EPA-540/1-86-020

Office of Emergency and
Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
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Cincinnati OH 45268

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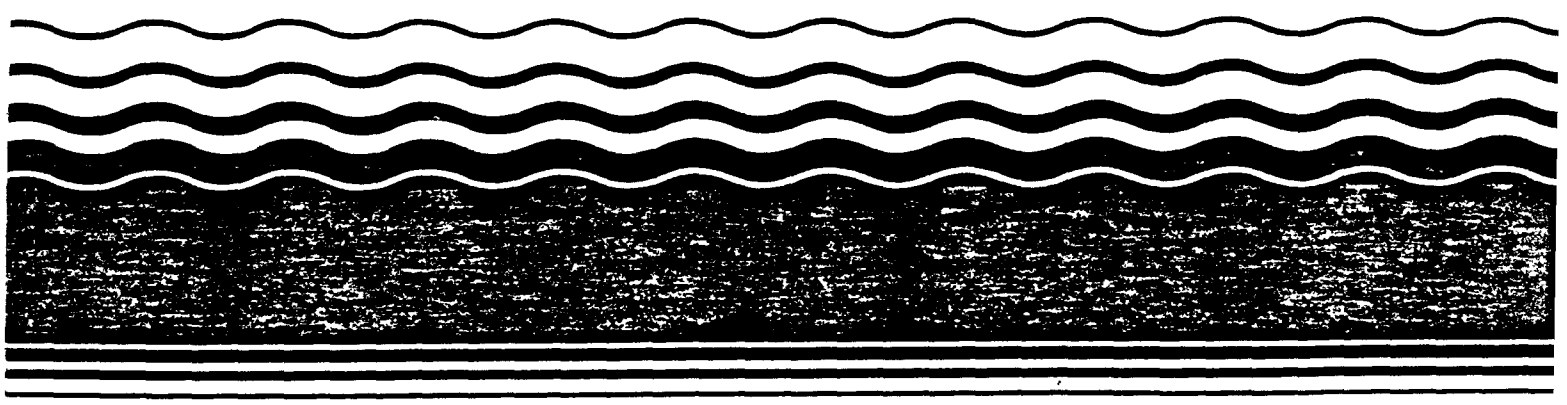
HEALTH EFFECTS ASSESSMENT FOR ARSENIC



EPA/540/1-86-020
September 1984

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U.S. Environmental Protection Agency
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Office of Solid Waste and Emergency Response
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with arsenic. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Arsenic. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-021. NTIS PB 81-117327.

U.S. EPA. 1983a. Reportable Quantity for Arsenic (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH., OHEA, for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicological Data in Support of Evaluation for Carcinogenic Potential of Arsenic and Compounds. Prepared by the Carcinogen Assessment Group, OHEA, Washington DC. for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA-600/8-83-021F. NTIS PB 84-190891.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983c).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented. In addition, the preface defines the terminology used in the text and summary tables.

Arsenic and compounds have been classified as Group A compounds based on evidence for excess cancer risk for skin and lung cancers in humans exposed to inorganic arsenic compounds. The evidence for the carcinogenicity of arsenic in experimental animals is equivocal. The U.S. EPA (1984) used data on skin cancer in people in Taiwan exposed to arsenic in the drinking water to estimate a unit risk based on oral exposure of 15.0 $(mg/kg/day)^{-1}$. A unit risk of 4.29×10^{-3} $(\mu g/m^3)$ for inhalation was estimated from four epidemiological studies concerning respiratory cancers in workers at two copper smelters. Applying the assumptions discussed in Section 6.3.2., this value corresponds to a unit risk of 50.1 $(mg/kg/day)^{-1}$.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
LD_{50}	Median lethal dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Arsenic (atomic weight 74.92) is a nonmetal or metalloid belonging to Group VA of the periodic table. Elemental arsenic has a CAS Registry number of 7440-38-2. The major stable valences of arsenic are 3-, 3+ and 5+.

Arsenic can enter aquatic media through atmospheric wet and dry deposition (Boyle and Jonasson, 1973), through runoff from soils and through industrial discharge into surface waters. The processes that are likely to dominate the fate of arsenic in aquatic media are chemical speciation, volatilization, sorption and biotransformation (Callahan et al., 1979). Generally, arsenate (As^{+5}) is the dominant species in aquatic systems. However, the speciation of arsenic in natural waters is significantly influenced by the presence of biota in the water bodies. The biological activities in water may reduce arsenate into arsenite (As^{+3}) and finally to methylated arsenicals (As^{-3}) (Callahan et al., 1979). In the presence of biological activity or a highly reducing condition, arsenic in water bodies may be converted to methyl arsenics (AsH_3). These latter compounds are volatile and may evaporate from water, accounting for some loss of arsenic. In polluted water bodies, arsenic may form complexes with organic compounds present in the water. Various sorption and subsequent precipitation of both arsenate and organic complexes of arsenic may reduce the level of arsenic in water bodies. Clay, iron oxides, and particulate matters high in organic content are excellent materials for the sorption of arsenic from aquatic media (Callahan et al., 1979). The precipitated arsenic may be metabolized by a number of organisms to organic arsenicals, thereby increasing arsenic mobility in the aquatic media (Callahan et al., 1979).

The major source of atmospheric arsenic is coal combustion (U.S. EPA, 1980b). Other sources include smelting operations, dust from the earth's crust, and vaporization of volatile compounds (Graedel, 1978). The dominant atmospheric species appears to be arsenic trioxide (As_2O_3) (Graedel, 1978). The principal removal mechanisms for atmospheric arsenic appear to be wet and dry precipitation (Graedel, 1978).

