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.

VI. REFERENCES

1. Schroeder HA, Balassa JJ: Abnormal trace metals in man: Arsenic. J Chronic Dis 19:85-106, 1966

2. Frost DV: Arsenicals in biology--Retrospect and prospect. Fed Proc 26:194-208, 1967

3. Browning E: Arsenic and arsine, in Toxicity of Industrial Metals. London, Butterworth & Co, 1961, pp 34-52

4. Schrenk HH, Schreibeis L Jr: Urinary arsenic levels as an index of industrial exposure. Am Ind Hyg Assoc J 19:225-28, 1958

5. Patty FA: Arsenic, phosphorus, selenium, sulfur, and tellurium, in Patty FA (ed): Industrial Hygiene and Toxicology, ed 2 rev; Toxicology (DW Fassett, DD Irish, eds). New York, Interscience Publishers, 1962, vol 2, pp 871-80

6. Vallee BL, Ulmer DD, Wacker WEC: Arsenic toxicology and biochemistry. Arch Ind Health 21:132-51, 1960

7. Weast RC, Selby SM (eds): Handbook of Chemistry and Physics, ed 48. Cleveland, Chemical Rubber Co, 1967, pp B-155, B-173, B-162, B-186, B-222

8. Minerals Yearbook 1969: Metals, Minerals, and Fuels. US Government Printing Office, 1971, vol I-II, p 1176

9. Gafafer WM (ed): Occupational Diseases--A Guide to Their Recognition, publication No 1097. US Dept Health, Education, and Welfare, Public Health Service, 1964, pp 83-84

10. Neubauer O: Arsenical cancer--A review. Br J Cancer 1:192-251, 1947

11. Harting FH, Hesse W: [Lung cancer, mine disease in the Schneeberger mines.] Vierteljahrschr Gerichtl Med 30:296-309, 1879 (Ger)

12. Doll R: Cancer of the lung and nose in nickel workers. Br J Ind Med 15:217-23, 1958

13. Amor AJ: Growths of the respiratory tract (preliminary notice). Report of the VIII International Congress for Industrial Accidents and Occupational Diseases, 1938, Leipzig. 2:941-62, 1939

14. Morgan JG: Some observations on the incidence of respiratory cancer in nickel workers. Br J Ind Med 15:224-34, 1958

15. Goldblatt MW: Occupational carcinogenesis. Br Med Bull 14:136-40, 1958

16. Hueper WC: Experimental studies in metal cancerigenesis--IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel. Arch Pathol 65:600-07, 1958

17. Kelynack TN, Kirkby W, Delepine S, Tattersall CH: Arsenical poisoning from beer-drinking. Lancet 2:1600-02, 1900

18. Mees RA: [A symptom of polyneuritis arsenicosa.] Ned Tijdschr Geneeskd 1:391-96, 1919 (Dut)

19. Dinman BD: Arsenic--Chronic human intoxication. J Occup Med 2:137-41, 1960

20. Buchanan WD: Toxicity of arsenic compounds, in Browning E (ed): Elsevier Monographs on Toxic Agents. New York, Elsevier Publishing Co, 1962

21. Delepine S: Observations upon the effects of exposure to arsenic trichloride upon health. J Ind Hyg 4:346-64, 410-23, 1923

22. Watrous RM, McCaughey MB: Occupational exposure to arsenic--In the manufacture of arsphenamine and related compounds. Ind Med 14:639-46, 1945

23. Webster SH: The lead and arsenic content of urines from 46 persons with no known exposure to lead or arsenic. US Public Health Service Report 56:1953-61, 1941

24. Holland RH, McCall MS, Lanz HC: A study of inhaled arsenic-74 in man. Cancer Res 19:1154-56, 1959

25. McCutchen JJ, Utterback RA: Chronic arsenic poisoning resembling muscular dystrophy. South Med J 59:1139-45, 1966

26. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics, ed 2. New York, Macmillan, 1958, pp 950-56

27. Kyle RA, Pease GL: Hematologic aspects of arsenic intoxication. N Engl J Med 273:18-23, 1965

28. Butzengeiger KH: [On peripheral circulatory disorders during arsenic intoxication.] Klin Wochenschr 19:523-27, 1940 (Ger)

29. Zettel H: [The effect of chronic arsenic damage on heart and blood vessels.] Z Klin Med 142:689-703, 1943 (Ger)

30. Butzengeiger KH: [Chronic arsenic poisoning--I. EKG alterations and other cardiovascular manifestations.] Dtsch Arch Klin Med 194:1-16, 1949 (Ger)

31. Barry KG, Herndon EG Jr: Electrocardiographic changes associated with acute arsenic poisoning. Med Ann D C 31:25-27, 65-66, 1962

