III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Arsenic is between germanium and selenium in the Periodic Table and as a member of Group V its physicochemical properties resemble those of phosphorus. [1,2] Its principal valences are 3 and 5, and it is ubiquitous, [1,3] being found in small amounts in soils and waters throughout the world, as well as in foods, particularly seafood. [1,4] Arsenic is a constituent of a number of minerals. For industrial and commercial uses, it is obtained primarily from the ores of metals in which it is present as an impurity, [5] removed as arsenic trioxide (arsenic (III) oxide, As203) during the smelting operation. This oxide is used in the manufacture of most other arsenic compounds, and is produced in the US as a byproduct in the smelting of copper ores. [6] Physical and chemical properties of arsenic and some of its more important inorganic compounds are given in Table X-1. [5,7]

Consumption of arsenic trioxide in the United States is estimated to range between 25,000 and 35,000 tons annually. Of this amount, 6,000-14,000 tons are produced in the United States. [8] Various arsenic compounds are used as pesticides. [1,3,5] Arsenic compounds are also used in pigment production, the manufacture of glass, textile printing, tanning, taxidermy, in antifouling paints, and to control sludge formation in lubricating oils. Metallic arsenic is used as an alloying agent to harden lead shot, and in lead-based materials. It is also alloyed with copper to improve its toughness and corrosion resistance. [3,6,9]

Some occupations which have or in the past have had potential

exposures to arsenic are listed in Table X-2. [9] NIOSH estimates that 1,500,000 workers are potentially exposed to inorganic arsenic, including arsine and lead arsenate.

Historical Reports

According to Vallee et al, [6] Paris reported in 1820 that exposure to the arsenical fumes from the copper smelters of Cornwall and Wales occasionally resulted in cancer of the scrotum. Neubauer [10] reviewed the history of the high mortality due to "mountain disease" among cobalt miners in Schneeberg and Joachimstal in Saxony, and credited Harting and Hesse [11] with first identifying the condition as lung cancer. According to Neubauer, [10] arsenic was first believed to be the carcinogen. He concluded that was not the case since Harting and Hesse did not report typical signs of arsenicalism (hyperpigmentation, keratoses, etc). In his opinion, the etiologic factor was ionizing radiation in the mines.

The significantly increased risk [12] of cancer both of the ethmoidal sinuses and of the lung experienced by workers refining nickel by the nickel carbonyl process in Swansea, South Wales, was attributed to arsenic present as an impurity in the sulfuric acid used prior to 1924. [13,14] Goldblatt [15] has suggested that finely divided nickel formed by decomposition of the gaseous carbonyl and deposited in the lung or on the mucosa of the sinuses was responsible. Hueper [16] has demonstrated the carcinogenicity of powdered metallic nickel when inhaled for prolonged periods by guinea pigs and rats.

Kelynack et al [17] in 1900 reported an outbreak in Manchester and the adjoining areas of Lancashire and Staffordshire, England, of arsenic

15

poisoning traced to arsenic-contaminated beer. Peripheral neuritis, initially thought to be "alcoholic peripheral neuritis," was the salient clinical manifestation. Ataxia, weakness, and sensations of "pins and needles" in the limbs were commonly observed. Patients generally had watery eyes, sometimes with distinct puffiness about the eyelids. In almost all cases a dusky, irregular pigmentation of the skin developed. Pigmentation was reportedly most marked on exposed parts, over pressure areas, and in the normally pigmented areas. Frost [2] reviewed the incident, including reports that selenium was also found in the beer. Tabulating symptoms described in a number of original reports and review articles between 1901 and 1943, he concluded that the incident was not likely due to arsenic alone, since not all symptoms reported in the papers he reviewed could be explained solely by arsenic toxicity, but were consistent with selenium poisoning.

Transverse white striae in the nails (Mees' lines) were first described in 1919 [18] as resulting from the ingestion of a large quantity of arsenic, and were reported to appear approximately 2 months after ingestion. Dinman [19] considered Mees' lines to be suggestive but not pathognomonic of chronic arsenic poisoning.

According to Buchanan, [20] 18 cases of poisoning due to arsenic trichloride were reported in Britain from 1915 to 1918. In the 1939 case reported by Buchanan, a quantity of liquid arsenic trichloride was spilled over the legs of a processman who was wearing a canister-type respirator. The splashed region of the skin was drenched thoroughly with water and all the clothing removed very soon after the accident. The man was transferred to a hospital within 15 minutes, where he was found to be suffering from

16

burns on both legs, conjunctivitis, and throat irritation. Despite the fact that he had been wearing a respirator, the man stated he had inhaled an irritating gas (a companion, also wearing a respirator, was unaffected). The throat irritation became worse and laryngitis developed, followed by bronchopneumonia resulting in death 5 days after the accident. Autopsy revealed redness and congestion of the larynx, trachea, and bronchial mucosae, red hepatization of the lower lobes of both lungs, and marked fatty degeneration of the liver. The liver was found to contain 3.0 ppm of arsenic trioxide, the hair 3.0 ppm, and the urine present in the bladder 3.5 ppm. Buchanan [20] reported that, in the opinion of the analyst making these estimations, the higher liver content 5 days after the accident indicated absorption over a period of time, probably through the skin, while the presence of arsenic in the hair suggested previous absorption.

Another fatality was reported by Delepine [21] after arsenic trichloride was spilled on 1 leg of a worker. After death, arsenic was found in high concentrations in all tissues examined (lung, liver, kidney, pancreas, stomach, heart, and blood), and it appeared that the trichloride had been inhaled as well as absorbed through the skin. The heart, liver, kidneys, pancreas, and stomach were in a state of acute granulo-fatty degeneration. The direct cause of death was kidney failure, but the damage to the lungs, liver, pancreas, and heart also would have been fatal.

In 1945, Watrous and McCaughey [22] reported on conditions in a pharmaceutical plant manufacturing arsphenamine and related compounds from the basic intermediate arsanilic acid, so that exposures in this plant were to organic arsenicals. In the manufacturing department, exposures varied from 0.02 to 0.60 mg As2O3/cu m (approximately 0.015-0.456 mg As/cu m) with

17

an overall average of 0.17 mg As2O3/cu m (0.129 mg As/cu m). In the packaging division, air concentrations ranged from 0.007 to 0.28 mg As2O3/cu m (0.005-0.213 mg As/cu m) with a mean of 0.065 mg As2O3/cu m (0.049 mg As/cu m).

Medical records dating from 1939 were available and were reviewed [22] for 35 workers in the manufacturing department, 31 workers in the packaging department, and a control group of 30 in a packaging department with no arsenic exposure. Records were examined and the number of visits to the medical department were tabulated for 5 types of complaints considered to be possible indicators of subclinical or borderline arsenicalism. These symptoms were: hyperkeratosis, including warts and cracking, chapped, dry, or thickened skin; gastrointestinal, including upset stomach, nausea, vomiting, abdominal pain, loss of appetite, etc; central nervous system, such as headache, dizziness, fainting, etc; optic nerve, such as blurring or diminution of vision, spots before the eyes, etc (there were no complaints of this type in any of the 3 groups); and peripheral neuropathy, including shooting pains in the extremities, numbness, tingling, or sudden loss of muscular power.

The overall total number of visits per person per year was markedly higher in the packaging group (21.2) than in the manufacturing (9.6) or control group (10.0). [22] The packaging department employees also had a significantly higher number of visits per person per year for peripheral neuritis complaints (0.13 compared to 0.05 and 0.02). The authors concluded that these differences were probably due to an unusual number of neurotic individuals in the packaging division since some records contained "page after page of vague and bizarre complaints unexplained by any

18

physical finding." Both the manufacturing and packaging groups had a lower number of visits per person per year for gastrointestinal (0.32 and 0.69) and central nervous system (0.22 and 0.19) complaints than did the control group (0.83 for GI and 0.76 for CNS complaints). However, both exposed groups also had significantly more complaints of hyperkeratosis (0.23 and 0.20 compared to 0.09).

In the manufacturing department, complete blood counts were made at 3-month intervals throughout an individual's employment. [22] For the 35 employees exposed to arsenic, 323 counts were available. From those workers in the manufacturing department who performed similar tasks but with no arsenic exposure, a control group was randomly selected, providing a total of 221 complete blood counts. There was no significant difference in white, red, neutrophil, or eosinophil counts or in hemoglobin values.

Effects on Humans

According to Frost [2] in his review of arsenic in biology, inorganic arsenicals are more toxic than the organic, and trivalent is more toxic than pentavalent arsenic, but he also pointed out that for any such generalization exceptions can be found. Arsenic is widely distributed throughout body tissues, but can be found in the hair and nails months after it has disappeared from the urine and feces. [3] Pentavalent arsenic is excreted faster than trivalent arsenic, [1,20] and some authorities [1,3] state that trivalent arsenic accumulates in the mammalian body, but Frost [2] reported rapid excretion of all arsenicals. Schroeder and Balassa [1] and Frost [2] stated that arsenicals are oxidized in vivo from trivalent to pentavalent, and not reduced from pentavalent to trivalent.

19

On the other hand, as an explanation for the toxicity of some pentavalent arsenicals, Buchanan [20] suggested that pentavalent arsenic is slowly reduced to trivalent.

The presence of arsenic was illustrated by Schroeder and Balassa [1] in a variety of foods purchased in food stores. Mean arsenic values, in μg As/g wet weight were: fish and seafood, 4.64; meats, 0.49; vegetables and grains, 0.41. The highest arsenic levels found were 15.3 μg As/g in shrimp shells and 8.86 μg As/g in kingfish. Other high levels were 2.71 in table salt, 1.6 in puffed rice, 1.4 and 1.07 in 2 samples of pork liver, and 1.3 in stewing beef. No arsenic was detected in pork kidney, chicken breast, egg lecithin, corn oil, and other items. No arsenic was found in the kidneys of 8 wild mice, but the livers and hearts contained 0.74 and 1.10 μg As/g wet weight. Arsenic was found in the urine of 2 humans in concentrations of 0.14 and 0.10 μg As/g of urine (approximately 0.143 and 0.102 mg As/liter, using a specific gravity of 1.024 for conversion). In the hair of 7 humans, the arsenic level ranged from 0.12 in a 3-year-old to 1.1 μg As/g of hair in an 80-year-old, with a mean of 0.536 μg As/g. Webster [23] also reported the urinary arsenic level of persons with no known exposure to arsenic. First morning specimens from 26 adults and 17 children contained 0.015 and 0.014 mg As/liter of urine, respectively. The overall average was 0.014 mg As/liter.

Schrenk and Schreibeis [4] collected 756 urine specimens from 29 persons with no known arsenic exposure. The average urinary excretion was 0.08 mg As/liter, with 79% of the samples below 0.1 mg As/liter. The 3 highest levels reported were 2.0, 1.1, and 0.42 mg As/liter, and were attributed to probable consumption of seafood. The 2 highest average

urinary excretions by individuals were 0.22 and 0.12 mg As/liter.

