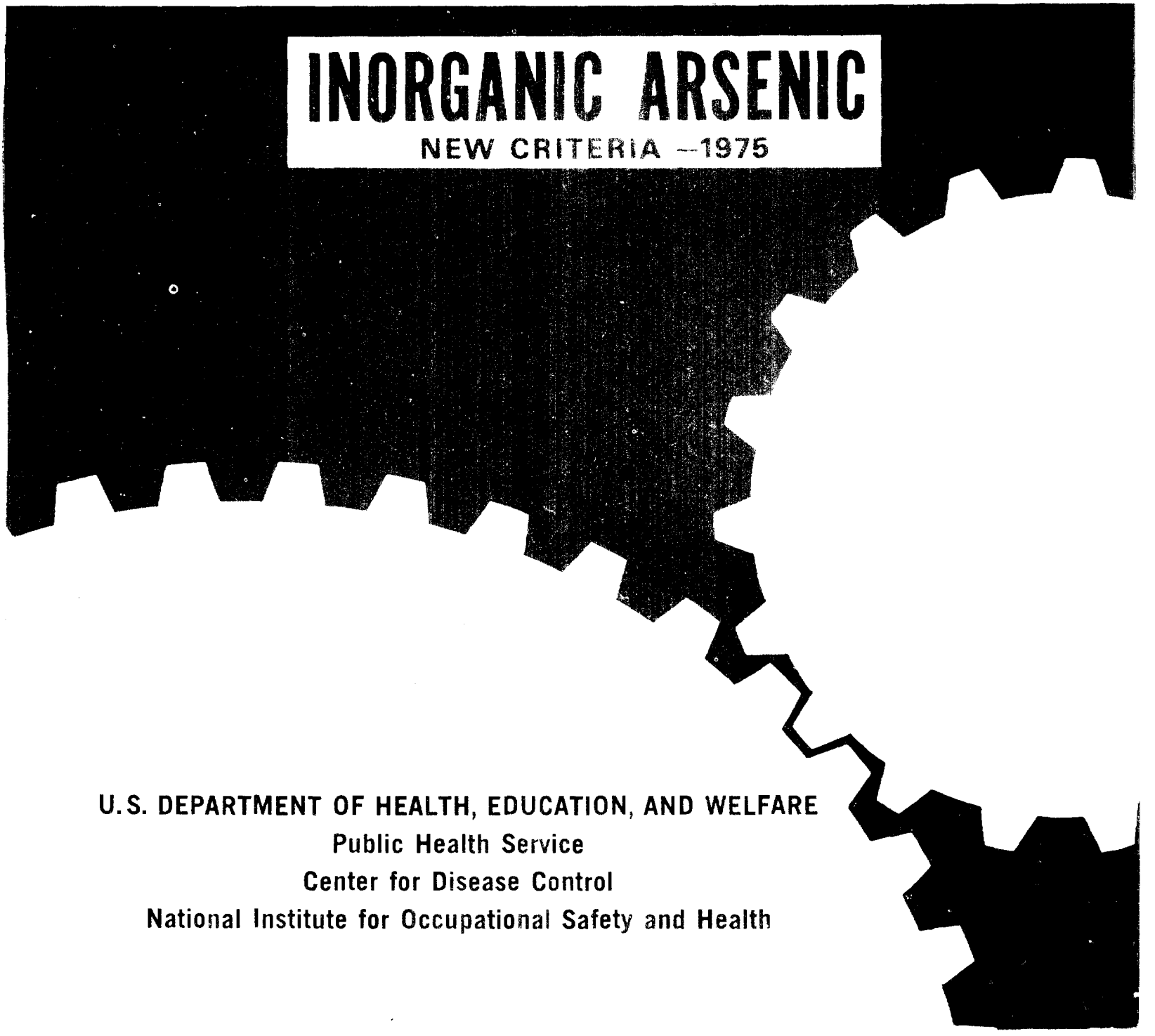
criteria for a recommended standard . . . .

OCCUPATIONAL EXPOSURE TO



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

criteria for a recommended standard . . . .

OCCUPATIONAL EXPOSURE TO INORGANIC ARSENIC

NEW CRITERIA —1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
1975

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

HEW Publication No. (NIOSH) 75–149

PREFACE TO THE REVISED RECOMMENDED STANDARD

When the document on Occupational Exposure to Inorganic Arsenic was originally developed, it was apparent that inorganic arsenic had been a factor in the development of occupationally related lung cancer, but the evidence was not unequivocal. Although data were not available which could validate any specific concentration as an occupational health limit, NIOSH acted because of the seriousness of the disease. Even in the absence of data demonstrating the absolute safety of the recommended environmental limit, a workroom limit was recommended which it was believed would "at the minimum, significantly reduce the incidence of arsenic-induced cancer."

Beginning in July, 1974, unpublished reports on occupational exposure to inorganic arsenic were made available to NIOSH by Allied Chemical Corporation, The Dow Chemical Corporation, and Kennecott Copper Corporation. After reviewing these papers and several additional reports that were subsequently published, NIOSH on November 8, 1974, transmitted to the Department of Labor modified recommendations for an inorganic arsenic standard. As new information continued to accumulate, NIOSH further modified its recommendations at the public hearing held by the Occupational Safety and Health Administration on April 8, 1975. This new Criteria Document contains the modified recommendations for an inorganic arsenic standard and incorporates discussions of the additional information that has been considered. The revised criteria and recommended standard were prepared in the Office of Research and Standards Development with the valuable assistance of Elliot S. Harris, Ph.D., Director, Division of Laboratories and Criteria Development; J. William Lloyd, Sc.D., Director, Office of Occupational Health Surveillance and Biometrics; William L.

Wagner, Industrial Hygiene Engineer, Western Area Occupational Health Laboratory; and of Joseph K. Wagoner, S.D. Hyg., Director, Division of Field Studies and Clinical Investigations.

When the inorganic arsenic criteria document was first published, arsine and lead arsenate were excluded from the provisions of the recommended standard. They are included in these revised recommendations, although the inclusion of arsine poses some difficulties in that specific work practices for arsine are needed, and sampling methods for arsine and other arsenical gases need to be refined. NIOSH is working on these areas and will transmit recommendations directly to the Occupational Safety and Health Administration, but these difficulties should not be cited as cause for permitting continued worker exposure to arsine at concentrations above 0.002 mg (2.0 (u)g) As/cu m. NIOSH also recognizes that the stringent occupational exposure limit recommended, based on our evaluation of the health hazards, presents a difficult regulatory problem for agencies such as the Environmental Protection Agency and the Occupational Safety and Health Administration. However, it is not possible at present to determine a safe exposure level for carcinogens. In the interest of worker safety and health, NIOSH has recommended restricting exposure to very low levels that can be reliably measured.

John F. Finklea, M.D.

