PLAINTIFF'S
EXHIBIT
DUP-2494

Reprinted from the Archives of Environmental Health
June 1971, Volume 22
Copyright 1971, American Medical Association

Mortality in the Chrysotile Asbestos Mines and Mills of Quebec

J. Corbett McDonald, MD; Alison D. McDonald, MD;
Graham W. Gibbs, MSc; Jack Siemiatycki; and
Charles E. Rossiter, MA, Montreal

Of 11,788 persons born between 1891 and 1920 employed in the Quebec asbestos mining industry, 88.4% were traced. Of these 2,457 (23.6%) had died. Exposure indexes for each worker were calculated from job dust levels and duration of employment. The overall mortality was lower than expected for the population of Quebec but in the highest dust category, comprising 5% of the cohort, the age-standardized rate was 20% higher than in the other groups. Respiratory, cardiovascular, and malignant disease in equal proportions accounted for the excess. There were 101 deaths from respiratory cancer including three from malignant mesothelioma, an estimated excess of about 15 deaths. The difference in rates for respiratory cancer between those maximally and minimally exposed was fivefold and, though perhaps exaggerated, was apparently determined by accumulated dust exposure and duration of employment.

THE REMARKABLE qualities of the asbestos group of fibrous minerals have been recognized since antiquity, but mining and milling on an industrial scale began only at the end of the 19th century. In the Eastern Townships region of Quebec, deposits of chrysotile asbestos in serpentine rock were noted in the 1847 Canadian Geological Survey. The first mine was opened at Thetford in 1878, and within 30 years the region was producing most of the world's asbestos. The proportion fell as Russian, South African, and Italian mines came into operation, but Quebec still produces about 40% of the world's supply, now estimated at about 4 million tons a year.[1]

There are two main mining areas, one at Thetford Mines and neighboring towns of Black Lake and Broughton, and the other at Asbestos. The Thetford area was developed by many different companies, but with amalgamation the number has now been reduced to six. At Asbestos, the mining has been carried out since 1882 by one large company which also operates a small factory in the town for the manufacture of mixed asbestos products. There is a small mine owned by another company a few miles away.

Concern for the health effects of asbestos has paralleled growth in its production, and the main available evidence was reviewed fully by Wright[2] in 1969. The first cases of diffuse pulmonary fibrosis after prolonged exposure were noted by Murray in 1907, and by 1930 asbestosis was recognized as an important occupational hazard. Controls introduced since then have reduced considerably the dust concentration to which workers in the mines, mills, and primary manufac-

Submitted for publication Aug 17, 1970; accepted Nov 10.

From the Department of Epidemiology and Health, McGill University, Montreal. Mr. Rossiter is presently with the Medical Research Council Pneumoconiosis Unit, Penarth, South Wales.

Reprint requests to 3775 University St, Montreal 112 (Dr. J. C. McDonald).

DU 011557

DUP 0821141

turing industries are exposed. Though the prevention of asbestosis is far from complete in these industries, it is still generally believed that this can be achieved by more strict environmental control. Another aspect of the problem appeared in 1947 when Merewether[1] showed a link between asbestos exposure and lung cancer. The potential extent of this hazard was increased by reports of Wagner and others[4] during the last ten years that malignant tumors of the pleura and peritoneum are related to certain types of industrial work and perhaps also to neighborhood exposure.

The association between lung cancer and asbestos was first found in the British textile industry. Merewether's inquiry showed an unduly high proportion of lung cancers at autopsy in cases of asbestosis, and other observations among textile workers have confirmed the association.[5-8] Two studies in particular which take some account of the degree of exposure suggest a dose-response relationship. Knox et al[6] found a considerable excess of lung cancer in persons exposed before 1933 when asbestos control regulations were enforced, but none in persons exposed for ten years or more in the most dusty areas since then. These findings must be reviewed when a longer period of observation has elapsed, since Newhouse[8] (also in a textile factory) found an excess of lung cancer in persons heavily exposed 20 years earlier for periods of less than two years. Workers exposed to light or moderate dust concentrations showed no excess of bronchogenic cancer even after 20 years of exposure.

Selikoff and his colleagues[9] found an eightfold increase in lung cancer compared with national figures in a cohort study among the members of an American insulation workers union who had been exposed for 20 years or more. He also found a gross excess of pleural and peritoneal mesotheliomas. On the other hand, in a national survey of all known mesothelial tumors in Canada, 1960 to 1968, McDonald and her colleagues[10] found a history of occupational contact with asbestos in a relatively small proportion of cases. This exposure was mainly in insulation and allied trades, rather than in the asbestos-producing industry.

Of the four main types of asbestos fiber—chrysotile, crocidolite, amosite, and anthophyllite, the two textile factories referred to above[6,8] used mainly chrysotile fiber, together with some crocidolite, and in one of the two, some amosite. As in most industrial applications different types of fibers are mixed, the carcinogenic effects of a single fiber type in practice can only be studied in mining and milling. Chrysotile fiber is of greatest importance because of its qualities and extensive usage. The only studies of lung cancer in chrysotile miners and millers were reported by Braun and Truan in 1958[11] and by Kogan et al in 1966.[12] In the first of these, nine deaths from lung cancer were observed in the Quebec industry compared with six expected from provincial rates. The second was in the Soviet Union and showed that compared with the general population the mortality from lung cancer was increased by a factor of 1.9 for miners, 3.1 for millers, and 2.3 for factory workers. The present investigation forms part of a comprehensive epidemiological survey of the entire Quebec asbestos-producing industry since its inception. Using the considerable volume of data available, our primary aim has been to define as accurately as possible the quantitative relationship between exposure to chrysotile asbestos and the incidence of lung cancer. The results from parallel studies concerned with the relationship of dust exposure to radiographic appearances, pulmonary function, and respiratory symptoms will be reported separately.

Materials and Methods

Registration.—A register was compiled in the personnel department of each asbestos mining company in the Eastern Townships region of Quebec listing all persons currently or previously employed, as of Nov 1, 1966. A card was made out for each employee on which was recorded his name, date of birth, address, and a detailed work history which included the department and mine, dates of starting and finishing, for every job, and all periods of leave.