Arsenic can enter the soil from wet and dry precipitation of atmospheric arsenic, from runoff of surface waters and from disposal of arsenic-containing waters. The fate of arsenic in soil is inadequately studied. However, the fate may be dependent on the nature of soil. The factors that may significantly determine the fate of soil arsenic are organic matter content, clay content and microbial activity capable of metabolizing arsenic. Soil containing high levels of sorptive materials, such as clay or organic matter, are likely to retard the leachability of arsenic in soils. However, arsenic may leach into groundwater from soils with low sorptive capacity. Indirect evidence suggests that leaching of arsenic from soils into groundwater may be quite common (Page, 1981).

The BCFs for arsenic in aquatic organisms have been determined by a few investigators and have been found to vary from 333-6000 (Callahan et al., 1979).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Absorption of arsenic from the GI tract is predominantly governed by the solubility of the specific compound administered and the dosing rate. Coulson et al. (1935) reported that solutions of either trivalent or pentavalent soluble inorganic arsenic compounds were almost completely absorbed from the GI tracts of rats. Solutions of arsenic trioxide have been reported to be 88% absorbed in rats (Urakabo et al., 1975; Dutkiewicz, 1977), 90% absorbed in pigs (Munro et al., 1974), and 98% absorbed in monkeys (Charbonneau et al., 1978). Absorption is reduced when the arsenic trioxide is administered as a suspension, with 40% of the administered dose being absorbed by rabbits and 30% by rats (Ariyoshi and Ikeda, 1974).

Coulson et al. (1935) and Ray-Bettley and O'Shea (1975) estimated that >95% of the inorganic arsenic that man consumes is absorbed. Slightly lower estimates may be obtained from the study of Mappes (1977), who observed that one human subject given a daily dose of ~0.8 mg trivalent arsenic excreted ~70% of the daily dose in the urine each day. Mappes (1977) reported that, in contrast to the high absorption of soluble inorganic arsenic, insoluble arsenic triselenide (As_2Se_3) passed through the GI tract with negligible absorption. Buchet et al. (1981) reported that human volunteers treated with sodium meta arsenite that provided arsenic at 125-1000 µg/day excreted 60% of their daily dose in the urine. Steady state was achieved within 5 days.

Arsenic is present in crustaceans and fish in a highly complexed organic form known as "shrimp" arsenic. The pharmacokinetics of this form of arsenic have been investigated recently in considerable detail (LeBlanc and Jackson, 1973; Westoo and Rydalv, 1972; Munro, 1976; Edmonds et al., 1977;

Penrose et al., 1977; Crecelius, 1977; Edmonds and Francesconi, 1977). Collectively, these studies suggest that "shrimp" arsenic appears to be extensively absorbed and rapidly excreted as an intact organoarsenical complex by man and animals and, therefore, does not appear to be a health threat.

2.2. INHALATION

Absorption of arsenic from the respiratory tract is governed by the specific chemical compound and, in the case of aerosols or dusts, the particle size. Particles smaller than 1-2 μm in diameter are deposited in the alveoli and may, thus, be absorbed through the respiratory epithelium. Larger particles are predominantly deposited in the upper respiratory tract, expelled by retrociliary movement, and swallowed.

The effect of solubility on the pulmonary retention of arsenic compounds was investigated by Inamasu et al. (1982), who administered single intratracheal doses of ~2 mg of arsenic as arsenic trioxide (slightly soluble) or calcium arsenate (nearly insoluble) to rats. Groups of 4-5 rats were killed at intervals from 15 minutes to 7 days after treatment and the amount of arsenic retained in the lungs was measured. At 15 minutes after treatment, the amounts of arsenic recovered from the lungs were 1146 and 620 μg, respectively, in the calcium arsenate and arsenic trioxide treated rats. By 24 hours post-treatment, almost all the arsenic trioxide had been cleared from the lungs, but ~50% of the calcium arsenate was retained. Very little additional clearance of calcium arsenate was observed by 7 days post-treatment, while the small amount of arsenic trioxide remaining at the end of 24 hours had been cleared. These data suggest that arsenic trioxide is absorbed by the lung to a much greater extent than is calcium arsenate.

Similar conclusions were reached by Pershagen et al. (1982), who administered 4 weekly intratracheal doses of arsenic trioxide, arsenic trisulfide

and calcium arsenate at doses of 0.3, 0.5 and 0.5 mg arsenic, respectively, to Syrian golden hamsters. In animals sacrificed immediately after treatment, the lung contents of arsenic were 386, 755 and 866 mg/kg in the above three treatment groups, respectively. At the end of the fourth treatment, lung contents of arsenic were ~0.3, 3.0 and 800 mg/kg, respectively. Mortality and severe lung damage occurred only in the calcium arsenate treated hamsters.

