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AN ASSESSMENT OF THE HEALTH EFFECTS OF ARSENIC GERMANE TO LOW-LEVEL EXPOSURE

NOTICE

This document is a preliminary draft. It has been released by EPA for public review and comment and does not necessarily represent Agency policy.

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WASHINGTON, D.C. 20460

PREFACE

The Environmental Protection Agency has prepared three documents concerning the health effects of arsenic on the general population:

1. A health effects assessment,
2. An environmental exposure assessment, and
3. A population risk assessment based on the data presented in the first two documents.

This report, the health effects document, will be used by the Environmental Protection Agency's Office of Air and Waste Management, and by the Administrator, to determine the scientific basis for possible actions regarding arsenic under the Clean Air Act. The report was prepared under the direction of the Criteria Development and Special Studies Division, Office of Health and Ecological Effects, with participation by the following Division personnel:

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Drafts of the three documents were reviewed by the Environmental Protection Agency's Science Advisory Board Study Group on Arsenic as a Hazardous Air Pollutant in public session on May 22-23, 1978. Members of this panel were:

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Review copies of this document were also provided to other government agencies and to industrial and public interest groups, as the result of a notice that appeared in the Federal Register April 26, 1978, on page 18246.

Comments and criticisms received at these meetings and in response to the Federal Register notice have been reviewed and incorporated into the report as deemed appropriate.

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ACKNOWLEDGMENTS

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SUMMARY

Arsenic, which occurs naturally in the environment, may present a health hazard to humans when it is released into the environment as a consequence of industrial, manufacturing, and agricultural processes. The preponderance of clinical and epidemiological evidence regarding the effects of arsenic pertains to trivalent inorganic arsenic. Much of this evidence suggests that trivalent inorganic arsenic is a carcinogen. Some limited evidence suggests that pentavalant inorganic arsenic may also be carcinogenic.

The main routes by which arsenic enters the human body are inhalation and ingestion. Experimental studies show that following injection of trivalent inorganic arsenic, arsenic is concentrated initially in the liver, kidneys, lungs, and spleen. After 24 hours the level in the liver and kidneys decreases, while that in the skin increases.

Both trivalent and pentavalent arsenic are mutagenic and teratogenic in animal tests. Attempts to induce tumors in experimental animals by arsenic usually have been unsuccessful, although, significantly in some instances, positive results have been obtained. Animal toxicity studies indicate that trivalent arsenic is several times more toxic than pentavalent arsenic.

Epidemiological studies of smelter workers show excess lung cancer risk in individuals exposed to arsenic trioxide, and several studies indicate that the risk increases with increasing duration and level of exposure. Risk increases of up to 8-fold have been reported. It is possible that the increased risk is not due to arsenic alone, since smelter workers are exposed concomitantly to sulfur dioxide and other toxic substances. Workers engaged in the manufacture of arsenical pesticides also

showed elevated risk for pulmonary cancer. Such workers, though not exposed to sulfur dioxide, may be exposed to other toxic substances. Similar results have been recorded in vineyard workers in France and Germany, where the workers were exposed to pesticides containing trivalent and pentavalent arsenic. In the United States, agricultural workers exposed to lead arsenate spray (pentavalent) evidenced excess lung cancer associated with this process.

The currently available experimental and epidemiological evidence does not provide an adequate basis for gauging the effects of chronic low-level exposure to arsenic compounds. A clear dose-response effect has been noted in a large-scale study in which ingestion of drinking water containing arsenic was associated with subsequent development of skin cancer. It is reasonable to assume that smaller dosages of inhaled arsenic could be involved with the development of cancer, since inhalation is a more efficient route of entry to the body than ingestion. In addition, as noted above, dose-response relationships have been reported in smelter workers.

It is difficult to determine a specific level of exposure associated with a specific level of risk because the precision of ambient air measurements is low; the level may be incorrect by as much as one order of magnitude. Nevertheless, the air levels yielding standard mortality ratios of 800 (i.e., an 8-fold increase in lung cancer deaths) have been estimated at 23 to 323 μg of arsenic per cubic meter of air.

SECTION 1
INTRODUCTION

Arsenic is a metal that occurs naturally in compounds with sulfur and with other metals (copper, cobalt, iron, lead, zinc, etc.). In its various forms arsenic occurs in trace amounts throughout the environment in water, solids, rocks, and living organisms. Arsenic is the 20th most common trace element in the earth's crust (Schroeder and Balassa, 1966). In addition to its occurrence in natural forms, arsenic trioxide is produced by smelters and by coal-burning power plants, and refined arsenic trioxide is used as the raw material for a large number of industrial and agricultural products, both inorganic and organic.

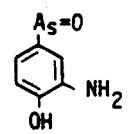
Some of the important natural and commercial arsenic compounds are shown in Table 1 with their chemical structures. Some of the sources of arsenic in various phases of the environment are shown in Table 2.

The toxicity of arsenic compounds varies greatly, depending on valence state, chemical structure, and route of entry. Elemental arsenic is considered nontoxic (Buchanan, 1962), whereas arsine gas and lewisite [dichloro (2-chlorovinyl) arsine] are extremely toxic (Buchanan, 1962). The arsenic in seafood (sometimes referred to as "shrimp arsenic") appears to be organically bound, is excreted rapidly in humans, and is generally thought to be nontoxic (National Academy of Sciences, 1977).

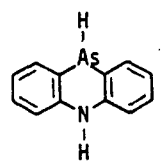
Since this report deals with the human health effects of airborne arsenic, the complex questions of the distribution and circulation of arsenic throughout the environment and the possible hazards to wildlife and humans by arsenic in the soil, foodstuffs, and drinking water are beyond its scope. Case studies involving ingestion of arsenic in beverages, drinking

TABLE 1. SELECTED ARSENIC COMPOUNDS AND THEIR CHEMICAL STRUCTURES[a]

AsS, AsS_4 REALGAR SULFURET		As_2S_3 AURIPIGMENTUM ORPIMENT	FeAsS ARSENOPYRITE MISPICKEL
$Cl-CH=CH-As-Cl_2$ LEWISITE		As_2O_3 ARSENOUS OXIDE WHITE ARSENIC	As_2O_5 ARSENIC OXIDE



MAPHARSIDE ARSENOXIDE MAPHARSEN OXOPHENARSINE



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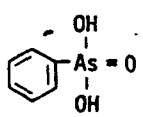
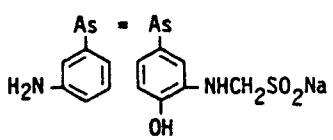
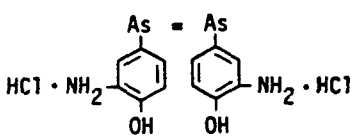


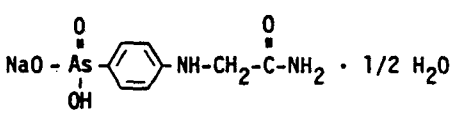
PHENYL ARSONIC ACID



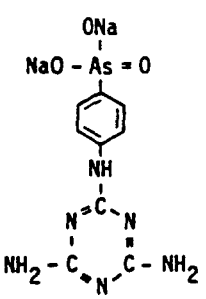
NEOARSPHENAMINE



ARSPHENAMINE "606" SALVARSAN



TRYPARSAMIDE



MELARSEN OXIDE

[a] Taken from: Vallee et al. (1960).

TABLE 2. ARSENIC IN THE ENVIRONMENT

Milieu	Compound	Source	Levels reported (as elemental arsenic)
Air	Arsenic trioxide	Milling and refining; smelters; coal-burning power plants; petroleum	Up to 2.5 $\mu g/m^3$ at property line of Tacoma smelter[a]
Soil		Weathering of arsenic - containing rocks	
	Lead arsenate Arsenic acid Sodium arsenite Calcium arsenate, etc.	Pesticides; insecticides	Less than 10 ppm to 500 ppm[b]
	Cacodylic acid MSMA DSMA, etc.	Herbicides	
Water	Unidentified arsenic compounds	Dissolution of pyrites, minerals and ores; industrial effluents containing arsenic	1100 µg/liter downstream from an industrial complex;[b] 0.14-1.0 ppm in seawater near mouths of estuaries draining industrial areas[c]
Food	Arsenic compounds in fruits and vegetables	Arsenical herbicides and pesticides; arsenical feed additives	
	Unidentified arsenic in seafood (thought to be organically bound)	Weathering and leaching of minerals containing arsenic.	Up to 174 ppm in prawns[c]

[a] Nelson (1977)

[b] Luh et al. (1973)

[c] Vallee (1960)

water, and medicinal preparations are mentioned only as they pertain to the association between arsenic and cancer.

This report is concerned primarily with inorganic arsenic. None of the scientific evidence to date implicates organic arsenic as a carcinogen, and few scientific studies have dealt with the effects of long-term exposure to organic arsenic compounds, such as the herbicides monosodium methanearsonate, disodium methanearsonate, and cacodylic acid. For these reasons it is difficult to draw conclusions as to whether organic arsenic compounds pose a hazard to the general population. The available evidence and its implications are discussed in Section 6.

Most of the available data on the human toxicity of inorganic arsenic relate to human exposure to trivalent arsenic. Much of this information indicates that inorganic trivalent arsenic is a human carcinogen, and that at high levels it can induce other serious, irreversible effects, such as cardiovascular disease and severe peripheral neuropathy. Trivalent inorganic arsenic is emitted into the air along with sulfur dioxide and other contaminants by smelters and coal-burning power plants.

Although there is more clinical and epidemiological evidence for the carcinogenicity of trivalent than pentavalent inorganic arsenic, several studies suggest that pentavalent inorganic arsenic may also be a carcinogen (Frohn, 1938; Roth, 1957; Ott et al., 1974; NIOSH, 1975: reevaluation of Nelson et al., 1973). This evidence is discussed in a recent EPA report (Carcinogen Assessment Group, 1978).

It has been demonstrated that both valency forms of inorganic arsenic interfere with normal genetic functioning, although the trivalent form is more toxic than the pentavalent.

This document pertains to arsenic in particulate matter in the air, rather than to the levels of both inorganic and organic arsenic compounds in waterways, soils, and foods, a concern that deserves consideration elsewhere. A recent review of arsenic toxicity (Luh et al., 1973) points out that no standard has been set for arsenic levels in industrial effluents. The authors

further note that organisms in the aquatic food chain concentrate arsenic by factors of hundreds to thousands over the amounts present in the surrounding water. The only incidents related to human ingestion of contaminated drinking water have resulted from contamination with inorganic arsenic, and these are discussed in this report.

SECTION 2
PHYSICAL AND CHEMICAL PROPERTIES

ROUTE OF ENTRY, DISTRIBUTION, ELIMINATION

The main routes by which arsenic can enter the body are inhalation and ingestion, although absorption through the skin is also a possible minor route of entry (Sollman, 1964; Oehme, 1972; Garb and Hine, 1977). Arsenic compounds are generally absorbed onto particulate matter. The biological fate of the arsenic thus depends on particle size and rate of solution (i.e., solubility). The optimum range for deposition in the lower tracheobronchial tree, where it can either lodge or be absorbed into the blood stream, is 0.1 to 2 μm. Particles smaller than 0.1 μm remain in suspension in the inhaled air and are exhaled. Particles larger than 2 μm are trapped by the mucous membranes of the nose and throat and can be swallowed; these enter the gastrointestinal tract, either to be absorbed or to be excreted (Falk and Kotin, 1961).

Emissions of arsenic and other toxic trace elements from high-temperature combustion sources such as smelters have been observed to be mainly in the size range of less than 1 μm in diameter. Thus they are respirable and are capable of being absorbed through the lungs, the most efficient route of entry (Natusch and Wallace, 1974).

Some information on the distribution of arsenic and its elimination is available from experimental studies involving administration of specific arsenic compounds (usually radioactively labelled) and measurement of arsenic levels in specific tissues and in urine and feces. Arsenic metabolism is poorly understood, however, owing primarily to the scarcity of information

about the form in which arsenic occurs normally in the diet and in human tissues and the interconversions (reduction, oxidation, methylation) of different arsenic compounds in the body (Crecelius, 1977).

Vallee et al. (1960), who reviewed the literature on the toxicology of arsenic in animals and man, report that in most species arsenic concentrates in the liver, kidneys, lung, spleen, and skin in the first 24 hours following oral and parenteral administration. Thereafter, the concentration in the skin increases while that in the liver and kidneys decreases. Low levels of arsenic are distributed throughout the body tissues, but bone, muscle, and skin contain proportionately greater amounts because of their greater mass. They represent the "major storage areas." Following oral administration high levels of arsenic appear temporarily in the gastrointestinal tract. Arsenic is excreted predominantly in the urine and to a much lesser degree in the feces. Excretion takes place rapidly during the first 2 days following intake and more slowly for 7 to 10 days thereafter. Small amounts of arsenic are excreted at a much lower rate through ectodermal tissue (mainly the hair and nails) (Vallee et al., 1960).

The general pattern, then, is rapid clearance from the blood; short-term concentration in the liver, kidneys, lung, and spleen; and rapid excretion of the bulk of the administered dose in the urine. This pattern appears to apply to trivalent arsenic in the rabbit, mouse, guinea pig, and man, and to pentavalent arsenic in the rabbit (DuPont et al., 1942) and cow (Peoples, 1964). Excretion of arsenic by the rat is much slower than in other species owing to the rat's ability to store arsenic in its red blood cells.

A study of inhaled sodium arsenite (^{74}As) in humans has shown that the rate of absorption from the bronchial tree was rapid for the first several days and then decreased slowly. Three patients excreted 45 percent of the inhaled arsenic in the urine in 10 days and excreted 2.5 percent in the feces. The

remainder was assumed to have been deposited in the body, exhaled, or excreted over a long period of time (Holland et al., 1959).

Hunter et al. (1942) found that subcutaneously injected potassium arsenite (^{74}As) was concentrated in the blood in rats but was generally distributed throughout the tissues of guinea pig, rabbit, chimpanzee, one baboon, and man. Excretion took place mainly through the kidney and was essentially complete in 6 days. On examining different fractions of tissues from this experiment, Lowry et al. (1942) found that most of the arsenic was in the protein fraction, a small amount in the acid-soluble fraction, and a trace amount in the lipid fraction.

Ducoff et al. (1948) compared the distribution and excretion of sodium arsenite (^{76}As) in rat, rabbit, mouse, and man. They confirmed the observation that arsenic concentrates in the blood of the rat and found that in the rabbit it is distributed by the bloodstream and concentrates in liver, kidneys, and lungs.

In a woman with carcinoma of the parotid, arsenic concentration was highest in the liver and kidney 20 hours after injection of sodium arsenite (^{76}As).

Cumulative excretion as a percentage of the administered dose was most rapid in rabbits (more than 90% within 96 hours following injection), slower in two human subjects (40 and 50% within 96 hours following injection), and slowest in rats (10% within 72 hours following injection). (No exact measurements were made on excretion rates in mice.)

Lanz et al. (1950) administered sodium arsenate (^{74}As) intramuscularly in the rat, dog, cat, chick, guinea pig, and rabbit. After 48 hours, less than 0.27 percent of the arsenic was present in the organs studied in all species except the rat and cat, which retained 79 and 5.6 percent, respectively, in the blood. Arsenic in the blood of rats was primarily in the hemoglobin. Because of this storage of arsenic in the red blood cells, where it remains for the lifetime of the cell, the rat is a poor model for the fate of arsenic in man.

Dutkiewicz (1977) observed the effects of the route of administration on the distribution and elimination of pentavalent arsenic in rats. Both intravenous and intratracheal administration of sodium arsenate caused immediate distribution of arsenic to most tissues, whereas skin application and gastrointestinal administration caused much lower arsenic concentrations in tissues. These data are summarized in Table 3.

Peoples (1964) fed arsenic acid (pentavalent arsenic) at levels of 0, 0.05, 0.25, and 1.25 mg/kg daily for 8 weeks to lactating cows in order to determine whether arsenic appeared in their milk. After 8 weeks the arsenic levels in tissue were low, even in cows receiving the highest doses. Highest concentrations were in the liver, kidneys, and spleen. Analysis of the blood showed no increase in arsenic. Lack of arsenic storage in the tissues was explained by the arsenic acid content of the urine, which nearly equalled the daily intake. Peoples concluded that the tissues store little arsenic and that "these low levels are rapidly depleted . . . and represent a 'transit' period rather than true storage of arsenic." Peoples found that all tissue-bound arsenic was in the pentavalent form and that none was reduced to the trivalent form. No arsenic appeared in the milk, an indication of a blood-mammary barrier to arsenic in cows.

Mealey et al. (1959) administered radioactive arsenic trioxide to 11 patients dying of intracranial disease and found that arsenic accumulated mainly in the liver, kidneys, and spleen and disappeared rapidly from the blood.

METBOLISM

It is generally accepted that trivalent arsenic is largely oxidized and excreted in the urine in the pentavalent form (Overby and Frederickson, 1963; Peoples, 1964; Schroeder and Balassa, 1966). Winkler (1962) examined the livers of rats fed with sodium arsenite and found that most of the arsenic was pentavalent. While oxidation of trivalent arsenic appears to take place in vivo, it is not clear whether the reverse reaction

TABLE 3. EFFECT OF ROUTE OF ADMINISTRATION ON DISTRIBUTION AND EXCRETION OF PENTAVALENT ARSENIC IN RATS[a]

Route of administration	Percentage of dose/g tissue at various times after administration					
	1 h	2 h	5 h	24 h	120 h	240 h
	Distribution in liver					
Intravenous	3.85	3.73	3.47	2.75	2.17	1.73
Intratracheal	2.49	2.59	3.25	3.08	1.69	1.02
Gastrointestinal	0.34	0.27	0.32	0.26	0.19	0.37
Skin resorption				0.066	0.36	0.23
	Distribution in spleen					
Intravenous	1.60	1.96	2.15	1.72	1.90	1.70
Intratracheal	0.71	1.07	1.55	1.69	2.48	2.75
Gastrointestinal	0.19	0.40	0.65	1.07	0.78	1.20
Skin resorption				0.29	0.63	0.96

	Elimination in urine and feces after 10 days, % of absorbed dose	
	Urine	Feces
Intravenous	39	5
Intratracheal	35	15
Gastrointestinal	20	30
Skin	30	30

[a] Taken from Dutkiewicz (1977).

occurs, i.e., reduction of the pentavalent to the trivalent form. When sodium arsenate and sodium arsanilate (both pentavalent) were fed to rats, the livers contained only pentavalent arsenic (Winkler, 1962). Peoples (1964) also found only pentavalent arsenic in the urine of cows fed arsenic acid (pentavalent). Ginsburg (1965) found, however, that in dogs arsenate was in part reduced to arsenite, which appeared in the urine and blood. It has been suggested that such reduction of the pentavalent organic arsenicals used as medicines may be necessary for their medicinal effects (Vallee et al., 1960).

Urinary excretion following human ingestion of known arsenic species shows that biomethylation occurs. When sodium arsenate and potassium arsenite were fed to cows and dogs, more than 50 percent of the trivalent and pentavalent inorganic arsenic was methylated in the urine (Lakso and Peoples, 1975). After ingestion of arsenite-rich wine, approximately 10 percent of the arsenic was excreted as arsenite, but most of the arsenic was excreted as methylarsonic acid and dimethylarsinic acid. Of 63 µg of arsenic ingested, approximately 80 percent was excreted in the urine within 61 hours. After ingestion of arsenate-rich water, analyses showed higher levels of both arsenate and dimethylarsinic acid in the urine. After ingestion of crabmeat (containing an as-yet-unidentified organo-arsenic compound), elevated levels of dimethylarsinic acid were observed, but only after the urine had been heated in 2N NaOH (Crecilius, 1977).

BIOCHEMISTRY AND TOXICITY

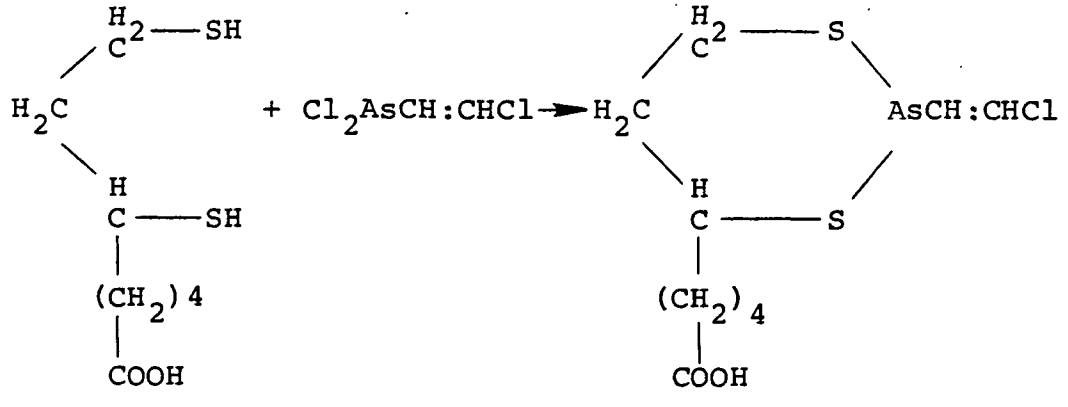
The toxicity of arsenic compounds varies with their valence state and structure. On the basis of experimental studies with animals, trivalent arsenic appears to be considerably more toxic than pentavalent (Webb, 1966; Luh et al., 1973). Pentavalent arsenic does not readily bind to tissues and is excreted rapidly in the urine, whereas trivalent arsenic binds readily and is excreted more slowly (Webb, 1966). Toxicity is thought to be a function of binding of various arsenicals (Vallee et al., 1960).

Inorganic arsenic has been said to be generally more toxic than organic arsenic, but Webb, in an exhaustive review of the biochemistry of arsenic compounds, notes that certain organic compounds (lewisite and phenylarsenoxide) are 50 to 1000 times more potent than arsenite (Webb, 1966, p. 655).

Trivalent arsenic (arsenite), can, owing to its tetrahedral structure with a lone electron pair, complex with hydroxyl groups in biologically important monosaccharides and in catechol (which occurs in epinephrine). Pentavalent arsenic, on the other hand, was found not to complex with hydroxyl groups (Roy et al., 1957). Trivalent arsenic has also been found to inhibit the activity of many enzymes containing sulfhydryl groups by binding to the sulfhydryl groups, with which it has been postulated to form an arsenical-thiol mercaptide (Vallee et al, 1960).

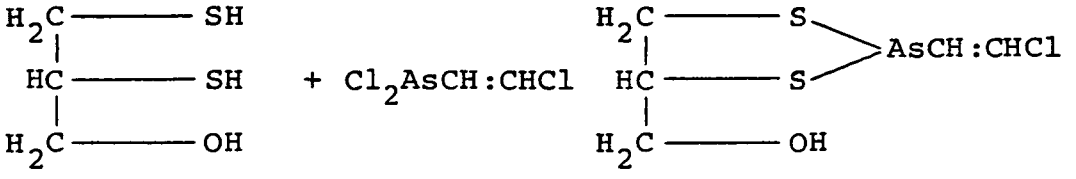
It is thought that such sulfhydryl binding occurs with lipoic acid, thereby inhibiting the pyruvate oxidase system. By blocking pyruvate oxidation, arsenite interferes with cellular respiration, the main energy-producing process in aerobic cells. An extreme example of such binding is the war gas, lewisite, which binds to two thiol groups in lipoic acid to form a stable ring. Inhibition of pyruvate oxidase probably accounts for some of the most obvious acute effects of arsenic poisoning.

The reaction between lipoic acid and lewisite can be represented as:



Lipoic acid Lewisite

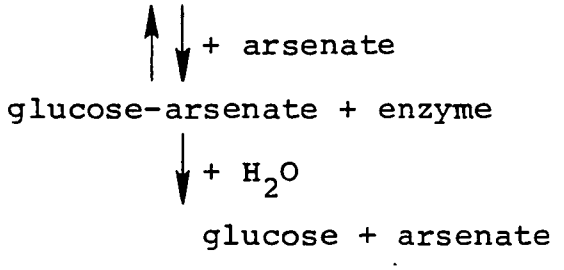
British antilewisite (BAL), which resembles lipoic acid, binds more readily to arsenicals and forms an even more stable five-member ring with lewisite. Thus it can be used as a remedy for arsenic poisoning.