In one of the 44 mining companies represented in our survey, the records of at least 560 persons had been destroyed. These were of ex-employees and others not transferred when ownership of the company changed in 1964. The work histories of a small number of older men who had been employed partly in this company and partly in others were also incomplete.

DUP 0821142

DU 011558

Table 1.—*Subjects of Study and Results of Tracing by Age and Sex*

Year of Birth	Persons M	Persons F	Persons Total	Traced M	Traced F	Traced Total	% Traced	Dead	% of Persons Traced
1891-1895	1,553	14	1,567	1,179	13	1,192	76.1	611	51.3
1896-1900	1,982	31	2,013	1,588	28	1,616	80.3	655	40.5
1901-1905	2,027	50	2,077	1,724	45	1,769	85.2	498	28.2
1906-1910	1,897	99	1,996	1,741	92	1,833	91.8	330	18.0
1911-1915	1,837	117	1,954	1,773	113	1,886	96.5	221	11.7
1916-1920	2,027	154	2,181	1,976	149	2,125	97.4	142	6.7
All	11,323	465	11,788	9,981	440	10,421	88.4	2,457	23.6

Table 2.—*Subjects of Study and Results of Tracing by Dust Index and Years of Employment*

Years		Dust Index <10	10-	100-	200-	400-	800-	All
<1	No.	3,043	654	38	3	0	0	3,738
	% traced	76.6	75.1	76.3	66.7	...	...	76.3
1-	No.	1,025	1,975	450	264	122	64	3,900
	% traced	86.3	88.6	89.3	90.5	91.0	90.6	88.3
10-	No.	55	1,117	566	522	432	255	2,947
	% traced	100.0	99.0	98.9	99.0	99.3	99.6	99.1
30-	No.	0	204	181	250	303	265	1,203
	% traced	...	100.0	100.0	100.0	100.0	99.6	99.9
All	No.	4,123	3,950	1,235	1,039	857	584	11,788
	% traced	79.9	89.9	94.9	97.0	98.4	98.6	88.4

There was of course some movement of labor from one mining company to another. This necessitated bringing together and matching the records of all the companies, to obtain complete work histories. In the course of tracing ex-employees, the matching process could often be confirmed or amended. In all, 27,669 men and women were registered, including 6,415 currently employed on Nov 1, 1966. Of this total, 1,039 persons had been employed by more than one company.

Using the occupational histories, a list was compiled of all named jobs in each company from the beginning of its operation. A description of each of the 13,346 jobs listed in this way was obtained from existing evaluation systems and by interviewing employees with long service. Jobs with several names but involving the same work and dust exposure were combined and the codes finally needed for classification thus reduced to 5,783. For each of these and for each year of operation, the average dust exposure was estimated on a 13-point scale. Throughout the industry in the dryers, crushers, and mills, the concentrations of dust at working places had been measured annually since 1949 by Maurice Lachance, Eng, and since 1946 by various investigators in the small factory. All measurements were made with either a midget impinger or Greenburg-Smith, impinger and recorded in millions of dust particles per cubic foot (mpcf). Levels of exposure in mining and maintenance jobs and in other operations where no dust measurements had been made were estimated by investigating present-day dust levels and adjusting these according to changes in operating procedure reported by mining and maintenance personnel. A full description of geological and environmental features and of the methods and results of dust measurement are to be published by G. W. Gibbs, MSc, and Mr. Lachance.

Before 1949, few dust measurements were recorded, and estimates of exposure for that period are, therefore, only approximate. Interviews with employees of long service enabled comparisons of dustiness to be made with conditions since 1949. The dates of installation or modification of dust control systems were also taken into account.

Duration of exposure for each person was expressed in years or fractions of years after subtraction of all periods of leave, and was corrected to a working week of 40 hours. A dust index was calculated for each employee by adding together the products of time spent on each job and estimated average dust concentration. For example, suppose the dust index for a man was 600; this might mean that he had worked for five years at 40 mpcf, 15 years at 20 mpcf, and 20 years at 5 mpcf (ie, 200 + 300 + 100). It would be useful if it could be assumed

DUP 0821143

DU 011559

had been included incorrectly, 47 were confirmed pathologically, 28 hospital diagnoses were presumed correct, and in 17 no further information was obtained.

The following steps were taken to discover cases of lung cancer that had not been mentioned as such on the death certificate:

1. A letter was sent to the certifying physicians whenever it was stated that an autopsy had been or would be performed. These numbered 306 in all; 33 deaths were certified as due to lung cancer and 273, as due to other causes. In 18 replies, it was stated that there had been no autopsy; in 175, that the certified diagnosis was confirmed at autopsy; and in 18, that it was incorrect. These 18 yielded five additional cases of lung cancer. The diagnoses for these had been certified as renal tumor (ICD 180), infectious hepatitis (ICD 092), pulmonary fibrosis (ICD 519), diabetes (ICD 260), and asbestosis (ICD 523).

2. We asked the physicians in charge of the industrial clinics at Thetford Mines and Asbestos for lists of all deaths known to be due to lung cancer. Their records included only employees who had given up work because of ill health, those who were pensioned, and those who had applied for workmen's compensation. They listed 24 of the 96 lung cancer deaths found by the methods already described plus three additional cases. These three deaths had been certified as due to tuberculosis (ICD 019), asbestosis (ICD 523), and coronary heart disease (ICD 420), and though there had been autopsies for the purpose of compensation, no mention of this was made on the death certificate. In addition, there were three autopsies for compensation purposes in which a small lung cancer was noted as an incidental finding. The pathologist had not considered these cancers to have contributed to death and the causes certified were asbestosis (ICD 523) in two cases and cardiac infarction (ICD 420) in a third.

3. A search was made for any case of primary malignant mesothelial tumor of the pleura that might have been given a code other than 162. One additional case coded as a benign pleural tumor was found.

4. We reviewed cases reported by pathologists in the national survey of primary malignant mesothelial tumors in Canada between 1960 and 1968, and five were in men who had worked in the Quebec asbestos-producing industry. Two were born in 1922 and were, therefore, not in our cohort, and two died in 1967 after the present study had ended. A fifth case, diagnosed by biopsy, was eligible for both studies.

To summarize the results of all these inquiries, three cases were removed from the group of 95 malignant neoplasms of the bronchus, trachea, or lung (ICD 162 and 163) and nine were added, making 101 in all (100 men and one woman). Included in the total were the following: cancer of the trachea, in one case; malignant mesothelial tumor, in three; and cancer of the bronchus or lung, in 97.