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Director, National Institute for
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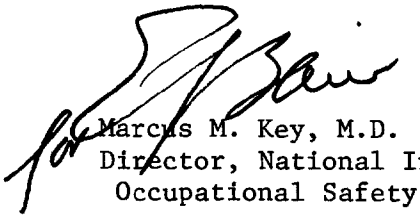
PREFACE

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 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 will prevent noncarcinogenic adverse effects of exposure to inorganic arsenic in the workplace air and by skin exposure, and should at the minimum materially reduce the risk of arsenic-induced cancer. 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. "Exposure to arsenic" is defined as exposure at or above 0.002 mg (2.0 μg) As/cu m. Arsine and other arsenical gases should be controlled to the same concentration as other forms of inorganic arsenic. Suitable sampling and analytical methods for arsenical gases are not yet available but are being developed.

Section 1 - Environmental (Workplace air)

(a) Concentration

Inorganic arsenic shall be controlled so that no worker is exposed to a concentration of arsenic in excess of 0.002 mg (2.0 μg) per cubic meter of air as determined by a 15-minute sampling period.

(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 and related records kept as specified below for all workers occupationally exposed to arsenic.

(a) Preplacement and annual medical examinations shall include:

(1) Comprehensive preplacement or annual interim work history.

(2) Comprehensive preplacement or annual interim medical history.

(3) 14" x 17" posterior-anterior chest X-ray, giving particular attention to parenchymal and hilar changes.

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

(5) Palpation of superficial lymph nodes to detect indications of neoplastic changes.

(6) Complete blood count to include differential.

(7) An evaluation of the advisability of the worker's using

negative- or positive-pressure respirators.

(b) A periodic sputum cytology examination is recommended for all workers occupationally exposed to inorganic arsenic. The frequency of this procedure should be determined by the responsible medical authority.

(c) Proper medical management shall be provided for workers adversely affected by occupational exposure to inorganic arsenic compounds.

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

(e) 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 pertinent occupational medical records. Physicians designated and authorized by any employee or former employee shall have access to that worker's medical records.

(f) Medical records shall be maintained by the employer or successors thereto for persons employed one or more years in work involving exposure to arsenic. Preplacement X-rays, X-rays for the 5 years preceding termination of employment, and all other medical records with pertinent supporting documents shall be maintained at least 30 years after the individual's employment is terminated. In the event that the employer ceases business without a successor, records shall be forwarded by registered mail to the Director, National Institute for Occupational Safety and Health.

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
CANCER CAUSING AGENT
HARMFUL IF INHALED OR SWALLOWED, OR UPON SKIN CONTACT
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.

ARSENIC
DANGER! CANCER CAUSING AGENT

Dust or spray mist may be hazardous to health.
Provide adequate ventilation.

This sign shall be printed both in English and in the predominant language of non-English-speaking workers unless they are otherwise trained and informed of the hazardous area. All illiterate workers shall receive such training.

Section 4 - Personal Protective Equipment and Work Clothing

(a) Protective Clothing

(1) Where there is occupational exposure to inorganic arsenic compounds, protective clothing shall be provided by the employer. This may include underwear, gloves, coveralls, 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.

(b) Respiratory Protection

(1) Engineering controls shall be used wherever feasible to maintain arsenic concentrations below the prescribed limit. Compliance with the permissible exposure limit may not be achieved by the use of respirators except:

(A) During the time period necessary to install or test the required engineering controls.

(B) For nonroutine operations such as a brief exposure to concentrations in excess of the permissible exposure limit as a result of maintenance or repair activities.

(C) During emergencies when air concentrations of arsenic may exceed the permissible limit.

(2) When a respirator is permitted by paragraph (b)(1) of this Section, it shall be selected and used pursuant to the following requirements:

(A) The employer shall ensure that no worker is being exposed to arsenic in excess of the environmental limit because of improper respirator selection, fit, use, or maintenance.

(B) A respiratory protection program meeting the requirements of 29 CFR 1910.134 as amended shall be established and enforced by the employer.

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

(D) Respiratory protective devices described in Table I-1 shall be those approved under the provisions of 30 CFR 11 as amended.

(E) The employer shall ensure that respirators are adequately cleaned, and that employees are instructed in the use of respirators assigned to them, and how to test for leakage.

(F) Where an emergency may develop which could result in employee exposure to arsenic, the employer shall provide respiratory protection as listed in Table I-1.

TABLE I-1

1) Combination supplied air respirator, pressure demand type, with auxiliary self-contained air supply.

2) Self-contained breathing apparatus with positive pressure in the facepiece

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 the hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and precautions for safe use. Instruction shall include, as a minimum, all information in Appendix III 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 the "Material Safety Data Sheet" shown in Appendix III or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Readily accessible standby rooms under positive air pressure and in which the concentration of arsenic in the air is less than 2.0 μg As/cu m shall be provided where there is occupational exposure to inorganic arsenic.

(b) 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.

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

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

(e) 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.

(f) 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.

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

(h) 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.

(i) Due to potential skin irritation associated with respirator use and arsenic dust exposure, workmen shall be permitted to leave the work area every 2 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 shower bathe before changing into street clothes. Shower baths shall be cleaned following use after each work shift.

(d) Employees exposed to arsenic shall wash their hands and exposed skin 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

Workroom areas shall not be considered to have arsenic exposure if environmental levels, as determined on the basis of a professional industrial hygiene survey, are less than 2.0 μg As/cu m. Records of these surveys, including the basis for concluding that air levels are less than 2.0 μg As/cu m, shall be maintained in accordance with Section 8 (e). In workrooms where inorganic arsenic compounds are handled or processed, surveys shall be repeated at least annually and when any process change indicates a need for reevaluation. Requirements set forth below apply to areas in which 1 or more 15-minute breathing zone samples have indicated exposure at or above 2.0 μg As/cu m.

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

(a) In all monitoring, sufficient breathing zone samples shall be collected to characterize the potential exposure of workers at each operation or process.

(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 first operation of a new process or process changes.

(d) Samples shall be collected at least every 2 months for those work areas in which there is occupational exposure to inorganic arsenic.

(e) Records of all sampling and of medical examinations shall be maintained by the employer or successors thereto for at least 30 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 exposure information is available for individual employees, and each employee shall be able to obtain information on his own exposure. In the event that the employer ceases business without a successor, records shall be forwarded by registered mail to the Director, National Institute for Occupational Safety and Health.

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. 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 are in a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of inorganic arsenical products as applicable under the Occupational Safety and Health Act of 1970. When the inorganic arsenic criteria document was first published in January 1974, arsine and lead arsenate were excluded from the provisions of the recommended standard. They are included in these revised recommendations. The inclusion of arsine and other gaseous arsenicals poses some difficulties in that specific work practices are needed, and

sampling methods need investigation. However, these difficulties should not be cited as cause for permitting continued exposure to arsine at concentrations above 0.002 mg (2.0 μg) As/cu m. NIOSH is working on these areas and will transmit recommendations directly to the Occupational Safety and Health Administration as soon as possible.

