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Mortality among Workers at a Talc Mining and Milling Facility

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Background: This study evaluated mortality among workers at a talc mining and milling facility.

Methods: Subjects were white men actively employed between 1948 and 1989 and known to have been alive in or after 1950. Analyses assessed cancer mortality during the period 1950–89 (809 subjects) and non-cancer mortality during 1960–89 (782 subjects).

Results: Comparisons with regional general population death rates for 1960–89 indicated that the workers had more than expected deaths from all causes combined [209 observed/160 expected, standardized mortality ratio (SMR) = 131, 95% confidence interval (CI) = 114–150], due mainly to increased mortality from lung cancer (31/13, SMR = 232, CI = 157–329) and non-malignant respiratory disease (NMRD) (28/13, SMR = 221, CI = 147–320). The lung cancer excess was concentrated in miners (18/4.6, SMR = 394, CI = 233–622); millers had only a small increase (7/5.5, SMR = 128, CI = 51–263). An excess of NMRD occurred both in miners (10/4.2, SMR = 241, CI = 116–444) and in millers (11/4.8, SMR = 227, CI = 113–407). The median estimated exposure to respirable dust was 511 mg/m^3-days for all exposed employees, 739 mg/m^3-days for mine workers and 683 mg/m^3-days for mill workers. Employees with high, compared with low, estimated exposure to dust had a rate ratio of 0.5 (CI = 0.2–1.3) for lung cancer and of 11.8 (CI = 3.1–44.9) for pulmonary fibrosis.

Conclusions: Exposure to talc ore dust may not have been responsible for the lung cancer excess among these workers but probably contributed to the elevated rate of NMRD, particularly pulmonary fibrosis.

Keywords: epidemiology; lung neoplasms; occupational exposure; talc

INTRODUCTION

This study evaluated mortality among workers at an industrial grade (tremolitic) talc mining and milling facility in upstate New York. Four retrospective follow-up studies (Brown and Wagoner, 1978; Stille and Tabershaw, 1982; Lamm *et al.*, 1988; Brown *et al.*, 1990) and one nested case–control study of lung cancer (Gamble, 1993) previously assessed the mortality experience of these workers. The most recent of these included observations through 1983 (Brown *et al.*, 1990). The present study extended follow-up through 1989 and examined mortality in the overall group of workers and in subgroups specified on the basis of work area, years since hire, years worked and estimated cumulative exposure to respirable dust. Of particular interest were lung cancer and non-malignant respiratory disease (NMRD) mortality patterns.

MATERIALS AND METHODS

Subjects were white men who worked for at least 1 day at the plant from the start of its operations in 1948 through to the end of 1989, whose vital status was

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known in or after 1950 and who had known birth and employment dates. We restricted the study to white men because women and black men comprised only about 5% of the workforce.

Data files from previous studies, plant personnel records and Internal Revenue Service Forms 941 identified 818 men actively employed at the facility from 1948 to 1989 and provided information on personal and employment characteristics. We later excluded nine men who were lost to follow-up before 1950, leaving 809 eligible subjects (see below). For each job held by a subject, detailed work history information included the title, work location and the start and termination dates. Information on specific jobs was not available for 37 short-term employees (5% of 809), who had an average work duration of only 0.14 yr. We included these men in most analyses, counting them as having worked in an unknown plant location, but excluded them from cumulative exposure analyses (see below).

Because the quantity and utility of historical exposure data available for these facilities were limited, we estimated workers' cumulative exposures. Although we identified 1322 exposure measurements over the 38 yr of the study, they were collected by a variety of methods and agencies or organizations, and measurements were not available for most of the work area/year combinations of the study period. Thus, we estimated cumulative respirable dust exposure estimation for individual subjects from a job–exposure matrix consisting of estimates of respirable dust concentrations for all work area and calendar year combinations throughout the study period (Oestenstad *et al.*, 2002).

To develop this matrix we first classified subjects' jobs into one of 12 work areas, specified on the basis of similarity in tasks, production activities and respirable dust exposure potential. A panel of seven long-term employees, relying on personal knowledge of operations, production records, dust control information and historical environmental reports, specified time periods during which exposures in each area would have been relatively uniform. For each area and time period combination they assigned exposure scores on a scale from 0 to 10. Because only one rater, a long-term supervisor, had personal experience in both mines as well as in the milling operations, we decided to use only this rater's estimates of relative exposure levels over time. The use of his exposure scores alone, as compared with the average of all available scores for work area and time period, resulted in slightly, but not significantly, lower exposure estimates (Oestenstad *et al.*, 2002). Finally, we conducted baseline exposure surveys to determine current respirable talc dust concentrations in the work areas. Historical respirable dust concentrations for each work area/calendar year category were then estimated as the product of the average baseline concentration and the ratio of the time-specific exposure score to the baseline exposure score. To validate the estimated exposures, we compared them with available measured historical exposure concentrations.

The final job–exposure matrix contained a total of 462 work area/year combinations. Estimated average respirable talc dust concentrations ranged from 0.1 to 1.7 mg/m^3 for the 11 work areas with non-zero exposure. When compared with available historical measured concentrations, these estimates had a correlation coefficient of 0.50.

Vital status information came from company records, the National Death Index and Pension Benefit Information, which maintains mortality data from the Social Security Administration death master file and other sources. We also used personal contact, credit bureau records and linkage with the New York Division of Motor Vehicles to determine the vital status of some subjects.

The company provided some death certificates. We obtained additional death certificates from the State of death for subjects who died outside New York. A trained nosologist classified the underlying cause of death using the Eighth Revision of the International Classification of Diseases (ICD) and the coding rules in effect at the time of death. For most decedents dying in New York, the State provided cause of death data from its computerized decedent database. We converted the cause of death codes from this database, which were coded according to the ICD revision in effect at the time of death, to Eighth Revision codes.

The standardized mortality ratio (SMR) was the measure of association used to compare workers' mortality rates with the rates of the general population of the region consisting of the county in which the plant was located and five other counties that lay, at least partly, within 50 miles (presumed commuting distance) of the plant. The combined 1970 male population of the six counties was about 185 072 (US Bureau of the Censes, 1972). We computed SMRs as the ratio of observed to expected numbers of deaths multiplied by 100, using the Occupational Mortality Analysis Program (Marsh *et al.*, 1998). We obtained expected numbers of deaths by multiplying the age- and calendar time-specific person-years of follow-up of the workers by the corresponding mortality rates of the regional white male general population and summing over the stratifying variables. We calculated 95% confidence intervals (CIs) of the SMRs assuming a Poisson distribution for the observed number of deaths.

Regional general population death rates needed for most analyses were available beginning in 1950 for cancers and in 1962 for non-cancer causes of death (Marsh *et al.*, 1998) and we used 1962–64 rates to estimate general population rates for 1960–64. The follow-up period for assessing cancer mortality

began on the hire date or 1 January 1950, whichever was later; whereas the follow-up period for assessing overall and non-cancer mortality began on the hire date or 1 January 1960, whichever was later. Follow-up ended on 31 December 1989, on the death date or on the loss-to-follow-up date, whichever was earliest. Analyses of the 1950–89 time period included 809 men. Analyses of the 1960–89 time period included 782 men. The 27 exclusions from the 809 subjects eligible for the 1950–89 time period were 16 men who died before 1960 and 11 who were lost to follow-up before 1960.

For certain causes of death, we analyzed subgroups specified on the basis of period of hire, years since hire, years worked, work area and cumulative dust exposure, beginning person-years accumulation on the later of the first date in a particular category of each variable or on the default follow-up start date mentioned above. We combined work areas into five non-mutually exclusive groups (mills, mines, minimal exposure potential, no exposure potential and unknown). We also carried out Poisson regression analyses with an internal referent group to obtain maximum likelihood estimates of rate ratios (RRs) and their 95% CIs (Callas *et al.*, 1990). In the latter analyses all models included terms for age (<35, 35–54, 55–64, 65+) and either years since hire (<10, 10–19, 20+) or calendar year (1950–59, 1960–69, 1970–79, 1980–89), as well as for the other occupational variables of interest. Causes of death examined in Poisson regression analyses included: (i) lung cancer; (ii) ischemic heart disease; (iii) all NMRD; (iv) 'other NMRD', excluding pneumonia, influenza, asthma, emphysema and bronchitis and including chronic obstructive pulmonary disease (COPD) and 'pulmonary fibrosis' (talcosis, pneumoconiosis, asbestosis and unspecified pulmonary fibrosis); (v) pulmonary fibrosis alone. Other NMRD comprises a pathologically heterogeneous group of diseases but was examined because it is a standard cause of death category in SMR analyses (Marsh *et al.*, 1998).

Poisson regression analyses incorporating exposure to respirable dust included 772 subjects for whom exposure estimates were available. For these analyses, we specified cumulative exposure categories as exposure tertiles among exposed decedents in the disease group being analyzed, combining the 0 exposure group and lowest tertile to form the referent category. The death certificates of 16 decedents indicated COPD ($n = 8$) or pulmonary fibrosis ($n = 8$) as a contributory, rather than underlying, cause of death. We included these decedents in certain Poisson regression analyses.