Results

Female Mortality.—There were only 465 women in the cohort; almost all had short exposures and all but 33 were in the two lowest dust-index categories. In all, 440 (94.6%) were traced, and of those, 45 had died. Tuberculosis (11), malignant neoplasms (12), circulatory (nine) and respiratory (one) diseases, and trauma (one) were the causes of death in 34. Death was due to other causes in eight cases, and the cause of death was unknown in two; there was one death from lung cancer. Apart, perhaps, from tuberculosis, these figures are not unusual and will not be considered further.

Male Mortality.—To permit comparisons of mortality by dust index and years of exposure, death rates were calculated in five-year cohorts by date of birth. Equivalent average death rates[13] were then calculated using a standard population with equal numbers in each age group. Since the actual number at risk in each cohort was similar, this method of age standardization was particularly appropriate. The standardized rates are shown by dust index and main disease groupings in Table 3. In the lower five dust categories, equivalent average death rates for "all causes" were approximately the same, but in the top category, containing 5% of the total cohort, mortality was about 20% higher than the rest. Malignant neoplasms, circulatory diseases, and respiratory diseases, in approximately equal proportions, accounted for the excess. Two groups showed the opposite trend: "trauma," probably because rates fell with advancing age, and "unknown causes," probably because death certificates were difficult to find for older men with short periods of employment.

Table 4 shows that the main contribution to the excess in malignant disease was from cancer of the bronchus, trachea, and lung

DUP 0821145

DU 011561

Table 3.—*Equivalent Average Death Rates per 1,000 Men by Dust Index*

	Dust Index						
	<10	10-	100-	200-	400-	800-	All
No. of men	3,006	3,408	1,148	1,002	842	575	9,981
Tuberculosis (ICD 001-019)	18.8	19.9	31.6	23.8	28.5	25.8	22.5
Malignant neoplasms (ICD 140-209)	38.8	39.3	32.2	27.5	45.1	61.8	38.6
Circulatory diseases (ICD 400-469)	85.0	80.8	82.5	83.5	94.8	107.3	85.8
Respiratory diseases (ICD 470-529)	9.5	15.3	19.5	16.7	15.3	41.6	15.6
Trauma (ICD 800-999)	34.7	30.8	36.3	35.2	33.8	13.7	31.5
Other causes	46.8	52.9	39.0	47.7	38.3	58.9	48.4
Unknown causes	30.6	21.4	16.5	6.2	7.2	3.4	20.8
All causes	264.1	260.4	257.6	240.6	262.9	312.5	263.1

Table 4.—*Equivalent Average Death Rates per 1,000 Men for Malignant Neoplasms (ICD 140-209) by Dust Index*

	Dust Index						
Location	<10	10-	100-	200-	400-	800-	All
Esophagus & stomach (ICD 150-151)	10.2 (32)	4.5 (13)	1.7 (2)	7.0 (5)	11.3 (8)	13.7 (8)	7.5 (68)
Intestine & rectum (ICD 152-154)	2.5 (8)	4.9 (15)	3.2 (3)	3.9 (3)	5.6 (4)	8.7 (5)	4.0 (38)
Other abdominal areas (ICD 155-159)	4.0 (13)	3.0 (9)	1.7 (1)	1.3 (1)	2.8 (2)	1.7 (1)	2.9 (27)
Bronchus, trachea & lung (ICD 162-163)	7.6 (25)	8.6 (26)	11.2 (10)	8.9 (8)	15.8 (11)	24.2 (14)	9.9 (94)
Other malignant neoplasms	14.4 (47)	18.6 (54)	14.5 (11)	6.4 (5)	9.5 (6)	13.5 (8)	14.4 (131)
All malignant neoplasms (ICD 140-209)	38.8 (145)	39.3 (117)	32.2 (27)	27.5 (22)	45.1 (31)	61.8 (36)	38.6 (358)

(ICD 162 and 163). In this group there was little difference between rates in the four lower dust categories, but the fifth and sixth groups showed an upward trend. A similar trend with years of exposure was found (Table 5), but the figures within the body of the table suggest a closer relationship with dust than with years. Subtraction of the three incorrectly coded cases and addition of the nine lung cancer cases found at autopsy increased slightly the rate among persons with highest dust and longest exposure, but did not materially change the picture (Table 5). Further analyses to distinguish better the relative importance of years of exposure and dust index are described as follows.

Rates for cancer of the intestine were about one third of those for cancers of the bronchus, trachea, and lung, but showed a very similar trend. Rates for cancer of the esophagus and stomach, on the other hand, did not appear related to dust in any consistent manner. Other abdominal neoplasms were less frequent still and also unrelated to dust. This is important since it might be expected that unrecognized peritoneal mesotheliomas would be found within this group.

Most of the excess mortality from respiratory disease was ascribed to pneumoconiosis (Table 6). There was little evidence that dust-associated deaths were included in other respiratory categories. Of the 28 deaths coded under the pneumoconioses, one was described as anthracosis, four as silicosis, and the remaining 23 as asbestosis. The greatest excess mortality from pneumoconiosis was among persons in the highest dust group who had been employed between ten and 29 years.

In the circulatory diseases group, there was also excess mortality in the highest two dust categories, mainly in persons employed

DUP 0821146

DU 011562

between ten and 29 years. It was present equally in the "arteriosclerotic and degenerative heart disease" group (ICD 420 to 422 [which included more than three quarters of all circulatory deaths]) and in the group of "other circulatory diseases" (ICD 400 to 419 and 423 to 469).

Comparison With Quebec Mortality.—The number of deaths from all causes which would have been expected if Quebec death rates had applied was calculated in the following way. Age-specific death rates for the province were applied for each year, 1950 to 1966, to all the men traced who were alive in 1950, with an adjustment for those who started work after 1950. The expected number of deaths among men, thus, was 1,824, whereas the observed number in the cohort was 1,674.

A similar calculation was made for lung cancer deaths. The expected number was 91, whereas 94 male deaths certified as due to this cause were observed. Correction for coding errors and additional autopsy information was not appropriate, since certificates for the general population were uncorrected.

