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Arsenic—State of the Art

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Approximately 1.5 million workers in the United States are exposed to arsenic. Occupational exposure is primarily by inhalation. NIOSH recommends that time-integrated exposure to arsenic in air not exceed 2 $\mu g/m^3$. Recent exposure is accurately measured by urine assay; urine arsenic concentrations above 50 μg/liter indicate increased absorption. Hair assay is a semiquantitative index of past exposure. Toxicity is associated primarily with the trivalent (3+) form of arsenic. Acute poisoning is caused most commonly by contaminated food or drink; it is rarely occupational. Chronic intoxication is characterized by dermatitis, hyperpigmentation, keratoses, peripheral neuropathy (primarily sensory), irritation of the upper and lower respiratory tract, and occasionally by hepatic toxicity and peripheral vasculopathy (blackfoot disease). Arsenic is not carcinogenic in animal species, but is mutagenic in Syrian hamster cells. In man, arsenic is known definitely to cause cancer of skin, lung, and liver (angiosarcoma) and possibly to cause lymphoma.

Key words: arsenic, mutagenesis, lung cancer, angiosarcoma of liver, skin cancer, neuropathy

INTRODUCTION

Arsenic is a metalloid element, a member of group V of the periodic table [National Academy of Sciences, Committee on Medical and Biological Effects of Environmental Pollutants, 1977].

Consumption of arsenic in the United States is estimated to range from 25,000 to 35,000 tons per year [National Institute for Occupational Safety and Health, 1975]. Of this amount, 6000–14,000 tons are produced domestically. The principal sources are the ores of copper, as well as of lead and zinc, from which arsenic is removed as an impurity during smelting. The National Institute for Occupational Safety and Health (NIOSH) estimates that 1.5 million workers in the United States have the potential for occupational exposure to inorganic arsenic, including arsine and lead arsenate; 660,000 of these workers

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are directly involved in the commercial cycle of arsenic. Approximately 80% of the arsenic consumed each year in the United States is used in the manufacture of pesticides, herbicides, and other agricultural products.

HUMAN EXPOSURE

Human exposure to arsenic and its compounds occurs mainly either through ingestion, particularly of seafood [Jelinek et al, 1977], or through inhalation of arsenic-containing airborne particulates. Major occupational exposure occurs in smelting [Milham, Jr et al, 1974], but has been reported also in the chemical [Hill et al, 1948], pesticide [Mabuchi et al, 1979], and pharmaceutical industries [Watrous et al, 1945]. NIOSH has recently observed an increased exposure to airborne arsenic and elevated urinary arsenic excretion in workers using lead-arsenic alloys ("hard lead") in the manufacture of lead-acid batteries [Costello et al, 1980]. In populations without occupational or other unusual exposure to arsenic, the daily absorbed dose is calculated to be less than 40–50 μg. [Nordberg et al, 1979].

Excretion of arsenic is mainly via the urine. In primates, excretion after a single injected dose is essentially complete in six days [Charbonneau et al, 1978]. In man, the biological half-life of arsenic in blood was measured by Mealey et al after intravenous injection of radioactive arsenic (^{74}As) to patients with terminal cancer [1959]. Excretion proceeded in three phases: plasma was cleared in 10 hours, the main portion of the dose was excreted in 30 hours, and a small residual fraction had a half-life of eight days. The overall half-life of ingested inorganic arsenic in man has been calculated to be 10 hours. Those observations are corroborated by the data of Milham and Strong [1974], who found that arsenic levels in the urine of children living downwind of an arsenic-emitting copper smelter in Tacoma, Washington, decreased sharply within 2–3 days following a change in the prevailing wind direction.

Human absorption or the "body burden" of arsenic has been assessed through the measurement of the total arsenic concentrations in blood, hair, and urine [Harrington et al, 1978]. Because of the short half-life of arsenic in blood [Mealey et al, 1959; Charbonneau et al, 1978], the blood arsenic determination has been found to be of little practical value [Nordberg et al, 1979].