BAL Lewisite

In addition to pyruvate oxidase, some of the other enzyme systems inhibited by trivalent arsenic are: cholinesterase, deoxyribonuclease, d-amino acid oxidase, 2-glutamic acid oxidase, monoamine oxidase, transaminase, liver choline oxidase, choline dehydrogenase, glucose oxidase (Buchanan, 1962). An exhaustive list if given by Webb (1966).

Owing to its similarity to phosphorus, it has been suggested that arsenic, in both its trivalent and pentavalent states, competes with phosphate in many enzymatic reactions. Arsenite uncouples oxidative phosphorylation. Arsenate can replace phosphate in phosphoglyceraldehyde dehydrogenase (Vallee et al., 1960). The arsenical esters formed in these reactions are unstable and are immediately hydrolyzed. This phenomenon is known as "arsenolysis." The uncoupling by arsenite has been explained as follows: "the unstable arsenlyated oxidation product rapidly undergoes irreversible hydrolysis and allows oxidation to proceed at an increased rate, but without the formation of the high energy phosphate bond" (Vallee et al., 1960). The reaction can be represented as:



Rosen (1971) has suggested that arsenic can substitute for phosphorus in DNA. It has been hypothesized that arsenic inhibits dark repair in human epidermal cells by binding to DNA-polymerase (Jung and Trachsel, 1970).

SECTION 3
EXPERIMENTAL STUDIES

CARCINOGENICITY

In an EPA-commissioned project, the National Academy of Sciences (1977) has reviewed the data on the carcinogenicity of arsenic; the Academy concludes that: "In general, animal studies have not shown carcinogenicity for arsenic compounds, even when administered at near the maximally tolerated dosage for long periods." The important experimental studies of carcinogenesis and cocarcinogensis with arsenic are reviewed by NAS (1977) and IARC (1973) and are summarized in Tables 4 and 5.

The NAS cites two exceptions to the generally negative findings. One is a study by Halver (1962), reviewed by Kraybill and Shimkin (1964), in which 50 trout were exposed to carbasone at 480 mg/100 g of diet; five developed heptomas, whereas no heptomas were found in a large control group fed the same diet but without carbasone. The second exception, a study by Osswald and Goerttler (1971), reported a considerable increase in the incidence of leukemia in female Swiss mice given daily subcutaneous injections of sodium arsenate during pregnancy and in their offspring. Pregnant mice were given a total of 20 injections, each containing arsenic at 0.5 mg/kg of a 0.005 percent aqueous sodium arsenate solution. Some groups of offspring from the treated females were given an additional 20 subcutaneous injections of arsenic (0.5 mg/kg) at weekly intervals and others were left untreated. Eleven of 24 mothers (46%) developed leukemia or lymphoma within 24 months after the beginning of the experiment, whereas none of 20 untreated mothers that died during the 2-year period developed lymphoma.

TABLE 4. EXPERIMENTAL CARCINOGENESIS STUDIES WITH ARSENIC

Study	Species	Route of admin.	Compound	Concentration	Frequency	Duration	Results
Hueper and Payne (1962)	Rat	Oral	Arsenic trioxide	0.0004% solution of 12% aqueous ethanol in drinking water	Daily	15 months	No excess tumors
Baroni et al. (1963)	Mouse	Oral	Arsenic trioxide	0.01% in drinking water		60 weeks	No excess tumors
Knoth (1966)	Mouse	Oral	Fowler's solution (potassium arsenite)	Total dose of 7 mg As as As_2O_3	1 drop/week	5 months	Adenocarcinomas of the skin, lung and lymph nodes; tumors were observed in offspring
Kanisawa and Schroeder (1967)	Mouse	Oral	Sodium arsenite	5 mg As/ml	Ad libitum	Lifespan of the mice	No tumors
Fairhall and Miller (1941)	Rat	Oral	Lead arsenate	10 mg/day		Up to 2 years	No tumors
			Calcium arsenate	Equivalent amount			
Hueper and Payne (1962)	Rat	Oral	Arsenic trioxide	0.0004% in drinking water		22-24 months	No tumors
				0.0004-0.0034% in 12% aqueous ethanol			
Byron et al. (1967)	Rat	Oral	Sodium arsenite	0, 15.6, 31.2, 62.5 125, 250 ppm As as sodium arsenite		2 years	No excess tumors
			Sodium arsenate	0, 31.2, 62.5, 125, 250, 400 ppm As as sodium arsenate			
Kanisawa and Schroeder (1969)	Rat	Oral	Sodium arsenite	5 ppm	Ad libitum	Lifespan	No excess tumors "Pretumorous lesions of the liver" in treated rats

(continued)

TABLE 4 (continued)

Study	Species	Route of admin.	Compound	Concentration	Frequency	Duration	Results
Leitch and Kennaway (1922)	Mouse	Skin applications	Potassium arsenite in alcohol (containing 1.8% arsenous oxide; later reduced to 0.12%)		3 times/week	3-5.5 months	Negative
Osswald and Goerttler (1971)	Mouse	Subcutaneous	Sodium arsenate	0.6 mg/kg body weight as 0.005% aqueous solution of sodium arsenate	Daily throughout pregnancy	2-year observation period	11 treated mice (45%) developed lymphocytic leukemia or lymphoma
		Intramuscular					13 of the 71 untreated progency of the arsenate-mothers developed lymphoma during a 2-year observation period compared with 41 of 97 progency given weekly subcutaneous injections of 0.5 mg/kg body weight (as sodium arsenate)
Osswald and Goerttler (1971)	Mouse	Intravenous	Sodium arsenate	0.5 mg As (as 0.005% solution of sodium arsenate)	Weekly	20 weeks	11 of 19 mice had lymphoma
Heuper (1954)	Rat	Intramedullary injection in the femur	Metallic arsenic in lanolin	0.43 mg arsenic			1 sarcoma at site of injection
	Rabbit			0.64 mg	Single injection		No tumors
Holland and Acevedo (1964)	Rabbit	Inhalation	Arsine gas	Small doses	Daily	20-26 months	One rabbit developed a malignant mesothelioma of the pleura after 17 months exposure

TABLE 5. EXPERIMENTAL STUDIES OF COCARCINOGENESIS, TUMOR PROMOTION, AND INITIATION

Study	Species	Route of admin.	Compound	Concentration	Frequency, duration	Promoter or initiator	Results
Salaman and Roe (1956)	Mouse	Skin application	Potassium arsenite	1% solution in methanol	Once/week for 10 weeks	Promoter 0.17% or 0.085% croton oil in acetone	Three treated mice developed skin papillomas, but controls receiving only croton oil also developed skin tumors
Baroni (1963)	Mouse	Oral	Arsenic trioxide	0.01% solution	40-60 weeks	Croton oil, DMBA, or urethane	No excess tumors
		Skin application	Sodium arsenate			Initiators: urethane DMBA	
						Promoter: croton oil	
Boutwell (1963)	Mouse	Oral	Potassium arsenate	2.4 mg $KAsO_2$/ mouse	Over 5-day period	Promoter: croton oil	No excess tumors in test mice receiving potassium arsenite compared with control mice receiving only croton oil or DMBA + croton oil
				676 mg $KAsO_2$/kg of diet	2 weeks	Initiator: DMBA croton oil	
				169 mg $KAsO_2$/kg diet	48 weeks		
		Skin application		1.24 mg/ mouse	Over 5-day period	Promoter: croton oil in benzene	
				2.2 mg/ weeks	29 weeks	Initiator: DMBA	

(continued)

TABLE 5 (continued)

Study	Species	Route of admin.	Compound	Concentration	Frequency, duration	Promoter or initiator	Results
Milner (1969)	Mouse	Oral	Arsenic trioxide	0.01% in drinking water	4-13 weeks	Initiator: MCA	No enhancement of skin cancer
Kroes et al. (1974)	Rat	Oral	Lead arsenate Sodium arsenate	463 and 1850 ppm in diet 416 ppm in diet	Up to 29 months	DENA	No evidence of carcinogenicity of sodium arsenate; inconclusive evidence for lead arsenate; no enhancement of carcinogenic effect attributable to DENA

[a] DMBA = dimethylbenz (a) anthracene;
MCA = methylocholanthrene;
DENA = diethylnitrosamine.

Among the untreated offspring, 7 of 34 males (21%) and 6 of 37 (16%) females developed leukemia. Among the treated offspring 17 of 41 males (41%) and 24 of 50 females (48%) developed leukemia. Eleven of 19 treated offspring (58%) also developed lymphoma. Among untreated control mice only 3 of 35 male (9%) and none of 20 female offspring developed leukemia.

IARC (1973) comments that this study is "difficult to interpret since 20 out of the 55 control animals and some of the experimental animals were still alive at the date of reporting." The NAS criticism that the credibility of this study is limited by the "failure to give the vehicle solution to the controls" is difficult to understand because the sodium arsenate was administered in aqueous solution.

Two other reports that may indicate positive effects are those of Knoth (1966) and Kanisawa and Shroeder (1969).

Knoth (1966) reported in a preliminary study that oral administration of one drop of Fowler's solution (containing potassium arsenite) per week for 5 months to groups of 30 mice (equivalent to a total dose of 7 mg calculated as As_2O_3) caused a significant increase in the number of tumor-bearing mice. Tumors including adenocarcinomas of the skin, lung, and lymph nodes were observed at 14 months, the time at which the experiment was ended. Fifteen control mice showed no tumors. Offspring of the treated mothers also showed some tumors, whereas the offspring of the control mice showed no tumors. Knoth's data are difficult to interpret because the preliminary report is very brief and the followup study he mentioned was not published.

Kanisawa and Schroeder (1969) fed 91 Long Evans rats sodium arsenite in their drinking water at a concentration of 5 ppm over their lifespan. The incidence of tumors in treated rats was similar to that in untreated controls. The authors note, however, that 19 of 91 rats given arsenic developed unspecified "pretumorous lesions" of the liver, whereas only 10 of 82 controls developed such lesions. IARC (1973) called attention to the very low level of arsenic used in this experiment.

Thus, some evidence can be taken to indicate that arsenic causes cancer in test animals. These interesting leads should be followed-up, refined, and replicated in order to fully substantiate the experimental carcinogenicity of arsenic. The NAS (1977) discusses factors to be considered in future efforts to find an experimental model for arsenic carcinogenesis.

MUTAGENICITY

Both point mutational and chromosomal tests indicate that trivalent and pentavalent inorganic arsenic are mutagenic. Furthermore, both forms of arsenic appear to interfere with DNA repair in a variety of cell types, and sodium arsenate has this effect in human epidermal cells. These studies are summarized in Table 6.

Jung et al. (1969) found that exposure of living human epidermal cells to inorganic arsenic causes a temporary reduction in enzymatic repair of DNA. They hypothesized that prolonged inhibition by arsenic of repair of DNA damage caused by ultraviolet radiation, chemical agents, or viruses could lead to scattered lesions, which "may constitute the starting point of carcinogenic changes."

Burgdorf (unpublished Master's Thesis, 1977) studied sister chromatid exchange (the exchange of genetic material between the two chromatids of a single chromosome during mitosis) in six patients with histories of arsenic use and with multiple skin malignancies and other signs of chronic arsenicism. In all six the frequencies of sister chromatid exchange were significantly elevated. Burgdorf notes, however, that the meaning of elevated sister chromatid exchange is not yet understood. It may reflect either DNA damage or successful DNA repair.

Paton and Allison (1972) tested the effects of sodium arsenite, sodium arsenate, and acetylarsan in cultures of human leukocytes and diploid fibroblasts. Subtoxic doses of the arsenic compounds were added to leukocyte cultures and fibroblast cells at various times between 2 and 24 hours of fixation. A

TABLE 6. SUMMARY OF STUDIES ON INORGANIC ARSENIC MUTAGENICITY[a]

Study	Author(s)	Chemical(s)	Cell type	Effects
Dominant lethal effects	Sram and Bencko (1974)	Sodium arsenite	ICR-SP mice	An acute oral dose (250 mg/kg) given to the male produced negative results. Chronic application over 4 generations of males at 10 mg/liter of drinking water gave positive results (increase in overall dominant and preimplantation lethality); subtoxic dose (100 mg/liter) gave no change in frequency of dominant lethality or male fertility
DNA repair (Microbial)	Rossman et al. (1975, 1976)	Sodium arsenite	E. coli (uv-exposed)	Decreased mutation frequency of irradiated cells that were excision-repair deficient; decreased survival rate of uv-exposed cells (wild type, excision-repair deficient); no effect was found on strain deficient in post-replication repair
(Mammalian)	Jung et al. (1969)	Sodium arsenate	Human epidermal cells (exposed to xenon lamp)	DNA dark repair activity decreased in presence of sodium arsenate
	Jung and Trachsel (1970)	Sodium arsenate	Human epidermal cells (exposed to xenon lamp)	DNA synthesis (reduced mitotic index) and DNA dark repair both inhibited in presence of sodium arsenate
Metabolic and cellular toxicity effects	Skipper et al. (1951)	Potassium arsenite	Mice	Reduced incorporation of ^{14}C-formate (precursor of mouse DNA-purines) into nucleic acid purines
(In vivo)	Sawada and Rebhun (1969)	Sodium arsenite	Annelid worm eggs	Inhibition of the formation of the mitotic apparatus (before fertilization)

(continued)

TABLE 6 (continued)

Study	Author(s)	Chemical(s)	Cell type	Effects
Point mutation	Ficsor and Piccolo (1972)	Sodium arsenate	E. Coli	No reversions induced
	Moore (1976)	Arsenic trioxide	S. typhimurium	Negative Ames' test (without metabolic activation)
	Nishioka (1975)	Sodium arsenate	Bacillus subtilis	Positive mutagen
		Sodium arsenite	Bacillus subtilis and E. coli	Positive mutagen > effect stronger than sodium arsenate
				Positive mutagen > effect stronger than sodium arsenate
	Casto (1977 letter)	Sodium arsenite	Hamster lung cells	Positive mutagen; increased the frequency of mutation in 8-asaguanine resistant cells
Chromosomal effects In vitro	Oppenheim and Fishbein (1965)	Potassium Arsenite	Human peripheral leukocytes	Chromosome gaps, breaks translocation, dicentrics, ringforms; cell division suppressed; increased number of broken metaphase plates
	Patton and Allison (1972)	Sodium arsenite	Human diploid fibroblasts	Chromatid breakage
		Sodium arsenite	Human diploid	Chromatid breakage > effect higher with sodium arsenite
		Sodium arsenate	Fibroblasts and leukocytes	Chromatid breakage > effect higher with sodium arsenite
In vivo cytogenetics	Petres et al. (1970)	Unspecified (probably potassium arsenite and lead arsenate)	Human leukocytes (from psoriasis patients and winegrowers)	Compared with controls, arsenic treatment yielded a much higher percentage of secondary chromosomal constrictions, achromatic lesions, chromosome gaps, chromatid breaks, acentric fragments, dicentric chromosomes, and aneuploidy
Sister chromatid exchange	Burdorf et al. (1977)	$KASO_2$ (Fowler's solution)	Human lymphocytes	Compared with controls, patients treated with Fowler's solution had elevated rates of sister chromatid exchange

(continued)

TABLE 6 (continued)

Study	Author(s)	Chemical(s)	Cell type	Effects
(In vitro)	Tsuda (1974)	Sodium arsenate	Mouse fibroblasts	Indices for prophase, metaphase, and mitosis increased; but indices for telophase decreased
	Petres and Hundeiker (1968)	Sodium arsenate	Human peripheral lymphocytes	Number of mitoses reduced to 1/5 the expected number; chromosome pulverization occurred consistently
	Petres and Berger (1972)	Sodium arsenate	Same	At high concentrations, the mitotic index decreased; metaphase plate pulverizations at low doses; inhibition of ^{3}H-thymidine incorporation into DNA
	Petres et al. (1974)	Sodium arsenate	Same	Inhibition of ^{3}H-thymidine and ^{14}C-thymidine incorporation into DNA at lower doses than inhibition of ^{3}H-uridine and ^{14}C-uridine into RNA
	Petres et al. (1975)	Sodium arsenate	Same	After 1 h of exposure, increasing inhibition of ^{14}C-thymidine incorporation into DNA
	Baron et al. (1975)	Sodium arsenate	Same	Inhibition of ^{14}C-TTP into DNA and ^{14}C-UTP RNA; inhibition of corporation of labeled alanine and leucine into cellular proteins

[a]Source: EPA Carcinogen Assessment Group.

(continued)

significantly increased incidence of chromosome breakage was found in leukocytes treated with sodium arsenite (2.9×10^{-9} to 1.8×10^{-8} M) and acetylarsan (6.0×10^{-8} M) in the last 48 hours of the culture period. In the leukocytes treated with sodium arsenite 60 percent of 148 metaphases examined had chromatid breaks. In leukocytes treated with acetylarsan, 20 percent of 50 metaphases observed had chromatid breaks. Sodium arsenate, however, administered in the highest nontoxic concentration, caused no significant increase in the number of breaks. Diploid fibroblast cultures exposed to sodium arsenite (2.9×10^{-9} to 5.8×10^{-8} M) in the last 24 hours of culture showed a significantly increased incidence of chromosomal damage.

Beckman et al. (1977) looked at chromosomal aberrations in short-term cultured lymphocytes from nine employees exposed to arsenic at the Rönnskär smelter works. In lymphocytes from smelter workers there were 87 aberrations in 819 mitoses. The frequency of aberrations was significantly higher ($p<0.001$) among the arsenic-exposed workers than among controls. Individual variations ranged from 0 to 25 aberrations per 100 cells. Since the arsenic-exposed workers also experienced concomitant exposure to other chemicals, it could not be determined whether arsenic alone or arsenic in conjunction with other agents was responsible.

Petres et al. (1977) examined lymphocytes from 31 patients at a dermatological clinic. These patients had been exposed to arsenic and displayed the characteristic arsenical hyperkeratoses of the hands and feet. Thirty-one people with no known arsenic exposure served as a control group. The group with arsenic exposure showed a frequency of chromosomal aberrations significantly above that of the controls. The frequency of chromatid breaks was especially high (34 times greater than in the controls). Petres et al. also found that <u>in vitro</u> addition of sodium arsenate to cultured lymphocytes from healthy subjects induced the same chromosome changes that were found in the exposed group. Radioactive incorporation studies indicated that

arsenate inhibited the incorporation of radioactively labelled nucleotides in RNA and DNA, and the inhibitory effect increased with increased dose. Finally, Petres et al. noted that arsenic blocked the lymphocytes in the S- and G_2 phases. Petres et al. suggested that arsenic interferes with enzyme systems involved in nucleic acid metabolism by binding to the sulfhydryl groups in certain enzymes and possibly by uncoupling phosphorylation or substituting for phosphorus in nucleic acids.

Rossman et al. (1977) showed that the presence of sodium arsenite significantly decreased survival of wild type E. coli after ultraviolet irradiation, an indication that arsenite is mutagenic in E. coli normally capable of carrying out post-replication repair. This finding would support the hypothesis that arsenite may act as a cocarcinogen by interfering with DNA repair, although no strong experimental evidence of such cocarcinogenicity is available.

Administration of arsenic together with the referential mutagen (chemosterilant TEPA, tris(1-aziridinyl) phosphine oxide) resulted in a significant increase in dominant lethal mutations in F_3 generation mice. This effect, seen only at high dosages, has been explained by the possible interference of arsenic in chromosome repair by its blocking sulfhydryl groups (Bencko, 1977).

Negative results have been reported (Hodge, 1977) in tests for a dominant lethal effect by administering (intraperitoneally) to male mice single doses of sodium arsenate (5 mg/kg), sodium arsenite (5 mg/kg), sodium cacodylate (200 mg/kg), arsenoacetic acid (50 mg/kg), methane arsenic acid (250 mg/kg), and a composite flue dust (2 mg/kg). The implications of a negative dominant lethal test are thought to be limited.

TERATOGENICITY

Several investigators have shown that sodium arsenate induces developmental malformations in a variety of test animals:

embryo chick, hamster, rat, and mouse (Ancel, 1946; Ridgeway and Karnovsky, 1952; Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974).

Pregnant golden hamsters injected with sodium arsenate (15 to 25 mg/kg body weight) produced offspring with a range of developmental malformations including anencephaly, renal agenesis, rib malformation, cleft lip and palate, and anophthalmia. The percentages of living embryos with various selected malformations followed maternal treatment with 20 mg/kg sodium arsenate on the 8th day of gestation were as follows: nearly 90 percent with all malformations; over 80 percent with anencephaly; nearly 70 percent with rib malformations; 30 percent with exencephaly. The spectrum of malformations varied with the time of injection during critical stages of embryogenesis. Malformations induced by arsenate differed from those induced by other teratogenic agents including certain heavy metals (Ferm et al., 1971).

In another study, single intraperitoneal injections of sodium arsenate (45 mg/kg) in Swiss-Webster mice between the 6th and 11th days of gestation consistently caused an increase in fetal resorptions, a significant decrease ($p<0.05$) in fetal weights compared to controls, and a number of fetal malformations, most frequently the following: exencephaly, shortening of the jaws with consequent protrusion of the tongue, exophthalmos, missing pinna, cleft lip, hydrocephalus, umbilical hernia, eventration, ectrodactyly, micromelia, and shortened or twisted tail or limb, or both. Malformations were dependent on the stage of embryogenesis. Exencephaly occurred in 54 percent of the fetuses when the injection was administered on day 9 of gestation; fusion of the ribs occurred in 100 percent of the fetuses when the injection was given on day 9; and fusion of the vertebrae occurred in 73 percent when the injection was given on day 10 (Hood and Bishop, 1972).

In a later report, Ferm (1977) demonstrated that administration of 20 mg/kg of sodium arsenate intravenously or intraperitoneally to Golden hamsters during day 8 to 9 of gestation

induced a specific spectrum of malformations including exencephaly, encephaloceles, skeletal defects, and malformations of the genitourinary system. The last effect, which appears to be unique to arsenate occurred in both sexes and with high frequency.

Ferm (1977) further showed that sodium arsenate (^{74}As) injected intravenously into Golden hamsters on day 8 of gestation was transmitted across the placenta during the critical stage of embryogenesis and appeared in the fetal tissues. Ferm refers to a report by Lugo et al. (1969) concerning a case of arsenic trioxide poisoning during human pregnancy, which demonstrated the "ease with which inorganic arsenic crosses the human placenta at term with extremely high levels in the fetal liver, brain, and kidneys" (Ferm, 1977). Introduction of arsenic into fertilized bird eggs has led to malformations of beak and brain (Peterkova and Puzanova, 1975).

Hood et al. (1977) compared the prenatal effects of oral and intraperitoneal administration of sodium arsenate in mice. Intraperitoneal administration had a considerably greater effect than oral administration on prenatal mortality, reduction of fetal weights, and occurrence of fetal malformations. The dosages were 40 mg/kg (intraperitoneal) and 120 mg/kg (oral).

Hood et al. further noted that although arsenite is considerably more toxic than arsenate, it has received less attention from teratologists. Intraperitoneal injection of mice <u>in utero</u> with 10 to 12 mg/kg of sodium arsenite on one of days 7 to 12 of pregnancy caused significant increases in prenatal mortality ($p<0.05$), and treatment on days 8, 9, and 10 resulted in gross and skeletal malformations similar to but less frequent than those induced by comparably toxic levels of arsenate (Hood et al., 1977).

SECTION 4
EFFECTS OF HUMAN EXPOSURE TO ARSENIC

We have noted that the respiratory tract represents a major route of entry for arsenical compounds. Much of the evidence regarding the toxic potential of inhaled arsenic derives from data on occupationally exposed populations, although epidemiological investigations of the relative cancer rates in communities near arsenic smelters have also been reported. Epidemiological and clinical studies of worker groups and of communities located near smelters are presented below.

The National Institute of Occupational Safety and Health (NIOSH) has estimated that 1.5 million workers are potentially exposed to inorganic arsenic (National Institute of Safety and Health, 1975). Occupational exposure to arsenic occurs principally in workers employed in the smelting and refining of nonferrous ores containing arsenic, in workers employed in producing arsenical pesticides and insecticides, and in agricultural workers using arsenical desiccants and pesticides. A relatively small number of workers and communities is exposed to organic and inorganic arsenic used as desiccants in cotton-ginning operations.

Environmental exposure to airborne arsenic may be a cause for concern in the vicinity of smelters, coal-fired power plants, glass-manufacturing plants, and other sources of arsenical air pollution.

