

criteria for a recommended standard

OCCUPATIONAL EXPOSURE TO

INORGANIC ARSENIC

**U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health**

ERRATA SHEET
FOR
CRITERIA FOR A RECOMMENDED STANDARD....
OCCUPATIONAL EXPOSURE TO INORGANIC ARSENIC

p 36 Lines 8 & 9 now read " Plants A and Z (1938 [86] and 1945,
[87] respectively)...."

SHOULD READ "....Plants A and Z (1938 [43] and 1945, [44] re-
spectively)...."

p 105 HEADING: FIGURE XI-2 ARSINE GENERATOR

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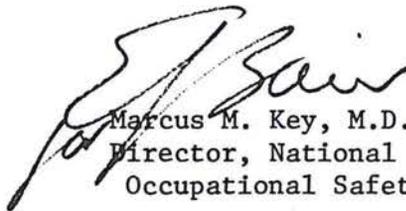
1973

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytic methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on inorganic arsenic by members of my staff, by the Review Consultants on Inorganic Arsenic, by the ad hoc committees of the American Industrial Hygiene Association and of the Society of Toxicology, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Edwin C. Hyatt on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on inorganic arsenic. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.



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The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for inorganic arsenic. Tabershaw-Cooper Associates, Inc. developed the basic information for consideration by NIOSH staff and consultants under contract No HSM-99-72-127. Bryan D. Hardin had NIOSH program responsibility and served as criteria manager.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN
OCCUPATIONAL EXPOSURE STANDARD FOR INORGANIC ARSENIC

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I. RECOMMENDATIONS FOR AN INORGANIC ARSENIC STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to arsenic and its inorganic compounds, with the exception of arsine and lead arsenate, be controlled by requiring compliance with the following sections. The standard is designed to protect the health and safety of workers for a 40-hour week over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of exposure to inorganic arsenic in the workplace air and by skin exposure. The standard is measurable by techniques that are valid, reproducible, and available. Sufficient technology exists to permit compliance with the recommended standard. The standard will be subject to review and will be revised as necessary.

"Arsenic" is defined as elemental arsenic and all of its inorganic compounds except arsine and lead arsenate. "Exposure to arsenic" is defined as exposure above 0.01 mg As/cu m.

Section 1 - Environmental (Workplace air)

(a) Concentration: Occupational exposure shall be controlled so that no worker is exposed to a concentration of arsenic greater than 0.05 mg As/cu m of air determined as a time-weighted average (TWA) exposure for up to a 10-hour work day, 40-hour work week.

(b) Sampling and Analysis: Procedures for sampling, calibration of equipment, and analysis of arsenic samples shall be as provided in Appendices I and II, or by any method shown to be equivalent in precision, accuracy, and sensitivity to the methods specified.

Section 2 - Medical

Medical surveillance shall be made available as specified below for all workers occupationally exposed to arsenic.

(a) Replacement and annual medical examinations shall include:

(1) Comprehensive or interim work history.

(2) Comprehensive or interim medical history.

(3) 14" x 17" posterior-anterior chest X-ray.

(4) Careful examination of the skin for the presence of hyperpigmentation, keratoses, or other chronic skin lesions. Skin examinations shall be repeated bimonthly. Care shall be taken to observe and record the location, condition, appearance, size, and any changes in all such lesions.

(5) An evaluation of the advisability of the worker's using negative- or positive-pressure respirators.

(b) Proper medical management shall be provided for workers exposed to arsenic.

(c) Initial annual examinations for presently employed workers shall be offered within 6 months of the promulgation of a standard incorporating these recommendations.

(d) The medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, and of the employer shall have access to all medical records. Physicians designated and authorized by any employee or former employee shall have access to that worker's medical records.

(e) Medical records shall be maintained for persons employed one or more years in work involving exposure to arsenic. X-rays for the 5 years preceding termination of employment and all medical records with pertinent supporting documents shall be maintained at least 20 years after the individual's employment is terminated.

Section 3 - Labeling (Posting)

(a) Containers of arsenic compounds shall bear the following label in addition to or in combination with labels required by other statutes, regulations, or ordinances.

NAME OF COMPOUND

DANGER! CONTAINS ARSENIC

HARMFUL IF INHALED OR SWALLOWED

AVOID CONTACT WITH SKIN, EYES, AND CLOTHING

WASH THOROUGHLY AFTER HANDLING

Avoid breathing dust or spray mist

Keep container closed

Use only with adequate ventilation

(b) The following warning sign shall be affixed in a readily visible location at or near entrances to areas in which there is occupational exposure to arsenic. This sign shall be printed both in English and in the predominant primary language of non-English-speaking workers, if any.

ARSENIC

DANGER!

High concentrations of dust or spray mist
may be hazardous to health.
Provide adequate ventilation.

Section 4 - Personal Protective Equipment and Work Clothing

Subsection (a) shall apply whenever a variance from the standard recommended in Section 1 is granted under provisions of the Occupational Safety and Health Act, or in the interim period during the application for a variance. Until the arsenic exposure limit prescribed in Section 1 is met, an employer must establish and enforce, as provided in subsection (a) of this Section, a respiratory protection program to effect the required protection of every worker exposed.

(a) Respiratory Protection: Engineering controls shall be used to maintain arsenic concentrations at or below the prescribed limit. Appropriate respirators shall be provided and used when a variance has been granted to allow respirators as a means of control of exposure in routine operations and while the application for variance is pending. Administrative controls can also be used to reduce exposure. Respirators shall also be provided and used for nonroutine operations (occasional brief concentrations above the time-weighted average or for emergencies). For these instances a variance is not required, but the requirements set forth below continue to apply. Appropriate respirators as described in Table I-1 shall only be used pursuant to the following requirements:

Table I-1

Multiples of TWA Limit
for up to 10-hour day

Respirator Type

| | |
|-----------------------|--|
| less than 10x | (1) Half-mask respirator with replaceable dust or fume filter(s) (2) Type C demand type (negative pressure) supplied air respirator with half-mask facepiece |
| less than 100x | (1) Full facepiece respirator with replaceable dust or fume filter(s) (2) Type C demand type (negative pressure) supplied air respirator with full facepiece |
| less than 200x | Powered air-purifying (positive pressure) respirator with high efficiency filter |
| less than 1000x | Type C continuous flow (positive pressure) supplied air respirator |
| greater than 1000x | (1) Combination supplied air respirator, pressure-demand type, with auxiliary self-contained air supply. (2) Self-contained breathing apparatus with positive pressure in facepiece |

(1) For the purpose of determining the type of respirator to be used, the employer shall measure the atmospheric concentration of arsenic in the workplace when the initial application for variance is made and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the arsenic concentration; this requirement shall not apply when only atmosphere-supplying positive pressure respirators are used. The employer shall ensure that no worker is being exposed to arsenic in excess of the standard because of improper respirator selection, fit, use, or maintenance.

(2) Filters used shall be of the appropriate class, determined on the basis of exposure to arsenic dust or fume. If exposure is to gases and vapors in addition to arsenic dust or fume, appropriate respirators shall be selected and used for protection against these agents, also.

(3) A respiratory protective program meeting the general requirements outlined in section 3.5 (Minimal Acceptable Program) of American National Standard Practices for Respiratory Protection Z88.2-1969 shall be established and enforced by the employer. In addition, Sections 3.6 (Program Administration), 3.7 (Medical Limitations), and 3.8 (Approval) shall be enforced.

(4) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided.

(5) Respiratory protective devices described in Table I-1 shall be those approved under the provisions of 30 CFR 11, published in the Federal Register March 25, 1972.

(6) Respirators specified for use in higher concentrations of arsenic may be used in atmospheres of lower concentrations.

(7) The employer shall ensure that respirators are adequately cleaned, and that employees are instructed on the use of respirators assigned to them and on testing for leakage.

(b) Protective Clothing:

(1) Where needed to prevent contact dermatitis from arsenic compounds, protective clothing shall be provided by the employer. This may include underwear, gloves, coveralls, dust-proof goggles, and a hood over the head and neck. When liquids are being processed in a manner that may result in splashes, impervious gloves, aprons, and splash goggles shall be used.

(2) Protective clothing shall be changed at least daily at the end of the shift.

(3) Work clothing shall not be taken home by employees. The employer shall provide for maintenance and laundering of protective clothing.

(4) The employer shall ensure that precautions necessary to protect laundry personnel are observed when soiled protective clothing is laundered.

Section 5 - Informing Employees of Hazards from Inorganic Arsenic

At the beginning of employment in an arsenic area, employees exposed to arsenic compounds shall be informed of all hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and

precautions for safe use or exposure. Instruction shall include, as a minimum, all information in Appendix IV which is applicable to the specific arsenic containing product or material to which there is exposure. The information shall be posted in the work area and kept on file and readily accessible to the worker at all places of employment where arsenic is involved in unit processes and operations.

A continuing educational program shall be instituted to ensure that all workers have current knowledge of job hazards, proper maintenance procedures and cleanup methods, and that they know how to correctly use respiratory protective equipment and protective clothing.

Information as required shall be recorded on US Department of Labor Form OSHA-20 "Material Safety Data Sheet" or a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Arsenic shall be removed from work areas by vacuum cleaning or wet methods. Cleaning may be performed by washing down with a hose, provided that a fine spray of water has first been laid down. Sweeping or other methods which can stir the dust into the air shall not be used.

(b) Waste material shall be disposed of in a manner which will prevent exposure of humans and animals as well as air and water pollution.

(c) Arsenic trichloride shall be handled only in enclosed systems sufficient to prevent skin contact and to prevent worker exposure in excess of the environmental standard.

