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RESPIRATORY CANCER AND ARSENICALS
A RELATIONSHIP BASED ON PROPORTIONATE MORTALITY ANALYSIS

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ABSTRACT

RESPIRATORY CANCER AND ARSENICALS: A RELATIONSHIP BASED ON PROPORTIONATE MORTALITY ANALYSIS. Ott, M. Gerald, Holder, Benjamin B., Gordon, Harold L.

The proportionate mortality experience of 173 decedents exposed primarily to lead arsenate and calcium arsenate was compared with that of 1809 decedents not exposed to those compounds. A significant increase in respiratory cancer was found among the exposed employees. The relationship between accumulated arsenic exposure and the ratio of observed to expected respiratory malignancy deaths was estimated using a least squares approach. The predicted ratio exceeded six-to-one for individuals exposed to compounds containing an equivalent level of 1 mg/cm³ arsenic for a period of more than eight years. For the more heavily exposed individuals, a liability to respiratory cancer remains 35+ years after the initial exposure. Observations based on the proportionate study were supported by an analysis of the same target population, employing prospective rather than retrospective methods.

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RESPIRATORY CANCER AND ARSENICALS

A RELATIONSHIP BASED ON PROPORTIONATE MORTALITY ANALYSIS

Arsenical compounds have long been suspected of causing cancer in humans. ⁽¹⁾ Most recently, Lee and Fraumeni ⁽²⁾ reported an overall three-fold increase in respiratory cancer among 3000 smelter workers exposed to arsenic trioxide. The increase ran as high as sixfold among employees who were heavily exposed to arsenic for 12 or more months. The authors were careful to note that the influence of sulfur dioxide or unidentified chemicals varying concomitantly with the arsenic exposure could not be discounted.

In a number of British and German articles, excess cancer has been reported to be associated with exposure to arsenicals. ^(3,4,5,6) Lung cancer and clinical arsenical were found together among German vineyard workers who used insecticides containing arsenic in spraying and dusting operations between 1925 and 1942. In addition, a significant increase in lung cancer was found among inhabitants of the wine producing areas of the Moselle River, but not among residents of the wine producing areas of the Ahr River where pesticides containing arsenic were not used.

This investigation examines the proportionate mortality experience of a group of industrial workers engaged in the production of insecticides containing arsenic. All available exposure information was incorporated into the analysis in an effort to determine if the proportion of respiratory cancer deaths was related to exposure dosage.

METHODS

The Exposure Environment. During the period from 1919 through 1956, a production unit of the company was engaged in formulating and packaging a line of insecticides containing arsenic. The product line included lead arsenate,

calcium arsenate, copper aceto-arsenite and magnesium arsenite. The lead arsenate was produced from 1919 through 1956, calcium arsenate from 1920 to 1951, copper aceto-arsenite from 1932 through 1943, and magnesium arsenate from 1919 through 1943. The breakdown of arsenical production over the entire 37 years was estimated to be 59% lead arsenate, 34% calcium arsenate, 5% copper aceto-arsenite, and 2% magnesium arsenate. The unit, in addition, processed and packaged several other products, the most important of which were powdered sulfur and dry lime sulfur. The size of the work force varied from 30 in 1928 to approximately 100 in 1948. Turnover rates were rather high, with less than 25% of the men remaining with the unit for more than one year. This was partially due to the seasonality of the work, and due to the nature of the jobs. The packaging jobs required few skills and were often assigned to new employees. Transfer to better jobs within the company occurred rapidly for most of these employees.

The lead arsenate process typified the processes used to manufacture each of the other arsenicals. This process began by slurring lead oxide in water. The slurry was pumped into a mixing tank, where arsenic acid was added. This solution was then transferred to an adjacent building for drying, milling, and bagging. In 1943, the packaging operations were surveyed, with 15 breathing zone samples taken. The readings varied from .18 to 19.0 milligrams arsenic per cubic meter of air, depending on the location of the sampler. In 1952, the highest exposures occurred in the area of the drum dryers where breathing zone samples ranged from 1.7 to 40.8 milligrams arsenic per cubic meter of air, and in the area of the packaging machines where samples ranged from .26 to 7.5 milligrams arsenic per cubic meter of air. Excessive exposure was also noted during cleanup operations, such as sweeping of floors.

