PART 1

INHALED PARTICLES SYMPOSIUM

SECTION 7

EPIDEMIOLOGY-FIBROUS DUSTS

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MORTALITY OF VERMICULITE MINERS EXPOSED TO TREMOLITE

H. E. AMANDUS,* R. WHEELER,* B. G. ARMSTRONG,† A. D. MCDONALD,† J. C. MCDONALD* and P. SEBASTIEN†

*The Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, W.VA., U.S.A. 26505, † School of Occupational Health, McGill University, 1110 Pine Ave. West, Montreal, PQ, Canada H3A 1A3

Abstract—Closely similar cohort mortality studies were conducted independently and in parallel by groups from NIOSH and McGill University among past and present employees of a Montana mine and mill where the vermiculite ore is contaminated by amphibole fibres, mainly of the tremolite-actinolite series. The NIOSH cohort consisted of 569 men hired before 1970, while the McGill cohort consisted of 406 men hired before 1963, and men in both cohorts were employed at least 1 year.

Exposures were estimated for each man in fibre-years (f-y) from work histories and all available samples of airborne dust tested by governmental agencies or the company since 1956.

A man-years analysis against U.S. white male mortality showed increased SMR's from lung cancer and non-malignant respiratory disease (NIOSH:2.15 and 2.46; McGill: 2.45 and 2.55). In relation to exposure, the SMR for lung cancer was estimated to increase 0.6% by NIOSH and 1.1% by McGill with each unit increase in f-y. Mortality from mesothelioma was reported as the underlying cause of death in 2 cases in the NIOSH cohort, and as the underlying or contributing cause of death in 4 cases in the McGill cohort.

INTRODUCTION

IN DECEMBER, 1981 the National Institute for Occupational Safety and Health (NIOSH) initiated a study of the mortality and morbidity among employees of a Montana mine and mill where the vermiculite ore is contaminated by tremolite-actinolite fibres. In April 1983 McGill University began a parallel but independent study. The primary objective of both studies was to estimate the relationship between cumulative fibre exposure and morbidity and mortality. This report covers the mortality findings.

METHODS

Exposure estimates

Production methods have changed over the years at the mine and mill. However, at present ore is extracted in the mine by drilling, blasting, loading with front end loaders and hauling to a transfer site. The coarse fraction is then separated while the fine fraction is transferred by belt to the mill. From the mill, the processed concentrate is transferred (called skipping) to a transfer site, loaded into trucks and hauled to a screening plant and loading dock by the Kootenai river. Screened concentrate is loaded into railroad cars, and a smaller quantity is hauled to a bagging facility in the town of Libby, Montana.

Prior to 1974 both milling and screening were located in the same building at the mine site. From 1935 to 1954 the milling was a totally dry process, and a wet mill was added in 1954. In 1973 a new wet mill and screening plant were completed and the old mills were closed in 1974.

An estimate of the cumulative fibre/cc-years exposure (f-y), was calculated for each worker in a similar manner by NIOSH and McGill. Results of air sampling were available to NIOSH (McGill) from 336(376) midget impinger samples collected before 1970, and 4116 (4128) membrane filter samples collected after 1967. For the period before 1975 air samples were either static or short term personal samples reflecting more the general air concentrations than the individual TWA exposure. To estimate individual cumulative exposure on the basis of existing air sample measurements for the period before 1975, McGill designed a strategy based upon the concept of 'location-operation'. A location-operation defined a type of work in a certain area. NIOSH grouped and averaged (arithmetic mean) the results in 25 location-operations, while McGill used the technique described by OLDHAM (1965) to estimate the arithmetic mean in 28 location-operations.

Job exposure estimates were then computed as an average of area exposure estimates weighted by the proportion of time spent in different areas. Finally, the f-y estimate was computed as a sum of job tenures weighted by job exposure estimates.

Prior to 1968, samples were primarily collected in the dry mill and exposures were measured in million particles per cubic foot. Exposures were converted to f/cc using conversion factors computed from the data to be 4.0 by NIOSH and 4.6 by McGill. Prior to 1968, samples were unavailable in many areas, and assumptions were made as to exposure levels.