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 the noncarcinogenic effects of inorganic arsenicals, (2) materially reduce the risk of arsenic-induced cancer, (3) be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (4) 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 3 and 5, and it is ubiquitous, [1,3] being found in small amounts in soils and waters throughout the world, as well as in foods, particularly seafood. [1,4] Arsenic is a constituent of a number of minerals. For industrial and commercial uses, it is obtained primarily from the ores of metals in which it is present as an impurity, [5] removed as arsenic trioxide (arsenic (III) oxide, As203) during the smelting operation. This oxide is used in the manufacture of most other arsenic compounds, and is produced in the US as a byproduct in the smelting of copper ores. [6] Physical and chemical properties of arsenic and some of its more important inorganic compounds are given in Table X-1. [5,7]

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

Some occupations which have or in the past have had potential

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

Historical Reports

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

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

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

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

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

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

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

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

In 1945, Watrous and McCaughey [22] reported on conditions in a pharmaceutical plant manufacturing arsphenamine and related compounds from the basic intermediate arsanilic acid, so that exposures in this plant were to organic arsenicals. In the manufacturing department, exposures varied from 0.02 to 0.60 mg As203/cu m (approximately 0.015-0.456 mg As/cu m) with

an overall average of 0.17 mg As203/cu m (0.129 mg As/cu m). In the packaging division, air concentrations ranged from 0.007 to 0.28 mg As203/cu m (0.005-0.213 mg As/cu m) with a mean of 0.065 mg As203/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 μg As/g wet weight were: fish and seafood, 4.64; meats, 0.49; vegetables and grains, 0.41. The highest arsenic levels found were 15.3 μg As/g in shrimp shells and 8.86 μg As/g in kingfish. Other high levels were 2.71 in table salt, 1.6 in puffed rice, 1.4 and 1.07 in 2 samples of pork liver, and 1.3 in stewing beef. No arsenic was detected in pork kidney, chicken breast, egg lecithin, corn oil, and other items. No arsenic was found in the kidneys of 8 wild mice, but the livers and hearts contained 0.74 and 1.10 μg As/g wet weight. Arsenic was found in the urine of 2 humans in concentrations of 0.14 and 0.10 μg As/g of urine (approximately 0.143 and 0.102 mg As/liter, using a specific gravity of 1.024 for conversion). In the hair of 7 humans, the arsenic level ranged from 0.12 in a 3-year-old to 1.1 μg As/g of hair in an 80-year-old, with a mean of 0.536 μg As/g. Webster [23] also reported the urinary arsenic level of persons with no known exposure to arsenic. First morning specimens from 26 adults and 17 children contained 0.015 and 0.014 mg As/liter of urine, respectively. The overall average was 0.014 mg As/liter.

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

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

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

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

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

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

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

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

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

In all 6 cases anemia and leukopenia were present, with 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 1 case. Basophilic stippling was a prominent finding. The bone marrow of 4 patients was examined, and in 3 of these increased, disturbed erythropoiesis was observed. Depressed or disturbed myelopoiesis was seen in all 4. Hematologic abnormalities disappeared within 2-3 weeks after cessation of arsenic ingestion.

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

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

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

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

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

More recently, Barry and Herndon [31] described characteristic electrocardiographic changes of nonspecific T-wave inversion and 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 blood serum electrolytes, serum chemistries, neurologic or respiratory systems were present. In 1 case, an ECG had been performed 3 months before arsenic was ingested and was normal. This patient, a 21-year-old male, died and post-mortem examination showed "subendocardial hemorrhage and fibrosis with subepicardial petechiae and myocardial perivascular mononuclear infiltration." The ECG changes in the

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

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

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

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

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

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

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

Epidemiologic Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

mortality of plant employees.

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

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

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

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

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

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

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

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

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

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

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

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

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

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 2 groups, increases in cardiovascular and cancer mortality are unrelated to arsenic exposure. The increase in overall cancer mortality was not statistically significant, but the respiratory cancer mortality in the smelter group was 18 of 229 deaths (7.9%) compared to 518 of 13,759 deaths (3.0%) in the state as a whole. Similarly, overall deaths due to cardiovascular disease were increased in the smelter group, but not significantly so. The increase, however, was entirely concentrated in the 45-64 age group (63 deaths compared to 38.52 expected) and was partially offset by a decrease in the 65-94 age group (82 deaths compared to 106.54 expected).

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

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

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

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

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 <u>alone</u> 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.

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

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

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

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

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

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

from Rencher and Carter [52]

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

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

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

TABLE III-2
Lung Cancer Deaths as a Percentage of Total Deaths in Smokers and Nonsmokers

	Smokers	Nonsmokers
Smelter	9.2	3.3
Mine	3.3	0.7
Concentrator	3.3	0.8

from Rencher and Carter [52]

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

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

TABLE III-3
Age-Adjusted Death Rates per 10,000 At Risk

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

from Rencher and Carter [52]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE III-4
Respiratory Cancer Deaths by Exposure Category

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

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

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

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

Animal Toxicity

The acute oral toxicity of arsenic trioxide in mice and rats was tested by Harrisson et al [63] using both "crude" or commercial grade (97.7% As203 with 1.18% Sb203) and highly purified arsenic trioxide (99.999+% As203). Solutions were administered intraesophageally using an oral feeding tube. Test animals had been previously fasted for 24 hours. The acute oral LD50 for young Webster Swiss mice was estimated as 39.9 mg As/kg for the purified trioxide and as 42.9 mg As/kg for the commercial grade. For Sprague Dawley albino rats the LD50 was 15.1 mg As/kg and 23.6 mg As/kg for the pure and crude preparations, respectively. Despite its lower LD50, the purified arsenic was found to be less severe as a gastrointestinal irritant than was the crude trioxide. Retching during life and marked gastrointestinal damage at autopsy were observed only in animals receiving the crude arsenic trioxide. This was attributed to the antimony in the crude preparation.

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

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

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

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

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

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

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

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

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

Rozenshtein [70] conducted an experimental inhalation study using albino rats. He was concerned with the effects of atmospheric pollution by arsenic trioxide on the community at large, so 3 groups of female albino rats were exposed 24 hours a day for 3 months to a condensation aerosol of freshly sublimed arsenic trioxide at levels of 0.06, 0.0049, and 0.0013 mg As203/cu m (approximately 0.046, 0.004, and 0.001 mg As/cu m). The animals were studied biochemically and neurophysiologically during each month of exposure and during the recovery period after the termination of exposure. Some animals were killed 1 month after exposure ended and tissues were examined histologically and histochemically. The author did not state how many animals were involved in the study.

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

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

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

The animals exposed to only 0.0013 mg As203/cu m (0.001 mg As/cu m) showed none of the foregoing ill effects. On this basis the author [70] proposed 0.001 mg As203/cu m as the "mean diurnal maximum permissible concentration of this compound in the atmosphere...." This was apparently intended to be a standard for the population-at-large implying 24-hour exposure.

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

extrapolation to this from the continuous exposure used by Rozenshtein is uncertain. If linearity is assumed, since there is no validated conversion formula, the exposure cited would be equivalent to 4.2 times higher levels on the 40-hour week basis, or 0.252, 0.021, and 0.005 mg As203/cu m (0.192, 0.016, and 0.004 mg As/cu m). The threshold apparently was between the 2 lower exposure levels.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE III-5
Arsenate Study Design

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

from Kroes et al [81]

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

Correlation of Exposure and Effect

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 on a cellulose membrane filter with a pore size of 5.0 μm or less. Satisfactory methods are not avaliable for collecting arsine and other arsenical gases.