RESULTS

Of the 782 men included in the analyses of the 1960–89 time period, 159 (20%) were active employees at the close of the study and 623 (80%) had their employment terminated or retired. Five hundred and sixty-seven (73%) were classified as alive, 209 (27%) as deceased and six (1%) as having an undetermined vital status. Of the 809 men included in the analyses of the 1950–89 time period, 159 (20%) were active employees at the close of the study and 650 (80%) had their employment terminated or retired. Five hundred and sixty-seven (70%) were presumed living, 225 (28%) were deceased and 17 (2%) had an undetermined vital status. We obtained the underlying cause of death information from death certificates ($n = 134$) or from the New York decedent file ($n = 86$) for 220 (98%) of the 225 decedents.

For the 1960–89 time period, subjects had a total of 15050 person-yr of follow-up, an average of 19 yr per man, and median values of 1962 for hire year, 27 yr for age at hire and 3.0 yr for duration of employment. For the 1950–89 time period, subjects had a total of 18 048 person-yr of follow-up, an average of 22 yr per man and median values of 1960 for hire year, 27 yr for age at hire and 2.3 yr for duration of employment.

Compared with the regional general population of white men, the 782 talc workers followed-up in 1960–89 experienced a 31% increase in overall mortality, based on 209 observed/160 expected deaths (SMR = 131, CI = 114–150) (Table 1). Excesses were largest for tuberculosis (3/0.4, SMR = 788, CI = 163–2303), all cancer (53/35, SMR = 151, CI = 113–198) and NMRD (28/13, SMR = 221, CI = 147–320). There were about 10% more deaths than expected from ischemic heart disease (69/63, SMR = 110, CI = 86–139).

The overall increase in NMRD deaths was not limited to a particular form of respiratory disease but was greatest for other NMRD (COPD and fibrosis) (17/5.7, SMR = 291, CI = 173–475). This category included chronic obstructive pulmonary disease ($n = 10$), asbestosis ($n = 1$), pneumoconiosis ($n = 5$) and chronic pulmonary fibrosis ($n = 1$).

The excess of cancer deaths during the 1950–89 follow-up period (54/37, SMR = 146, CI = 110–191) (Table 2) was similar to that in 1960–89 and was attributable mainly to increased mortality from respiratory cancer (34/14, SMR = 239, CI = 165–334), including lung cancer (31/13, SMR = 232, CI = 157–329) and larynx cancer (2/0.6, SMR = 316, CI = 38–1142). The death certificate for the remaining respiratory cancer decedent indicated that he had 'adenocarcinoma of the mediastinum'. There were several more deaths than expected from lymphohematopoietic cancer (7/3.7, SMR = 192, CI = 77–395). This category included two decedents with non-Hodgkin's lymphoma, two with Hodgkin's disease, two with leukemia and one with multiple myeloma. Decedents' death certificates reported two deaths from mesothelioma. New York nosologists had coded one

Table 1. Observed and expected numbers of deaths, SMR and 95% CI by cause of death (1960–89, 782 subjects, 15 050 person-yr)

	Observed/expected	SMR	95% CI
All causes	209/160	131	114–150
Tuberculosis	3/0.4	788	163–2303
All cancer	53/35	151	113–198
Cerebrovascular disease	6/8.8	68	25–148
Rheumatic heart disease	2/1.1	175	21–633
Ischemic heart disease	69/63	110	86–139
Hypertension	2/0.9	224	27–807
Other heart disease	5/4.6	108	35–252
Non-malignant respiratory disease (NMRD)	28/13	221	147–320
Influenza and pneumonia	7/3.8	185	74–381
Bronchitis, emphysema, asthma	4/3.3	122	33–312
Other NMRD[a]	17/5.7	297	173–475
Cirrhosis of liver	5/3.7	137	44–319
External causes of death	16/15	104	60–169
Other known causes	16/18	89	51–144
Unknown causes	4		

[a]Observed number includes chronic obstructive pulmonary disease ($n = 10$) and pulmonary fibrosis ($n = 7$).

Table 2. Observed and expected numbers of cancer deaths, SMR and 95% CI (1950–89, 809 subjects, 18 048 person-yr)

	Observed/expected	SMR	95% CI
All cancer	54/37	146	110–191
Digestive organs and peritoneum	10/9.9	102	49–187
Stomach	2/1.4	144	17–520
Colon and rectum	2/4.8	42	5–150
Respiratory system	34/14	239	165–334
Larynx	2/0.6	316	38–1142
Lung	31/13	232	157–329
Lymphatic and hematopoietic tissue	7/3.7	192	77–395
Other cancer	3/9.3	32	7–95

Table 3. Observed and expected numbers of deaths, SMR and 95% CI for selected causes of death by year of hire (1960–89 for causes other than cancer, 1950–89 for cancer)

	Hired before 1955			Hired after 1955		
	Observed/expected	SMR	95% CI	Observed/expected	SMR	95% CI
All causes	169/113	150	128–174	40/47	85	61–116
All cancer	46/27	172	126–229	8/10	79	34–155
Cancer of the lung	28/9.8	286	190–414	3/3.6	83	17–242
Ischemic heart disease	56/46	122	92–158	13/17	77	41–132
Non-malignant respiratory disease (NMRD)	23/9.5	242	153–363	5/3.1	160	52–373
Other NMRD	15/4.2	355	199–586	2/1.5	133	16–479

of these as ICD code 212 (benign neoplasm of the respiratory system) and the other as ICD code 162.9 (malignant neoplasm of bronchus and lung, unspecified), despite specific mention of mesothelioma.

Increases in mortality from all causes combined, all cancer, lung cancer and ischemic heart disease were limited to men hired before 1955 (Table 3). This subgroup had 28 lung cancer deaths compared with 9.8 expected (SMR = 286, CI = 190–414), while men hired in or after 1955 had three deaths compared with 3.6 expected. For all NMRD and for other NMRD, both period-of-hire subgroups experienced

Table 4. Observed and expected numbers of deaths, SMR, RR[a] and 95% CI for selected causes of deaths by years since hire and years worked

Years since hire	Years worked		Lung cancer	Ischemic heart disease	Non-malignant respiratory disease (NMRD)	Other NMRD
<20	<5	Observed/expected	3/2.4	11/13.2	5/2.2	2/0.7
		SMR (CI)	126 (26–370)	83 (42–149)	224 (73–524)	294 (36–1062)
		RR (CI)	1.0[b]	1.0[b]	1.0[b]	1.0[b]
<20	5+	Observed/expected	2/1.6	9/8.8	2/1.4	2/0.5
		SMR (CI)	126 (15–454)	103 (47–195)	140 (17–506)	417 (51–1507)
		RR (CI)	1.0 (0.2–5.9)	1.3 (0.5–3.1)	0.6 (0.1–3.1)	1.4 (0.2–10.2)
20+	<5	Observed/expected	19/5.8	30/23.6	11/5.0	7/2.6
		SMR (CI)	331 (199–516)	127 (86–181)	222 (111–397)	271 (109–558)
		RR (CI)	3.0 (0.7–11.8)	2.0 (0.9–4.5)	1.2 (0.3–4.1)	1.4 (0.2–8.8)
20+	5+	Observed/expected	7/3.7	19/17.2	10/4.0	6/2.0
		SMR (CI)	190 (76–392)	111 (67–173)	248 (119–456)	302 (111–657)
		RR (CI)	1.8 (0.4–8.1)	2.0 (0.8–4.7)	1.6 (0.4–5.9)	1.8 (0.3–11.8)

[a]RR for each category of years since hire and years worked adjusting for age (<35, 35–54, 55–64, 865) and calendar year (1960–69, 1970–79, 1980–89).
[b]Referent category for the RR for each category of years since hire and years worked computed using the subgroup with <20 yr since hire and <5 yr worked as the referent.