(d) Where there is possibility of arsenic trichloride contact with the skin, emergency showers shall be provided in readily accessible locations. Eye-wash facilities shall also be conveniently located.

(e) Procedures for emergencies, including fire fighting, shall be established to meet foreseeable events. Necessary emergency equipment, including appropriate respiratory protective devices, shall be kept in readily accessible locations. Only self-contained breathing apparatus with positive pressure in the facepiece shall be used for fire fighting. Appropriate respirators should also be available for use during evacuation.

(f) Exhaust ventilation and enclosure of processes shall be used wherever practicable to control workplace concentrations.

(g) Air from the exhaust ventilation system shall not be recirculated into work areas, and necessary measures shall be taken to ensure that discharge outdoors will not produce a health hazard to humans or animals.

(h) Due to potential skin irritation associated with respirator use and arsenic dust exposure, workmen shall be permitted to leave the work area every two hours to wash their face and obtain a clean respirator.

Section 7 - Sanitation Practices

(a) Employees exposed to arsenic shall be provided with separate lockers or other storage facilities for street clothes and for work clothes.

(b) Employees exposed to arsenic shall not wear work clothing away from the plant.

(c) Facilities for shower baths shall be provided for employees exposed to arsenic. Workers shall bathe before changing into street clothes.

(d) Employees exposed to arsenic shall wash before eating or smoking during the work shift.

(e) No food shall be permitted in areas where arsenic is handled, processed, or stored.

(f) Employees shall not smoke in areas where arsenic is handled, processed, or stored.

Section 8 - Monitoring and Recordkeeping Requirements

Workroom areas shall not be considered to have arsenic exposure if environmental levels, as determined on the basis of an industrial hygiene survey or by the judgment of a compliance officer, do not exceed 0.01 mg As/cu m. Records of these surveys, including the basis for concluding that air levels are below 0.01 mg As/cu m, shall be maintained until a new survey is conducted. Surveys shall be repeated when any process change indicates a need for reevaluation or at the discretion of the compliance officer. Requirements set forth below apply to areas in which there is arsenic exposure.

Employers shall maintain records of environmental exposures to arsenic based upon the following sampling and recording schedules:

(a) In all monitoring, samples representative of the exposure in the breathing zone of employees shall be collected. An adequate number of samples shall be collected to permit construction of a time-weighted

average (TWA) exposure for every operation or process. The minimum number of representative TWA determinations for an operation or process shall be based on the number of workers exposed as provided in Table I-2.

(b) The first environmental sampling shall be completed within 6 months of the promulgation of a standard incorporating these recommendations.

(c) Environmental samples shall be taken within 30 days after installation of a new process or process changes.

TABLE I-2

| <u>Number of Employees Exposed</u> | <u>Number of TWA Determinations</u> |
|------------------------------------|--|
| 1-20 | 50% of the number of workers |
| 21-100 | 10 TWAs plus 25% of the excess over 20 workers |
| over 100 | 30 TWAs plus 5% of the excess over 100 workers |

(d) Samples shall be collected at least bimonthly (every 60 days) in accordance with Appendix I for the evaluation of the work environment with respect to the recommended standard.

(e) Environmental monitoring of an operation or process shall be repeated at 15-day intervals when the arsenic concentration has been found to exceed the recommended environmental standard. In such cases, suitable controls shall be initiated and monitoring shall continue at 15-day intervals until two consecutive surveys indicate the adequacy of these controls.

(f) Records of all sampling and of medical examinations shall be maintained for at least 20 years after the individual's employment is terminated. Records shall indicate the type of personal protective devices, if any, in use at the time of sampling. Records shall be maintained so that they can be classified by employee. Each employee shall be able to obtain information on his own environmental exposure.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to arsenic and its inorganic compounds other than arsine and lead arsenate. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents.

These criteria for a standard for arsenic and its inorganic compounds other than arsine and lead arsenate are in a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of arsenical products as applicable under the Occupational Safety and Health Act of 1970. Arsine (AsH_3) is not included in this standard since its toxicity is markedly different, as are the nature and occurrence of occupational exposures to it and the types of control measures required. Including lead arsenate in this standard would, in effect, increase the allowable concentration since the current Federal

standard of 0.15 mg $Pb_3(AsO_4)_2$ /cu m is approximately equivalent to 0.026 mg As/cu m. Furthermore, this compound poses the double threat of lead poisoning as well as arsenic intoxication and is therefore best considered separately.

The standard was not designed for the population-at-large, and any extrapolation beyond general occupational exposures is not warranted. It is intended to (1) protect against injury from inorganic arsenicals, (2) be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (3) be attainable with existing technology.

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 three and five, 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, As_2O_3) 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 XI-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 to 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 XI-2. [9] NIOSH estimates that 1,500,000 workers are potentially exposed to inorganic arsenic.

Historical Reports

According to Vallee et al, [6] Dr. J. Ayrton 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 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 (Mee's lines) were first described in 1919 [18] as resulting from the ingestion of a large quantity of arsenic, and were reported to appear approximately two months after ingestion. Dinman [19] considered Mee's 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 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 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 reported [20] that, in the opinion of the analyst making these estimations, the higher liver content five 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 one 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, kidney, 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 more or less rapidly.

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 to 0.456 mg As/cu m) with 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 to 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 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. 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 $\mu\text{g As/g}$ wet weight were: fish and seafood, 4.64; meats, 0.49; vegetables and grains, 0.41. The highest arsenic levels found were 15.3 $\mu\text{g As/g}$ in shrimp shells and 8.86 $\mu\text{g As/g}$ in kingfish. Other high levels were 2.71 in table salt, 1.6 in puffed rice, 1.4 and 1.07 in two 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 $\mu\text{g As/g}$ wet weight. Arsenic was found in the urine of 2 humans in concentrations of 0.14 and 0.10 $\mu\text{g As/g}$ 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 $\mu\text{g As/g}$ of hair in an 80-year-old, with a mean of 0.536 $\mu\text{g As/g}$. 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 three highest levels reported were 2.0, 1.1, and 0.42 mg As/liter, and were attributed to probable consumption of seafood. The two highest average urinary excretions by individuals were 0.22 and 0.12 mg As/liter.

These authors considered [4] seafood to be the main source of dietary arsenic. Shellfish in particular elevated the arsenic of test subjects. In one test, three 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 fourth 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 an attack 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 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 to 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 macular-papular 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 pigmentation, and in 3 cases there was hyperkeratosis of the palms and soles. However, in 2 cases neither hyperpigmentation nor hyperkeratoses were observed. Average urinary arsenic excretion was 1.87 mg As/liter, with a range of 0.348 to 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 to 42.0 mg As/100 g of nails.

In all 6 cases anemia and leukopenia were present, with thrombocytopenia 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 one 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 four. Hematologic abnormalities disappeared within 2 to 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 to 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 mm Hg. 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 of causes such as age, arteriosclerosis, or 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 prolongation 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 serum electrolytes, serum chemistries, neurologic or respiratory systems were present. In one case, 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 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 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 to 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 one the patients exhibited multiple keratoses of the palms and soles. In the one 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 two 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 new employees, continue work since this often resulted in hyposensitivity. 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 one 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 to 12 hours a day away from the community did not have dermatitis. Nine of eighteen 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 "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 Fanning. [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 four 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 four groups. The average arsenic excretion was 0.24, 0.10, 0.11, and 0.09 mg As/liter of urine, and 108, 85, 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 three 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 from 1 to 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 is 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.

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 to 1949, 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 [86] and 1945, [87] 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 two 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 Plant 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 three 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, liver sarcomas 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 one-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 to 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 one 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 two 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 to 0.4 miles, and 0.02 ppm at a distance of 2.0 to 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 to 0.4 miles to 70 ppm at a distance of 2.0 to 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. Neverthe-

less, the authors stated that the mortality figures "truly represent the 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 cardiovascular 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 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 two groups, increases in cardiovascular and cancer mortality are unrelated to arsenic exposure. The increase in overall cancer mortality was shown to be statistically not 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 1950-1971, 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 communication, October 1973] The increased respiratory cancer mortality, 40 observed compared to 18 expected, was statistically significant (P less than 0.001).

Lee and Fraumeni [49] conducted a mortality study of 8,047 white male smelter workers exposed to arsenic trioxide during 1938 - 1963. 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 to 14 years, (4) 5 to 9 years, (5) 1 to 4 years. No specific environmental data were provided, but the smelter workers also were divided occupationally into three 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 two individuals at the Division of Occupational Health, USPHS, based on unpublished data. The data used had been collected in a 1965 survey of one US copper smelter and are presented in Table XI-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 XI-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 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 degree of arsenic or sulfur dioxide exposure.

Animal Toxicity

The acute oral toxicity of arsenic trioxide in mice and rats was tested by Harrison et al [50] using both "crude" or commercial grade (97.7% As₂O₃ with 1.18% Sb₂O₃) and highly purified arsenic trioxide (99.999% As₂O₃). 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 [51] 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 one of two concentrations. In the one 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. [51] 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 [51] 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 [52] 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 seleniferous 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 [53] 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 [54] 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 [55] 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 two arsenicals could be detected.

Using weanling Long-Evans rats, Schroeder et al [56] evaluated the effects of arsenic by feeding diets low in arsenic (0.46 $\mu\text{g As/g}$ wet weight) and administering sodium arsenite in the drinking water of experimental animals at a level of 5 $\mu\text{g As/ml}$. 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 two 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 ($\mu\text{g As/g}$ 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 [57] 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 three groups of female albino rats were exposed 24 hours a day for three 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 one 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 two highest exposure groups, and was still apparent one 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 two highest exposure groups. In the most heavily exposed animals these organs retained a high arsenic content one 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 shrivelling of neurons in the middle pyramidal tract. [57] In the bronchi of these animals there was accumulation of leukocytic exudate, 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 proposed [57] 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.