Dutkiewicz (1977) observed similar tissue distribution dynamics in rats following either intratracheal or intravenous administration of pentavalent arsenic, indicating extremely rapid absorption across the respiratory epithelium. Rapid absorption has also been observed in rats and mice following exposure to condensation aerosols of arsenic trioxide (1.0, 3.7 or 46 $\mu g/m^3$) (Rozenshtein, 1970) or a solid aerosol of fly ash containing 180 μg arsenic/m^3 (Bencko and Symon, 1970). Pinto et al. (1976) found that, in workers at a copper smelter, urinary excretion of 38-55 μg arsenic/ℓ occurred in men exposed to atmospheric concentrations ranging from 3-295 $\mu g/m^3$. Smith et al. (1977) reported that urinary levels of trivalent, pentavalent, methyl- and dimethylarsenic in copper smelter workers were directly correlated with atmospheric concentrations. In a quantitative study, Holland et al. (1959) found that, within 4 days, 75-85% of the deposited arsenite was absorbed from the lungs of a group of lung cancer patients who inhaled arsenite-containing aerosols or smoke from arsenite-containing cigarettes.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

In general, the rat is not a good model for arsenic toxicity. Lanz et al. (1950) found that, in contrast to other mammals, the rat stored 79% of an intramuscularly administered arsenic dose bound to hemoglobin in red blood cells. Cats were found to accumulate 5.6% in the blood, and dogs, chicks, guinea pigs and rabbits stored <0.27% in the blood. This binding results in an extremely slow excretion of arsenic by rats as compared with other species, including man, following intravenous administration (Ducoff et al., 1948; Mealey et al., 1959). Blood levels are much higher in rats (125 ppm) than in guinea pigs (4 ppm), rabbits (1.5 ppm) or hamsters (2.5 ppm) following administration of diets containing 50 mg arsenic trioxide/kg diet for 21 days (Peoples, 1975). For this reason, toxicity data in rats cannot be reliably extrapolated to man. The subchronic and chronic toxicity of arsenic depends principally on the chemical form, physical state, particle size and solubility of the material tested. Generally, inorganic trivalent arsenic is regarded to be more toxic than the pentavalent form. Methylated forms appear to be less toxic and "shrimp" or "fish" arsenic is generally regarded as non-toxic (NAS, 1977; Pershagen and Vahter, 1979; WHO, 1981).

3.1. SUBCHRONIC

3.1.1. Oral. The subchronic oral toxicity of arsenic is summarized in Table 3-1. Byron et al. (1967) administered diets containing 0, 5, 25, 50 or 125 mg arsenic/kg diet, as either sodium arsenite or sodium arsenate, to groups of three male and three female beagle dogs for up to 2 years. Sodium arsenite was more toxic than sodium arsenate, with 5/6 dogs in the high-dose group dying or becoming moribund following 3-9 months of treatment. The no-effect level was 50 mg/kg diet for both compounds.

TABLE 3-1

Subchronic Oral Toxicity of Arsenic

Compound	Species/ Strain	Dose	Length of Exposure	Effects	Reference
Sodium arsenite	dog/beagle	0, 5, 25, 50 or 125 mg arsenic/kg diet	up to 2 years	Slight to moderate anemia, anorexia, listlessness, and decreased body weight in high-dose group. 5/6 died between 3 and 9 months, and all were dead by 19 months. No effects at doses of ≤50 mg/kg diet.	Byron et al., 1967
Sodium arsenate	dog/beagle	0, 5, 25, 50 or 125 mg arsenic/kg diet	up to 2 years	At a dose of 125 mg/kg diet, one dog had severe weight loss and died by 13.5 months. All had mild anemia and granular iron-positive pigment in liver macrophages. No effects at a dose of ≤50 mg arsenic/kg diet.	Byron et al., 1967
Arsenic(III) oxide	rat/Wistar	0, 0.125, 12.5 or 62.5 mg arsenic/ℓ H_2O	7 months	Slightly decreased water consumption in high-dose group. Dose-related increase in absolute and relative liver weight, degenerative changes in liver, and sloughing of the kidney tubular epithelium.	Ishinishi et al., 1980; Hisanaga, 1982
Calcium arsenate (probably)	human	3 mg/day	2-3 weeks	Facial edema and anorexia in 187/220. Less than 10% with exanthemata, desquamation, and hyperpigmentation. Approximately 20% with peripheral neuropathy.	Mizuta et al., 1956
NR	human/ infants	NR	"a few months"	Coughing, rhinorrhea, conjunctivitis, vomiting, diarrhea, melanosis, fever, abdominal swelling, hepatomegaly, anemia, granulocytopenia, abnormal electrocardiograms, increased density at epiphyseal ends of long bones. Symptoms were reversible, except for a retardation of ulnar growth. Follow-up indicated increased incidences of leukomelanoderma, keratosis, mental retardation, growth retardation and epilepsy.	Masahiki and Hideyasu, 1973; Okamura et al., 1956; Satake, 1955; Nagai et al., 1956
Arsenic(III) oxide or arsenic trisulfide	human	2.5 mg arsenic/ day or 10.3 mg arsenic/day, respectively	daily for several months or "intermit-tently" for up to 15 years	Polyneuropathies in ~50% of 74 patients. Hyper-pigmentation and hyperkeratosis.	Tay and Seah, 1975

Ishinishi et al. (1980) and Hisanaga (1982) administered 0, 0.125, 12.5, or 62.5 mg arsenic/ℓ drinking water, as arsenic(III) oxide, to Wistar rats for 7 months. Most of the arsenic-treated rats had cloudy swelling of the hepatocytes, spotty coagulative necrosis, proliferation of interlobular bile ducts, and angitis of adjacent blood vessels. Sloughing of the tubular epithelium was observed in the kidneys from all three treatment groups.