Table 5. Observed and expected numbers of deaths, SMR, RR and 95% CI for selected causes of deaths by non-mutually exclusive work area, (1960–89)

Work area (no. of subjects)		Lung cancer	Ischemic heart disease	Non-malignant respiratory disease (NMRD)	Other NMRD
Mills (n = 379)	Observed/expected	7/5.5	31/26	11/4.8	6/2.3
	SMR (CI)	128 (51–263)	122 (83–173)	227 (113–407)	266 (98–579)
	RR [a] (CI)	0.6 (0.2–1.8)	1.2 (0.6–2.3)	0.9 (0.3–2.5)	1.2 (0.3–4.4)
Mines (n = 311)	Observed/expected	18/4.6	23/22	10/4.2	8/1.84
	SMR (CI)	394 (233–622)	104 (66–156)	241 (116–444)	434 (189–856)
	RR[b] (CI)	2.1 (0.8–5.5)	1.1 (0.6–2.1)	1.0 (0.4–2.7)	2.0 (0.6–7.2)
Minimal exposure (n = 182)	Observed/expected	3/3.9	13/22	9/4.6	5/2.0
	SMR (CI)	77 (15–224)	60 (32–102)	194 (89–369)	255 (83–596)
No exposure (n = 87)	Observed/expected	3/1.1	4/6.6	2/1.3	1/0.5
	SMR (CI)	281 (58–821)	60 (16–154)	158 (19–572)	217 (5–1207)
Unknown area (n = 67)	Observed/expected	2/1.3	7/6.4	3/1.2	3/0.6
	SMR (CI)	151 (18–547)	109 (44–225)	242 (50–708)	546 (113–1597)

[a]RR for mill workers compared with all other employees, adjusting for age, calendar period and employment in mines.
[b]RR for mine workers compared with all other employees, adjusting for age, calendar period and employment in mills.

increased mortality, but the larger increase occurred in men hired before 1955 (all NMRD, 23/9.5, SMR = 242, CI = 153–363; other NMRD, 15/4.2, SMR = 355, CI = 199–586). Men hired in or after 1955 had five NMRD deaths compared with 3.1 expected.

In analyses of mortality patterns by years since hire and years worked, data on lung cancer, all NMRD and other NMRD were sparse for the subgroups with <20 yr since hire (Table 4). In the subgroup with 20+ yr since hire, there was some suggestion that SMRs and RRs increased consistently, although weakly, with increasing length of employment for NMRD. This was not seen for lung cancer or for ischemic heart disease.

Among the 782 men included in analyses of the 1960–89 time period, 48% had worked in the talc mills for a median of 1.8 yr, 40% had worked in the mines for a median of 2.0 yr, 23% had worked in areas involving minimal exposure for a median of 1.7 yr and 11% had worked in areas involving no exposure to talc for a median of 10 months (Table 5). A total of 67 subjects (9%) had spent a median of less than 3 months in an unknown work area.

The overall excess of lung cancer was concentrated among men ever employed in the mines (18/4.6,

SMR = 394, CI = 233–622) (Table 5). In contrast, mill workers had only a small increase in lung cancer (7/5.5, SMR = 128, CI = 51–263). Overall NMRD mortality was elevated both in mill workers (11/4.8, SMR = 227, CI = 113–407) and in miners (10/4.2, SMR = 241, CI = 116–444). Other NMRD deaths were also elevated in mill workers (6/2.3, SMR = 266, CI = 98–579) and in miners (8/1.8, SMR = 434, CI = 189–856). Results of Poisson regression analyses were consistent with these patterns. Some of the other work area groups had slight increases in deaths from lung cancer and/or NMRD, but these results were based on small numbers. Mutually exclusive work area analyses confirmed these patterns (data not shown). For example, the SMR for overall NMRD was 257 (11/4.8, CI = 128–460) for men employed in mills but never in mines and was 277 (10/3.6, CI = 133–510) for men employed in the mines but not the mills. For ischemic heart disease, there were 22% more than expected deaths among mill workers (31/26, SMR = 122, CI = 83–173) and 40% fewer than expected deaths in the group with minimal exposure potential (13/22, SMR = 60, CI = 32–102). Other work area groups had trivial differences in observed and expected numbers of deaths in this disease category.

Among 772 men with work history information adequate for estimating exposure to respirable dust, the median estimated cumulative dust level was 511 mg/m^3-days for all exposed subjects combined, 739 mg/m^3-days for men ever employed in mines and 683 mg/m^3-days for men ever employed in mills (Table 6). Among exposed decedents, the median estimated cumulative respirable dust exposure was 520 mg/m^3-days for all decedents combined, 347 mg/m^3-days for men with lung cancer, 376 mg/m^3-days for men with ischemic heart disease, 888 mg/m^3-days for men with any form of NMRD as the underlying cause of death, 1199 mg/m^3-days for men with other NMRD as the underlying or a contributing cause and 3759 mg/m^3-days for men with pulmonary fibrosis as the underlying or a contributing cause. Thus, estimated cumulative exposure was 33% lower for lung cancer decedents and over seven times higher for decedents with pulmonary fibrosis than for the overall group of decedents.

Duration of employment in exposed jobs, rather than average intensity of exposure, was the primary determinant of estimated cumulative exposure. Among the exposed, the median average daily exposure intensity was 0.7 mg/m^3 for all subjects, 0.9 mg/m^3 for all decedents, and 0.9 mg/m^3 for persons dying of lung cancer, IHD and all categories of NMRD. Most subjects' average exposure intensity fell within a narrow range. For example, the proportion with estimated average exposure intensities between 0.8 and 1.1 mg/m^3 was 65% for lung cancer decedents, 63% for decedents with other NMRD as the underlying or contributory cause of death and 65% for decedents with pulmonary fibrosis as the underlying or contributory cause of death.

Poisson regression analyses indicated that there was an inverse association between estimated cumulative respirable dust exposure and lung cancer, with an RR of 0.5 (CI = 0.2–1.3) for men in the highest cumulative exposure tertile compared with men in the lowest tertile (Table 7). Ischemic heart disease was not associated with dust exposure. For the series of all NMRD coded as the underlying cause of death, the RR was elevated in the two higher tertiles of estimated cumulative respirable dust exposure as compared with the lowest exposure tertile, but the dose–response pattern was irregular. In contrast, when the analysis was limited to other NMRD (i.e. excluding pneumonia, influenza, emphysema, asthma and bronchitis) and expanded to include those with other NMRD as a contributory cause of death, the RR increased regularly with increasing cumulative

Table 6. Median estimated cumulative exposure to respirable dust among selected subgroups of 772 subjects with adequate work history data

Group (median years worked)	Number	Percent exposed	Median cumulative exposure among exposed (mg/m^3-days)
All subjects (2.6)	772	96	511
Mill workers, ever (3.0)	389	100	683
Mine workers, ever (3.6)	331	100	739
All decedents (2.3)	213	94	520
Ischemic heart disease (2.4)	70	94	376
Lung cancer decedents (1.0)	29	90	347
All non-malignant respiratory disease (NMRD) decedents[a] (2.3)	27	96	888
Other NMRD decedents[b] (8.3)	20	100	1199
Pulmonary fibrosis decedents[b] (11.5)	7	100	3759

[a]Non-malignant respiratory disease as the underlying cause of death.
[b]Non-malignant respiratory disease as the underlying or a contributory cause of death.

Table 7. RR and 95% CI for selected causes of death by tertile[a] of cumulative respirable dust exposure, adjusted for age and years since hire[b]

Cause of death	Cumulative exposure (mg/m^3-days)	Deaths	Person-yr[b]	RR	95% CI
Lung cancer					
	0–<95.1	11	2625	1.0	[c]
	95.1–<987.0	9	2660	0.8	0.3–1.9
	987.0+	9	3796	0.5	0.2–1.3
				df = 12, D = 11.6[d]	
Ischemic heart disease	0–<131.8	25	3931	1.0	[c]
	131.8–<2456.8	23	5083	0.7	0.4–1.2
	2456.8+	22	2927	1.0	0.6–1.8
				df = 19, D = 17.7	
All non-malignant respiratory disease (NMRD) (underlying)	0–<488.8	9	6023	1.0	[c]
	488.8–<2554.7	9	3058	2.2	0.9–5.6
	2554.7+	9	2860	1.6	0.6–4.1
				df = 19, D = 14.0	
Other NMRD (underlying/contributory)	0–<519.7	10	6124	1.0	[c]
	519.7–<4110.5	10	3948	1.8	0.8–4.4
	4110.5+	10	1869	2.1	0.9–5.1
				df = 19, D = 17.5	
Pulmonary fibrosis (underlying/ contributory)	0–<863.3	5	6990	1.0	[c]
	863.3–<7529.6	6	4437	2.2	0.7–7.4
	7529.6+	6	514	11.8	3.1–44.9
				df = 16, D = 14.0	

[a]Tertiles are based on the cumulative exposure distribution of cases in the cause of death category.
[b]Age categories were 35–54, 55–64, 65+ yr for all disease groups evaluated. Years since hire categories were <10, 10–19 and 20+ for ischemic heart disease, all NMRD, other NMRD and pulmonary fibrosis and were 10–19 and 20+ for lung cancer.
[c]Referent category for the RR.
[d]df, model degrees of freedom; D, model deviance.

exposure and was 1.0, 1.8 (CI = 0.8–4.4) and 2.1 (CI = 0.9–5.1) for the lowest, middle and highest tertiles, respectively. The RR also increased with increasing exposure for pulmonary fibrosis and was 1.0, 2.2 (CI = 0.7–7.4) and 11.8 (3.1–44.9) for the lowest, middle and highest tertiles, respectively.

