ARSENIC TOXICOLOGY AND INDUSTRIAL EXPOSURE

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The Occupational Safety and Health Act of 1970 tremendously enlarged the field of health care in industry in the United States. It directs the Secretary of Labor "to set the standard which most adequately assures . . . that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" (1).

The secretary's task in setting standards involves great problems, because it assumes knowledge of pharmacology and toxicology of substances not yet developed in spite of the cumulative experience of centuries in some cases and of scientific research for decades. Arsenic is an example of a substance for which it has been difficult to set standards. In this paper we review the challenging and divergent views met with when an attempt is made to set a standard for airborne inorganic arsenic.

Inorganic arsenic is widely used in industry. The National Institute of Safety and Health (NIOSH) has estimated that about 1.5 million people in industry are potentially exposed to arsenic at least part of the time during the course of their work. (2) NIOSH is authorized to "conduct such research and experimental programs . . . as are necessary for the development of criteria for . . . improved health standards" and to "make recommendations concerning new . . . health standards." NIOSH has been most concerned with the possibility of inorganic airborne arsenic acting as a respiratory carcinogen. This, or course, is just part of a larger question, that is, does arsenic cause cancer?

Buchanan (3) and Vallee (4) have reviewed the problem and state that the idea was first proposed in the publications of Paris in 1820. However, Paris's work has not been confirmed. In 1887 Hutchinson showed a relationship between prolonged oral administration of arsenical preparations and skin cancer. Neubauer (5) in 1947 brilliantly reviewed all prior literature on the question of arsenical cancer and stated that only a very few persons of the thousands receiving oral arsenical preparations ever developed epitheliomas. He suggests that "in arsenical cancer, arsenic is not the only aetiological factor." Neubauer collected 143 published cases of medicinal

arsenical epithelioma in man. Many of these cases had an "affection of the skin, and especially psoriasis [which] gives a predisposition for arsenical cancer although there is no real definite proof." The great majority of the cases developed after the drug had been given for about 15 years, and the average patient received 28 grams of arsenic during the entire course of treatment. Roth (6) studied cancer in German vintners who were exposed to arsenic from inhalation of insecticide sprays and dusts as well as from drinking a wine that contained a high level of arsenic (0.2–8.9 mg/100 ml). He estimated that the workers had a 12–17 year exposure and an intake of about 53 grams of arsenic over a 12 year period. The latent period for tumor development was estimated to be 13–22 years after first exposure.

Regelson (7) described an instance of hemangioendothelial sarcoma of the liver seven years after the discontinuation of treatment with Fowler's solutions. In this report, a case of psoriasis is described which had been treated with Fowler's solution for 17 years.

Hill & Fanning (8) studied mortality data on employees working in a factory that produced sodium arsenate. Mortality data for workers in the factory between 1910 and 1943 were compared with mortality data for other workers in the community. Among 75 deceased factory workers there were 22 deaths from cancer (29.3%), while workers in other occupations in the community showed 157 deaths from cancer in 1216 deceased workers (12.9%). Workers engaged in handling sodium arsenate had an increased percentage of their deaths from cancer of the respiratory system. Thus 31.3% of their deaths from cancer were in the respiratory system while 15.9% of the control group had respiratory cancer. The factory workers also had an increase in skin cancer compared to the control group.

Perry et al (9) investigated the clinical and environmental aspects of the factory and its employees in 1946. Appreciable arsenic absorption was evidenced by skin changes (pigmentation and warts), which were observed clinically in all chemical workers. Atmospheric concentrations of arsenic in different parts of the factory were found to range from a high of 1034 μg per cubic meter, to a low of 384 μg of arsenic per cubic meter.

Hill & Fanning describe their conclusions as "guarded but suggestive." A twofold excess of deaths from all cancer was observed in the factory workers; the organ systems especially affected were the respiratory and skin.

Snegireff & Lombard in 1951 (10) published a study of deaths from cancer in two plants, one in which arsenic trioxide was produced, the other in which no arsenic was handled. No apparent difference between the two plants in cancer death experiences was found, but NIOSH has suggested that the lack of inter-plant differences could be due to an unsuspected arsenic exposure in the control plant. (11) In the arsenic-exposed plant 39% of all cancer deaths were due to lung cancer while 50% of all cancer deaths in the non-arsenic exposure plant were due to lung cancer. The sample size limitations in this study make it of questionable significance in evaluating the problem of arsenic and cancer.

Pinto & Bennett (12) in 1963 studied the mortality data in the deaths of 229 individuals who worked at a copper smelter where arsenic trioxide was produced as a by-product. The deaths covered the period 1946–1960. The total number of

deaths from lung cancer in this group was compared with a list of such deaths prepared by the Washington State Division of Vital Statistics. The cases that were classed as lung cancer cases by the state were the same cases of lung cancer used in the Pinto-Bennett study, and there was no under-reporting of cases as has been suggested (11).