SMELTER WORKERS AND COMMUNITY RESIDENTS

Smelter workers are a population exposed to high levels of arsenic trioxide fumes in conjunction with high levels of sulfur

dioxide. Other air contaminants, such as lead and other heavy metals, are also present but in smaller quantities. Toxic exposures of smelter communities and workers have been much greater in the past than they are now (Nelson, 1977), so that epidemiological evidence relating to workers with a long history of smelter work is of particular significance. This evidence is summarized in Table 7.

The working population at the smelter in Tacoma, Washington, has been studied extensively over the years. ASARCO, which operates the smelter, has collected and published a great deal of data on atmospheric and biological exposure levels; the series of reports based on these studies represent an important contribution to the available knowledge about the effects of arsenic on humans. The papers are especially interesting when presented in chronological order because they illustrate the changes in recognition of the effects of chronic arsenic exposure. Milham and others not employed by ASARCO have also studied this population, and their results are relevant.

In early study Pinto and McGill (1953) reported the urinary arsenic levels of 348 workers exposed to arsenic trioxide dust at the Tacoma smelter and concluded from physical examinations of the population that the urinary arsenic levels were not associated with systemic arsenic poisoning. The values ranged from 0.10 to 6.44 mg arsenic/liter. The average urinary arsenic level for the whole group was 0.82 mg/liter. In 147 men actively working in the industry, but considered by Pinto and McGill not to have exposure to arsenic trioxide, the average urinary level of arsenic was 0.13 mg/liter.

Pinto and Bennett (1963) reported on an investigation of the causes of death among 229 active smelter workers and retirees from the Tacoma plant over the period 1946 to 1960 and calculated proportional mortality rates (PMR). The PMR's calculated for the male population of the State of Washington between the ages of 15 and 95 in the year 1950 served as a reference rate. Among the smelter workers 43 cancer deaths were observed whereas 36.7 were

TABLE 7. SUMMARY OF EPIDEMIOLOGICAL STUDIES OF SMELTER WORKERS

Study	Type of study, and period of observation	Process	Number in cohort	Findings	Exposure data
Pinto and McGill (1953)	Clinical	Smelter producing As_2O_3 as byproduct			Urine levels; but "nonexposed" smelter workers might have had some exposure to arsenic
Pinto and Bennett (1963)	Proportionate mortality, 1946-1960	Smelter workers at same plant as Pinto and McGill	229 deaths reported among 904 active plant employees and 209 pensioners	Smelter workers had increased incidence of deaths due to lung cancer as a proportion of cancer deaths (41.9% vs. 23.7% in the state as a whole)	
Milham and Strong (1974)	Proportionate mortality, 1950-1971	Smelter workers at same smelter as Pinto and McGill	>241 deaths	Increased lung cancer; 40 observed deaths, 18 expected ($p< 0.001$)	Urine levels
Lee and Fraumeni (1969)	Retrospective cohort analysis, 1938-1963	Smelter workers with exposure to As_2O_3	1877 deaths among 8047 white male smelter workers	6.7, 4.8, and 2.4-fold lung cancer excess for heavy, medium, and light exposure	Heavy, medium, and light exposure groups (concomitant exposure to SO_2)
Kuratsune et al. (1974)	Case-control, 1917-1965		Case group: 19 males who died of lung cancer; 19 males who died of diseases other than lung, urinary, bladder, or skin cancer	11 lung cancer deaths occurred in former copper smelter workers vs. only 3 deaths in former copper smelters in the control group ($p=0.01$)	Exposure to SO_2 and PAH
Milby and Hine (unpublished, 1974)	Proportionate mortality, 1950-1972	Same company as studies by Rencher and Carter (Utah smelter)	1910 deaths among persons who had worked at least 10 years with company (including mine, concentrator, refinery) with no increased risk according to Rencher and Carter	No excess lung cancer	

(continued)

TABLE 7 (continued)

Study	Type of study, and period of observation	Process	Number in cohort	Findings	Exposure data
Tokudome and Kuratsune (1976)	Retrospective cohort, 1949-1971	Metal refinery	157 deaths among 839 copper smelter workers	Significant excess mortality for lung cancer (SMR=1189) among smelter workers with heavy exposure for 15 or more years; this exposure reached SMR=2500	Dose-response relationship demonstrated between lung cancer mortality and degree of exposure
Pinto, Enterline, Henderson, and Varner (1977)	Historical prospective, 1949-1973	Copper smelter workers with exposure to As_2O_3	324 deaths among 527 male retirees from copper smelter	Significant excess mortality for all causes (SMR=112.2) for cancer (SMR=148.4) for lung cancer (SMR=304.8). Highest exposure category SMR=833.3	Measurements of urinary arsenic for all plant workers showed direct correlation between airborne As and urinary As values; time-weighted index of total lifetime exposure to As was linearly related to respiratory cancer mortality
Rencher and Carter (1971)	Retrospective 1959-1969	Copper smelter workers	651 deaths	Smelter workers exhibited highest % of deaths from lung cancer (7.0% based on 17 deaths); both smoking and nonsmoking smelter workers experienced a higher relative frequency of lung cancer deaths than their counterparts at the mine and the concentrator	Based on average exposure in each of 12 work areas and amount of time worked in each of these areas, 5 exposure indices (for SO_2 sulfuric acid mist, arsenic, lead, copper) were computed for each worker and averaged over the number of persons in each of the three categories of cause of death; all 5 of these average cumulative exposure indices were substantially higher for lung cancer group, indicating that these persons had either worked longer in the smelter or in areas of higher exposure to the contaminants than persons dying of other causes; average hourly exposure level for the 12 work areas ranged from a reported 0 in the engineering building and warehouse to 22.0 $\mu g/m^3$ in the reverberating furnace area; overall average was 7.38 $\mu g/m^3$

expected. For lung cancer the rates were 41.9 percent (18 out of 43) for smelter workers and 23.7 percent for Washington males. The significance levels of these calculations are not reported.

When the smelter population was divided into exposed and unexposed workers on the basis of urinary arsenic levels measured in the Pinto and McGill study, the authors calculated that unexposed workers had a higher proportion of deaths from all cancer (37 versus 6) and from lung cancer (15 versus 3) than exposed workers. The age at death of exposed workers did not correlate with arsenic exposure. Pinto and Bennett concluded that the levels of arsenic trioxide to which the workers were exposed did not cause systemic cancer or cardiovascular disease.

According the Milham and Strong (1974), however, the 39 lung cancer deaths among the Tacoma smelter workers between 1950 and 1971 represent a significant excess ($p<0.001$) over the number expected (18) on the basis of U.S. mortality rates.

A recent study of the mortality of retired Tacoma smelter workers by Pinto et al. (1977) confirms the Milham and Strong results. Pinto et al. found evidence of a dose-response relationship between exposure to airborne arsenic and lung cancer mortality. The study group consisted of 527 pensioners from the Tacoma copper smelter. Overall mortality rate of the retirees was 12 percent higher than that of all Washington males. Mortality due to lung cancer showed the greatest excess (32 deaths observed vs. 10.5 expected; standardized mortality rate (SMR) = 304.8; $p<0.05$). Smoking histories obtained for most retirees did not appear to account for the elevated lung cancer rate.

An "index of exposure" based on urinary arsenic levels was calculated for each retiree. The "index" did not indicate an absolute exposure rate, but rather represented the relative exposure rates among the cohort members. Intensity of exposure was better correlated with lung cancer mortality than was length of exposure; a gradient of increasing lung cancer mortality corresponded to the increasing exposure gradient. Among the group with highest exposure, the SMR for lung cancer was 833.3.

Although the smoking histories that were obtained with respect to most of the retirees did not appear to be correlated with the elevated lung cancer rate in this report, Pinto et al. later reported that among 377 retirees alive on January 1, 1961, the SMR for the 189 smokers was 287 ($p<0.05$). The SMR for 119 nonsmokers was 507 ($p<0.05$) (Pinto et al., in press).

Pinto et al. (1977) also observed that among workers with less than 25 years of exposure the lung cancer rates were lower than those of workers with more than 25 years. Also, the risk for lung cancer decreased with increasing age beyond 65. These observations are taken by the authors as possible evidence of a threshold value for arsenic trioxide, below which no adverse effect may be expected. This conclusion is discussed further in the health assessment section. The authors concluded that although other airborne contaminants were present in the atmosphere of the smelter, exposure to airborne arsenic was "closely related" to the excess lung cancer observed.

Milham (1977) examined the cause of death among 753 Tacoma smelter workers for the period 1940 to 1976. The study group included retirees and men who had worked in the smelter, but had not retired from it and had continued to reside in Pierce County after termination of employment. Former employees who died out of the State of Washington were not included.

The rates of deaths from all cancer, cancer of the large intestine, and lung cancer showed significant excesses when compared with the rates among Washington males. The respective PMR's are 128, 162, and 222 (for all threee, $p<0.05$). Excesses in deaths from circulatory diseases and nephritis/nephrosis were also significant (PMR's = 119 and 122, respectively; $p<0.05$ in both cases).

These investigations and their implications are discussed more fully in Section 6. The Tacoma smelter epidemiological data discussed here are summarized in Table 3.

An extensive study of workers in many smelters was carried out by Lee and Fraumeni (1969), who examined deaths among 8047

white male smelter workers with exposure of 1 year or more to arsenic trioxide during the period 1938 to 1963. The mortality of the smelter workers was compared with that of the white male population of the same states by use of the life-table method. Excess overall mortality among smelter workers was significant ($p<0.01$) and was attributable primarily to cancer and cardiac disease. Among specific causes of death, lung cancer showed a significant excess over the expected (SMR = 329; $p<0.01$). Excess of lung cancer reached 8-fold in workers with more than 15 years employment and heavy exposure to arsenic. On the basis of air measurements each work area was classified as involving "heavy," "medium," or "light" exposure. In general, excess lung cancer reflected the degree of exposure to both arsenic and sulfur dioxide. Distinguishing the effects of arsenic from those of SO_2 is not possible because most work areas with heavy arsenic exposure also involved medium SO_2 exposure and all jobs with heavy SO_2 exposure involved medium arsenic exposure. The highest excess of lung cancer, however, occurred among those workers with heaviest exposure to arsenic coupled with moderate or heavy exposure to SO_2. The authors conclude that their findings are consistent with the "hypothesis that exposure to high levels of As_2O_3, perhaps in interaction with SO_2 or unidentified chemicals in the work environment, is responsible for the excessive number of respiratory cancer deaths among smelter workers."

In their study of the mortality at the Kennecott smelter near Salt Lake City, Rencher and Carter (1977) also report a significant excess of deaths due to lung cancer among smelter workers (7.0% of all deaths). The lung cancer mortality among smelter workers is compared with that of mine workers (2.0%), concentrator workers (2.2%), and Utah males (2.7%). In addition to excess lung cancer mortality, a smaller excess due to other types of cancer was found among smelter workers. Data on smoking habits were examined, but gave no evidence of an increased risk for smokers. The excess lung cancer mortality occurred in those

with the greatest cumulative exposure to five contaminants: SO_2, H_2SO_4 mist, arsenic, lead, and copper.

All deaths among current and former employees in the 11-year period from 1959 to 1969 were included in the study. The life-table method was used in comparing the death rates of smelter and mine workers with those of State of Utah citizens. Each deceased employee was classified according to the length of time worked in each of 12 major work areas, and indices were developed for each employee for exposure to SO_2, H_2SO_4 mist, arsenic, lead, and copper. Information on smoking was obtained for nearly all deceased smelter workers and for random samples of mine and concentrator workers. Workers were classified in one of three groups: smokers, nonsmokers, and those of unknown smoking history. The proportion of smokers was similar in each of the operations (approximately 60%). To evaluate the increased risk of lung cancer among smelter workers with respect to the risk among smokers, the investigators compared the smelter/mine mortality ratios with the smoker/nonsmoker mortality ratios for U.S. males. They found that "any increased risk at the smelter is far less than the risk due to smoking in the population at large."

Rencher and Carter concluded that the excess of lung cancer mortality at the smelter might be due to high levels of airborne arsenic prevalent in the plant before 1959. They also noted that areas of the plant with high levels of airborne arsenic also had high levels of SO_2, similar to the situation reported by Lee and Fraumeni (1969).

Kuratsune et al. (1974) performed a case-control study of much smaller scope. The cases consisted of 19 males in one town who died of lung cancer. Eleven men (58%) had worked as smelters in a local copper smelter, where they were exposed to high levels of arsenic. The control group consisted of 19 men who had died of diseases other than cancer of the lung, bladder, or skin. The control group had only three smelter workers (15.8%).

Smoking habits were similar in the two groups, and the difference between the two groups was significant ($p=0.01$).

As a followup of the case-control study, Tokudome and Kuratsune (1976) conducted a retrospective cohort study of workers at the smelter in the town. The period of observation was 1949 to 1971. Observed deaths were compared with expected deaths based on age- and cause-specific death rates for Japanese males. Copper smelter workers had a significant excess of lung cancer deaths (29 deaths vs. 2.4 expected; SMR = 1189; $p<0.01$). In smelter workers with heaviest exposure the SMR for lung cancer mortality reached 2500. Furthermore, the SMR's for subgroups of copper workers showed a definite positive gradient with length of employment, level of exposure, and time when exposure occurred, although the numbers of deaths in each category were small. The authors took this as clear evidence of a dose-response relationship.

Smoking habits of the smelter workers were not thought to be different from those of other workers, and smoking alone could not account for the magnitude of the increased risk. The authors concluded that arsenic and sulfur dioxide were probably responsible for the observed excess mortality, although polycyclic aromatic hydrocarbons were also present in the operations at the time and cannot be ruled out as contributing to the lung cancer mortality.

One study that did not show an increased proportion of lung cancer deaths was carried out by Snegireff and Lombard (1951), who compared the mortality of workers in a plant (Plant A) that handled large amounts of arsenic trioxide with that of the population of the State. During a 25-year period, 18 deaths from cancer were reported among workers in the plant. Seven of these were ascribed to lung cancer. The deaths were not limited to workers in any specific work area within the plant or to any occupational group. The authors calculated that the proportion of cancer deaths among plant workers under 55 (9 cancer deaths

out of a total of 62, or 12.5%) was not significantly different from that for the State (6.1%).

At a second plant (Plant Z, the type of plant is not specified) in which arsenic was not present, the workers had an excess proportional mortality rate for cancer (in age groups below 55) similar to that of workers in the arsenic-handling plant.

NIOSH (1975) pointed out several deficiencies in this study. Snegireff and Lombard did not calculate the relative lung cancer mortality rates in the two plants, which accounted for 38.9 and 50.0 percent of cancer deaths in the "arsenic" plant and the "nonarsenic" plant, respectively. Furthermore, because they made no attempt to determine the status of former employees or retirees, the exposed cohorts are incomplete.

Using the total cancer deaths experienced in each plant, NIOSH calculated the expected number of lung cancer deaths, by age group, that should have occurred if the rates for the appropriate U.S. population were applied. Both plants showed large excesses of lung cancer deaths relative to mortality from all causes in 1938 (460% for Plant A; 350% for Plant Z). Both plants also showed large excesses when lung cancer deaths were compared to all cancer deaths (450% for Plant A; 550% for Plant Z). These excesses for lung cancer contrasted with the deficits that both plants showed for total cancer mortality relative to all causes of death (4% for Plant A; 25% for Plant Z). The excesses of lung cancer deaths in both plants indicate that it is lung cancer rather than all cancers that requires detailed examination and furthermore that Plant Z was an inappropriate control population since its workers were evidently exposed to some respiratory carcinogen.

COMMUNITY EXPOSURES

Mortality studies of inhabitants of communities near smelters emitting arsenic have also been reported. In a study comparing lung cancer mortality in 71 counties, Blot and Fraumeni

(1975) suggested an association between elevated lung cancer mortality and environmental air pollution from industrial sources of inorganic arsenic. The study compared the average mortality rates for lung cancer among white males and females in counties with copper, lead, or zinc smelting and refining industries and in counties with other nonferrous ore-processing industries. Copper, lead, and zinc ores contain substantial amounts of inorganic arsenic, whereas aluminum and other nonferrous metals contain much smaller amounts.

Seventy-one counties with manufacturing units engaged in primary smelting and refining (SR) of nonferrous ores (and with an estimated 50,855 persons employed in the SR industry in 1963) were selected for study. The 71 counties were divided into two groups according to the type of ore processed: 36 counties with copper, lead, or zinc processing units and 35 counties with installations processing aluminum or other nonferrous metals.

Average annual age-adjusted lung cancer mortality rates per 100,000 people in 1950 to 1969 were calculated for the 71 SR-industry counties and the other 2984 counties of the contiguous United States. A multiple-regression analysis permitted correction for differences in demographic and socioeconomic factors such as population density, degree of urbanization, schooling, income, and geographic region.

This analysis showed that the 36 counties with copper, lead, and zinc SR industries had a significantly higher lung cancer mortality among males ($p<0.001$) and females ($p<0.05$) than did counties in the rest of the United States. The mean excess in lung cancer for these counties, corrected for demographic and socioeconomic influences, was 17 percent for males and 15 percent for females. The rates for both sexes were high in each 5-year interval over the 20-year period. The 35 counties with industries processing nonferrous ores other than copper, lead, and zinc showed no excess lung cancer mortality.

The median SMR for all 36 counties with SR industries was 112 for males and 110 for females. Data from three counties with

the highest proportion of the total population employed in the SR industry (each had >5%) showed an average excess lung cancer mortality of 92 percent in males and 36 percent in females.

According to Blot and Fraumeni, occupational exposure alone cannot explain the increased mortality in both males and females. Although occupational exposure probably contributes to excess risk in males, the number of workers in the SR industries is small relative to the total population of the counties (less than 1% for more than half of the 36 counties and less than 3% for all but four). The relative risk for the workers would have to be 13-fold to account for the excess lung cancer observed. The authors believe that their correlations are not due to confounding social factors or to differences in smoking habits. They conclude that "the most likely explanation for the elevated lung cancer mortality in this study is neighborhood air pollution from industrial sources of inorganic arsenic." They do not, however, rule out contributory effects from other toxic substances. The implications of their results, together with criticisms of their study made by others, are discussed in detail in Section 6.

Milham and Strong (1974) confirmed that inhabitants of copper smelter communities absorb excessive arsenic. Their study of children living near the copper smelter in Tacoma, Washington, revealed elevated levels of urinary arsenic that decreased with distance of residence from the smelter stack. Analyses of vacuum-cleaner dust showed a decreasing arsenic content with increasing distance of residence from the smelter. Since the urinary arsenic levels in children living near the smelter are similar to those in smelter workers, it was argued that communities near the smelter might be exposed to an excess risk of lung cancer. It should be noted that the authors did not consider seafood ingestion as a source of arsenic, and they did not consider the specific gravity of the spot urine samples.

Newman et al. (1976) studied the histologic types of lung cancer in two Montana counties, one with a copper smelter (located in Anaconda) and the other with several copper mines

(adjacent to Butte). Vital statistics indicated an elevated lung cancer mortality in both counties. The investigators examined records of 143 lung cancer cases (114 males and 29 females) from the period 1959 to 1972 and classified them histologically. Occupational information was obtained for all males and for all but 2 of the 25 Butte females. The persons were in four groups: copper smelter workers (those with more than 1 years employment in the smelter); copper mine workers (with more than 1 years employment in a mine); "other" men (with less than 1 years employment in the smelter or mines, this group serving as a control for the smelter workers and miners); and females from Butte.

Lung cancer mortality of men from both Butte and Anaconda and women from Butte was significantly elevated. No arsenic exposure was apparent in Butte, and it was hypothesized that the excess lung cancer might be due to exposure to asbestos-like dust from a material used to sand the streets. The lung cancer rate of women from Anaconda also was significantly elevated relative to the rate for Montana women, in calculations over a period of 10 years (2.9/10,000 as compared with 1.4/10,000; $p<0.05$). It was noted that the average level of arsenic in Anaconda air was 0.45 mg/m^3.

Smelter workers were found to have a greater frequency of poorly differentiated epidermoid carcinomas than copper miners ($p<0.05$). Miners were found to have a distribution of histologic types of lung cancer similar to that of controls ("other" men), suggesting an etiologic agent in miners different from that in smelter workers. Butte women showed a distribution of histologic types similar to that of smelter workers. Histories of smoking, though incomplete, indicated that smoking habits did not differ significantly in the three male groups. The women smoked less than the men.

The high percentage of poorly differentiated epidermoid carcinomas among the smelter workers was unexpected. The authors noted that Robson and Jelliffe (1963) had reported poorly differentiated carcinomas in six patients with lung cancer who had

received arsenical medication. They concluded that the poorly differentiated epidermoid lung carcinoma among smelter workers was best explained by exposure to airborne arsenic and further suggested that poorly differentiated epidermoid lung carcinoma may serve as a "marker" indicating exposure to arsenic.

Pershagen et al. (1977) studied mortality from different causes among residents living near the Rönnskärsverken smelter works in northern Sweden, which for decades has emitted large amounts of arsenic as well as sulfur dioxide. Mortality ratios for the exposed population for the period 1960 to 1974 were compared with ratios for a reference population with similar degrees of urbanization, occupational profiles, and age distribution. Lung cancer mortality of men over 40 in the exposed area was significantly elevated (SMR = 250; $p<0.0016$). When the occupationally exposed Rönnskärsverken employees were excluded, however, the increase was no longer significant. Excess mortality from lung cancer among the Rönnskärsverken employees was large (SMR = 405). The authors are conducting a followup study that should yield more data on mortality rates of the nonoccupationally exposed.

MANUFACTURE OF ARSENICAL PESTICIDES

Several studies of workers exposed to various inorganic arsenic compounds used in the manufacture of arsenical pesticides and insecticides have showed an increased lung cancer incidence associated with such exposure. Unlike smelter workers, pesticide workers have no concomitant exposure to sulfur dioxide. In some plants, however, they do undergo exposure to a wide range of other chemicals.

In 1945 the Medical Research Council in Britain commissioned two studies to evaluate the relationship between arsenic and lung cancer. Hill and Faning (1948) conducted a proportional mortality study of workers in a factory that produced arsenic-containing sheep-dip, and Perry et al. (1948) measured the levels of arsenic and examined the workers in the same factory. Exposure

to sodium arsenite in the factory was considered heavy among 31 chemical workers and moderate among 20 maintenance workers and 12 packers. Chemical workers all exhibited skin changes that made it immediately apparent to the authors whether the person was a chemical worker, even before a work history was obtained. Most chemical workers were grossly pigmented, and one-third of them had hyperkeratinization of exposed skin, with a tendency to wart formation. Chemical workers had significantly higher arsenic content in their hair ($p<0.01$) and urine compared with unexposed workers (Perry et al., 1948).

In the period from 1910 to 1943 a total 75 of the factory workers died, 22 of them from cancer. The proportion of deaths due to cancer (29.3%, 22 out of 75 deaths) was compared with 12.9 percent in other occupations in the same town, yielding a statistically significant difference of 16.4 ± 4.1. In a grouping of the deaths into three periods (1910 to 1919, 1920 to 1929, 1930 to 1943) cancer deaths among the factory workers in each period were still significantly higher than among controls (sum of χ^2 for the three periods = 11.88; $p<0.01$). When deaths were standardized for three age groups (under 55, 44 to 59, 70 and over), the proportion of deaths due to cancer among factory workers (29.3%) was still markedly higher than that among other workers (12.9%; $p<0.01$) (Hill and Faning, 1948).

Analysis of the deaths by work area showed that the excess of cancer deaths was accounted for mainly by chemical workers (16 deaths), who had the heaviest exposure to arsenic dust, and by three deaths among engineers and packers. The difference between cancer deaths among the chemical workers and among persons in other occupations (nonfactory workers) was significant ($\chi^2 = 3.95$; $p = 0.047$).

Analysis of cancer deaths by site suggested a relative excess of lung and skin cancer among factory workers, although Hill and Faning (1948) state that the numbers of deaths in each category were too small to be conclusive.

Ott et al. (1974) reported the results of both a proportional mortality study and a retrospective cohort study of deaths among workers at a Dow Chemical plant that manufactured arsenical insecticides, primarily lead arsenate and calcium arsenate.

The proportional mortality study revealed that lung cancer accounted for a significantly higher proportion of all deaths in the exposed group of 173 decedents who had worked for one or more days with arsenical insecticides (16.2%) than in the controls, 1809 decedents who had worked at the same plant but without arsenic exposure (5.7%; $p<0.001$). Lymphatic and hematopoietic cancer (excluding leukemia) were also found to be significantly elevated in the exposed group (3.5%) relative to the controls (1.4%; $p<0.05$).