Another animal inhalation study with arsenic trioxide which in some respects more closely approaches human occupational exposure was conducted by Bencko and Symon. [58] 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. [58] 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 [59] 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 [60,61] and in mice [62] after injection of pregnant animals with sodium arsenate. A variety of effects were demonstrated, including anencephaly, renal agenesis, and rib malformations in the hamster, [61] and exencephaly, agnatha, and various skeletal defects such as fused and forked ribs in mice. [62] Holmberg et al [60] 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 [52] that sodium arsenite provided a degree of protection against selenium poisoning in rats.

Leitch and Kennaway [63] 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 [64] was unable to reproduce this result on a repetition of the experiment.

Roth reported [46] increased incidence of cancer among German vine-dressers who apparently ingested a significant amount of arsenic in contaminated wine. Using 4 groups each of Bethesda black rats and C57 black mice, Hueper and Payne [65] 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 one mouse receiving pure water, there were no cancers in mice. [65] 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 one 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 [66] 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, 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 three types of effect.

Osswald and Goerttler [67] 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. Injections of a 0.005% aqueous solution of the "sodium salt" (the valence of the arsenic was not specified) were given 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). 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. Among 35 male and 20 female controls, 3 of 20 deaths among the males and none of 16 deaths among the females were due to leukemia.

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 the study [40] of the 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 one 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 mg As/cu m 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.

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 to 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.

A study of a larger smelter population was reported 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 XI-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. 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.

The animal study with the most direct bearing on an occupational exposure standard is that by Rozenshtein [57] in which rats were exposed 24 hours a day to an aerosol of arsenic trioxide at concentrations of 0.06, 0.0049, and 0.0013 mg As₂O₃/cu m (approximately 0.046, 0.004, and 0.001 mg As/cu m). One difficulty with this study 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 As₂O₃/cu m (0.192, 0.016, and 0.004 mg As/cu m).

Rats exposed to the highest concentration of arsenic trioxide suffered damage to the central nervous system, a disturbed chronaxial ratio of antagonistic muscles, and fatty degeneration of the liver. Similar but less severe effects were observed in the intermediate exposure group, but no ill effects were seen in the lowest. Thus, the threshold apparently was between the two lower exposure levels which, with the assumptions stated, would have been approximately equivalent to 0.004 and 0.016 mg As/cu m on a 40-hour week basis.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analytical Methods

No direct reading instruments are available for determining arsenic in the field. The dusts and fumes of inorganic arsenic compounds can be collected by standard filtration including tape sampler, electrostatic precipitation, or impingement methods.

Several procedures have been developed for analysis of arsenic in air. Dubois and Monkman [68] compared three widely used methods on samples from a variety of sources. The methods tested were Gutzeit, silver diethyldithiocarbamate, and iodine microtitration. They concluded that the silver diethyldithiocarbamate method was superior to the others, and recommended it because of its sensitivity, accuracy, and suitability over a wide range of concentrations. The American Conference of Governmental Industrial Hygienists evaluated this method [69] by comparing test results obtained by eight cooperating laboratories. It was found [69,70] sensitive enough to detect, in a 10 cu m air sample, 0.1 $\mu\text{g As/cu m}$ or a maximum of 1.5 $\mu\text{g As/cu m}$. Thus, sampling times and flow rates must be adjusted to collect from 1.0 to 15.0 $\mu\text{g As}$ in the sample. Arsenic is reduced to the trivalent state and converted to arsine in a Gutzeit generator. The arsine is passed through a scrubber into an absorber containing silver diethyldithiocarbamate in pyridine. The resulting red color is measured photometrically. [69,70]

Engineering Controls

Significant exposures are encountered both in the production of arsenic compounds and in their use, and good industrial hygiene practices must be followed to prevent adverse health effects. Where fumes may be present, as in the sintering and roasting of arsenic-bearing ores, complete enclosure and exhaust ventilation of the operation is essential. [71] Operations that agitate arsenic trioxide dust, eg grinding, screening, shoveling, sweeping, and transferring, require control since the dust is very fine and disperses easily. [5] When the operation has not been sufficiently enclosed and ventilated, supplemental protective clothing and respiratory protection may be needed until adequate engineering controls are installed.

Arsenic trichloride can cause irritation or ulceration on contact or may be absorbed through the skin with fatal results. [20,21] Since its vapor pressure at 25 C is sufficient to produce an air concentration of 14,000 ppm (104,000 mg/cu m), [71] its handling requires complete enclosure.

Agricultural uses of arsenic compounds may produce potentially hazardous exposures for nearby personnel. Engineering control methods used will depend on the equipment and techniques used to apply the chemicals. Protective clothing and respiratory protection may be needed as supplemental controls.

Biologic Evaluation

Arsenic absorbed into the human body is excreted in the urine, feces, skin, hair, and nails, and possibly a trace from the lungs. [3,5,6,26] Even at low doses, a proportion of absorbed arsenic is deposited in the skin, hair, and nails where it is firmly bound to keratin. [6] Storage in these metabolically "dead" tissues represents a slow route of elimination from the body.

Arsenic in hair has been used to monitor workers' exposure, [22,41] but the significance of arsenic in hair is obscured by the difficulty of distinguishing externally deposited arsenic from that systemically deposited in the hair. Camp and Gant [72] reported that "there is no way to differentiate 'interior' and 'exterior' arsenic." Similarly, Watrous and McCaughey [22] reported that once arsenic was deposited on the hair, it resisted washing with ether and water, and they considered determinations of arsenic in hair to be completely unreliable. The level of arsenic in fingernail and toenail parings reflects past absorption and is therefore useful forensically, but is less useful if the goal is to monitor current absorption.

Most authors agree that the urine is a major route of arsenic excretion. [3,6,24] Arsenic can be detected in the urine of people with no known exposure to arsenic, apparently derived from dietary and general environmental sources. [2,4] However, the urine of workers occupationally exposed to arsenic may show much higher levels than that of the unexposed, even in the absence of signs of systemic arsenic poisoning. [4,39,22]

Webster [23] collected urine samples from 26 adults and 17 children and reported that the average arsenic content was 0.014 mg As/liter with an average specific gravity of 1.017. Corrected to a specific gravity of 1.024, Webster's average was 0.02 mg As/liter.

Schrenk and Schreibeis [4] collected 756 urine specimens from 29 persons with no known industrial exposure to or abnormal dietary uptake of arsenic. The overall average urinary excretion was 0.08 mg As/liter, and 79% of the samples were less than 0.1 mg As/liter. After the authors found that seafood could affect urinary arsenic levels, they excluded values when it was known that the subject had eaten seafood. However, some values, which apparently had been influenced by seafood, were included before seafood was recognized as a factor. Since no record of diet had been kept, these unusually high values could not be excluded (the three highest samples were 2.0, 1.1, and 0.42 mg As/liter).

Seafood was considered [4] to be the main source of dietary arsenic. Shellfish in particular elevated the arsenic of test subjects. In one test, three subjects with pretest levels of 0.01, 0.03, and 0.05 mg As/liter were given lobster tail for lunch. Four hours after eating, urinary levels were 1.68, 0.78, and 1.40 mg As/liter, respectively. Ten hours after eating, levels were 1.02, 1.32, and 1.19 mg As/liter. After 24 hours values were 0.39, 0.39, and 0.44 mg As/liter, and at 48 hours, values were approaching the pretest levels.

Rapid initial excretion of inhaled arsenic was reported by Holland et al, [24] with 28% of the absorbed As-74 being excreted in the urine within the first day after it was inhaled, and 45% within 10 days. An

additional 2.5% had been excreted in the feces after 10 days, but the remaining 52.5% was not accounted for.

Pinto and McGill analyzed [39] the urine of 348 men (845 spot samples) occupationally exposed to arsenic trioxide and reported a mean level of 0.82 mg As/liter. The median value was 0.58 mg As/liter, and 27.3% of the samples exceeded 1.0 mg As/liter. One hundred forty-seven urine samples from 124 active smelter employees considered to have no arsenic exposure averaged 0.13 mg As/liter. The three highest values were 0.53, 0.70, and 2.06 mg As/liter, but 88% of the samples were below 0.2 mg As/liter. Although it was stated that among the exposed workers there was only one dubious case of mild systemic arsenic poisoning, there were several cases (at least 17) of acute arsenical dermatitis. Over a 6-day period, sixteen of these had average urine arsenic levels, during or following British Anti-Lewisite (BAL) therapy, ranging from 0.30 to 0.93 mg As/liter. One individual with severe facial dermatitis of rapid onset received BAL every six hours for four days, but excreted an average of only 0.2 mg As/liter. It was surmised that this man was hypersensitive or allergic to arsenic. One individual who declined BAL therapy had urinary arsenic levels ranging from 3.15 to 5.76 mg As/liter over a two-day period. According to these authors, [39] individuals may show urinary arsenic levels in spot samples as high as 4 or 5 mg As/liter, without any evidence of systemic arsenic poisoning.

In the English sheep-dip factory, [41] urinary arsenic levels were determined for workers exposed to mixed arsenic trioxide and sodium arsenite dusts, and for unexposed controls. The urinalyses of exposed

personnel were repeated after an interval of six months. The mean urinary arsenic level for 54 controls was 0.085 mg As/liter, and in 58 determinations made on chemical workers (the most heavily exposed group), the mean was 0.231 mg As/liter (computed from the data given in Tables 6 and 7 by Perry et al [41]). The 3 highest levels recorded in the exposed group were equivalent to 0.73, 1.01, and 1.91 mg As/liter. Most of the chemical workers (28 of 31) had evidence, in the form of pigmentation and warts, of past systemic arsenicalism. Air samples were collected at a number of locations where chemical workers apparently were employed, and the mean arsenic concentration in these areas can be computed from data in Table 3 [41] as 0.562 mg As/cu m.