In the six counties of the province which include the mining region (Arthabaska, Beauce, Drummond, Megantic, Richmond, and Wolfe), the lung cancer death rate was about two-thirds the provincial rate and the expected number of deaths was correspondingly lower. However, many ex-employees were no longer living in this area when they died, and most of those who had moved had gone to cities where lung cancer death rates were higher. The best estimate of expected deaths probably lies between the numbers 61, derived from the mining region, and 91, from the province. The excess of observed over expected lung cancer deaths, therefore, lies somewhere between zero and 30 and is most probably between ten and 20.

Factor Evaluation.—Although the numbers of men in each cohort were about the same, their distribution by years of employment and dust index was uneven. In these circumstances, equivalent average death rates could be misleading. Berry[14] recently reviewed some of the methods used for analyzing the importance of factors in multiway tables and described a parametric approach which has the advantage that the adequacy of the model may be checked and statistical

Table 5.—*Equivalent Average Death Rates per 1,000 Men for Cancer of Bronchus, Trachea, and Lung**

Years	Dust Index <10	10-	100	200-	400	800	All
As certified							
<1	6.4	1.7	27.8	0.0	...	...	5.9
	(16)	(1)	(1)	(0)			(18)
1-	11.7	9.5	11.3	5.8	7.6	0.0	9.6
	(9)	(15)	(4)	(1)	(1)	(0)	(30)
10-	0.0	12.4	6.7	5.3	19.9	23.6	13.1
	(0)	(7)	(3)	(3)	(6)	(6)	(25)
30-	...	12.5	14.7	13.9	16.1	27.9	17.2
		(3)	(2)	(4)	(4)	(8)	(21)
All	7.6	8.6	11.2	8.9	15.8	24.2	9.9
	(25)	(26)	(10)	(8)	(11)	(14)	(94)
Using all available information							
<1	6.7	1.7	0.0	0.0	...	...	5.9
	(17)	(1)	(0)	(0)			(18)
1-	12.0	10.1	9.4	11.5	7.6	0.0	10.1
	(9)	(16)	(3)	(2)	(1)	(0)	(31)
10-	0.0	12.8	7.6	9.2	19.9	23.6	14.3
	(0)	(8)	(4)	(4)	(6)	(6)	(28)
30-	...	12.5	14.7	13.9	16.1	35.3	19.1
		(3)	(2)	(4)	(4)	(10)	(23)
All	7.8	9.1	10.1	10.6	15.8	27.7	10.6
	(26)	(28)	(9)	(10)	(11)	(16)	(100)

* By dust index and years of employment. Diagnosis was ICD 162 and 163.

significance evaluated. From the number of deaths from any particular cause in groups subdivided by date of birth and year of employment or dust index, expected rates may be calculated assuming no interaction between age and the other two factors. For this analysis, the complementary log log transformation was used.[15] This transformation is appropriate when increasing exposure is associated with proportional increases in the age-specific death rates.

The results of this parametric analysis for respiratory cancer (Table 7) agree remarkably closely with the equivalent average death rates shown in the lower half of Table 5. The rates for the first five dust index levels do not differ significantly but those for the first four are significantly different from the highest exposure group. There are, however, also differences between the rates by years of employment, those for the lower two categories being significantly less than that for men with the longest exposure.

The general fit of the complementary log log model is very good. In no cell of the 24 does the observed number of deaths differ significantly from expectation. Tests for interaction between the 24 cells and the six cohorts gave the following results: likelihood

DUP 0821147
DU 011563

Table 6.—Equivalent Average Death Rates per 1,000 Men for Respiratory Diseases (ICD 470-529) by Dust Index and Years of Employment

	Dust Index						
Years	<10	10-	100-	200-	400-	800-	All
Pneumonia and bronchitis (ICD 490-509)							
<1	2.6(7)	8.7(4)	0 (0)	166.7(1)	...	...	4.0(12)
1-	7.1(5)	3.7(6)	2.5(1)	4.4(1)	15.5(2)	16.7(1)	5.2(16)
10-	0	6.3(4)	5.9(2)	5.3(3)	5.6(3)	9.5(2)	6.3(14)
30-	...	0	4.9(1)	5.8(1)	0 (0)	3.4(1)	2.9(3)
All	3.8(12)	4.7(14)	4.2(4)	6.6(6)	5.6(5)	6.9(4)	4.9(45)
P. sumoconioses (ICD 523 and 524)							
<1	1.4(3)	4.5(2)	0	0	...	...	1.9(5)
1-	1.4(1)	1.5(2)	0	5.8(1)	0	0	1.5(4)
10-	0	2.3(1)	0	1.2(1)	1.6(1)	34.3(8)	6.3(11)
30-	...	0	0	3.6(1)	7.1(2)	17.9(5)	6.9(8)
All	1.5(4)	2.0(5)	0(0)	3.7(3)	3.9(3)	22.6(13)	3.2(28)
Other respiratory diseases (ICD 470-489, 510-522, 525-529)							
<1	4.5(10)	5.7(3)		0	0	0	4.6(13)
1-	3.8(3)	13.2(20)	29.0(5)	9.8(2)	7.9(1)	13.9(1)	12.5(36)
10-	0	2.7(2)	9.2(2)	7.9(2)	11.0(3)	7.8(2)	7.3(11)
30-	...	0	0	0	0	13.5(4)	3.6(4)
All	4.2(13)	8.6(25)	15.3(11)	6.3(4)	5.9(4)	12.1(7)	7.5(64)
All respiratory diseases (ICD 470-529)							
<1	8.6(20)	18.8(9)	0	166.7(1)	...	...	10.5(30)
1-	12.2(9)	18.4(28)	31.5(10)	20.0(4)	23.5(3)	30.6(2)	19.2(56)
10-	0	11.2(7)	15.1(4)	14.4(6)	18.2(7)	51.6(12)	19.9(36)
30-	...	0	4.9(1)	9.3(2)	7.1(2)	34.7(10)	13.4(15)
All	9.5(29)	15.3(44)	19.5(15)	16.7(13)	15.3(12)	41.6(24)	15.6(137)

ratio test, 88.9 and χ^2, 90.4, each with 95 degrees of freedom; and $P > 0.5$.