These authors [4] considered seafood to be the main source of dietary arsenic. Shellfish in particular elevated the arsenic of test subjects. In one test, 3 subjects with pretest levels of 0.01, 0.05, and 0.03 mg As/liter were given lobster tail for lunch. Four hours after eating, urinary levels were 1.68, 1.40, and 0.78 mg As/liter, respectively, but after 48 hours, values were approaching the pretest levels.

The excretion by humans of inhaled arsenic was studied experimentally by Holland et al. [24] Eight terminal lung cancer patients inhaled smoke from a cigarette contaminated with As-74, and 3 others inhaled an As-74 aerosol from an intermittent positive pressure machine. Uptake and distribution was determined by examining the chest with a radiation counter. The radioactive arsenic disappeared from the respiratory tract very rapidly during the first few days, falling by the 4th day to 20-30% of the original uptake. Thereafter, the rate of disappearance tapered off slowly. Approximately 28% of the absorbed As-74 was excreted in the urine the first day. By the end of 10 days, urinary and fecal excretion of the absorbed As-74 was approaching zero, with 45% having been excreted in the urine and 2.5% in the feces. The remainder was assumed to have been deposited in the body, exhaled, or eliminated over a long time period. Deposition in hair, skin, and nails or in organs such as the liver was not reported.

The typical symptoms of severe chronic arsenicalism were illustrated in a case history reported by McCutchen and Utterback. [25] The first symptoms were attacks of nausea, vomiting, diarrhea, hot flashes, and progressive anxiety. These symptoms gradually cleared over a period of 10 days. Similar episodes continued intermittently. Within the next 2 years

21

there was a gradual darkening of the skin, and a thickening and scaling of the skin on the soles of the feet. An almost constant pain and feeling of "pins and needles" appeared first in the feet and later in the hands. Muscular weakness became more apparent and the extremities became numb in a glove and stocking distribution. Three years after the first symptoms, the skin of the trunk had darkened markedly, there had been a gradual loss of vision, and increased pain. Attacks of the initial symptoms continued to occur 3-4 times annually for 10 years, until the patient was referred to specialists for management of severe heart failure and muscular dystrophy. At that time, ascites was evident and severe ankle edema had developed. The patient was constipated except during the episodes of nausea and vomiting, when he had diarrhea. He was emaciated and had a diffuse tan pigmentation over the trunk. The palmar and plantar surfaces were hyperkeratotic and Mees' lines were present on the nails. There was an erythematous maculopapular rash below the knees, with indolent, shallow ulcers up to 1 cm in diameter. All sensory functions were diminished in a diffuse peripheral nerve distribution with a definite increase in perception from distal to proximal. The patient could not walk.

Laboratory tests revealed [25] that urinary excretion was 0.140 mg/24 hours and that the hair contained 20.7 mg As/100 g of hair. The white count was low (2,174) with a slight increase in monocytes. Both the EEG and ECG were normal. In an effort to increase urinary excretion of arsenic, 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) was administered but failed to increase arsenic excretion. After 3 months of hospitalization, functional use of the hands returned and the patient could walk with the aid of leg braces and crutches. Urinary arsenic excretion

was approximately 0.040 mg/24 hours. A follow-up at 1 year revealed little, if any, improvement in the neuropathy. Deep tendon reflexes were still absent and there was no proprioception distal to the knees or elbows. Pigmentation was marked but the dermatitis had cleared completely.

At one time, arsenic was considered a beneficial stimulant to the erythropoietic system and was popular as a tonic. [1,26] More recently, Kyle and Pease [27] have shown hematologic abnormalities in association with chronic arsenic intoxication of 6 patients. Nausea, vomiting, diarrhea, and peripheral neuropathy were present in all cases. In 3 cases there was hyperpigmentation, and in 3 cases there was hyperkeratosis of the palms and soles. However, in 2 cases neither hyperpigmentation nor hyper-keratoses were observed. Average urinary arsenic excretion was 1.87 mg As/liter, with a range of 0.348-3.46 mg As/liter of urine. Arsenic in the hair averaged 4.88 mg As/100 g of hair, ranging from 1.76 to 8.5 mg As/100 g of hair. The nails contained an average of 9.12 mg As/100 g of nails, with a range of 0.0-42.0 mg As/100 g of nails.

In all 6 cases anemia and leukopenia were present, with thrombo-cytopenia in 3 cases. [27] White counts of less than 1000 were seen in 3 cases, with the major change an absolute neutropenia. All patients had relative eosinophilia, but the absolute eosinophil count was elevated in only 1 case. Basophilic stippling was a prominent finding. The bone marrow of 4 patients was examined, and in 3 of these increased, disturbed erythropoiesis was observed. Depressed or disturbed myelopoiesis was seen in all 4. Hematologic abnormalities disappeared within 2-3 weeks after cessation of arsenic ingestion.

Butzengeiger [28] examined 180 vinedressers and cellarmen with symptoms of chronic arsenic intoxication and reported that in 41 (22.8%) there was evidence of vascular disorders in the extremities. Arsenical insecticides were used in the vineyards and workers reportedly were exposed not only when spraying but also by inhaling arsenic-contaminated dusts and plant debris when working in the vineyards. The homemade wine consumed by most of the workers was believed to be contaminated with arsenic.

Fifteen cases were described in detail. [28] All had varying degrees of hyperpigmentation and all but 2 had palmar and plantar keratoses. Cold hands or feet or both were common to all and apparently preceded the development of gangrene on the toes or fingers in 6 of the 15 cases. Liver damage was reported in 9 of the 15 cases, but most of the workers consumed up to 2 liters of wine daily. Urinary arsenic levels were given in terms of arsenic trioxide either per liter or per 100 grams of urine. Converting all to milligrams of arsenic per liter of urine (assuming a specific gravity of 1.024), values ranged from 0.076 to 0.934 mg As/liter, with an average of 0.324 mg As/liter. Arsenic in hair ranged from 0.012 to 0.1 mg As2O3/100 g of hair (0.009-0.076 mg As/100 g) with an average of 0.051 mg As2O3/100 g (0.039 mg As/100 g).

In 1943 Zettel [29] observed 170 soldiers who had been chronically exposed to arsenic in their drinking water. Arsenic was demonstrated in the hair and nails, but the levels were not reported. Most patients had a feeling of weakness, lassitude, dizzy spells, and were easily fatigued. In many cases complaints developed of numbness and "pins and needles" in the limbs, and of cold hands and feet. In about 120 cases the systolic blood pressure at rest was less than 110 mmHg. Electrocardiograms were prepared

for 80 patients, 45 of whom displayed a broadened Q-R-S interval. The Q-T was almost always prolonged and, frequently, there was an S-T depression and flattening of the T-wave. Six to eight weeks after the first examination, repeat ECGs were obtained in 47 cases. The Q-R-S broadening initially observed was absent or reduced, and the S-T depression and flattened T-wave were observed less frequently.

Butzengeiger [30] reported that, of 192 ECGs from vinegrowers suffering chronic arsenic intoxication, 107 (55.7%) were normal, 30 (15.6%) showed slight changes which alone were insufficient for a definite diagnosis of cardiac damage, and that 55 (28.7%) revealed definite changes. Of the 55 with definite changes, in 19 cases the possibility existed that the changes were caused by age, arteriosclerosis, or intercurrent disease. In the remaining 36 cases, no possible causes other than arsenic poisoning were detected. ECG abnormalities included Q-T prolongation and flattened T-wave. Follow-up studies revealed a decline in ECG abnormalities along with the attenuation of other symptoms of arsenic intoxication.

More recently, Barry and Herndon [31] described characteristic electrocardiographic changes of nonspecific T-wave inversion and pro-longation of the Q-Tc interval. In the 3 cases reported, the changes were present on initial ECG's taken shortly after arsenic ingestion at a time when no significant alterations in blood serum electrolytes, serum chemistries, neurologic or respiratory systems were present. In 1 case, an ECG had been performed 3 months before arsenic was ingested and was normal. This patient, a 21-year-old male, died and post-mortem examination showed "subendocardial hemorrhage and fibrosis with subepicardial petechiae and myocardial perivascular mononuclear infiltration." The ECG changes in the

25

remaining 2 patients regressed coincidentally with clinical recovery, suggesting to the authors an "acute pharmacologic cardiac insult."

Prolongation of the Q-T interval and an abnormal T-wave was reported in 2 cases of chronic and 1 case of acute arsenic intoxication by Glazener et al. [32] The ECG changes could not be related to disturbances in blood serum electrolytes and were considered due to a toxic effect on the myocardium. In the acute case, approximately 24 hours after arsenic was ingested, the serum arsenic level was 0.0173 mg As/100 ml and the urinary level was 1.40 mg As/liter. Seventeen days after the arsenic was ingested, none could be detected in the serum but the urinary level was 0.5 mg As/liter. In the chronic cases, arsenic levels were: 0.060 and 0.059 mg As/100 g of hair; 1.92 and 2.61 mg As/100 g of nails; and, in the urine, 0.30 and 0.124 mg As/24 hours, respectively.

Franklin et al [33] observed 3 cases of portal cirrhosis which they attributed to prolonged use of Fowler's solution (potassium arsenite). One patient had taken Fowler's solution for 2 years for leukemia. The other patients had taken the medication for 2 and 6 years, respectively, for dermatologic conditions. All had generalized mottling and bronzing of the skin, palmar and plantar hyperkeratoses, ascites, and marked ankle edema. Portal cirrhosis was diagnosed in all 3 cases and confirmed in 1 case by biopsy. There was no history of alcoholism in these cases. Urinary arsenic was elevated in only 1 case at 1.68 mg As/liter. The urinary levels in the remaining 2 cases were said to be normal, these investigators considering 0.0-0.06 mg As/liter as normal.

Graham et al [34] determined the arsenic contained in lesions of Bowen's disease (an intra-epidermal carcinoma [35]) in 50 patients and in

the adjacent skin of 30 of these. For comparison, material was examined from 119 patients with skin lesions which included basal-cell carcinoma, senile keratosis, intra-epidermal epithelioma of Jadassohn, extramammary Paget's disease, seborrheic keratosis, and others. There was no known history of arsenic intake in 95% of the Bowen's disease and control patients. The normal level of arsenic was considered to be 1.0 μg As/g wet tissue or less. In the control group, arsenic in lesions and adjacent skin was "normal" in 71% of the patients. The arsenic level was "normal" in only 18% of the Bowen's disease patients. Statistically, this increased arsenic content in Bowen's lesions was highly significant. These arsenical keratoses were considered "practically indistinguishable from those of Bowen's disease" on a clinical and histological basis. Because of the increased concentration of arsenic in Bowen's lesions, the authors suggested arsenic as one of the causes of Bowen's disease.