Several procedures have been developed for analysis of arsenic in air. Dubois and Monkman [82] compared 3 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 [83] by comparing test results obtained by 8 cooperating laboratories. It was found [83,84] sensitive enough to detect, in a 10 cu m (10,000 liter) air sample, 0.1 μg As/cu m or a maximum of 1.5 μg As/cu m. However, at the recommended environmental limit of 2.0 μg As/cu m, only 0.06 μg (60.0 ng) of arsenic would be collected in the recommended 30-liter air sample.

In recent years, an analytical method involving arsine generation followed by analysis by atomic absorption spectrophotometry has show increased sensitivity for arsenic. [85-87] An absolute sensitivity of 0.005 μg (5.0 ng) of arsenic has been obtained using sodium borohydride reduction, a balloon collection technique, and an electrodeless discharge

arsenic lamp. [86] Other methods with increased sensitivity are the heated graphite furnace [88] and anodic stripping voltammetry. [89] Although these techniques are not in wide use, they show promise of attaining sensitivities equal to or greater than that achieved by atomic absorption. Atomic absorption spectrophotometry is the recommended analytical method because, in addition to possessing the required sensitivity, it is more widely known than alternative methods are at this time.

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 are essential. [90] 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), [90] 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 [91] 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. [4,22,39]

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 3 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, 3 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 [39] analyzed 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 3 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 1 dubious case of mild systemic arsenic poisoning, there were several cases (at least 17) of acute arsenical dermatitis. Over a 6-day period, 16 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 6 hours for 4 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 2-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 an English sheep-dip factory, [41] urinary arsenic levels were determined for workers exposed to mixed arsenic trioxide and sodium arsen-

ite dusts, and for unexposed controls. The urinalyses of exposed personnel were repeated after an interval of 6 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. [92] This was considered to be roughly consistent with a time-weighted average air level of 0.5 mg As/cu m. [93]

Of all the papers discussed in this document, only Webster [23] reported the specific gravity of the sample tested. Elkins, [92,93] Elkins and Pagnotto, [94] Buchwald, [95] and Levine and Fahy [96] 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 [95] reported the mean specific gravity was 1.016. However, in the United States, Elkins, [92,93] and Elkins and Pagnotto [94] recommend 1.024. This was based on the findings of Levine and Fahy, [96] who in 1945 reported 1.024 as the mean specific gravity of nearly 1,200 urine samples. According to Elkins and Pagnotto, [94] their laboratory has analyzed 1,000-2,000 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. [94,96]

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." 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."

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 qualitative 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. [97] However, the summary of standards compiled by Cook [98] 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. [98] 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 a MAC for arsenic of 0.1 mg/cu m, [99] but the following year this was raised to a Threshold Limit Value (TLV) of 0.5 mg As/cu m. [100] 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 a 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 [101] for TLVs in the 0.0-1.0 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," [101] but in 1974 a notice of intended change to 0.25 mg As/cu m was published, [101] and the ACGIH Plenary Committee has recently proposed [102] that the 1975 TLV book list inorganic arsenic compounds in Appendix A1.a (Human Carcinogens) with a TLV of 0.05 mg As/cu m.

In his 1959 textbook, Elkins [92] 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, calcium arsenate, and arsine have been recommended by the ACGIH for a number of years. A limit of 0.15 mg/cu m for lead arsenate was adopted tentatively in 1956, [103] confirmed in 1957, [104] and has remained unchanged since. [101] (No chemical formula is given in the TLV booklet, but the Documentation [105] gives the formula for lead ortho-arsenate--Pb3(AsO4)2--in which case 0.15 mg/cu m is equivalent to 0.025 mg As/cu m. It is not clear whether the 0.15 mg/cu m TLV is intended to apply to other forms of lead arsenate. If so, it is equivalent to 0.032, 0.033, 0.046, and 0.050 mg As/cu m for lead diortho-, pyro-, monoortho-, and meta-arsenate, respectively.) According to the ACGIH Documentation, [105] 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. [105]

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, [103] and was adopted in 1957. [104] In his review of standards, Smyth [106] 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 [105] cited Smyth [106] 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.

In 1946 the ACGIH adopted [107] a 1.0 ppm MAC for arsine which in 1947 was changed to 0.05 ppm. [99] In 1948 the terminology was changed to TLV, but the value remained at 0.05 ppm. According to the most recent Documentation of TLVs, [105] 250 ppm for 30 minutes has been reported as fatal and symptoms of toxicity have been reported after exposure at 3-10 ppm for a few hours. No data were given to document concentrations that result in chronic poisoning or to document the validity of the TLV of 0.05 ppm.

The Czechoslovak MAC Committee suggested a "mean MAC" of 0.3 and a "peak MAC" of 0.5 mg As/cu m. [108] 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, all determined as a time-weighted average, for calcium arsenate (1.0 mg Ca3(AsO4)2/cu m), for lead arsenate (0.15 mg Pb3(AsO4)2/cu m), and for arsine (0.05 ppm). [29 CFR 1910.93, published in the Federal Register, vol 39, dated June 27, 1974] These standards were based on the ACGIH recommendations.

In January, 1974, NIOSH transmitted to the Department of Labor a recommended standard for occupational exposure to inorganic arsenic that included an environmental limit of 0.05 mg As/cu m. Arsine and lead arsenate were excluded from the provisions of that recommended standard. Additional information that was published or made available after that document was published led to a review of the NIOSH recommendations, and in November, 1974, NIOSH transmitted a memorandum to the Department of Labor in which modified recommendations were made for an inorganic arsenic standard. Additional significant information has developed since late 1974, and, along with the earlier reports, has been the object of continuing review and evaluation within NIOSH. The rapid development of new information and the consequent alterations in NIOSH recommendations have made this new criteria document necessary.

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 [63] 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 leukopenia 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 [68] and fatty degeneration of the liver. [70] 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] of a smelter population reported significantly increased mortality due both to cirrhosis of the liver and to cardiovascular disease. Another study [48] of mortality among smelter workers found that cardiovascular mortality was not significantly increased in workers exposed to arsenic.

Mortality studies of orchardists exposed to lead arsenate spray [57] and of copper smelter workers [42,48,53] found no excessive cancer mortality. However, as discussed in the section on Epidemiologic Studies, the conclusions in each of these reports are questionable. Other studies have reported cancer of the skin, [40,46] lung, [40,46,49,50,52,60,61] lymphatic system, [60,61] and other organs. [46] In general, attempts to produce cancer experimentally in animals have failed, [68,69,78,79] but leukemia reportedly [80] has been induced experimentally and teratogenic effects have been observed in animals. [73-75]

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, and by Ott et al [61] who estimated total dosages of arsenic and showed an apparent dose-response relationship for respiratory cancer.

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 [68] and after inhalation of arsenic trioxide. [70] 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. A third paper [53] reported no excess cancer mortality in the smelter population studied. 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 Milham 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. Although Milby and Hine [53] found that cancer mortality was not excessive among all smelter workers employed by a copper company, an earlier study by Rencher and Carter [52] had shown excessive lung cancer mortality among the same company's smelter workers in Utah.