Cohorts

The NIOSH cohort includes 575 men hired before 1970, and the McGill cohort consists of 406 men hired before 1963; men in both cohorts were required to have worked at least 1 year at the Montana site. The average tenure (years) and f-y was 8.3 (8.7) and 200.3 (144.6) for NIOSH (McGill).

Vital status was traced to Jan. 1, 1982 for 569 men in the NIOSH cohort, and for 405 men in the McGill cohort. Additionally, 391 men in the McGill cohort were traced to July 1, 1983. Death certificates were obtained for 159 of the 161 deceased in the NIOSH cohort, and 163 of the 165 deceased in the McGill cohort. The underlying cause of death on the death certificates was coded independently by the same nosologist for both studies according to the eighth revision of the International Classification of Diseases.

Statistical analysis

The relationship between lung cancer mortality and cumulative fibre exposure was estimated in two ways by both groups. First using a man-years analysis (MONSON, 1974; BERRY, 1983), expected deaths were calculated by 5-year age groups and 5-year follow-up periods. The number of expected and observed deaths were then summed over the age groups and follow-up periods, and SMR's were calculated by exposure and time from hire.

For men with a least 20 years since hire, simple linear regression models were fitted to the SMR and average f-y of 4 exposure groups. Separate models were calculated, one

with the intercept restricted to 1.0 and another with the intercept unrestricted. NIOSH fitted a simple linear regression model using conventional unbiased estimates of the intercept and coefficient for f-y, while McGill fitted models using an iteratively weighted regression technique described by HANLEY and LIDDELL (1985).

In addition to the man-years analyses, NIOSH fitted a survival model described by COX (1972) to estimate the relationship between the conditional probability of dying from lung cancer and fibre-years, where the relative risk is estimated as exp [b(f-y)]. McGill also conducted a case-referent analysis using the method of THOMAS (1981) to estimate the linear increase in the relative risk (odds ratio) per fibre-year, where the relative risk is estimated as $1 + b$(f-y). Controls were matched to lung cancer cases based on surviving beyond the death of the case, date of birth, and date of hire within 3 years.

RESULTS

NIOSH (McGill) estimates of fibre concentrations prior to 1964 in the dry mill were 168 f/cc (101 f/cc) for working areas and 182 f/cc (125 f/cc) for sweeping, and 33 (22) and 36 f/cc (27 f/cc) respectively from 1964–1971 (Table 1). Prior to 1971, NIOSH estimates of fibre concentrations ranged from 9–23 f/cc for drilling, 17–88 f/cc in the skip area, 21–22 f/cc at the river station bin site, 17–116 f/cc at the loading dock, and 12–13 f/cc for baggers. The corresponding McGill figures were somewhat lower. Estimates of fibre concentrations from 1975–1982 in the new mill and screening plant were less than 1 f/cc. Additionally, the company reported that the average area exposures in 203 samples collected in 1984 were less than 0.1 f/cc.

The mortality of the NIOSH and McGill cohorts was compared with U.S. white males. Results are summarised in Table 2 with respect to years since hire and cause of death. The SMR for lung cancer is significantly increased in the overall cohorts (2.45 for McGill and 2.23 for NIOSH). Mortality from non-malignant respiratory disease was also increased in the overall group (2.55 for McGill and 2.43 for NIOSH). Mortality from accidents was increased among workers with greater than 20 years since hire. Mortality from digestive cancer and circulatory disease was not increased.

Mortality from malignant mesothelioma was found listed on the death certificates as an underlying or contributing cause of death in 4 cases in the McGill cohort. Only 2 had died by Jan. 1, 1982, the cut-off date for the NIOSH study.

Results for lung cancer mortality among workers with at least 20 years' latency are presented in Table 3 by exposure group. Compared with U.S. white males (NIOSH results), the lung cancer mortality was increased significantly above 399 f-y (p-value $< 5\%$), was increased from 50–399 f-y (but did not reach statistical significance), and was not increased below 50 f-y. Compared with Montana males (McGill results), lung cancer mortality was increased in each of 4 exposure groups (Table 3), and SMR's were higher than those based on comparison with U.S. white male rates.