Twenty-seven cases of multiple cancers of the skin and internal organs were reported by Sommers and McManus. [36] Arsenic was considered the etiological agent because in all cases but 1 the patients exhibited multiple keratoses of the palms and soles. In the 1 case without keratoses, the patient had been treated for psoriasis with Fowler's solution. Overall, 20 patients had some history of medical treatment with arsenicals, though very brief in some cases. Two of these also had possible occupational exposure. Two other patients without history of medical exposure were considered occupationally exposed--a chemist who had analyzed sprayed fruit for arsenic and who used arsenic as a gardener, and a farmer who used Paris green and lead sprays. Two patients were considered as possibly exposed occupationally--an electric welder and a mill

overseer. Three patients had no known arsenic exposure. Skin was the most common cancer site, but carcinomas were seen in the urogenital, oral, esophageal, and respiratory epithelium. Ten patients had multiple skin and visceral cancers. The remaining 17 had multiple skin cancers.

Epidemiologic Studies

Holmqvist [37] reported an extensive study of dermatitis problems in a Swedish copper smelter. Workers reported symptoms of burning and itching. The dermatitis was broadly classified into 2 types: eczematous type, with erythema, swelling, and papules or vesicles; and a follicular type, with erythema and follicular swelling or follicular pustules. The dermatitis was primarily localized on the most heavily exposed areas such as the face, back of the neck, throat, forearms, wrists, and hands. However, it also occurred on the scrotum, the inner surfaces of the thighs, the upper chest and back, the lower legs, and around the ankles. Once established, dermatitis continued as long as arsenic exposure continued. To permit the condition to clear up, sick leave was granted. The average length of sick leave required was 13.6 days for initial occurrences and 10.2 days for recurrences. Hyperpigmentation and keratoses were not reported.

Patch tests demonstrated that the dermatitis was due to arsenic, not to impurities present in the crude arsenic trioxide. [37] Tests with arsenic trioxide and pentoxide, sodium arsenite, and sodium, calcium, and lead arsenate demonstrated that all produced dermatitis. Many workers had been sensitized to both trivalent and pentavalent arsenic. However, Holmqvist also recommended that workers with mild dermatitis, especially

28

new employees, continue work since this often resulted in the loss of their hypersensitivity. The incidence of dermatitis was highest in those areas in which arsenic exposure was highest, but occurred in all areas, possibly in sensitized individuals where arsenic exposures were low. Dermatitis also was worse in the summer months, possibly because workers sweat more than in the winter.

An outbreak of arsenical dermatoses was reported by Birmingham et al [38] which involved cases in the community outside the plant. A reactivated gold mine began smelting ore which contained large amounts of sulfides of arsenic. It was estimated that 40 tons of arsenic and 100 tons of sulfur dioxide were burned off daily, but the dust-collecting system failed to operate at the expected 90% efficiency. Within a few months after operations began, children attending elementary school in the nearby mining camp community developed skin lesions, mostly on the exposed parts of the body. Thirty-two of the 40 elementary school students had 1 or more types of suspect arsenical dermatoses including eczematous contact dermatitis, folliculitis, furunculosis, pyodermas, and ulcerations. Conjunctivitis and rhinitis were common. The eczematous dermatitis was pruritic, usually involving the face and flexures, and was highly suggestive of atopic dermatitis. The follicular and pustular lesions were mostly on the face and neck, although some were on the extremities. Ulcerations were seen on the palms, fingers, toes, and webs. The high school students who spent 10-12 hours a day away from the community did not have dermatitis. Nine of 18 mill workers on the day shift had similar skin lesions. Two also had ulcerations and perforations of the nasal septum. The urinary arsenic levels of elementary school children and smelter workers reportedly

29

"compared favorably" with 0.82 mg As/liter reported by Pinto and McGill [39] for copper smelter workers exposed to arsenic. One urinary arsenic value was elevated, at 2.06 mg/liter, in an ore roaster worker.

The mortality experience in an English factory manufacturing a sodium arsenite sheep-dip was reported in 1948 by Hill and Faning. [40] Death registers were consulted for the town in which the factory was located and for a nearby town in which there was a hospital. Records indicated that, between 1910 and 1943, there were 75 deaths of factory workers and 1,412 deaths of other workers who were residents of the factory town. This latter group was subdivided by occupation into 4 groups: 319 agricultural workers, 701 skilled artisans or shop workers, 196 general laborers, and 196 other workers, in mainly professional, managerial, and clerical occupations. This last group was not used for comparison purposes, since it was not considered comparable on a social and industrial basis. Excluding that group left 1,216 deaths in the other 3 groups, with cancer deaths representing 14.4%, 13.8%, and 12.0%, respectively, or 12.9% overall.

The cancer deaths were classified into 6 broad site groups. There was no apparent difference between the factory workers and the other 3 occupational groups with respect to cancer of the buccal cavity and pharynx, genitourinary organs, and other or unspecified sites. However, there was an apparent excess among factory workers of deaths due to cancer of respiratory system (31.8% compared to 15.9%) and of the skin (13.6% compared to 1.3%), with a corresponding deficit in deaths due to cancer of the digestive organs and peritoneum (22.7% compared to 58.0%).

Based on factory records and the advice of factory personnel, the deaths among factory workers were subdivided [40] according to the

occupations within the factory. Three groups resulted: chemical workers, engineers and packers, and a general group including builders, printers, watchmen, carters, boxmakers, etc. Of 24 deaths in this last group, 3 (12.5%) were due to cancer, an incidence very similar to that observed in the 3 nonfactory groups. Sixteen of 41 deaths (39.0%) among chemical workers and 3 of 10 deaths (30.0%) among engineers and packers were due to cancer. Statistically, the cancer incidence in the engineers and packers group did not differ significantly from the control group, but the cancer mortality of the chemical workers was significantly higher ($p = 0.047$). All lung cancer and skin cancer deaths (5 and 3, respectively) recorded among factory workers occurred in the chemical worker group.

Perry et al [41] conducted clinical and environmental investigations at this sheep-dip factory during 1945 and 1946. On 5 occasions over a 12-month period, general room samples were collected in 4 work areas: in the packing room, drying room, sieving room, and near the kibbler operator. Median concentrations were 0.071, 0.254, 0.373, and 0.696 mg As/cu m, respectively. Arsenic analyses were made on urine and hair samples from 4 groups of workers: 31 chemical workers, 20 maintenance workers (engineers, builders, etc), 12 packers, and 56 unexposed controls consisting of office workers, men from a printing and bookbinding department, truck drivers, box makers, and chemical workers not recently exposed to arsenic. An effort was made to collect 24-hour urine samples twice and to collect 2 hair samples from each worker. However, not all workers cooperated, so that there was a total of 58, 32, 22, and 54 urine measurements and 27, 17, 11, and 44 hair samples, respectively, for the 4 groups. The average arsenic excretion was 0.24, 0.10, 0.11, and 0.09 mg As/liter of urine, and 108, 85,

31

64, and 13 ppm As in hair, respectively. With regard to arsenic both in hair and in urine, exposed workers had significantly higher levels than did the unexposed controls. The 3 exposed groups did not differ significantly with respect to arsenic in hair, but the urinary excretion of arsenic by chemical workers was significantly higher than the excretion by maintenance workers and packers.

The workers were given a full physical examination with particular attention to pigmentation and the number of warts. [41] They were given a chest X-ray, a vital capacity test, and an exercise tolerance test. One worker showed an enlarged mass at a hilum, but bronchoscopy did not reveal a neoplasm. Otherwise, no abnormal results of the X-ray, vital capacity tests, or exercise tolerance tests were mentioned. Pigmentation keratoses and wart formation were considered quite typical of arsenic exposure, and "changes were so evident that the person carrying out the physical examination could readily tell whether the man he was examining was a chemical worker without asking any questions." The degree of pigmentation was subjectively rated as from one to four plus and the number of warts was recorded. Nine of the 31 chemical workers examined had 1-6 warts, and their pigmentation was rated as negative in 3 workers, 1 plus in 10, 2 plus in 9, 3 plus in 7, and 4 plus in 2. Of 20 maintenance workers and 12 packers: 1 had 4 warts and pigmentation was rated as negative in 20 workers, 1 plus in 9, and 2 plus in 3. Of the 56 controls, 2 had 1 wart each and pigmentation was rated as negative in 46 workers, 1 plus in 8, and 2 plus in 2 (both of these were former chemical workers).

Snegireff and Lombard [42] conducted a statistical study of cancer mortality in the metallurgical industry. From 1922 to 1949, 146 deaths

were recorded among the employees at one plant (Plant A) handling large quantities of arsenic trioxide. No mention was made of methods used to trace former and retired employees, so it appears that only deaths among active plant employees were considered. Of the 146 deaths recorded, 18 were due to cancer and 7 of these were ascribed to cancer of the respiratory system. The 18 deaths due to all types of cancer represented a slightly higher proportionate cancer mortality (12.3 cancer deaths per 100 deaths) than observed in the state as a whole (10.0 cancer deaths per 100 deaths). A total of 72 deaths were reported among employees under age 55, and 9 of these were due to cancer of all types (12.5 cancer deaths per 100 deaths). In contrast, the proportionate cancer mortality for this age group in the state as a whole was 6.1 per 100 deaths. The authors showed that both of these increases in proportionate cancer mortality were not statistically significant. This apparently was due to the small sample size.

Also studied was the cancer mortality of Plant Z, comparable to Plant A except that no arsenic was handled. [42] In Plant Z from 1941-49, 12 of 109 deaths were due to cancer of all types (11.0 cancer deaths per 100 deaths), and 6 of the 12 cancer deaths were due to lung cancer. Compared to the state as a whole in which it was located, (9.6 cancer deaths per 100 deaths), Plant Z had a higher proportionate cancer mortality, but this was not statistically significant. In the under 55 age group, the mortality due to cancer of all types again was higher (8.3 compared to 5.7 cancer deaths per 100 deaths) in Plant Z, but was not statistically significant. On the basis of this evidence, they concluded that the handling of arsenic trioxide in industry did not produce significant change in the cancer

mortality of plant employees.

By examining only deaths among active plant employees, the authors failed to consider deaths among former employees, including those who retired or changed jobs after long exposure. Therefore, the true cancer mortality may have been higher. Furthermore, the authors did not attempt to compare respiratory cancer mortality in the plants with that in the state as a whole, despite the fact that cancer of the respiratory system in Plants A and Z represented 38.9% and 50.0%, respectively, of all cancer deaths.

Using the total cancer deaths experienced in each plant, NIOSH calculated the expected number of respiratory cancer deaths, by age group, that should have occurred if rates for the appropriate US population were applied. Mid-years were chosen for Plants A and Z (1938 [43] and 1945, [44] respectively) for application of the indirect method of standardization. Since data necessary for a reasonably sound evaluation of the respiratory cancer deaths were not available, numerous assumptions must be made keeping in mind the limitations they impose. Nevertheless, it is interesting to show, under these limitations, how the respiratory cancer in Plants A and Z compared to the US experience for a similar time period. Plant A experienced a 460% excess in respiratory cancer deaths relative to mortality from all causes in 1938. The Plant Z excess was somewhat less at 350%. When respiratory cancer deaths in the plants were compared to all cancer deaths, the excess was 450% and 550% in Plants A and Z, respectively. This was in sharp contrast to the total cancer mortality relative to all causes of death when using the same control populations for the 2 plants. In this case, the cancer death experience showed deficits for

Plants A and Z of 4% and 25%, respectively. Thus, even if the absolute figures used were inaccurate, the relative difference demonstrated here indicates that it was the respiratory cancer that required detailed investigation in the original study. A representative control population might also have shown an excess and could have indicated problems both in Plants A and Z. This would then make it inappropriate to compare Plant A to Plant Z, since Plant Z also demonstrated evidence of some type of carcinogen for respiratory cancer.