Thus, urinary arsenic levels of people with no known arsenic exposure have been reported as 0.014 (0.020 corrected to a specific gravity of 1.024), [23] 0.08, [4] 0.085, [41] 0.129, [22] and 0.13 mg As/liter. [39] Some of the unexposed individuals tested had urinary levels as high as 2.0 mg As/liter, [4,39] but these high levels may have been due to unusual dietary intake [4] or to unrecognized arsenic exposure. [39]

The urinary arsenic levels of exposed workers vary widely and levels above 4.0 mg As/liter have been reported [39] without apparent adverse effects. On the other hand, signs of mild systemic poisoning have been reported [22] in a worker excreting only 0.76 mg As/liter. This wide variability in urinary arsenic levels, even in an apparently unexposed population, combined with inability to demonstrate a definite association between urinary levels and either observed effects or atmospheric concentrations makes interpretation of urinary data difficult.

Nevertheless, a biological threshold limit value of 1.0 mg As/liter of urine was proposed by Elkins. [73] This was considered to be roughly consistent with a time-weighted average air level of 0.5 mg As/cu m. [74]

Of all the papers discussed in this document, only Webster [23] reported the specific gravity of the sample tested. Elkins, [73,74] Elkins and Pagnotto, [75] Buchwald, [76] and Levine and Fahy [77] all point out the importance of correcting to a mean specific gravity in order to obtain meaningful and consistent results. Testing persons in the United Kingdom, Buchwald [76] reported the mean specific gravity was 1.016. However, in the United States, Elkins, [73,74] and Elkins and Pagnotto [75] recommend 1.024. This was based on the findings of Levine and Fahy, [77] who in 1945 reported 1.024 as the mean specific gravity of nearly 1,200 urine samples. According to Elkins and Pagnotto, [75] their laboratory has analyzed 1,000 to 2,000 urine samples annually since the Levine and Fahy report, and 1.024 is still the mean specific gravity used. However, care must be exercised when making specific gravity corrections to express the specific gravity of the urine in relation to that of water at the same temperature. If a urinometer calibrated against water at 4 C is used, then a correction for temperature should also be employed. [75,77]

Citing urinary levels reported by Pinto and McGill [39] for exposed workers with no signs of poisoning, Schrenk and Schreibeis [4] concluded that, while no relationship could be shown between urinary arsenic levels and evidence of poisoning, "urinary arsenic levels in a group of exposed persons may serve to check the efficacy of control measures and indicate if excessive absorption of arsenic occurs." Referring to the inconsistency

with which the workers wore their respirators, Pinto and Bennett [48] wrote: "It is for this reason we depend on the urinary arsenic level as showing the men are exposed to arsenic-containing dusts. The simple measurement of arsenic dust in the air is not a good measure of how much arsenic has been absorbed by an individual."

Monitoring urinary arsenic cannot replace monitoring atmospheric concentrations as the primary method of characterizing the workers' exposure. It seems reasonable that group averages may be useful as a check on the adequacy of the overall program of engineering controls and work practices designed to protect the workers' health.

V. DEVELOPMENT OF THE STANDARD

Basis for Previous Standards

The American Standards Association (now the American National Standards Institute) in 1943 proposed 0.015 mg As/cu m as an American War Standard for inorganic arsenic. [78] However, the summary of standards compiled by Cook [79] shows that by 1945 the War Standard had been increased by a factor of 10 to 0.15 mg As/cu m, set on the basis of analogy with other metals such as cadmium and lead. The 0.15 mg As/cu m standard was also adopted by Connecticut, Massachusetts, New York, and Oregon, but Utah endorsed a Maximum Acceptable Concentration (MAC) of 0.5 mg/cu m. [79] In his discussion of the 0.15 mg As/cu m standard, Cook stated that "On the basis of long experience [undescribed] involving many occupational exposures, at least one large concern considers it permissible to increase the limit to 5. mg. per cubic meter."

In 1947 the American Conference of Governmental Industrial Hygienists (ACGIH) adopted an MAC for arsenic of 0.1 mg/cu m, [80] but the following year this was raised to a Threshold Limit Value (TLV) of 0.5 mg As/cu m. [81] The ACGIH gave no explanation for the change, but Pinto, commenting in a July 1972 written communication to ANSI on the 0.5 mg As/cu m standard, stated that arsenic trioxide was considered to be the primary arsenic compound to which there was industrial exposure, and the 0.5 mg As/cu m level was suggested as a safe concentration of arsenic trioxide, with "safe concentration" meaning that "it would not cause incapacitating dermatitis in a few hours." Whether the change from an MAC to a TLV constituted a change from a ceiling of 0.1 mg/cu m to a time-weighted

average of 0.5 mg/cu m is not clear. If that was the case and one applies the excursion factor of 3 presently recommended by the ACGIH [82] for TLVs in the 0.0 to 1.0 mg/cu m range, this change constituted a 15-fold increase. The present TLV recommended by the ACGIH is 0.5 mg As/cu m for "arsenic and compounds." [82]

In his 1959 textbook, Elkins [73] recommended a maximum allowable concentration of 0.25 mg/cu m for arsenic trioxide, equivalent to 0.19 mg As/cu m. There was little discussion given of safe exposure levels, but the Watrous and McCaughey [22] report of concentrations averaging almost 0.2 mg As₂O₃/cu m in the manufacturing department of a pharmaceutical plant apparently was a major consideration.

Separate TLVs for lead arsenate and calcium arsenate have been recommended by the ACGIH for a number of years. A limit of 0.15 mg/cu m for lead arsenate (equivalent to 0.026 mg As/cu m) was adopted tentatively in 1956, [83] confirmed in 1957, [84] and has remained unchanged since. [82] According to the ACGIH Documentation, [85] this compound was considered to present the double hazard of both lead and arsenic intoxication. The chronic toxicity was attributed to the lead content and the acute toxicity to the arsenic, although it was considered less acutely toxic than calcium arsenate. [85]

A limit of 0.1 mg/cu m (equivalent to 0.038 mg As/cu m) for calcium arsenate was originally recommended by the ACGIH in 1956, [83] and was adopted in 1957. [84] In his review of standards, Smyth [86] attributed the toxicity of calcium arsenate to the arsenic content. Considering it to be 20% arsenic, he recommended a standard of 2.5 mg/cu m to be consistent

with the ACGIH recommended standard of 0.5 mg As/cu m for "arsenic and compounds." The ACGIH documentation [85] cited Smyth [86] as attributing the toxicity to the arsenic content, but the TLV recommended for calcium arsenate was 1.0 mg/cu m (equivalent to 0.38 mg As/cu m). This discrepancy was not explained.

The Czechoslovak MAC Committee suggested a "mean MAC" of 0.3 and a "peak MAC" of 0.5 mg As/cu m. [87] The documentation did not give reasons for the levels chosen, but did state the following MACs for other countries: Great Britain, the United States, West Germany, and Yugoslavia, 0.5 mg As/cu m; East Germany, Hungary, and the USSR, 0.3 mg As/cu m; and Poland, 0.15 mg As/cu m. It was not stated whether these MACs were ceilings or time-weighted averages.

The present Federal standard for "arsenic and compounds" is 0.5 mg As/cu m as a time-weighted average. There are separate standards, both determined as a time-weighted average, for calcium arsenate (1.0 mg $\text{Ca}_3(\text{AsO}_4)_2/\text{cu m}$) and for lead arsenate (0.15 mg $\text{Pb}_3(\text{AsO}_4)_2/\text{cu m}$). [29 CFR 1910.93, published in the Federal Register, vol 37, dated October 18, 1972] These standards were based on the ACGIH recommendations.

Basis for Recommended Environmental Standard

A number of signs and symptoms are associated with arsenic poisoning. When ingested, arsenic compounds can cause nausea, vomiting, and diarrhea within a few hours, [25,27] although in at least one animal study [50] with arsenic trioxide, much of the gastrointestinal irritation was attributed to impurities. Dermatitis may be observed [25] after

chronic ingestion, but the typical signs of chronic arsenicalism are hyperpigmentation and hyperkeratosis, especially on the palmar and plantar surfaces, [25,27,33] and peripheral neuropathy [25,27] in a glove and stocking distribution with prickly sensations [25,29] and loss of distal proprioception and deep tendon reflexes. [25] Changes in the ECG have been reported after both acute [31,32] and chronic [29,32] intoxication, although in at least one report [25] of severe chronic arsenicalism, the patient's ECG was normal. ECG changes that were observed [29,31,32] regressed after arsenic exposure ceased. Anemia and leucopenia were reported [27] in cases of chronic intoxication, but these changes also regressed after arsenic ingestion ended. Effects on the liver include cirrhosis after prolonged use of Fowler's solution, [33] and, in animal studies, marked enlargement of the bile duct [55] and fatty degeneration of the liver. [57] Skin cancer has long been considered [10] a consequence of arsenic exposure, but multiple cancers of the viscera have also been reported. [36] However, the association too often was made because a cancer patient exhibited hyperpigmentation and hyperkeratoses. On this basis, cases were included both in Neubauer's review [10] in which 147 cases were collected and in the cases reported by Sommers and McManus [36] despite the fact that in some cases there was no known arsenic exposure.