DISCUSSION

Many of the mortality patterns seen in the present study were similar to patterns reported previously for workers at the same plant (Brown and Wagoner, 1978; Stille and Tabershaw, 1982; Lamm *et al.*, 1988; Brown *et al.*, 1990; Gamble, 1993). Compared with the regional general population, the employees experienced increased mortality rates for most diseases, particularly for lung cancer and NMRD. Men hired in 1955 or later had mortality rates that were similar to regional population rates for disease categories other than NMRD, including all causes, all cancer and lung cancer. These results could be interpreted as indicating that any exposure at the plant related to lung cancer or conditions except NMRD was removed or controlled effectively by the mid 1950s. However, data on subjects who began working in or after 1955 were too imprecise to exclude the possibility of a continuing small excess of deaths from all causes combined or a moderate lung cancer increase. Furthermore, subjects hired in or after 1955 have had a shorter period of time for the expression of exposure-related diseases with long induction times. Thus, additional follow-up will be required to determine if these subjects are free of excess disease.

The lung cancer excess in the overall study group was moderately strong and was concentrated in the follow-up period 20 or more yr since hire, results that suggest that some aspect of employment at the plant may have been associated with lung cancer. In a nested case–control study of 22 of the 31 lung cancer decedents identified in the present study, Gamble (1993) reported that all of the lung cancer cases and 73% of employee controls had been smokers. These smoking prevalences are high, but it is unlikely that the entire moderately strong lung cancer excess, particularly the nearly 4-fold increase among miners,

was attributable to smoking (Blair *et al.*, 1995). However, several observations from the present study indicate that exposure to talc at the facility may not have been responsible for the excess.

First, although men who worked in the underground mine, which is a high talc dust exposure area, experienced a greater than 4-fold increase in lung cancer, we found little evidence of an increase among mill workers, a group with similar exposure. In addition, the estimated dust exposure was low for lung cancer decedents compared with other workers and internal analyses of lung cancer rates by cumulative exposure indicated an inverse relationship. These findings do not support the hypothesis that talc dust at this facility has a carcinogenic potential similar to that of asbestos, which typically produces a moderate to strong positive dose–response relationship (Seidman *et al.*, 1986; Goodman *et al.*, 1999). Also, because internal analyses should be minimally subject to confounding by non-occupational exposures, the absence of a positive dose–response pattern does not support the hypothesis that the talc ore of the plant *per se* is a lung carcinogen.

Studies of other occupational groups have not provided evidence that talc ore causes lung cancer. A study of 389 Norwegian talc miners and millers exposed to non-asbestiform talc with low quartz content indicated no excess lung cancer incidence (6 observed/6.9 expected) (Wergelund *et al.*, 1990). Another investigation found a lung cancer deficit among Italian talc miners and millers exposed to non-asbestiform talc (12 observed/23 expected) (Rubino *et al.*, 1976, 1979). In that study, miners, who were exposed to silica as well as talc, experienced a 3-fold increase in NMRD deaths, whereas the millers, who had low silica exposure, did not experience such an excess. Straif *et al.* (2000) reported that German rubber industry workers with high talc exposure (≥10 yr of high exposure versus <0.5 yr of medium and high exposure levels combined) had increased lung cancer mortality (RR = 1.9, CI = 1.1–3.1); however, the results were not controlled for exposure to other raw materials present in the work environment or for smoking histories.

In recently published follow-up studies, Wild *et al.* (2002) found small lung cancer mortality increases among talc miners and millers in France who contributed person-years after 1968, the earliest year for which local mortality comparison rates were available (SMR = 123, CI = 76–189), and among a smaller group of workers in Austria (SMR 106, CI = 43–219). A case–control study of lung cancer, nested within those study groups, used semi-quantitative cumulative exposure estimates and adjusted for smoking. There was no evidence of an association between lung cancer and cumulative exposure to talc dust. Subjects in the highest cumulative exposure category (≥800 mg/m^3-yr) had a lung cancer odds ratio of 0.60 (CI not reported). Smoking data were missing for about 35% of cases, but among those for whom they were available only one was a non-smoker.

Because of the high non-asbestiform amphibole content of the ore and dust at the facility investigated in the present study, research on other workers exposed to amphiboles is particularly relevant to our findings (Wylie *et al.*, 1985, 1993; Kelse and Thompson, 1985; US Department of Labor, 2000). Retrospective follow-up studies of workers exposed to taconite, which contains the non-asbestiform amphibole cummingtonite-grunerite, reported no association with lung cancer or NMRD (Higgins *et al.*, 1983; Cooper *et al.*, 1992). Investigations of gold miners exposed to silica, in addition to cummingtonite-grunerite and small amounts of tremolite-actinolite, found an increase in NMRD deaths but no excess of lung cancer (McDonald *et al.*, 1978; Brown *et al.*, 1986).

In addition, several animal studies have evaluated the carcinogenicity of non-asbestiform amphiboles, talc *per se* and individual components of the talc ore found at the study facility (Wagner and Berry, 1969; Pott *et al.*, 1974; Smith *et al.*, 1979; Stanton *et al.*, 1981; McConnell *et al.*, 1983; Davis *et al.*, 1991). Results of these studies indicated that non-asbestiform amphibole minerals in general and talc ore in particular did not increase the incidence of tumors, whereas asbestos was carcinogenic under the same experimental conditions (Wagner and Berry, 1969; Pott *et al.*, 1974; Smith *et al.*, 1979). Both talc and asbestos are cytotoxic in cell culture; however, asbestos, but not talc, has demonstrated proliferative potential in some cells (Wylie *et al.*, 1997).

NMRD mortality patterns differed from those seen for lung cancer in several respects. NMRD was elevated both among subjects hired before 1955 and among subjects hired in 1955 or later, although the increase in the latter group was based on small numbers. NMRD was increased both among miners and among mill workers and was positively associated with increasing duration of employment. Moreover, NMRD decedents with pneumoconiosis or interstitial lung disease, the group most likely to include dust-related disease, had a median cumulative dust exposure that was eight times higher than the corresponding values for the overall study group. Internal comparisons indicated a positive relation between estimated cumulative dust levels and this category of NMRD.

As with lung cancer, patterns of smoking and occupational exposures in jobs before and after those held at the study facility may explain some of the overall excess of NMRD seen in our analyses. The observation of elevated SMRs among short-term workers is consistent with this interpretation. In addition, pre-employment records were available for 25 of the 23

men who had NMRD as the underlying cause of death. Of these, 20 had worked in other mining operations before starting work at the talc facility under study. Exposures sustained in these other mining operations are likely to have contributed to the development of respiratory disease. Similarly detailed non-facility work histories were not available for subjects who died of causes other than cancers and respiratory disease. The impact of potential confounding by such factors should have been reduced in internal analyses. Similarly, any observation bias due to selective reporting of NMRD on the death certificates of deceased talc workers should have been lower in the internal analyses than in the external analyses. On balance, the positive associations seen in these analyses support a causal association between exposure to the talc ore dust at this plant and NMRD. The fact that we observed excess NMRD mortality when our exposure estimates suggested concentrations of respirable talc dust lower than the current threshold limit value of 2 mg/m^3 is of concern (Oestenstad *et al.*, 2002). However, because workers may have sustained exposures in other jobs that contributed to the etiology of NMRD, doubt remains about the hazard associated with talc dust levels of <2 mg/m^3.

The results of the studies of French and Austrian talc miners and millers support the findings of the our investigation (Wild *et al.*, 2002). The French study group had a slightly elevated SMR for all NMRD that was due to a significant excess of deaths from pneumoconiosis (SMR = 556, CI = 112–1620). No excess was observed in the Austrian study group (NMRD, 1/3.7; pneumoconiosis, 0/0.1). The nested case–control study of NMRD reported increased mortality in the highest exposure group (odds ratio = 2.5 for cumulative exposures ≥800 mg/m^3-yr, CI not reported) with a statistically significant trend (odds ratio = 1.1, CI = 1.0–1.2) that was similar when analyses were restricted to pneumoconiosis cases and their controls but was not present in analyses of chronic obstructive pulmonary disease.

In our study, comparisons of the employees with the regional general population indicated a slight increase in ischemic heart disease deaths. Ischemic heart disease rates were not, however, associated consistently with employment duration, time since hire or cumulative exposure to respirable dust. Other results included a small increase in deaths from lymphohemopoietic cancer, based on 7 observed and 3.5 expected deaths. The latter deaths were not limited to any particular subtype of lymphohemopoietic cancer and it is likely that the increase was due to chance or to confounding by an unidentified factor.

The occurrence of two deaths from mesothelioma is difficult to interpret. Of the two men with mesothelioma, one worked at the talc facility for 15 yr, had a relatively high cumulative exposure and died 15 yr after starting work at the talc facility. His previous employment history (obtained by querying next of kin) included 16 yr as a carpenter and millwright, 8 yr as a lead miner and 5 yr as a repairman in a milk plant. The other decedent with mesothelioma worked only briefly at the facility as a draftsman during mill construction in 1948–49. His job would have entailed minimal exposure to talc dust. He previously had worked for several years on the construction of another talc mine and he subsequently installed and repaired oil burning heating systems and delivered fuel oil. Although medical records that we obtained for this subject reported no history of asbestos exposure, he may have been exposed from the insulating materials in his fuel oil business. Experimental animal studies of the talc ore of the study facility have not observed pleural tumors (Stanton *et al.*, 1981). For this reason, and because of the short amount of time between first exposure and death of the first case and the low exposure of the second case, it is unlikely that either of the two mesotheliomas was due to talc ore dust.