Two studies in humans present useful dose-response information (Mizuta et al., 1956; Tay and Seah, 1975). Tay and Seah (1975) investigated 74 patients in Singapore who had ingested arsenic-containing antiasthmatic herbal preparations for periods ranging from <6 months to (intermittently) 15 years. Doses were estimated to be 2.5 mg arsenic/day as arsenic(III) oxide or 10.3 mg arsenic/day as arsenic sulfides. The organ systems involved were cutaneous (91.9%), neurological (51.3%), GI (23%), hematological (23%) and renal and others (19%); 5.4% of the patients had internal malignancies. The major effects, occuring in more than 10% of the subjects, were generalized hyperpigmentation (arsenic melanosis), hyperkeratosis of palms and soles, "raindrop" depigmentations, palmar and plantar hyperhidrosis, multiple arsenical keratoses, sensorimotor polyneuropathy, fine finger tremors, persistent chronic headache, lethargy, weakness and insomnia, psychosis, gastritis or gastroenteritis, mild iron deficiency anemia as a result of toxic marrow suppression, and transient albuminuria without azotemia. The internal malignancies consisted of two squamous-cell carcinomas of the lungs, one squamous-cell carcinoma of the gall bladder and one hemangiosarcoma of the liver. Mizuta et al. (1956) observed similar neurological effects in people who consumed ~3 mg arsenic/day in contaminated soy sauce for 2-3 weeks.

3.1.2. Inhalation. A gaseous arsenic compound, arsine, has a high acute toxicity and can be formed in the environment under conditions of low pH, high reducing potential and low oxygen pressure, or as a by-product of industrial processes (Callahan et al., 1979; ACGIH, 1980). Other investigators have indicated that airborne arsenic compounds are associated with skin lesions, cardiovascular and respiratory effects, and peripheral neuropathy, but no adequate exposure information is available for any of these studies (Stokinger, 1981; IARC, 1980; ACGIH, 1980; U.S. EPA, 1980b; NIOSH, 1975).

3.2. CHRONIC

3.2.1. Oral. The chronic oral toxicity of inorganic arsenic compounds is summarized in Table 3-2. The most common effects observed in humans were skin lesions, peripheral vascular disease and peripheral neuropathy. In experimental animals, decreased survival without apparent cause was frequently observed. The only species, other than human, in which dermal pathologies were observed was the mouse, and these changes were relatively mild and did not include skin cancers. Peripheral neuropathies were not observed in any experimental animals tested. Hepatic degenerative changes and renal damage were frequently observed in rats, but not in other species.

Tseng (1977) investigated the relationship between blackfoot disease, a peripheral circulatory disease characterized by gangrene of the extremities, and the arsenic concentration in drinking water of residents of the southwest coast of Taiwan. A total of 40,421 individuals in 37 villages were included in the study. Arsenic concentrations ranged from 0.001 to 1.82 mg/ℓ. The overall prevalence rate for blackfoot disease was 8.9/1000, with a positive correlation between the prevalence rate and arsenic concentration and duration of intake. This study established a NOAEL of 0.001-0.017 mg/ℓ for blackfoot disease.

TABLE 3-2

Chronic Oral Toxicity of Arsenic

Compound	Species/ Strain	Dose	Length of Exposure	Effects	Reference
Arsenic(III) oxide	mice/Swiss	0.01% in drinking water	"lifetime"	Slight hyperkeratosis with occasional areas of epidermal hyperplasia.	Baroni et al., 1963; Shubik et al., 1962
Sodium arsenite	rats/NR	0, 15.63, 31.25, 62.5, 125 or 250 mg arsenic/ mg diet	2 years	Decreased survival and body weight and enlargement of common bile duct at high-dose level. Slight decrease in body weight and enlargement of common bile duct at 125 mg/kg diet.	Byron et al., 1967
Sodium arsenate	rats/NR	0, 15.63, 31.25, 62.5, 125, 250 or 400 mg arsenic/kg diet	2 years	400 mg arsenic from sodium arsenate produced approximately the same effects as 250 mg arsenic from sodium arsenite. Slight decrease in survival and body weights and enlargement of the common bile ducts in 250 mg/kg diet group.	
Sodium arsenite	rats/Long-Evans	5 µg/ml H_2O	~2 years	No effect on growth, longevity or histopathology. Increased serum cholesterol and decreased serum glucose in males.	Schroeder et al., 1968
Sodium arsenite	mice/CD	5 µg/ml H_2O	~2 years	Decreased survival rates and longevity. No treatment-related histopathological effects.	Schroeder and Balassa, 1967
Sodium arsenate	rats/Wistar	100 mg arsenic/ kg diet	29 months	No effects on survival, body weight gain, food consumption, blood hemoglobin levels, erythrocytes, gross anatomy or histology.	Kroes et al., 1974
Lead arsenate	rats/Wistar	100 or 399 mg arsenic/kg diet	29 months	In the high-dose group, males had decreases in blood hemoglobin values and packed cell volumes. Food consumption and body weight were decreased and mortality was increased in both sexes. Histopathological changes included enlarged bile ducts, bile duct proliferation, pericholangitis, cholangiofibrosis, and intranuclear eosinophilic inclusions in the kidneys. No effect at a dose of 100 mg/kg diet.	

TABLE 3-2 (cont.)