No reports were found of occupational exposure to arsenic compounds resulting in nausea, vomiting, diarrhea, or peripheral neuropathy. Occupational exposures have been reported to cause hyperpigmentation, [28,41] palmar and plantar hyperkeratoses, [28] warts, [28] contact dermatitis and sensitization, [37-39] ulceration and perforation of the nasal septum,

[38,39] and conjunctivitis. [39] Reversible ECG changes [30] and severely reduced peripheral circulation resulting in gangrene of the fingers and toes [28] have been reported. Cirrhosis of the liver has been observed, [28,46] and one epidemiological study [49] reported significantly increased mortality due both to cirrhosis of the liver and to cardiovascular disease. Two studies reported that cancer [42,48] and cardiovascular [48] mortality were not significantly increased in workers exposed to arsenic, but the mortality experience of workers in the same plant studied by one of these [48] was examined again [47] in 1973 and significantly increased lung cancer mortality was reported. Other studies have reported cancer of the skin, [40,46] lung, [40,46,49] and other organs. [46] In general, attempts to produce cancer experimentally in animals have failed, [55,56,65,66] but leukemia reportedly [67] has been induced experimentally and teratogenic effects have been observed in animals. [60-62]

Atmospheric data were not included in the studies reporting dermatitis, [37-39] ulceration and perforation of the nasal septum, [38,39] conjunctivitis, [39] ECG changes, [30] disturbed peripheral circulation, [28] or cirrhosis of the liver. [28,46] The question of air levels was approached only by Pinto and McGill, [39] who considered dust-in-air measurements to be of limited value for predicting skin reactions.

ECG changes reported after nonoccupational [29,31,32] and occupational [30] exposure to arsenic have apparently been reversible. One epidemiological study [48] of a copper smelter reported that observed deaths due to cardiovascular disease exceeded the expected, but the difference was not statistically significant. Another study [49] of a smelter population

found that, compared to statistics for the state in which the smelter was located, mortality due to heart disease was significantly increased. In terms of length of employment, cardiovascular mortality was significantly increased in 4 of 5 cohorts, and the excess mortality was approximately the same in each of these 4 cohorts. In both smelter studies, [48,49] exposures were to many compounds other than arsenic. However, the fact remains that arsenic apparently caused at least temporary ECG changes [29-32] and may have caused increased cardiovascular mortality. [48,49]

Cirrhosis of the liver has been reported as a result of prolonged use of Fowler's solution [33] and among German vineyard workers. [28,46] In the latter studies, ethyl alcohol may have been at least a contributor, since in one report [28] many of the vineyard workers were said to drink 2 liters or more of wine daily. A recent epidemiological study [49] of an American smelter population found increased mortality due to cirrhosis of the liver, but the increase apparently was not related to length of exposure. Animal studies have reported liver damage after ingestion of either sodium arsenite or arsenate [55] and after inhalation of arsenic trioxide. [57] Thus the potential for liver damage seems real, but it is not clear whether occupational exposures have actually resulted in damage, and if so, at what concentration.

Two mortality studies [42,48] of smelter populations have reported that observed cancer mortality exceeded the expected mortality but not significantly. These authors concluded that workers exposed to arsenic did not experience increased cancer mortality, but that conclusion is open to question. In the Snegireff and Lombard study, [42] the authors examined

and discussed only overall cancer mortality. However, according to a comparison made by NIOSH, respiratory cancer mortality as a proportion of total cancer deaths was 5.7 times expected in the plant at which arsenic trioxide was handled and 6.5 times expected in the comparison plant at which arsenic was not handled. Thus, both plants apparently had increased respiratory cancer mortality, although overall cancer mortality was not significantly increased.

The Pinto and Bennett study [48] was followed in 1973 by the Milhan and Strong report [47] of mortality among workers at the same plant. These authors [47] found that lung cancer mortality was significantly higher than expected. As reported by Hill and Faning, [40] the cancer mortality of chemical workers in the English sheep-dip factory was significantly increased. The small numbers involved made firm conclusions difficult, but the authors suggested that the excess could be attributed to increased lung and skin cancer mortality. Lee and Fraumeni [49] reported not only that respiratory cancer mortality was significantly increased, but also that the incidence of respiratory cancer increased with length of employment as well as with the degree of arsenic exposure.

These studies [40,47,49] strongly implicate arsenic as an occupational carcinogen. However, the relationship is obscured because, in the smelting industry, the workers were exposed to a variety of substances other than arsenic, one of which was sulfur dioxide. In the Lee and Fraumeni report, [49] lung cancer mortality increased with increasing arsenic exposure; but generally the sulfur dioxide levels increased with the arsenic levels. It was not possible to examine the mortality of a

subgroup exposed only to arsenic or only to sulfur dioxide, so a role by sulfur dioxide or some other substance cannot be ruled out in the smelting industry. However, the involvement of arsenic can hardly be denied. There was no suggestion of sulfur dioxide exposure in the sheep-dip factory, [40,41] but cancer mortality was still significantly increased. [40]

Environmental data with which to establish a safe exposure level are scant. In the English sheep-dip factory study, [40,41] increased cancer mortality was observed among chemical workers. [40] The average exposure of chemical workers can be computed as 0.562 mg As/cu m from the air concentrations reported by Perry et al [41] by assuming that all samples reported, with the exception of 6 samples from the packing room where workers apparently would be classified as packers, were collected in areas in which chemical workers were employed. Increased lung cancer mortality was reported by Lee and Fraumeni [49] in all cohorts, including the group with only 1 to 4 years of employment, and in all exposure groups, including those with light arsenic exposure. The sparse data (12 samples from three "light" exposure areas) with which to characterize these work areas range from 0.001 to 1.20 mg As/cu m with a mean and median of 0.206 and 0.01 mg As/cu m, respectively (Table XI-3). With the exception of the pharmaceutical plant study, [22] no environmental data were published in any of the other reports examined.

Even if contact dermatitis and systemic toxicity were the only bases for establishing a standard, it is evident that the existing Federal standard of 0.5 mg As/cu m is too high because, according to Pinto in a July 1972 written communication to ANSI, it was originally established to

prevent "incapacitating dermatitis in a few hours," clearly an inadequate basis from present-day considerations. However, more recent reports [40,47,49] associate inorganic arsenic with occupational cancer. The Lee and Fraumeni report [49] strongly suggests that exposure at or around 0.2 mg As/cu m [Table XI-3] can result in an increased incidence of cancer. Because of the seriousness of the disease, prudence dictates that the standard should be set at least as low as 0.05 mg As/cu m. It is believed that exposure at this level should, at the minimum, significantly reduce the incidence of arsenic-induced cancer.

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VII. APPENDIX I

AIR SAMPLING PRACTICES FOR ARSENIC

General Requirements

Air concentrations shall be determined within the worker's breathing zone and shall meet the following criteria in order to evaluate conformance with the standard:

(a) Samples collected shall be representative of the individual worker's exposure.

(b) Sampling data sheets shall include:

- (1) The date and time of sample collection
- (2) Sampling duration
- (3) Volumetric flowrate of sampling
- (4) A description of the sampling location
- (5) Other pertinent information

Breathing Zone Sampling

(a) Breathing zone samples shall be collected as near as practicable to the worker's face without interfering with his freedom of movement and shall characterize the exposure from each job or specific operation in each production area.

(b) A portable battery-operated personal sampling pump plus an unweighed 0.8 μ cellulose membrane filter (Type AA) mounted in either a 2- or 3-piece cassette shall be used to collect the sample.

(c) The sampler shall be operated at a flowrate of two liters per minute and samples taken for at least 15 minutes. A sampling time of 30 to 60 minutes is recommended.

(d) A minimum of three samples shall be taken for each operation (more samples if the concentrations are close to the standard) and averaged on a time-weighted basis.

(e) A minimum of three blank filters carried in closed cassettes to the sampling site shall be provided to the analytical laboratory to determine the background correction which must be applied to the analytical results.

Calibration of Sampling Trains

Since the accuracy of an analysis can be no greater than the accuracy of the volume of air which is measured, the accurate calibration of a sampling pump is essential to the correct interpretation of the volume indicated. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. In addition, pumps should be recalibrated if they have been subjected to misuse or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, more frequent calibration may be necessary.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a 1-liter burette or wet-test meter is recommended, although other standard calibrating instruments such as spirometer, Marriott's bottle, or dry-gas meter can be used. The actual set-up will be the same for these instruments.

Instructions for calibration with the wet-test meter follow. If another calibration device is used, equivalent procedures should be followed.

(a) The calibration device used shall be in good working condition and shall have been calibrated against a soapbubble meter, spirometer, or other primary standard upon procurement, after each repair, and at least annually.

(b) Calibration curves shall be established for each sampling pump and shall be used in adjusting the pumps prior to field use.

(c) The volumetric flowrate through the sampling system shall be spot checked and the proper adjustments made before and during each study to assure obtaining accurate airflow data.

(d) Flowmeter Calibration Test Method (see Figure XI-1)

(1) Apparatus

- (A) Wet test meter
- (B) Quick connector or by-pass valve
- (C) In-line filter holder cassette with Type AA filter
- (D) Tee
- (E) Manometer
- (F) Pump with rotameter
- (G) Rubber or vinyl tubing
- (H) Barometer
- (I) Thermometer
- (J) Stopwatch

(K) Small screwdriver

(L) Graph paper

(2) Procedures

(A) Level wet test meter. Check the water level which should just touch the calibration point at the left side of the meter. If water level is low, add water 1 to 2 F warmer than room temperature to fill point. Run the meter for 30 minutes before calibration.

(B) Check the voltage of the pump battery with a voltmeter. This test is most indicative of battery conditions when performed under full load, ie with the pump motor operating.

(C) Mount the filter to be calibrated in the in-line filter holder.