Comment

At face value, the findings suggest that our cohort of workers in the chrysotile mining industry had a lower mortality than the population of Quebec of the same age. This is generally true of employed persons, provided they are not subjected to an occupational hazard sufficient to offset the considerable selective advantage of being and remaining fit for work. This advantage was clearly lost by the men in the highest dust-index category whose standardized mortality was about 20% above that of the rest. Two thirds of the excess mortality in this group was probably due to pulmonary fibrosis, shown on the death certificate as either asbestosis or in the guise of various respiratory or cardiovascular diagnoses, and the remaining third to cancer, mainly of the respiratory tract.

The high rate of lung cancer in men heavily exposed to asbestos might be explained if such men also tended to smoke more heavily than others. We have no direct evidence on this point for ex-employees, since information on smoking was not routinely recorded by the companies or the medical clinics. However, in a survey of a selected random sample of over 1,000 current employees there was little or no relationship, after allowing for age, between smoking habits and either dust exposure or duration of employment.

Table 7.—Age-Corrected Death Rates per 1,000 Men for Cancer of the Bronchus, Trachea, and Lung by Dust Index and Years of Employment*

	Dust Index						
Years	<10	10-	100-	200-	400-	800-	All
<1	6.3	2.0	0.0	0.0	...	...	5.5
1-	11.4	9.4	8.1	8.3	9.6	0.0	9.5
10-	0.0	10.4	9.8	10.3	16.8	23.4	12.8
30-	...	13.3	9.9	14.6	13.7	34.4	17.9
All	7.5	8.7	8.9	11.0	14.6	26.3	10.0

* A complementary log log model was used, and diagnosis was based on all available information.

Our attempts to assess separately the importance of cumulative dust exposure and duration of exposure in relation to lung cancer are capable of more than one interpretation. As shown in Table 5, there is a fivefold difference between the mortality for those with the lowest amount and duration of exposure, 6.7, and that for those with the highest, 35.3. This is confirmed by the parametric analysis (Table 7) which further suggests that accumulated dust exposure and

DUP 0821148

DU 011564

Table 8.—*Comparison of Mesothelial Tumor Findings in Two Previous Studies and the Present Study*

	Selikoff et al[16]	Newhouse[8,17]	Present Study
No. of men studied	632	4,806	9,981
No. of deaths			
All causes	380	436	2,413
Lung cancer	72	42	97
Mesothelial tumors	22	20	3

duration of employment are about equally important in determining the difference. Unfortunately, there are possible sources of bias and error which may have contributed to both these effects.

In Table 5, the rates for men with less than one year of employment seem remarkably low; 18 deaths were observed, whereas 29 would have been expected on the basis of Quebec rates. It was in this group that tracing was least satisfactory (Table 2). Failure to ascertain even a small number of lung cancer deaths would have made an appreciable difference in the rates. Short-term employees who were traced tended to be those who had stayed in the neighborhoods where, in any case, lung cancer rates were much lower than in the urban areas of the province and elsewhere, to which those untraced may well have gone. Whatever the explanation, it is difficult to accept, without reserve, the low rate of lung cancer in this group.

A second source of error is related to the ascertainment of lung cancer as a cause of death. It is generally believed that this diagnosis is greatly aided by postmortem examination. In our study, 34% of the cases before correction and 40% after correction had had an autopsy, compared with 12% of all deaths. This might not matter if autopsies were evenly distributed in relation to exposure, but this was not so. The autopsy rates in ascending order of dust-index group were 11%, 11%, 9%, 10%, 16%, and 22%, and by years of employment, 12%, 9%, 17%, and 21%. This trend is also likely to have exaggerated the difference in lung cancer rates in relation to exposure, but by how much it is impossible to say.

Taking all these considerations into account we are inclined to conclude that the true difference between those maximally and minimally exposed may well be closer to threefold than fivefold and that this is partly dust-related and partly time-related. We propose in future analyses, when a longer period of observation will have yielded more data, to use an exposure index based on the concept of amount of dust inhaled and the time that it remains in the lung. Our findings so far appear compatible with such a model.

In the Canadian survey mentioned earlier,[10] primary malignant mesothelial tumors were rarely associated with chrysotile asbestos production in Quebec and the present survey bears this out. Three deaths from this cause were found among nearly 2,500 deaths from all causes in the cohort. This is probably more than would be expected in a comparable number of deaths in the general population, but quite out of line with the findings of Selikoff et al[16] in insulation workers and those of Newhouse[8,17] in a London asbestos factory. The magnitude of the difference can be inferred from the figures in Table 8. Though these figures are not entirely comparable, because of age, methods of ascertainment, or other factors, they suggest that the results of Newhouse[8,17] are similar to those of Selikoff et al[16] for mesothelial tumors and, perhaps, lung cancer. It is clear that the Quebec chrysotile workers have had nothing like the experiences of the American insulation workers or the London factory workers with respect to malignant mesothelioma, and it seems unlikely that they are compatible with respect to lung cancer. These findings strongly suggest either that chrysotile is less likely to cause malignant disease of the lung and pleura than other forms of asbestos, such as crocidolite, or that workers engaged in insulation and processing are exposed to additional factors which explain the difference.

This work was undertaken with the assistance of a grant from the Institute of Occupational and Environmental Health of the Quebec Asbestos Mining Association.

Paul M. Cartier, MD, medical director of the

DUP 0821149

DU 011565

Thetford Industrial Clinic, and T. Roger Grainger, MD, medical director of the Canadian Johns-Manville Company assisted and cooperated in this study. Members of unions and management personnel of the Quebec Asbestos Mining Industry gave their support. The Department of Demography, Quebec, and other departments of vital statistics helped us obtain death certificates. The Department of National Health and Welfare, Ottawa, and the Canadian Unemployment Insurance Commission assisted in the follow-up. Julienne Roy, Fernande Proulx, and Joseph-Albert Carrier, and others traced ex-employees, and Geraldine Jacobs and Jean Peabody helped with the data processing.

References

1. Asbestos: A review of the Canadian industry. *Mining in Canada*, Oct 1967, pp 17-38.

2. Wright GW: Asbestos and health in 1969. *Amer Rev Resp Dis* 100:467-479, 1969.

3. Merewether ERA: Asbestosis and carcinoma of the lung, in *Annual Report of the Chief Inspector of Factories for the Year 1947*. London, Her Majesty's Stationery Office, 1949, pp 79-87.