In addition, high lead concentrations were found in the production area. The 1952 measurements resulted in phasing out the lead arsenate process over the next several years. For analysis purposes, it was necessary to reduce the exposure information to a simplified structure, yet one which did not misrepresent the underlying exposure patterns. The first task was to construct a matrix of job classifications within the production unit by calendar years. This was done from annual personnel lists which enumerated the employees by job classification within department, and from the work history cards that are kept for each employee. Over the course of 37 years, numerous modifications in job classification terminology were encountered. Fifty different job titles were identified, including those which were later found to refer to the same job. Next, job descriptions and exposure measurements were used to combine the jobs into four exposure classifications. In assigning time weighted average concentrations to the various groupings, the emphasis was placed on arriving at a proper ratio between the exposure groups. The estimates shown in Table 1 were obtained through the consensus of two industrial hygienists familiar with the processes, the available industrial hygiene data, and job descriptions.

The exposure concentrations experienced by employees while in Group I jobs were quite variable, and included the likelihood of brief excursions to very high levels. Respirators were available, but were not worn consistently. Individuals on Group II jobs were exposed to dust levels generally at lower, less variable concentrations, but over longer periods of time. Some employees, for example, spent up to six hours a day performing tasks near the packaging machines. Few measurements were available for Group III or Group IV jobs because the exposure was apparently felt to be of less concern relative to the other jobs. Thus, the greatest subjectivity was used in estimating time

weighted average concentrations for these groups. Since no adjustments were made for the wearing of respirators, or the fact that production occurred on a somewhat intermittent basis, it is likely that actual exposure dosages were overstated rather than understated by the above estimates. However, the imprecision in the time weighted average estimates would not be expected to lead to appreciable distortions in the relative dosage exposure rankings since duration of exposure, which was determined quite precisely, varied considerably from individual-to-individual.

The dosage exposure to arsenic was calculated from the following formula:

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

where i represents the exposure group;

D_i represents the number of work days an employee spent in the i^{th} exposure category (21 working days per month were assumed in adjusting for nonwork days);

T_i represents the time weighted concentration for an 8-hour day in the i^{th} exposure group;

and,

B equals 4 cubic meters/8-hour day, the average breathing rate assumed for an 8-hour day.⁽⁷⁾ (The assumption of 4 cubic meters/8-hour day may be conservative; 10 cubic meters/8-hour day is commonly used.)

Study Design. For this study, the sampling frame consisted of nearly 2,000 employees who were known, through company records at that manufacturing location, to have died between 1940 and 1972. The employee work histories for the entire decedent population were examined to identify those decedents who

had spent one or more days assigned to the production unit of interest. The 173 men identified constituted the exposed population. The remaining decedents, less 13 who had worked with asbestos, served as controls.

The expected proportion of deaths due to respiratory malignancy in relation to year of death and age at death was estimated based on a weighted least squares analysis of the control population. The 1800 deaths among the controls were categorized by ten year age groups and intervals of five calendar years within each age group. An eight term equation, utilizing age and year of death, explained 58 percent of the variability between the categories and provided a reasonable fit to the data in the region of interest. Table 2 shows resulting estimates of the expected proportion of deaths due to respiratory malignancy for selected age at death and calendar years.

For the decedents in the exposed population, the following items of information were accumulated: a predicted probability that death would be due to respiratory malignancy; the observed cause of death; the career dosage exposure to arsenic in mgs.; the interval between first exposure and death; the age at death; and, the year of death. The strategy of the analysis was to determine if a dose response relationship existed between the proportion of deaths due to respiratory malignancies and exposure dosage, adjusting the observations for the expected proportion of respiratory malignancy deaths.

RESULTS

A summary of causes of death among the exposed workers and the controls is shown in Table 3. Malignant neoplasms of the respiratory system accounted for 16.2 percent of the deaths in the exposed group, as compared with 5.6 percent among the controls. A Mantel-Haenszel test statistic⁽⁸⁾ was calculated to compare the proportionate differences in respiratory cancer between the

two groups after subdividing the data into a 3 X 4 table of ages at death, by decade of death. The purpose of this procedure was to adjust for effects which might be associated with these variables. The normal approximation statistic for this test was 5.3 ($P < .001$). Cancer of the lymphatic and hematopoietic tissues, except leukemia, also occurred more frequently than expected. Six deaths were observed among the exposed group versus 2.8 deaths expected following the Mantel-Haenszel procedure ($P < .05$).

In relating the percent of respiratory cancer deaths to dosage levels, the expected probability that death would be due to respiratory cancer was determined from the regression equation described in the methodology section. The observed versus expected deaths by exposure category are presented in Table 4.

A weighted least squares procedure was employed to describe the relationship between the ratio of observed to expected respiratory cancer deaths and the natural logarithm of the dosage exposure in milligrams. This is shown in Figure 1. An approximate test for the significance of the fit yielded a P-value of $< .01$. Weights were assigned on a basis of the estimated variances of the ratio for each exposure group. It is important to note that, if the dosage scale had been expressed in months of exposure at 1 mg/cm^3 , the ratio of observed to expected deaths would have exceeded unity at one month of exposure.