The determination of arsenic in the hair has been found to be a useful, semiquantitative indicator of past exposure to arsenic. In a nationwide survey in the United States of children living near primary smelters, the Center for Disease Control (CDC) found that the mean hair arsenic concentration in 972 children from 11 towns with copper smelters was 2.60 μg/gram; the highest concentration (19.88 μg/gram) being found in Anaconda, Montana, the most heavily polluted town in the study [Baker et al, 1977]. By contrast, the mean hair arsenic content in 160 children from three comparison towns without smelters was 0.09 μg/gram ($t = 9.72$, $p < 0.01$). The major drawback to the determination of arsenic in hair is that it does not distinguish systemically absorbed from externally deposited arsenic. Thus the intrinsic arsenic content of hair can be modified by such external sources as bathing in arsenic-contaminated water, by contamination with arsenic excreted in sweat, or by exposure to airborne arsenic.

The urine arsenic concentration appears to be the best indicator of current or of recent (1–3 days) past exposure to arsenic [Harrington et al, 1978]. However, it is very important, as noted previously [Milham, Jr et al, 1974], to consider the timing of the

collection of samples in assessing the biological significance of the arsenic concentration in urine. A study conducted in Fairbanks, Alaska, found a high correlation coefficient ($r = 0.58$) between arsenic concentrations in the water and urine of drinkers of contaminated well water [Harrington et al, 1978]. Also, in studies of children who lived near smelters, the CDC group found a mean urine arsenic content of 18.7 μg/liter in 712 children from 11 towns with smelters and of 5.8 μg/liter in 193 children from three comparison towns ($t = 10.75$; $p < 0.01$) [Baker et al, 1977]. Milham and Strong [1974] found that the mean urine arsenic concentration was 300 μg/liter in children living at a distance of 0.0–0.4 miles from an arsenic-emitting copper smelter in Tacoma, Washington, and decreased to 20 μg/liter at a distance of 2.0–2.4 miles.

Although the range of values considered "normal" in previous studies of urine arsenic concentration has varied, due primarily to differences in laboratory methods, most urine arsenic concentrations in unexposed populations have been found to be below 50 μg/liter [Webster, 1941; Milham, Jr et al, 1974; Baker et al, 1977; Harrington et al, 1978; Morse et al, 1979; Rosenberg et al, 1980]. Three studies, one by Schrenk and Schreibeis [1958], one by Perry et al [1948], and a third by Pinto and McGill [1953] reported mean urinary arsenic concentrations in allegedly unexposed persons of 80, 85, and 130 μg/liter respectively; however, in each of those studies, persons in the control groups either worked in proximity to arsenic-contaminated areas or had had previous occupational exposure to arsenic.

ARSENIC TOXICITY

For the most part, the toxicity of trivalent ($+3$) arsenic has been found to be greater than that of the pentavalent ($+5$) form.

Acute Poisoning

Acute arsenic poisoning is rare in the occupational setting and results principally from the ingestion of contaminated food or drink. The major symptoms are those of profound gastrointestinal inflammation, sometimes with hemorrhage, and of cardiogenic shock [National Academy of Sciences, Committee on Medical and Biological Effects of Environmental Pollutants, 1977]. Symptoms resemble those of cholera and may include difficulty in swallowing, abdominal pain, projectile vomiting, "rice-water" diarrhea, dehydration, a weak irregular pulse, and a loss of blood pressure that is followed by the development of stupor, coma, convulsions, and death. The fundamental lesion appears to be dilation and increased permeability of the small blood vessels in the gastrointestinal tract and elsewhere. Pathological examination shows extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine. The necrosis sometimes progresses to perforation of the gut wall. Fatty degeneration of the liver and kidneys has been observed.

Subacute and Chronic Toxicity

Chronic arsenic intoxication is best discussed in terms of the organ systems affected—the skin, nervous system, liver, cardiovascular system, hematopoietic system, and respiratory tract.

Skin Toxicity

Chronic arsenic exposure has been found in many studies to be associated with dermatitis [Holmquist, 1951; Birmingham et al, 1965]. The dermatitides caused by arsenic have been classified as eczematous and follicular [Holmquist, 1951]. Conjunctivitis and rhinitis frequently may accompany arsenical dermatitis. Chronic exposure to arsenic has been shown to produce hyperpigmentation, warts (arsenical keratoses) [Perry et al, 1948], and hyperkeratosis of the palms and soles [Tseng, 1977; Nordberg et al, 1979].