The retrospective cohort analysis included 603 chemical workers with a minimum of 1 month exposure to arsenic. Although overall mortality of the cohort was low compared with mortality of U.S. white males, mortality due to lung cancer and lymphatic and hematopoietic cancer (excluding leukemia) were both considerably higher than expected on the basis of U.S. white male deaths (SMR = 345 and SMR = 385, respectively).

Four exposure groups were established, and time-weighted average concentrations were calculated for each group. From these average concentrations, the arsenic dosages were calculated. By both methods of analyses lung cancer mortality increased with increasing cumulative arsenic exposure. The methodology of this study is discussed in Section 6.

Baetjer et al. (unpublished study, summarized in NIOSH, 1975) did a preliminary proportional mortality study of retired workers from a Baltimore plant manufacturing arsenical pesticides. Cancer mortality among 22 retirees was almost four times the expected rate (based on age-sex specific proportional mortality ratios for the city of Baltimore): 17 cases vs. 4.43 expected. The SMR's were 671 for lung cancer, 300 for "lymphatic and hematological cancers" (lympho-sarcomas), and 149 for all other cancers. There is a problem in that workers experienced

concomitant exposure to several hundred chemicals, some of them known carcinogens, in the air of the plant.

When the observed death rates were compared with age-cause specific death rates calculated for the population of Baltimore, the retirees again showed an excess mortality from lung cancer, with an SMR of 1667 (95% confidence limits of 7.14 to 32.8%); from lymphatic cancer, with an SMR of 5000 (confidence limits of 6.05 to 180.50); and from all other cancers, with an SMR of 465 (confidence limits of 1.26 to 11.90). The number of deaths in this study was small. Baetjar et al. are currently conducting a broad retrospective cohort mortality study of the workers in this plant. This more thorough study has not borne out the reported excess mortality from lymphatic cancer.

These studies are summarized in Table 8.

AGRICULTURAL WORKERS

Agricultural workers engaged in the application of arsenical insecticides constitute another occupational group with exposure to inorganic arsenic. Some of these workers are known to be exposed both through inhalation of insecticide sprays and through ingestion of wine contaminated by arsenic.

Many cases of chronic arsenic poisoning occurred in Germany in the 1930's among winegrowers who used arsenical insecticides including calcium arsenate and copper acetoarsenite (Frohn, 1938). The studies described here provide clinical evidence of the carcinogenic effects of arsenic exposure, probably by both inhalation and ingestion. The use of arsenical insecticides was banned in Germany in 1942. Roth (1957) reported on 27 autopsies he performed on Moselle vintners between 1950 and 1956. All 27 workers had been exposed 20 to 30 years earlier, between 1925 and 1938, and their exposures had lasted several years. Symptoms of arsenic poisoning appeared in most of the workers after 1935.

Sixteen of the 27 Moselle winegrowers had a total of 38 malignant tumors. Six had "arsenic cirrhosis" of the liver. Eleven (or 40%) had lung cancer. All of the lung cancer cases

TABLE 8. SUMMARY OF EPIDEMIOLOGICAL AND CLINICAL STUDIES OF NONSMELTER OCCUPATIONAL EXPOSURE TO ARSENIC

Study	Type of study, and period of observation	Process	Number in cohort	Findings	Exposure data
Hill and Faning (1948)	Proportionate mortality, 1910-1943	Sodium arsenite sheep-dip manufacturing plant	75 deaths	Two-fold excess for lung cancer; 16 deaths from cancer out of 41 deaths among chemical workers	
Perry et al. (1948)	Environmental and clinical	Same plant as Hill and Faning			Median concentrations (mg/m^3) of As were 0.071 (packing room); 0.254 (drying room); 0.373 (sieving room); 0.696 (near kibbler operation); urine samples and hair samples of exposed workers had significantly higher As levels than controls; pigmentation and keratosis
Snegireff and Lombard (1951)	Proportionate mortality, 1922-1949	Plant handling large quantities of As_2O_3	146 deaths	No significant excess of cancer deaths determined by proportionate mortality	
Roth (1957)	Clinical	German vinegrowers with exposure to arsenical insecticides and As-contaminated wine		18 lung cancer deaths out of 47 deaths. 7 hemangiosarcomas of the liver; cancer of esophagus	Exposure to arsenical insecticide containing 4.3 to 56% As_2O_3; As found in urine of living patients
Daetjer et al. (1974)	Proportionate mortality, 1960-1972	Arsenical pesticide among workers	27 deaths	Proportionate mortality ratio of observed to expected lung cancer deaths was 6.71; 3.0 for lymphatic and hematological cancer (lymphosarcoma); death rate compared with age-cause specific death rates for Baltimore showed significantly increased cancer mortality for lung cancer with O/E ratio of 16.67 (95% confidence limits of 7.14-32.84); mortality from lymphatic cancer (5.0 O/E ratio, 6.05-180.50 confidence limits)	

(continued)

TABLE 8 (continued)

Study	Type of study, and period of observation	Process	Number in cohort	Findings	Exposure data
Ott et al. (1974)	Proportionate mortality	Lead and calcium arsenate, copper acetoarsenite, magnesium arsenate	173 deaths with exposure; 1809 decedents with no exposure	Proportionate mortality for lung cancer significantly higher among exposed group (16.2%) than in controls (5.7%); lymphatic cancer also significantly higher in exposed group (3.5% vs. 1.4% expected)	Dose-response shown between As exposure for respiratory cancer mortality
Ott et al. (1974)	Retrospective cohort		Cohort of 603 chemical workers with at least 1 month of work in As production	Overall mortality lower than U.S. white male mortality; lung cancer mortality (O/E ratio of 3.45) and cancer of lymphatic and hematopatic tissues expect leukemia (O/E ratio 3.85) were significantly higher than expected in cohort of exposed workers	
Newman et al. (1975)	Clinical			Significantly increased lung cancer among men of Anaconda and Butte and in women of Butte as compared with Montana as a whole	
Nelson et al. (1973)	Followup to 1938-1969	People exposed occupationally or otherwise to lead arsenate pesticide spray or residue		No excess lung cancer	

also showed the typical signs of chronic arsenic poisoning. Roth concluded that they could not be attributed to the increase in lung cancer in the general population, but must be regarded as occupational lung cancers caused by arsenic. In only one of the cases was there a history of heavy smoking. The latent period he observed for malignant tumors (of the skin, liver, bile duct, esophagus, and respiratory tract) was 13 to 25 years.

Since Moselle vintners were thought to have a high consumption of wine, some of which contained high levels of arsenic, Roth explicitly stated that his findings "cannot be explained by chronic alcoholism, nor do they provide evidence of combined poisoning" (i.e., via inhalation and ingestion), but he does not present a quantitative defense of this reasoning. He concluded that "the late manifestations of chronic poisoning, particularly cirrhosis of the liver and multiple neoplasms, are occupational diseases."

In a second article, Roth (1958) added 20 autopsies of winegrowers to the earlier 27. Among the total of 47 cases, 30 deaths were attributed to cancer and 3 to malignancies. In 18 cases lung cancer was listed as the cause of death. There were also six cases of hemangio-sarcomas of the liver, five cases of cancer of the esophagus, and one of cancer of the bile duct.

Roth also compared the proportional mortality rates of six rural and urban districts of the Moselle and one district of the Ahr. Mortality due to lung cancer was higher in winegrowing areas of the Moselle, where arsenical insecticides had been used, than in urban and nonwinegrowing areas. In winegrowing areas of the Ahr, where arsenical insecticides had never been used, the rate for lung cancer was lower than in the winegrowing areas of Moselle. Roth took this as added evidence of a causal connection between arsenical insecticides and lung cancer.

Braun (1958) performed another clinical study in which 16 vintners from the Palatine region of Germany were examined between 1951 and 1957. These workers had definite histories of occupational exposure to arsenical pesticides (from about 1925 to

1942) and of frequent wine consumption. All 16 showed palmar and plantar keratoses characteristic of chronic arsenic poisoning; 9 had pigmentation, 9 had inoperable lung cancer, 1 had bile-duct cancer, and another had a malignant lymph node tumor. Two of the lung cancer patients also had skin cancer (squamous cell carcinoma), and two other lung cancer patients had Bowen's disease. Only 3 of 16 vintners with arsenical skin lesions had no neoplastic changes.

In the whole period from 1939 to 1952 only one vineyard worker with lung cancer was reported. Braun explains the dramatic increase in lung cancer cases among vintners in the years following 1952 by the long latent period for arsenic-induced cancer. Unlike Roth, Braun does not refer to the smoking histories.

Galy et al. (1963) reported three cases of lung cancer among winegrowers in the Beaujolais region of France. The three had handled arsenic pesticides (lime arsenate and lead arsenate) 20 years earlier. All three had keratosis. The authors note that in spite of the ingestion of a "nonnegligible quantity of arsenic, . . . ingestion of arsenic seems to be secondary to inhalation."

Nelson et al. (1973) did an epidemiologic study of the effects of exposure to arsenical pesticides in a followup of an earlier morbidity study among 1231 residents of the Wenatchee Valley, Washington, some of whom were exposed to lead arsenate spray. The original Public Health Service study in 1938 to 1939 divided the study group into three exposure groups: "orchardists, who had prepared and used lead arsenate sprays during 1938; "consumers," who were not exposed to the spray (mainly women and children), and "intermediates," a mixed group including former orchardists, warehouse workers, and people with occasional exposure to lead arsenate spray.

The followup study, which covered the 30-year period from 1938 to 1968, included more than 98 percent of the original cohort. Standard mortality ratios (SMR's) for different exposure

groups and for different lengths of exposure were calculated with the population of the State of Washington as a standard. The life-table method was used to calculate expected deaths. The cohort as a whole had an SMR of 70, indicating mortality rate that is favorable relative to the Washington average. The mortality rates for the three exposure groups did not reflect exposure. "Intermediates" had the highest SMR (78) and "orchardists" had the lowest (65). Mortality rates also failed to reflect increased length of exposure. No excess deaths were found to be due to specific causes of death (heart disease, cancer, stroke).

Nelson et al. point out several limitations in their study: (1) a small number of workers in the original study; (2) the lack of adequate exposure data; and (3) the possible loss of the most susceptible workers, who may either have left orchard work or died before 1938.

Because results of this study conflicted with evidence of the effects of chronic exposure to arsenic, NIOSH (1975) reassessed the mortality experience of Wenatchee Valley residents exposed to lead arsenate, using independent sources of data. Information on occupation and cause of death in all deaths among adult white males in the State of Washington over the period 1950 to 1971 showed that the lung cancer rate of orchardists was 19 percent higher than expected. Over the 11-year period (1961 to 1971) lung cancer showed a "statistically significant increase of 27 percent" (NIOSH, 1975).

These studies are summarized in Table 8.

MEDICINAL USE OF ARSENIC COMPOUNDS

The medical use of arsenic compounds in the treatment of diseases such as psoriasis, eczema, dermatitis, anemia, asthma, and epilepsy provides data on the effects of chronic ingestion of relatively high doses of arsenic compounds. Such effects include pigmentation, keratoses on the hands and feet (characteristic of chronic arsenicism), skin cancer, and, possibly, lung cancer.

Despite the fact that the first association between arsenical treatment and skin cancer was made in 1887 by Hutchinson, the use of arsenicals in medicine continued until recently (NAS, 1977).

In 1947 Neubauer published an extensive review of the literature on arsenical cancer. Of the 143 cases of skin cancer included in his review, nearly all had been treated with arsenic in the inorganic trivalent form, most often as Fowler's solution (potassium arsenite). Approximately 90 percent of the patients had taken Fowler's solution for more than 1 year, and 50 percent for more than 5 years. On the average, a total quantity of 28 g of arsenic was ingested by each patient (NAS, 1977).

Ninety percent of the patients treated with Fowler's solution had keratoses, typically on the hands and feet, and many had hyperpigmentation. The period from the beginning of treatment to the appearance of skin cancer averaged 18 years, with a range of 3 to 40 years. The latent period for keratosis averaged 9 years. In these patients treated with arsenic, skin cancer appeared at a relatively early age (one third were 40 or younger; 70% were 50 or younger). Thirteen of the 143 patients developed cancers at other sites (NAS, 1977).

There is clinical evidence for the induction of lung cancer, as well as skin cancer, from treatment with arsenicals. Robson and Jelliffe (1963) described six cases of lung cancer in patients who had been treated with arsenic. Four of the six had received arsenic in the form of Fowler's solution for periods ranging from 3 to 15 years; the remaining two patients had received an unspecified form of arsenic for several years. All of the patients showed keratoses; three showed intraepidermal epitheliomas, and one showed intraepidermal carcinomas. All six had poorly differentiated bronchial carcinoma, the same type observed by Newman et al. (1976) and taken by them to be a "marker" for arsenic exposure. Two of the patients were moderate cigarette smokers, one was a light pipe-smoker, and three were nonsmokers.

The average latent period before the clinical onset of lung cancer was 32 years.

Fierz (1964) carried out a followup study of 262 patients who had received Fowler's solution within the previous 26 years. Knowledge of the amount of Fowler's solution received by each patient enabled Fierz to establish a clear dose-response relationship between the quantity of arsenic ingested and the frequency of keratosis and skin cancer. As a group, the patients received from 10 to 2600 ml of Fowler's solution. Hyperkeratoses were present in 106 of the 262 subjects (or in 40%); melanosis occurred in only 5 cases; and skin cancer occurred in 21 cases of the subjects (or 8%). The cancers were multiple in 13 of the 21 cases. Fierz calculated an average latency period of 14 years for skin cancer, 4 years shorter than that calculated by Neubauer.

As in the cases reviewed by Neubauer (1947), Fierz's skin cancer cases were relatively young (20 to 21 patients were less than 60 years old at the time of appearance of skin cancer). Fierz, however, purposely examined only patients under 65 years of age to avoid "distortion of the picture by any old-age cancer." Since some of the patients had begun arsenic treatment only 6 years before examination and the latency period for arsenic-induced skin cancer is 14 years or longer, Fierz notes that additional cases of skin cancer might appear (Fierz, 1964). These studies are summarized in Table 9.

INGESTION OF ARSENIC FROM CONTAMINATED FOOD AND WATER

Clinical and epidemiological studies of accidental ingestion of arsenic-contaminated food and water are summarized in Table 9. An early report was that of Reynolds (1901), in which he studied an unusual number of cases of skin eruptions (including erythema, keratosis, and pigmentation) in a Manchester infirmary. He attributed these to arsenic poisoning by beer containing approximately 2 to 4 ppm of arsenious oxide (As_2O_3) from brewing sugars. Because of the large number of cases that Reynolds examined and his detailed descriptions of symptoms, this article has been

TABLE 9. SUMMARY OF EPIDEMIOLOGICAL AND CLINICAL STUDIES OF EFFECTS OF INGESTED ARSENIC

Study	Study population	Numbers and types of disease	Degree of exposure	Form of arsenic	Arsenic in hair or urine	Histology	Dose-response	Control
Reynolds (1901)		500 cases seen by Reynolds (13 deaths); most prominent symptoms erythromelalgia, keratosis, pigmentation, neuritis, cardiac failure, cirrhosis of the liver	2-4 ppm in contaminated beer; patients had drunk 2-16 pints of beer daily for many months	Arsenious oxide				
Tseng et al. (1968)	40,421 90.8% of the population were examined; total population at risk 103,154	7418 cases of hyperpigmentation (18.4%) 2860 of keratosis (7%); 428 of skin cancer (1%); 360 of Blackfoot disease (0.9%)	0.01-1.82 ppm in water from artesian wells; most well water had an arsenic content around 0.4-0.6 ppm			131 cases of skin cancer out of 420 were proved by biopsy specimens; permission to perform biopsies was refused in remaining 297 patients but the lesions had all the characteristics of arsenical cancer	Clear dose-response relationship: the greater the arsenic content of the water, the higher the prevalence of skin cancer, keratosis, hyperpigmentation, and Blackfoot disease	7500 persons whose drinking-water contained no detectable arsenic or water containing 0.001-0.017 ppm had not a single case of melanosis, keratosis, or skin cancer

(continued)

TABLE 9 (continued)

Study	Study population	Numbers and types of disease	Degree of exposure	Form of arsenic	Arsenic in hair or urine	Histology	Dose-response	Control
Fierz (1964)	262	Hyperkeratosis-106 or 40% melanoderma-5 cases; skin cancer-21 cases or 8%; 5 deaths from malignant tumors including 3 from bronchial carcinoma	10 to 2000 ml of Fowler's solution	Potassium arsenite As_2O_3 in Fowler's solution		All skin changes were tested histologically	Both hyperkeratosis and skin cancer showed increase with increasing arsenic dose	
Regelson et al. (1968)		1 patient with hemangioendothelial sarcoma of the liver, plantar and palmer keratoses.	17 years of treatment with Fowler's solution	Potassium arsenité	Not found (not surprising 7 years after ingestion)	Interpreted variously as "cirrhosis with acute hepatitis" and as "hemangioendothelial sarcoma"		

(continued)

TABLE 9 (continued)

Study	Study population	Numbers and types of disease	Degree of exposure	Form of arsenic	Arsenic in hair or urine	Histology	Dose-response	Control
Hamamoto (1955)		Of 61 babies hospitalized 98% had melanosis, 26% had hyperkeratosis, 100% had liver swelling	1.5-2.4 mg As/100 g of powdered milk	Trivalent arsenic	Hair			
Neubauer (1947)		Keratoses in 90% of patients who received Fowler's solution; skin cancer in all 143 patients	Average total quantity of 28 g; 90% of patients received Fowler's solution for <1 year; 50% for <5 years	Nearly all received inorganic trivalent arsenic (most often Fowler's solution)		Half of skin cancers were aquamous carcinomas; half were basal cell epitheliomas		
Robson and Jelliffe (1963)		Six cases of lung cancer; all 6 had keratoses, 3 had intraepidermal epithelioma, 1 had intraepidermal carcinoma	All received arsenic for 3 to 15 years	4 had received Fowler's solution	3.5 ppm in hair of 1 patient; 1.5 ppm in hair of another patient	All tumors were poorly differentiated carcinomas		

(continued)

TABLE 9 (continued)

Study	Study population	Numbers and types of disease	Degree of exposure	Form of arsenic	Arsenic in hair or urine	Histology	Dose-response	Control
Yeh (1973)						303 lesions in 184 patients studied histologically		
Bergoglio (1964)	2355 deaths, 556 from cancer and malignant tumors (23.8%)	35% of cancer deaths were due to respiratory cancer; 35%, digestive tract; 2.3%, skin					Departments with higher cancer mortality also have higher arsenic content in drinking water	137,702 deaths among entire population of Cordoba Province of 1,759,997 inhabitants (1949-1959). 15.3% of all deaths were due to cancer and malignant tumors (average for 11-year period)
Bargono and Greiber (1972)	27,088 children	12% had cutaneous changes; 1/4 - 1/3 had systemic symptoms; 11% had acrocyanosis;	0.8 ppm in drinking-water					
	180 inhabitants of Antofagasta	80% had abnormal skin pigmentation; 36% had hyperkeratosis; 30% had Raynaud's syndrome						No cases of abnormal skin pigmentation, hyperkeratosis, or Raynaud's syndrome

referred to as "the definitive medical description of subacute poisoning with ingested arsenic" (NAS, 1977). Reynolds personally examined 500 patients suffering from arsenical poisoning, each of whom had each drunk 2 to 16 pints a day of contaminated beer for many months. He classified the patients into four groups: (1) those with skin lesions principally; (2) those with cardiac and hepatic lesions principally; (3) those with paralytic lesions principally; and (4) those with all symptoms. The major cause of death was cardiac failure.

A more recent and more quantitative study of accidental arsenic ingestion was done by Tseng et al. (1968), who examined the incidence of melanosis, keratosis, skin cancer, and Blackfoot disease (a peripheral vascular disorder resulting in gangrene of the extremities) in 37 villages on the southwest coast of Taiwan where the population had been exposed for over 40 years to the high levels of arsenic in the drinking water. The concentrations of arsenic in the drinking water ranged from 0.01 to 1.82 ppm. The arsenic content of most well water was 0.4 to 0.6 ppm.

Among the 40,421 inhabitants studied, the overall incidence of melanosis was 183.5/1000; the incidences were 71.0/1000 for keratosis, 10.6/1000 for skin cancer, and 8.9/1000 for Blackfoot disease. (Incidence of skin cancer among Chinese in Taiwan is normally low, 2.9 percent.) On the whole, the rate of all four conditions increased steadily with age, though women over 69 showed a lower rate of cancer and melanosis. Over 10 percent of the people above age 59 had skin cancer.

The youngest cancer patient was 24, the youngest with melanosis was 3, and the youngest with keratosis was 4; these observations were taken to indicate that there is a latency period even at high dose levels. The association of Blackfoot disease with melanosis, keratosis, and skin cancer was significantly higher than expected, suggesting a causal relationship between Blackfoot disease and chronic arsenicalism. Among the 428 cases of skin cancer, 89.7 percent had melanosis, and 71.7 percent had keratosis.

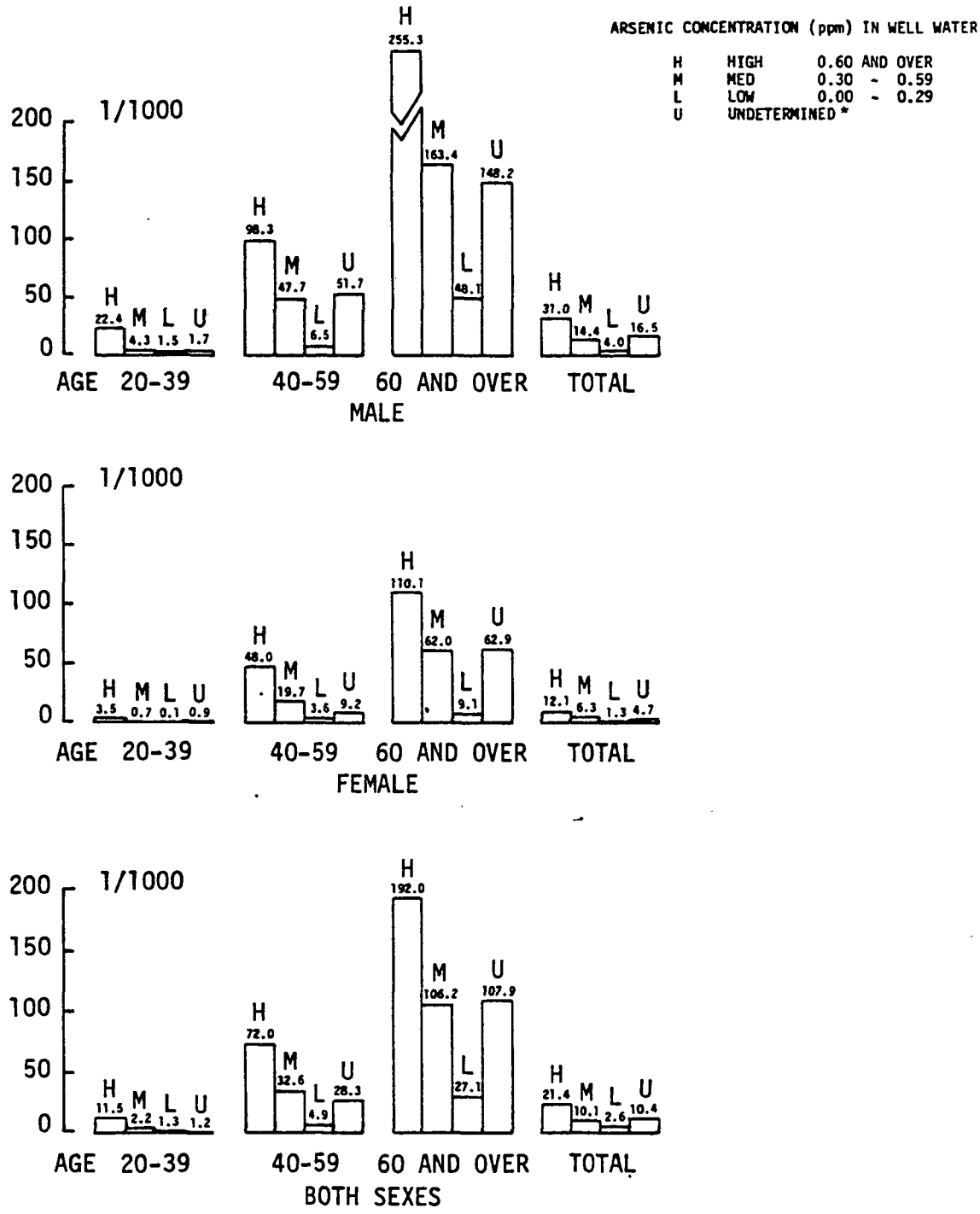
When villages were grouped by the arsenic content of their well water ("low," below 0.3 ppm; "mid," 0.3 to 0.6 ppm; and "high," above 0.6 ppm) the incidence of all four conditions rose with increased arsenic concentration. This was taken as evidence of a dose-response relationship. The dose-response data for skin cancer are shown in Figure 1.