Table 5 shows, for two dosage categories, the observed and expected number of respiratory cancer deaths by interval between exposure and death. Among the decedents in the low exposure group, the excess of observed to expected deaths occurs 15 to 34 years after initial exposure; whereas, in the high exposure group the excess persists among individuals dying more than 35 years after their initial exposure to arsenic.

For the 28 decedents who died from respiratory cancer, a regression of interval between initial exposure and death, on age of employee at first exposure, was performed. The age at first exposure to arsenic was negatively correlated with the lag time between exposure and death due to respiratory cancer. The observed intervals between first exposure and death were then adjusted for the age at first exposure effect and were plotted against the cancer dosage levels for each of the 28 decedents. As seen from Figure 11, there is no clear association between exposure dosage and the interval between first exposure and death.

DISCUSSION

The positive dose response relationship and the overall increase in respiratory cancer serve to further implicate arsenical compounds as a cause of respiratory cancer. No other common denominator was found among these employees to explain the observations. The exposed population examined proportionately did include four decedents who had worked with asbestos subsequent to their arsenic exposure. Two of these decedents died from respiratory cancer. The effects of including these four decedents in the exposed group were felt to be immaterial to the conclusions. Three of the eight deaths that have occurred during 1973 were due to respiratory cancer. These results were not included in the proportionate analysis. The medical records for the respiratory cancer decedents were reviewed with respect to smoking and familial cancer histories. No analysis of the incomplete information found was attempted. However, in view of the partial information available, it was deemed unlikely that these variables would be highly correlated with the arsenic exposure.

Malignant neoplasms of the lymphatic and hematopoietic tissues, except leukemia, was the only other category for which the exposed group differed

from the controls. The ratio of observed to expected deaths for this category was 2.1. Specifically, the six cases of lymphoma were classified on the death certificates as one lymphoblastoma, one reticulum cell sarcoma, and four cases of Hodgkin's Disease. No clear dosage relationship could be drawn from these observations and no association could be found in the literature relating lymphomas to chronic chemical exposure. The data are summarized only as a clinical observation by the authors.

It was possible to follow 580 of the insecticides employees utilizing prospective study in retrospect techniques. Total observed deaths were 9 percent higher than for a corresponding population of company employees, but 11 percent below the number of deaths expected based on a corresponding U.S. white male population.

On the other hand, respiratory malignancy death rates were 3.3 times higher than for other company employees, and ten times higher among more heavily exposed employees 35 or more years after initial exposure (7 observed versus .7 expected). These results did not conflict with the proportionate results to any significant degree, but did indicate that the number of deaths due to all causes exceeded the expected number by a relatively small number.

Until the early 1950's, arsenical pesticides had been sprayed on tobacco crops in the United States. The use of these insecticides has led to contamination of cigarettes with arsenic. Satterlee⁽⁹⁾ summarized the problem in 1956. The arsenic content of cigarettes had risen from 12.6 micrograms per cigarette in 1932 to 42 micrograms in 1950-51. These levels could lead to rather high concentrations of arsenic in the lung during smoking. In recent years, arsenic levels in American cigarettes have declined to an average of 7.7 micrograms per gram of tobacco.⁽¹⁰⁾

In Peruvian tobaccos, arsenic levels were found to be 22 micrograms per cigarette as recently as 1966.⁽¹¹⁾ Satterlee also reported that background arsenic levels of 10 to 40 micrograms per cubic meter of air were found in New York City. Thus, arsenic is a widespread environmental contaminant which, in view of the results of this study, deserves considerable investigation.

Table 1. Estimated Arsenic Levels By Job Category

Job Category	8-Hour TWA Concentration of Arsenic (Milligrams per cubic meter)
Group I	5.0
Group II	3.0
Group III (Jobs associated with arsenical production out of the area of high dust exposure)	1.0
Group IV (Jobs involving either the formulation of non-arsenicals within the production unit or re- quiring only intermittent time in the areas of high exposure)	0.1

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Table 2. Expected Proportion of Respiratory Malignancy
Deaths By Age and Date of Death (Based on
Company Control Population).

Year of Death	Age at Death					
	30	40	50	60	70	80
1950	.006	.024	.033	.034	.026	.010
1960	.006	.034	.050	.054	.046	.026
1970	.004	.068	.105	.117	.104	.063

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Table 3. Number and Percent of Deaths Among the
Exposed Group and Controls, 1940-1972.