Results from linear model fitting were similar whether the intercept was restricted or unrestricted (Fig. 1). NIOSH results indicate that the regression coefficient for f-y is 0.006, and that the percentage increase in the estimated SMR would be 0.6% for a unit increase in f-y. Corresponding results from McGill indicate that the estimated f-y coefficient is 0.013, and that the percentage increase in the SMR would be 1.3% for a unit increase in f-y.

TABLE 1. ESTIMATES OF FIBRE CONCENTRATIONS (f/cc) BY LOCATION-OPERATION AND YEAR FROM NIOSH AND MCGILL

	NIOSH Year						McGill Year					
Location-operation	< 50	60	65	70	75	80–82	< 50	60	65	70	75	80–82
Mine: non-drilling	2.6	2.6	2.6	2.6	0.6	0.6	2.3	2.3	2.3	2.3	0.6	0.6
drilling	23.0	23.0	23.0	9.2	0.6	0.6	12.5	12.5	12.5	5.2	5.3	0.8
Transfer point	2.2	2.2	2.2	2.2	0.6	0.6	2.8	2.8	2.8	2.8	0.6	0.6
Tailsbelt	7.3	7.3	7.3	7.3	0.7	0.7	7.9	7.9	7.9	7.9	0.7	0.7
Drymill: sweeping	182.1	182.1	35.9	35.9			124.9	124.9	27.2	27.2		
working	168.4	168.4	33.2	33.2			101.5	101.5	22.1	22.1		
Old wet mill +		3.7	3.7	3.7				5.1	5.1	5.1		
New wet mill					2.0	0.8					1.5	0.8
Skipping	88.3	88.3	17.4	17.4	0.6	0.6	68.8	68.8	15.0	15.0	0.6	0.6
Quality control lab.	13.1	13.1	2.6	2.6	0.6	0.6	2.9	2.9	2.9	2.9	0.6	0.6
Service area shops	1.9	1.9	3.8	1.9	0.2	0.2	1.0	1.0	2.0	0.9	0.2	0.2
Concentrate hauling	5.5	5.5	5.5	5.5	0.4	0.4	5.4	5.4	5.4	5.4	0.4	0.4
River Station: bin	21.2	21.2	21.2	21.2	0.7	0.7	12.0	12.0	12.0	12.0	0.7	0.7
office	10.6	10.6	10.6	10.6	0.2	0.2	4.7	4.7	4.7	4.7	0.2	0.2
loading	82.5	10.7	10.7	3.2	0.2	0.2	24.0	9.0	9.0	9.0	0.2	0.2
dock	116.9	17.0	17.0	17.0	0.5	0.5	36.0	6.0	6.0	6.0	0.5	0.5
Bagging	12.9	12.9	12.9	12.9	1.2	1.2	24.0	24.0	24.0	24.0	1.2	1.2

+ Mill-wright samples were excluded from NIOSH estimates

TABLE 2. DEATHS AND SMR BY CAUSE AND YEARS SINCE HIRE +

Cause of Death (ICDA)	Years Since Hire: < 10		10–19		> 20		Total	
	0	SMR	0	SMR	0	SMR	o	SMR
McGill								
All Causes	17	0.79	45	1.11	103	1.31	165[c]	1.17
Respiratory cancer (160–163)	4	5.02*	4	1.66	15	2.42*[a]	23	2.45*[b]
Digestive cancer (150–159)	1	0.86	1	0.44	5	1.11	7	0.88
Circulatory disease (390–458)	3	0.31	20	0.93	42	0.97	65	0.87
Non-malignant respiratory disease (460–519)	0	—	7	3.36*	14	5.30*	21	2.55*
Accidents (800–949)	5	1.80	4	1.46	9	3.11*	18	2.14*
NIOSH								
All Causes	22	0.74	46	1.02	93	1.30	161[c]	1.10
Carcinoma trachea, bronchi, lung (162–163)	4	3.51	4	1.53	12	2.30*	20	2.23*
Digestive cancer (150–159)	1	0.67	1	0.40	4	0.98	6	0.74
Circulatory disease (390–458)	6	0.48	20	0.86	40	1.02	66	0.88
Non-malignant respiratory disease (460–519)	1	0.85	7	3.05*	12	2.53*	20	2.43*
Accidents (800–949)	5	1.13	2	0.62	8	2.96*	15	1.45

