CASE STUDY 4: INORGANIC ARSENIC—AMBIENT LEVEL APPROACH TO THE CONTROL OF OCCUPATIONAL CANCERIGENIC EXPOSURES

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INTRODUCTION

Arsenic, known and used since antiquity, is one occupational substance which is truly ubiquitous from both natural and industrial sources. A current estimate is that in the U.S.A. alone 1,500,000 workers in dozens of occupations are potentially exposed to inorganic arsenic.[1]

HISTORICAL BACKGROUND

In 1820, 45 years after Percivall Pott started the field of cancer research, J. A. Paris ascribed the first association of arsenic and cancerigenesis as also occupational. While practicing in Cornwall, this English physician had observed that ". . . a cancerous disease in the scrotum, similar to that which infests chimney sweeps . . ." occasionally affected smelters exposed to the arsenical fumes of a local copper smelting works. The works closed many decades ago, and Paris' original specific observation was never confirmed.[3-6] It still remains a subject of dispute and controversy. By 1930, it had been firmly established clinically that occupational contact with inorganic arsenicals could produce *skin cancer*—particularly among sheep-dip workers involved in the production of sodium arsenite, a veterinary pesticide.[3, 7, 8] The causal relationship between medical or environmental arsenical exposure and skin carcinogenesis was equally well established by 1930.[8]

Medical reports had postulated in 1903 that lung damage and, in 1934, *lung cancer* among sheep-dip workers might be due to inhalation of inorganic arsenicals.[9, 10] The first strong implication of a causative role between occupational exposure to these arsenicals and lung carcinogenesis emerged in 1943, when four fatal cases of lung cancer were reported in Britain among, again, sheep-dip workers.[11]

EPIDEMIOLOGICAL STUDIES

The above evidence prompted the first epidemiological study of an occupational group exposed to inorganic arsenicals. In 1948, Hill and Faning[12] reported on a study of the mortality experience among workers exposed to sodium arsenite sheep-dip, a topical veterinary pesticide. From that time to the present (1975), ten epidemiological studies are known to have been carried out to eluci-

date further the mortality and carcinogenic risk among other occupations exposed to various inorganic arsenicals.[3, 4, 13-20]

Selected salient findings from these 11 studies are summarized in TABLE 1.

SUMMARY OF EPIDEMIOLOGICAL FINDINGS

Seven studies were carried out of occupations in the metallurgical industry (copper smelting and arsenic trioxide production),[4, 5, 13-17] three in the production of arsenical pesticides,[12, 19, 20] and one in the agricultural application of arsenical pesticides.[18]

Initially, or upon review of the data by the U.S. National Institute for Occupational Safety and Health (NIOSH), excess mortalities from respiratory cancer were observed to have occurred in all but one of the occupational groups studied.[21] The findings of one study, that of orchardists,[18] remain inconclusive.

Three studies revealed an excess mortality from overall cancer among occupations involved in the production of arsenical pesticides.[12, 19, 20] This finding was not observed in any of the eight metallurgical occupations studied, although it must be noted that two of these studies were not designed to evaluate this type of mortality experience.[14, 15]

Excess mortalities from cancer of the lymphatic system were observed among the occupational groups that produced arsenical pesticides.[19, 20]

Excess mortality from skin cancer was observed only among sheep-dip workers.[12]

Workers in the metallurgical industries had been exposed in each case to arsenic trioxide and, at least, to sulfur dioxide. Pesticide production workers were exposed to various inorganic arsenicals, but not to sulfur dioxide. The common denominator in the exposures of all these occupational group was therefore an inorganic arsenical.

Both the trivalent arsenic compounds, such as arsenic trioxide, and the pentavalent, such as lead and calcium arsenates, were found to be cancerigenic in the lung, lymphatic system, and/or skin.

DOSE-RESPONSE RELATIONSHIPS

The studies by Lee and Fraumeni [13] and Ott et al.[20] correlated work exposure levels of inorganic arsenicals with observed mortality experience.