Compound	Species/ Strain	Dose	Length of Exposure	Effects	Reference
NR	human/NA	0.598 mg arsenic/ℓ H_2O	15 years	Leukomelanoderma, hyperkeratosis, chronic coryza, abdominal pain, Raynaud's syndrome	Zaldivar and Ghai, 1980; Borgono and Greiber, 1972; Zaldivar, 1974; Borgono et al., 1977
NR	human/NA	0.01-1.82 mg arsenic/ℓ H_2O	>45 years	Hyperpigmentation, keratosis, skin cancer, blackfoot disease	Tseng et al., 1968; Tseng, 1977
Arsenic(III) oxide	human/NA	8.8 mg/day	28 months	Characteristic dermal lesions and peripheral neuropathy	Silver and Wainman, 1952

NR = Not reported

NA = Not applicable

3.2.2. Inhalation. Chronic inhalation exposure to arsenic compounds results in symptoms similar to those observed following oral exposure. For example, Landau et al. (1977) reported a direct relationship between the length and intensity of exposure of smelter workers to airborne arsenic, predominantly as arsenic trioxide, and alterations in peripheral nerve function. No studies were available in which exposure levels are characterized to an extent sufficient for the determination of dose-response relationships.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Hood et al. (1977) reported that oral administration of 120 mg sodium arsenate/kg bw to mice during pregnancy had less of an effect on prenatal mortality, reduction in fetal weight, or the occurrence of fetal malformations than did intraperitoneal administration of 40 mg/kg bw. Matsumoto et al. (1973a,b) reported that oral doses of up to 40 mg/kg bw/day for 3 consecutive days resulted in decreased fetal weights; however, administration of diets containing up to 100 mg arsenite/kg diet (~5 mg/kg bw/day) throughout pregnancy had no effect on the offspring (Kojima, 1974). Baxley et al. (1981) indicated that a single oral dose of 40-45 mg/kg bw on any gestation day between days 8-15 will produce adverse effects in developing mice.

3.3.2. Inhalation. No data pertinent to the teratogenicity or other reproductive effects of inhaled arsenic were located in the available literature.

3.4. TOXICANT INTERACTIONS

The best-known interactive effect of arsenic involves a protective effect in cases of selenium poisoning. Moxon (1938) found that 5 mg arsenic/ℓ H_2O, as sodium arsenite, prevented liver damage in rats fed

diets containing 15 mg selenium/kg diet. In a later study Dubois et al. (1940) determined that sodium arsenite and sodium arsenate were equally effective, but that the arsenic sulfides were ineffective.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Numerous arsenic compounds, particularly trivalent inorganics, have been associated with lung and skin carcinomas in humans. Tseng et al. (1968) and Tseng (1977) surveyed 40,421 residents of Taiwan who consumed artesian well water containing 0.01-1.8 mg arsenic/ℓ for 45-60 years. A dose-response relationship (Table 4-1) was established between the prevalence of skin cancer and arsenic consumption, based on arsenic concentrations in different wells and length of exposure (age). The overall incidence of skin cancer was 10.6/1000, with a maximum incidence of 209.6/1000 in males over 70 years of age.

Arsenic sulfides and arsenic trioxide have also been associated with the development of malignancies in 74 patients in Singapore (Tay and Seah, 1975). These patients had consumed herbal preparations containing arsenic for up to 15 years. Malignancies of the skin were reported in 6/74 patients, and malignancies of the visceral organs in 4/74.

In contrast, Morton et al. (1976) found no increase in skin cancer incidences in an area of Oregon where arsenic levels in the drinking water are high. No increase in internal malignancies was observed in patients treated with arsenicals for various skin diseases, although an increased incidence of basal-cell carcinoma was observed in females (Reymann et al., 1978).

Cuzick et al. (1982) reported on a cohort study of patients treated with Fowler's solution (potassium arsenite). They found an excess of both fatal and nonfatal skin cancers, often associated with other signs of chronic arsenic poisoning. They hypothesized the existence of a susceptible subpopulation that initially develops dermatological symptoms, followed by the development of skin cancers.

TABLE 4-1

Age-Exposure-Specific Prevalence Rates for Skin Cancer[a]

Exposure in ppm[b]	Age		
	20-39 (30)	40-59 (50)	≥60 (70)
0-0.29 (0.15)	0.0013	0.0065	0.0481
0.30-0.59 (0.450)	0.0043	0.0477	0.1634
≥0.6 (1.2)	0.0224	0.0983	0.2553

[a]Source: Tseng et al., 1968

[b]Range given by authors. Midpoint is in parentheses.

4.1.2. Inhalation. Numerous investigators have reported an association between occupational exposure to arsenic and the development of tumors. This exposure is presumably largely by the respiratory route. Pinto and Bennett (1963) failed to find an association between arsenic exposure and tumor formation in copper smelter workers; however, a follow-up study found an increase in deaths from all cancers, particularly respiratory cancer, at this smelter (Pinto et al., 1978). Numerous other investigators have reported an increase in lung cancer among arsenic-exposed workers, but the exposure concentrations are insufficiently characterized for use in risk assessment (Axelson et al., 1978; Lee and Fraumeni, 1969; Rencher et al., 1977; Tokudome and Kuratsune, 1976; Osburn, 1969; Pershagen et al., 1977; Hill and Faning, 1948; Perry et al., 1948; Ott et al., 1974).

The U.S. EPA (1984) used an absolute-risk linear model applied to the data from four epidemological studies involving copper smelters. Those studies are briefly reported here; however, U.S. EPA (1984) provides a more exhaustive discussion of these studies and other studies that did not lend themselves to quantitative risk assessment.

The four studies from which the U.S. EPA (1984) derived unit risks for respiratory cancer all deal with different cohorts of workers at the Anaconda copper smelter in Montana (Brown and Chu, 1983; Lee-Feldstein, 1983; Higgins et al., 1982) or the ASARCO smelter in Tacoma, WA (Enterline and Marsh, 1980, 1982).