+ Reference population: U.S. white males

* SMR significantly greater than 100, p-value < 5%

[a] The SMR calculated from Montana State rates was 2.85

[b] The SMR calculated from Montana State rates was 3.03

[c] The McGill cohort was a subset of the NIOSH cohort. The greater number of deaths in the McGill cohort was due to the longer period of follow-up.

TABLE 3. LUNG CANCER DEATHS (O) AND SMR's BY FIBRE/CC-YEARS EXPOSURE (f-y) FOR AT LEAST 20 YEARS FROM HIRE

McGill				NIOSH			
f-y Group	Mean	O	SMR*	f-y Group	Mean	O	SMR+
0–25	12.5	4	1.68				
				0–50	28.1	2	0.85
ts25–200	77.3	3	1.85	50–100	72.7	2	2.25
				100–399	209.6	1	1.09
200–500	332.4	5	9.80				
⩾ 500	836.1	3	6.77	⩾ 400	957.1	7	6.71

* Reference Population: Montana males
\+ Reference Population: U.S. White male rates

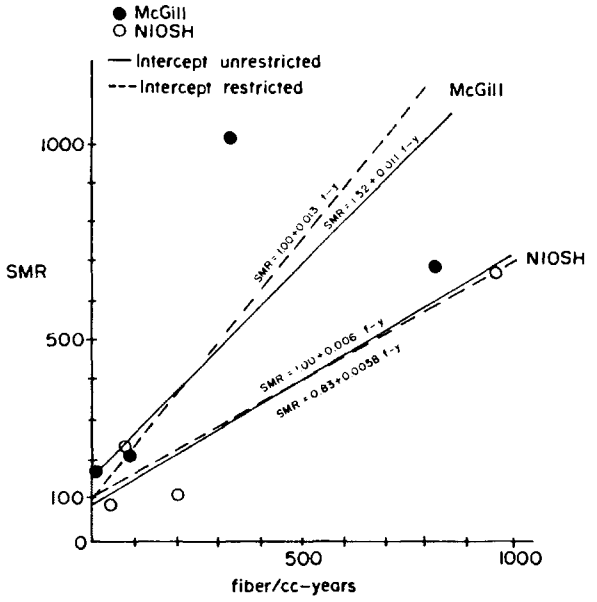

FIG. 1. Respiratory Cancer SMRs 20 or more years from first employment and cumulative exposure (fibre/cc-years)

NIOSH results from fitting the survival model indicate that the estimated f-y coefficient is 0.0011, giving the relative risk = exp(0.0011 f-y). Compared to zero f-y, the percentage change in the relative risk in calculated as 0.1% at 1 f-y, 0.6% at 5 f-y and 5.7% at 50 f-y. McGill results from the case-referent analysis show that the linear increase in the odds ratio for lung cancer is estimated as 1.0% for each f-y, i.e. the relative risk = 1 + 0.010 f-y. Differences in estimates of the relative risk between the NIOSH survival and linear models are in part due to the form of the models (exponential versus linear).

DISCUSSION

Results have implications for dust control on the amphibole fibres contaminating the vermiculite ore. If smoking is not considered a confounding factor, the linear form of the model is accepted, and the effect of cumulative exposure is the same whether accumulated in 'high' or 'low' average exposure situations, the results of these studies suggest that an 8-hour TWA exposure of 0.1 f/cc over a working life time of 50 years (i.e. 5 f-y) would increase the relative risk of lung cancer by about 3.0% (NIOSH) to 5.5% (McGill).