Using unpublished data supplied by Lull and Wallach, Hueper [45] reported the cancer mortality in several Montana counties in which copper smelters and mines were operated for many years. In 3 counties in which the major industry was copper smelting and/or mining, the annual lung cancer death rate per 100,000 male population ranged from 46.3 to 145.7 for 1947-48. In contrast, a rate of 5.2 per 100,000 was reported for a county in which the major industry was agriculture. The estimated [45] lung cancer death rate among white males in the United States as a whole in 1947 was 10.9 per 100,000.

Roth [46] reported the results of 47 autopsies of German vinegrowers. Autopsies were conducted because the individuals had been chronically poisoned by exposure to arsenical insecticides in the vineyards and by arsenic contaminated common wine. Cancer was listed as the cause of death of 30 of the 47 cases (64%), and malignancies were observed in an additional 3 cases. A total of 75 malignant tumors (40 of which were skin cancers) of various tissues were observed in these 33 cases with malignancies. Lung cancer was listed as the cause of death in 18 cases, hemangiosarcoma of the liver in 6 cases, carcinoma of the esophagus in 5 cases, and

bile duct carcinoma in 1 case. There were 10 cases of multiple tumors of the skin and internal organs, and 4 cases of multiple tumors of internal organs. "Arsenic cirrhoses" were listed as the cause of death in 8 cases, and were observed in an additional 15 cases.

The lung cancer mortality of 6 rural and urban districts of the Moselle and 1 district of the Ahr were compared. A statistical treatment was not attempted, but Roth [46] reported that, in general, vineyard areas of the Moselle had a higher proportionate mortality due to lung cancer than did the urban and nonvineyard areas. The vineyard areas of the Ahr also had lower incidence of bronchial cancer, which was attributed to the fact that arsenical insecticides had never been used there. Roth considered that, in combination with his autopsy findings, this strengthened an etiological link between the arsenical insecticides and bronchogenic carcinoma. He did not consider it appropriate to propose such a link in an individual case unless there was a history of arsenic exposure and unless there were symptoms of chronic arsenic poisoning, such as melanosis and hyperkeratosis of the skin, single or multiple skin cancers, or peripheral disturbances of circulation.

Pinto and McGill [39] studied the effects of arsenic exposure in a smelter producing arsenic trioxide as a byproduct. Much qualitative information on the plant environment was reported, but no actual air measurements were made, and the necessity for protective clothing and respirators was stressed. Work clothes used were underwear, socks, and a 1-piece denim coverall with attached hood for covering the scalp, ears, and back of the neck. Dust-tight goggles were recommended to prevent conjunctivitis in high dust concentrations. Respirators consisted of a

hard metal frame holding layers of surgical sheetwadding. These respirators were reportedly 99% effective when tested against arsenic trioxide dust loadings of 99-1740 mg/cu m. No further details of this testing were given. Perry et al [41] described very similar respirators that were used in the English sheep-dip factory as "masks of cotton wadding held in place by a wire frame."

Urinary arsenic levels were reported [39] for exposed and nonexposed workers employed in the smelter. In 147 samples from 124 nonexposed workers, urinary arsenic levels ranged up to 2.07 mg As/liter in 1 case (the second highest sample reported was 0.7 mg As/liter) and the mean was 0.13 mg As/liter. The average of 835 samples from 348 exposed workers was 0.82 mg As/liter with 7 samples reported as 4.0 mg As/liter or more. There is a distinct difference in the 2 groups, and the urinary level for the "nonexposed" workers is consistent with that reported by Watrous and McCaughey [22] for 13 job applicants with no known arsenic exposure. However, other studies have shown considerably lower normal urinary arsenic levels. For example, Schrenk and Schreibeis [4] reported an average of 0.08 mg As/liter based on 756 specimens from 29 persons with no known exposure, Perry et al [41] reported a mean of 0.085 for 54 controls, and Webster [23] reported an average of 0.014 mg As/liter based on samples from 43 adults and children. Furthermore, Milham and Strong [47] measured the urinary arsenic levels of residents on a downwind transect from the smelter studied by Pinto and McGill, [39] and found arsenic levels decreased with distance from the smelter. Levels were 0.3 ppm at a distance of 0-0.4 miles, and 0.02 ppm at a distance of 2.0-2.4 miles. Samples of vacuum cleaner dust were also collected, and arsenic was reported to decline from

1300 ppm at a distance of 0-0.4 miles to 70 ppm at a distance of 2.0-2.4 miles. This suggests that arsenic exposure was not confined to one section of the smelter, but extended also to the surrounding community. Thus, the "nonexposed" smelter workers might also have had a degree of arsenic exposure.

Effects observed, [39] presumably among the "exposed" workers, were dermatitis, perforation of the nasal septum, conjunctivitis, turbinate inflammation, and pharyngitis. Blond and reddish skinned persons were reported to be more sensitive to the irritating action of arsenic. Some cases of dermatitis were attributed to hypersensitivity. The authors considered dermatitis to be dependent on the sensitivity of the individual and on the degree of skin contact with arsenical dusts. Dust-in-air measurements were considered of limited value in predicting skin reactions, as were levels of arsenic in urine. However, based on a study of 127 individuals, the authors reported that dermatitis was observed in 80% of those excreting 1.0-3.0 mg As/liter and in 100% of those excreting more than 3.0 mg As/liter. No excessive pigmentation or keratoses were seen, and all observed effects were considered preventable by faithful use of the protective clothing and respirators described.

In a later paper based on the same plant population, Pinto and Bennett [48] analyzed the causes of death for a total of 229 active plant employees and pensioners. The pensioners were defined as being at least 65 years of age at the time of the study, and as having had at least 15 years service in the plant. The total population at risk is not known since the study excluded all workers who left the plant before retirement. Nevertheless, the authors stated that the mortality figures "truly represent the

38

causes of death in this plant for the individuals who stay long enough to have significant contact with industrial dusts and fumes." The 1958 cause-specific proportionate mortality of males aged 15-94 in the same state was used for comparison. The age range of the smelter group was 19-95. A slight excess of cancer deaths was observed in the smelter group (18.8% of all deaths compared to 15.9% in the state as a whole), but the increase was not statistically significant. Subdividing cancer deaths by site, the smelter group was shown to have an increased incidence of deaths due both to cancer of respiratory system (41.9% vs 23.7% of cancer deaths) and of the breast and genitourinary tract (18.8% vs 11.6% of cancer deaths). There was a decrease in the proportion of deaths due to cancer of the digestive organs and peritoneum (18.6% vs 34.5%). The deaths in the smelter group were also classified into deaths among "exposed" and "nonexposed" workers, revealing that relatively more cancer deaths occurred among the "nonexposed" (19.4% of all deaths) than among those "exposed" to arsenic (15.8%).

Compared to the data for the state as a whole, the smelter workers were also shown [48] to have slightly increased mortality due to cardio-vascular disease (65.5% of all deaths compared to 59.0% in the state as a whole), but the increase was not statistically significant. An excess was observed in the 45-64 age bracket for both "exposed" and "nonexposed" workers (36.8% and 25.7%, respectively, compared to 15.2% for this age group in the state as a whole), with a reduction in cardiovascular mortality in the 65-94 age bracket for both groups (31.6% and 36.6%, respectively, compared to 41.9% in the state). Because the cardiovascular mortality was similar in both "exposed" and "nonexposed" groups, the

39

authors concluded that arsenic exposure had no effect.

The "exposed" and "nonexposed" categories are suspect, however, since the urinary arsenic levels reported by Pinto and McGill [39] and cited by Pinto and Bennett [48] indicate that the "nonexposed" group did in fact have a degree of exposure to arsenic. Consequently, one must also question the conclusions that, because the mortality experience was similar in the 2 groups, increases in cardiovascular and cancer mortality are unrelated to arsenic exposure. The increase in overall cancer mortality was not statistically significant, but the respiratory cancer mortality in the smelter group was 18 of 229 deaths (7.9%) compared to 518 of 13,759 deaths (3.0%) in the state as a whole. Similarly, overall deaths due to cardiovascular disease were increased in the smelter group, but not significantly so. The increase, however, was entirely concentrated in the 45-64 age group (63 deaths compared to 38.52 expected) and was partially offset by a decrease in the 65-94 age group (82 deaths compared to 106.54 expected).

A recent study of mortality among workers at this plant was reported by Milham and Strong. [47] In this case, death certificates for the county in which the smelter is located were examined. In the years 1950-71, 39 deaths due to respiratory cancer were recorded among county residents listed as employed at the smelter. Records at the smelter revealed one employee who was not a resident of the county but who died of respiratory cancer. Since the average annual population at risk (904 active employees and 209 pensioners) and their age distribution as published by Pinto and Bennett [48] was essentially unchanged, the 1960 age-cause specific mortality statistics for white males in the US were applied to compute an expected total respiratory cancer mortality of 18. [S Milham, written

40

communication, October 1973] The increased respiratory cancer mortality, 40 observed compared to 18 expected, was statistically significant (p < 0.001).

Lee and Fraumeni [49] conducted a mortality study of 8,047 white male smelter workers exposed to arsenic trioxide during 1938-63. The smelter workers were classified into 5 cohorts based on total years of smelter work completed: (1) 15 or more years completed before 1938, (2) 15 or more years completed between 1938 and 1963, (3) 10-14 years, (4) 5-9 years, (5) 1-4 years. No specific environmental data were provided, but the smelter workers also were divided occupationally into 3 categories with respect to relative level of arsenic trioxide exposure: arsenic kitchen, Cottrell, and arsenic roaster workers were classified as a heavy exposure group; converter, reverberatory furnace, ore roaster and acid plant, and casting workers as a medium exposure group; and all other smelter workers were classified as a light exposure group. According to Lee and Fraumeni, [49] this classification was made for them by 2 individuals at the Division of Occupational Health, USPHS, based on unpublished data. The data used had been collected in a 1965 survey of 1 US copper smelter and are presented in Table X-3. The "heavy," "medium," and "light" exposure categories were based on these exposure data and on these individuals' experience with the smelting industry. Urinary arsenic levels collected in the 1965 survey are listed in Table X-4.