In the Tacoma, WA, case, Enterline and Marsh (1980, 1982) studied the vital statistics of a cohort of male workers who were employed in the period 1940-1964. Since work-related exposure for $\geq$1 year was required for inclusion in the cohort, follow-up did not begin until 1941 and extended through

1976. The cohort initially contained 2802 individuals. The vital statistics of 51 could not be verified, so final studies involved 2751 persons; results are presented in Table 4-2. During this period, 1061 deaths occurred. A significant increase in deaths due to cancers (all respiratory) was noted. Arsenic exposure for each worker was estimated on the basis of average urinary arsenic of workers in each department factored by the length of time each worker remained in that department. When estimated this way, Enterline and Marsh (1980, 1982) observed a dose-related response between estimated arsenic exposure and the incidence of lung cancer.

The other epidemiological studies concern statistics that were gathered from workers at the Anaconda copper smelter in Montana. Lee-Feldstein (1983) studied the mortality of workers from this plant from 1938-1977. The 8045 workers were assigned to cohorts on the basis of length of exposure: cohort 1 worked $\geq$25 years, cohort 2, 15-24 years, cohort 3, 10-14 years, cohort 4, 5-9 years and cohort 5, 1-4 years. SMRs were calculated by comparing the incidences of 13 causes of death among the workers to those of the combined male populations of three western states. Of the 13 causes of death considered, only death due to respiratory cancer showed a significant increase in the ratio of observed to expected deaths coupled with a positive gradient related to length of employment (Table 4-3).

Brown and Chu (1983) further discussed the data and conclusions of the Lee-Feldstein (1983) study, particularly regarding the suitability of applying the multistage theory of cancer to these data (Table 4-4). They indicated that the observation of an increasing risk of lung cancer mortality at increasing age of initial exposure and the observation that mortality appeared to be independent of time after exposure ceased were evidence that arsenic acts as a late-stage carcinogen.

TABLE 4-2

Data from Table 8 of Enterline and Marsh (1982)
with Person-Years of Observation Added

Cumulative Exposure[a] μg/m³-years	Person-Years of Observation[b]	Observed Deaths	Expected Deaths
	0 Lag		
91.8	10,902	8	4.0
263	21,642	18	11.0
661	14,623	21	10.3
1381	13,898	26	14.1
4091	9398	31	12.7
	10-Year Lag		
91.8	27,802	10	6.4
263	16,453	22	12.5
661	11,213	26	11.5
1381	9571	22	12.4
4091	5423	24	9.7

[a]Exposures are in μg/m³ -- years estimated by the formula (I μg/ℓ-years) (0.304) where I is mean urinary exposure index from Enterline and Marsh (1982) and 0.304 is the relation between urinary and airborne arsenic estimated by Pinto et al. 1977.

[b]Furnished by Dr. Enterline (personal communication to U.S. EPA, 1984)

TABLE 4-3

Observed and Expected Deaths from Respiratory Cancer, with Person-Years of Follow-up, by Cohort and Degree of Arsenic Exposure[a]

Years of Exposure	Maximum Exposure to Arsenic (≥12 months)[b]					
	Heavy		Medium		Light	
	Obs/Exp[c]	P-Y[d]	Obs/Exp	P-Y	Obs/Exp	P-Y
25 years+	13/2.5	2400	49/7	6837	51/16.3	14,573
15-24	9/1.3	2629	13/4.0	6509	16/ 8.6	12,520
<15 years	11/2.4	6520	31/9.3	24,594	69/31	78,245

[a]Source: Lee-Feldstein, 1983

[b]The 1562 men who worked <12 months in their category of maximum arsenic exposure were not included in this table.

[c]Observed/Expected

[d]Person-years of follow-up furnished by Dr. Lee-Feldstein (personal communication to U.S. EPA, 1984).

TABLE 4-4

Observed and Expected Lung Cancer Deaths and Person-Years by Level of Exposure, Duration of Employment, and Age at Initial Employment*

Age at Initial Employment		Duration of Employment (years) 0-9	10-19	20-29	30-39	40+
High Exposure Level Group						
<20	Obs	0	0	0	3	0
	Exp	0.001	0.009	0.065	0.249	0.193
	Pyr	206	408	588	499	172
20-29	Obs	0	0	2	0	2
	Exp	0.008	0.051	0.164	0.277	0.082
	Pyr	624	637	495	308	64.4
30-39	Obs	0	0	3	0	0
	Exp	0.030	0.077	0.106	0.053	0.001
	Pyr	398	207	155	59.1	0.86
40-49	Obs	0	0	0	0	0
	Exp	0.083	0.054	0.034	0.007	0.0
	Pyr	210	80.0	49.1	6.88	0.0
50+	Obs	0	0	0	0	0
	Exp	0.066	0.027	0.0	0.0	0.0
	Pyr	78.0	23.2	0.0	0.0	0.0
Medium Exposure Level Group						
<20	Obs	0	0	1	4	1
	Exp	0.010	0.039	0.171	0.591	0.597
	Pyr	1801	1763	1500	1206	579
20-29	Obs	0	0	2	4	7
	Exp	0.035	0.118	0.331	0.717	0.514
	Pyr	2636	1622	1099	951	654
30-39	Obs	0	0	1	3	0
	Exp	0.167	0.473	0.329	0.161	0.045
	Pyr	1939	1137	438	194	68.2
40-49	Obs	0	0	1	3	0
	Exp	0.167	0.414	0.098	0.010	0.0
	Pyr	1190	448	98.9	12.1	0.0

TABLE 4-4 (cont.)

