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The Morbidity and Mortality of Vermiculite Miners and Millers Exposed to Tremolite-Actinolite: Part II. Mortality

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The vermiculite ore and concentrate of a mine and mill located near Libby, Montana was found to be contaminated with a fiber of the tremolite/actinolite series. A study was conducted to estimate the exposure-response relationship for mortality for 575 men who had been hired prior to 1970 and employed at least 1 year at the Montana site. Individual cumulative fiber exposure (fiber-years) was calculated. Results indicated that mortality from nonmalignant respiratory disease (NMRD) and lung cancer was significantly increased compared to the U.S. white male population. For those workers more than 20 years since hire, the standard mortality rate (SMR) for lung cancer (ICDA 162-163) was 84.7, 225.1, 109.3, and 671.3 for less than 50, 50-99, 100-399, and more than 399 fiber-years respectively. Corresponding results for NMRD (ICDA 460-519) were 327.8, 283.5, 0, and 278.4. Based on a linear model for greater than 20 years since hire, the estimated percentage increase in lung cancer mortality risk was 0.6% for each fiber-year of exposure. At 5 fiber-years, the estimated percentage was 2.9% from an unrestricted (nonthreshold) linear model and 0.6% from a survival model.

Key words: tremolite-actinolite, fiber-years exposure, mortality, lung cancer risk

INTRODUCTION

In 1978, 12 cases of benign pleural effusion were reported among employees of an Ohio fertilizer plant that had processed vermiculite concentrate from South Africa, and from a mine and mill near Libby, Montana [Lockey et al, 1983]. These cases have led to studies of exposure to the tremolite-actinolite contaminating the Montana vermiculite ore and its health effects [Lockey et al, 1984; Amandus et al, 1987a,b; McDonald et al, 1986a,b; Atkinson et al, 1982].

There is little published information regarding the health effects in humans from exposure to fibers of the tremolite-actinolite series. Baris et al [1978] and Yazicioglu et al [1978, 1980] reported on Turkish populations exposed to tremolite from the soil and stucco of homes. They reported a high prevalence of radiographic pleural abnormalities and mesothelioma, but information was not available concerning the

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exposure–response curve. Moreover, findings reported by Barris et al may be due partly to erionite, a fibrous zeolite [Rohl et al, 1982].

Other worker populations with exposure to tremolite include New York talc miners and millers and Quebec chrysotile miners and millers. In talc workers, the carcinogenicity of tremolitic talc is unclear. Brown and Wagoner [1980] reported that the lung cancer risk increased with latency among New York talc workers. However, Lamm [1985], in a reanalysis of an extended follow-up of Brown and Wagoner's cohort, reported that the lung cancer risk was inversely related to exposure indices, and was likely due to occupational exposures other than in the talc industry. However, individual exposure was either not classified or was not classified precisely in these studies. Thus, the association between lung cancer mortality and tremolite in talc is yet to be substantiated epidemiologically.

With regard to Quebec miners and millers, tremolite appears as a contaminant of Canadian chrysotile asbestos [J.C. McDonald et al, 1980]. Thus, the effect of tremolite among Canadian miners and millers cannot be measured separately from that due to chrysotile.

Results from a literature review indicate that there are no published results of mortality studies of workers exposed to tremolite–actinolite, or any other amphibole, in which cumulative fiber or dust exposure was estimated for each individual [Liddell and Hanley, 1985]. The Montana vermiculite miners and millers are appropriate to investigate the effects of tremolite–actinolite without confounding from other fiber types.

In 1982, this laboratory initiated studies of the environmental exposures, mortality, and morbidity of workers employed at the Libby site [Amandus et al, 1987a,b]. J.C. McDonald et al [1986a,b] also have conducted parallel but separate studies of the Libby workers. The purpose of this paper is to estimate the exposure–response association between cumulative fiber exposure and mortality.

METHODS

Description of Cohort

The study cohort included 575 men hired prior to 1970 and employed at least 1 year at the Libby site. The vital status of 569 men was determined as of December 31, 1981. A person was considered living if he (1) was actively employed at the Libby facility, (2) was contacted by telephone, (3) was reported to be living in a personal interview with the person, a friend, or next-of-kin, (4) was receiving retirement benefits from the Social Security Administration (SSA), or (5) was paying into the SSA's retirement fund. A person was considered dead as of December 31, 1981 if a certificate was obtained or a date of death was reported to the SSA.