Lee and Fraumeni Study

Deaths were classified by length and degree of exposure to arsenic trioxide and sulfur dioxide. Excess mortality from lung cancer was found to increase with increasing duration of exposure, the excess ranging from two to five times the expected. When these groups were further subdivided into "Heavy," "Medium," and "Light" exposures to arsenic trioxide, the lung cancer mortality was found to increase for each group with increasing degrees of exposure to arsenic trioxide. Similarly, when the deaths were classified by length and degree of exposure to sulfur dioxide, excesses of mortality from lung cancer were shown with increasing exposure to sulfur dioxide. The largest excesses of lung cancer

TABLE 1

SUMMARY OF EPIDEMIOLOGICAL INVESTIGATIONS OF OCCUPATIONS WITH EXPOSURE TO INORGANIC ARSENIC

Epidemiological Study Date and Occupation	Period of Observation	Number of Deaths Studied	Significant Cancer Mortality Excess *			Main Exposure Compound	
			Overall	Lung	Other	Arsenical	Other
Hill-Faning, 1948 Sheep-dip Production	1910–43	75	+	+	skin	sodium arsenite	
Snegireff-Lombard, 1951 Copper Smelting	1922–49	146	–	(+)	–	arsenic trioxide (As_2O_3)	sulfur dioxide (SO_2)
Pinto-Bennett, 1963 Copper Smelting †	1946–60	229	–	(+)	–	As_2O_3	SO_2
Lee-Fraumeni, 1969 Copper Smelting	1938–63	1,877	+	+	–	As_2O_3	SO_2
Nelson et al., 1973 Pesticide Application	1938–69	344	–	(i)**	–	lead (Pb) arsenate	
Karatsune et al., 1974 Copper Smelting	1917–65	11	NE ¶	+	NE	As_2O_3	SO_2
Milham-Strong, 1974 Copper Smelting †	1950–71	>241	NE	+	NE	As_2O_3	SO_2
Baetjer et al., 1974 Pesticide Production	1960–72	27	+	+	lymphatic	As_2O_3; Pb & Ca arsenates?	
Ott et al., 1974 Pesticide Production	1940–72	173	+	+	lymphatic	As_2O_3; Pb, Ca & Mg arsenates	dry sulfurs
Milby-Hine, 1974 Copper Smelting ‡	1950–72	1,910	(i)	(i)	–	As_2O_3	SO_2
Rencher-Carter, 1971 § Copper Smelting	1959–69	561	–	+	–	As_2O_3	SO_2

* Parentheses indicate which results changed after evaluation by NIOSH or independent sources.

† Same smelter.

‡ Includes smelter studied by Rencher-Carter.

§ Released in 1974.

¶ Not evaluated.

** Inconclusive.

TABLE 2

OBSERVED AND EXPECTED DEATHS DUE TO RESPIRATORY CANCER BY EXPOSURE CATEGORY *

Exposure Levels			Respiratory Cancer Deaths		
TWA Concentration X Months of Exposure	Average Log_e (Dosage), mg	No. of Total Deaths (N=173 *)	Observed (N=28)	Expected	Observed / Expected
<1	3.74	26	1	1.77	0.6
1–1.9	4.84	17	2	1.01	2.0
2–3.9	5.53	24	4	1.38	2.9
4–5.9	6.04	22	3	1.36	2.2
6–11.9	6.68	27	3	1.70	1.8
12–23.9	7.35	18	2	0.97	2.1
24–59.9	8.17	13	3	0.77	3.9
60–95.9	8.78	13	5	0.79	6.3
96+	10.30	13	5	0.72	7.0

* 138 worked in the exposure area <1 year; 16 of these died of respiratory cancer.
† After Ott et al. 1974. Arch. Env. Health **29:** 250.

mortality were found among those exposed to high arsenic trioxide concentrations and high or medium sulfur dioxide concentrations. The conclusion was that a *semi-quantitative* dose-response relationship existed between high arsenic trioxide exposure and lung cancer, possibly in interaction with sulfur dioxide or other, unidentified, chemicals in the work environment.