For comparison, the mortality statistics were used for the white male population of the states in which the various smelters were situated. [49] The total mortality of smelter workers was significantly increased. The specific causes of death which were significantly elevated were

41

tuberculosis, respiratory cancer, diseases of the heart, and cirrhosis of the liver. Respiratory cancer mortality was significantly increased in all 5 cohorts. Mortality due to diseases of the heart was significantly increased in cohorts 2, 3, 4, and 5. Deaths due to cirrhosis of the liver were significantly elevated to cohorts 2 and 5, while tuberculosis mortality was significantly higher only in cohort 5.

When respiratory cancer deaths were grouped according to relative level of arsenic exposure, the observed mortality was significantly higher than expected in all 3 groups: approximately 6.7, 4.8, and 2.4 times expected in the heavy, medium, and light exposure groups, respectively. [49] In addition to arsenic trioxide, the smelter workers were simultaneously exposed to sulfur dioxide in over 5,000 of the cases, to silica in an unstated number of cases, to lead fume in 35 cases, and to ferromanganese dust in 317 cases. Therefore, a similar classification was made for relative sulfur dioxide exposure. Respiratory cancer mortality was directly related, with observed deaths ranging from 6.0 to 2.6 times expected in heavy, medium, and light exposure groups. Most work areas having heavy arsenic exposure were also medium sulfur dioxide and all jobs with heavy sulfur dioxide exposure were medium arsenic areas. It was observed that workers with heaviest exposure to arsenic and moderate or heaviest sulfur dioxide exposure were most likely to die of respiratory cancer. Smoking histories were not available for the workers in this study, but the authors discounted smoking as the major factor, concluding that "it is highly unlikely that smoking alone would account for the excessive respiratory cancer mortality observed." Furthermore, there was no reason to expect that the amount smoked would be related to either the

42

degree of arsenic or sulfur dioxide exposure.

Kuratsune et al [50] reported increased respiratory cancer mortality among workers at a Japanese copper smelter. Because a remarkably high lung cancer mortality rate was noted among males in one town, a case control study was conducted based on mortality information derived from death certificates. The case group consisted of 19 males who died of lung cancer and the control group of 19 males who died of diseases other than lung, urinary bladder, or skin cancer. The only significant difference between the groups was that 11 of the lung cancer deaths occured in men formerly employed as copper smelters, compared to only 3 deaths in former copper smelters in the control group (p = 0.01). No arsenic exposure levels or other environmental data were included so this report does not contribute information on a safe exposure level, but it does serve to confirm the results of studies conducted in American smelters.

Rencher and Carter [51,52] analyzed causes of death among active and retired employees of the Utah division of a copper company who died during the period 1959-69. A total of 965 deaths were identified during this period from company records. These were subdivided into 4 categories according to the specific plant at which the decedents worked (no indication was given of how persons with employment at more than one plant were classified). The distribution by plant and average ages at death are given in Table III-1.

The relative frequencies (percentages) of deaths from specific causes among decedents from each location were compared to those for the state of Utah in 1968. [52] It should be noted that no adjustment for age was made in these comparisons. Smelter workers exhibited the highest percentage of

TABLE III-1
Deaths in the Utah Division of a Copper Company (1959-64)

Location	No. of Deaths	Average Age at Death
Smelter	244	63.9
Mine	317	62.2
Concentrator	318	64.9
Other*	86	59.0

*included refinery, Salt Lake City offices, and Research Center

from Rencher and Carter [52]

deaths from lung cancer (7.0% based on 17 deaths). For both mine and concentrator employees, the frequency of cancer was 2.2% (7 deaths in each group). No deaths from lung cancer were observed among refinery and office employees. The corresponding figure for the State in 1968 was 2.7%.

The influence of smoking habits among the decedents on lung cancer mortality was investigated. [52] Smoking habits for all deceased smelter workers and for random samples of deceased mine and concentrator workers were obtained. The proportions of smokers at the smelter, mine, and concentrator were found to be nearly the same (approximately 60%). The percentages of lung cancer deaths among smokers and nonsmokers for the 3 major locations are given in Table III-2. These data indicate that both smoking and nonsmoking smelter workers experienced a higher relative frequency of lung cancer deaths than their counterparts at the mine and at the concentrator.

Age-adjusted mortality rates for major causes of death were computed for smelter and mine employees. [52] While the number at risk by age was fully known for all active and retired mine workers, the number of persons at risk within the smelter for ages over 66 had to be estimated. The

TABLE III-2

Lung Cancer Deaths as a Percentage of Total Deaths in Smokers and Nonsmokers

	Smokers	Nonsmokers
Smelter	9.2	3.3
Mine	3.3	0.7
Concentrator	3.3	0.8

from Rencher and Carter [52]

results in terms of age-adjusted death rates per 10,000 at risk are given in Table III-3.

Deaths among smelter workers were divided by cause into 3 categories: lung cancer, nonmalignant respiratory disease, and all other causes. [52] Based on average exposures in each of 12 work areas and the amount of time worked in each of these areas, 5 exposure indices (for sulfur dioxide, sulfuric acid mist, arsenic, lead, copper) were computed for each worker and averaged over the number of persons in each of the 3 categories of cause of death. All 5 of these average cumulative exposure indices were substantially higher for the lung cancer group, indicating that these persons had either worked longer at the smelter or in areas of higher exposure to the contaminants than persons dying of other causes. An examination of work histories for the 17 smelter workers dying of lung cancer revealed that all but one had worked in at least 1 of the 4 work

TABLE III-3

Age-Adjusted Death Rates per 10,000 At Risk

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

from Rencher and Carter [52]

areas having the highest average exposure levels for the 5 contaminants. (The smelter had been subdivided into 12 distinct work areas for the total study.) The average duration of employment at the smelter for the 17 former workers dying of lung cancer was roughly 29 years.

It was reported that prior to 1959 a different company had operated the facility as a custom smelter serving several customers with various sources of ore. [51] Since 1959, processing has been limited to ore from a mine which has a relatively low arsenic content. Although no measurements of arsenic concentrations within the smelter prior to 1959 were given, stack emission data were reported for arsenic as far back as 1944. These data indicated that average daily arsenic stack emissions (in tons) were at least 3 times higher prior to 1959 than during recent years. Current arsenic levels (circa 1970) within the smelter were given in the morbidity part of the Rencher and Carter report. [51] Average hourly exposure levels for the 12 work areas ranged from a reported zero in the engineering building and warehouse areas to 22.0 μg/cu m in the reverberatory furnace area. The overall average was 7.38 μg/cu m.

Milby and Hine [53] surveyed proportionate mortality patterns among active and retired employees of the company operating the smelter studied by Rencher and Carter. [51,52] The study group consisted of 1,910 persons who had worked at least 10 years with the company and who died between 1950 and 1972. The original purpose of the study was to investigate the extent of respiratory diseases (especially cancer) among employees of this company. No mention was made of arsenic or arsenical compounds. However, the question of respiratory cancer related to smelter employment was mentioned. The analysis consisted of comparing the proportion of deaths

46

due to cancer (all sites), respiratory cancer, and nonmalignant respiratory diseases in employees with the corresponding figures derived from the general populations of the US and the State of Utah. Contrasts were also provided with results of 3 earlier studies of copper smelter workers. [42,48,49] No adjustment was made for age at death or calendar-year of death in the analyses.

Overall, the proportion of respiratory cancer deaths among the company's employees (2.88%) was not very different from the US experience (3.2% in 1969) and that of Utah (2.7% in 1968). [53] With respect to respiratory cancer mortality, these employees were well below what has been reported for smelter workers. [42,48,49] When the data were subdivided into mining operations vs reduction plants, the proportion of respiratory cancer deaths was 2.7% and 3.0%, respectively. Excess mortality was noted for nonmalignant respiratory disease and was due primarily to an increased frequency of deaths from emphysema. When results were subdivided into 4 geographic subdivisions of the company, the proportion of respiratory cancer deaths was found to be 2.1, 3.5, 4.6, and 4.3%. The subdivision having the lowest proportion of lung cancer deaths consisted of a concentrator, mine, refinery, and smelter. The 3 subdivisions having a higher relative frequency of lung cancer were each composed solely of a mine and a reduction plant. Individual results, eg for smelters, were not given for any one of the 10 plants. No mention was made of the extent of exposure to arsenic within these 10 facilities nor was there mention of exactly how many of the workers studied were exposed to arsenic.

Although this study [53] showed no excess lung cancer, it utilized a relatively insensitive technique (analysis by proportionate mortality

ratios), it excluded some of the exposed population (workers who quit work before retirement), and it apparently included many workers who did not have significant arsenic exposure (eg, miners and concentrator workers). It is possible that a more sensitive method (ie, computation of age-specific mortality rates based on the population at risk and comparison to similar rates in the general population) might detect an increase in cancer mortality not revealed by this study. Should the results of this study be confirmed by a more comprehensive one, they would suggest that inorganic arsenic exposure as experienced by these workers did not cause cancer. However, no environmental data were presented to describe this exposure, and data from other sources are inadequate.

There are 2 major differences between the Rencher and Carter [52] and the Milby and Hine [53] studies which could account for the apparently conflicting results. In the Milby and Hine [53] study, all of the company's Utah facilities were lumped together in the analysis of lung cancer risks. This would result in a dilution effect, since the mine, concentrator, and refinery work environments were not associated with an increased risk, according to Rencher and Carter. [52] Approximately 80% of the Milby and Hine study group was employed at these facilities. Hence, an increased risk for the smelter would be masked by the more heavily weighted experience of the other facilities. The Milby and Hine [53] study included deaths occurring during the period 1950-72. Inclusion of deaths occurring during the 1950's could also dilute the results for lung cancer from the standpoint of latency, ie arsenic-related lung cancer would not normally be manifested until many years after individuals were first exposed. If sufficient time had not elapsed as of the 1950's for arsenic lung cancer to

48

occur among the population at risk at the Utah smelter, deaths occurring during the period 1950-58 among former smelter workers would not be expected to reflect the presence of an increased risk. Hence, the presence of an increased risk for lung cancer during the more recent period would be somewhat offset by a normal risk during the 1950's.

At any rate, neither study can reliably assess the lung cancer risk associated with arsenic air levels in the smelter since the present operator took over in 1959. The influence of these lower arsenic levels on the cancer incidence could be demonstrated only after a long period elapsed, eg 20-30 years.

Newman et al [54] examined the incidence of lung cancer and classified the cell types that occurred in 2 Montana counties from 1969 to 1971. In Silver Bow County there are several copper mines adjacent to the principal city, Butte, but there is no smelter. In Deer Lodge County there is a large smelter in Anaconda, the major city. Newman et al reported that lung cancer was significantly increased among the men of Anaconda and Butte, and in the women of Butte when compared to Montana as a whole (using a 10-year observation period, 1964-73, lung cancer was also increased among Anaconda women). Excluding the cities of Anaconda and Butte, the men and women of Deer Lodge and Silver Bow Counties did not have excessive lung cancer mortality. In a preliminary survey of 36 US counties in which there is a nonferrous metal smelter, Fraumeni [55] found increased lung cancer mortality for females in 24 of the counties and for males in 28 counties.