Death certificates were obtained for 159 of the 161 deceased, and the date of death was confirmed for the 2 with missing certificates. The certified underlying cause of death was coded for statistical analysis according to the International Classification of Diseases, Eighth Revision [National Center for Health Statistics, 1968].

Fiber–Exposure Estimates

Individual cumulative fiber exposure estimates (fiber–years) were computed from job exposure estimates and work histories. The mine and mill were divided into 25 "location–operations" (LO) according to a scheme designed by J.C. McDonald et

al [1986a]. For the years after 1968, an estimate of the fiber exposure for each LO was computed as an arithmetic average of fiber concentrations (fibers per cubic centimemter, f/cc) from membrane filter samples. For the years before 1968, an estimate of the fiber exposure for each LO was computed as an arithmetic mean of dust concentrations (million particles per cubic foot, mppcf) from midget impinger samples employing a conversion ratio (4.0 f/cc:mppcf). Details of the computation of the fiber exposure estimates for each LO and the conversion ratio are described elsewhere [Amandus et al, 1987a].

An estimate of the 8-hour TWA fiber exposure was computed for each job as an average of LO exposure estimates weighted by the proportion of time spent in the LO. Work histories were collected from company personnel records, and tenure in a job was calculated as the consecutive number of days employed in the job including weekends, leave, and holidays. An estimate of individual cumulative exposure (fiber-years) was computed as a sum of job tenures weighted by job exposure estimates.

Because samples were unavailable for some LOs before 1968, a range of fiber exposure estimates was derived for these LOs. Similarly, a range of cumulative fiber exposure (a high and low estimate) was computed for workers employed in jobs within these LO. The difference in the cohort's average high and low fiber-years (f-y) estimate was 4 f-y, and because this difference was slight, the high estimate was chosen for this paper. The cohort's average cumulative exposure was 200 f-y and the average net tenure was 8.3 years.

Statistical Methods

Man-years at risk of dying were accumulated from date of hire to December 31, 1981, or to date of death for those who died before December 31, 1981, by year of follow-up, age, latency, and f-y [Monson, 1974]. Man-years were tallied across age, time, exposure, and latency strata as a person moved from one stratum to another. The cohort contributed 13,502 man-years of follow-up, the average age at hire was 32.3 years, and the average age at death was 61.8 years.

The number of expected deaths during the follow-up period was calculated from U.S. white male death rates. The Standardized Mortality Ratio (SMR) was computed by dividing the number of observed by the number of expected deaths, and the ratio was multiplied by 100. A statistical test of whether the SMR was significantly different from 100 was made assuming that the observed number of deaths was Poisson distributed [Bailar and Ederer, 1964].

Two methods were used to estimate the exposure-response curve among workers with at least 20 years latency (time since hire). Employing the first method, the cohort was stratified into four cumulative exposure groups (less than 50, 50–99, 100–399, and more than 399 f-y). This stratification provided a reasonable and similar number of man-years of follow-up in the higher exposure categories (7373, 2073, 2353, and 1701 man-years respectively). Then, threshold and nonthreshold simple linear regression models were calculated from the SMR and the average f-y of the groups. For the nonthreshold model, the intercept was set at 100 and the regression coefficient for f-y was derived from the data. For the threshold model, the intercept and the regression coefficient for f-y were computed from the data.

Employing the second method, the conditional probability of dying of lung cancer by time from hire was estimated using the model suggested by Cox [1972]. The model provided an estimate of the instantaneous relative risk (RR) of dying of

lung cancer by time from hire based on values of age at hire and f-y, i.e. RR = exp(b f-y).

RESULTS

Results of the man-years analysis are presented for the cohort in Table I. The SMR was increased significantly ($p < .05$) for lung cancer (223) and nonmalignant respiratory disease (243), but was not increased significantly for other selected causes of death. The average latency was 21.8 years for lung cancer and 23.1 years for nonmalignant respiratory disease (NMRD).

Man-Years Analysis by Fiber-Years

Results of the man-years analysis are presented in Table II by selected causes of death and f-y exposure group. In the more than 399 f-y group, the SMR was significantly increased for all causes (157), all malignant neoplasms (268), lung cancer (576), and NMRD (401).

In the 50–99 and 100–399 f-y groups, mortality was not significantly increased for any selected cause of death but tended to be elevated for lung cancer, digestive cancer, and NMRD. In the less than 50 f-y group, the SMR was significantly increased for NMRD (220), was increased for lung cancer (151) but did not reach statistical significance, and was decreased for digestive cancer (56), ischemic heart disease (61), and diseases of the circulatory system (67).