Ott et al. Study

A part of this study calculated the total dosage of arsenic inhaled during the duration of employment ‡ and compared the dosage, by exposure category, to the respective mortality from respiratory cancer deaths.[20] When, as presented in TABLE 2, the dosage was compared with the ratio of observed to expected deaths from respiratory cancer by exposure category, the data indicated a dose-response relationship. (Although Ott et al. did not discuss it in relation to the findings presented in TABLE 2, they did mention the fact that 138 decedents had worked in the exposure area for less than one year; of these 138 deaths, 16 were due to respiratory cancer; that is, 16 of the 28 deaths from respiratory cancer occurred among workers who had been exposed to arsenic for less than one year.)

‡ The dosage of arsenic received during the length of employment of each worker at that plant was calculated by Ott et al. from the following formula:

$$\text{Dosage in milligrams} = (\Sigma\, D_i\, T_i)\, B,$$

where i represents the arsenic exposure group; D_i, the number of working days each worker spent in the i^{th} exposure group category (21 working days/month); T_i, the time-weighted average (TWA) concentration of arsenic for an 8-hour day in the i^{th} exposure group; and B, four cubic meters of air (M^3) as the average respiratory volume assumed for an 8-hour working day/worker. Results were expressed in the natural logarithm (log_e) of the dosage in milligrams.

TABLE 3

RATIO OF OBSERVED TO EXPECTED RESPIRATORY CANCER DEATHS BY 40-YEAR DOSAGE AND DAILY EXPOSURE CATEGORIES *

Projected Exposure Levels		Respiratory Cancer Deaths Observed/ Expected
40-Year Dosage, Log_e mg	Daily TWA Dose, $\mu g/M^3$	
3.74	1	0.6
4.84	3	2.0
5.53	6	2.9
6.04	10	2.2
6.68	20	1.8
7.35	40	2.1
8.17	90	3.9
8.78	160	6.3
10.30	740	7.0

* Modified from Ott et al. 1974. Arch. Environ. Health **29:** 250.

Projection from Ott et al. Data

Because of the dose-response relationship indicated by the Ott et al. data, we attempted to estimate what the *daily* 8-hour time-weighted average (TWA) arsenic concentrations would have been *if the arsenic dosages in question were taken to represent those inhaled by exposed workers over a 40-year working life.* First, we calculated the 40-year respiratory volume which was the same in all cases, viz 40,320 cubic meters of air (M^3), based on the respiratory volume of four M^3 per 8-hour working day used by Ott et al.§ Then we converted the dosage categories given in TABLE 2 from logarithmic to arithmetic units and, by dividing each by 40,320 M^3, arrived at the projected daily TWA concentration categories in micrograms of arsenic per cubic meter of air ($\mu g/M^3$). To reiterate, we used the same method and figures Ott et al. did to calculate the accumulated dosages except, as indicated, that we divided the dosages by a projected 40-year breathing volume. TABLE 3 presents our construction of the projected daily 8-hour TWA doses of arsenic which would have had to exist to have resulted in those accumulated dosages during a 40-year working life.

By reinterpreting the Ott et al. data in this manner, another view emerges from the dose-effect response which Ott et al. derived from analysis of their data. In this new form, the dose-response suggests that a no-effect level, vis-à-vis an increased respiratory cancer mortality risk, might lie in the very low microgram range of arsenic/M^3. It must be noted, however, that 16 (56.3%) of the 28 total deaths from respiratory cancer reported by Ott et al. occurred among workers who were exposed to arsenic for less than one year. Ott et al. did not indicate in their report in which of the exposure categories these 16 deaths occurred. Nevertheless, even if all of the 16 deaths had occurred in the exposure categories of greatest dosage, at least three had to have occurred in the fourth