Other studies have also shown increased respiratory cancer mortality in smelter populations. Kuratsune et al [50] found that of 19 men who died of lung cancer, 11 had been employed at a copper smelter, compared to only 3 who were so employed in a case control group of 19 with other causes of death. Lee and Fraumeni [49] demonstrated an increased incidence of respiratory cancer mortality in the smelter population they studied, and

they showed that the cancer risk increased with the degree of arsenic exposure as well as with the length of exposure.

As reported by Hill and Faning, [40] the cancer mortality of chemical workers in an 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. A definite excess in respiratory cancer mortality was reported by Baetjer et al [60] and by Ott et al [61] among American workers exposed to arsenates and some arsenites in pesticide plants. These American pesticide plant employees were also shown to have experienced excessive lymphatic cancer mortality. [60,61]

These studies [40,47,49,50,52,60,61] 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 also 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 cannot be denied. Furthermore, there was no suggestion of sulfur dioxide exposure in the sheep-dip factory [40,41] or in the American pesticide plants, [60,61] but cancer mortality still was significantly increased. [40,60,61]

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. Moreover, recent reports [40,47,49,50,52,60,61] undeniably associate occupational exposure to inorganic arsenic with increased cancer mortality.

Although their environmental data were scanty, Ott et al [61] calculated total arsenic dosages received by exposed workers and showed an apparent dose-response relationship for respiratory cancer mortality. Using these data, Blejer and Wagner [62] calculated 8-hour TWAs that would produce the same dosages after a 40-year working life (Table III-4). For the group with the lowest total arsenic dosage, the O/E ratio for respiratory cancer was 0.6, and their exposure on an equivalent 8-hour TWA basis was calculated as 1.0 μg As/cu m. The next higher exposure group had an O/E ratio of 2.0, and an arsenic dose equivalent to 3.0 μg As/cu m on an 8-hour TWA basis.

Arsenic is one of the pollutants produced in varying degrees by most nonferrous metal smelters, and there is evidence suggesting that in some areas arsenic air pollution may have been responsible for increased lung cancer mortality in the general population. Hueper [45] in 1955 reported excessive respiratory cancer mortality in 3 Montana counties in which the major industry was copper mining and/or smelting. Fraumeni [55] reported that lung cancer mortality was increased in 26 of 38 US counties with nonferrous metal smelters, and Newman et al [54] attributed increased respiratory cancer mortality in Anaconda, Montana to arsenic air pollution. No environmental data were available in these studies, but in a 1961-62

survey, [56] 24-hour averages in Anaconda ranged up to 2.5 μg As/cu m.

These data [45,54-56] suggest that exposure on an 8- to 24-hour TWA basis at concentrations of 2-3 μg As/cu m has resulted in increased cancer mortality. This conclusion is supported by the reports of Ott et al [61] and Blejer and Wagner. [62] In the absence of information for a safe level of exposure to a carcinogen such as inorganic arsenic, protection of the worker should be effected by requiring that airborne concentrations not exceed minimally detectable levels. Inorganic arsenic, however, presents a serious complication by its ubiquity in the environment. Limited data on background atmospheric concentrations are available from a 1964-65 EPA air quality survey. [109] In this report, concentrations in most nonurban areas were less than 0.01 μg As/cu m, while the concentrations averaged over 0.02 μg As/cu m in urban areas. The highest concentration reported was 1.4 μg As/cu m in El Paso, Texas, where a nonferrous metal smelter is located.

NIOSH recommends that worker exposure to inorganic arsenic be controlled to prevent exposure in excess of 2.0 μg As/cu m of air as determined by a 15-minute sampling period. This short-term limit is intended to achieve the greatest practicable reduction in worker exposure while avoiding spurious sampling results produced by natural background concentrations of inorganic arsenic. Although there may be enforcement problems in heavily polluted areas, background levels in such places cannot be considered natural, and may be unsafe. Inorganic arsenic compounds can have a direct effect on the skin or may be absorbed through the skin. They also may be absorbed from the lungs, from the tracheobronchial tree, and from the gastrointestinal tract (most nonrespirable particles deposited in

the upper respiratory tract are ingested). Since a toxicologic response can be elicited by arsenic absorbed by any of these routes, the recommended environmental limit is intended to apply to total dust samples, rather than only the respirable fraction.

Since the studies by Baetjer et al [60] and Ott et al [61] demonstrate an association between lymphatic cancer and inorganic arsenic exposure, chest X-rays should be examined for changes that can be suggestive of lymphoma as well as lung cancer. Two additional provisions that can be indicative of lymphoma are also recommended: palpation of the superficial lymph nodes and a complete blood count with differential. Although not included as part of the recommended mandatory medical surveillance program, periodic sputum cytology examinations are suggested for exposed workers. Based on the association between inorganic arsenic and cancer, records should be retained for at least 30 years. Recommendations are also made to ensure that records pertaining to individual worker's exposure and medical history are maintained even when the employer goes out of business. The recommended labels and warning signs have statements to advise of the cancer risk, and the recommended respiratory protective devices include only supplied air or self-contained devices.

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VII. APPENDIX I

AIR SAMPLING PRACTICES FOR ARSENIC

General Requirements

In order to evaluate conformance with the standard, 15-minute breathing zone samples representative of the individual worker's exposure shall be collected. Sampling data sheets shall include:

(a) The date and time of sample collection

(b) Sampling duration

(c) Volumetric flowrate of sampling

(d) A description of the sampling location

(e) Other pertinent information

Air Sampling

(a) Fifteen-minute breathing zone samples representative of worker exposure shall be collected to characterize the exposure from each job or specific operation in each production area.

(b) Samples shall be collected using a portable sampling pump plus a cellulose membrane filter with a pore size of 5.0 μm or less mounted with backup pad in a 2- or 3-piece closed face cassette.

(c) The sampler shall be operated at a flowrate of 2 liters/min and samples taken for 15 minutes.

(d) A minimum of 3 samples shall be taken for each operation or process.

(e) For 20 or fewer samples, 3 blank filters carried in closed cassettes to the sampling site shall be provided to the analytical laboratory for determination of the background correction which must be applied to the analytical results. One additional blank shall be provided for each 10 samples after the first 20.

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 for 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- or 2-liter buret or wet test meter is recommended, although other standard calibrating instruments such as spirometer, Marriott's bottle, or dry-gas meter can be used.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be used. The calibration setup for personal sampling pumps with a cellulose

membrane filter is shown in Figure X-1. Since the flowrate given by a pump is dependent on the pressure drop of the sampling device, in this case a membrane filter, the pump must be calibrated while operating with a representative filter and backup pad in line.

(1) While the pump is running, the voltage of the pump battery is checked with a voltmeter to assure adequate voltage for calibration. The battery is charged if necessary.

(2) Place the cellulose membrane filter with backup pad in the filter cassette.

(3) The sampling train is assembled as shown in Figure X-1.

(4) The pump is turned on and the inside of the soapbubble meter is moistened by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire buret length without bursting.

(5) The pump rotameter is adjusted to provide a flowrate of 2.0 liters/min.

(6) The water manometer is checked to insure that the pressure drop across the sampling train does not exceed 13 inches of water at 2 liters/min.

(7) A soapbubble is started up the buret and the time it takes the bubble to transit a minimum of 1.0 liter is measured with a stopwatch.