TABLE I. Observed and Expected Number of Deaths, and Standardized Mortality Ratio (SMR) by Cause of Death

				95% Confidence interval for SMR	
Cause (ICDA Code)	Observed	Expected	SMR	Lower	Upper
Any cause (1-999)	161	146.1	110.2	93.8	128.6
All malignant neoplasms (140–209)	38	28.4	133.9	94.7	183.7
Digestive (150–159)	6	8.1	74.3	27.3	161.8
Stomach (151)	2	1.6	124.4	15.1	449.3
Lung (162–163)	20	9.0	223.2[b]	136.3	344.7
DCS (390–458)[c]	66	75.1	87.9	68.0	111.9
IHD (410–413)[c]	45	52.7	85.3	62.2	114.2
NMRD (460–519)[c]	20	8.2	243.0[a]	148.4	375.3
Pneumonia (480–486)	1	3.0	32.9	0.8	183.4
Tuberculosis (10–19)	1	1.3	79.7	2.0	444.0
Emphysema (492)	4	2.1	190.0	51.8	486.4
Lesions of central nervous system (430–438)	10	9.8	101.6	48.7	186.9
External causes (800–998)	23	15.2	151.0	95.7	226.5
Accidents (800–998)	15	10.4	144.6	80.9	238.4
Suicide (950–959)	6	3.5	169.9	62.4	369.8

[a]$p < 0.05$.
[b]$p < 0.01$.
[c]DCS; Diseases of circulatory system; IHD; ischemic heart disease; NMRD; nonmalignant respiratory disease.

TABLE II. Observed and Expected Number of Deaths, and Standard Mortality Ratio (SMR), by Fiber-Years and Cause of Death

Cause of death	Fiber - years			
	<50	50-99	100-399	>399
Any cause				
Observed	58	24	34	45
Expected	66.4	21.5	29.5	28.6
SMR	87.3	111.6	115.2	157.1[c]
All malignant neoplasms				
Observed	13	4	6	15
Expected	12.7	4.3	5.9	5.6
SMR	102.7	93.6	102.4	268.1[c]
Digestive cancer				
Observed	2	2	0	2
Expected	3.8	1.2	1.7	1.6
SMR	56.4	165.9	—	121.7
Lung cancer				
Observed	6	2	2	10
Expected	4.0	1.4	1.9	1.7
SMR	151.2	145.8	106.2	575.5[c]
DCS[a]				
Observed	22	12	16	16
Expected	35.9	10.9	15.5	15.8
SMR	66.9[b]	110.5	103.2	101.3
IHD[a]				
Observed	14	9	10	12
Expected	23.1	7.7	11.0	11.1
SMR	60.7[b]	117.6	91.2	108.6
NMRD[a]				
Observed	8	2	3	7
Expected	3.6	1.2	1.7	1.8
SMR	220.0[b]	170.2	179.5	400.7[c]

[a]DCS, Diseases of circulatory system; IHD, ischemic heart disease; NMRD, nonmalignant respiratory disease.
[b]$p < 0.05$.
[c]$p < 0.01$.

Man-Years Analysis by Fiber-Years and Latency

Mortality from lung cancer and NMRD was further evaluated by f-y with control for latency (Table III). The lung cancer SMR for greater than 20 years latency was increased significantly in the greater than 399 f-y group (671), and was increased in the 50-99 f-y group (225) but did not reach statistical significance. The SMR was not increased in the 100-399 f-y group (109), and was decreased in the less than 50 f-y group (85).

The exposure-response association is less clear for NMRD than for lung cancer (Table III). For 10-19 years latency, the NMRD SMR was significantly increased in the 100-399 f-y (460) and the more than 399 f-y (775) groups. However, for greater than 20 years latency, the SMR was increased for most f-y groups, but only reached statistical significance in the less than 50 f-y group.