§ That is, ($4M^3$/day) × (21 days/month) × (12 month/year) × 40 years $=40{,}320\ M^3$.

of the nine exposure categories shown in TABLE 2 and, by our projection, in TABLE 3; i.e., where $\log_e$ dosage in milligrams was 6.04.¶

DISCUSSION AND CONCLUSIONS

In every case, each of the epidemiological and other findings reviewed or presented herein has valid limitations *per se*. Taken together, however, they demonstrate firmly that occupational exposure to inorganic arsenicals is cancerigenic in three different tissues. Moreover, in many areas of the U.S.A. and other countries, concentrations of arsenic in the urine and hair or tissues of children and adults have been found to be elevated due to ambient contamination from urban and natural sources, but mostly as a direct result of industrial contamination.[8, 14] In some of these areas, increases in lung cancer mortality risk have been found or suspected among the general community as a result of environmental contamination from industrial or agricultural sources of inorganic arsenicals.[14, 22]

Occupationally, there are no data to document a noncancerigenic exposure level for inorganic arsenic. Moreover, our evaluation of the occupational dose-response relationship appears to indicate that a nonresponse level of exposure may not exist. Therefore, because of the ubiquity of arsenic in the environment and because of the necessity of preventing occupational exposures from increasing the arsenic body burden, the most prudent and logical approach would be to limit these occupational exposures to those of approximately the *natural ambient level*. In setting a national standard anywhere, especially in a country as vast as the U.S.A., it is imperative that the standard be uniform. Since the highest 24-hour average ambient concentration for arsenic reported during any quarter in the U.S.A. was 1.41 $\mu g/M^3$,[23] it would seem appropriate that the standard for occupational exposure to inorganic arsenic in this country be set at 2 $\mu g/M^3$, on an eight-hour time-weighted average basis.

We make this statement with full acknowledgment of the following facts:

1) The ambient level used as the basis for a recommended standard was the quarterly average of 24-hour samples, which, by its nature, does not reveal what the 8-hour fluctuations were during that trimester.
2) The ambient level at the particular location where that quarterly average was recorded to be highest is not necessarily a *natural background*.
3) Some cases of occupationally induced respiratory or other cancer *might* occur at this level of exposure to inorganic arsenic.

¶ Personal communications with Mr. M. G. Ott, after this paper was presented, revealed that the 16 deaths from respiratory cancer observed among workers who had been exposed for less than one year were distributed among the nine exposure-level categories in TABLE 2 as follows:

Exposure Level Category	3.74	4.84	5.53	6.04	6.68	7.35	8.17	8.78	10.30
Number of Respiratory Cancer Deaths	1	2	4	3	3	2	1	0	0

SUMMARY

In 1820 the first malignancies ascribed as due to occupational arsenic exposure were reported as scrotal cancers among smelters. A century later the causal relationship between chronic occupational, environmental or medical arsenical exposure and skin carcinogenesis was firmly established

From 1948 to 1975, nine out of eleven epidemiological studies have shown, initially or upon review, significant excess mortality from respiratory cancer among diverse occupations exposed to various inorganic arsenicals. Two of the nine studies have shown concommitant, significant excess mortality from lymphatic cancer, and another, from skin cancer. Additionally, two such studies have revealed a dose-response relationship between arsenical exposure and lung carcinogenesis. In the first, reported in 1969, the relationship was semi-quantitative, with a possible interactive role by sulfur dioxide or other contaminants. The other demonstrated a dose-response which was quantitative for arsenic *per se*. Upon our reinterpretation, this dose-response also demonstrated an increased lung cancer mortality risk apparently at arsenic concentrations above 1 $\mu g/M^3$, calculated as the 8-hour TWA daily exposure over a 40-year working life. However, these and related data do not reveal a definite no-effect exposure level. Thus, in the absence of data documenting a cancerigenically safe level of occupational exposure and because of the environmental ubiquity of arsenic, the conclusion is drawn that the arsenic body burden of workers should not be occupationally increased above that produced by the ambient level.

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