For classification of histologic types, Newman et al [54] classified the men in 3 groups: copper smelter workers, copper mine workers, and "other" men (less than 1 year of employment in the copper smelter or mines,

but resident in the same general area). The distribution of histologic types of bronchogenic carcinoma of the copper miners and other men was very similar. However, the smelter workers had significantly more poorly differentiated epidermoid carcinomas. The data that were available on smoking habits indicated that there was no difference in the 3 groups with respect to smoking. Newman et al suggested that arsenic was responsible for the increased lung cancer mortality in Anaconda men and women, and they proposed that an excess of poorly differentiated epidermoid carcinoma might be characteristic of arsenic-induced lung cancer. According to an air pollution survey, [56] the atmospheric concentration of arsenic in Anaconda during 1961-62 was 0.0-2.5 μg As/cu m (0.45 μg As/cu m average) compared to 0.0-0.55 μg/cu m (0.07 μg/cu m average) in Butte. For 5 other Montana cities, the yearly average was 0.001-0.07 μg As/cu m. Newman et al [54] offered no explanation for their observation that the histologic type distribution of bronchogenic carcinoma in Butte women was "surprisingly similar" to that of the smelter workers. They did suggest that the excess cancer mortality in Butte might be attributable to community air pollution arising from the sanding material used on city streets during the winter.

In 1973 Nelson et al [57] studied the long-term mortality of a sample of residents of the Wenatchee Valley area in the State of Washington. Members of the cohort were originally enrolled in a medical survey conducted in 1938-39 by the US Public Health Service [58] to assess the health status of persons exposed occupationally and otherwise to lead arsenate pesticide spray or spray residue. This chemical had been and was still being used extensively in that area to protect the substantial apple crop.

The population sample was categorized into 3 subgroups for the medical survey reflecting the degree of exposure to lead arsenate. [57] Orchardists comprised those persons who were actively engaged in the preparation and application of lead arsenate sprays during 1938. Consumers denoted persons who never had an active part in orchard work and consisted mainly of women and children. Intermediates were either former orchardists, warehouse workers, or persons whose exposure to spray materials was irregular and infrequent.

These 3 groups were followed for a 30-year period (1938-68) and their mortality experience was compared to that of the general population of the State of Washington. [57] All 3 subgroups exhibited substantial deficits in total mortality which persisted throughout the 30 years of observation. Death rates for 3 broad cause-categories (heart disease, cancer, and stroke) closely paralleled the pattern of deficits seen for total mortality relative to the state as a whole. The authors reported that the frequency of deaths from kidney disease, liver disease, and lung cancer was not excessive.

Because the results of the study by Nelson et al [57] were at variance with previous evidence on the long-term effects of arsenic exposure, NIOSH reviewed data from other sources and used alternative procedures in an attempt to verify these findings. One approach was to utilize other data sources regarding the cancer experience of Wenatchee Valley residents exposed to lead arsenate. One readily available data source consisted of occupational and cause of death information for all deaths among adult white males in the State of Washington for the period 1950-71. The Washington Department of Social and Health Sciences has coded

and entered these data into an automated retrieval system permitting comparisons of disease frequency among some 400 distinct occupational groups. [S Milham, written communication, October 1974] For decedents classified as orchardists, respiratory cancer was found to be 19% higher than expected as an underlying cause of death over the 22-year period. During the most recent 11 years (1961-71), a statistically significant increase of 27% was noted for this disease. Most of the excess mortality from respiratory cancer occurred between the ages of 20 and 64. It was reported by Milham that male residents of the Wenatchee Valley comprise about 50% of the orchardist population in the State of Washington.

Another approach was to review age-adjusted mortality rates for cancers at specific sites for the 3-county area comprising the locale from which the orchardist sample was drawn by Nelson et al. [57] Cancer mortality rates (1950-69) for Chelan, Douglas, and Okanogan counties [59] were compared to the state rates to identify unusual cancer patterns. For the area as a whole, respiratory cancer was 7% higher than expected among white males. Chelan county accounted for all of the excess (31%, p < 0.01). The rate for Douglas county was similar to the state rate while Okanogan experienced a significant 28% deficit (p < 0.01). These results reflect the residence distribution of the EPA orchardist sample, ie, the majority of persons participating in the EPA study were from Chelan county while Okanogan was the least represented county. Respiratory cancer rates for white females in the 3-county area were consistently lower than the State rate. Both sexes in this area experienced increased mortality from cancers of the skin, bone, and brain. Only Chelan county exhibited a consistent pattern for these sites, but since the number of deaths for these sites is

small, it is difficult to draw firm conclusions as to their significance. It is noted that current mortality data on orchardists and male residents of Chelan County indicate a significant excess for lung cancer.

As pointed out by Nelson et al, [57] the deficits in mortality that they reported might be explained by a self-screening process whereby the workers most vulnerable to lead arsenate spray left orchard work before 1938, so they either were not in the study or were classified as intermediates. Similarly, the more susceptible individuals might have died or moved away before 1938, leaving behind a selected group of better mortality risks. Because the independent sources of information that NIOSH investigated contradicted rather than confirmed the report by Nelson et al, it appears that the report did not accurately depict the cancer experience of persons exposed to lead arsenate spray in the Wenatchee valley.

Baetjer et al [60] examined the mortality experience of retirees who had been exposed to arsenic at a Baltimore chemical plant manufacturing arsenical pesticides. Seventeen of 22 deaths among male retirees were due to cancer, compared to 4.43 expected cancer deaths (expected numbers based on age-sex specific proportionate mortality ratios for the city of Baltimore). By site, the ratio of observed to expected (O/E) cancer deaths was 6.71 for respiratory cancer, 3.0 for "lymphatic and hematological cancers" (sometimes referred to as lymphosarcomas), and 1.49 for all other neoplasms.

To conduct a death rate analysis, age-cause-specific death rates were calculated for the population of Baltimore. [60] These rates were then applied to the person-years at risk of dying for each retiree age group. Once again, significantly increased cancer mortality was noted for

respiratory cancer, with an O/E ratio of 16.67 (95% confidence limits of 7.14-32.84). Mortality from lymphatic cancer (50.0 O/E ratio, 6.05-180.50 confidence limits) and from all remaining neoplasia (4.65 O/E ratio, 1.26-11.90 confidence limits) were also excessive but the small numbers of deaths in these groups made interpretation difficult.

Ott et al [61] compared the proportionate mortality experience of 173 decedents who had been primarily exposed to lead and calcium arsenate with that of 1,809 decedents without arsenic exposure. As a percentage of total deaths, cancer of the respiratory system was significantly higher as a cause of death in the exposed group (16.2%) than in the controls (5.7%). Cancer of the lymphatic and hematopoietic tissues (described as not including leukemia) was also significantly higher in the exposed group (3.5% compared to 1.4% expected). Specifically, the 6 cases of lymphoma were classified on death certificates as 1 lymphoblastoma, 1 reticulum cell sarcoma, and 4 cases of Hodgkin's disease.

To supplement this proportionate analysis, the authors also examined the mortality in a cohort of 603 chemical workers with at least 1 month of work in the arsenic production areas. [61] Person-years lived by the cohort were used to compute the expected number of deaths by cause, based on the US white male mortality. Total deaths were lower than expected (O/E ratio of 0.84), and this was consistent with overall mortality at this company location where mortality from all causes varied from 60-85% of US mortality. However, mortality due to respiratory cancer (O/E ratio of 3.45) and cancer of the lymphatic and hematopoietic tissues except leukemia (O/E ratio of 3.85) was significantly higher than expected in the cohort of exposed workers.

TABLE III-4
Respiratory Cancer Deaths by Exposure Category

Average ln Dosage (in mg Arsenic)	Projected 8-hour TWA (μg Arsenic)	Total Deaths (n = 173)	Respiratory Cancer Deaths		
			Observed (n = 28)	Expected	O/E
3.74	1.0	26	1	1.77	0.6
4.84	3.0	17	2	1.01	2.0
5.53	6.0	24	4	1.38	2.9
6.04	10.0	22	3	1.36	2.2
6.68	20.0	27	3	1.70	1.8
7.35	40.0	18	2	0.97	2.1
8.17	90.0	13	3	0.77	3.9
8.78	160.0	13	5	0.79	6.3
10.30	740.0	13	5	0.72	7.0

Adapted from Ott et al [61] and Blejer and Wagner [62]

Four job categories were established and 8-hour TWA exposures were estimated for each category. [61] Using these estimates and work histories, the authors calculated arsenic dosages for the workers included in the proportionate analysis and in the retrospective cohort analysis. In both cases, an apparent dose-response relationship was shown between arsenic exposure and respiratory cancer mortality. The authors estimated the O/E ratio for respiratory cancer would be 7:1 for individuals exposed for more than 8 years at an "equivalent level of 1 mg/cu m arsenic." The authors reported they could find "no common denominator," other than arsenic, to explain the observed excess cancer mortality. Blejer and Wagner [62] used the total arsenic dosages as published by Ott et al [61] to calculate what the daily 8-hour time-weighted average (TWA) exposure would have been if the total arsenic dosages were taken to represent those inhaled by workers over a 40-year working life. As shown in Table III-4,

these calculations suggest that respiratory cancer mortality was twice the expected at a dosage equivalent to exposure for 40 years at 3.0 μg As/cu m on an 8-hour TWA basis, while the O/E ratio was 0.6 at the equivalent to 1.0 μg As/cu m.

Animal Toxicity

The acute oral toxicity of arsenic trioxide in mice and rats was tested by Harrisson et al [63] using both "crude" or commercial grade (97.7% As_2O_3 with 1.18% Sb_2O_3) and highly purified arsenic trioxide (99.999+% As_2O_3). Solutions were administered intraesophageally using an oral feeding tube. Test animals had been previously fasted for 24 hours. The acute oral LD50 for young Webster Swiss mice was estimated as 39.9 mg As/kg for the purified trioxide and as 42.9 mg As/kg for the commercial grade. For Sprague Dawley albino rats the LD50 was 15.1 mg As/kg and 23.6 mg As/kg for the pure and crude preparations, respectively. Despite its lower LD50, the purified arsenic was found to be less severe as a gastrointestinal irritant than was the crude trioxide. Retching during life and marked gastrointestinal damage at autopsy were observed only in animals receiving the crude arsenic trioxide. This was attributed to the antimony in the crude preparation.

Sharpless and Metzger [64] conducted a series of feeding experiments to investigate the relationship between arsenic and iodine. Young rats were fed basal diets with arsenic trioxide or pentoxide and potassium iodide added in varying ratios. Two control groups received the basal diet plus potassium iodide at 1 of 2 concentrations. In the 1 group receiving arsenic trioxide and potassium iodide, no effects were observed relative to

the controls. The authors considered it "probable that insufficient arsenic was absorbed to exert either a toxic or goiterogenic effect."