Age at Initial Employment		Duration of Employment (years) 0-9	10-19	20-29	30-39	40+
<50+	Obs	0	0	0	0	0
	Exp	0.262	0.076	0.011	0.0	0.0
	Pyr	295	71.2	14.5	0.0	0.0
Low Exposure Level Group						
<20	Obs	0	0	1	1	3
	Exp	0.056	0.117	0.478	1.59	1.57
	Pyr	8524	5249	4038	3175	1376
20-29	Obs	0	0	2	5	6
	Exp	0.115	0.334	0.892	1.74	0.796
	Pyr	9951	4724	2965	2117	834
30-39	Obs	0	3	1	0	1
	Exp	0.390	0.802	0.937	0.662	0.062
	Pyr	5218	2218	1364	715	74.6
40-49	Obs	2	1	1	1	0
	Exp	1.29	1.18	0.344	0.035	0.001
	Pyr	3703	1319	386	52.7	2.00
50+	Obs	3	2	0	0	0
	Exp	1.62	0.385	0.041	0.0	0.0
	Pyr	1945	371	65.4	0.0	0.0

*Source: Brown and Chu, 1983

In another study of the same smelter, Higgins et al. (1982) reported on a sample of 1800 workers, 277 from a "heavy exposure category" and a random sample (20%) of the remaining known workers. Workers with at least 1 year of work experience were entered into the study. Smoking histories were obtained. SMRs were calculated by comparison with the white male population of Montana and also of the United States. Estimates of workroom atmospheric concentrations of arsenic for 52 smelter departments were based on industrial hygiene records for the years 1943-1965 or by analogy with those areas in which the concentrations were known. The departments were classified into four categories based on atmospheric arsenic concentration: low, <100 $\mu g/m^3$; medium, 100-499 $\mu g/m^3$; high, 500-4999 $\mu g/m^3$; or very high, >5000 $\mu g/m^3$

The data were analyzed by five exposure/follow-up methods that differed primarily in the amount of overlap permitted between exposure period and follow-up period. Data analysis method I was the primary method used by the authors and included the worker's arsenic exposure up to the time he was entered into the cohort with follow-up from day of entry until 1978. No overlap between exposure and follow-up occurred. Method IV, exposure from date hired until 1964 and follow-up from 1964-1978, also had no overlap. Complete overlap was permitted in methods II and V. Method II involved exposure from date hired through 1964 and follow-up from 1938-1964 and method V involved exposure from date hired to termination and follow-up from 1938-1978. Partial overlap occurred with method III; exposure from date of hire to 1964 and follow-up from 1938-1978.

Analysis of the data obtained (presented in Table 4-5) resulted in the following conclusions: (1) that exposure to arsenic in the workroom was strongly correlated with excess mortality due to respiratory cancer; (2)

TABLE 4-5

Respiratory Cancer Mortality 1938-1978 from Cumulative Exposure to Arsenic for 1800 Men Working at the Anaconda Copper Smelter[a]

Cumulative Exposure $\mu g/m^3$-years	Person-Years of Observation	Observed Deaths	Expected Deaths
0-500 (250)[b]	13,845.9	4	5.8
500-2000 (1250)	10,713.0	9	5.7
2000-12,000 (7000)	11,117.8	27[c]	6.8
≥12,000 (16,000)	9015.5	40[c]	7.3

[a]Source: Higgins et al., 1982

[b]Numbers in parentheses indicate assumed average exposures.

[c]Significant at 0.01 level

exposure to other occupational contaminants, such as sulfur dioxide and asbestos did not appear to cause excess deaths due to respiratory cancer; (3) smoking accounted for only a small fraction of excess respiratory cancer deaths; (4) the SMRs reflected increased incidences of excess lung cancers positively correlated with exposure category; and (5) that SMRs dropped subsequent to 1923 when additional methods were instituted that resulted in increased arsenic fume and dust recovery.

4.2. BIOASSAYS

4.2.1. Oral. Animal bioassays with a variety of arsenic compounds have generally produced negative results. Hueper and Payne (1962) and Baroni et al. (1963) administered 0.0034% or 0.01% arsenic trioxide in the drinking water to mice. No increase in tumor incidence was observed at either dose level. In a similar study, Kanisawa and Schroeder (1967, 1969) administered 5 mg sodium arsenite/ℓ drinking water to mice or 5 mg sodium arsenate/ℓ to rats over their entire lifespan without producing any increase in tumor incidence. Hueper and Payne (1962) found that drinking water levels of up to 34 mg arsenic trioxide/ℓ had no effect on tumor incidences in rats. Both sodium arsenate and sodium arsenite were found to be ineffective in a 2-year feeding study in dogs fed diets containing arsenic, as at levels between 5-125 mg/kg diet (Byron et al., 1967). Shirachi et al. (1983) reported that sodium arsenite did not induce renal tumors (species unspecified) but did increase the incidence of dimethylnitrosamine-initiated kidney tumors. These authors, therefore, considered arsenite to be a tumor promoter.

Other investigators have reported tumorigenic effects of arsenic treatment. Schrauzer et al. (1978) reported that an unspecified arsenic compound, at a concentration of 2 mg/ℓ drinking water, failed to increase the

number of treated female mice bearing mammary adenocarcinomas, but the growth rate and incidence of multiple tumors in tumor-bearing animals were increased. Knoth (1966/1967), in a brief and incomplete report, found an increase in adenocarcinomas of the skin, lung, peritoneum and lymph nodes of mice dosed with arsenic trioxide or Fowler's solution (1% arsenic trioxide) orally once per week for 5 months.