The study showed that workers in the plant had the same total incidence of cancer as in the state of Washington for the population of the same sex and age. However, within the cancer group there was a twofold increase in respiratory cancer for both the group exposed to high arsenic levels and the group exposed to low arsenic levels. In a previous study Pinto & McGill (13) had studied two groups of employees in the plant. One group worked in an area of high potential arsenic exposure, and the other in an area with presumably minimal arsenic exposure. The high exposure group had an average urinary arsenic value of 820 μg/liter, while the minimal exposure group had an average urinary excretory value of 130 μg/liter.

In a more recent study Pinto & Enterline (14) analyzed the causes of death among 530 male retirees from the same smelter who retired between January 1, 1949 and December 31, 1973. Pensioners were specifically studied because each member of the group had been exposed to arsenic trioxide for a definite period of time that ended with retirement. Thus, exposure and follow-up period did not overlap. Total arsenic exposure for each individual was calculated from personnel records, and was obtained by multiplying the average arsenic exposure in each department by the time spent in that department. An excess of respiratory cancer deaths was found and there appeared to be a linear relationship between the increase in deaths from respiratory cancer and degree of exposure to arsenic or some closely related material. No excess in deaths from lymphatic cancer was found.

Further analysis of the data indicated that there was a measure of arsenic exposure below which no excess respiratory cancer was found if the period of exposure was shorter than 25 years. The safe level of exposure to arsenic was indicated to be of the order of 100 μg per m^3 of air. It was noted there were other air contaminants in the industrial atmosphere and that their possible synergistic action cannot be overlooked. The proposed exposure level cannot be considered as based solely on arsenic trioxide. Rather, arsenic trioxide is used as an indicator of a complex industrial airborne exposure. After 25 or more years of exposure, there were statistically significant respiratory cancer excesses that were related to the intensity of exposure.

This study also developed histories of the smoking patterns of 377 men in the total pensioner group who were alive on January 1, 1961. Their mortality experience was followed through 1973. Analyses showed some interaction between smoking and arsenic exposure but not the multiplying effect observed for some other substances. The figures indicate that the excess mortality ratio due to respiratory cancer in the group was not due entirely to smoking.

Weir (14) has pointed out a number of factors that must be considered in evaluating lung cancer presumably due to occupational factors. These include smoking pattern, urban-rural residence, foreign born/native born population proportions, and socioeconomic variations. He further pointed out that the age-adjusted lung

cancer rate for white males for 1950–1969 in the state of Washington is 34.61 per 100,000 yet the county rates for this same period range from 10.4–46.0. It is evident that a variety of factors influencing rates of death from lung cancer fluctuate by county of residence and account for this variation in death rate.

Lee & Fraumeni (15) in 1969 compared the mortality data of 8047 white male smelter workers who were exposed to both arsenic trioxide and sulfur dioxide from 1933 to 1963. They found 1877 deaths compared to 1634 expected deaths. Classifying the deaths into three groups according to intensity of arsenic exposure, Lee & Fraumeni found that deaths from lung cancer increased with higher degrees of arsenic trioxide exposure. When workers were grouped according to duration and degree of exposure to sulfur dioxide, excess lung cancer mortality was found with increasing exposure to sulfur dioxide. Lee & Fraumeni's studies also indicated that there was more respiratory cancer among the foreign-born sample than in the native-born sample. However, figures on the incidence of lung cancer for the two groups are not presented in the paper and cannot be generated from the published tables.

The authors conclude that their findings are "consistent with the hypothesis that exposure to high levels of arsenic trioxide, perhaps in interaction with sulfur dioxide or unidentified chemicals in the work environment, is responsible for the threefold excess of respiratory cancer deaths among smelter workers." In an attempt to find the levels of arsenic that might have been present in this smelter, air analyses were made in various departments of a smelter in 1965. The validity of applying an air-contamination figure of 1965 to a similar operation in 1940 is open to question. It has been our experience that air contamination in the non-ferrous smelting industry was less in 1965 than it was in the period before 1948. After 1948, structural building material was available, and the processes learned for reducing harmful air contaminants in industry during World War II were applied more widely throughout the United States smelting industry.

Nelson et al (16) studied the long-term effect of lead arsenate spray on the users rather than on the producers. This was a follow-up mortality study for a cohort of 1231 individuals who had participated in a 1938 mortality survey of the effects of exposures to lead arsenate insecticide spray. Over 97% of the original 1938 group were located. The authors concluded that excess mortality did not occur. In fact, the orchardists, the most highly exposed group, had the lowest standard mortality ratio of the three groups analyzed. It should be noted that the authors report having used as cause-of-death the primary cause listed on death certificates. This action usually results in underestimating the true frequency of death due to lung cancer.