Arsenic exposure has been associated with three types of skin cancer—Bowen's disease, basal cell carcinoma, and squamous cell carcinoma [Nordberg et al, 1979]; these cancers are frequently multiple in origin and develop primarily from arsenical keratoses. The prevalence of arsenic-related skin cancer appears to be related to the total absorbed dose of arsenic [Tseng, 1977; Nordberg et al, 1979]. Excess mortality due to arsenic-induced skin cancer has been observed in the chemical [Perry et al, 1948] and wine-producing industries [Roth, 1958], as well as from the consumption of contaminated water [Tseng, 1977]. Numerous cases of skin cancer have been attributed to the use of medications containing arsenic [Nordberg et al, 1979].

Neurologic Toxicity

Peripheral neuropathy affecting primarily sensory function has been encountered in several studies of persons with chronic exposure to arsenic [Heyman et al, 1956; Hindmarsh et al, 1977]. A very large outbreak occurred in England in 1900 as the result of widespread consumption of arsenic-contaminated beer (Royal Commission on Arsenical Poisoning, 1901). In a study conducted in Nova Scotia of 92 persons chronically exposed to arsenic in well water, Hindmarsh et al [1977] found that the prevalence of sensory and motor symptoms correlated positively with the concentration of arsenic in well water as well as with the arsenic content in hair. Also, a positive association was found between well water and hair arsenic concentrations and the prevalence of electromyographic (EMG) abnormalities. Clinical experience suggests that the neuropathy which follows exposure to arsenic is at least partially reversible [Nordberg et al, 1979].

Hearing loss, possibly reflecting arsenic toxicity to the eighth cranial nerve, was reported in a study conducted in Czechoslovakia among 56 children who lived near a power plant that burned coal with a high arsenic content and released arsenic-contaminated fly ash [Bencko et al, 1977]. However, no hearing impairment was observed by Milham in children living near the arsenic-emitting copper smelter in Tacoma, Washington [Milham, Jr, 1977].

Liver Toxicity

The chronic absorption of arsenic occasionally produces hepatocellular toxicity which may be the result of an inhibition by arsenic of the enzymes involved in cellular respiration [Fowler, 1977]. Trivalent arsenic binds readily to sulfhydryl groups of enzymes and has been shown to inhibit pyruvate dehydrogenase function [Schiller et al, 1977]; that alteration has been correlated with the swelling and distortion of the hepatic mitochondria [Fowler et al, 1979]. Chronic exposure to arsenic has been reported to produce reversible liver enlargement and has been associated with cirrhosis of the liver [Lee et al, 1969; Nordberg et al, 1979].

Angiosarcoma of the liver has been associated with arsenic exposure. Exposure in those cases has been through the drinking of contaminated wine [Roth, 1958] or through use of Fowler's solution [Falk et al, 1980]. Angiosarcoma of the liver was observed recently in a two-year-old girl who had been exposed to arsenic in the air, dust, soil, and water near an arsenic-emitting-copper smelter in Ajo, Arizona [Falk et al, 1980].

Cardiovascular Toxicity

Peripheral vascular disease has been observed among persons in Chile [Borgono et al, 1971] and in Taiwan [Tseng, 1977] who had had chronic exposure to arsenic in drinking water. Early symptoms included acrocyanosis and Raynaud's phenomenon. Those changes were associated with hyperpigmentation and hyperkeratosis. They progressed in severe cases to frank gangrene of the extremities ("blackfoot disease") [Tseng, 1977], associated with endarteritis obliterans. In Chile, infants and children showed more pronounced vascular symptoms than adults, and myocardial infarction was reported even in children [Borgono et al, 1971]. The prevalence and severity of blackfoot disease appeared to be related to the dose of ingested arsenic [Tseng, 1977].

Hematopoietic Toxicity

Chronic exposure to arsenic has been associated with disturbed erythropoiesis, and megaloblastic formation has been noted [Nordberg et al, 1979]. These changes may reflect the inhibitory effects of arsenic on cellular respiration [Schiller et al, 1977]. Depression of delta aminolevulinic acid synthetase and of ferrochelatase activity in experimental animals dosed with arsenic has been reported [Woods et al, 1977].