Compared with previous investigations of the same workers, the present study had several advantages. These included longer follow-up, larger size, analyses by work area and estimated cumulative exposure to respirable dust, comparisons of subjects' mortality rates with regional general population rates and use of an internal referent group in some analyses.

Limitations of our study included the exclusion from analyses of work areas and cumulative dust exposure of a small proportion (6%) of subjects because work histories were unavailable. Most of these subjects were short-term workers whose cumulative exposure would have been low. Potential misclassification of subjects by cumulative exposure was inherent in the exposure estimation approach used for the study (Oestenstad *et al.*, 2002). However, because we developed the work area/time period exposure estimates using procedures that did not involve any reference to disease outcome, misclassification errors should have been non-differential, blunting any true dose–response relation. Another limitation of exposure estimation was our lack of information on subjects' peak exposure intensities and exposure to respirable fibers, either of which might be more biologically relevant than cumulative exposure. Although we intended to examine the joint effects of duration and intensity of exposure, average daily intensity scores showed little variability.

We also lacked comprehensive information on potential confounders such as cigarette smoking and other occupational exposures. Because data on the smoking habits of subjects were unavailable, we cannot rule out the possibility that the lung cancer and NMRD patterns observed were due, at least in

part, to heavier and/or more prevalent smoking by the subjects than by the comparison population. The recent study of French and Austrian talc workers suggests that the prevalence and role of smoking may be dissimilar in subjects with NMRD and those with lung cancer (Wild *et al.*, 2002). Similarly, work in other mining operations and construction jobs may have contributed to the respiratory disease mortality patterns observed.

Some misclassification of NMRD, resulting both from difficulties with the clinical diagnosis of various respiratory diseases and with the possible overlap between NMRD and cardiovascular disease, may have occurred. In addition, NMRD that was present at death may not be mentioned on the death certificate. If the tendency to list NMRD as a cause of death is greater for talc worker decedents than for decedents in the general population who died with the same set of medical conditions, observation bias would elevate SMRs for NMRD.

In summary, the reason for the increased lung cancer mortality among plant workers compared with the general population remains unclear. The association may be due, in part, to confounding by smoking and by other unidentified risk factors. It is unlikely to be related to respirable talc ore dust *per se*. An unidentified constituent of the ore or of the underground mine environment, exposure to which is poorly correlated with total respirable dust exposure, may have been responsible for some of the excess lung cancer. We have no information, apart from the disease patterns seen in this study, to substantiate or refute this speculation. The study found an increased rate of NMRD among workers that is probably related to exposure to the talc ore dust at the facility, as well as to dust exposures encountered in other work environments and to smoking. Other causes of death among the plant workers did not appear to be related to the occupational factors.

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A nested case control study of lung cancer among New York talc workers

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Summary: This nested case control study assessed the relationship of lung cancer and time exposed to talc, while controlling for smoking, other talc exposures, and nontalc exposures. There were 22 lung cancer cases (91% smokers and 9% former smokers) and 66 controls (27% nonsmokers, 9% former smokers, and 64% smokers). Smokers were at sixfold increased risk compared to nonsmokers and ex-smokers. When stratified by smoking status, risk of lung cancer decreased with talc tenure and remained negative when excluding cases with < 20 years' latency and short-term workers. These data suggest that nontalc exposures are not confounding risk factors while smoking is, and that temporal and exposure-response relationships are consistent with a smoking etiology but not an occupational etiology for lung cancer.

Key words: Talc – Lung cancer – Amphiboles – Case control study – Tremolite

Introduction

In 1980 the National Institute of Occupational Safety and Health (NIOSH) published a morbidity, mortality, and environmental study of miners and millers at the Gouverneur Talc Company (GTC) (Dement et al. 1980). Ten years later an updated portion of the earlier report was published as a health hazard evaluation (HHE) (Brown et al. 1990). During this period there were two other mortality studies of basically this same cohort (Stille and Tabershaw 1982; Lamm et al. 1988) as well as considerable discussion regarding the mineralogical composition of the talc and the cause of the excess lung cancer mortality. Various causes for the excess were suggested including the amphibole minerals in the talc, prior employment in other industries and/or in other New York talc companies, and smoking (Brown et al. 1983; Tabershaw and Thompson 1983; Dement and Brown 1982; Thompson 1984; Taylor 1981; Campbell et al. 1979; Campbell 1978; Kelse and Thompson 1989, 1990; Dement 1990; Virta 1985; Reger and Morgan 1990).

The original design of the HHE included updating the original cohort and conducting a nested case control study (Gamble and Piacitelli 1988). The nested case control study reported here investigates the confounding potential of non-GTC risk factors and exposure-response relationships while controlling for these risk factors and using tenure as the surrogate for exposure. Analysis by cumulative exposure remains to be published.

Materials and methods

All cases and controls were from the cohort of 710 white males of GTC talc workers employed between 1947 and 1978 with follow-up through 1983 (Gamble and Piacitelli 1988; Brown et al. 1990). All persons with lung cancer (ICD 162–163, 8th Revision) certified as the underlying cause of death on the death certificate were defined as cases. Each case was matched with three controls in whom all categories of nonneoplastic respiratory disease (ICD 460–519) and accidents (ICD E800–E949) had been excluded; controls were selected from survivors and deceased by reference to the closest match with respect to date of birth and date of hire. Controls must have survived the case, and control history ended at date of death of the case.

Information on each case and control concerning tobacco use and work history was obtained from interviews of the person himself (if living) or from relatives or friends. Interviews were conducted over the phone whenever possible, or by mail if not. Also, verification from other sources was done whenever possible. For example, several relatives were asked about smoking and work history. Information from GTC personnel records provided some pre-GTC employment history. Confirmation of previous employment was obtained when possible by contacting the previous employer directly.

Talc mining has gone on in this region of New York for many years, and some of the cases and controls had worked at other talc mines in addition to the GTC talc mine and mill. One analysis therefore adds non-GTC talc employment to that of years worked at the GTC talc mine or mill.

To control for possible confounding due to nontalc exposure, a panel of nine epidemiologists and industrial hygienists rated the risk of lung cancer associated with nontalc jobs as listed in the work histories without knowledge of case and control status. Each nontalc job was rated as "probable," "possible," or "no" risk of job-associated lung cancer; each category was given a score of 3, 1,

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and 0 respectively. A composite score for each job was compiled from the nine ratings. An individual's total score was the composite score for each job multiplied by years in that job, and summed over all jobs. Total scores were divided into four categories of roughly comparable size. Estimates of the odds ratios (OR) for each category and trend analysis were used to assess whether non-talc exposure represented a risk factor deserving control in the exposure-response analysis.

The cases and controls were divided into two tenure groups (< 5, 5–15, 15–36; < 1, 1–9, 10–19, 20–36) for the major analyses of exposure-response relationships (Gamble and Piacitelli 1988). Since the results for both tenure analysis were similar only one tenure grouping is reported here. This analysis was done using GTC tenure with all cases and controls, and then repeated including only smokers. Additional analysis by GTC tenure for smokers only was done with exclusion of all cases and controls with: < 1 year's tenure; < 20 years' latency; < 20 years' latency and < 3 months' tenure. A similar analysis was repeated using all talc tenure (GTC plus non-GTC).

A linear trend in the OR by exposure was estimated following the methods described by Rothman (1986). Using a least squares approach to a weighted regression where $b' = b_1/b_0$, the slope b' was estimated from the equation case control $OR = b_0 + b_1x$. The slope b' describes mathematically the change in OR for each year of tenure. Using the standard error (SE) of b', a 95% confidence interval (CI) for b' was calculated.

In addition, means of exposure were compared for cases and controls using paired and independent sample t-tests as appropriate. All tests were performed at the 0.05 significance level. Except for the comparison of exposure levels for cases and controls, all testing and confidence interval estimation may depend on the assumption of a large sample size.

Results

Table 1 summarizes descriptive information on the cases and controls. All of the 22 cases were either smokers (91%) or ex-smokers (9%), while of the controls, 42 (64%) were smokers, 6 (9%) ex-smokers, and 18 (27%) nonsmokers. Cases and controls who smoked were quite comparable in age, year of hire, and age at hire. Controls were somewhat heavier smokers than cases, and controls who smoked had almost twice the tenure of cases who smoked. Tables 2 and 3 present more detailed information on the 22 cases.