Ott et al (17) in 1974 presented a study of exposure to lead arsenate and calcium arsenate occurring between 1919 and 1956. Arsenic trioxide was the basic material from which the arsenates were made. The relationship between cumulative arsenic exposure and the ratio of observed to expected respiratory malignancy deaths was estimated by the method of least squares. The predicted ratio was 7:1 for individuals exposed for more than eight years to compounds that contained an equivalent level of 1 mg/m^3 arsenic. In the more heavily exposed individuals, an excess of respiratory cancer was observed 35+ years after the initial exposure. An increase in malignant neoplasms of the lymphatic and hematopoietic tissues, except leuke-

mia, was also found in the exposed group. No clear dose-response relationship was found.

Baetjer, Levin & Lillienfield (11) studied the mortality experience of retirees from an Allied Chemical plant that had been engaged in manufacturing dry arsenicals for pesticides. Arsenic trioxide was the starting compound for the subsequent syntheses of lead arsenate and calcium arsenate. Analysis of the death rates among male retirees of this plant showed an increase of observed over expected deaths from all cancer, as well as respiratory and leukemia-lymphatic cancers. It should be noted that a survey of materials used in the manufacturing processes of this plant was made. Several of these materials are well recognized as being carcinogenic, but no significance seems to have been attached to their presence.

Kuratsune et al (18) in 1974 reported on lung cancers in some employees of a Japanese copper smelter. The most significant information presented was that all the workers who died of lung cancer were "engaged in the dirtiest pre-war operations," when the amount of arsenic contained in the ores processed was estimated to be four to eight times higher than in recent years.

Newman et al (19) studied the histologic characteristics of lung cancers found in a copper-mining city and in a group of copper smelter workers in another city. Both areas had a higher than normal lung cancer rate. Poorly differentiated epidermoid bronchogenic carcinomas were found among the smelter workers. The authors believe that such a cell type may be related to exposure to arsenic. In the area presumably not exposed to arsenic, the predominant cell type of the cancer was "well differentiated" in the majority of the cases studied. The authors believe this type of cancer may have been caused by exposure to finely ground dust containing biotite, sericite, chlorite, and hornblende. These results should be of significant help in charting a course for further studies of lung cancer and its possible relationship to environmental factors.

Toxicologists who are concerned with the occupational cancer problem are anxious to find experimental confirmation of their theory by producing cancers in one animal or another. At the OSHA fact-finding hearing (September 1974), Dr. Herman Kraybill (11) said "arsenic stands out as the one substance for which human carcinogenicity has been demonstrated but for which an animal model has yet to be found to reproduce this effect."

The work of Milner (20) on arsenic and experimentally induced skin tumors in mice shows the problems encountered in this field. Cutaneous tumors were initiated by topical methylcholanthrene and promoted by transplantation. In one strain of mice the number of papillomas produced appeared to increase after feeding arsenic although the effect was not statistically significant. In another strain of mice the arsenic treatment resulted in a decrease in the number of papillomas produced, and the result was statistically significant.

DISCUSSION

These papers almost uniformly point to some low-grade carcinogenic activity by arsenic although not confirmed by any animal model (11) yet suggest that various cocarcinogenic factors must be studied much more thoroughly (2).

Regelson (7) points out that the antimitotic effect of arsenic is clinically useful since it is used in treating psoriasis and chronic myelocytic leukemia. Arsenic also is an antiparasitic agent and is an inhibitor of insect fecundity. Arsenic possesses both carcinogenic- and tumor-inhibitory properties, a characteristic seen in other clinically useful antimitotics.

We feel it is highly unlikely that a single scientifically sound level for all inorganic compounds of arsenic in air can be established from the data at hand. Arsenical compounds differ in toxicity, so why not in carcinogenicity? Fields of investigation that should be pursued in developing an understanding of the arsenic-respiratory cancer problem include (*a*) smoking history of subject as well as amount of arsenic exposure; (*b*) level and chemical nature of respirable arsenic compounds in the air; (*c*) investigation of other airborne contaminants that may be present, including such materials as sulfur dioxide, chromium, asbestos, and recognized organic carcinogens; (*d*) more histological studies of types of lung cancer and their relationship to known occupational carcinogens; (*e*) socioeconomic variations of lung cancer incidence. Although the academician trained in toxicology has become very important in helping to develop the rules and regulations for modern industry, his awareness of the pressing nature of the problem should be further increased.

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