REFERENCES

BERRY, G. (1983) The analysis of mortality by the subject-years method. *Biometrics* **39**, 173–184.

COX, D.R. (1972) Regression models and life-tables. *J. R. Statist. Soc. B.* **34**, 187–202.

HANLEY, J. and LIDDELL, F.D.K. (1985) Fitting relationship between exposure and standardized mortality ratios. *J. Occup. Med.* **27**, 555–560.

MONSON, R. (1974) Analysis of relative survival and proportional mortality. *Computers and Biomedical Research 1*, 325–332.

OLDHAM, P.D. (1965) On estimating the arithmetic means of lognormally-distributed populations. *Biometrics* **21**, 235–239.

THOMAS, D.C. (1981) General relative-risk models for survival time and matched case-control analysis, *Biometrics* **37**, 673–686.

DISCUSSION

D. B. DOUGLAS: What influence, if any, does vermiculite itself have on the results of your study?

H. E. AMANDUS: There has been only one animal study of the carcinogenicity of vermicule (HUNTER *et al.*), and in that study vermiculite was not shown to be carcinogenic. Whether or not it is fibrogenic with radiographic changes and lung function abnormalities is unknown.

There is little information available on the health effects of vermiculite, it is considered a nuisance dust. The effects we're seeing among vermiculite miners is likely due to the asbestos in the ores; certainly with regard to lung cancer.

R. SARACCI: What is the reason for the marked discrepancies (by a factor of about 10) in the per cent estimated increase in lifetime risk of lung cancer between linear model and survival model?

H. E. AMANDUS: There was a difference between the results from our survival model and linear model, while the McGill group showed consistent results between their case-referent analysis and their linear model. The results from our survival analysis were estimates of the instantaneous relative risk from the Cox regression model, rather than a relative risk based on the cumulative hazard.

I think that might partially explain some of the differences. However, it is primarily due to differences between the exponential and linear contribution to risk at low exposure.

F. D. K. LIDDELL: I would certainly expect the case-referent analysis to accord fairly closely with the ordinary subject-years analysis, and I also wonder whether your survival model is in fact a good one, since it produces such different results.

M. J. GARDNER: Would you comment on the very different estimates of exposures produced for all parts of the mines by NIOSH and McGill, the latter being some 30% lower ? This difference presumably affects markedly the positioning of points on the exposure-response relationship and hence the slopes of the fitted lines. As a further consequence, any predictions of lung cancer rates for given fibre levels will be affected, and it would be informative to know which is preferred.

H. E. AMANDUS: Our exposure estimates were slightly higher than the McGill estimates for most location operations. Our estimates were markedly higher for the loading area and shipping area. For some of areas, assumptions had to be made as to the exposure levels. For areas where samples were not available, (drilling, loading, and bagging area), we picked a range of possible exposures. Although I may be corrected by Dr Sebastien or Dr McDonald, McGill selected estimates at the lower end of the range. Our estimates were at the higher end of the range.

B. ARMSTRONG: Just a comment on Dr. Saracci's question. The classical Cox regression model used by NIOSH assumes an exponential relationship between hazard (relative risk) and exposure, implying a less steep slope at low exposures than the linear relative risk model used in the McGill case-referent analysis. This may explain the lower predicted relative risks from the NIOSH survival analysis.

G. MAJOR: Are you really happy in giving us information on lung cancer, without material on cigarette-smoking?

H. E. AMANDUS: Am I unhappy? (Laughter!). Yes, it would have been helpful to have data to control for the effect of cigarette-smoking. We only had 20 cases of lung cancer. We considered doing a case-control study, collecting cigarette-smoking information for cases and controls but I don't believe the numbers are large enough to provide sufficient power for that study.

R. W. WHEELER: The present respirable levels of respirable particulate at Libby were very small in the range of 0.1–0.2 mg/m^3 of material, with 16 hours of sampling.