4. Wagner JC, Sleggs CA, Marchand P: Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Brit J Industr Med* 17:260-271, 1960.

5. Doll R: Mortality from lung cancer in asbestos workers. *Brit J Industr Med* 12:81-86, 1955.

6. Knox JF, Holmes S, Doll R, et al: Mortality from lung cancer and other causes among workers in an asbestos textile factory. *Brit J Industr Med* 25:293-303, 1968.

7. Enterline PE, Kendrick MA: Asbestos-dust exposures at various levels and mortality. *Arch Environ Health* 15:181-186, 1967.

8. Newhouse ML: A study of the mortality of workers in an asbestos factory. *Brit J Industr Med* 26:294-301, 1969.

9. Selikoff IJ, Hammond EC, Churg J: Asbestos exposure, smoking and neoplasia. *JAMA* 204:106-112, 1968.

10. McDonald AD, Harper A, El Attar OA, et al: Epidemiology of primary malignant mesothelial tumors in Canada. *Cancer* 26:914-919, 1970.

11. Braun DC, Truan TD: An epidemiological study of lung cancer in asbestos miners. *Arch Industr Health* 17:634-653, 1958.

12. Kogan FM, Troitsky SY, Gulevskaya MR: On the carcinogenic effect of asbestos dust. *Gig Tr Prof Zabol* 8:28-33, 1966.

13. Hill AB: *Principles of Medical Statistics*, ed 8. London, Lancet Ltd, 1966, p 209.

14. Berry G: Parametric analysis of disease incidences in multiway tables. *Biometrics* 26:572-579, 1970.

15. Yates F: The use of transformations and maximum likelihood in the analyses of quantal experiments involving two treatments. *Biometrika* 42:382-403, 1955.

16. Selikoff IJ, Hammond EC, Churg J: Mortality experiences of asbestos insulation workers, in *Proceedings of the International Conference on Pneumoconiosis Johannesburg, 1969*, to be published.

17. Newhouse ML, Wagner JC: Validation of death certificates in asbestos workers. *Brit J Industr Med* 26:302-307, 1969.

Printed and Published in the United States of America

DUP 0821150

DU 011566

Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States*

E. Cuyler Hammond, Sc.D., and Irving J. Selikoff, M.D.

SUMMARY

We conclude that employment in asbestos insulation work greatly increases the lung cancer risk of cigarette smokers. It is uncertain whether such employment increases the risk of lung cancer among nonsmokers. Cigarette smoking may also increase the risk of death from asbestosis, although to a much lesser extent. It is of interest that the risk of death among nonsmoking asbestos insulation workers is greater for asbestosis than for lung cancer. This indicates that even if asbestos workers were to stop cigarette smoking, it would still be necessary to reduce dust exposure below those concentrations associated with the occurrence of asbestosis.

Data have been reported indicating that cigarette smoking greatly increases the risk of death of lung cancer among asbestos insulation workers (Selikoff, Hammond and Churg, 1968). It was calculated that asbestos insulation workers with a history of regular cigarette smoking had eight times the risk of lung cancer deaths compared with cigarette smokers who did not do such work, and approximately ninety times the risk of men who neither worked with asbestos nor smoked cigarettes.

We have obtained further evidence on this matter, bearing on aspects of asbestos associated disease for which data were previously scant or incomplete.

Lung cancer among cigarette smoking asbestos insulation workers.

Recent experiences have confirmed that lung cancer among insulation workers is largely confined to those men with a history of cigarette smoking. Data are derived from observation of two cohorts of insulation workers. Since they differ in age of distribution and work experience, it is advantageous to consider them separately.

First, we have followed a group of 370 insulation workers from Jan. 1, 1963. These were survivors of 632 men who were members of the insulation workers union in the New York area on Jan. 1, 1943 (Selikoff, Churg and Hammond, 1964). Therefore, in 1963 these men were all at least 20 years from onset of employment (indeed, 333 had reached thirty or more years from onset) (Table 1). 283 of these men had a history of regular cigarette smoking; by April 30, 1967, 24 had died of lung cancer although, given their smoking habits, only 2.98 such deaths had been expected. No deaths of lung cancer occurred among the 87 men with no history of cigarette smoking. (Selikoff, Hammond and Churg, 1968).

The cohort has now been traced for an additional 56 months. Table 2 shows findings for the nine-year period January 1, 1963-December 31, 1971. Of 283 men who ever smoked cigarettes regularly 41 died of lung cancer while of 87 men who never smoked cigarettes regularly only 1 died of lung cancer. This man was a cigar smoker. Expected number of deaths shown in Table 2 are based upon United States mortality data for white males disregarding smoking habits. We are presently unable to calculate smoking-specific expected rates for this group, since death rates related to smoking are not yet available for the period 1967-1971.**

We have obtained data in a second far larger study of insulation workers. On January 1, 1967, we registered all members of the insulation workers union in the United States and Canada (including the New York-New Jersey locals mentioned above).*** There were 17,800 men so enrolled on that day (Table 3). 11,656 completed a questionnaire providing, among other details, information concerning their smoking habits (Table 4). We have followed this cohort

*From the Environmental Cancer Research Project, American Cancer Society and the Mount Sinai School of Medicine of the City University of New York. This research was supported in part by U.S. Public Health Service grant OH00320 to the Mount Sinai School of Medicine.

**We have reported smoking-specific death rates, 1959-1965, in a prospective study of 1,000,000 people (Hammond, 1966). This cohort is now being retraced, and rates, 1966-1971, will be available.

***International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO.

DUP 0821151

DU 011567

through December 31, 1971 (Selikoff and Hammond, 1972). Although the total group differed from the cohort described above in being, on the average, significantly younger and with shorter duration of exposure, its lung cancer experience has been very much in the same direction.

1,092 deaths occurred during the period January 1, 1967-December 31, 1971 (See Table 5). Of these, 213 were due to lung cancer; whereas only 44.4 were expected, had the experience of these men been the same as other U.S. white males of the same age distribution. Among the 9,590 men with a history of regular cigarette smoking, there were 596 deaths, 134 of which were due to lung cancer. Again, we are at this time unable to calculate smoking-specific expected and observed rates because, as noted, death rates related to smoking habits of individuals are unavailable for this period of years.