(D) Assemble the calibration train as shown in Figure XI-1. Leave the quick connector disconnected.

(E) Turn the pump on, adjusting the rotameter with a screwdriver to a reading of 10 (read middle of the float).

(F) Connect the wet test meter to the train. The pointer on the meter should run clockwise and a pressure drop of not more than 1.0 inch of water indicated. If the pressure drop is greater than 1.0 disconnect and check the system.

(G) Operate the system ten minutes before starting the calibration.

(H) Record the following on calibration data sheets:

(i) Wet test meter reading, start and finish

(ii) Elapsed time, start and finish

- (iii) Pressure drop at manometer
- (iv) Air temperature
- (v) Barometric pressure
- (vi) Serial number of pump and rotameter

(I) Adjust the rotameter reading to 9.0, 8.0, and 7.0, respectively, and repeat step (H) at each reading. For each point, the system should run for 10 minutes or sample at least 0.5 cubic foot of air.

(J) Record the name of the person performing the calibration, the date, serial number of the wet test meter, and the numbers of the pump and flowmeter system being calibrated.

(K) Corrections to the flow rate may be necessary if the pressure or temperature when samples are collected differs significantly from that when calibration was performed. Flow rates may be calculated using the following formula:

$$q(\text{actual}) = q(\text{indicated}) \cdot \sqrt{\frac{P(\text{calibrated})}{P(\text{actual})} \cdot \frac{T(\text{calibrated})}{T(\text{actual})}}$$

where q = volumetric flowrate

P = pressure

T = temperature (in degrees Kelvin or Rankine)

(L) Use graph paper to record the actual airflow as the ordinate and the rotameter readings as the abscissa.

VIII. APPENDIX II
ANALYTICAL METHOD FOR
ARSENIC IN AIR [69,70]

Treatment of Sample: The filter or precipitator sample is rinsed into a beaker with a stream of 1% sodium hydroxide solution, followed by a distilled water rinse. The volumes of both rinse liquids are kept at a minimum. The alkali is neutralized by dropwise addition of concentrated hydrochloric acid using phenolphthalein indicator. The cooled solution is transferred and made up to 50 ml in a volumetric flask. Impinger samples are made up to a 50 or 100 ml final volume as convenient. If water was used in the impinger no neutralization is required.

Analysis: Known microgram amounts of arsenic (1-15 μg) in the form of standard arsenic solution, are pipetted into 125 ml Erlenmeyer flasks. Distilled water is added to make the total volume 35 ml. To the flasks are added 5 ml hydrochloric acid, 2 ml 15% potassium iodide solution, and 8 drops of stannous chloride solution. The flasks are swirled, and allowed to stand for 15 minutes to ensure reduction of all arsenic to the trivalent form.

Three milliliters of the pyridine solution of silver diethyl-dithiocarbamate are placed in the absorbing tube, which is attached to the scrubber containing glass wool impregnated with lead acetate.

The ground joints are lubricated with stopcock grease, 3 g of granulated zinc are added to the solution in the flask, and the receiving tube is inserted immediately. Arsine evolution is completed in about 30 minutes.

At the end of this time the absorbing solution is transferred to a square 1 cm cell and the absorbance measured at 560 nanometers in a spectrophotometer. Plotting measured absorbances against micrograms of arsenic taken produces the standard curve. Care should be taken when preparing standard curves, since some arsenic can leach from new glassware and could influence a standard curve.

Air samples, after the previously described preparation treatment, are treated in the same manner as the standards. Depending upon the operator's knowledge of the sampling conditions, a sample or aliquot of a sample representing from 1.0 to 15.0 μg of arsenic should be taken for analysis. From previous experience with known amounts of arsenic the operator can decide from the color of the absorbing solution whether the sample aliquot taken will be within the range of the calibration curve. If necessary, the prepared sample may be diluted, or the volume of the absorbing solution may be varied to adjust the color intensity to the scale of the standard curve.

Chemical Reaction: Arsenic, in the form of arsine, displaces an equivalent amount of silver from silver diethyldithiocarbamate in pyridine solution.

Calculations: If a 25 ml aliquot of a 50 ml prepared sample is taken for analysis, and 3 ml of absorbing solution are used, the arsenic concentration in milligrams per cubic meter is:

$$\frac{2 \text{ X micrograms arsenic from curve}}{1000 \text{ X volume of air sampled in cubic meters}}$$

Range and Sensitivity: If suitable samples (10 cu m of air) are available, concentrations as low as 0.1 $\mu\text{g As/cu m}$ can be measured. The maximum measureable concentration with a comparable sample is 1.5 $\mu\text{g As/cu m}$. Higher concentrations can be measured if smaller samples are used.

Precision and Accuracy: Samples containing 0.1, 1.0, 5.0, and 10.0 $\mu\text{g As}$ were analyzed [70] with an accuracy of $\pm 0.04 \mu\text{g}$ based on 7 replicate determinations at each concentration. Four samples containing arsenic were analyzed [70] by eight laboratories and the percent average deviation from the arsenic actually present was calculated:

| Sample | Arsenic present $\mu\text{g As/ml}$ | Percent average deviation |
|--------|--|------------------------------|
| 1 | 0.05 | 9.1 |
| 2 | 0.50 | 3.5 |
| 3* | 1.00 | 6.1 |
| 4 | 1.50 | 4.0 |

*Contained 0.5 $\mu\text{g Sb/ml}$

Interferences: The only substances likely to interfere with the test are hydrogen sulfide, which is normally removed by the lead acetate glass wool plug, and stibine. Sample 3 above [70] contained 0.5 $\mu\text{g Sb/ml}$ in addition to the arsenic present. The results indicate that stibine, due to antimony present in the sample, does not interfere in the amount present.

Special Equipment: The equipment illustrated in Figure XI-2 has been found convenient, easy to construct and clean, and suitable for mass

production of results. It is available commercially or may be built. Other arrangements of glassware have been used with success, such as a standard borosilicate glass Gutzeit generator connected to a glass delivery tip extending into absorbing solution contained in a Kahn tube. A spectrophotometer, with or without photomultiplier, or any good colorimeter may also be used.

Reagents: Silver diethyldithiocarbamate $[\text{AgSCSN}(\text{C}_2\text{H}_5)_2]$ reagent: Dissolve 4.0 g of silver diethyldithiocarbamate in 800 ml of pyridine. The useful life of this reagent can be extended to at least two months by storing in a dark brown bottle or in the dark.

Stannous chloride reagent: Dissolve 10.0 g of fresh supply of stannous chloride dihydrate in 25 ml of 12N (specific gravity 1.19) hydrochloric acid. Place in a separatory funnel with a layer of pure mineral oil 5 mm thick on top to minimize oxidation. Drain a small quantity of the solution out of the stopcock before use. This solution is stable for 2 weeks.

Lead acetate solution: Dissolve 10 g of $\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$ crystals in 100 ml of water. The solution will be slightly turbid as a small amount of the basic salt is formed, but this will not affect its usefulness. The glass wool in the scrubber may be soaked in this solution, drained, and dried, or a few drops may be placed on the glass wool before the evolution of arsine.

Potassium iodide solution: Dissolve 15 g of KI in 100 ml of water. The solution should be stored in a brown glass bottle.

Zinc: Reagent grade, granular 20 mesh.

Arsenic standard stock solution: 1.320 g arsenic trioxide is dissolved in 10 ml of 40% sodium hydroxide and diluted to 1 liter with distilled water. Various strengths of standard solutions are prepared by further diluting this stock solution with suitable volumes of water.

The water used to make up the reagents, and throughout the analysis, is triple distilled in borosilicate glass. Naturally, all reagents used should be checked to ensure a low individual and a low total reagent blank.

IX. APPENDIX III
ANALYTICAL METHOD FOR
ARSENIC IN URINE [68-70]

At least 100 ml of urine should be collected. Determine the specific gravity of the sample before further treatment.

Oxidation: Place 100 ml of urine in a 300 ml Kjeldahl flask, add 5 ml concentrated H₂SO₄ and 25 ml concentrated HNO₃. Boil over a full flame under the hood. The addition of acid may cause the sample to darken, but the heating will lighten the color. Continue the heating to concentrate the sample. No trouble should be experienced with bumping. As the sample becomes quite concentrated, it will foam considerably. At this point it should be watched carefully for signs of darkening. If there is darkening, add a few drops of concentrated HNO₃ from a pipette dipped into a tube of the acid. Only sufficient acid should be added to overcome the darkening. Finally, the liquid should be water-white and fumes of sulfuric acid will be evolved. Further bleaching of the solution may be obtained by cautiously adding 2 ml of a 1:1 mixture of nitric and perchloric acids, and reheating to produce white fumes. Cool slightly and add 5 ml of saturated ammonium oxalate. Heat again until white fumes appear. This oxidation may be completed in less than two hours.

Analysis: Transfer the oxidized sample with the aid of 25 ml of water to a 100 ml conical flask. Cool to room temperature. Add 5 ml of 10% potassium iodide and 4 drops of stannous chloride. Let stand 15 minutes. Add 3.0 g of zinc and, using the same equipment as in determining

arsenic in air (see Figure XI-2), follow the same procedures as for air samples.

Calculations: Determine absorbance produced by 10 or 20 μg As at 560 nm. For example, if the increase in absorbance produced by 10 μg As is found to be 0.440, then:

$$\frac{(A-B)}{0.044} = \mu\text{g in aliquot}$$

where A = absorbance in sample, and B = absorbance of blank run on reagents. Calculate as mg As/liter of urine. Adjust to mean specific gravity of 1.024.

Reagents: Prepare as in analysis for determination of arsenic in air.