TABLE III. Observed and Expected Number of Deaths, and Standard Mortality Ratio (SMR) From Lung Cancer and Nonmalignant Respiratory Disease by Fiber-Years and Latency

Latency (years since hire)	Fiber-years				
	<50	50–99	100–399	>399	Total
			Lung cancer		
<10					
Observed	2	0	0	2	4
Expected	0.6	0.2	0.3	0.2	1.1
SMR	338.7	0	0	1370.2[a]	351.8
10–19					
Observed	2	0	1	1	4
Expected	1.0	0.3	0.7	0.6	2.6
SMR	196.5	0	139.2	182.2	152.8
⩾20					
Observed	2	2	1	7	12
Expected	2.4	0.9	0.9	1.0	5.2
SMR	84.7	225.1	109.3	671.3[b]	230.4[a]
Total					
Observed	6	2	2	10	20
Expected	4.0	1.4	1.9	1.7	9.0
SMR	151.2	145.8	106.2	575.5[b]	223.2[b]
			Nonmalignant respiratory disease		
<10					
Observed	1	0	0	0	1
Expected	0.6	0.2	0.2	0.2	1.2
SMR	162.1	0	0	0	84.5
10–19					
Observed	0	0	3	4	7
Expected	0.9	0.3	0.6	0.5	2.3
SMR	0	0	459.9[a]	774.5[b]	304.9[a]
⩾20					
Observed	7	2	0	3	12
Expected	2.1	0.7	0.8	1.1	4.8
SMR	327.8[a]	283.5	0	278.4	252.6[b]
Total					
Observed	8	2	3	7	20
Expected	3.6	1.2	1.7	1.8	8.2
SMR	220.0	170.2	179.5	400.8[b]	243.0[b]

[a]$p < 0.05$.
[b]$p < 0.01$.

Modeling the Exposure–Response Association

Equations to predict the lung cancer SMR were computed as described previously, and the regression coefficient (standard error) for f-y was 0.58 (0.08) for the nonthreshold model and 0.60 (0.13) for the threshold model (Table IV). The standard error of the estimate for the predicted SMR was 83.17 and 100.09 for the models respectively. Because only four points were used to estimate these models, statistical tests on the coefficients are of limited value. In any event, the coefficient for f-y in both equations was significantly different from zero.

Employing the Cox survival model (Table IV) to estimate the relative risk for lung cancer, the regression coefficient (standard error) was 0.0011 (0.0004) for f-y

TABLE IV. Linear Regression Equations to Predict the Lung Cancer Standard Mortality Ratio From Fiber-Years for Men With at Least 20 Years Latency

	Threshold model	Nonthreshold model	Survival model
Threshold model			
Intercept	82.53	100.00	
(SE)[a]	(65.55)	—	
f-y coefficient	0.60[b]	0.58[b]	0.0011[b]
(SE)[a]	(0.13)	(0.08)	(0.0004)
Age at hire coefficient			(0.0212)[b]
(SE)[a]			(0.0353)

[a]SE, Standard error (value in parentheses).
[b]Significantly different from zero, $p < 0.05$.

and −0.0212 (0.0353) for age at hire. (The regression coefficients in the survival model must be multiplied by 100 to be comparable to the coefficients in the linear models). The contribution of age and f-y were statistically significant ($p < .05$) based on a likelihood ratio test.

The estimated proportional increase (over zero f-y) in the lung cancer RR or SMR at 50 f-y was 5.7% from the survival model, and 29.6% from the nonthreshold model. The proportional increase in the RR or SMR from these models at 5 f-y was 0.6% and 2.9% respectively.

Mesothelioma

With regard to mesothelioma, two cases were observed by December 31, 1981. Both cases were hired in 1946, died between 1979–1980, had a latency of 33 years, had a tenure less than 20 years, had an exposure greater than 300 f-y, and worked more than 70% of their tenure in the dry mill. The proportional mortality rate for mesothelioma was 1.2% (2/161) of all deaths and 2.2% (2/93) of the deceased with greater than 20 years latency.

DISCUSSION

The estimated percentage increase in lung cancer mortality risk among workers achieving at least 20 years since hire was 0.6% for each f-y based on the linear models, and at 5 f-y, it was 2.9% from the nonthreshold linear model and 0.6% from the survival model.

We modeled the lung cancer mortality risk only for workers achieving at least 20 years latency, but this does not imply that lung cancer could not have been caused by fiber exposure within 20 years since hire. However, the exposure–response relationship in the less than 20-year latency group is unclear. The number of expected deaths was small in each f-y latency subgroup, and the lung cancer SMR in the 10–19 year latency group was not significantly increased and was not associated with f-y.

An association between cumulative fiber exposure and NMRD mortality was not found, and conclusions as to the exposure–response association are unclear for several reasons. First, there was no consistent association between f-y and NMRD mortality under control for latency. For greater than 20 years latency, an inverse relationship is suggested (Table III). Competing risks from lung cancer and accident

mortality may be a partial explanation for this inverse trend, since accident mortality was significantly elevated for men with greater than 20 years latency (SMR = 296). Additionally, for greater than 20 years latency, accident mortality was significantly increased in the 100–399 (SMR = 635) and more than 399 f-y groups (SMR = 567).