Evaluation of a control population of 7500 persons whose drinking water contained no detectable arsenic or very low amounts (0.001 to 0.017 ppm) revealed no cases of melanosis, keratosis, or skin cancer.

Results of biopsies taken during the study by Tseng et al. are discussed by Yeh (1973). Yeh also calculated standardized mortality ratios for the patients with skin cancer and those with Blackfoot disease and found that both groups had a much higher mortality rate than the study population, especially in the total age group below 49 years. The numbers of cases were small: 7 skin cancer patients below age 49; 16 Blackfoot disease patients below age 49. The most common cause of death among skin cancer patients was carcinoma of various sites (skin cancer having the highest incidence) and that among patients with Blackfoot disease was cardiovascular disease.

Irgolic (1978, unpublished report supplied by EPA) has analyzed samples of well water from two locations in Taiwan by flameless atomic absorption spectrometry and neutron activation analysis. Both arsenite and arsenate (in a ratio of 1:10 in one sample and in a ratio of 1:7 in a second sample) were detected, but the ratio of arsenite to arsenate may have changed from the time of collection to the time of analysis, since some of the well waters are known to be anaerobic and since some oxidation may have occurred during transit.

Recently, fluorescent compounds have been detected in samples of well water from areas of Taiwan where Blackfoot disease is endemic (Lu, et al., 1975, 1977a, 1977b). One of these fluorescent compounds appeared to be lysergic acid or alkaline hydrolysate of ergotamine tartrate, or a related compound. Lu et



*"Undetermined" exposures refer to villages where arsenic polluted wells were no longer used or where the levels of arsenic in different wells varies too widely to allow classification.

Figure 1. Age-specific and sex-specific prevalence rate (1/1000) for skin cancer by arsenic concentration in well water (from Tseng et al., 1968).

al. (1977a) reported that one of the fluorescent compounds (as yet unidentified) produced abnormalities in developing chick embryos.

Another report relating cancer to the ingestion of arsenic in water is that of Bergoglio (1964). Arguello et al. (1938) had reported a high rate for skin cancer in Cordoba Province, Argentina, where well water was known to have contained high levels of arsenic for at least 40 years, but this report was not definitive. Bergoglio examined the specific cause of death among all deaths occurring in the 11-year period between 1949 and 1959 in a region of Cordoba Province with well waters known to have high arsenic levels. He also classified deaths in Cordoba Province by geographic department.

During the 11-year period, there were 2355 deaths in the study region; 556 (or 23.8%) were attributed to cancer and malignant tumors. Thirty-five percent of all cancers were respiratory cancer; 35 percent, digestive tract cancer; and 2.3 percent, skin cancer. The proportion of deaths due to cancer (23.8%) was significantly higher than that of the province of Cordoba as a whole over the 11-year period (15.3%), with no significance level stated. Respiratory cancer and skin cancer accounted for a greater-than-expected proportion of the total cancer deaths among the study population, but corresponding figures for the control population are not given. Fifty percent of the deaths from lung cancer occurred among females. The higher proportion of mortality from cancer and malignant tumors corresponded to those regions with high levels of arsenic in the drinking water.

In Antofagasta, Chile, in the early 1960's, dermatological symptoms, especially among children, drew attention to high levels of arsenic contamination (0.88 ppm) of the drinking water. Of 27,088 schoolchildren surveyed in this city, Borgono and Greiber (1972) found that 12 percent showed skin changes characteristic of arsenicism; one fourth to one third had systemic symptoms, and 11 percent had acrocyanosis (a circulatory

disorder affecting the hands). The authors compared the records of 180 inhabitants of Antofagasta with those of 98 people of Iquique, a city with no arsenic in its water supply. Among the 180 Antofagasta residents, most of whom were under 20 years old, 80 percent had abnormal skin pigmentation; 36 percent had hyperkeratosis; 30 percent had Raynaud's syndrome; 22 percent had acrocyanosis; and 15 percent had bronchopulmonary disease. There were no cases of these disorders among the control group. The authors do not discuss cancer, but since the latent period for arsenic-induced skin cancer is long, one would not expect to find an increase of cancer within the period of the study.

In the midfifties, two incidents of arsenic food poisoning occurred in Japan. In 1955, more than 10,000 infants who had been fed powdered milk contaminated with pentavalent inorganic arsenic showed signs of poisoning, and 130 infants died. The major acute symptoms, reported in the many papers published between 1955 and 1975, were fever, diarrhea, vomiting, and anorexia. Incidence of melanosis was also high. The reports are summarized in Tsuchiya (1977).

Hamamoto (1955) recorded the symptoms of 61 hospitalized infants who had been fed the tainted milk. Melanosis was observed in 98 percent, liver swelling in 100 percent, and hyperkeratosis in 26 percent. Heart palpitations or instability were noted in 60 percent of the cases. Laboratory tests revealed anemia and granulocytopenia. No neuritis was observed. Hamamoto calculated that the infants of 3 months or older developed symptoms after ingesting from 90 to 140 mg of arsenous acid. Hamamoto further noted the remarkably rapid disappearance of symptoms following BAL therapy.

It is unclear from the various reports whether the arsenic in the powdered milk was in the trivalent or pentavalent form. Tsuchiya (1977) indicates it was pentavalent, whereas Hamamoto (1955) and Ohira and Aoyama (1973) indicate that it was trivalent.

The Japanese Pediatric Society (1973) summarized the findings of regional investigations of the long-term effects among those who were fed the tainted milk in 1955. They reported high rates for mental retardation, for epilepsy and other abnormalities suggestive of brain damage, and for skin changes (melanosis). The Japanese Pediatric Society stressed the need for epidemiologic studies of the cohort exposed to the contaminated milk to assess the relationship between arsenic and long-term effects. Followup studies on the long-term effects of the children who were exposed to the contaminated milk are complicated by incomplete records and the difficulty of discovering who was in the exposed cohort (Tsuchiya, 1977).

In 1956, 417 patients who had eaten arsenic-contaminated soy sauce were examined. The estimated dosage was 0.1 mg/ml arsenic, thought to be calcium arsenate. Mizuta et al. (1956) reported on the acute symptoms of 220 of the patients. The duration of arsenic ingestion was from 2 to 3 weeks in most cases; symptoms included edema of the face, disturbances of the gastrointestinal tract and upper respiratory tract, skin lesions, neuritis, and swelling of the liver. Laboratory findings included slight anemia, leukopenia, and relative lymphocytosis. Abnormal EKG findings were noted in 80 percent of the 220 persons examined. There were no fatalities in this incident, and no long-term followup has been reported.

SECTION 5
NONCARCINOGENIC TOXIC EFFECTS OF ARSENIC ON HUMANS

This section summarizes the major noncarcinogenic toxic effects of arsenic.

Cases of acute poisoning with solid trivalent inorganic arsenic have occurred most frequently from the accidental ingestion of contaminated food or drink. Acute poisoning from industrial exposure is relatively rare. Arsenic causes an increased permeability of the capillaries and withdrawal of water from the body. Initial symptoms are inflammation of the stomach and intestine, vomiting, profuse and painful diarrhea, and difficulty in swallowing. Nervous symptoms include vertigo, headache, and pain in the limbs, with poor circulation in the extremities. Later symptoms include syncope, coma, clonic and tonic spasms, and general paralysis. Death usually occurs from exhaustion due to the prolonged gastroenteritis (Sollmann, 1964). Skin reactions are rare in cases of acute arsenic poisoning (NAS, 1977).

In cases of subacute, nonfatal poisoning, the prominent symptoms are inflammation of the mucous membranes of the gastrointestinal tract, conjunctivitis, coryza, stomatitis, and pharyngitis. If the poisoning is prolonged, abnormalities of the skin and nervous system (including neuritis) appear (Sollman, 1964). Autopsy findings on cases with acute arsenic poisoning reveal gastroadenitis and cell infiltration (Sollman, 1964).

The symptoms of chronic arsenic poisoning generally fall into three stages:

1. Weakness, loss of appetite, nausea, and occasional vomiting, sometimes accompanied by diarrhea and pain in the stomach.

2. Conjunctivitis and catarrhal state of exposed mucous membranes of the nose, larynx, and respiratory passages; coryza; hoarseness of voice; and mild tracheitis or bronchitis. (Perforation of the nasal septum is the most characteristic lesion of the upper respiratory tract in workers exposed to arsenical dusts and is more indicative of local irritation rather than chronic systemic poisoning.)

3. Peripheral neuritis, mainly of the hands and feet (Buchanan, 1962).

Table 10 summarizes the major noncarcinogenic toxic effects of different forms of arsenic. Some of the acute and chronic effects reported in various case studies of exposure to arsenic are noted below.

The syndrome known as Rönnskär Disease, a chronic "rhino-pharyngo-tracheo-bronchitis" (reported at the smelting works at Rönnskär, Sweden) corresponds to Buchanan's second stage of chronic arsenic poisoning (Buchanan, 1962). Skin manifestations (especially keratoses and melanosis), hepatitis, and jaundice have been reported at this stage.

Arsenic causes nephritis that is at first mainly vascular, but always involves the epithelium (Sollmann, 1964). Arsenic is hepatoxic, causing fatty swelling which may compress the bile ducts, resulting in an increase in the bilirubin content of the blood and in visible icterus (Sollmann, 1964). Cases of cirrhosis of the liver have been reported following ingestion or medicinal administration of arsenic. Acute hepatitis has been reported in patients undergoing arsphenamine therapy (Buchanan, 1962; Hine et al., 1977).

Systemic arsenic poisoning has been reported to affect production and survival time of red and white blood cells. Specific abnormalities include normochromic anemia, neutropenia, a relative eosinophilia, and thrombocytopenia (Hine et al., 1977).

In the 41 cases of neuropathy described by Heyman et al. (1956), recovery of sensory and motor functions was slow, and the course of recovery was not improved by treatment with BAL. The

TABLE 10. TOXIC EFFECTS OF ARSENIC[a]

Compound	Route of entry	Acute effects
Trivalent inorganic arsenic	Ingestion	Throat constriction, difficulty swallowing, violent abdominal pain, vomiting, muscular cramp, possible death within 1-4 days
		Fatty infiltration of cells (especially liver cells); direct toxic action on cardiac muscle; ECG abnormalities
Arsphenamine	IV injection	Stomatitis, albuminuria, jaundice, blood dyscrasias, dermatitis, severe cerebral symptoms, acute hepatitis, ascites
Arsine	Inhalation	Enlargement of the liver, hemoglobinuria, jaundice, hemolytic anemia, abdominal pain, vomiting; acute uremia is a common cause of death (from 4th day onwards); fatty degeneration of cells, particularly those of the liver, kidneys, and cardiac musculature
		Chronic effects
Inorganic arsenic	Ingestion	Nausea, vomiting, conjunctivitis and catarrhal state of exposed mucous membranes of the nose, larynx and respiratory passages, keratoses, melanosis
	Inhalation	Perforation of the nasal septum; Rönnskär Disease (chronic "rhino-pharyngo-tracheo-bronchitis") hepatitis, jaundice, peripheral neuritis

[a] Source: Buchanan (1962).

degree of recovery was an inverse function of the severity of the neuropathy. Biopsies taken from seven of the patients showed various degrees of degeneration, the severity increasing with increasing duration of disease. Unfortunately, no data are available on whether neurological sequellae follow low-level chronic exposures, and no dose-response information is available.

Electrocardiographic changes have been reported in cases of both acute and chronic arsenic exposure. Specific effects are: broadening of Q-R-S intervals, prolongation of Q-T interval, S-T depression, and flattening of T-waves (Hine et al., 1977; Glazener et al., 1968). Similar electrocardiographic abnormalities have been noted in acute cases (Barry and Herndon, 1962). Abnormalities have not been associated with disturbances of the serum electrolytes, but rather with a direct toxic effect on the myocardium. The clinical reports are that the myocardial effect is reversible and recovery is accelerated with administration of BAL.

A variety of symptoms (including bronchopneumonia, hyperkeratosis, peripheral vascular disorders) and some deaths were reported among children in Antofagasta, Chile, where the water supply contained 0.8 ppm arsenic (Borgono and Greiber, 1972). As a whole, inhabitants of Antofagasta had an increased incidence of bronchopulmonary disease, pigmentation, hyperkeratosis, chronic coryza, abdominal pain, Raynaud's syndrome, and acrocyanosis (Borgono and Greiber, 1972).

A high incidence of Blackfoot disease was found in the population of southwestern Taiwan where drinking water contained high levels of arsenic (Tseng et al., 1968).

Various sensory and motor neurologic abnormalities have been observed in cases of acute and chronic arsenic poisoning. These have been evidenced by measurements of nerve conduction, chronaxie, and electromyographic activity, which serve as sensitive indicators of neurological changes. An earlier report by Heyman

et al. (1956) describes peripheral neuropathy caused by arsenical intoxication.

Arsine gas, which is evolved when trivalent arsenic comes in contact with nascent hydrogen, is extremely toxic. It is a powerful hemolytic agent and can cause oliguric renal failure (Fowler and Weissberg, 1974). Acute symptoms include abdominal cramp, nausea, vomiting, jaundice, and anemia. In fatal cases there may be delirium followed by coma. Death usually results from myocardial failure a few days after the onset of anuria. The symptoms of chronic exposure to arsine gas include vomiting, dark urine, severe anemia, jaundice, and peripheral neuritis (Browning, 1969).

EFFECTS OF LOW-LEVEL ARSENIC EXPOSURE

Bencko and Symon (1977) reported changes in the hearing among 56 10-year-old Czechoslovakian children living near a power plant burning coal of high arsenic content. Hearing losses were detected in both air and bone conduction, especially at low frequencies in the exposed group as compared with a control group of 51 children of the same age living outside the polluted area. The differences between the two groups in tests at low frequencies had a high statistical significance ($p<0.01$). The authors concluded that the observed losses may be due to toxic neural damage caused by arsenic.

Milham and Strong (1974) noted that children living near the Tacoma smelter had elevated levels of arsenic in the hair and urine, but Milham (1977) reported that their school attendance, hearing, and hematologic indices were within normal limits. No adverse effects were associated with chronic, low-level exposure to arsenic.

Attendance at the Ruston School, less than 100 yards from the smelter, was similar to attendance at six other Tacoma elementary schools in the period 1969 to 1974. The hearing functions of 556 Ruston schoolchildren was favorable compared with those of 17,623 Tacoma schoolchildren. Blood counts of 33

Ruston schoolchildren were similar to those of children at a school located 8 miles from the smelter (no p-values are given).

ORGANIC ARSENIC

Few studies have dealt with the effects of long-term low-level exposure to organic arsenic compounds such as the herbicides cacodylic acid, monosodium methanearsonate (MSMA) and disodium methanearsonate (DSMA). Tarrant and Allard (1972), studying forest workers who applied cacodylic acid and MSMA, found significantly elevated (at the 5% level of probability) urinary arsenic levels in exposed workers as compared with controls. Urinary arsenic content was highest on Fridays and in most cases had returned to normal by Monday. There was no indication of a continuing increase over a 9-week study period.

In all but one of the 15 men applying cacodylic acid and MSMA the urinary arsenic levels were above 0.3 ppm at least once during the period of exposure. The highest level recorded was 2.5 ppm. No health problems were noted among these workers. The amount of arsenic absorbed by workers could not be correlated with different arsenic compounds or different methods of application. The authors note that the urinary arsenic level at which "concern for matters of health should begin is not well known."

Another study (Wagner and Weswig, 1974) of forest workers exposed to cacodylic acid during a 2-month period also found that urinary arsenic levels increased in the course of the work week. Removal from exposure led to a rapid drop in urinary arsenic. No workers in this study showed a sign of arsenic poisoning. The authors note the lack of studies of long-term low-level exposure to organic arsenic compounds and the need for animal studies as a means of obtaining dose-response data.

Chronic toxicity resulting from reasonable levels of exposure to MSMA and cacodylic acid should not be expected for the following reasons:

1. Their toxicity is 1/100 that of arsenite.

2. They are rapidly excreted in the urine.

3. The dog and cow methylate both arsenate and arsenite, thus detoxifying them (NAS Arsenic, 1977).

4. Creciluis (1977) showed that the arsenate ingested by man by drinking well water is rapidly converted to cacodylic acid and excreted in the urine.

SECTION 6
ASSESSMENT OF THE HEALTH EFFECTS OF ARSENIC

INTRODUCTION

A quantitative assessment of the health effects of exposure to arsenic and its compounds is difficult for many scientific reasons. Nonetheless, despite the limitations on interpretation of the data base, and particularly on the extrapolation of a dose-response relationship, the overwhelming weight of the epidemiological and clinical evidence, when taken together, is that exposure to inorganic arsenic compounds, particularly trivalent arsenic, is related to an increased risk for the development of skin cancer, lung cancer, and various skin disorders; some diseases of the cardiovascular system; and peripheral neuropathy and other nervous system manifestations. If these diseases occur, they are generally serious and irreversible. Such diseases have been associated with high levels of arsenic, and there is no evidence that they arise from low-level environmental exposures.

It must be noted, however, that the dose-response relationship between lung cancer and arsenic alone, observed in the epidemiological studies already cited, can technically be considered only highly suggestive since other contaminants, usually sulfur dioxide, have also been present. Such contaminants must thus be considered possible factors or cofactors in the disease etiology. This is particularly true in view of the observation by Lee and Fraumeni (1967) of an apparent dose-response relationship between lung cancer and concomitant exposure to sulfur dioxide and arsenic. The ability of sulfur dioxide to act

synergistically with other carcinogens such as benzo(a)pyrene has been demonstrated experimentally (Laskin et al., 1970).

Perhaps the major limitation in assessment of the carcinogenicity of arsenic is the lack of a consistent experimental model. Although many experiments have been performed, principally with rats and mice, few have met with success. Those studies that have shown positive effects (e.g., Knoth, 1966; Kanisawa and Schroeder, 1969; Osswald and Goerttler, 1971) have not been replicated or followed to completion. Difficulties in experimental design and differences in metabolism and in the skin of humans and animal species may account in part for the lack of success in inducing arsenical cancer in animals under experimental conditions. Also, storage of arsenic in the red blood cells of the rat may render it an unsuitable species for modeling arsenic carcinogenesis.

The lack of consistent positive evidence of animal carcinogenicity attributable to arsenic is offset somewhat by experimental evidence of mutagenicity, as discussed earlier, as well as evidence of chromosomal abnormalities in human populations, where both *in vivo* and *in vitro* studies have shown chromosomal aberrations among people with histories of exposure to arsenic. Sodium arsenite has been shown to inhibit postreplication DNA repair in *E. coli*. These reports suggest that arsenic interferes with fundamental genetic processes, possibly by binding to the sulfhydryl groups of enzymes involved in genetic repair. The effects on health of such interference are not clear, but Jung and Trachsel (1969) hypothesize that prolonged inhibition of DNA repair by arsenic could lead to lesions that "may constitute the starting point of carcinogenic changes." Since there is high correlation between mutagenicity and carcinogenicity (Hollaender, 1976), these results lend credence to the idea that the inability to demonstrate experimentally that arsenic is a carcinogen may be a function of experimental design.

In addition to data on mutagenicity and carcinogenicity there is a body of evidence demonstrating that inorganic arsenic

is teratogenic. It is known that arsenic can cross the human placenta and that the fetus can absorb and distribute it (Lugo and Palmisano, 1969). Here, too, the health ramifications are not understood, and there are no dosage data, or indeed any data at all, on the effects of low-level human exposure on reproduction. It should be noted that no adverse reproductive effects were reported in the studies of human acute ingestion summarized in this document.

The distribution of arsenic and its metabolism in animals and in humans are also incompletely understood. Distribution and storage vary with different animal species and with route of entry. Studies indicate, however, that arsenic inhibits a large number of enzyme systems by binding to enzymes containing sulfhydryl groups, as discussed previously. The implications of these findings for human health are not clear.

In addition to incomplete knowledge of the chemical and biological action of arsenic, we have little information with which to assess the effects on humans of low-level chronic exposure to arsenic. Only effects resulting from relatively high levels of exposure have been reported. There are virtually no studies of morbidity associated with low-level exposure to arsenic except for those by Benko, which have not been confirmed by others.

INGESTION OF ARSENIC

Several reports of the effects of ingesting high levels of inorganic arsenic have been described. These reports leave little room for doubt that ingestion of inorganic arsenic produces a variety of skin disorders, including skin cancer. In a well-documented epidemiological investigation (Tseng et al., 1968) established a clear dose-response relationship between the amoung of arsenic ingested and the occurrence of skin cancer, as noted previously.

Figure 1, taken from this study, shows some of the observed relationships. It also shows that the levels of arsenic in this

study are extremely high. The report does not give enough data to enable one to estimate the range of the arsenic dosage required to produce skin cancer.

The characteristic sequence of melanosis, keratosis, and skin cancer reported by Tseng has also been observed in widely different situations and different areas of the world, among populations exposed to contaminated drinking water and in patients receiving Fowler's solution during medical treatment. Some rough approximations of dosage can be made. As previously noted, Neubauer's (1947) review of skin cancer in 143 patients undergoing medicinal treatment with arsenical preparations (most often Fowler's solution) affords the estimate that on the average each patient ingested a total quantity of 28 g of arsenic (NAS, 1977), with an average induction period of about 18 years. The effects of similar quantities of inhaled and ingested arsenic cannot be easily equated since it has been demonstrated that absorption of arsenic from the gastrointestinal tract is far less effective than from the respiratory tract (Dutkiewicz, 1977; Stevens et al., 1977). Data on rats administered radio-labeled arsenic are given in Table 3. Despite the ability of the rat to store arsenic in the red blood cells, these data are still useful for demonstrating the differences in absorption by different routes. That there is a difference is, of course, not surprising, since a basic parameter of the toxicity of heavy metals (and other substances) is route of entry. The toxicity of airborne mercury vapor, for example, is markedly greater than that of ingested mercury in humans (Browning, 1969).

We note that others have assumed that ingested and inhaled arsenic are toxicologically equivalent (NIOSH, 1975; Smith et al., 1977). NIOSH has recommended that the concentration of all airborne particles, respirable and irrespirable, is to be determined for compliance with the occupational exposure standard. Irrespirable particles may become trapped in the mucociliary defense system and swallowed and then enter the gastrointestinal

tract; these particles do not enter the bloodstream as effectively as inhaled respirable particles.

OCCUPATIONAL EXPOSURE

Unlike the reports relating to ingestion of high levels of arsenic, the literature on populations occupationally exposed to airborne arsenic clearly shows that arsenic is related to development of lung cancer. Unfortunately, many of the available epidemiological studies that give disease rates among the exposed populations use the proportional mortality ratio (PMR) to calculate disease rates. In a PMR study the number of deaths in a population is expressed relative to the number of all deaths, rather than to the population of the group. As noted by McMahon (1970), a proportional rate determined in this way is only <u>suggestive</u> of differences that may exist between a study population and a comparison population, but no direct comparison can be made. The PMR does not express the <u>risk</u> of members of the exposed population and "until rates can be computed against a population base, it will not be known whether the [observed] differences relate to differences in the sizes of the numerators or the denominators of the compared rates." Thus the absence of quantifiable risk in such PMR studies presents a major stumbling block to a health assessment and to the calculation of a dose-response relationship, since a dose-response relationship is defined as an increase in disease risk with an increase in amount of exposure (McMahon, 1970).

As discussed earlier and summarized in Tables 3 and 4, many of the studies of populations of arsenic-exposed workers were PMR studies. The report of Hill and Faning (1948) of sheep-dip workers should still be considered highly suggestive that lung cancer and arsenic exposure are related, despite the limitations in design. The air and urine levels measured by Perry et al. (1948) and the evident signs of arsenicism make it clear that this population was heavily exposed to arsenic. Unfortunately, no dose-response data can be derived from this investigation.