X. APPENDIX IV

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material containing arsenic or arsenic compounds shall be provided in the appropriate section of the Material Safety Data Sheet or other approved form. If a specific item of information is inapplicable (eg, flash point), the initials "n.a." (not applicable) should be inserted.

(a) The product designation in the upper left hand corner of both front and back to facilitate filing and retrieval. Print in upper case letters as large as possible.

(b) Section I. Name and Source.

(1) The name, address, and telephone number of the manufacturer or supplier of the product.

(2) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(c) Section II. Hazardous Ingredients.

(1) Chemical or widely recognized common name of all hazardous ingredients.

(2) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, eg, 10-20% V; 10% max. W.

(3) Basis for toxicity for each hazardous material such as established OSHA standard (TLV), in appropriate units and/or LD50, showing amount and mode of exposure and species or LC50 showing concentration and species.

(d) Section III. Physical Data.

Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure, in millimeters of mercury, vapor density of gas or vapor (air = 1), solubility in water in parts per hundred parts of water by weight; specific gravity (water = 1); percent volatile, indicate if by weight or volume, at 70 Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether = 1); and appearance and odor.

(e) Section IV. Fire and Explosion Hazard Data.

Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits, in percent by volume in air; suitable extinguishing media or agents; special fire fighting procedures; and unusual fire and explosion hazard information.

(f) Section V. Health Hazard Data.

Toxic level for total compound or mixture, relevant symptoms of exposure, skin and eye irritation properties, principal routes of absorption, effects of chronic (long-term) exposure and emergency and first aid procedures.

(g) Section VI. Reactivity Data.

Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(h) Section VII. Spill or Leak Procedures.

Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers containing residues, contaminated absorbants, etc.

(i) Section VIII. Special Protection Information.

Requirements for personal protective equipment, such as respirators, eye protection and protective clothing, and ventilation such as local exhaust (at site of product use or application), general, or other special types.

(j) Section IX. Special Precautions.

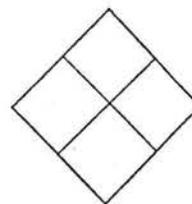
Any other general precautionary information such as personal protective equipment for exposure to the thermal decomposition products listed in Section VI, and to particulates formed by abrading a dry coating, such as by a power sanding disc.

(k) The signature of the responsible person filling out the data sheet, his address, and the date on which it is filled out.

| |
|---------------------|
| PRODUCT DESIGNATION |
|---------------------|

MATERIAL SAFETY
DATA SHEET

Form Approved
Budget Bureau No.
Approval Expires
Form No. OSHA



| SECTION I SOURCE AND NOMENCLATURE | |
|---|-------------------------|
| MANUFACTURER'S NAME | EMERGENCY TELEPHONE NO. |
| ADDRESS (Number, Street, City, State, ZIP Code) | |
| TRADE NAME AND SYNONYMS | CHEMICAL FAMILY |
| CHEMICAL NAME AND SYNONYMS | FORMULA |

| SECTION II HAZARDOUS INGREDIENTS | | | | | | |
|----------------------------------|--|---------------------------------|----------|---------|----------|-------|
| BASIC MATERIAL | APPROXIMATE OR MAXIMUM % WT. OR VOL. | ESTABLISHED OSHA STANDARD | LD 50 | | LC 50 | |
| | | | ORAL | PERCUT. | SPECIES | CONC. |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

| SECTION III PHYSICAL DATA | | | |
|---------------------------------------|------------------------------|------------------------------|-----------------------------------|
| BOILING POINT | °F. | VAPOR PRESSURE | mm Hg. |
| MELTING POINT | °F. | VAPOR DENSITY (Air=1) | |
| SPECIFIC GRAVITY (H ₂ O=1) | | EVAPORATION RATE (_____ =1) | |
| SOLUBILITY IN WATER | Pts/100 pts H ₂ O | VOLATILE | % Vol. % Wt. |
| APPEARANCE AND ODOR | | | |

| SECTION IV FIRE AND EXPLOSION HAZARD DATA | | |
|---|------------------------------------|-------|
| FLASH POINT | FLAMMABLE (EXPLOSIVE) LIMITS | UPPER |
| METHOD USED | | LOWER |
| EXTINGUISHING MEDIA | | |
| SPECIAL FIRE FIGHTING PROCEDURES | | |
| UNUSUAL FIRE AND EXPLOSION HAZARDS | | |

PRODUCT DESIGNATION

SECTION V HEALTH HAZARD DATA

| | |
|------------------------------------|-------------------------|
| TOXIC LEVEL | CARCINOGENIC |
| PRINCIPAL ROUTES OF ABSORPTION | SKIN AND EYE IRRITATION |
| RELEVANT SYMPTOMS OF EXPOSURE | |
| EFFECTS OF CHRONIC EXPOSURE | |
| EMERGENCY AND FIRST AID PROCEDURES | |

SECTION VI REACTIVITY DATA

| |
|---|
| CONDITIONS CONTRIBUTING TO INSTABILITY |
| CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION |
| INCOMPATIBILITY (Materials to Avoid) |
| HAZARDOUS DECOMPOSITION PRODUCTS |

SECTION VII SPILL OR LEAK PROCEDURES

| |
|---|
| STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED |
| WASTE DISPOSAL METHOD |

SECTION VIII SPECIAL PROTECTION INFORMATION

| | |
|---|---|
| VENTILATION REQUIREMENTS LOCAL EXHAUST | PROTECTIVE EQUIPMENT (Specify Types) EYE |
| MECHANICAL (General) | GLOVES |
| SPECIAL | RESPIRATOR |
| OTHER PROTECTIVE EQUIPMENT | |

SECTION IX SPECIAL PRECAUTIONS

| |
|---|
| PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE |
| OTHER PRECAUTIONS |

Signature _____

Address _____

Date _____

TABLE XI-1

PHYSICAL AND CHEMICAL PROPERTIES OF
IMPORTANT INORGANIC ARSENICALSArsenic, As

Physical state: gray metal, hexagonal-rhombic crystals
also yellow cubic crystals (As₄)
Atomic weight: 74.9216
Specific gravity: 5.727
Melting point: sublimes at 613 C
Solubility: insoluble in water

Arsenic Trichloride, AsCl₃

Physical state: oily liquid or needle shaped crystals
Formula weight: 181.28
Specific gravity: 2.163 (20 C)
Melting point: -8.5 C
Boiling point: 130.2 C
Vapor density: 6.25 (air = 1)
Vapor pressure: 10 mm Hg (23.5 C)
Solubility: decomposes in water
Percent arsenic: 41

Arsenic Trioxide, As₂O₃ (White Arsenic, Arsenous Oxide)

Physical state: transparent crystals or amorphous white powder
Formula weight: 197.84
Specific gravity: 3.738
Melting point: 315 C
Solubility, in g/100cc water: 3.7 at 20 C, 10.14 at 100 C
Percent arsenic: 76

Arsenic Pentoxide, As₂O₅ (Anhydride of Arsenic Acid)

Physical state: deliquescent, white amorphous powder
Formula weight: 229.84
Specific gravity: 4.32
Melting point: decomposes at 315 C
Solubility, in g/100cc water: 150 at 16 C, 76.7 at 100 C
Percent arsenic: 65

Calcium Arsenate, Ca₃(AsO₄)₂

Physical state: colorless amorphous powder
Formula weight: 398.08
Specific gravity: 3.62
Melting point: 1455
Solubility, in g/100cc water: 0.013 at 25 C
Percent arsenic: 38; also occurs with 3 moles of water,
in which case the molecular weight is 452.11, and the percent
arsenic is 33.

TABLE XI-1 (CONTINUED)

| |
|---|
| <u>Copper Acetoarsenite</u> , $3 \text{ Cu}(\text{AsO}_2)_2\text{-Cu}(\text{COOCH}_3)_2$ (approx) (Copper Acetate Metarsenate, Imperial, Schweinfurth, Vienna, Parrot or Paris Green) |
| Physical state: emerald green powder |
| Formula weight: 1013.77 |
| Solubility: insoluble in water |
| Percent arsenic: 44 |
| <u>Cupric Arsenite</u> , CuHAsO_3 (approx) (Scheele's Green, Swedish Green) |
| Physical state: yellowish green powder |
| Formula weight: 187.47 |
| Melting point: decomposes |
| Solubility: insoluble in water |
| Percent arsenic: 40 |
| <u>Lead Arsenate</u> , $\text{Pb}_3(\text{AsO}_4)_2$ (Lead Orthoarsenate) |
| Physical state: white crystals |
| Formula weight: 899.41 |
| Melting point: 1042 C, slightly decomposes at 1000 C |
| Solubility: very slightly soluble in cold water |
| Specific gravity: 7.8 |
| Percent arsenic: 17 |
| <u>Lead Arsenite</u> , $\text{Pb}(\text{AsO}_2)_2$ (Lead Metarsenite) |
| Physical state: white powder |
| Formula weight: 421.03 |
| Specific gravity: 5.85 |
| Solubility: insoluble in cold water |
| Percent arsenic: 36 |
| <u>Ortho-Arsenic Acid</u> , $\text{H}_3\text{AsO}_4\text{-}1/2\text{H}_2\text{O}$ |
| Physical state: white translucent hygroscopic crystals |
| Formula weight: 150.95 |
| Specific gravity: 2.0 to 2.5 |
| Melting point: 35.5 C |
| Boiling point: 160 C |
| Solubility, in g/100cc: 16.7 in cold water 50 in hot water |
| Percent arsenic: 50 |
| <u>Sodium Arsenite</u> , NaAsO_2 (Sodium Metarsenite) |
| Physical state: gray-white powder |
| Formula weight: 129.91 |
| Specific gravity: 1.87 |
| Solubility: very soluble in water |
| Percent arsenic: 58 |