A second reason that makes the results for NMRD mortality difficult to interpret is that few deaths were certified due to asbestos-related respiratory disease. Fibrosis was certified as the underlying or contributing cause of death in only 10 of 20 NMRD cases.

An analysis of the association between asbestos exposure and lung cancer mortality is not complete without controlling for cigarette smoking. The proportion of current and former smokers (Table V) was 15.5% higher among 161 vermiculite workers (161 men employed from 1975–1982 with at least 5 years tenure) than among U.S. white males in 1975. Thus, part of the study cohort's excess lung cancer mortality could be attributable to confounding from smoking.

Employing the method of Axelson [1978], a crude estimate of the confounding effect of cigarette smoking was made. Assuming the proportion of smokers was 84% for the vermiculite cohort and 67% for U.S. white males, and the relative risk of lung cancer due to smoking is 14 [Steenland et al, 1984], the confounding effect due to smoking would result in a 23% increase in the crude risk ratio. The 23% increase due to smoking would be similar to the estimated increase at 50 f-y from our linear model (29%). This adjustment for smoking is imprecise, and our estimates of the increase in the lung cancer risk at exposures less than 50 f-y may perhaps be confounded.

The exposure–response curves from seven other asbestos studies in which individual exposures were estimated are presented in Table VI and Figure 1. Curves were recomputed for several studies from published data employing a simple linear

TABLE V. Proportion of Current and Former Smokers Among U.S. White Males and Vermiculite Workers

Year	Current (%)	Former (%)	Total (%)
U.S. white males[a]			
1955	52.6	10.9	63.5
1957	52.0		
1964	52.9	22.2	75.1
1965	51.1		
1966	51.9	23.6	75.1
1967	49.1		
1968	47.0		
1969	44.0		
1970	42.3	32.6	74.9
1971	47.0		
1972	48.0		
1974	42.7		
1975	39.3	29.2	68.5
1976	41.9		
1977	41.0		
1978	37.5		
Vermiculite workers[b]	35.0	49.0	84.0

[a]Information from U.S. Public Health Service [1979].
[b]Sample of 161 men with at least 5 years tenure employed during 1975–1982.

TABLE VI. Results of the Exposure–Response Association for Lung Cancer Mortality From Asbestos Studies

Weill et al [1979]						Dement et al [1983]		J.C. McDonald et al [1980]		This study		Henderson and Enterline [1979]		A.D. McDonald et al [1982, 1983, 1984]			
Chrysotile only		Chrysotile and Crocidolite		Total group													
mppcf-yrs	SMR	mppcf-yrs	SMR	mppcf-yrs	SMR	mppcf-yrs[a]	SMR	mppcf-yrs	SMR	mppcf-yrs[b]	SMR	mppcf-yrs	SMR	mppcf-yrs	PA SMR	SC SMR	CT SMR
6	56	11	100	5	77	0.5	140			7	77	62	198	<10	67	143	167
						5	279					182	180	10–20	84	183	102
						23	352	30	104	38	164	352	328	20–40	156	304	105
64	77	77	53	30	70	64	1099	100	140			606	450	40–80	160	420	163
				125	144	137	1818	300	142	239	671	976	778	>80	416	1032	55
654	182	698	241	400[c]	226			500	170								
								1200	268								

[a]Exposure is calculated as the midpoint of exposure groups reported by Dement et al [1979].
[b]Fiber–years was converted to mppcf–years using a conversion factor of 4.0 f/cc:mppcf.
[c]Weill et al [1979] used 400 to represent this group with >200 mppcf–years.