(8) The procedure in (7) above is repeated at least 3 times, the results averaged, and the flowrate calculated by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the distance.

(9) Data for the calibration include the volume measured, elapsed time, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

VIII. APPENDIX II

ANALYTICAL METHOD FOR ARSENIC IN URINE AND AIR

PRINCIPLE OF METHOD

Samples are ashed with a mixture of nitric, perchloric, and sulfuric acids to destroy the organic matrix, and taken to fumes of sulfur trioxide to ensure that all traces of nitric acid are removed. The sample is transferred to an arsine generator where the arsenic is converted to the trivalent form. The arsine is generated from the sample either by the addition of metallic zinc or by the addition of sodium borohydride. The arsine is flushed through the burner of an atomic absorption spectrophotometer for the determination of arsenic content.

RANGE AND SENSITIVITY

For a 25-ml urine sample, the range extends from 0.001 to 0.040 mg As/liter. The range can be extended by taking smaller (or larger) aliquots for analysis. For a 30-liter air sample, the range extends from 0.001 to 0.060 mg As/cu m. Fernandez [86] reported an absolute sensitivity of 0.005 μg (5.0 ng) of arsenic using sodium borohydride reduction, a balloon collection technique, and an electrodeless discharge arsenic lamp.

INTERFERENCES

Organic arsenic compounds would cause a positive interference. Appropriate background correction techniques must be applied in order to

eliminate nonspecific absorption at 1937 A.

PRECISION AND ACCURACY

At the 95% confidence level, the precision of the atomic absorption method using a continuous flow system is 9% for 1.0 μg As/sample, and is 25% for 0.10 μg As/sample. NIOSH calculated these values from 15 data points, each obtained over several independent runs. The precision of the present balloon technique may be different.

Fernandez [86] reported a coefficient of variation of 3.2% for 0.25 μg As/sample using the balloon collection method. However, the coefficient of variation at the recommended standard (0.060 μg or 60.0 ng As/sample) is expected to be greater.

The accuracy of the method has not been determined at this time.

ADVANTAGES AND DISADVANTAGES OF THE METHOD

This method has the advantage of being free of interference by antimony. It is somewhat faster, and several times as sensitive as the colorimetric method for arsenic. The disadvantages include the requirement of specialized equipment and the use of rather large volumes of expensive gases. This analytical procedure does not distinguish between pentavalent and trivalent arsenic compounds. Specialized research methods which are not widely used reportedly can distinguish between these valence states. [110,111]

APPARATUS

(a) Atomic absorption spectrophotometer equipped with arsine generator, deuterium arc background correction, and argon-hydrogen system. (Figure X-2) An electrodeless discharge arsenic lamp is recommended.

(b) 125-ml borosilicate Phillips beakers.

(c) Hood facilities capable of handling perchloric acid fumes.

(d) Specific gravity meter or hydrometer capable of measuring specific gravities in the range of 1.000-1.040 ± 0.001.

(e) 25-ml borosilicate volumetric flasks.

REAGENTS AND GASES

All chemicals must be ACS reagent grade or better. Double deionized water or equivalent must be used.

(a) Nitric acid, distilled reagent grade.

(b) Perchloric acid, 72%.

(c) Sulfuric acid, 90%.

(d) Hydrochloric acid, 36%.

(e) Potassium iodide solution. Dissolve 20 g of potassium iodide in 100 ml double distilled water.

(f) Stannous chloride solution. Dissolve 20 g of stannous chloride dihydrate in 100 ml of concentrated hydrochloric acid.

(g) Zinc, 20 mesh granular, low arsenic.

(h) Sodium borohydride, 11/32-inch pellets.

(i) Arsenic standard stock solution, 1,000 ppm. Dissolve 1.320 g of arsenic trioxide in 10 ml of 40% sodium hydroxide and dilute to 1 liter with distilled water. Commercially prepared stock solutions are also

available. Working standards are made by diluting the stock solution.

(j) Gases. Hydrogen, electrolytic grade. Argon, high purity.

PROCEDURE

(a) Cleaning Equipment

All glassware must be cleaned with a detergent solution followed by both tap water and distilled water rinses. Then the glassware is cleaned with hot concentrated nitric acid and thoroughly rinsed with tap water followed by distilled water. (Arsine generators are rinsed with concentrated hydrochloric acid following the nitric acid wash.)

(b) Collection of Urine Samples

Urine samples are collected in polyethylene bottles which are precleaned in nitric acid. About 0.1 g EDTA is added as a preservative. At least 75 ml of urine should be collected. Care should be taken to prevent leaking of bottles in transit.

(c) Collection of Air Samples

Air samples are collected in accordance with Appendix I.

ANALYSIS OF SAMPLES

Determine the specific gravity of the urine sample at room temperature. This may be done with the use of a specific gravity meter or a reliable hydrometer.

Transfer 25 ml of the urine sample, or the membrane filter for air samples, into a 125-ml Phillips beaker. Wet-ash the sample by treating with 5 ml of a mixture of 3 parts nitric acid, 1 part sulfuric acid, and 1

part perchloric acid and heating on a hot plate at 130-150 C. Keep adding small amounts of redistilled nitric acid until a colorless (liquid) ash is obtained. If the ashing is still incomplete, additional perchloric acid can be added dropwise. Continue heating to fumes of sulfur trioxide.

Allow the mixture to cool, then transfer to a 25-ml volumetric flask and make up to volume with distilled water. For urine samples, pipet a 5-ml aliquot of the 25-ml sample into an arsine generation flask with balloon attached. For air samples, transfer the entire sample to the arsine generation flask. The arsine can be generated by either of the following 2 methods.

(a) Reduction with zinc. Add in order 15 ml of distilled water, 10 ml of concentrated hydrochloric acid, 2 ml of potassium iodide solution, and 2 ml of stannous chloride solution. (Swirl solution after the addition of each reagent for homogeneous mixing.) Mix well and allow to stand for 15 minutes to insure the conversion of arsenic to the trivalent form. Attach the flask to the generating system and open the 4-way stopcock for 15 seconds to flush the air out of the system with argon. Add 1.5 g of zinc to the sample solution via the addition stopcock.

(b) Reduction with sodium borohydride. Add 35 ml of distilled water, 5 ml concentrated hydrochloric acid, and mix well. Connect the sample flask to the generating system and open the 4-way stopcock for 15 seconds to flush air out of the system with argon. Add to the sample solution, via the addition stopcock, a single sodium borohydride pellet (11/32-inch diameter, 200-mg).

The reaction is vigorous and the balloon fills with the evolved gases thus acting as a reservoir for the generating system. After one minute,

open the 4-way stopcock allowing the pressure in the balloon to flush the gases into the flame of the atomic absorption instrument. The absorbance is recorded on a rapid response strip chart recorder. Larger (or smaller) aliquots of the sample solution may be taken if the signal is not in the proper range.

CALIBRATION AND STANDARDS

Prepare working standards of 0.25, 0.50, 1.0, 3.0, 5.0, and 7.0 μg of arsenic in 25 milliliters of solution by dilution of the standard stock solution. These standards should be prepared fresh each time.