From references [5,7]

TABLE XI-2
OCCUPATIONS WITH POTENTIAL ARSENIC EXPOSURE

| | |
|-----------------------|-------------------------------|
| alloy makers | hide preservers |
| aniline color makers | insecticide makers |
| Babbitt metal workers | lead shot makers |
| boiler operators | lead smelters |
| brass makers | leather workers |
| bronze makers | paint makers |
| bronzers | painters |
| cattle dip workers | petroleum refinery workers |
| ceramic enamel makers | pigment makers |
| ceramic makers | printing ink workers |
| copper smelters | rodenticide makers |
| defoliant applicators | semiconductor compound makers |
| defoliant makers | sheep dip workers |
| drug makers | silver refiners |
| dye makers | taxidermists |
| enamellers | textile printers |
| farmers | tree sprayers |
| fireworks makers | type metal workers |
| glass makers | water weed controllers |
| gold refiners | weed sprayers |
| hair remover makers | wood preservative makers |
| herbicide makers | wood preservers |

From reference [9]

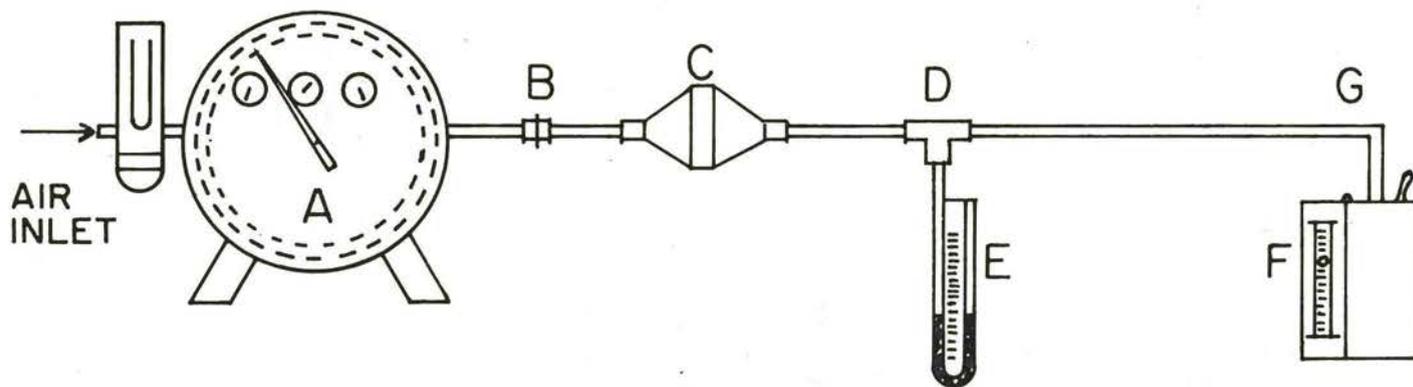
TABLE XI-3
 1965 SMELTER SURVEY
 ATMOSPHERIC ARSENIC CONCENTRATIONS (mg As/cu m)

| | | |
|--|-------|---------------|
| "Heavy exposure area" as classified by Lee and Fraumeni [49] | | |
| <u>Arsenic Roaster Area</u> | | Mean: 1.47 |
| 0.10 | 0.20 | Median: 0.185 |
| 0.10 | 0.22 | |
| 0.10 | 0.25 | |
| 0.10 | 0.35 | |
| 0.10 | 1.18 | |
| 0.10 | 5.00 | |
| 0.17 | 12.66 | |
| "Medium exposure areas" as classified by Lee and Fraumeni [49] | | |
| <u>Reverberatory Area</u> | | Mean: 1.56 |
| 0.03 | 0.93 | Median: 0.88 |
| 0.22 | 1.00 | |
| 0.23 | 1.27 | |
| 0.36 | 1.60 | |
| 0.56 | 1.66 | |
| 0.63 | 1.84 | |
| 0.66 | 1.94 | |
| 0.76 | 2.06 | |
| 0.78 | 2.76 | |
| 0.78 | 3.40 | |
| 0.80 | 4.14 | |
| 0.83 | 8.20 | |
| <u>Treater Building and Arsenic Loading</u> | | Mean: 1.50 |
| 0.10 | 0.48 | Median: 0.295 |
| 0.10 | 0.62 | |
| 0.10 | 3.26 | |
| 0.11 | 7.20 | |
| "Light exposure areas" as classified by Lee and Fraumeni [49] | | |
| <u>Copper Concentrate Transfer System</u> | | Mean: 0.70 |
| 0.25 | | Median: 0.65 |
| 0.65 | | |
| 1.20 | | |
| <u>Samples from Flue Station</u> | | Mean: 0.17 |
| 0.10 | | Median: 0.17 |
| 0.24 | | |
| <u>Reactor Building</u> | | Mean: 0.004 |
| 0.001 | 0.003 | Median: 0.002 |
| 0.002 | 0.009 | |
| 0.002 | 0.010 | |
| 0.002 | | |

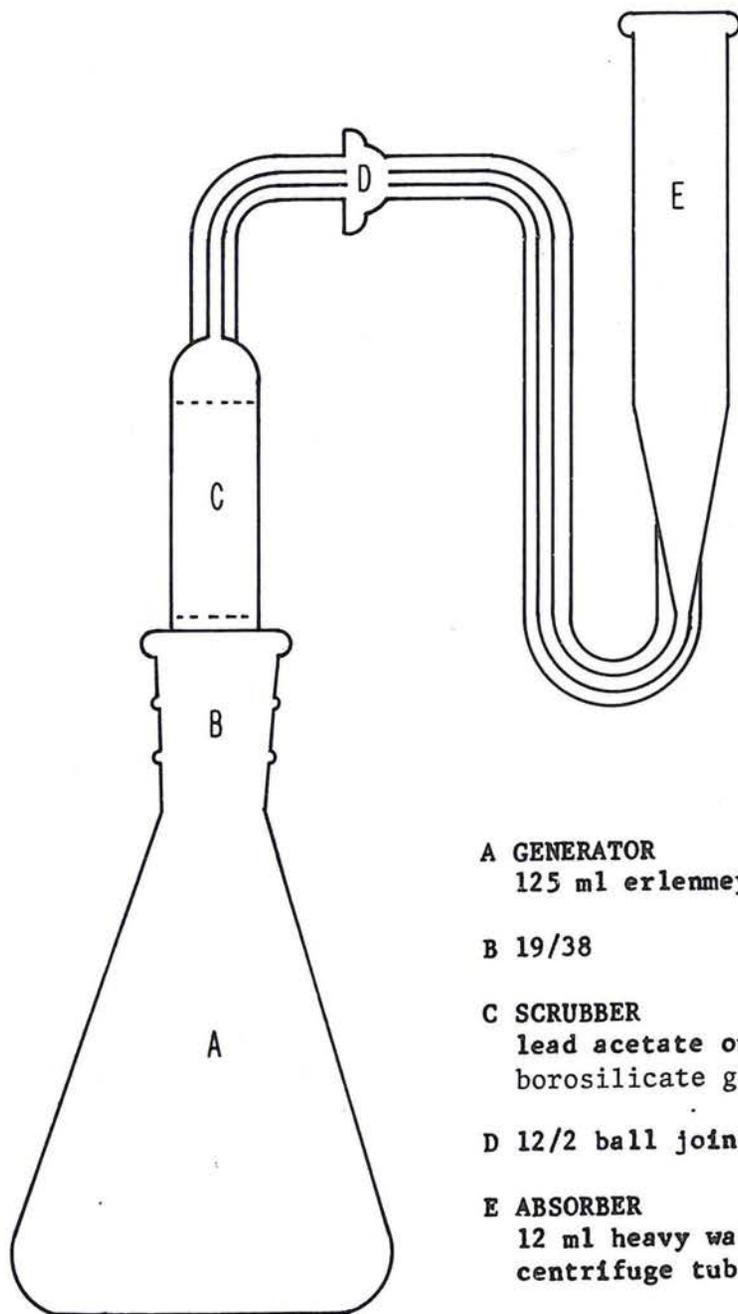
TABLE XI-4
 1965 SMELTER SURVEY
 URINARY ARSENIC

| <u>Job Title</u> | <u>mg As/liter of urine</u> |
|---------------------------|-----------------------------|
| Rapper | 0.06 |
| Stack foreman | 0.15 |
| Station man | 0.36 |
| Station man | 0.46 |
| Scraper operator | 0.19 |
| Scraper operator | 0.47 |
| Treaterman | 0.24 |
| Louvre man (treater) | 0.11 |
| Louvre man (treater) | 0.12 |
| Dump floorman | 0.40 |
| Dump floorman (main flue) | 0.17 |
| Furnace operator | 0.15 |
| Furnaceman | 0.17 |
| Repairman | 0.48 |
| Change floor operator | 0.32 |
| Cleaner | 0.27 |
| Funnel loader | 0.43 |
| Arsenic roaster foreman | 0.17 |
| Arsenic loader | 0.04 |
| Arsenic loader | 0.06 |
| Arsenic loader | 0.14 |
| Arsenic loader | 0.19 |
| Arsenic loader | 0.29 |
| | Mean 0.24 |
| | Median 0.17 |

FIGURE XI-1



CALIBRATION SETUP FOR PORTABLE PUMPS WITH FILTERS.



A GENERATOR
125 ml erlenmeyer

B 19/38

C SCRUBBER
lead acetate on
borosilicate glass wool

D 12/2 ball joint

E ABSORBER
12 ml heavy wall
centrifuge tube

74-110