Table 1. Characteristics of lung cancer cases and controls

	Cases ($n = 22$)	Controls ($n = 66$)
Mean year of first employment	1949.7	1949.5
Mean age at first employment	34.6	34.1
Mean year of birth	1915	1915
Mean years worked		
Mean (SD)	6.6 (8.6)	9.2 (11.1) ($P = 0.08$)
Range	(0.003–23.5)	(0.003–35.3)
Mean years worked, all talc	7.7 (9.2)	9.9 (12.1) ($P = 0.12$)
Ex-smokers		
No. (%)	2 (9)	6 (9)
Mean cig/day (SD)	20 (9)	48.3 (13.3)
Mean pack years (SD)	29.5 (9.2)	87.5 (35.0)
Year of hire	1953.5	1950.0
Age at hire (SD)	37.5 (9.2)	32.5 (8.7)
Year of birth	1915.5	1916.8
Years worked [mean (SD)]		
GTC	18.3 (2.3)	4.6 (9.8) ($P = 0.11$)
All talc	18.3 (2.3)	4.9 (9.6) ($P = 0.11$)
Smokers		
No. (%)	20 (91)	42 (64)
Mean cig/day (SD)	25.7 (12.0)	27.4 (12.7)
Mean pack years (SD)	53 (31.9)	61.9 (34.1)
Mean age began smoking (SD)	18.0 (3.7)	16.7 (3.5)
Year of hire	1949.3	1949.2
Age at hire (SD)	34.3 (8.5)	32.7 (7.02)
Year of birth	1914.7	1916.3
Years worked [mean (SD)]		
GTC	5.4 (8.1)	10.4 (11.4) ($P = 0.08$)
All talc	6.6 (8.9)	11.5 (12.8) ($P = 0.13$)
Non-smokers		
No. (%)	0 (–)	18 (27)

Table 2. Case review of lung cancer deaths among talc miners and millers

Case no.	Age at death	Smoking					Talc work history			
		Status	Age started	Latency	Cig./day	Pack years	Age at hire	GTC latency	Tenure in years	
									GTC	All talc
1	79	S	Unk	Unk	20	62	57	22	0.02	0.02
2	77	S	17	60	40	120	42	35	0.20	0.20
3	63	S	18	45	40	90	42	21	0.05	0.05
4	75	S	Unk	Unk	20	Unk	41	34	23.5	23.5
5	52	S	19	33	3	5	47	5	5.31	5.31
6	55	S	29	26	10	8	39	16	2.83	2.83
7	62	Ex	17	45	20	36	44	18	16.7	16.7
8	68	S	12	56	20	56	35	33	0.35	3.35
9	58	S	Unk	Unk	20	Unk	34	24	0.64	1.06
10	64	S	25	39	20	38	34	30	1.49	2.02
11	59	S	14	45	30	56	36	23	11.78	23.5
12	62	S	20	42	40	84	32	30	22.51	23.5
13	63	S	Unk	Unk	20	Unk	31	32	0.003	0.003
14	53	S	Unk	Unk	20	Unk	31	22	0.15	0.15
15	65	Ex	Unk	Unk	20	Unk	31	34	20.0	20.0
16	63	S	15	48	50	120	30	33	16.67	16.67
17	54	S	19	35	20	33	30	24	2.51	9.59
18	39	S	14	25	20	25	27	12	2.58	2.58
19	53	S	Unk	Unk	20	Unk	26	27	0.21	0.21
20	45	S	20	25	40	50	24	21	0.15	0.15
21	49	S	17	32	20	23	25	24	17.38	17.38
22	56	S	18	38	40	76	23	33	0.16	0.16

Unk. Unknown

Three potentially confounding risk factors are of primary concern: nontalc exposure, smoking, and non-GTC talc employment. Table 4 presents ORs for all cases and controls by estimated risk from nontalc exposure. The highest and medium-low scores showed a decreased risk while the medium-high score was slightly elevated. The slope of the OR (b') was negative (-0.0008). At the midpoint of the high nontalc exposure group (score = 377), the estimated OR from the regression model OR = $1 + b'$ (exposure) was 0.70, with 95% CI of 0.25 and 1.08. Since there was no trend for the risk of lung cancer to increase with nontalc exposure and therefore no apparent confounding, this factor is not controlled in further analyses.

Table 5 presents the risk of lung cancer by smoking category and cigarettes/day. Smoking cigarettes increased the OR for lung cancer almost sixfold compared to combined nonsmokers and ex-smokers, and 1.4 times compared to ex-smokers. There was little apparent difference in the OR for lung cancer by the number of cigarettes smoked per day. Smoking is controlled in some of the subsequent analyses by including only cases and controls who smoked.

Table 6 presents the relative odds of lung cancer by tenure group for all cases and controls. ORs were around the null value with increasing tenure. The point estimates for the slope of the OR was negative, but the upper 95% confidence limit was positive. At 25 years' tenure the estimated OR from the regression model was 0.80 (0.55, 1.06).

When only smokers were considered, ORs were less than 1 with increasing tenure (Table 7). The point estimate of the slope and the upper 95% CI were both negative. At 25 years' tenure the estimated Or was 0.39 (0.11, 0.67).

Tables 8–10 present data for smokers only and include only cases and controls with ≥ 1 year's tenure (Table 8), ≥ 20 years' latency (Table 9), and ≥ 20 years' latency and > 3 months' tenure (Table 10). The results are similar to those observed in Table 7: the ORs all decline with increasing tenure, the slopes are negative, and the upper 95% CIs are negative, except in Table 10, where the upper 95% CI is positive.

Another possible confounder is employment at non-GTC talc mines and mills. Table 11 compares the risk of total talc employment (GTC plus non-GTC) for all cases and controls. The only change was one more case in the ≥ 15 year tenure group and one less case in the < 5 year tenure group. The OR slope was positive, and at 25 years' tenure the estimated OR was 1.03 (0.73, 1.33).

Table 12 compares the risk of total talc employment stratified by smoking. The slope and upper 95% CI are negative. At 25 years' tenure the estimated OR is 0.54 (0.21, 0.87).

Discussion

The primary reason for this nested case control study was to try and determine whether talc exposure was the

Table 3. Case review of lung cancer deaths among talc miners and millers

Case no.	GTC employment	Non-GTC employment[a]
1	Carpenter	Construction carpenter (37), lumber camp (2) iron Mine (1)
2	Painter	Painter (35), Purchasing clerk (iron, St. Joes) (16)
3	Millwright	Welder (steel mill) (10), paper mill (5)
4	Miller, oiler, forklift op.	Driller (16)
5	Laborer, oiler	Mine (>9), foundry (molder) (12), construction carpenter
6	Blacksmith and welder	Road construction (5), mine blacksmith and welder (6), car mechanic (3), welder (10)
7	Miner	Dairy farmer (35)
8	Mucker, machine man	Driller (talc, coal, zinc) (18), St. Lawrence Seaway (5)
9	Mucker and driller	St. Joe lead (2), paper co. (2), Int. Talc (1), farm (5), army (4), unknown (13)
10	Mucker and driller	Military (7), Int. Talc (1), manufacturing (?) (18), truck driver (17)
11	Trammer, electrician, driller, Eimco op., scraper op., mucker	Paper mill (1), hosiery mill (3), Loomis Talc (driller, foreman) (12), construction (1), TV repair (10)
12	Mucker, Eimco op., driller hoistman, trammer	Mucker, driller (St. Joe Lead) (2), packer (Talc) (1), farm (3), sinking shafts (1)
13	Mucker	Driller (iron) (20), dairy farm (3), carpenter (1), construction (31)
14	Mucker	Army (4), ALCOA (5), driller (6 mo), sawmill, unknown (3), const. driller (3), Farm (11)
15	Mucker, scraper op., Eimco op., shaft mucker, driller	Farm, feed mill (1), operator (aluminum company) (1)
16	Miner	Farm (23), zinc miner (3), heavy equipment op. (5), zinc mill (5)
17	Mucker, driller	Farm, mucker/driller (talc) (7), blaster (iron Mine) (19)
18	Mucker, Eimco op.	Mucker (1), ALCOA (3 mo), military (1), manufacturing bowling pins (1), unknown (1)
19	Mucker	Army (7), manufacturing (1), miner (3 mo), farm, (4 mo), sawmill (1), radio repair, TV repair (5)
20	Blacksmith	Quarry (>1), ALCOA (5), driller (iron) (4 mo), roofer (hot tar) (2), machinist (5), foundry (1)
21	Laborer, miller, cal, process op., wheeler mill, process air op., car liner	Paper mill (9), stock clerk (7)
22	Laborer	Road crew (3 mo), St. Joes Mineral (1), iron mine (6 mo), Foundry (molder) (4 mo), construction (1 mo); navy (3), custodian (22)