Increased mortality due to malignant neoplasms of lymphatic and hematopoietic tissues has been noted in two studies of workers exposed to arsenic [Ott et al, 1974; Axelson et al, 1978]. The number of cases cited in each of those reports was, however, small and further evaluation will be required.

Respiratory Toxicity

In the smelting industry, inflammatory and erosive lesions of the respiratory mucosa, including perforation of the nasal septum, have been observed in workers exposed to airborne arsenic [Pinto et al, 1953]. Frequently in smelting there are, however, concomitant exposures to sulfur dioxide and to other metallic and unspecified particulates. Thus it is difficult in that environment to distinguish among the irritative effects of the various agents.

Lung cancer has been found to account for excess mortality in several populations of smelter workers exposed to arsenic trioxide. In Anaconda, Montana, Lee and Fraumeni found a threefold excess mortality from respiratory cancer over statewide rates in a group of 8047 white male workers [1969]. There was a systematic gradient in lung cancer mortality according to the duration and intensity of arsenic exposure within that population, and in the subgroup of workers with the heaviest and longest (>15 years) exposure, excess mortality from lung cancer was found to be increased eightfold over expected. In the Lee and Fraumeni study, because of the nature of smelter operations, exposures to arsenic and to sulfur dioxide were inextricably linked.

Previous studies of workers at the Tacoma, Washington, smelter produced conflicting results in regard to lung cancer mortality [Pinto et al, 1963; Milham, Jr et al, 1974]. However, a more recent analysis of mortality patterns at the plant showed a threefold excess mortality from lung cancer (standardized mortality ratio, SMR = 300.3) in all workers aged 65 and over [Pinto et al, 1977]. When workers were subdivided according to the extent of their exposure, SMRs for respiratory cancer were found to increase from 165.6 in the least heavily exposed group to 810.5 in the most heavily exposed (Fig. 1).

At the smelter in Garfield, Utah, Rencher and Carter [1971] found a threefold excess mortality from lung cancer in smelter workers as compared to statewide Utah rates and a fivefold excess as compared to miners employed by the same company (Table I). Among the smelter workers, cumulative exposure indices for persons who died of lung cancer were high not only for arsenic but also for sulfur dioxide, sulfuric acid mist, lead, and copper. Rencher and Carter found evidence for interactive effects on lung cancer mortality between occupational exposures and smoking (Table II). A subsequent analysis of mortality at the Utah smelter by Milby and Hine found no increase in lung cancer rates when compared to United States or Utah rates [1974]. However, the study by Milby and Hine excluded from analysis certain categories of exposed workers and included many workers who did not have a significant exposure to arsenic.

Excess mortality from lung cancer has been reported in smelter workers exposed to arsenic trioxide in Japan [Kuratsune et al, 1974] and in Sweden [Pershagen et al, 1977; Axelson et al, 1978]. In the Swedish studies, the overall SMR for lung cancer mortality in smelter workers was 504.

A criticism of the studies of lung cancer in smelter workers exposed to arsenic is that they do not resolve the question of whether arsenic alone is a lung carcinogen or whether concomitant exposure to sulfur dioxide or to other dusts is necessary for the development of lung cancer [National Academy of Sciences, Committee on Medical and Biological Effects of Environmental Pollutants, 1977]. Evidence from studies in other industries helps, however, to resolve that issue. Pesticide manufacturing workers in the United Kingdom [Hill et al, 1948] and in the United States [Ott et al, 1974] who were exposed to arsenic but who had no occupational exposure to sulfur dioxide were found in separate studies to have a three to fourfold excess mortality from respiratory cancer. Likewise, a study of 1393 pesticide workers in Baltimore found a significant excess mortality (SMR = 168) over Baltimore city rates in all workers exposed to arsenic [Mabuchi et al, 1979]. A positive dose-response relationship was noted in that study between lung cancer mortality and the duration of arsenic exposure; SMRs ranged less than 100 in workers exposed for under one year to 2750 (2 observed vs. 0.1 expected) in workers heavily exposed for 25 or more years. Excess lung cancer mortality has also been observed in arsenic-exposed workers employed as vineyard-sprayers in Germany [Roth, 1958] and as underground gold miners in Rhodesia [Osburn, 1969].