Lung cancer deaths among insulation workers who do not smoke cigarettes.

At the time of our initial report, we had had limited opportunity of studying the incidence of lung cancer among insulation workers with no history of cigarette smoking. There were 87 such men in our 1963 New York-New Jersey group, and by 1967, only 16 deaths had occurred, none of lung cancer. Only 0.18 lung cancer deaths were expected, however, and with such scant experience we concluded that our information "...does not prove that exposure to asbestos dust has no influence on the risk of lung cancer among nonsmokers. However, it does suggest that exposure to asbestos dust does not lead to an extremely high risk of lung cancer among nonsmokers." (Selikoff, Hammond and Churg, 1968.) Obviously, it was important to obtain further information on the lung cancer risk among nonsmoking insulation workers. This is now available, from experience of the cohort described above.

Among the 2,066 non-cigarette smokers in the nation-wide study, 73 deaths occurred January 1, 1967-December 31, 1971. Two were due to lung cancer. One of these two men was a cigar and pipe smoker and the other never smoked regularly. (Table 5)

It seems clear, then, that lung cancer is uncommon among asbestos insulation workers who have no history of cigarette smoking and that if the risk is increased, such increase is not great.

Pleural Mesothelioma.

In our previous report, we were unable to suggest whether or not pleural mesothelioma was related to cigarette smoking. Only three deaths occurred of this disease in our New York-New Jersey group from 1963 through April 1967. While all three of these men were cigarette smokers, the number was too small for reliable evaluation. Since then 2 more deaths of pleural mesothelioma have occurred, again among cigarette smokers. (Table 2)

In the larger cohort (see Table 5) there were 1,092 deaths of which 26 were due to a pleural mesothelioma. Of these 26 men, 17 had a history of regular cigarette smoking, 1 was a pipe smoker, 1 never smoked regularly and 7 were unknown as to smoking habits. We still refrain from drawing definite conclusions because of small numbers.

Peritoneal Mesothelioma.

As with pleural disease, no definitive statement could be made in 1968 concerning the relation of peritoneal mesothelioma to cigarette smoking. Of seven deaths of peritoneal mesothelioma, two occurred among men with no history of cigarette smoking.

In the large cohort (See Table 5) there were 51 deaths of peritoneal mesothelioma; 9 among the 2,066 never smoked cigarettes regularly, and 29 among the 9, 590 cigarette smokers. 13 occurred among 6,144 insulation workers for whom smoking histories were not available (Table 5).

These experiences suggest that cigarette smoking does not increase the already high risk of peritoneal mesothelioma among asbestos insulation workers.

Asbestosis.

Studies indicate that radiologically evident pulmonary fibrosis is augmented in asbestos workers by cigarette smoking (Weiss, 1971, Selikoff, 1972).

Data now at hand suggest that the risk of death of asbestosis (respiratory insufficiency and cor pulmonale) may be increased by cigarette smoking. These data are reported with the realization that there must be a mixture of cigarette smoking effects in such cases, including increased asbestotic fibrosis, and the emphysema, bronchitis and smoking-associated fibrosis associated with cigarette smoking in general (Auerbach, Stout, Hammond and Garfinkel, 1963). These effects could be additive or less than additive, or multiplicative, in specific cases. Complex histological and physiological variations are possible.

In the nationwide study, of the 73 deaths among the 2,066 nonsmokers, 4 were due to asbestosis, as were 45 of the 596 deaths among the 9,590 smokers. (Table 5). We computed expected numbers of asbestosis deaths from age specific

DUP 0821152

death rates for the total study population disregarding smoking habits. The ratio of observed to expected asbestosis deaths was almost three times as high for men with a history of cigarette smoking as for men without a history of cigarette smoking. This was of borderline statistical significance.

Gastro-intestinal cancer.

There seems to be a definite, albeit limited, association between employment in asbestos insulation work and increased risk of death of cancer of stomach, colon-rectum, and esophagus. Data in this regard were first reported in 1963. (Selikoff, Churg and Hammond, 1964.)

Experiences since 1963 continue in the same direction with increased death rates of approximately the same magnitude. In the large cohort (See Table 5) there were 16 observed vs. 6.62 expected deaths from cancer of the stomach, 26 observed vs. 17.51 expected deaths from cancer of the colon-rectum, and 13 observed vs. 3.21 expected deaths from cancer of the esophagus. Because of small numbers of expected and observed deaths from cancer of these sites among the 2,066 men with no history of cigarette smoking, we will draw no conclusion concerning the possible interaction of cigarette smoking and asbestos exposure. However, these data are consistent with findings in other studies of high degree of relationship between smoking and the occurrence of cancer of the esophagus.

References

1. Auerbach, O., Stout, A.P., Hammond, E.C., and Garfinkel, L. (1963) Smoking habits and age in relation to pulmonary changes: rupture of alveolar septums, fibrosis, and thickening of walls of small arteries and arterioles. *New Engl. J. Med.;* 269, 1045-1054.
2. Hammond, E.C. (1966) Smoking in relation to the death rates of 1,000,000 men and women, in Epidemiological Study of Cancer and Other Chronic Diseases, Bethesda, Md., *National Cancer Institute.* monograph 19, pp. 127-204.
3. Selikoff, I.J. (1972) Asbestos exposure and cigarette smoking: Synergism in cardinogenesis. Proc. Skytop Conference on Respiratory Disease in Industry. *In press.*
4. Selikoff, I.J., Churg, J. and Hammond, E.C. (1964) Asbestos exposure and neoplasia. *J. Amer. Med. Assoc.,* 188, 22-26.
5. Selikoff, I.J. and Hammond, E.C. (1972) Cancer risk of insulation workers in the United States. *This conference.*
6. Selikoff, I.J., Hammond, E.C. and Churg, J. (1968) Asbestos exposure, smoking and neoplasia. *J. Amer. Med. Assoc.,* 204, 106-112.
7. Weiss, W. (1971) Cigarette smoking, asbestosis and pulmonary fibrosis. *Amer. Rev. Resp. Dis.* 104, 223-227.

DU 011569

DUP 0821153

Table 1

Members of New York-New Jersey Locals of Insulation Workers Union Classified by Age as of Jan. 1, 1963, and by Years From First Occupational Exposure to Asbestos Dust up to Jan. 1, 1963.