In rats receiving nontoxic amounts (0.005% of the diet) of arsenic pentoxide, "a slight, but not significant" goiterogenic effect was observed. [64] When arsenic was 0.02% of the diet, growth was decreased by 50% and the authors calculated that the iodine requirement was more than doubled. Thyroid weights were significantly increased while the iodine concentration in the thyroid decreased, even when iodine was administered at 5 times the minimum requirement. The authors suggested [64] that in man, arsenic in nontoxic amounts has an insignificant effect, but that in areas where the iodine intake is relatively low, a goiterogenic effect could be expected if the arsenic intake were sufficient to be slightly toxic.

Similarly, Dubois et al [65] reported antagonistic effects between arsenic and selenium. Albino rats given sodium arsenite or arsenate either in drinking water or in the diet were protected against toxic effects of seliniferous wheat, sodium selenite, and selenium-cystine. Arsenic sulfides (AsS2 and AsS3) in the diet did not prevent selenium poisoning. Arsenic in drinking water was effective if administration began within the first 20 days of selenium administration. After 30 days of selenium in the diet, arsenic provided no protection.

Ginsburg and Lotspeich [66] investigated the mechanisms of renal arsenate excretion in the dog and reported similarities between arsenate and phosphate excretion. Net tubular reabsorption of arsenate was observed, inhibited by increased plasma phosphate concentrations. The authors interpreted this as indicating a competitive interaction between

these ions. Reduction of arsenate to arsenite was reported, but whether this occurred in the urine, either in the lumen of the kidney tubules or in the bladder, or intracellularly could not be determined. Ginsburg [67] later reported that reduction to arsenite occurred intracellularly. Arsenite then diffused across both luminal and antiluminal faces of the tubular cell, resulting in higher plasma arsenite levels in renal venous than in renal arterial blood.

Byron et al [68] conducted a 2-year feeding study of the effects of sodium arsenite and sodium arsenate administered in the food of Osborn-Mendell rats and beagle dogs. Weight records were kept, blood samples were taken periodically, and animals were autopsied at death. At the end of 2 years, survivors were killed and autopsied. Many post-mortem tissues were preserved for microscopic study.

In rats, marked enlargement of the common bile duct was observed at the highest dosage of both compounds (250 and 400 ppm for the arsenite and arsenate, respectively). At the next lower dosages of both (125 and 250 ppm), enlargement was present but less pronounced. Arsenate slightly reduced survival and both compounds caused reduced weight. Some changes were noted in the hematologic study. None of the dogs on the highest arsenite dosage (125 ppm) survived for 2 years, but 5 of 6 on the highest arsenate dosage (125 ppm) did survive. In the nonsurvivors, gross and microscopic changes were essentially those of inanition. All dogs on the high dosages lost much weight, but those at levels of 50 ppm or less did not differ from controls. No carcinogenic effect of these 2 arsenicals could be detected.

Using weanling Long-Evans rats, Schroeder et al [69] evaluated the effects of arsenic by feeding diets low in arsenic (0.46 μg As/g wet weight) and administering sodium arsenite in the drinking water of experimental animals at a level of 5 μg As/ml. The experiment continued until the natural death of the animals. No specific disorders were observed in the control or experimental groups, nor was there a carcinogenic or tumorigenic effect. No arsenical keratoses were observed. The growth rates and life spans of the 2 groups did not differ. However, male rats had elevated serum cholesterol levels and lower glucose levels than did the controls. Arsenic accumulated with age in all tissues analyzed. Levels (μg As/g of wet tissue) in control and experimental rats, respectively, were: kidney, 0.0 and 27.63; liver, 0.21 and 46.92; heart, 0.53 and 34.53; lung, 0.25 and 46.19; spleen, 0.31 and 39.79.

Rozenshtein [70] conducted an experimental inhalation study using albino rats. He was concerned with the effects of atmospheric pollution by arsenic trioxide on the community at large, so 3 groups of female albino rats were exposed 24 hours a day for 3 months to a condensation aerosol of freshly sublimed arsenic trioxide at levels of 0.06, 0.0049, and 0.0013 mg As2O3/cu m (approximately 0.046, 0.004, and 0.001 mg As/cu m). The animals were studied biochemically and neurophysiologically during each month of exposure and during the recovery period after the termination of exposure. Some animals were killed 1 month after exposure ended and tissues were examined histologically and histochemically. The author did not state how many animals were involved in the study.

Inhibition of blood cholinesterase activity was detected during the exposure and recovery periods only in the high exposure group. In this

same group, an increase in blood pyruvic acid concentration was detected. Free -SH groups in whole blood also were lower and remained low after a month's recovery period. A disturbance of the normal chronaxial ratio of antagonistic muscles was seen in the 2 highest exposure groups, and was still apparent 1 month after exposure in the highest exposure group. Some accumulation of arsenic, mostly in the lungs and liver, was shown at the end of the exposure period in the 2 highest exposure groups. In the most heavily exposed animals these organs retained a high arsenic content 1 month after exposure.

Microscopic examination of the brains of animals in the highest exposure group showed pericellular edema and plasma-cell infiltration of vascular walls, plasmolysis, and karyolysis in addition to shriveling of neurons in the middle pyramidal tract. [70] There was an accumulation of leukocytic exudate in the bronchi, and in the liver there was fatty degeneration of hepatic cells. There were less marked changes in the tissues of the intermediate exposure group. Unexposed animals were used as controls for the above observations.

The animals exposed to only 0.0013 mg As2O3/cu m (0.001 mg As/cu m) showed none of the foregoing ill effects. On this basis the author [70] proposed 0.001 mg As2O3/cu m as the "mean diurnal maximum permissible concentration of this compound in the atmosphere...." This was apparently intended to be a standard for the population-at-large implying 24-hour exposure.

One difficulty with this study [70] is that, as grooming animals, the rats may have ingested arsenic trioxide from the fur. Another difficulty is that occupational standards are based on a 40-hour week, and any

extrapolation to this from the continuous exposure used by Rozenshtein is uncertain. If linearity is assumed, since there is no validated conversion formula, the exposure cited would be equivalent to 4.2 times higher levels on the 40-hour week basis, or 0.252, 0.021, and 0.005 mg As_2O_3/cu m (0.192, 0.016, and 0.004 mg As/cu m). The threshold apparently was between the 2 lower exposure levels.

Another animal inhalation study with arsenic trioxide, which in some respects more closely approaches human occupational exposure, was conducted by Bencko and Symon. [71] In this case hairless mice were used to eliminate the possibility of ingesting fur-retained dust during grooming. The animals were exposed 6 hours daily, 5 days a week for up to 6 weeks to fly ash containing 1% arsenic trioxide. Particle size was less than 10 microns, and the mean air concentration of arsenic was 0.1794 mg/cu m. Mice were killed serially after 1, 2, 4, and 6 weeks of exposure, and the liver, kidney, and skin analyzed separately for arsenic content. No microscopic examination of tissues was performed and there was no statement as to whether the animals were pathologically affected in any way.

Arsenic levels in liver and kidney peaked at 2 weeks' exposure. [71] At 4 and 6 weeks arsenic content fell to much lower levels, only slightly higher than in nonexposed controls despite continuing exposure. This implies that, after an initial latent period, the excretory mechanisms for arsenic increase in capacity and maintain an increased level for at least 6 weeks in the mouse, preventing accumulation of arsenic in liver and kidney. In the skin, the arsenic content continued to rise until the fourth week of exposure. By the sixth week, the arsenic level had declined by about one-third and remained a little higher than at the end of the first week of

exposure. It does not appear that any of the mice died from the effects of their exposure during the experiments.

These results confirmed an earlier paper by Bencko and Symon [72] in which they reported studies of arsenic in the skin and liver of hairless mice given arsenic in their drinking water. Arsenic trioxide was administered in a 32-day subchronic experiment and in a 256-day experiment. In both experiments, the maximum arsenic content of the skin and liver was reached on the 16th day. Thereafter, arsenic values decreased in the skin and liver, being particularly manifest in the long-term experiments.

Teratogenic effects have been observed in golden hamsters [73,74] and in mice [75] after injection of pregnant animals with sodium arsenate. A variety of effects were demonstrated, including anencephaly, renal agenesis, and rib malformations in the hamster, [74] and exencephaly, agnatha, and various skeletal defects such as fused and forked ribs in mice. [75] Holmberg and Ferm [73] reported that simultaneous injections of sodium selenite and sodium arsenate significantly reduced the teratogenic effect of sodium arsenate in the golden hamster. This evidence of metabolic antagonism between selenium and arsenic is consistent with the earlier report [65] that sodium arsenite provided a degree of protection against selenium poisoning in rats.

Leitch and Kennaway [76] reported a metastasizing squamous epithelioma in 1 of 100 mice receiving 86 twice-daily applications of alcoholic 0.12% potassium arsenite on the shaved skin. Leitch [77] was unable to reproduce this result on a repetition of the experiment.

Roth [46] reported increased incidence of cancer among German vine-dressers who apparently ingested a significant amount of arsenic in contam-

inated wine. Using 4 groups each of Bethesda black rats and C57 black mice, Hueper and Payne [78] administered arsenic trioxide in drinking water and in a 12% aqueous solution of ethyl alcohol. Control groups received either pure water or the 12% alcohol solution. The rats tolerated the arsenic solutions well and gained weight, but the mice died rather early.

With the exception of leukemia in 1 mouse receiving pure water, there were no cancers in mice. [78] The highest number of cancers in rats occurred among those on the alcoholic solution of arsenic, but they did not differ in type from those in the control groups. The rats receiving pure water had the highest incidence of reticulum cell sarcomas of the liver. There was 1 skin cancer (a squamous cell carcinoma of the cheek) in this control group, identical in site and type to the 2 skin cancers observed in the principal experimental group, the group receiving arsenic in alcoholic solution.

Baroni et al [79] tested both arsenic trioxide and sodium arsenate for primary carcinogenic effect, for cancer initiating effect in combination with the promoter croton oil, and for cancer promoting effect following administration of the carcinogens 7, 12-dimethyl benz(a)anthracene and urethan, in mice. The arsenic trioxide was administered as a 0.01% solution in the drinking water, and the sodium arsenate was applied to the skin of the mice as a 1.58% solution in a 2.5% solution of detergent. The results were entirely negative for all 3 types of effect.

Osswald and Goerttler [80] observed a marked increase in the incidence of lymphocytic leukemias and malignant lymphomas in female Swiss mice and their offspring following subcutaneous injections of arsenic. Among 35 male and 20 female untreated controls, 3 of 20 deaths in the males

63

and none of 16 deaths in the females were due to leukemia. Test animals were given injections of a 0.005% aqueous solution of the "sodium salt" (the valence of the arsenic was not specified) daily during gestation (a total of 20 injections) in a dose of 0.5 mg As/kg. The leukemia rate was increased both in the females (11 of 22 deaths due to leukemia) and in their offspring (13 of 59 deaths) that received no additional arsenic treatment. The leukemia rate was further increased when arsenic was injected subcutaneously into the offspring themselves (41 of 92 deaths). In 20 females receiving 20 once-weekly intravenous injections of 0.3 mg As, 11 of 19 deaths were due to leukemia. Since the controls did not receive injections of the vehicle solution, these results are of questionable significance.