Ott et al. (1974) calculated a dose-response relationship for arsenic and lung cancer. This study involves exposure to arsenicals without concomitant sulfur dioxide exposure. Certain problems in the study design, however, limit the applicability of the dose-response relationship derived.

First, entry into the study population was based on employment for only 1 or more days in the arsenical work area of the plant. Further, 138 of the 173 decedents in the study were exposed to the pesticides for less than 1 year, and 16 of the 28 observed deaths due to respiratory cancer were among this group. Another of these 28 decedents was a worker with occupational asbestos exposure, and one of the decedents with more than 1 year arsenic exposure was also occupationally exposed to asbestos. Serious questions can be raised about inclusion of workers with such short-term exposure in the study population. The study population also included only those workers who had died while employed by the company or had retired from the company. The retrospective study also reported about one-third of the cohort had been lost to followup. It is not unreasonable to expect the same loss of workers in the PMR study, and it is difficult to estimate the direction of the bias introduced. Since the work with arsenical exposure was an entry-level job with often disagreeable conditions, authors believe it likely that job transfer could be expected, but whether the workers transferred to another job or simply left the company is not known. This loss of workers is, of course, the reason that the authors resorted to a PMR evaluation.

A more serious drawback is that to predict the expected number of deaths as a function of age and year of death, Ott et al. derived and used the following regression equation:

$$P(x_1,x_2) = -0.069 + 0.0037x_1 - 0.00035x_1^2 - 0.014e^{x2} + 0.00051x_1e^{x2} - 0.0000050x_1^2e^{x2}$$

where x_1 = age at death and x_2 = (year of death - 1,940)/10.

Despite its complicated six terms, the predictor equation explains only 57 percent of the variability of the data. The authors provide no further statistical analysis of the equation, such as a calculation of the least squares residuals, which might indicate those ages at which the predictor equation fits the data well and those at which it fits poorly. Furthermore, the standard deviation of the predicted proportion of deaths from respiratory cancer among the control population is between about 25 and 33 percent of the predicted value, a wide error limit.

Because of the relatively poor fit of the predictor equation, it has limited usefulness for providing the expected numbers of deaths for calculation of an observed/expected ratio. Hence, quantitative estimates of a "response" for a dose-response relationship cannot readily be made from this paper. The estimations of dosages also are of limited value because they are highly approximate. Ott and coworkers relied on 15 breathing-zone samples taken in 1952. The samples ranges from 1.7 to 40.8 mg As/m^3 in the drum dryer area and 0.26 to 7.5 mg As/m^3 in the packaging area. These measurements, which cover a range greater than one order of magnitude, were used to derive time-weighted averages, which were then extrapolated according to employee work histories.

In summary, the study design, the predictor equation, and the dosage estimates are such that the report cannot be used as the basis for extrapolating a dose-response relationship. The work of Ott et al. is, however, highly suggestive of a causal relationship between lung cancer and arsenic exposure and is in accord with other available evidence.

SMELTER WORKER MORTALITY RATE STUDIES

The strongest evidence that arsenic is a lung carcinogen, possibly in conjunction with sulfur dioxide, comes from the mortality studies of smelter workers. Lee and Fraumeni (1969); Pinto et al. (1977); Pinto et al. (unpublished); Tokudome and Kuratsune (1976); and Rencher and Carter (1977), for example,

present similar results, derived from different smelter cohorts, indicating an excess risk associated with exposure to arsenic (and to sulfur dioxide). These studies further confirm that the risk for lung cancer increases with exposure; that is, they provide additional support for a dose-response relationship. Blot and Faumeni (1975) obtained evidence of an increased rate of lung cancer when they calculated an increased risk for lung cancer among residents of counties in which copper smelters or refineries are located.

The results of these smelter-worker studies are analyzed in some detail here to develop an estimate of the extent of the risk observed and the dosages with which these risks can be correlated. The estimates of dosages also involve an analysis of serious deficiencies in both environmental and biological monitoring of arsenic exposure.

The rates calculated by several authors for respiratory cancer are given in Table 11. They are all significantly elevated. When rates are calculated as a function of duration and degree of exposure in Table 12, a definite gradient is observed. All the authors state that a similar gradient is observable with respect to concurrent sulfur dioxide exposure. It is important to note that the gradients shown in Table 12 should not be compared, since the classifications "heavy," "medium," and "light" do not refer to the same degrees of arsenic exposure. They are purely relative indices taken from the original sources.

Once a dose-response gradient is observed, it is important to quantify the dose leading to the response. Accurate quantification depends on accurate environmental and/or biological assays. For this reason, it is appropriate to discuss relevant parameters of such monitoring before doses are extrapolated.

BIOLOGICAL MONITORING

Inherent in the assumption that one can extrapolate an index of exposure from urinary arsenic levels to ambient arsenic is reliance on a correlation between urinary arsenic levels and

TABLE 11. STANDARDIZED RESPIRATORY CANCER MORTALITY RATES OBSERVED AMONG SEVERAL SMELTER-WORKER COHORTS

	No. of cases	SMR	Comments
Tokudome and Kuratsune (1976)	29	1189[a]	Dose-response relationship obtained for length of employment and degree of exposure; no relationship observed between latency period and dose
Lee and Fraumeni (1969)	61 (>15 yr before 1930)	469[b]	Dose-response relationship obtained for length of employment and degree of exposure
	37 (>15 yr 1938-63)	370[b]	
	10 (10-14 yr)	233[a]	
	15 (5-9 yr)	268[b]	
	24 (1-4 yr)	203[b]	
Pinto et al. (1977)	32	305	Dose-response relationship obtained for length of employment and degree of exposure; only deaths among retirees included
Rencher and Carter (1976)	17	10.1/10,000[c] Utah 3.3/10,000	Cohort included all workers

[a] Significant at 5% level.

[b] Significant at 1% level.

[c] Statistically significant level not stated.

TABLE 12. RESPIRATORY CANCER SMR's AS A FUNCTION OF DURATION AND DEGREE OF EXPOSURE

All cohorts:	Heavy[a]	Medium[a]	Light[a]
Tokudome and Kuratsune (1976)	1485[b]	1250[b]	615[b]
Lee and Fraumeni (1969)	667[b]	478[b]	239[b]
Cohorts by length of exposure:			
Tokudome and Kuratsune (1976)	2048[b] >15 yr prior to 1948	1064[b] >15 yr	614[b] 1-14 yr
Lee and Fraumeni (1969)	800[b] >15 yr prior to 1938	667[b] >15 yr	250[b] 1-14 yr
Pinto et al. (1977)	600[c] <25 yr	267 <25 yr	95 <25 yr
	833[c] >25 yr	364[c] >25 yr	278[c] >25 yr

[a] Exposure categories are not strictly comparable because they represent different actual values. They are taken from the authors' estimates and should be considered relative to each other in each report.

[b] Significant at 1% level.

[c] Significant at 5% level.

airborne arsenic. The recent epidemiological investigations of Pinto et al. (unpublished) explicitly derive an arsenic exposure index from urinary arsenic levels. The air/urine correlation cited in Figure 2 is that of Pinto et al. (1976). Our examination of the data presented in Pinto et al. (1976) shows, in fact, a poor correlation between urinary arsenic levels and airborne arsenic for all exposures less than 60 $\mu g/m^3$, despite the statistically significant correlation reported. Figure 2 illustrates the correlation presented by Pinto et al.

Although Pinto and coworkers calculated a significance level of $p<0.01$, this significance level has little meaning for the lower end of the regression line, since it does not correlate well with the data. At these values, the nonrandom scatter of the points in Figure 2 illustrates this poor fit.

The mean and standard deviation of the data, 170 and 113, respectively, also show wide variability in the relationship between airborne arsenic levels and urinary arsenic levels. A similar conclusion has been reached by others (NIOSH, 1975). Thus, in order to estimate the exposure indices and dosages of workers at risk for lung cancer, wide error limits must be applied to the calculated exposures. For purposes of this document a 7-fold to 10-fold variation will be assumed, since that is the approximate range of the urinary arsenic values corresponding to very small changes in airborne levels shown in Figure 2.

AIR SAMPLING

Even greater error limits must be applied to the urine/air correlations to account for errors in the methods of air analysis. Lao et al. (1974) clearly demonstrate that the physical properties of arsenic require a differential between temperatures of the ambient air and of the collector. If the collector is not at a lower temperature, volatilization of the As_2O_3 collected (as As_4O_6) will occur and as much as 90 percent of the sample may be

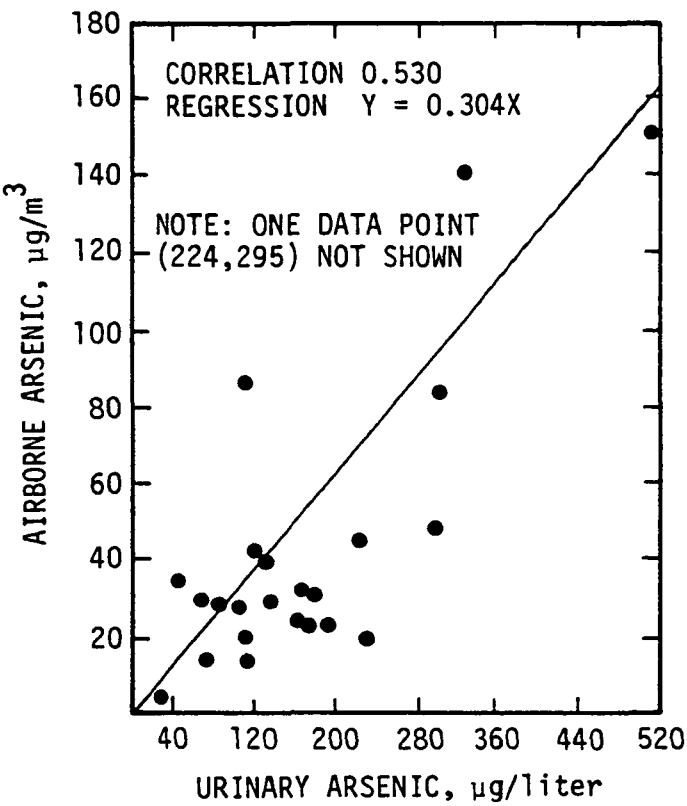


Figure 2. Comparison of urinary arsenic excretion and concentration of inhaled arsenic calculated by Pinto et al. (1977).

lost. The National Academy of Sciences (1977) warns in its Recommendations that unless the methods of Lao et al. are followed, air sampling measurements will be seriously deficient.

The purpose of this assessment is to extrapolate the health effects of arsenic in the best way feasible and not simply to dismiss the data. Thus air sampling data presented here will be considered to be within an order of magnitude of the correct value, a justifiable approximation given the constraints pointed out by Lao and others. Although such precision is of little value to an analytical chemist charged with determining compliance with ambient air levels, it is certainly within the degree of precision with which all the epidemiological and clinical data presented here can be evaluated.

Thus, taken together, approximately a 70- to 100-fold range and variability must be considered for urine/air correlations and the indices derived from them.

EVALUATING THE EXPOSURE

With the constraints of a 70- to 100-fold range for urine/air correlations and 7- to 10-fold and 10-fold ranges for urine and air measurements, respectively, extrapolations of dosages can be made on the basis of the reports cited in Table 12. The dosages are given in Tables 13 and 14.

Table 13, taken from NIOSH (1975), gives the ranges used by Lee and Fraumeni (1969) for their classification of exposures. There is great variability in the data. The calculated standard deviations for the areas numbered 1, 2a, 2b, and 3a, respectively, are 3.47, 1.74, 2.54, and 0.48.

Exposure levels are not given by Tokudome and Kuratsune (1976), and those of Rencher and Carter (1977) are not well defined, with no units given.

Table 14 is taken from Pinto et al. (1976). The exposure index calculated is a relative index constructed from the average urinary arsenic levels found in workers in 33 departments of the Tacoma smelter and the employment history for each of the 525

TABLE 13. ATMOSPHERIC ARSENIC CONCENTRATIONS IN 1965 SMELTER SURVEY[a]

($mg\ As/m^3$)

"Heavy exposure area" as classified by Lee and Fraumeni		
Arsenic roaster area		Mean: 1.47
0.10	0.20	Median: 0.185
0.10	0.22	
0.10	0.25	
0.10	0.35	
0.10	1.18	
0.10	5.00	
0.17	12.66	
"Medium exposure areas" as classified by Lee and Fraumeni		
Reverberatory area		Mean: 1.56
0.03	0.93	Median: 0.88
0.22	1.00	
0.23	1.27	
0.36	1.60	
0.56	1.66	
0.63	1.84	
0.66	1.94	
0.76	2.06	
0.78	2.76	
0.78	3.40	
0.80	4.14	
0.83	8.20	
Treater building and arsenic loading		Mean: 1.50
0.10	0.48	Median: 0.295
0.10	0.62	
0.10	3.26	
0.11	7.20	
"Light exposure areas" as classified by Lee and Fraumeni		
Copper concentrate transfer system		Mean: 0.70
0.25		Median: 0.65
0.65		
1.20		
Samples from flue station		Mean: 0.17
0.10		Median: 0.17
0.24		
Reactor building		Mean: 0.004
0.001	0.003	Median: 0.002
0.002	0.009	
0.002	0.010	
0.002		

[a] Source: National Institute of Occupational Safety and Health, 1975.

TABLE 14. RELATIONSHIP BETWEEN ARSENIC EXPOSURE AND LUNG CANCER MORTALITY CALCULATED BY PINTO et al. (1977)

Exposure index (mean index)	Respiratory cancer deaths			
	No. of men	Observed	Expected	SMR
<2000(1514)	36	1	0.9	111.1
2000-2999(2513)	109	4	2.1	190.5
3000-5999(4317)	205	11	3.9	282.0[a]
6000-8999(7473)	109	7	2.3	304.3[a]
9000-11,999(10,135)	38	4	0.7	571.4[a]
>12,000(14,712)	29	5	0.6	833.3[a]

[a] $p < 0.05$

retirees included in the study. Thus the index is a measure of intensity, not arsenical exposure. Table 15 gives the corresponding mean urinary levels, which appear in Pinto et al. (unpublished).

Applying the regression fit calculated by Pinto et al. (1977) to data also provided by Pinto et al. (1977), which calculates SMR as a function of duration and intensity of exposure, we obtain the air levels shown in Table 16. In order to be most conservative in the extrapolation and thus ensure the greatest margin of safety, we shall use the correspondence between an SMR of 833 and an air level of 106 $\mu g/m^3$ for further calculation.

Assuming that the worker experiencing a mortality rate of 833 is exposed to the workplace environment about 22 percent of the year (40 hours/week; 3 weeks vacation and leave), the 106 $\mu g/m^3$ is equivalent to an air level of 23 $\mu g/m^3$ in the environment for 24 hours per day all year. This figure must be further tempered because Pinto et al. (1977) reported only on the mortality experience of retirees. An upward bias is thus introduced, because some men who worked at the refinery but left may also have died of respiratory cancer. It can also be argued that such reporting pushes the estimate downward, in that smelter workers probably tend to live in arsenic-polluted environments and hence continue to be exposed to levels of arsenic greater than that to which the general population is exposed when not at work. It is difficult to weigh these biases quantitatively.

If we next consider the Lee and Fraumeni report, we see that, taking the heaviest exposure and the corresponding SMR, a median of 0.185 mg As/m^3 and a mean level of 1.47 mg As/m^3 resulted in an SMR of 800 (significant at the 1% level). Using the same approximation of 22 percent (see above) this is equivalent to a 24-hour exposure level between 41 and 323 $\mu g/m^3$.

Considering the approximations, the unreliability of the measurement methods, the loss of followup of cohort, the variability in the air levels used by Lee and Fraumeni and Pinto et

TABLE 15. MEAN URINARY ARSENIC VALUES USED TO CONSTRUCT TABLE 14[a]

Department	Number of samples		Concentration in urine, μg As/liter		Percent change
	1948-52	1973	1948-52	1973	
Cottrell	62	48	553	526	- 5
Arsenic plant	222	85	804	516	-36
Roaster	77	103	556	414	-26
Boiler room (waste heat)	7	30	787	409	-48
Janitor	10	7	176	289	+64
Repair	25	41	328	288	-12
Steel shop	81	46	624	272	-56
Reverberatory	36	38	346	269	-22
Mason	5	20	270	260	- 4
Carpenter	94	41	219	255	+16
Yard	85	17	506	226	-55
Crushing plant	0	16		222	
Pipe shop	6	22	1258	218	-83
Slimes	27	26	127	207	+63
Laundry	6	3	115	201	+75
Acid plant	6	13	142	180	+27
Electric shop	10	24	354	171	-52
Lead burners	9	8	2144	166	-92
Converter	6	52	161	160	0
Fire	0	2		140	
Mobile equipment	0	23		119	
Martin mill	0	20		115	
Track	0	6		112	
Machine shop	5	16	120	102	-15
Mobile equipment repair	0	9		101	
Anode	4	36	103	98	- 5
Refinery	13	157	103	98	- 5
Office	30	58	108	88	-19
Warehouse	2	5	80	82	+ 3
Sample dept.	10	16	215	81	-62
Watchman	7	13	135	77	-43
Refined casting	7	56	67	58	-13
Average for 26 departments in which samples were taken in both periods.			400	220	-95

[a] Pinto et al. in press. Values are averages by department.

TABLE 16. DERIVATION OF AIR LEVEL EQUIVALENTS FROM URINARY ARSENIC LEVELS AND CORRESPONDING SMR's AS A FUNCTION OF DURATION

Calculated air level, μg/m^3	Intensity of exposure, μg/liter urine	Duration					
		<25 years			>25 years		
		Obs.	Exp.	SMR	Obs.	Exp.	SMR
15.2 - 60.5	50 - 199	2	2.1	95	10	3.2	278
60.8 - 106	200 - 349	4	1.5	267	8	2.2	364
>106	≥350	3	0.5	600	5	0.6	833

[a] Using the regression fit y = 0.304X, calculated from Pinto, et al. (1976).

al., as well as all the other constraints already mentioned, the ratios obtained from the Pinto et al. and the Lee and Fraumeni studies of air levels per SMR of 23 μg As/m^3 per 833 and 41 to 323 μg As/m^3 per 800, respectively, are still in reasonable agreement with each other.

Other Cancer Risks

There is evidence that arsenic exposure is related to cancer of the digestive tract, possibly arising from the swallowing of irrespirable particles trapped by the muco-ciliary defense system. Tokudome and Kuratsune (1976) calculated an SMR of 508 for digestive tract cancer, significant at the 1 percent level, among copper smelter workers; Milham (1977) obtained a PMR of 162, for cancer of the large intestine, significant at the 5 percent level. Lee and Fraumeni (1969) did not calculate an elevated SMR (101); however, they did not classify the deaths by exposure and an effect observable among those with the greatest and longest exposure may have been obscured. This is plausible since they did obtain such an exposure/duration gradient for lung cancer. Pinto et al. (1977) calculated an SMR of 122 for digestive cancer, but it was not statistically significant. At this point it is not possible to calculate an equivalent dose because corresponding air levels are not available.

It is also interesting to note that Rencher and Carter (1977) and Pinto et al. (unpublished) calculate that nonsmokers are at greater risk of lung cancer than smokers, as shown in Table 17. Since the mortality rate from lung cancer of the smoking retirees is more than 3-fold that of the nonsmoking retirees, it is still an open question as to whether this is a true observation or just the result of earlier death among smoking smelter workers with resultant loss to followup.

ASSESSMENT OF THE EFFECTS OF COMMUNITY EXPOSURE

Throughout this assessment we have stressed that one cannot state categorically that arsenic alone induces lung cancer and

TABLE 17. RESPIRATORY CANCER MORTALITY AND SMOKING AMONG SMELTER WORKERS

Observed respiratory cancer deaths among 377 men alive on January 1, 1961[a]

Smoking status	No. of retirees	No. of deaths	SMR
Smokers	189	15	287.3[b]
Ex-smokers	69	3	245.1
Nonsmokers	119	3	506.5[b]

Percentage of deaths due to lung cancer by location[c]

	Smelter	Mine	Other
Nonsmokers	3.3	0.7	0.8
Smokers	9.2	3.3	3.3

[a] Source: Pinto et al. (in press).

[b] $p<0.05$.

[c] Source: Rencher, Carter, and McKee (1977).

that the presence of ubiquitous contaminants must also be considered. The major environmental sources of airborne arsenic, such as smelters and coal-fired generators, usually do not emit arsenic alone to the community, but also emit the contaminants encountered in the workplace environments studied. Thus it can be expected that the etiological relationships observed in the workplace between arsenic and lung cancer in the presence of contaminants will be observed wherever such contaminants occur together, including the general environment. It is relevant that high-temperature generation of arsenic and heavy metals, such as from power plants, produces particles that are in the respirable size range and hence can effectively penetrate the respiratory system and enter the bloodstream (Natusch and Wallace, 1974). Further confirmation of this point is provided by Pinto and McGill (1953), who state that a "substantial part" of the arsenic trioxide emitted by smelters is over 5.5 μm in diameter. This means that 77 percent is below 5.5 μm and much of this is in the respirable range.

Additional evidence of community exposure to arsenic is found in the elevated levels of urinary arsenic reported in communities near copper smelters. Milham and Strong (1974) found that urinary arsenic levels of schoolchildren residing near the Tacoma smelter were comparable to those of smelter workers. As noted earlier, however, this study failed to take into account ingestion of arsenic in seafood or specific gravity of the spot urine samples. Elevated community levels are also confirmed in a fashion by Pinto and McGill (1953), who give 0.13 μg/liter urinary arsenic as the background level among nonsmelter workers assumed not to be exposed to arsenic; later studies suggest that this level is indicative of exposure. Apparently these workers lived in the community near the Tacoma smelter, which may account for their exposure. Furthermore, high levels of sulfur dioxide were noted in the area surrounding the Rönnskär smelter works (Pershagen et al., 1977), and it is likely that communities

adjacent to smelters are exposed to significant amounts of sulfur dioxide in combination with arsenic.

The report by Blot and Fraumeni (1975) supports the conclusion that the elevated ambient levels of arsenic and the elevated urinary levels of arsenic observed in communities near smelters lead to an excess of lung cancer. Their results, discussed earlier, are summarized in Table 18.

Nelson (1977) has criticized the findings of Blot and Fraumeni on the basis that they made no distinction between smelters and refineries. This is a valid criticism, since smelters are responsible for the greatest amount of arsenic pollution. When the data of Blot and Fraumeni are recalculated leaving out the four counties not cited by Nelson as containing smelters, the figures in Table 19 are obtained, showing that removal of counties with refineries does not affect the result.

Nelson also cites the data in Table 18 and derives the data shown in Table 20 (the mortality rates shown as SMR's are just mortality rates and not SMR's) in order to establish that there is no relationship between arsenic levels and community rates. No direct extrapolation can be made, however, for several reasons. One is that the use of national mortality rates for comparison purposes is not as good as the use of demographically derived comparison rates. The second is that distribution of the arsenic in the entire county is a function of the size of the county, the geographical location of the smelter, and meteorological factors. For example, the Tacoma smelter, which has the highest percentage of arsenic in the feed, is located in the northwest corner of a large county. If we look at the county/state/SMR breakdowns (Table 20) provided by Blot and Fraumeni in their original draft, but not published in the final report, the relative populations become apparent. For these geographical and demographic reasons it is also inappropriate to calculate the ambient levels that may correspond to the increased mortality rates.

TABLE 18. LUNG CANCER MORTALITY RATES AMONG WHITE MALES IN COUNTIES WITH COPPER SMELTERS[a] (showing national average)

County	Lung cancer mortality rate
Deer Lodge, Montana	65.2
Gila, Arizona	46.3
Pima, Arizona	39.7
Cochise, Arizona	38.1
National average	38.0
Pierce, Washington	35.8
El Paso, Texas	33.9
Greenlee, Arizona	32.0
Pinal, Arizona	31.7
Ontonagon, Michigan	29.2
Polk, Tennessee	28.8
Grant, New Mexico	26.3
Salt Lake, Utah	26.2
White Pine, Nevada	20.0

[a] Source: U.S. Cancer Mortality by County: 1950-1969, U.S. DHEW, Publication No. (NIH) 74615.