H. E. AMANDUS: As Dr. Armstrong mentioned in the NIOSH series that were 18 cases of fibrosis, that is workers with small opacities of profusion greater than ILO radiograph category 1/0. In 17 of the 18 cases there was agreement between at least two readers that irregular lesions were present. Most cases did not have a background of rounded opacities, and were found among older smokers who had over 100 fibre-years. There was only one case among non-smokers. Therefore, due to such a small number of cases in non-smokers, smoking was not found to be a significant variable.

M. J. GARDNER: I would like to make a comment about the presentation of Dr. Amandus. He was asked whether he had smoking data, to which he said he didn't and if so could the smoking data explain his results? From what Dr. Amandus showed it would be unlikely that smoking was an explanation anyway, for at least two reasons. The first is that he found an exposure-response relationship between the dust levels and lung cancer. This is similar to that found in many asbestos studies, and for smoking to be an explanation you would have to argue that the people with the highest exposures (or cumulative doses) were those with higher

smoking levels. Because of the consistency of finding a dose-response relationship in many studies, I think that possibility is unlikely. The second point is that some of Dr. Amandus' SMRs are very high, many about 200 or more.

These are much larger that you could reasonably expect to be caused by confounding from smoking, as has been demonstrated by the work of Axelson in Sweden. I think that it is not unreasonable to do these kinds of studies without smoking data. Although it would be better to have it, of course, there are lines of reasoning for determining whether or not smoking is likely to be the cause of what you find.

I would like to ask Dr. Amandus one question. On one of your slides, you showed that the lung cancer rate was high in people who had worked for a short period of time, as well as those who worked for longer periods of time. Would you comment on whether there is any potential for some of the overall lung cancer excess to be due to short-term workers who might have different smoking habits?

H. E. AMANDUS: You are quite correct; mortality from lung cancer was significantly increased among workers who had less than 10 years since hire. There was also an increased mortality among workers with 10–19 years since hire. However it did not reach significance. In the 10–19 year group, and in the less than 10 year group, there was no trend with exposure, and the numbers were small. We have no information on smoking habits of the short-term group to answer this question.

C. McDONALD: Can I just add a comment to what Dr. Amandus has said, that in the under 10 year exposure, (this applies anyway to the McGill study, and probably to NIOSH) I think there were only 4 lung cancers observed and 2 were in men who joined the industry aged about 50. At least one of them joined the industry at 65 and died two years later. When you get down to these small numbers, there are all sorts of oddities which occur.

H. E. AMANDUS: In addition, of those two people with less than 10 years who died, one died at the age of 28. The other one had zero fibre years.

G. MAJOR: My quarrel with Dr. Amandus is not so much that he gives us no data on cigarette-smoking, but his conclusion that 0.1 fibres/ml is not sufficient to protect a worker from lung cancer. His conclusion might more be that his work neither confirms nor denies an association between vermiculite and lung cancer.

S. LAMM: Dr. Gardner has raised a question as to what might explain the high risk in short-term employees. We reported at the WMO International Conference on Health of Miners, last May, on a study that we conducted on New York State talc-workers, with the question of tremolite exposure in there. There we found that the risk of lung cancer was essentially found in those people who had less than one year employment at the mine, mill operation; that when we compared the mortality risk for those with greater than one year employment, either in the New York State mine, or in the Vermont State mine, we found no difference in the mortality rate. When we looked at how the workers who had worked for less than one year differed from those who had worked for more than one year, we reviewed the prior employment histories given on the job application, and we found that the workers who had worked for less than one year had come from high carcinogenic employments prior to their employment at the mine, as opposed to those people who had tended to stay for a longer employment. Thus, our interpretation of their data seemed to indicate that the short-term employees brought with them a risk that was different than the risk for those people who tended to stay on in employment in the mine. I think its another factor which should be investigated in a number of these reports.

H. E. AMANDUS: I don't think that you should imply that the results for the tremolite talc population are applicable to the Libby vermiculite population. The tremolite in New York talc is different from that in Libby vermiculite. The tremolite in talc is blocky with low aspect ratio fibres; and the Libby tremolite fibres are long and thin with a high aspect ratio.