.

Arsine. Arsine gas is formed by the reaction of hydrogen with arsenic and is generated as a by-product in the refining of nonferrous metals. Arsine is a potent hemolytic agent, producing acute symptoms of nausea, vomiting, shortness of breath, and headache accompanying the hemolytic reaction. Exposure may be fatal and may be accompanied by hemoglobinuria and renal failure, and even jaundice and anemia in nonfatal cases when exposure persists (Fowler and Weissberg, 1974).

Biological Indicators. Biological indicators of arsenic exposure are blood, urine, and hair (Table 23-3). Because of the short half-life of arsenic, blood levels are only useful within a few days of acute exposure but are not useful in assessing chronic exposure. Urinary arsenic is the best indicator of current on recent exposure and has been noted to be several hundred micrograms per liter with occupational exposure. However, some marine organisms may contain very high concentrations of organoarsenicals which do not have significant toxicity and are rapidly excreted in urine without transformation (Lauwerys, 1983). Workers should be advised not to ingest seafood for a day or two before testing. Hair or even fingernail concentrations of arsenic may be helpful in evaluating past exposures, but interpretation is made difficult because of the problem of differentiating external contamination.

There are no specific biochemical parameters that reflect arsenic toxicity, but evaluation of clinical effects must be interpreted with a knowledge of exposure history.

Treatment. BAL is used to treat acute dermatitis and the pulmonary symptoms of excess arsenic exposure. BAL has also been used for the treatment of chronic arsenic poisoning, but there are no established biological criteria or measures of effectiveness. BAL has been used most often in cases of dermatitis, but there is usually no change in the keratotic lesions or influence on the progression to skin cancer.

Arsine toxicity is best treated symptomatically. BAL is not considered helpful (Fowler and Weissberg, 1974).

Beryllium

Beryllium is an uncommon metal with a few specific industrial uses. Environmental sources and toxicological effects of beryllium are reviewed in detail in an EPA Health Criteria Document (EPA, 1987a; WHO, 1990a). Beryllium in the environment largely results from coal combustion. Illinois and Appalachian coal contains an average of about 2.5 ppm; oil contains about 0.08 ppm. The combustion of coal and oil contributes about 1250 or more tons of beryllium to the environment each year (mostly from coal), which is about five times the annual production for industrial use. The major industrial processes that release beryllium into the environment are beryllium extraction plants, ceramic plants, and beryllium alloy manufacturers. These industries also provide the greatest potential for occupational exposure. Currently, the major use for beryllium is as an alloy, but about 20 percent of world production is for applications utilizing the free metal in nuclear reactions, x-ray windows, and other special applications related to space optics, missile fuel, and space vehicles.

Table 23-3
Biological Indicators of Arsenic Exposure

	NORMAL	EXCESSIVE EXPOSURE
Whole blood	1–4 μg/L	Up to 50 μg/L
Urine*	< 10 μg/L	> 100 μg/L
Hair	< 1 μg/kg	

* Best indicator of current or recent exposure.