TABLE 19. DISTRIBUTION OF LUNG CANCER SMR's IN U.S. COUNTIES WITH COPPER SMELTERS AND REFINERIES (SR), AND WITH ONLY COPPER SMELTERS[a]

Male SMR	-90	90-110	110+	Total
-90	1 1	0 0	2 2	3 3
90 - 110	0 0	1 2	1 2	2 4
110+	3 3	1 3	4 5	8 11
Total	4 4	2 5	7 9	14 18

[a] Values for counties with both smelters and refineries are in upper portion of each box. Table calculated and adapted from Blot and Fraumeni (1969).

TABLE 20. ARSENIC IN SMELTER FEEDS AND LUNG CANCER RATES

Smelter (company)	Arsenic in feed, %	Lung cancer SMR[a]	
		Male	Female
Tacoma (Asarco)	5.200	35.8	6.4
Anaconda (Anaconda)	0.96	65.2	4.3
El Paso (Asarco)	0.800	33.9	7.6
Garfield (Kennecott)	0.135	26.2	3.5
Hayden (Asarco)	0.040	46.3	7.3
Hayden (Kennecott)	0.015	46.3	7.3
San Manuel (Magma)	0.007	31.7	7.8
Hurley (Kennecott)	0.005	26.3	10.8
White Pine (Copper Range)	0.002	29.2	2.0
U.S. average		37.98	6.29

[a] (sic) taken from Nelson (1977).

Lyon et al. (1977) recently reported on community lung cancer rates and arsenical pollution. The authors found no excess lung cancer mortality among residents of Salt Lake County, Utah. This finding agrees with those of Blot and Fraumeni for this county (Table 19). There is currently no explanation of the differences between this smelter county and the others shown in Table 21.

TABLE 21. U.S. COUNTIES ENGAGED IN THE PRIMARY SMELTING AND REFINING OF NONFERROUS ORES IN 1963[a]

County/State	Population in 1960	Estimated No. of smelter-refiner workers in 1963	1950-69 Lung cancer SMR	
			Male	Female
Cochise, Arizona	55,039	750	161	130
Gila, Arizona	25,745	1300	154	145
Greenlee, Arizona	11,509	175	138	46
Pima, Arizona	265,660	175	136	121
Pinal, Arizona	62,673	350	106	156
Anne Arundel, Maryland	206,634	750	118	108
Baltimore City, Maryland	939,024	750	109	102
Roughton, Michigan	35,654	210	105	132
Ontonagon, Michigan	10,584	175	130	43
Cascade, Montana	73,418	1160	134	110
Deer Lodge, Montana	18,640	925	246	85
White Pine, Nevada	9,808	375	78	123
Middlesex, New Jersey	433,856	4685	121	93
Grant, New Mexico	18,700	210	114	238
Polk, Tennessee	12,160	75	115	90
El Paso, Texas	314,070	1500	89	115
Salt Lake, Utah	383,035	2250	75	58
Pierce, Washington	321,590	760	100	97

[a] Source: Blot and Fraumeni (1975).

SECTION 7

REFERENCES

1. American Conference of Industrial Hygienists. Documentation of the Threshold Substances Added or Changed Since 1971. Cincinnati: Amer. Con. of Ind. Hygienists, 1976.

2. Ancel, P. Recherche Experimentale Sur Le Spina Bifida. Arch. Anat. Mier. Morph. Exp 36:45, 1946.

3. Argentine Association of Dermatology and Syphilology and Its Affiliates. Argentine Review of Dermatosyphilology. Buenos Aires: Frascolli & Bindi, 1938. (Trans. for EPA by Nundus Systems, Washington, D.C.)

4. Arguello, R.A., D.D. Cenget, E.E. Tello. Y Cancer Arsenicismo Regional Endemico En Cordoba. Argentine Dermatosifilol 22: 461-487, 1938.

5. Arsenault, R.D. Health Aspects of C.C.A. Wood Preservatives-- A Review of Arsenates and Cancer. BWPA Annual Convention, 1977.

6. Baetjar, A.M., M.L. Levin, A. Lilienfeld. Analysis of Mortality Experience of Allied Chemical Plant -- 2000 Race Street, Baltimore, Maryland. Unpublished report submitted to the Allied Chemical Corp., Morristown, New Jersey, July 16, 1974. (Summarized in NIOSH, 1975.)

7. Baron, D., I. Kunick, I. Frischmuth, J. Petres. Further In Vitro Studies on the Biochemistry of the Inhibition of Nucleic Acid and Protein Synthesis Induced by Arsenic. Arch Derm Res 253:15-22, 1975.

8. Baroni, C., G.J. Van Esch, U. Saffiotti. Carcinogenesis Tests of Two Inorganic Arsenicals, Arch of Environ. Health 7:668-673, 1963.

9. Barry, K.G., E.G. Herndon. Electrocardiographic Changes Associated with Acute Arsenic Poisoning. Med Ann Dist of Columbia 31:25-27, 76-66, 1962.

10. Beaudoin, A.R. Teratogenicity of Sodium Arsenate in Rats. Teratology 10:153, 1974.

11. Beckman, G., L. Beckman, I. Nordenson. Chromosome Aberrations in Workers Exposed to Arsenic. pp. 145-146. In National Institute of Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Department of HEW, Public Health Service, National Institute of Health. Publication Number (NIH) 77-218, 1977.

12. Bencko, V. Arzen Vo Vlasoch Neprofesionalne Exponovanej Populacie (Arsenic In Hair of Professionally Not Exposed Population). Ceskoslovenska Hygiena, 11:539-543, 1966.

13. Bencko, V., K. Nejedly, J. Scmora. Histological Examination of Some Organs After the Peroral Administration of Arsenic to Hairless Mice. C.S. Hyg. 13:344, 1968.

14. Bencko, V., A. Dobisova, M. Macaj. Arsenic in the Hair of a Non-Occupationally Exposed Population. Atmos. Envir. Pergamon Press 5:275-279, 1971.

15. Bencko, V. Carcinogenic, Teratogenic, and Mutagenic Effects of Arsenic. pp. 179-182. In National Institute of Environmental Health Sciences (Ed.), Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, National Institute of Health. Publication Number (NIH) 77-218, 1977.

16. Bencko, V., K. Symon. Test of Environmental Exposure to Arsenic and Hearing Changes in Exposed Children. pp. 95-101. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Department of HEW, Public Health Service, National Institute of Health. Publication Number (NIH) 77-218, 1977.

17. Bergoglio, R.M. Mortality From Cancer in Regions of Arsenical Waters of the Province of Cordoba Argentine Republic. Pren. Med. Argent. 51:994-998, 1964.

18. Biomedical Studies Group. Review of the Environmental Effects of Arsenic. Oak Ridge National Laboratory, Oak Ridge, Tennessee. Operated by Union Carbide Corp., for the Energy Research and Development Administration, Contract No. W-7405-Eng.-26, 1976.

19. Blejer, H.P., W. Wagner. Case Study 4. Inorganic Arsenic Ambient Level Approach to the Control of Occupational Cancerigenic Exposures. pp. 179-186. In Saffiotti, U., J.K. Wagoner, Occupational Carcinogenesis. Annals of the New York Academy of Sciences, Vol. 271. New York, New York, 1976.

20. Blot, W.J., J.F. Fraumeni. Arsenical Air Pollution and Lung Cancer. Lancet: 142-144, July 26, 1975.

21. Borgono, J.M., R. Greiber. Epidemiological Study of Arsenicism in the City of Antofagasta. pp. 13-24. In Hemphill, D.D. (Ed.). Trace Substances in Environmental Health V. Proceedings of Univ. of Missouri's 5th Annual Conference on Trace Substances in Environmental Health. June 29 - July 1, 1971. Columbia Univ. of Missouri, 1972.

22. Borgono, J.M., P. Vicent, H. Venturino, A. Infante. Arsenic in the Drinking Water of the City of Antofagasta. Epidemiological and Clinical Study Before and After the Installation of the Treatment Plant. pp. 103-105. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

23. Boutwell, R.K. A Carcinogenicity Evaluation of Potassium Arsenite and Arsanilic Acid. Agr. Food Chem. 11:381-385, 1963.

24. Braman, R.S., C.C. Foreback. Methylated Forms of Arsenic in the Environment. Science 182:1247-1249, 1973.

25. Braun, W. Carcinoma of the Skin and the Internal Organs Caused by Arsenic. Germ. Med. Monthly 3:321-324, 1958.

26. Browning, E. Toxicity of Industrial Metals. New York. Appleton-Century-Crofts, 1969.

27. Buchanan, R.J.M. Cases of Arsenical Peripheral Neuritis. Lancet 170-172, January 19, 1901.

28. Buchanan, W.D. Toxicity of Arsenic Compounds. Amsterdam: Elsevier Pub. Co., 1962.

29. Buechley, R.W. Bibliography on Health Effects of Arsenic. U.S. Department of Health, Education, and Welfare, 411 West Chapel Hill Street, Durham, North Carolina 27701. Unpublished.

30. Burgdorf, W.H. Sister Chromatid Exchanges in Patients with Chronic Arsenic Use. Unpublished Masters Thesis, 1977. University of Minnesota.

31. Butzengeiger, K.H. Uber Die Chronische Arsenvergiftung. Deut Arch Fur Klinische Medizin 194:1-16, 1947.

32. Byron, W.R., G.W. Bierbower, J.B. Brouwer, W.H. Hansen. Pathologic Changes in Rats and Dogs From Two-Year Feeding of Sodium Arsenite or Sodium Arsenate. Tox. and App. Phar. 10:132-147, 1967.

33. Carcinogen Assessment Group, Assessment of Cacodylic Acid. (Unpublished report supplied by EPA.)

34. Carcinogen Assessment Group, Preliminary Report on Inorganic Arsenic. (Unpublished report supplied by EPA.)

35. Carnow, B.W., ed. Health Effects of Occupational Lead and Arsenic Exposure. U.S. Department of Health, Education, and Welfare. Washington, D.C. Superintendent of Documents, U.S. Government Printing Office, 1976.

36. Clay, J.E., I. Dale, J.D. Cross. Arsenic Absorption in Steel Bronze Workers. J. Soc. Occup. Med. 27:102-104, 1977.

37. Colucci, A.V. Epidemiology of Pesticide and Metal Residues. pp. 1043-1051. In Comm. of the European Communities; WHO; EPA (Eds.). International Symposium Proceedings. Recent Advances in the Assessment of the Health Effects of Environmental Pollution, Vol. 2. Paris: Comm. of the European Communities; WHO; EPA, 1974.

38. Crecelius, E.A., M.H. Bothner, R. Carpenter. Geochemistries of Arsenic, Antimony, Mercury, and Related Elements in Sediments of Puget Sound. Environ. Sc. & Tech. 9:325-333, 1975.

39. Crecelius, E.A. Arsenite and Arsenate Levels in Wine. Bull. Environ. Contamination and Toxicology, 1977.

40. Crecelius, E.A. Changes in the Chemical Speciation of Arsenic Following Ingestion by Man. pp. 147-150. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

41. Crema, A. Distribution et élimination de l'arsenic 76 chez la souris normale et cancéreuse. Arch. int. pharmacodyn. 103: 57-70, 1955.

42. Currie, A.N. The Role of Arsenic in Carcinogenesis. Brit. Med. Bull. 4: 402-405, 1947.

43. Dubois, L., T. Teichman, J.L. Monkman. The Normal Value of Arsenic in Human Hair. Proc. Canadian Soc. of Forensic Science 4:217-231, 1965.

44. Ducoff, H.S., W.B. Neal, R.L. Straube, L.O. Jacobson, A.M. Brues. Biological Studies With Arsenic. II. Excretion and Tissue Localization. Proc. Soc. Exp. Biol. Med. 69:548-554, 1948.

45. DuPont, O., I. Ariel, S.L. Warren. The Distribution of Radioactive Arsenic in the Normal and Tumor-bearing (Brown-pearce) Rabbit. Am. J. Syphilis. 26:96-118, 1942.

46. Dutkiewicz, T. Experimental Studies on Arsenic Absorption Routes in Rats. pp. 173-177. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

47. Eiji, H. Funnyu Ni Yoru Nyuji Hiso Chudokusho (Infant Arsenic Poisoning by Powdered Milk). Nihon Iji Shimpo Japan Med. J. 1649:3-12, 1955. Translated for EPA by Leo Kanner Assoc. TR105-74.

48. Enterline, P.E., S.S. Pinto, V. Henderson. Cancer Among Arsenic Exposed Workers in a Copper Smelter.

49. Fairhall, L., J.W. Miller. A Study of the Relative Toxicity of the Molecular Components of Lead Arsenate. Publ. Hlth. Report, 56:1610-1625, 1942.

50. Falk, H.L., P. Kotin. An Assessment of Factors Concerned With the Carcinogenic Properties of Air Pollutants. Nat. Cancer Inst. Mon. 9:81-89, 1961.

51. Feinglass, E.J. Arsenic Intoxication From Wellwater in the United States. New Eng. J. of Med. 288:828-830, 1973.

52. Ferm, V.H., S.J. Carpenter. Malformations Induced by Sodium Arsenate. J. Reprod. Fertil. 17:199, 1968.

53. Ferm, V.H., A. Saxon, B.M. Smith. The Teratogenic Profile of Sodium Arsenate in the Golden Hamster. Arch. Environ. Health 22:557-560, 1971.

54. Ferm, V.H. Arsenic as a Teratogenic Agent. pp. 215-217. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

55. Fierz, L. Katamnestische Untersuchungen Uber Die Nebenwirkungen Der Therapie Mit Anorganischem Arsen Bei Hautkrankheiten (Catamnestic Investigations of the Side Effects of Therapy of Skin Diseases With Inorganic Arsenic). Schweiz Ges Derm Verner, 46th Annual Meeting, Lausanne, 1964. Dermatologica 131:41-58, 1965. Translated for EPA by SCITRAN - TR251-75.

56. Fowler, B.A. International Conference on Environmental Arsenic. An Overview. pp. 239-242. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Rsearch Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

57. Fowler, B.A., J.B. Weissberg. Arsine Poisoning. New Eng. J. Med. 291:1171-1174, 1974.

58. Fowler, B.A., J.S. Woods, C.M. Schiller. Ultrastructural and Biochemical Effects of Prolonged Oral Arsenic Exposure on Liver Mitochondria of Rats. pp. 197-204. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

59. Franseen, C.C., G.W. Taylor. Arsenical Keratoses and Carcinomas. Am. J. Cancer 22:287-307, 1934.

60. Fraumeni, J.F. Respiratory Carcinogenesis: An Epidemiologic Appraisal. J. Natl. Cancer Inst. 55:1039-1046, 1975.

61. Friedrich, E.G. Vulvar Carcinoma In Situ in Identical Twins-- An Occupational Hazard. Obstetrics and Gynecology 39:837-841, 1972.

62. Frohn, W. Occupational Arsenic Poisoning of Wine Growers. Munchener Medizinishe Wochenschrift 42: 1630-1635, 1938.

63. Frost, D.V. Arsenicals in Biology - Retrospect and Prospect. Fed. Proc. 26:194-208, 1967.

64. Gainer, J.H. Effects of Arsenicals on Interferon Formation and Action. Am. J. Vet. Res. 33:2579-2586, 1972.

65. Gainer, J.H., T.W. Pry. Effects of Arsenicals on Viral Infections in Mice. Am. J. Vet. Res. 33:2299-2307, 1972A.

66. Galy, P., R. Touraine, J. Brune, P. Roudier, P. Gallois. Le Cancer Pulmonaire D'Origine Arsenicale Des Vignerons Du Beaujolais. J. Fran De Med Et Chir Thorac 17:303-311, 1963.

67. Garb, L.G., C.H. Hine. Arsenical Neuropathy: Residual Effects Following Acute Industrial Exposure. J. Occ. Med. 19:567-568, 1977.

68. Ginsburg, J.M. Renal Mechanism for Excretion and Transformation of Arsenic in the Dog. Amer. J. Physiol. 208:832-840, 1965.

69. Glazener, F.S., J.G. Ellis, P.K. Johnson. Electrocardiographic Findings with Arsenic Poisoning. Cal. Med. 109:158-162, 1968.

70. Hamamoto, E. Funnyu Ni Yoru Nyuji Hiso Chudokusho (Infant Arsenic Poisoning by Powdered Milk. Nihon Iji Shimpo (Japan Med. J.) 1649:3-13, 1955. Trans. for EPA by Leo Kanner Assoc. -- TR 105-74.

71. Hamilton, A., H.L. Hardy. Industrial Toxicology, 2nd Ed. New York. Paul B. Hoeber, Inc., 1949.

72. Harkins, W.D., R.E. Swain. Papers on Smelter Smoke (First Paper). J. Amer. Chem. Soc. 29:970-998, 1907.

73. Harkins, W.D., R.E. Swain. The Chronic Arsenical Poisoning of Herbivorous Animals. (Papers on Smelter Smoke, Third Paper.) J. Amer. Chem. Soc. 30:928-946, 1908.

74. Harrisson, J.W.E., E.W. Packman, D.D. Abbott. Acute Oral Toxicity and Chemical and Physical Properties of Arsenic Trioxides. Ama. Arch. Ind. Health 17:118-123, 1958.

75. Haywood, J.K. Injury to Vegetation and Animal Life by Smelter Fumes. J. Amer. Chem. Soc. 29:998-1009, 1907.

76. Heyman, A., J.B. Pfeiffer, R.W. Willett, H.M. Taylor. Peripheral Neuropathy Caused by Arsenic Intoxication. New Eng. J. of Med. 254:401-409, 1956.

77. Hideo, T., K. Kazuo, S. Tsutomu, S. Hideaki, S. Heiichiro, S. Chukichi, T. Yoshiro, H. Shigeru, W. Giigichi, H. Kazuo, O. Tatsuo, S. Chukichi. Mansei Hiso Chudokusho No Rinshoteki Kansatsu Dai-I-Po (Clinical Observations of Chronic Toxicosis by Arsenic). Nihon Rinsho Jap. J. of Clin. Med. 18:118-127, 1960. Translated for EPA for Leo Kanner Assoc. - TR106-74.

78. Hill, A.B., E.L. Faning. Studies in the Incidence of Cancer in a Factory Handling Compounds of Arsenic: Part I, Mortality Experience in the Factory. Brit J. Indust. Med. 5:1-6, 1948.

79. Hine, C.H., S.S. Pinto, K.W. Nelson. Medical Problems Associated With Arsenic Exposure. J. Occ. Med. 19:391-396, 1977.

80. Hodge, H.C., J.W. Embree. Estimation of the Mutagenicity of Arsenic Compounds Utilizing Dominant Lethal Mutations of Mice. San Fran. Toxicology Research Laboratory, University of California, 1977. Contract No. SERA-HI-2, 1977.

81. Holland, R.H., M.S. McCall, H.C. Lanz. A Study of Inhaled Arsenic74 in Man. Cancer Res. 19:1154-1156, 1959.

82. Holland, R.H., A.R. Acevedo. Carcinogenicity of Inhaled Arsine and Triphenylarsine in Rabbits, Abstract From Proc. Am. Assoc. Cancer Res. 4:28, 1964.

83. Hollaender, A. Chemical Mutagens, Vol. IV. Plenum Press 1976.

84. Holmovist, I. Investigations of the Absorption of Some Metals Among People in the Surrounding Area of a Smelting Plant. pp. 613-629. In International Symposium Proceedings: Recent Advances in the Assessment of the Health Effects of Environmental Pollution, Vol. 2. Paris: Comm. of the European Communities, WHO, EPA, 1974.

85. Hood, R.D., S.L. Bishop. Teratogenic Effects of Sodium Arsenate in Mice. Arch Environ. Health 24:62-65, 1972.

86. Hood, R.D., S.L. Bishop. Teratogenic Effects of Sodium Arsenate in Mice. Arch Environ. Health 6:235, 1972.

87. Hood, R.D., G.T. Thacker, B.L. Patterson. Effects in the Mouse and Rate of Prenatal Exposure to Arsenic. pp. 219-222. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

88. Hueper, W.C. Experimental Studies in Metal Carcinogenesis. V. Tissue Reactions in Rats and Rabbits After Parenteral Introduction of Arsenic, Beryllium, or Asbestos in Lanolin. J.N.C.I., 15: 113-124, 1954.

89. Hueper, W.C., W.W. Payne. Experimental Studies in Metal Carcinogenesis. Chromium, Nickel, Iron, Arsenic. Arch Environ. Health 5:455-564, 1962.

90. Hunter, F.T., A.F. Kip, J.W. Irvine, Jr. Radioactive Tracer Studies on Arsenic Injected as Potassium Arsenite. J. Pharmacol Exp Ther 76:207-220, 1942.

91. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Vol. 2. Some Inorganic and Organometallic Compounds. Lyon, France: WHC, IARC, 1973.

92. Ireland, F.A. Reactions Following the Administration of the Arsphenamines and Methods of Prevention. Am. J. Syphilis 16:22-35, 1932.

93. Irgolic, K.J. Speciation of Arsenic in Water Supplies. EPA report, 1978.

94. Irvine, H.G., D.C. Turnacliff. Study of a Group of Handlers of Arsenic Trioxide. Arch Derm. Syph. 33:306-315, 1936.

95. Ishinishi, N., Y. Kodama, K. Nobutomo, A. Hisanaga. Preliminary Experimental Study of Arsenic Poisoning in Rat Lung. pp. 191-196. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

96. Ishinishi, N., Y. Kodama, K. Nobutomo, T. Inamasu, E. Kunitake, Y. Suenage. Outbreak of Chronic Arsenic Poisoning Among Retired Workers From an Arsenic Mine in Japan. pp. 121-125. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

97. Japanese Pediatric Society. Nihon Shonika Gakkai Morinaga Hiso Miruku Chudoku Chosa Shoiinkai (Tokubetsu I Inkai) Katsudo Hokoku Yoshi. [Summary of Report of Activities of the Morinaga Arsenic-Tainted Powdered Milk of Poisoning Investigation Subcommittee (Special Committee) on the Japanese Pediatric Society.] May 26, 1973. Translated for EPA by SCITRAN - TR124-74).

98. Jelinek, C.F., P.E. Corneliussen. Levels of Arsenic in the United States Food Supply. pp. 83-87. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

99. Jung, E.G., B. Trachsel, H. Immich. Arsenic As An Inhibitor of The Enzymes Concerned in Cellular Recovery (Dark Repair). Germ. Med. Mon. 12:614-616, 1969.

100. Jung, E.G., B. Trachsel. Molckularbiologische Untersuchungen Zur Arsencarcinogeneses. Arch Klin Exp Derm 237:819-826, 1970.

101. Kanisawa, M., H.A. Schroeder. Life Term Studies on the Effect of Trace Elements on Spontaneous Tumors in Mice and Rats. Cancer Res. 29:892-895, 1969.

102. Kjeldsberg, C.R., H.P. Ward. Leukemia in Arsenic Poisoning. Ann. of Int. Med. 77:935-937, 1972.

103. Knoth, W. Arsenbehandlung. Arch. Klin. Exp. Dermatol. 227:228-238, 1966/1967.

104. Konetzke, G.W. Die kanzerogene Wirkung von Arsen und Nickel. Arch. Geschwulstforsch 44: 16-22, 1974.

105. Kroes, R., M.J. VanLogten, J.M. Berkvens, T. DeVries, G.J. VanEsch. Study on the Carcinogenicity of Lead Arsenate and Sodium Arsenate and on the Possible Synergistic Effect of Diethylnitrosamine. Food Cosmet Toxical 12:671-679, 1974.

106. Kuratsune, M., S. Tokudome, T. Sjoralisa., Toshida, U. Tokumitsu, T. Hayano, M. Seita. Occupational Lung Cancer Among Copper Smelters. Int. J. Cancer 13:552-558, 1974.

107. Kyle, R.A., G.L. Pease. Hematologic Aspects of Arsenic Intoxication. New Eng. J. Med. 273:1823, 1965.

108. Lakso, J.U., S.A. Peoples. Methylation of Inorganic Arsenic by Mammals. J. Agric. Food Chem. 23:674-676, 1975.

109. Lancet: 414, February 9, 1901.

110. Lancet. The Beer-Poisoning Epidemic. 801, March 16, 1901.

111. Lancet. Peripheral Neuritis of Arsenical and Alcoholic Origin. 340-341, February 2, 1901.

112. Lancet. Arsenical Poisoning by Beer in the County Borough of Salford. 954, March 30, 1901.

113. Lander, H., P.R. Hodge. Arsenic in the Hair and Nails: Its Significance in Acute Arsenical Poisoning. J. of Forensic Med. 12:52-67, 1965.