4.2.2. Inhalation. Ishinishi et al. (1976, 1977) administered 15 weekly intratracheal instillations of arsenic trioxide (0.26 mg), copper ore (3.95% arsenic), or refinery flue condensate (10.5% arsenic) to Wistar-King rats. Tumor incidences were not increased over those of controls during the lifespan of the animals. Berteau et al. (1978) exposed female mice to a 1% aqueous aerosol of sodium arsenite, 20-40 minutes/day, 5 days/week, for 55 weeks. No significant increase in tumor incidence was observed. In contrast, a single intratracheal instillation of Bordeaux mixture (4% calcium arsenate) resulted in the induction of lung tumors in 9/15 rats (Ivankovic et al., 1979).

4.3. OTHER RELEVANT DATA

Singh (1983) tested sodium arsenite for mitotic gene conversion and reverse mutation in Saccharomyces cerevisiae D7. Under the conditions of this assay, sodium arsenite was weakly positive for reverse mutation and negative for mitotic gene conversion.

Arsenic compounds have been observed to produce chromosomal damage both in vitro and in vivo (Petres and Hundeiker, 1968; Petres et al., 1970, 1972). Walker and Bradley (1969) reported that arsenate increased the total frequency of exchange chromosomes in Drosophilia melanogaster treated with selenocystine. Petres et al. (1970) studied lymphocytes from 34 patients at the University of Freiburg Skin Clinic, 13 of whom had received extensive

arsenic therapy up to 20 years before. There was a remarkable increase in the frequency of aberrations observed in the arsenic-treated group. Beckman et al. (1977) found an increase in gaps, chromatid aberrations, and chromosome aberrations in short-term cultured leukocytes from mine workers exposed to arsenic at the Ronnskar smelter in northern Sweden.

4.4. WEIGHT OF EVIDENCE

IARC (1980) has found that "there is inadequate evidence for the carcinogenicity of arsenic compounds in animals. There is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans." Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for calculating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), arsenic is most appropriately classified in Group A - Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1980) has established a TWA of 0.2 mg/m³ for arsenic and soluble arsenic compounds, as measured as arsenic, and the compound arsine. Arsenic trioxide is classified as an "Industrial Substances Suspect of Carcinogenic Potential for Man" and no TWA has been established. NIOSH (1973) recommended a TWA of 0.05 mg arsenic/m³ as a workplace air standard. This was changed to a 15-minute ceiling of 0.002 mg/m³ (NIOSH, 1975). In 1978, OSHA established a standard of 0.01 mg/m³ for airborne inorganic arsenic (U.S. EPA, 1980b).

The U.S. PHS established a maximum allowable level of 50 µg/ℓ for arsenic in drinking water supplied by interstate carrier water supplies in 1942. This standard was continued when the U.S. EPA Drinking Water Standards became effective in June of 1977. The U.S. EPA (1980b) has subsequently recommended a criterion of 22 ng/ℓ, which would result in an estimated excess cancer risk of 10^{-5}.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Arsenic has been determined to be carcinogenic to humans and data exist from which carcinogenic potencies have been estimated. It is, therefore, inappropriate to determine an AIS for arsenic.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Arsenic has been determined to be carcinogenic to humans and data exist from which carcinogenic potencies have been estimated. It is, therefore, inappropriate to determine an AIC for arsenic.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. As described in Chapter 4, numerous studies have implicated arsenic in the etiology of human cancer. Since arsenic has not consistently produced tumors in animals, it is necessary to rely on human data for the derivation of a unit risk. Tseng et al. (1968) found a positive correlation between the levels of arsenic ingestion and the development of skin cancer in southwest Taiwan. The U.S. EPA (1984) fit the incidence of skin cancer data to a model generated for estimating the cancer rate as a function of drinking water arsenic concentration. A unit risk of 15.0 $(mg/kg/day)^{-1}$ was estimated, assuming that humans drink 2 ℓ of water/day and that absorption of arsenic is 100%. A detailed discussion of the data and assumptions employed in the estimation of this carcinogenic potency can be found in U.S. EPA (1984).

The issue of risk associated with oral arsenic exposure is currently being reevaluated (U.S. EPA, 1985). This assessment should be evaluated for possible impact on the present document when it becomes available in reviewed, final form.

6.3.2. Inhalation. The U.S. EPA (1984) applied the data from the epidemiological studies of copper smelting in Montana (Brown and Chu, 1983; Lee-Feldstein, 1983; Higgins et al., 1982) and Washington (Enterline and Marsh, 1980, 1982) to an absolute risk linear model and estimated unit risks for these studies as summarized in Table 6-1. The U.S. EPA (1984) provides an in-depth discussion of this risk assessment. The geometric mean of the several unit risks is 4.29×10^{-3} $(\mu g/m^3)^{-1}$. Applying the assumptions that humans weigh 70 kg, inhale 20 m^3/day and absorb 30% of inhaled arsenic, a unit risk of 50.1 $(mg/kg/day)^{-1}$ is calculated (U.S. EPA, 1984).

TABLE 6-1

Combined Unit Risk Estimates for Absolute Risk Linear Models[a]

Exposure Source	Unit Risk[b]	Geometric Mean Unit Risk[b]	Final Estimated Unit Risk[b]	Reference
Anaconda (Montana) smelter	1.25×10^{-3}			Brown and Chu, 1983
	2.80×10^{-3}	2.56×10^{-3}		Lee-Feldstein, 1983
	4.90×10^{-3}			Higgins et al., 1982
			4.29×10^{-3}	
ASARCO (Washington) smelter	6.81×10^{-3}[c]	7.19×10^{-3}		Enterline and Marsh, 1980
	7.60×10^{-3}[c]			

[a]Source: U.S. EPA, 1984

[b]Unit risk values presented as $(\mu g/m^3)^{-1}$

[c]Unit risk estimated from data gathered using two different follow-up periods

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