Kroes et al [81] in 1974 published a lifetime carcinogenicity study in which SPF-derived Wistar rats were given lead or sodium arsenate in their diet. The experimental diet was also fed to their dams until the experimental animals were weaned. To investigate the possibility of a synergistic effect with a known carcinogen, some groups of rats received diethylnitrosamine (DENA) by esophageal intubation 5 days a week. Food intake levels (for the first 12 weeks) and body weights were recorded, and hematological studies were conducted after 12 months. Complete gross and microscopic examinations were made of animals dying during the experiment and of survivors, which were killed at the 27th month. The experimental design is outlined in Table III-5.

At 1850 ppm lead arsenate caused intra- and extrahepatic bile-duct lesions, significantly reduced weight gain, and caused increased mortality. [81] The only blood changes that seemed relevant were observed in this

TABLE III-5
Arsenate Study Design

| | In Diet | | By Intubation | | Animals/Group | |
Group no.	Lead arsenate (ppm)	Sodium arsenate (ppm)	DENA µg/day	Water (ml)	Males	Females
1a	--	--	--	0.3	50	60
1b	--	--	5	0.3	50	60
2	1850	--	--	--	29	19
3a	463	--	--	0.3	40	40
3b	463	--	5	0.3	40	40
4a	--	416	--	0.3	40	40
4b	--	416	5	0.3	40	40

from Kroes et al [81]

group--reduced hemoglobin, packed cell volume, and erythrocyte count. No difference was observed either in the tumor incidence of the groups or in the times at which tumors were detected. No carcinogenic action was attributable to sodium arsenate and DENA, alone or in combination, but in group 2 an adenoma in the renal cortex and a bile duct carcinoma were found. The authors suggested that these tumors might be "indicative of a very weak carcinogenic action" by lead arsenate, but they also recognized that no definite conclusion can be drawn from these data.

Correlation of Exposure and Effect

There are no environmental data in the reports by Holmqvist [37] and Birmingham et al [38] on the effects of arsenic on the skin, but a dose-response relationship is implied in both. Despite sensitization problems, Holmqvist [37] reported that the incidence of dermatitis was highest in areas with heaviest arsenic exposure. Similarly, Birmingham et al [38]

reported no dermatitis among high school students who attended school elsewhere, but younger children attending school in the mining camp did have dermatitis. Urinary arsenic levels of the elementary school children were said to "compare favorably" with those reported by Pinto and McGill [39] for exposed smelter workers. Thus, dermatitis apparently was seen in association with a urinary excretion of 0.8 mg As/liter.

In a study [40] of an English sheep-dip factory, chemical workers were shown to have increased cancer mortality while the other 2 occupational groups did not. The plant was the subject of an environmental-clinical survey [41] during which air samples were collected on 5 occasions from 4 work areas: in the packing room, drying room, sieving room, and near the kibbler operator. Additionally, on 1 occasion 7 samples were collected on the mixing platform, by and between the kneading machine, while loading and unloading a kiln, and during the blending of ingredients. Neither in the epidemiological [40] nor in the environmental [41] portion of the study was the "chemical worker" grouping defined or associated with particular jobs in the factory. However, based on the job titles included in the other 2 groups--packers, engineers (also called maintenance workers [41]), builders, printers, watchmen, etc--it appears that those workers in the drying room and sieving room, operating the kibbler, kneading, and blending machines, and the kilns would be classified as "chemical workers" rather than in one of the other occupational groups. Combining all air samples from these areas (31 samples) indicates that chemical workers' exposure ranged from 0.110 to 4.038 mg As/cu m with a mean of 0.562 and a median of 0.379 mg As/cu m. The 4.038 mg As/cu m level was almost 4 times the next higher level (1.051 mg As/cu m). Hyperpigmentation was observed

in 28 of 31 chemical workers examined, and 9 had warts. Chemical workers were excreting 0.23 mg As/liter of urine, and had 108 ppm in hair.

Among former employees of 2 American chemical plants manufacturing arsenite and arsenate pesticides, Baetjer et al [60] and Ott et al [61] observed excessive respiratory and lymphatic cancer mortality. Ott et al [61] demonstrated an apparent dose-response relationship, based on their estimation of the total arsenic dose which workers in this study had inhaled. Ott et al reported that the natural logarithms of total dosage ranged from 3.74 to 10.30, and that the O/E ratio for lung cancer mortality ranged from 0.6 to 7.0. Using the data and assumptions as published by Ott et al, [61] Blejer and Wagner [62] calculated the 8-hour TWA exposure or dose that, after a 40-year working life, would result in the same total arsenic dosages. The projected equivalent 8-hour TWAs ranged from 1.0 to 740.0 μg As/cu m (Table III-4).

Pinto and McGill [39] reported the effects of exposure to arsenic trioxide in a copper smelter, but did not report the concentrations to which workers were exposed. Effects observed included dermatitis, perforation of the nasal septum, and conjunctivitis. Urinary arsenic levels were reported for "exposed" and "nonexposed" workers. The average excretion reported for "nonexposed" workers (0.13 mg As/liter) is the same as that reported by Watrous and McCaughey [22] for 13 unexposed job applicants; but it is 10 times the level reported (0.014 mg As/liter) by Webster [23] for 43 persons and is almost twice that reported (0.08 mg As/liter) by Schrenk and Schreibeis [4] for 29 persons and by Perry et al [41] for 54 persons (0.085 mg As/liter). Additionally, Milham and Strong [47] reported that, among people living on a downwind transect from the smelter, urinary

arsenic levels averaged 0.3 ppm near the smelter but decreased with distance from the smelter, falling to 0.02 ppm at a distance of 2.0-2.4 miles. The arsenic content of vacuum cleaner dust also declined with distance from the smelter. This suggests that there may have been a degree of arsenic exposure in the "nonexposed" group since arsenic apparently escaped to the community outside the smelter. The "exposed" workers' average excretion was 0.82 mg As/liter. Of those found to be excreting 1.0-3.0 mg As/liter, 80% had dermatitis. Everyone excreting over 3.0 mg As/liter had dermatitis.

Studying the same plant population, Pinto and Bennett [48] reported increased mortality due to respiratory cancer and cardiovascular disease, but the increase was not statistically significant. The incidence of deaths for these causes was similar among "exposed" and "nonexposed" workers, so the authors concluded that the deaths were not related to arsenic exposure. As already pointed out, however, the urinary arsenic levels reported by Pinto and McGill [39] suggest that there was a degree of arsenic exposure in the "nonexposed" group. A 1973 study of this plant population by Milham and Strong [47] demonstrated significantly increased lung cancer mortality. No environmental data were collected in this study, so the incidence of cancer cannot be related to exposure.

Other studies have also indicated no increased cancer risk after occupational exposure to inorganic arsenic. Based on their comparison of 2 plants, Snegireff and Lombard [42] concluded that in the metallurgical industry arsenic exposure did not affect cancer mortality. However, NIOSH has studied the data (see Epidemiologic Studies) and has concluded that both worker populations had excessive respiratory cancer mortality when the

Snegireff and Lombard data are compared to data for the US as a whole. Similarly, Nelson et al [57] reported no excessive mortality among orchardists exposed to lead arsenate spray. Independent data sources investigated by NIOSH (see Epidemiologic Studies), sources that should confirm this observation, in fact indicate that there has been excessive respiratory cancer mortality among these orchardists. Therefore, it seems that these studies may not have accurately depicted the cancer mortality of these exposed workers. The Milby and Hine [53] study of deaths among all employees of a copper company has methodologic weaknesses that preclude any definitive decision concerning the presence or absence of risk. This is especially true in view of the increased lung cancer mortality reported by Rencher and Carter [52] among workers at that company's Utah smelter.

A study of a large smelter population was reported in 1969 by Lee and Fraumeni. [49] In this case, overall mortality was significantly higher than expected. Specific causes of death which were significantly higher than expected were diseases of the heart, tuberculosis, cirrhosis of the liver, and respiratory cancer. Of these, only respiratory cancer was significantly higher in all cohorts. Furthermore, respiratory cancer mortality was directly related to length of employment, and to both the degree of arsenic exposure and the degree of sulfur dioxide exposure. Because there was considerable overlap between these exposure groups, it was not possible to separate effects due to each, but it was found that workers with heavy arsenic exposure and moderate or heavy sulfur dioxide exposure were most likely to die of respiratory cancer.

The data used in part to classify work areas in terms of relative arsenic exposures are listed in Table X-3. These data are highly variable

and did not form the sole basis for classification, which makes interpretation difficult. One area sampled, the arsenic roaster area, would be in the heavy exposure classification used by Lee and Fraumeni. [49] In this area, samples ranged from 0.10 to 12.66 mg As/cu m with a mean of 1.47 and a median of 0.185 mg As/cu m. The reverberatory area and the treater building and arsenic loading area, classified as medium arsenic exposure areas, ranged from 0.03 to 8.20 mg As/cu m with a mean and median of 1.54 and 0.79 mg As/cu m, respectively. The remaining 3 areas sampled were areas classified as light exposure areas and ranged from 0.001 to 1.20 mg As/cu m with a mean and median of 0.206 and 0.010 mg As/cu m, respectively.

Assuming these data to be representative, they indicate that arsenic exposures in the "heavy" and "medium" exposure areas were very similar overall, although concentrations reached higher levels in the heavy exposure area. However, even in the "light" exposure areas, where in these samples the average air concentration was 0.206 mg As/cu m, respiratory cancer mortality was significantly increased over the expected incidence.

Hueper [45] in 1955 reported excessive lung cancer mortality in 3 Montana counties in which the major industry was copper smelting and/or mining. More recently, Newman et al [54] disclosed that lung cancer mortality was excessive in 2 Montana cities, 1 of which is near several copper mines. There is a large copper smelter in the second city. Exclusive of the populations of these 2 cities, the incidence of lung cancer in the counties in which they are located did not differ from the incidence in Montana as a whole. [54] Based on differences in the distribution of histologic type of bronchogenic carcinoma, Newman et al

70

suggested that arsenic in the community air might have been responsible for the increased lung cancer mortality in the smelter city. Similarly, Fraumeni [55] has observed increased lung cancer mortality among males in 28 of 36 US counties with nonferrous metal smelters, and among females in 24 of these 36 counties.

These reports [45,54,55] suggest that arsenic pollution of community air may in some places be sufficient to produce excessive lung cancer mortality in the general population. A 1961-62 study [56] found 24-hour average concentrations of 0.0-2.15 μg As/cu m in Anaconda, Montana. In 6 other Montana cities, the range was 0.0-0.55 μg As/cu m. The range of quarterly averages in Anaconda was 0.26-0.54 μg As/cu m, while the highest quarterly average reported for the remaining 6 cities surveyed was 0.09 μg/cu m in Butte.