Age, Yr.	Total No. of Members	No. of Years Since First Exposure to Asbestos						
		20-24	25-29	30-34	35-39	40-44	45-49	50+
35-39	2	2	...	...	...	...	...	...
40-44	13	12	1	...	...	...	...	...
45-49	32	17	2	13	...	...	...	...
50-54	109	...	1	80	28	...	...	...
55-59	60	...	1	16	34	8	1	...
60-64	42	...	1	3	11	19	8	...
65-69	49	...	...	1	10	18	18	2
70-74	38	...	...	...	3	12	6	17
75-79	21	...	...	...	...	1	5	15
80-84	4	...	...	...	...	1	1	2
Total	370	31	6	113	86	59	39	36

Members Classified by Age and by Smoking Habits on or about Jan. 1, 1963

Age, Yr.	Total No.	Never Smoked Regularly	Pipe, Cigar, Only	Ex-Cigarette Smokers*	Current Cigarette Smokers*			
					1-9 A Day	10-19 A Day	20-39 A Day	40+ A Day
35-39	2	1	...	1	...	...	...	...
40-44	13	2	...	2	...	...	5	4
45-49	32	2	1	5	...	...	12	12
50-54	109	12	6	26	3	5	33	24
55-59	60	6	5	16	...	3	20	10
60-64	42	7	4	15	1	...	11	4
65-69	49	6	8	17	...	4	9	5
70-74	38	7	7	12	1	4	4	3
75-79	21	3	7	6	...	1	3	1
80-84	4	2	1	1	...	...	...	...
Total	370	48	39	101	5	17	97	63

*Includes cigarette smokers who also smoked pipes or cigars.

DU 011570

DUP 0821154

Table 2

Expected** and Observed Deaths among 370 New York-New Jersey Asbestos Insulation Workers, Jan. 1, 1963-Dec. 31, 1971

	Total		No history of cigarette smoking*		History of cigarette smoking	
Number of men Jan. 1, 1963	370		87		283	
Person years of observation	2,520		608		1,912	
	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths
Cancer all sites	15.74	94	4.75	15	10.99	79
Lung cancer	4.57	42	1.26	1	3.31	41
Pleural mesothelioma	***	5	***	–	***	5
Peritoneal mesothelioma	***	20	***	7	***	13
Cancer of stomach	0.94	6	0.30	2	0.64	4
Cancer of colon, rectum	2.15	6	0.69	2	1.46	4
Cancer of esophagus	0.37	–	0.11	–	0.26	–
Asbestosis	***	21	***	5	***	16
All other causes	69.22	53	22.28	15	46.94	38
Total deaths	84.96	168	27.03	35	57.93	133

* Included 39 men who smoked pipe or cigars.

** Expected deaths based upon age specific U.S. mortality for white males, disregarding smoking habits. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163.

*** United States data not available, but these are rare causes of death in the general population.

DUP 0821155

DU 011571

Table 3

Membership of Asbestos Insulation Workers' Union,* Jan. 1, 1967
Classified by Age and by Years from First Exposure to Asbestos Dust

Age-Yr.	Total No. of Members	Number of years since first exposure to asbestos								
		0-9	10-14	15-19	20-24	25-29	30-34	35-39	40-49	50+
15-19	244	244								
20-24	1,695	1,695								
25-29	2,412	2,066	345	1						
30-34	2,762	1,065	1,356	341						
35-39	2,987	313	1,140	1,342	192					
40-44	2,260	79	424	1,026	591	139	1			
45-49	1,589	49	131	433	442	487	47			
50-54	1,297	27	88	214	332	377	182	77		
55-59	983	12	49	129	206	176	146	193	72	
60-64	704	1	21	59	131	126	87	100	179	
65-69	417		6	18	40	57	46	28	200	22
70-74	255			6	14	22	21	16	105	71
75-79	111		1		4	8	4	7	37	50
80-84	52					2	1	2	16	31
85+	32							2	8	22
Total	17,800	5,551	3,561	3,569	1,952	1,394	535	425	617	196

*Membership in the United States and Canada of the International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO.

DUP 0821156

DU 011572

Table 4

Smoking Habits of 17,800 Asbestos Insulation Workers in the United States and Canada, on Jan. 1, 1967.

Age	Total	No History of Cigarette Smoking*	History of Cigarette Smoking	Smoking history not known
< 25	1,939	281	782	876
25-29	2,412	285	1,182	945
30-34	2,762	314	1,435	1,013
35-39	2,987	309	1,640	1,038
40-44	2,260	223	1,395	642
45-49	1,589	172	964	453
50-54	1,297	134	821	343
55-64	1,687	201	965	521
65-74	672	122	314	236
75+	195	25	92	78
Total	17,800	2,066	9,590	6,144

*Included 609 men who smoked pipes or cigars.

DU 011573

DUP 0821157

Table 5

Expected and Observed Deaths among 17,800
U.S. and Canada Asbestos Insulation Workers,
Jan. 1, 1967-Dec. 31, 1971*

	Total		No history of cigarette smoking**		History of cigarette smoking		Smoking habits not known	
Number of men Jan. 1, 1967	17,800		2,066		9,590		6,144	
Person-years of observation	86,300		10,163		46,615		29,522	
	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths
Cancer all sites	144.09	459	19.92	33	79.58	265	44.49	161
Lung cancer	44.42	213	5.98	2	25.09	134	13.35	77
Pleural mesothelioma	***	26	***	2	***	17	***	7
Peritoneal mesothelioma	***	51	***	9	***	29	***	13
Cancer of stomach	6.62	16	0.95	1	3.60	8	2.07	7
Cancer of colon, rectum	17.51	26	2.52	4	9.53	14	5.46	8
Cancer of esophagus	3.21	13	0.44	0	1.80	7	0.97	6
Asbestosis	***	78	***	4	***	45	***	29
All other causes	661.54	555	92.67	36	356.67	286	212.20	233
Total deaths	805.63	1,092	112.59	73	436.25	596	256.79	423

* Expected deaths based upon age specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163.

** Included 609 men who smoked pipes or cigars.

*** United States data not available, but these are ...re causes of death in the general population.

DU 011574

DUP 0821158