[a]Figures within parentheses represent years of employment, unless otherwise indicated

cause of the elevated standardized mortality ratios (SMRs) for lung cancer which were observed in the previous cohort studies (Dement et al. 1980; Stille and Tabershaw 1982; Lamm et al. 1988), and which remained after 8 more years of follow-up (Gamble and Piacitelli 1988; Brown et al. 1990). To do this it is necessary to address the issues of possible confounding from other occupational exposure, non-GTC talc exposures, and smoking and to evaluate exposure-response. There was no apparent confounding from other exposures as the ORs showed no trend to increase with increasing risk scores from nontalc employment. As expected, smoking was a risk factor for lung cancer and was more prevalent among cases than controls, thereby confounding the analysis and elevating the observed risk ratio in the cohort studies. The exposure-response relationship for all cases and controls was slightly negative, but not statistically significant. When controlling for smoking the trend was negative and statistically significant; that is, as tenure increased, the ORs for lung cancer decreased and the upper 95% confidence limits were negative. The finding of a decreased risk ratio with increasing tenure was not materially affected by non-GTC talc exposure and remained when cases and controls with less than 20 years' latency,

Table 4. Lung cancer risk by nontalc exposure (panel score × years worked): all cases and controls

Score (panel score × years employed)	Cases	Controls	Odds ratio
221–533	3	13	0.55
121–220	6	13	1.10
51–120	5	21	0.57
0– 50	8	19	1.00
	22	66	

Slope of OR b' (SE) = −0.0008 (0.0005); $b' = b_1/b_0$; 95% CI of $b' = -0.002, +0.0002$; $b = 0.82$; $b_1 = -0.0007$
Estimated OR at midpoint of high exposure group (score = 377) = $1 + b'$(score) = $1 + (-0.0008)$ (377) = 0.70; 95% CI: $1 + (-0.002)$ (377) = 0.25 (lower); $1 + (+0.0002)$ (377) = 1.08 (upper); $\chi^2 = 0.266$ (NS)

< 1 year's tenure, and less than 20 years' latency and 3 months' tenure were excluded.

There is a potential for misclassification of nontalc exposures and smoking history. Nontalc exposures were collected from several sources including personnel records and questionnaires administered to subjects or surrogates. Assessment of risk by the panel was done blind. The incompleteness of the non-GTC work history should be similar for both cases and dead controls. If there is a recall bias it should be greater recall for the controls than cases. If present, this would tend to increase the risk away from the null.

Smoking history was obtained by questionnaire, and from several surrogates for cases and dead controls. Two studies (Kolonel 1977; Lerchen and Samet 1986) indicate 96% and 100% agreement of smoking status when comparing wives' responses to those of their husbands. Thus classification by smoking status is likely to be quite good. If there is recall bias it is most likely to be less recollection among cases than among controls.

Increased risk of lung cancer was present among workers with short tenures (Dement et al. 1980; Brown et al. 1990; Lamm et al. 1988). Several possible explanations have been given for this observation (Brown et al. 1990). One is that exposure to other lung carcinogens may have occurred via non-GTC employment. Six of the 22 cases had some known non-GTC talc employment. No increased risk was found for either nontalc employment nor for total talc employment (both GTC and non-GTC) when controlling for smoking. Second, it has been suggested that short-term employees may have had very high exposures. In this study cases were matched on date of hire and so controls had as great an opportunity of high exposure as did cases. Further, removing short-term workers (≤ 1 year's tenure) from the analysis did not affect the results. Thus these hypothetical explanations do not appear to be valid.

Another purpose for conducting the case control study was to adjust for possible confounding effects of smoking. In an SMR analysis using the U.S. population as a standard, the smoking habits of the exposed and referent populations may differ, thereby in part explaining the high risk ratio for the talc workers. It has been suggested that smoking alone does not account for the excess as the 1976 smoking habits of the GTC workers "were not much different from those of U.S. white males" (Brown et al. 1990). However, the smoking habits of the 1976 GTC workforce do not necessarily reflect the smoking habits of the cases. One way to employ a more appropriate reference group is to use workers drawn from the same population as the cases, as was done in this study. Such an internal comparison population shows quite different smoking patterns from the cases: 91% smokers among cases vs 64% among controls, and 0% nonsmokers among cases vs 27% among controls.

Another argument against smoking explaining the excess risk is "even if 100% of the cohort were smokers, the risk for lung cancer would have been increased only by 60% or an SMR of 160" (Brown et al. 1990). As it

Table 5. Lung cancer risk by smoking status and cigarettes smoked/day: all cases and controls [smokers compared to (1) ex-smokers and nonsmokers and (2) ex-smokers only]

	Cases	Controls	Odds ratio (95% CI)	
Smoker	20	42	5.71 (0.36, 7.81)	1.43 (0.31, 9.07)
Ex-smoker	2	6	1.0 (Ex-smoker and nonsmoker)	1.00 (Ex-smoker only)
Nonsmoker	0	18		
	22	66		
Cigarettes/day				
> 40	6	11	6.55	1.64
20–39	12	27	5.33	1.33
1–19	2	4	6.0	1.5
Ex-smokers	2	6		1.00 (ex-smoker only)
Nonsmokers	0	18	1.00 (ex-smoker and nonsmoker)	
	22	66		

Slope of OR when reference group = ex-smokers and nonsmokers: b' (SE) = −0.12 (0.008); 95% CI = 0.10, 0.14; $b_0 = 1.09$; $b_1 = 0.13$
Estimated OR for 20 ci/day smoker = $1 + (0.12)(20) = 3.42$ (3.10, 3.75); $\chi^2 = 4.68$

Table 6. Lung cancer risk by tenure at GTC: all cases and controls

Tenure-years	Cases	Controls	Odds ratio
15–36	6	21	0.82
5–15	2	5	1.14
< 5	14	40	1.00
	22	66	

Slope of OR b' (SE) = −0.008 (0.003): $b' = b_1/b_0$; 95% CI of b' = −0.018, +0.002: $b_0 = 1.03$; $b_1 = -0.008$
Estimated OR (95% CI) at 25 years' tenure = 1 − (−0.008) (25) = 0.80 (0.55, 1.06): $\chi^2 = 0.13$ (NS)

Table 7. Lung cancer risk by tenure at GTC: smokers only

Tenure-years	Cases	Controls	Odds ratio
15–36	4	15	0.42
5–15	2	5	0.63
< 5	14	22	1.00
	20	42	

Slope of OR b' (SE) = −0.024 (0.006): 95% CI = −0.04, −0.01: $b_0 = 1.04$; $b_1 = -0.03$
Estimated OR (95% CI) at 25 years' tenure = 1 + (−0.02) (25) = 0.39 (0.11, 0.67): $\chi^2 = 1.78$ (NS)

Table 8. Lung cancer risk by tenure at GTC: smokers only with ≥ 1 year's tenure

Tenure-years	Cases	Controls	Odds ratio
15–36	4	15	0.53
5–15	2	5	0.80
1–5	4	8	1.0
	10	28	

Slope of OR b' (SE) = −0.019 (0.007): 95% CI = −0.03, −0.006: $b_0 = 1.04$; $b_1 = -0.02$
Estimated OR (95% CI) at 25 years' tenure = 1 + (−0.019) (25) = 0.52 (0.19, 0.84): $\chi^2 = 0.577$

Table 9. Lung cancer risk by tenure at GTC: smokers only with ≥ 20 years latency

Tenure-years	Cases	Controls	Odds ratio
15–36	4	15	0.49
5–15	1	4	0.46
< 5	12	22	1.0
	17	41	

Slope of OR b' (SE) = −0.021 (0.006): 95% CI = (−0.03, −0.01): $b_0 = 1.01$; $b_1 = -0.02$
Estimated OR at 25 years' tenure = 1 − (−0.021) (25) = 0.47 (0.19, 0.75): $\chi^2 = 1.152$

turns out, 100% of the cases were smokers. The overall SMR for lung cancer was 207, with a lower 95% CI of 120; in the ≥ 20 year latency group, the SMR was 260 with a lower 95% CI of 137. Thus one cannot distinguish between the hypothetical SMR of 160 and the actual

Table 10. Lung cancer risk by tenure at GTC: smokers only with ≥ 20 years latency and > 3 months tenure

Tenure-years	Cases	Controls	Odds ratio
15–36	4	15	0.73
5–15	1	4	0.69
3 mo–5 yr	4	11	1.0
	9	30	

Slope of OR b' (SE) = −0.01 (0.01): 95% CI = (−0.02, +0.003): $b_0 = 0.98$; $b_1 = -0.01$
Estimated OR at 25 years' tenure = 1 + (−0.01) (25) = 0.74 (0.40, 1.08): $\chi^2 = 0.120$

Table 11. Lung cancer risk by total talc tenure: all cases and controls

Tenure-years	Cases	Controls	Odds ratio
15–41	7	21	1.03
5–15	2	5	1.23
< 5	13	40	1.0
	22	66	

Slope of OR b' (SE) = +0.001 (0.006): 95% CI = −0.01, +0.01: $b_0 = 1.03$; $b_1 = 0.001$
Estimated OR at 25 years' tenure = 1 + (0.001) (25) = 1.03 (0.73, 1.33): $\chi^2 = 0.002$ (NS)

Table 12. Lung cancer risk by total talc tenure: smokers only

Tenure-years	Cases	Controls	Odds ratio
15–41	5	15	0.56
5–15	2	5	0.68
< 5	13	22	1.0
	20	42	

Slope of OR b' (SE) = −0.02 (0.01): 95% CI: −0.03, −0.005: $b_0 = 1.03$; $b_1 = -0.02$
Estimated OR at 25 years' tenure = 1 + (−0.02) (25) = 0.54 (0.21, 0.87): $\chi^2 = 0.84$ (NS)

SMR for either all the lung cancer cases or for those with ≥ 20 years' latency. The inverse and statistically significant exposure-response trend found in the case control analysis points up the confounding effect of smoking in the cohort analyses. The lack of an exposure-response trend with talc tenure is contrary to conventional wisdom and to the conclusion that workplace talc exposures account for the increased risk of lung cancer.