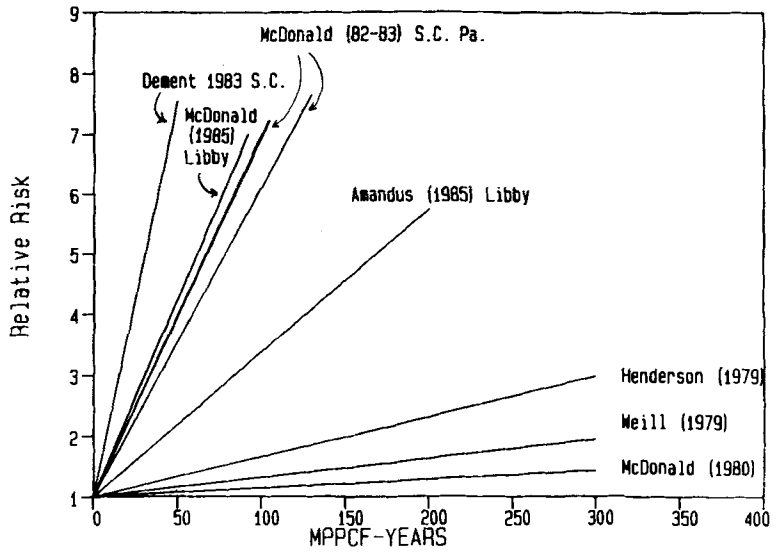

Fig. 1. Exposure-response curves for lung cancer mortality from asbestos studies.

regression model. Results were similar to those reported by Liddell and Hanley [1984] who used an iterative, weighted least-squares method.

Our slope for the lung cancer exposure-response curve was higher than for workers exposed predominantly to chrysotile [Weill et al, 1979; J.C. McDonald et al, 1980; A.D. McDonald et al, 1984; and Henderson and Enterline, 1979] and for workers exposed to chrysotile, amosite, and crocidolite [Weill et al, 1979; Henderson and Enterline, 1979]. However, our slope was lower than for workers exposed to chrysotile in asbestos textile plants [Dement et al, 1983; A.D. McDonald et al, 1982, 1983]. Differences in the slope between studies may be partially explained by a greater risk of lung cancer attributable to differences in fiber type and dimensions, cohort effect, competing risks, and misclassification of exposure and disease.

Amandus et al [1987a] suggested that perhaps Libby tremolite fibers are longer and thinner than crocidolite and amosite. Results from Langer et al [1974] indicated that the aspect ratio was higher for Libby tremolite fibers than samples of UICC amosite and crocidolite fibers. If the tremolite fibers are longer and thinner than crocidolite and amosite, this would offer a possible explanation for a higher slope for lung cancer in this study than in the studies of Henderson and Enterline [1979], Weill et al [1979], McDonald et al [1984], and A.D. McDonald et al [1980]. This cannot be substantiated from our data, and requires further evaluation of Libby tremolite fibers using electron microscopy.

A source of bias in any study is the choice of the standard population. Lung cancer SMRs were calculated employing death rates from the State of Montana and from surrounding counties in Montana and Idaho (Table VII). For this analysis, person-years were tallied from 1950-1981, periods in which these rates were readily available. The lung cancer SMR was similar using state (279) and county (278) rates, and was lowest using federal rates (236). The SMR using federal, state, or county rates was not significantly greater than 100 at exposures less than 400 f-y.

TABLE VII. Lung Cancer Mortality for More Than 20 Years Since Hire by Comparison Group and Fiber/cc-Years

Comparison group	Fiber/cc-years									
	<50		50–99		100–399		>399		Total	
	0	SMR[a]	0	SMR[a]	0	SMR[a]	0	SMR[a]	0	SMR[a]
NIOSH (this study)										
U.S. white males[b]	2	85	2	225	1	109	7	671[d]	12	230[d]
U.S. white males[e]									12	236[d]
Montana white males[c]	2	103	2	272	1	130	7	814[d]	12	279[d]
Idaho/Montana white males[c]	2	102	2	273	1	132	7	806[d]	12	278[d]
McDonald et al, 1986										
Montana white males[b]	4	168	3	185	5	980[d]	3	677[d]	15	242[d]
(fiber-years)	(≤25)		(25–200)		(200–500)		(≥500)		(total)	

[a]SMR, Standard mortality ratio.
[b]Person-years tallied from 1930–1981.
[c]Person-years tallied from 1950–1981.
[d]SMR was significantly different from 100 ($p < 0.05$).

Because conclusions as to the intercept of the exposure-response curve may vary with the standard population, the slope rather than the intercept of the exposure-response curve becomes a more reasonable parameter upon which to base recommendations for health standards [Liddell and Hanley, 1984]. In any event, the risk estimate at low exposure (<50 f-y) is still unclear based on the stratified analysis.

A parallel but independent mortality study was conducted by J.C. McDonald et al [1986a] who also used state rates (Table VII). The slope of the exposure-response curve was lower in our study than in the study by McDonald et al, and at less than 50 f-y, we found a lower lung cancer SMR. Differences in results are likely due to differences in exposure estimates [Amandus et al, 1987c]. In any event, nonthreshold linear models derived in both studies predict a 3–7% increase in lung cancer risk at 5 fiber-years exposure.

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