32. Glazener FS, Ellis JG, Johnson PK: Electrocardiographic findings with arsenic poisoning. Calif Med 109:158-62, 1968

33. Franklin M, Bean WB, Hardin RC: Fowler's solution as an etiologic agent in cirrhosis. Am J Med Sci 219:589-96, 1950

34. Graham JH, Mazzanti GR, Helwig EB: Chemistry of Bowen's disease--Relationship to arsenic. J Invest Dermatol 37:317-32, 1961

35. Fraser JF: Bowen's disease and Paget's disease of the nipple--Their relation to dyskeratosis. Arch Dermatol Syphilol 18:809-28, 1928

36. Sommers SC, McManus RG: Multiple arsenical cancers of skin and internal organs. Cancer 6:347-59, 1953

37. Holmqvist I: Occupational arsenical dermatitis--A study among employees at a copper ore smelting work including investigations of skin reactions to contact with arsenic compounds. Acta Derm Venereol 31 [Suppl 26]:1-214, 1951

38. Birmingham DJ, Key MM, Holaday DA, Perone VB: An outbreak of arsenical dermatoses in a mining community. Arch Dermatol 91:457-64, 1965

39. Pinto SS, McGill CM: Arsenic trioxide exposure in industry. Ind Med Surg 22:281-87, 1953

40. Hill AB, Faning EL: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic--I. Mortality experience in the factory. Br J Ind Med 5:1-6, 1948

41. Perry K, Bowler RG, Buckell HM, Druett HA, Schilling RSF: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic--II. Clinical and environmental investigations. Br J Ind Med 5:6-15, 1948

42. Snegireff LS, Lombard OM: Arsenic and cancer--Observations in the metallurgic industry. Arch Ind Hyg Occup Med 4:199-205, 1951

43. Vital statistics of the United States, 1938, Part I--Natality and mortality data for the United States tabulated by place of occurrence with supplemental tables for Hawaii, Puerto Rico, and the Virgin Islands. US Dept Commerce, Bureau of the Census, 1940, pp 178-79, 184-87

44. Vital statistics of the United States, 1945, Part I--Natality and mortality data for the United States tabulated by place of occurrence with supplemental tables for Hawaii, Puerto Rico, the Virgin Islands, and Alaska. Federal Security Agency, US Public Health Service, 1947, pp 54-55, 60-61, 64-65

45. Hueper WC: A Quest Into the Environmental Causes of Cancer of the Lung, Public Health monograph No. 36. US Dept Health, Education, and Welfare, Public Health Service, 1955, pp 27-29

46. Roth F: [Concerning bronchial cancers in vine-growers injured by arsenic.] Virchows Arch [Pathol Anat] 331:119-37, 1958 (Ger)

47. Milham S Jr, Strong T: Human arsenic exposure in relation to a copper smelter. Environ Res 7:176-82, 1974

48. Pinto SS, Bennett BM: Effect of arsenic trioxide exposure on mortality. Arch Environ Health 7:583-91, 1963

49. Lee AM, Fraumeni JF Jr: Arsenic and respiratory cancer in man--An occupational study. J Natl Cancer Inst 42:1045-52, 1969

50. Kuratsune M, Tokudome S, Shirakusa T, Yoshida M, Tokumitsu Y, Hayano T, Seita M: Occupational lung cancer among copper smelters. Int J Cancer 13:552-58, 1974

51. Rencher AC, Carter MW: A retrospective epidemiological study at Kennecott's Utah smelter--Phase I Morbidity. Unpublished report submitted to the Kennecott Copper Corporation, New York, NY, April, 1971

52. Rencher AC, Carter MW: A retrospective epidemiological study at Kennecott's Utah smelter--Phase II Mortality. Unpublished report submitted to the Kennecott Copper Corporation, New York, NY, April, 1971

53. Milby TH, Hine CH: A survey of mortality due to respiratory diseases among employees of the Kennecott Corporation. Unpublished report submitted to the Kennecott Copper Corporation, New York, NY, October 4, 1974

54. Newman JA, Archer VE, Saccomanno G, Kuscher M, Averbach O, Grondahl RD, Wilson JC: Bronchogenic carcinoma in the copper smelting and mining industry. Presented by JA Newman at the Conference on Occupational Carcinogenesis, New York City, March 24-27, 1975.

55. Fraumeni JF Jr: Remarks made during discussion following the Carcinogenesis in the Metal Industry session, at Conference on Occupational Carcinogenesis, New York City, March 24-27, 1975.