Cause of Death	Exposed Group		Controls	
	Number	Percent	Number	Percent
All Causes	173	100.0	1809	100.0
Malignant Neoplasms, Total	57	32.9	374	20.7
Digestive Organs & Peritoneum	10	5.8	128	7.1
Respiratory System	28	16.2	102	5.6
Genital Organs	4	2.3	36	2.0
Urinary Organs	1	.6	13	.7
Lymphatic & Hematopoietic Tissues, Except Leukemia	6	3.5	25	1.4
Leukemia	2	1.2	18	1.0
All Others	6	3.5	52	2.9
Diseases of Cardiovascular System	81	46.8	101	55.9
Diseases of Respiratory System	11	6.4	73	4.0
Diseases of Digestive System	7	4.0	59	3.3
External Injury	12	6.9	200	11.1
All Others	5	2.9	91	5.0

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Table 4. Observed and Expected Deaths Due to Respiratory
Malignancies by Exposure Category

Exposure Levels		Number of Total Deaths	Respiratory Malignancy Deaths		
TWA Concentration X Months of Exposure	Average ln _c (dosage) in mgs.		Observed	Expected	Ratio $\frac{\text{Observed}}{\text{Expected}}$
<1	3.74	26	1	1.78	.6
1 - 1.9	4.84	17	2	1.02	2.0
2 - 3.9	5.53	24	4	1.43	2.8
4 - 5.9	6.04	22	3	1.42	2.1
6 - 11.9	6.68	27	3	1.79	1.7
12 - 23.9	7.35	18	2	.95	2.1
24 - 59.9	8.17	13	1	.75	4.0
60 - 95.9	8.78	13	5	.79	6.3
96+	10.30	13	5	.78	6.4

Table 5. Observed and Expected Deaths Due to Respiratory
Malignancies by Interval Between Exposure and
Death.

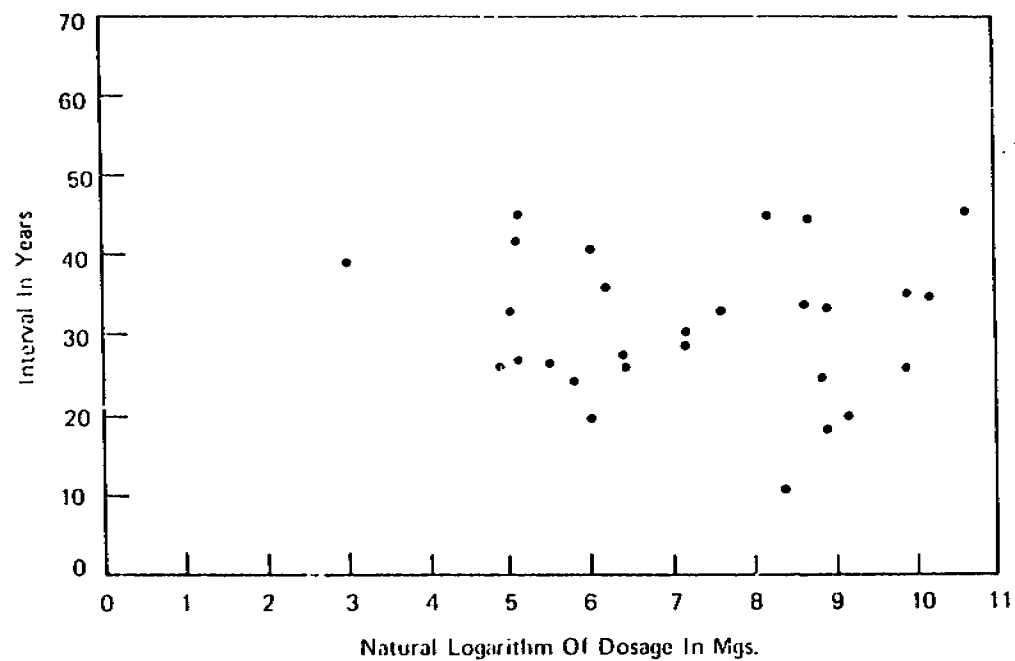
Interval Between First Exposure and Date of Death	$\ln_e$ (Dose) In Mgs.			
	0 - 6.9		6.9+	
	Observed	Expected	Observed	Expected
Total	13	7.8	15	3.0
<15 Years	0	.3	0	.1
15 - 34 Years	9	3.4	9	1.6
35+ Years	4	4.1	6	1.3

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FIGURE 2.
INTERVAL IN YEARS BETWEEN INITIAL EXPOSURE AND DEATH
DUE TO RESPIRATORY CANCER BY DOSAGE.
ADJUSTED FOR AGE AT FIRST EXPOSURE



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