In toto, the results from these studies indicate that neither sulfur dioxide nor other smelter dusts nor cigarette smoking are essential co-factors for the respiratory carcinogenicity of arsenic. Although each of these factors may interact with arsenic in the production of respiratory cancer, the data from these studies provide sufficient evidence that arsenic is itself a lung carcinogen in man. Further epidemiologic studies of possible interactions between arsenic and other materials might be of considerable academic interest. There is, however, no reason to delay reduction of occupational or environmental exposure to arsenic while awaiting the results of such studies.

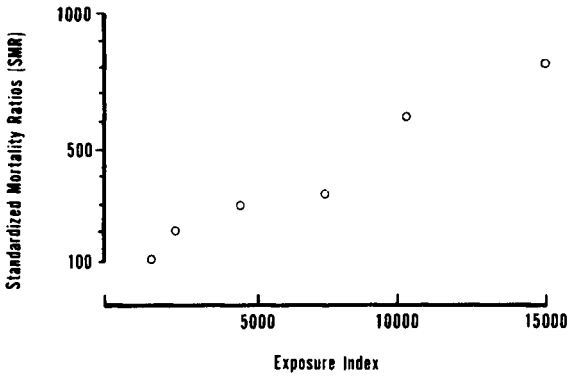

Fig. 1.—Standardized mortality ratios (SMRs) related to total arsenic exposure in smelter workers—Tacoma, Washington. Source: Pinto et al [1977].

TABLE I. Age-Adjusted Death Rates per 10,000 at Risk (Kennecott Mine and Smelter, Garfield, Utah, and State of Utah)

	Smelter	Mine	State
All causes	149.8	121.8	121.2
Lung cancer	10.1	2.1	3.3

From Rencher, Carter, and McKee [1977].

TABLE II. Lung Cancer Deaths as a Percentage of Total Deaths in Smokers and Nonsmokers (Kennecott Mine and Smelter, Garfield, Utah)

	Smokers	Nonsmokers
Smelter	9.2	3.3
Mine	3.3	0.7
Concentrator	3.3	0.8

From Rencher, Carter, and McKee [1977].

Animal Studies of Arsenic Carcinogenicity

A continuing paradox in the study of the carcinogenicity of arsenic has been an inability to establish a model of arsenic carcinogenicity in any animal species [National Academy of Sciences, Committee on Medical and Biological Effects of Environmental Pollutants, 1977]. The basis for this failure is not known. A recent Japanese study in which either arsenic trioxide or smelter dust was administered to groups of rats by intratracheal instillation showed an increased occurrence of lung cancer in the animals given smelter dust, but not in those administered the pure arsenic compound (although

one benign pulmonary adenoma was observed in the arsenic-trioxide treated group) [Ishinishi et al, 1977]. Good inhalation toxicity studies of animals exposed to arsenic have, however, not been reported.

Mutagenic Effects of Arsenic

Studies of mutagenesis due to arsenic have not been uniformly positive in bacterial cell systems (eg, Ames test)[Sunderman, Jr, 1979], possibly because of the toxicity of arsenical compounds to such systems. However, in Syrian hamster embryo cells, arsenic was found to cause cell transformation [DiPaolo et al, 1979] and also to enhance the frequency of transformation induced by the SA7 virus [Casto et al, 1979]. In addition, arsenic has been found to induce aberrant DNA synthesis and to produce chromosomal aberrations in tissue culture cells [Sunderman, Jr, 1979].

Smelter workers exposed to arsenic were found in a Swedish study to have an increased frequency of chromosomal aberrations as compared to controls [Nordenson et al, 1978]. Although the mechanism which may have accounted for that observation is not known, the authors speculated that arsenic may have acted by inhibiting DNA repair.

In conclusion, the available epidemiologic and toxicologic data, despite the absence of an animal model for arsenic carcinogenesis, indicate that arsenic is a toxin and carcinogen in man. Arsenic has been found to cause cancer of the skin, liver, and lung, and possibly of the hematopoietic and lymphatic tissues. It should be treated accordingly.

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