Construct a calibration curve by pipetting 5 ml of each of the working standards into arsine generators and proceeding with the analysis. A calibration curve of absorbance versus micrograms of arsenic is plotted and used for the determination of arsenic content of the samples.

CALCULATIONS

(a) Urine Samples

The concentration of arsenic in the urine sample can be expressed as mg As/liter of urine.

$$\text{mg As/liter} = \frac{\mu\text{g As}}{\text{ml of urine}} \quad \text{(from calibration curve)}$$

The use of a specific gravity correction factor to normalize values to 1.024, the average specific gravity of urine, has been proposed. [92-94,96] The following correction is recommended. Specific gravities less

than 1.010 are unreliable and these samples should be discarded.

$$\text{corrected mg As/liter} = \text{mg As/liter} \times \frac{(1.024-1.000)}{(\text{specific gravity} - 1.000)}$$

(b) Air Samples

The concentration of arsenic in air can be expressed as milligrams As per cubic meter of air, which is numerically equal to micrograms As per liter of air.

$$\text{mg As/cu m} = \mu\text{g As/V}$$

where:

μg As = micrograms As from calibration curve

V = volume of air sampled (in liters) at 25 C and 760 mmHg.

IX. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters in as large type size as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, "An Identification System for Occupationally Hazardous Materials." The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone number (including area code), are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be 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, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, ie, "100 ppm LC50-oral-rat," "25 mg/cu m LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.93," or if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute, Inc. Flammable or reactive data

could be flash point, shock sensitivity, or other brief data indicating nature of the hazard.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and exposion data for the product, including flash point and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special fire fighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a time-weighted average (TWA) concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, mild irritation and possibly some blistering.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal anti-pollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If Necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," "Suitable for dusts not more toxic than lead," etc. Protective equipment must be specified as to type and materials of construction.

(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Undersigning and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers potentially exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION

MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS

MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA

BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT.	
% VOLATILES BY VOL.		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES:

SKIN:

INHALATION:

INGESTION:

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY:

ADDRESS:

DATE:

TABLE X-1

PHYSICAL AND CHEMICAL PROPERTIES OF
IMPORTANT INORGANIC ARSENICALS

Arsenic, 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 mmHg (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

Arsine, AsH3

(Arsenic Hydride, Arseniuretted Hydrogen)
Physical state: colorless gas
Formula weight: 77.95
Density: 2.695
Boiling point: -55 C
Percent arsenic: 96

TABLE X-1 (CONTINUED)

Calcium Arsenate, $Ca_3(AsO_4)_2$
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.

Cupric Arsenite, $CuHAsO_3$ (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

Lead Arsenate, $Pb_3(AsO_4)_2$ (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

Lead Arsenite, $Pb(AsO_2)_2$ (Lead Metarsenite)
Physical state: white powder
Formula weight: 421.03
Specific gravity: 5.85
Solubility: insoluble in cold water
Percent arsenic: 36

Ortho-Arsenic Acid, H_3AsO_4-1/2H_2O
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

Sodium Arsenite, $NaAsO_2$ (Sodium Metarsenite)
Physical state: gray-white powder
Formula weight: 129.91
Specific gravity: 1.87
Solubility: very soluble in water
Percent arsenic: 58

from Patty [5] and Weast and Selby [7]

TABLE X-2
OCCUPATIONS WITH POTENTIAL ARSENIC EXPOSURE

acetylene workers
acid dippers
alloy makers
aniline color makers
aniline workers
arsine workers
Babbitt metal workers
bleaching powder makers
boiler operators
brass makers
bronze makers
bronzers
cadmium workers
cattle dip workers
ceramic enamel makers
ceramic makers
copper smelters
defoliant applicators
defoliant makers
dimethyl sulfate makers
drug makers
dye makers
electrolytic copper makers
electroplaters
enamelers
etchers
farmers
ferrosilicon workers
fertilizer makers
fireworks makers
galvanizers
glass makers
gold extractors
gold refiners
hair remover makers
herbicide makers
hide preservers
hydrochloric acid workers
illuminating gas workers
insecticide makers
jewelers
lead burners
lead shot makers
lead smelters
leather workers
lime burners
metal cleaners
metal refiners
nitrocellulose makers
ore smelter workers
organic chemical synthesizers
paint makers
painters
paper makers
petroleum refinery workers
pigment makers
plastic workers
plumbers
printing ink workers
rayon makers
rodenticide makers
semiconductor compound makers
sheep dip workers
silver refiners
soda makers
solderers
submarine workers
sulfuric acid workers
taxidermists
textile printers
tinners
tree sprayers
type metal workers
water weed controllers
weed sprayers
wood preservative makers
wood preservers
zinc chloride makers

from Gafafer [9]

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

"Heavy exposure area" as classified by Lee and Fraumeni [49]

Arsenic Roaster Area		Mean:	1.47
0.10	0.20	Median:	0.185
0.10	0.22		
0.10	0.25		
0.10	0.35		
0.10	1.18		
0.10	5.00		
0.17	12.66		

"Medium exposure areas" as classified by Lee and Fraumeni [49]

Reverberatory Area		Mean:	1.56
0.03	0.93	Median:	0.88
0.22	1.00		
0.23	1.27		
0.36	1.60		
0.56	1.66		
0.63	1.84		
0.66	1.94		
0.76	2.06		
0.78	2.76		
0.78	3.40		
0.80	4.14		
0.83	8.20		

Treater Building and Arsenic Loading		Mean:	1.50
0.10	0.48	Median:	0.295
0.10	0.62		
0.10	3.26		
0.11	7.20		

"Light exposure areas" as classified by Lee and Fraumeni [49]

Copper Concentrate Transfer System		Mean:	0.70
0.25		Median:	0.65
0.65			
1.20			

Samples from Flue Station		Mean:	0.17
0.10		Median:	0.17
0.24			

Reactor Building		Mean:	0.004
0.001	0.003	Median:	0.002
0.002	0.009		
0.002	0.010		
0.002			

TABLE X-4
1965 SMELTER SURVEY
URINARY ARSENIC

Job Title		mg As/liter of urine
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 X - 1. CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH FILTER CASSETTE