114. Lander, J.J., R.J. Stanley, H.W. Sumner, D.C. Boswell, and R.D. Aach. Angiosarcoma of the Liver Associated With Fowler's Solution (Potassium Arsenite). Gastroenterology 68:1582-1586, 1975.

115. Lanz, H., P.W. Wallace, J.G. Hamilton. The Metabolism of Arsenic in Laboratory Animals Using AS-74 As a Trace. Univ. Calif. Pub. Pharmacol 2:263-282, 1950.

116. Laskin, S., M. Kuschner, R.T. Drew. Studies in Pulmonary Carcinogenesis, pp. 321-350. In: Hanna, M.G., Jr., P. Nettlesheim, J.R. Gilbert. Eds. Inhalation Carcinogenesis. AEC Symposium Series, No. 18. Washington, D.C., U.S. Atomic Energy Commission, 1970.

117. Lao, R.C., R.S. Thomas, T. Teichman, L. Dubois. Efficiency of Collecting Arsenic Trioxide in High Volume Sampling. The Science of Total Environ. 2:373-379, 1974.

118. Lee, A.M., J.F. Fraumeni. Arsenic and Respiratory Cancer in Man: An Occupational Study. J. Natl. Cancer Inst. 42: 1045-1052, 1969.

119. Leitch, A., E.L. Kennaway. Experimental Production of Cancer by Arsenic. Br. Med. J. 2: 1107-1108, 1922.

120. Lowry, O.H., F.T. Hunter, A.F. Kip, J.W. Irvine, Jr. Radioactive Tracer Studies on Arsenic Injected as Potassium Arsenite. Vol. II. Chemical Distribution in Tissues. J. Pharmacol Exp. Ther. 76:221-225, 1942.

121. Lu, F.J., C.K. Yang, K.H. Lin. Physico-Chemical Characteristics of Drinking Water in Blackfoot Endemic Areas in Chia-I and Tainan Hsiens. J. Formosan Medical Assoc. 74: 596605, 1975.

122. Lu, F.J., M.H. Tsai, K.H. Ling. Studies on Fluorescent Compound in Drinking Water of Blackfoot Disease Endemic Areas: 1. The Toxic Effects of Fluorescent Compound on the Chick Embryos. J. Formosan Medical Assoc. 76: 58-63, 1977a.

123. Lu, F.J., M.H. Tsai, K.H. Ling. Studies on Fluorescent Compounds in Drinking Water of Blackfoot Endemic Areas: 2. Isolation and Identification of Fluorescent Compounds. J. Formosan Medical Assoc. 76: 209-217, 1977b.

124. Lugo, G., G. Cassady, P. Palmisano. Acute Maternal Arsenic Intoxication With Neonatal Death. Amer. J. Dis. Child 117, 1969.

125. Luh, M.D., R.A. Baker, D.E. Henley. Arsenic Analysis and Toxicity -- A Review. The Science of the Total Environ. 2:1-12, 1973.

126. Lyon, J.L., J.L. Fillmore, M.R. Kluber. Arsenic Air Pollution and Lung Cancer. Lancet, p. 869, October 22, 1977.

127. MacMahon, B., T.F. Puch. Epidemiology: Principles And Methods. Boston, Little, Brown & Co., 1970.

128. Mchaffey, K.R., B.A. Fowler. Effects of Concurrent Administration of Lead Cadmium, and Arsenic in The Rat. pp. 165-171. In: National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina, NC:U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

129. Mealey, J., Jr., G.L. Brownell, W.H. Sweet. Radioarsenic in Plasma, Urine, Normal Tissues, and Intracranial Neoplasms. Arch. Neurol Psychiatry 81:310-320, 1959.

130. Milby, T.H., C.H. Hine. A Survey of Mortality Due to Respiratory Diseases Among Employees of the Kennecott Corp. Unpublished Report Submitted to the Kennecott Corp., New York, New York, October 4, 1974. (Summarized in NIOSH, 1975.)

131. Milham, S., Jr., T. Strong. Human Arsenic Exposure in Relation to a Copper Smelter. Envir. Res. 7:176182, 1974.

132. Milham, J., Jr. Studies of Morbidity Near a Copper Smelter. pp. 131-132. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina, U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

133. Milham, S., Jr. Occupational Cancer Related to Nonferrous Metal Smelting. Presented at 1977 International Conference on Cancer and Environment, October 13, 1977.

134. Miller, R.W. Relationship Between Human Teratogens and Carcinogens. J. Natl. Cancer Inst. 58:471-474, 1977.

135. Milner, J.E. The Effect of Ingested Arsenic on Methylcholanthrene-Induced Skin Tumors in Mice. Arch. Environ. Health 18:7-11, 1969.

136. Mizuta, N., M. Mizuta, F. Ito, H. Uchida, Y. Watanabe, H. Akama, T. Murakami, F. Hayashi, K. Nakamura, T. Yamaguchi, W. Mizuta, S. Oishi, H. Matsumura. An Outbreak of Acute Arsenic Poisoning Caused by Arsenic Contaminated Soy Sauce (SHOYU): A Clinical Report of 220 Cases. Bull. Yamaguchi Med. Sch. 4:131150, 1956.

137. Musil, J., V. Dejmal. Experimental and Clinical Administration of Radioarsenic. Casopis lekaru ceskych 96:1543-1546, 1957.

138. National Academy of Sciences. Arsenic. Washington, D.C., 1977.

139. National Institute For Occupational Safety and Health. Criteria for a Recommended Standard: Occupational Exposure to Inorganic Arsenic. U.S. Department of Health, Education, and Welfare: HEW Pub. No. (NIOSH), pp. 75-149, 1975.

140. Natusch, D.F.S., J.R. Wallace, C.A. Evans, Jr. Toxic Trace Elements: Preferential Concentration in Respirable Particles. Science 183:202-204, 1974.

141. Nelson, K.W. Industrial Contributions of Arsenic to the Environment. pp. 31-34. National Institute of Environmental Health Sciences (ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

142. Nelson, W.C., M.H. Lykins, J. Mackey, V.A. Newill, J.F. Finklea, D.I. Hammer. Mortality Among Orchard Workers Exposed to Lead Arsenate Spray: A Cohort Study. J. Chron. Dis. 26:105-118, 1973.

143. Neubauer, O. Arsenical Cancer: A Review. Brit. J. Cancer 1:192-251, 1947.

144. Newman, J.A., V.A. Archer, G. Saccamanno, M. Kuschner, O. Auerbach, R.D. Grondauhl, J.C. Wilson. Histologic Types of Bronchogenic Carcinoma Among Members of Copper-Mining and Smelting Communities. pp. 260-268. In Saffiotti, U., J.K. Wagoner (ed.). Occupational Carcinogenesis. Annals of the N.Y. Academy of Sciences, Vol. 271.

145. Nieberle, K. Uber Endemischen Krebs Im Siebbein Von Schafen. Zeitschrift Fur Krebsforschung 49:137-141, 1939.

146. Nose, Y. Hiso Konnyu Shoyu Chuddku Jiken No Ekigakuteki Kansatsu. Tuku No Shoyu Chudoku To Hantei Suru Made No Keika Ni Oite (Epidemiological Observations of the Poisoning Incident Caused by Soy Sauce with Admixtures of Arsenic). Koshu Eisei (Public Health) 21:29-43, 1957. (Trans. for EPA by trans. consul., Arlington, Virginia. 1964.)

147. Occupational Safety and Health Administration. Proposed Regulation on Inorganic Arsenic. United States Department of Labor, Occupational Safety and Health Administration Office of Planning, Evaluation, and Research, Room 1162, 1826 M Street, N.W., Washington, D.C. 20210, 1975.

148. Oehme, F.W. Mechanisms of Heavy Metal Toxicities. Clin. Toxico 5:151-167, 1972.

149. Oppenheim, J.J., W.N. Fischbein. Induction of Chromosome Breaks In Cultured Normal Human Leukocytes by Potassium Arsenite, Hydroxyurea, and Related Compounds. Cancer Pres. 25:980, 1965.

150. Osburn, H.S. Cancer of the Lung in Gwanda. Central African J. Med. 3:215-223, 1957.

151. Osburn, H.S. Lung Cancer in a Mining District in Rhodesia. S. Afr. Med. Journal. 43:1304-1312, 1969.

152. Osswald, H., K. Boerittler. Leukosen Bei Der Maus Nach Diaplacentarer Und Postnataler Arsenik-Applikation. Dtsch. Gesamte. Path. 55:289-293, 1971.

153. Ott, M.G., B.B. Holder, H.L. Gordon. Respiratory Cancer and Occupational Exposure to Arsenicals. Arch. Environ. Health 29:250-255, 1974.

154. Overby, L.R., R.L. Frederickson. Metabolic Stability of Radioactive Arsenilic Acid in Chickens. J. Agric. Food Chem. 11:378-381, 1963.

155. Paton, G.R., A.C. Allison. Chromosome Damage in Human Cell Cultures Induced by Metal Salts. Mutation Res., 16:332-336, 1972.

156. Patty, F.A. (ed.). Industrial Hygiene and Toxicology. New York: Interscience Pub., 1963.

157. Pelfrene, A. Arsenic and Cancer: The Still Unanswered Question. J. Toxicol and Environ. Health, I: 1003-1016, 1976.

158. Peoples, S.A. Arsenic Toxicity in Cattle. Ann. N.Y. Acad. Sci. 111:644-649, 1964.

159. Perry, K., R.G. Bowler, H.M. Buckell, H.A. Druett, R.S.F. Schilling. Studies in the Incidence of Cancer in a Factory Handling Inorganic Compounds of Arsenic: Part II, Clinical and Environmental Investigations. Brit. J. of Ind. Med. 5:6-15, 1948.

160. Pershagen, J., C.G. Elinder, A.M. Bolander. Mortality in a Region Surrounding an Arsenic Emitting Plant. pp. 133-137. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina. U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH) 77-218, 1977.

161. Peterkova, R., L. Puzanova. An Effect of Tri- and Pentavalent Arsenic on the Early Development of Chicken Embryos. Folia Morphol 24:5, 1976.

162. Peters, J., K. Schmidt-Ulrich, U. Wolf. Chromosomen Aberrationen An Menchlichen Lymphocyten Bei Chronischen Arzenschaden. Deut Med. Wochenschr. 95:79, 1970.

163. Peters, R.A., H.M. Sinclair, R.H.S. Thompson. An Analysis of the Inhibition of Pyruvate Oxidation by Arsenicals In Relation to the Enzyme Theory of Vesication. Biochem. 40:516-524, 1948.

164. Peters, R.A., R.W. Wakelin. Observations Upon the Relation Between Sulfhydryl Groups and Pyruvate Oxidation in Brain Tissues. Biochem. 40:513-516, 1946.

165. Petres, J., A. Berger. Zum Eingluss Anorganischem Arzens Auf Die DNA-Symthese Menschlicher Lymphocyten In Vitro. Arch. Dermat. Forsche 242:343, 1972.

166. Petres, J., D. Baron, M. Hagedorn. Effects of Arsenic Cell Metabolism and Cell Proliferation: Cytogenetic and Biochemical Studies. pp. 223-227. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: U.S. Department of HEW, Public Health Service, Nat. Inst. of Health, Pub. No. (NIH), 77-218, 1977.

167. Pinto, S., P.E. Enterline, V. Henderson, M.O. Varner. Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure. pp. 127-130. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina, U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH), 77-218, 1977.

168. Pinto, S.S., C.M. McGill. Arsenic Trioxide Exposure in Industry. Ind. Med. and Surg. 22:281-287, 1953.

169. Pinto, S.S., B.M. Bennett. Effect of Arsenic Trioxide Exposure on Mortality. Arch. of Envir. Health 7:583-591, 1963.

170. Pinto, S.S., K.W. Nelson. Arsenic Toxicology and Industrial Exposure.

171. Pinto, S.S., M.O. Varner, K.W. Nelson, A.L. Labbe, L.D. White. Arsenic Trioxide Absorption and Excretion in Industry. J. Occ. Med. 18:677-680, 1976.

172. Pinto, S.S. Arsine Poisoning: Evaluation of the Acute Phase. J. Occ Med., 18: 633-635, 1976.

173. Pinto, S.S., V. Henderson, P.E. Enterline. Mortality Experience of Arsenic Exposed Workers. (Unpublished)

174. Pinto, S.S., K.W. Nelson. Arsenic Toxicology and Industrial Exposure. Annal. Rev. Pharm. and Toxico 15, 6:95-100, 1976.

175. Regelson, W., U. Kim, J. Ospina, J.F. Holland. Hemangiendothelial Sarcoma of Liver From Chronic Arsenic Intoxication by Fowler's Solution. Cancer 21:514-522, 1968.

176. Rencher, A.C., M.W. Carter, D.W. McKee. A Retrospective Epidemiological Study of Mortality at a Large Western Copper Smelter. J. Occp. Med. 19:754-758, 1977.

177. Reynolds, E.S. An Account of the Epidemic Outbreak of Arsenical Poisoning Occuring in Beer-Drinkers in the North of England and the Midland Counties in 1900. Lancet 1:166-170, 1901.

178. Ridgway, L.P., D.A. Karnofsky. The Effects of Metals on the Chick Embryos: Toxicity and Production of Abnormalities in Development. Ann. N.Y. Acad. Sci. 55:203, 1952.

179. Robson, A.O., A.M. Jelliffe. Medicinal Arsenic Poisoning and Lung Cancer. Brit. Med. J. 2:207-209, 1963.

180. Rosen, P. Theoretical Significance of Arsenic as a Carcinogen. J. Theor. Biol. 32:425-426, 1971.

181. Rossman, T.G., M.A. Meyn, W. Troll. Effects of Arsenite on DNA Repair in Escherichia Coli. pp. 229-233. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina, U.S. Dept. of HEW, Public Health Service, Nat. Inst. of Health. Pub. No. (NIH), 77-218, 1977.

182. Roth, F. The Sequelae of Chronic Arsenic Poisoning in Moselle Vintners. Germ. Med. Monthly 2:172-175, 1957.

183. Roth, F. Uber Den Bronchialkrebs Arsengeschadigter Winzer. Virchows Archiv 331:119-137, 1958.

184. Roy, G.L., A.L. Laferriere, J.O. Edwards. A Comparative Study of Polyol Complexes of Arsenite, Borate, and Tellurate Ions. J. Inorg. Nucl. Chem. 4:106-114, 1957.

185. Royal Commission on Arsenical Poisoning. Wednesday, March 6, 1901. Lancet: 828-829, March 16, 1901.

186. Royal Commission on Arsenical Poisoning. Lancet: 672-673, March 2, 1901.

187. Royal Commission on Arsenical Poisoning. Lancet: 980-981, March 30, 1901.

188. Royal Medical and Chirurgical Society. Epidemic of Arsenical Poisoning in Beer Drinkers in the North of England During the year 1900. Lancet: 98-100, January 12, 1901.

189. Rozenshtein, I.S. Sanitarno-Toksikologicheskaya Otsenka Nizkikh Kontsentratsii Myshyakovistogo Angigrida U Atmosfernom Vozkukhe (Sanitary Toxicological Assessment of Low Concentrations of Arsenic Trioxide in the Atmosphere.) Hyg Sanit 35: 1621, 1970.

190. Salaman, M.H., F.J.C. Roe. Further Tests for Tumor-Initiating Activity: N,Ndi-(2-chloroethyl)-p-aminophenyl butyric acid (CB 1348) as an Initiator of Skin Tumor Formation on Mouse Skin. Brit. J. Cancer, 10: 363378, 1956.

191. Schiller, C.M., B.A. Fowler, J.S. Woods. Effects of Arsenic on Pyruvate Dehydrogenase Activation. pp. 205-207. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: U.S. Dept. of Health, Education, and Welfare, Public Health Service National Institute of Health Pub. No. (NIH) 77-218, 1977.

192. Schrenk, H.H., L. Schreibeis, Jr. Urinary Arsenic Levels as an Index of Industrial Exposure. Ind. Hyg. J. :225-228, 1958.

193. Schroeder, H.A., M. Mitchener. Toxic Effects of Trace Elements on the Reproduction of Mice and Rats. Arch. Environ. Health 23:102-106, 1971.

194. Schroeder, H.A., J.J. Balassa. Abnormal Trace Metals in Man: Arsenic. J. Chron. Dis. 19:85-106, 1966.

195. Schroeder, H.A., M. Kanisawa, D.V. Frost, M. Mitchener. Germanium, Tin, and Arsenic in Rats: Effects on Growth, Survival, Pathological Lesions and Life Span. J. Nutrition 96:37-45, 1968.

196. Shapiro, H.A. Arsenic Content of Human Hair and Nails, Its Interpretation. J. of Forensic Med. 14:65-71, 1967.

197. Shearer, S.D. Personal communication to the Environmental Protection Agency.

198. Smith, T.J., E.A. Crecelius, J.D. Reading. Airborne Arsenic Exposure and Excretion of Methylated Arsenic Compounds. pp. 89-93. In National Institute of Environmental Health Sciences (ed.). Environmental Health Perspectives. Vol. 19. Research Triangle Park, North Carolina: U.S. Dept. of Health, Education and Welfare, Public Health Service, National Institute of Health. Pub. No. (NIH) 77-218, 1977.

199. Snegireff, L.S., O.M. Lombard. Arsenic and Cancer. AMA Arch. Ind. Hyg. 4:199-205, 1951.

200. Sollmann, T. A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. Phil: W.B. Saunders Co., 1964.

201. Sommers, S.C., R.G. McManus. Multiple Arsenical Cancers of Skin and Internal Organs. Can 6:347-359, 1953.

202. Sram, R.J., V. Bencko. A Contribution to the Evaluation of the Genetic Risk of Exposure to Arsenic. CS Hyg. 19:308, 1974.

203. Stevens, J.T., L.L. Hall, J.D. Farmer, L.C. Dipasquale, N. Chernoff, W.F. Durham. Disposition of C-14 and/or As-74-Cacodylic Acid in Rats After Intravenous, Intratracheal, or Peroral Administration. pp. 151-157. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, NC: U.S. Dept. of Health, Education and Welfare, Public Health Service, National Institute of Health, Pub. No. (NIH) 77-218, 1977.

204. Stocken, L.A., R.H.S. Thompson. British Anti-Lewisite: 1. Arsenic Derivatives of Thiol Proteins. Biochem 40: 529-535, 1946.

205. Strategies and Air Standards Division, Office of Air Quality Planning and Standards. Air Pollutant Assessment Report on Arsenic. Office of Air and Waste Management, EPA. Research Triangle Park, North Carolina 27711; 1976.

206. Sullivan, R.J. Air Pollution Aspects of Arsenic and Its Compounds. Bethesda, Maryland: Litton Systems, Inc., Environmental Systems Division, 7300 Pearl Street, Bethesda, Maryland 20014, September 1969.

207. Sunderman, F.W., Jr. A Review of the Carcinogenicities of Nickel, Chromium, and Arsenic Compounds in Man and Animals. Prev. Med. 5:279-294, 1976.

208. Sunderman, F.W. Jr. Metal Carcinogenesis. In: Advances in Modern Toxicology, R.A. Gover and M.A. Mehlman, Eds., 1977.

209. Suta, B.E., R. McGaughy, A. Pines. Population Exposures to Arsenic. Stanford Research Institute, Menlo Park, California 94025. Environmental Protection Agency Contract No. 68-OL-2940, Task 30.

210. Swain, R.E., W.D. Harkins. Papers on Smelter Smoke (Second Paper). J. Amer. Chem. Soc. 30:915-928, 1908.

211. Tarrant, R.F., J. Allard. Arsenic Levels in Urine of Forest Workers Applying Silvicides. Arch. Environ. Health 24:277-280, 1972.

212. Thiers, H., D. Colomb, G. Moulin, L. Colin. Arsenical Cutaneous Cancer of the Vinegrowers of Beaujolais. Ann. Dermatol. Syphilol. 94: 133-158, 1967.

213. Thompson, R.H.S. The Effect of Arsenical Vesicants on the Respiration of Skin. Biochem. 40:525-529, 1946.

214. Tokudome, S., M. Kuratsune. A Cohort Study of Mortality from Cancer and Other Causes Among Workers at a Metal Refinery. Int. J. Cancer 17:310-317, 1976.

215. University of California, Toxicology Research Laboratory. Estimation of the Mutagenicity of Arsenic Compounds Utilizing Dominant Lethal Mutations of Mice. Contract No. SERA-HI-2, 1977.

216. Tseng, W. Effects and Dose-Response Relationship of Skin Cancer and Blackfoot Disease with Arsenic. pp. 109119. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: US Dept. of Health, Education and Welfare, Public Health Service, National Institute of Health. Pub. No. (NIH) 77-218, 1977.

217. Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin, S. Yeh. Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenicism in Taiwan. J. National Cancer Institute 40:453-463, 1968.

218. Tsuchiya, K. Various Effects of Arsenic in Japan Depending on Type of Exposure. pp. 3542. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Nat. Institute of Health. Pub. No. (NIH) 77-218, 1977.

219. Tunnicliffe, F.W., O. Rosenheim. Selenium Compounds as Factors in the Recent Beer Poisoning Epidemic. Lancet: 318, February 2, 1901.

220. Vallee, B.L., D.D. Ulmer, W.E.C. Wacker. Arsenic Toxicology and Biochemistry. AMA Arch. Ind. Health 21:132-151, 1960.

221. Von Pein, H. Carcinogenesis in Chronic Arsenic Poisoning. Archie f. Klinische Medizin, 190: 429443, 1943.

222. Wadkins, C.L. Stimulation of Adenosine Triphosphatase Activity of Mitochondria and Submitochondrial Particles by Arsenate. J. of Bio. Chem. 235: 3300-3303, 1960.

223. Wagner, S.L., P. Weswig. Arsenic in Blood and Urine of Forest Workers. Arch. Environ. Health 28: 77-79, 1974.

224. Wagner, W.L. Environmental Conditions in U.S. Copper Smelters. U.S. Dept. of Health, Education and Welfare; Public Health Service, Center for Disease Control; National Institute for Occupational Safety and Health; Division of Technical Services, Salt Lake City, Utah, 1975.

225. Watrous, R.M., M.B. McCaughey. Occupational Exposure to Arsenic. Indust Med. 14: 639-645, 1945.

226. Webb, J.L. Enzyme and Metabolic Inhibitors, Vol. 2. Malonate, Analogs, Dehydroacetate, Sulfhydryl Reagent, O-Iodosobenzoate, Mercurials. New York: Academic Press, 1966.

227. Weissburger, J.H., G. Williams. Metabolism of Chemical Carcinogens. In Becker, F.F. (Ed.). Cancer. Plenum Press, 1975.

228. Whanger, P.D., P.H. Weswig, J.C. Stoner. Arsenic Levels in Oregon Waters. pp. 139-143. In National Institute of Environmental Health Sciences (Ed.). Environmental Health Perspectives, Vol. 19. Research Triangle Park, North Carolina: U.S. Dept. of Health, Education and Welfare, Public Health Service, National Institute of Health. Pub. No. (NIH) 77-218, 1977.

229. Willcox, W.H. Toxicological Detection of Arsenic and the Influence of Selenium on its Tests. Lancet: 778, March 16, 1901.

230. Winkler, W.O. Identification and Estimation of the Arsenic Residue in Livers of Rats Ingesting Arsenicals. J. Assoc. of Anal Chem. 45: 80-91, 1962.

231. Yeh, S. Relative Incidence of Skin Cancer in Chinese in Taiwan: With Special Reference to Arsenical Cancer. Natl. Cancer Inst. Monogr. 10: 81-107, 1963.

232. Yeh, S. Skin Cancer in Chronic Arsenicism. Human Path. 4: 469-485, 1973.

233. Yeh, S., S.W. How, C.S. Lin. Arsenical Cancer of Skin: Histologic Study With Special Reference to Bowen's Disease. Cancer 21: 312-339, 1968.

234. Yoshikawa, T., J. Utsumi, T. Okada, M. Moriuchi, K. Ozawa, T. Kaneko. Concerning the Mass Outbreak of Chronic Arsenic Toxicosis in Niigata Prefecture. Chiryo 43: 1739-1749, 1960. Translated from the Japanese by Leo Kanner Associates, October 1973 for the Environmental Protection Agency.

235. Zachariae, H. Arsenik og cancerrisiko. Ugeskr. Laeg. 134: 27202721, 1972.

236. Zettel, H. Der Einfluss Chronischer Arsenschadigung Auf Herz and Gefasse. Z.F. Klin Medizin 142: 687-703, 1943.