56. A study of air pollution in Montana--July 1961-July 1962. Montana State Board of Health, Division of Disease Control, and Dept Health, Education, and Welfare, Public Health Service, Division of Air Pollution, p 94

57. Nelson WC, Lykins MH, Mackey J, Newill VA, Finklea JF, Hammer DI: Mortality among orchard workers exposed to lead arsenate spray--A cohort study. J Chron Dis 26:105-18, 1973

58. Neal PA, Dreessen WC, Edwards TI, Reinhart WH, Webster SH, Castberg HT, Fairhall LT: A study of the effect of lead arsenate exposure on orchardists and consumers of sprayed fruit, Public Health bulletin No 267. Federal Security Agency, Public Health Service, National Institute of Health, 1941, pp 181

59. US Cancer Mortality by County: 1950-1969. DHEW Publication no (NIH) 74-615. US Dept Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, Md, pp 247, 262, 425, 439, 445, 459, 479, 494, 529, 543, 728, 729

60. Baetjer AM, Levin ML, Lilienfeld A: Analysis of mortality experience of Allied Chemical plant--2000 Race St., Baltimore, Md. Unpublished report submitted to the Allied Chemical Corporation, Morristown, NJ, July 16, 1974

61. Ott MG, Holder BB, Gordon HL: Respiratory cancer and occupational exposure to arsenicals. Arch Environ Health 29:250-55, 1974

62. Blejer HP, Wagner W: Inorganic arsenic--Ambient level approach to the control of occupational carcinogenic exposures. Presented at the Conference on Occupational Carcinogenesis, New York City, March 24-27, 1975.

63. Harrisson JWE, Packman EW, Abbott DD: Acute oral toxicity and chemical and physical properties of arsenic trioxides. Arch Ind Health 17:118-23, 1958

64. Sharpless GR, Metzger M: Arsenic and goiter. J Nutr 21:341-46, 1941

65. Dubois KP, Moxon AL, Olson OE: Further studies on the effectiveness of arsenic in preventing selenium poisoning. J Nutr 19:477-82, 1940

66. Ginsburg JM, Lotspeich WD: Interrelations of arsenate and phosphate transport in the dog kidney. Am J Physiol 205:707-14, 1963

67. Ginsburg JM: Renal mechanism for excretion and transformation of arsenic in the dog. Am J Physiol 208:832-40, 1965

68. Byron WR, Bierbower GW, Brouwer JB, Hansen WH: Pathologic changes in rats and dogs from two-year feeding of sodium arsenite or sodium arsenate. Toxicol Appl Pharmacol 10:132-47, 1967

69. Schroeder HA, Kanisawa M, Frost DV, Mitchener M: Germanium, tin, and arsenic in rats: Effects on growth, survival, pathological lesions, and life span. J Nutr 96:37-45, 1968

70. Rozenshtein IS: Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere. Hyg Sanit 35:16-21, 1970

71. Bencko V, Symon K: The cumulation dynamics in some tissue of hairless mice inhaling arsenic. Atmos Environ 4:157-61, 1970

72. Bencko V, Symon K: Dynamics of arsenic cumulation in hairless mice after peroral administration. J Hyg Epidemiol Microbiol Immunol 13:248-53, 1969

73. Holmberg RE Jr, Ferm VH: Interrelationships of selenium, cadmium, and arsenic in mammalian teratogenesis. Arch Environ Health 18:873-77, 1969

74. Ferm VH, Saxon A, Smith BM: The teratogenic profile of sodium arsenate in the golden hamster. Arch Environ Health 22:557-60, 1971

75. Hood RD, Bishop SL: Teratogenic effects of sodium arsenate in mice. Arch Environ Health 24:62-65, 1972

76. Leitch A, Kennaway EL: Experimental production of cancer by arsenic. Br Med J 2:1107-08, 1922

77. Leitch A: The experimental inquiry into the cause of cancer. Br Med J 2:1-7, 1923

78. Hueper WC, Payne WW: Experimental studies in metal carcinogenesis--Chromium, nickel, iron, arsenic. Arch Environ Health 5:445-62, 1962

79. Baroni C, van Esch GJ, Saffiotti U: Carcinogenesis tests of two inorganic arsenicals. Arch Environ Health 7:668-74, 1963

80. Osswald H, Goerttler K: [Arsenic-induced leukemia in mice after diaplacental and postnatal application.] Dtsch Gesell Pathol 55:289-93, 1971 (Ger)

81. Kroes R, van Logten MJ, Berkvens JM, de Vries T, van Esch GJ: Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosamine. Food Cosmet Toxicol 12:671-79, 1974

82. Dubois L, Monkman JL: Determination of arsenic in air and biological materials. Am Ind Hyg Assoc J 22:292-95, 1961

83. ACGIH Committee on Recommended Analytical Methods: Determination of arsenic in air, in Manual of Analytical Methods, Recommended for Sampling and Analysis of Atmospheric Contaminants. Cincinnati, American Conference of Governmental Industrial Hygienists, 1958, pp Arsenic 1-6