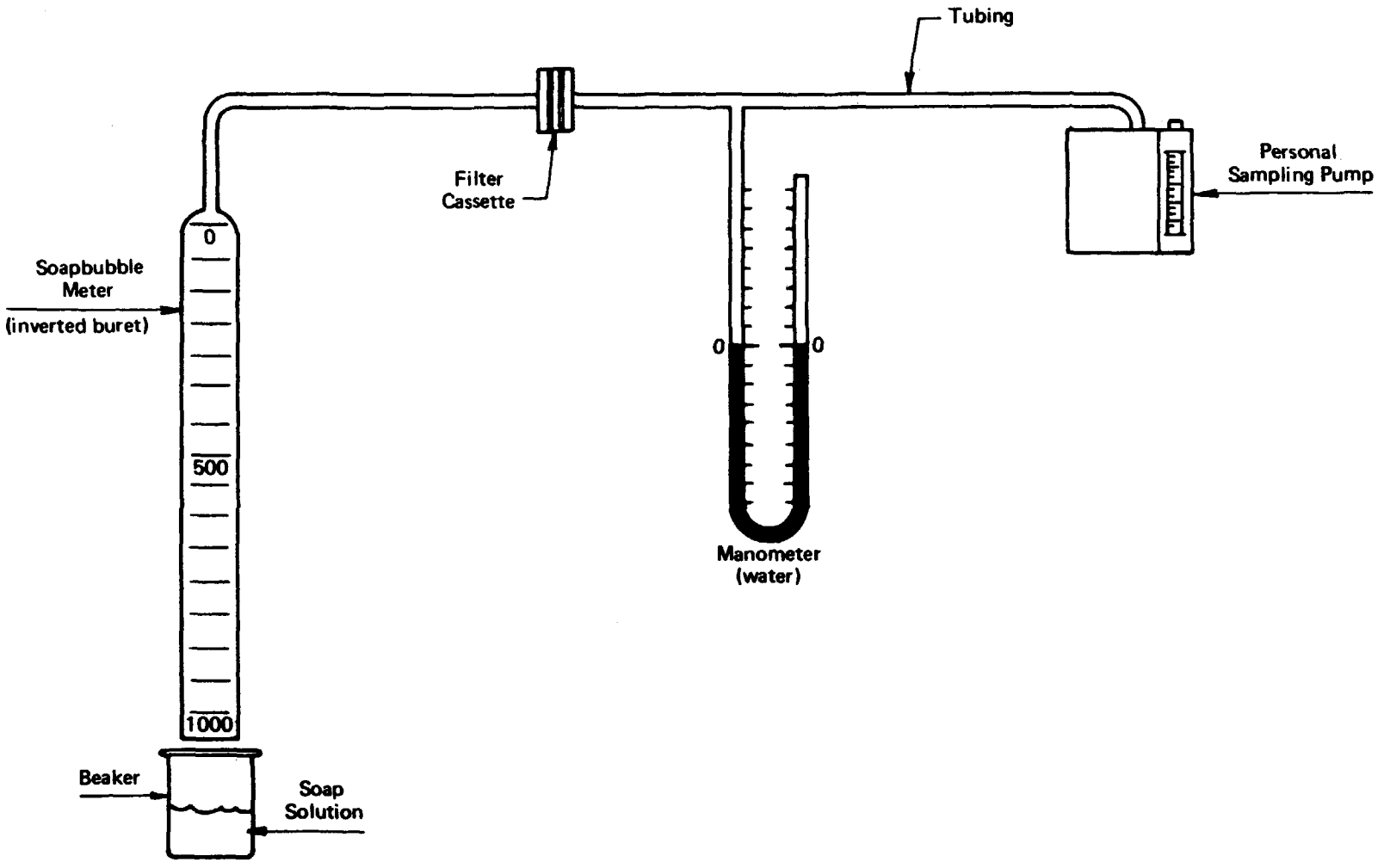
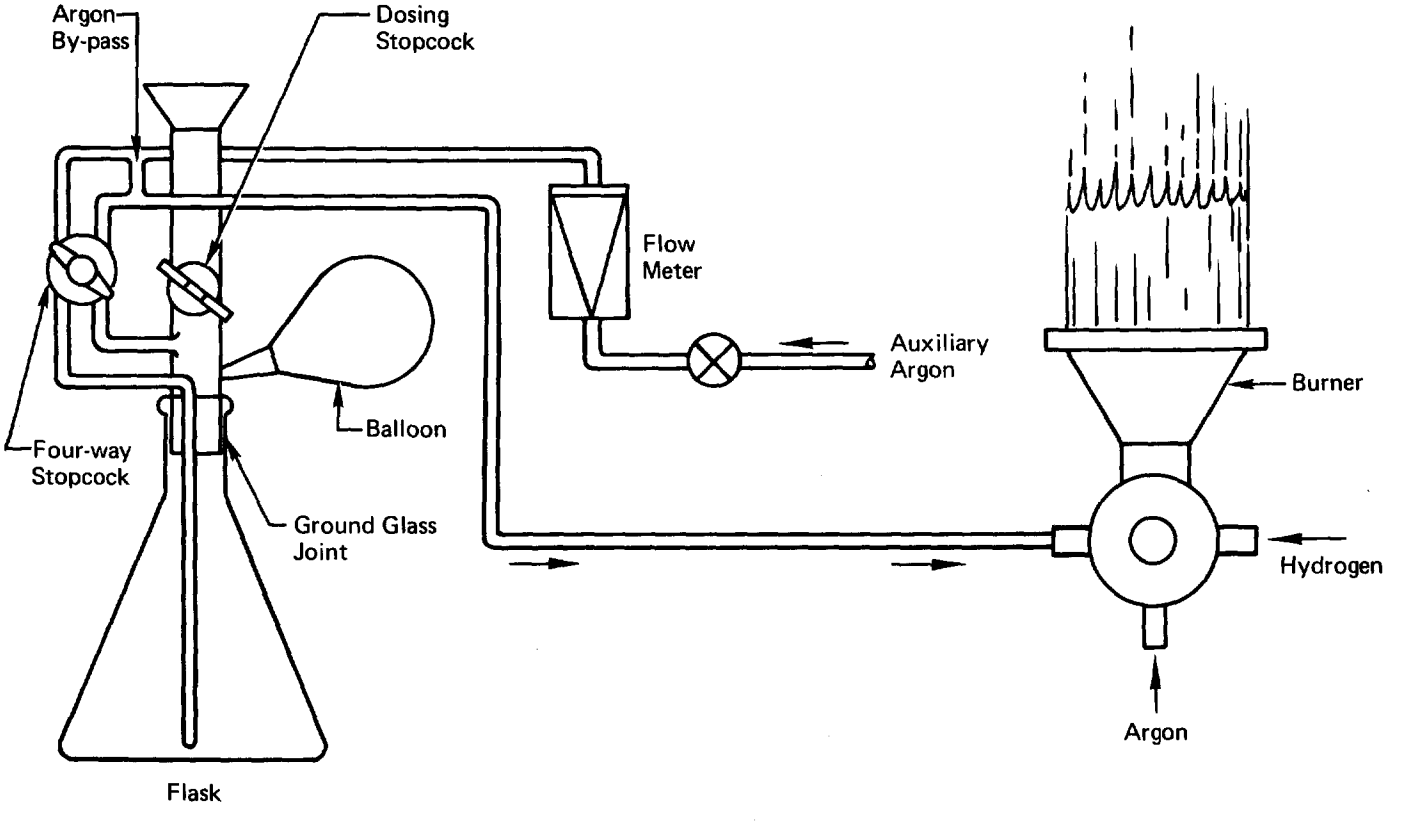


FIGURE X - 2. APPARATUS FOR ARSINE GENERATION



Instrument conditions to use for arsine measurement by atomic absorption.

wavelength – 1937 Å
slit - 7 Å
burner – three slot
Argon Flow – 8 scfh
H_2 Flow – 3 scfh
Recorder – fast response
Aspirate water continuously during analysis.

☆ U. S. GOVERNMENT PRINTING OFFICE 1975-657-696/5507 Region No. 5-11

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