84. Intersociety Committee: Tentative method of analysis for arsenic content of atmospheric particulate matter, in Methods of Air Sampling and Analysis. Washington, American Public Health Association, 1972, pp 289-92

85. Fernandez FJ, Manning DC: Atomic absorption application study no. 468--The determination of arsenic and selenium at sub-microgram levels. The Perkin-Elmer Corporation, Instrument Division, Norwalk, Conn, June, 1971, 10 pp

86. Fernandez FJ: Atomic absorption determination of gaseous hydrides utilizing sodium borohydride reduction. Atomic Absorption Newsletter 12:93-97, 1973

87. National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development: Arsenic in Urine and Air--Physical and Chemical Analysis Branch Method 139, in NIOSH Manual of Analytical Methods, HEW publication No (NIOSH) 75-121, Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, Center for Disease Control, NIOSH, 1974, pp 139-1 to 139-8

88. Barnett W: Atomic absorption application study no. 523--Determination of As and Se with the HGA. The Perkin-Elmer Corporation, May, 1973

89. General Method--Arsenic Analysis by Anodic Stripping Voltammetry (ASV): Environmental Sciences Associates, Inc, Burlington, Mass, (n.d.)

90. Arsenic and its compounds (except arsine), revised 1964, AIHA Hygienic Guide Series. Am Ind Hyg Assoc J 25:610-13, 1964

91. Camp WJR, Gant VA: Arsenic content of normal hair in the Chicago area. Fed Proc 8:279, 1949

92. Elkins HB: The Chemistry of Industrial Toxicology, ed 2. New York, Wiley & Sons, 1959, pp 62-63, 256, 295-98

93. Elkins HB: Maximum permissible urinary concentrations--Their relationship to atmospheric maximum allowable concentrations. Pure Appl Chem 3:269-73, 1961

94. Elkins HB, Pagnotto LD: The specific gravity adjustment in urinalysis. Arch Environ Health 18:996-1001, 1969

95. Buchwald H: The expression of urine analysis results--Observations on the use of a specific gravity correction. Ann Occup Hyg 7:125-36, 1964

96. Levine L, Fahy JP: Evaluation of urinary lead determination. J Ind Hyg Tox 27:217-223, 1945

97. Arsenic fumes. National Safety News, December, 1943, pp 34, 36

98. Cook WA: Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14:936-46, 1945

99. 1947 M. A. C. Values. Ind Hyg Newsletter, Division of Industrial Hygiene, US Public Health Service, August 1947, p 15

100. American Conference of Governmental Industrial Hygienists: Transactions of the 10th Annual Meeting. Boston, ACGIH, 1948, pp 30-32

101. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1974. Cincinnati, ACGIH, 1974, pp 11-12, 22, 37, 52-53

102. Threshold Limits 1975--Notice of Intended Changes, in ACGIH Jan-Feb 1975 Bulletin Board. Cincinnati, American Conference of Governmental Industrial Hygienists, 1975, vol 19, p 1

103. American Conference of Governmental Industrial Hygienists: Transactions of the 18th Annual Meeting. Philadelphia, ACGIH, 1956, pp 76-78

104. American Conference of Governmental Industrial Hygienists: Transactions of the 19th Annual Meeting. St. Louis, Mo, ACGIH, 1957, pp 53-55

105. ACGIH Committee on Threshold Limit Values: Documentation of Threshold Limit Values, ed 3. Cincinnati, American Conference of Governmental Industrial Hygienists, 1971, pp 16, 36, 145

106. Smyth HF Jr: Hygienic standards for daily inhalation--The Donald E. Cummings Memorial Lecture. Am Ind Hyg Assoc Quarterly 17:129-85, 1956

107. Report of the Sub Committee on Threshold Limits, in Proceedings of the Eighth Annual Meeting of the American Conference of Governmental Industrial Hygienists, Chicago, April 7-13, 1946, p 54

108. Czechoslovak Committee of MAC (J Teisinger, Chmn): Documentation of MAC in Czechoslovakia. Prague, The Committee, 1969, pp 15-16

109. Air Quality Data from the National Air Sampling Networks and Contributing State and Local Networks 1964-1965. US Dept of Health, Education, and Welfare, Public Health Service, 1966, pp 61-63

110. Meyers DJ, Osteryoung J: Determination of arsenic (III) at the parts-per-billion level by differential pulse polarography. Anal Chem 45:267-71, 1973

111. Braman RS, Foreback CC: Methylated forms of arsenic in the environment. Science 182:1247-49, 1973