Temporality is the only standard that may provide indisputable evidence that an association is not causal (Rothman 1986). A period of 20 or more years is a commonly used period between first exposure and the induction of lung cancer (Selikoff et al. 1980). Since death often occurs fairly shortly after diagnosis of the disease, the time between date of hire (or date of starting smoking) and date of death is used as the latency period.

The range of latency for asbestos workers at highest risk (textiles, insulation) and with long exposure is about 28–34 years (Selikoff et al. 1980; Knox et al. 1968; Dement et al. 1983). For a cohort exposed to high levels of

amosite for short periods, the mean latency is lower (21 years), (Seidman et al. 1986), as it is for vermiculite and asbestos cement workers (Weill et al. 1979; Amandus and Wheeler 1987). Chrysotile miners and millers, regardless of smoking habits or asbestos exposure, have a mean latency of about 40 years (Liddell 1980).

For mining cohorts exposed to nonasbestiform amphiboles (and for which there are no apparent exposure-response or causative relationships), the mean latency ranges from 22 to 32 years (Brown et al. 1986; Cooper et al. 1988). Smokers have a latency of about 40 years (Liddell 1980; Wynder and Stellman 1977).

The mean time from date of hire till death in GTC cases was 25 years; the length of time since starting smoking was 40 years. Thus the criterion of temporality suggests smoking is a more plausible risk factor for lung cancer than talc.

Analysis of exposure-response is an important element in the assessment of causality in this study. Misclassification of exposure will generally reduce the risk toward the null. The use of tenure as a surrogate estimate of exposure will not result in misclassification if subjects have the same exposure over time (Johnson 1986). If exposure is not the same over time then it may be difficult to show an exposure-response relationship or observe decreased risk with increased tenure. By matching for the period of exposure, there is some control for changes in exposure over time. To reduce the possibility of exposure misclassification, analysis of exposure-response using as the exposure variables net tenure (actual hours each employee worked) and cumulative quantitative estimates of dust exposure should be completed. The lack of such analyses does not, however, negate the observed inverse exposure-response relationship.

Another important criterion for evaluating causality is consistency. There is evidence the talc contains nonasbestiform amphiboles and a minor talc fiber component (Campbell et al. 1979; Campbell 1978; Kelse and Thompson 1989, 1990; Virta 1985). Mineral content of the talc varies somewhat but is generally in the range of 40%–60% tremolite, 1%–10% anthophyllite, 20%–40% talc, 20%–30% serpentine (antigorite-lizardite), and 0%–2% quartz (Kelse and Thompson 1989). NIOSH in 1980 reported over 70% tremolite and anthophyllite fibers in bulk and airborne samples from the talc mine that satisfied the regulatory definition of $\geq 3:1$ aspect ratio and $>5\,\mu m$ length (Dement et al. 1980). A mineralogical definition of asbestiform mineral fiber populations requires the presence of many particles $>5\,\mu m$ long with aspect ratios greater than 20:1 and thin fibrils $<0.5\,\mu m$ in width. Analysis of both bulk and airborne particles from the talc mine traditionally show little to no particles with an aspect ratio of 20:1 or greater, and none showed such asbestiform characteristics as splayed ends, curvature, or parallel fibers occurring in bundles for the amphibole components. For comparison, about 70% (37%–67%) of airborne fibers from asbestos mining and bagging operations had aspect ratios $>20:1$. About 3% (0%–6%) of airborne cleavage fragments from other nonasbestiform amphibole mines (cummingtonite, actinolite grunerite/actinolite) have aspect ratios $>20:1$. The width of airborne cleavage fragments and asbestos fibers is also distinctly different. About 65% of amphibole asbestos and chrysotile fibers are $>0.25\,\mu m$ wide while 100% of amphibole and tremolite talc cleavage fragments are $>0.25\,\mu m$ in width (Kelse and Thompson 1989). Based on these mineralogical characteristics, this cohort of talc miners is considered to be exposed to talc containing nonasbestiform tremolite.

Other cohort studies of workers exposed to nonasbestiform amphiboles (Brown et al. 1986; Cooper et al. 1988) show a lack of relationship between tenure and risk of lung cancer similar to that shown by the talc cohort. No causal relationship is postulated in these cohorts mining nonasbestiform amphiboles.

Asbestos-exposed cohorts do show increased risk with increasing tenure (Seidman et al. 1986; Weill et al. 1979; Amandus and Wheeler 1987; McDonald JC et al. 1980, McDonald AD et al. 1983a,b, 1984; Hobbs et al. 1980; Hughes et al. 1987; Ohlson and Hoystedt 1985) and a causal relationship is postulated. Workers exposed to asbestos were used to compare the consistency of the tenure-lung cancer association because of the contention that the talc contains asbestos (Dement et al. 1980; Dement and Brown 1982; Dement 1990). Thus the negative slope of the exposure-response curve (using tenure as a surrogate for exposure) is opposite to the effect one would expect if talc exposure were to increase the risk of lung cancer, is consistent with exposure-response relationships observed in populations mining nonasbestiform amphiboles, and is inconsistent with results from asbestos-exposed populations.

The SMRs for lung cancer (as well as for several other causes of death) are elevated in this group of talc workers. However, after adjustment for the confounding effect of smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure. The lack of an exposure-response gradient is not consistent with a causal relationship. The time occurrence of lung cancer among these talc workers is more congruent with a smoking than a talc etiology.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ■ Public Health Service
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NIOSH

Health Hazard Evaluation Report

HETA 90-390-2065
MHETA 86-012-2065
R.T. VANDERBILT COMPANY
GOUVERNEUR, NEW YORK

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to Federal, state, and local agencies; labor; industry and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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R.T. VANDERBILT COMPANY
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I. SUMMARY

The study conducted for this health hazard evaluation adds eight years of observation to the mortality study of miners and millers at the Gouverneur Talc Company (GTC) that was published by NIOSH researchers in 1980. The current study was based on 710 white male workers who were employed any time at GTC between 1947 and 1978 and whose vital status was determined as of 1983. When compared to U.S. white male mortality rates, there were statistically significant increases in all causes combined (SMR=128, 161 obs.), all non-malignant respiratory disease (SMR=251, 17 obs.), and lung cancer (SMR=207, 17 obs.). The SMR for lung cancer was slightly higher for the workers with tenure of employment less than 1 year (SMR=222, CI 96, 438) compared to workers with tenure greater than one year (SMR=194, CI 89, 369). The lung cancer risk was higher in those with 20 or more years of latency (SMR=258, CI 137, 441) than in those with less than 20 years of latency (SMR=126, CI 34, 322). The SMR for non-malignant respiratory disease was significantly elevated among those with more than one year of tenure (SMR=290, CI 144, 518).

The magnitude of the risk for both lung cancer and non-malignant respiratory disease indicate that the workplace exposures at GTC are, in part, associated with these excesses in mortality. Possible confounding factors, such as cigarette smoking and other occupational exposures from employment elsewhere, may have contributed to these risks as well. Although the contribution of these confounding factors could not be totally quantified in this study, it is unlikely that they, alone, could account for the observed excess risks.

The principal limitations in this study are; (1) the size of the cohort (especially for those workers with long tenure), (2) the inability to precisely characterize past occupational exposures at GTC or occupational exposures from employment elsewhere, and (3) the lack of reliable smoking data. The elevated risks observed in this study are similar to those in one other study of talc miners in New York State.

In summary, the results of this updated study support the findings of an excess risk for lung cancer and non-malignant respiratory disease which was observed in these workers by NIOSH researchers in 1980. The recommendations for control of exposure made in the 1980 report remain appropriate. It is recommended that this cohort be updated and reanalyzed after ten more years of observation.

Keywords: (SIC 1499) talc, amphiboles, cohort mortality study, mining, lung cancer, non-malignant respiratory disease.

II. INTRODUCTION

Researchers from the National Institute for Occupational Safety and Health (NIOSH) have previously conducted studies of mortality and morbidity patterns and occupational exposures among talc miners and millers.[1-8] In February 1980, NIOSH researchers published a Technical Report entitled "Occupational Exposure to Talc Containing Asbestos"[1], which dealt specifically with talc ore mined by the Gouverneur Talc Company (GTC) in the Gouverneur Talc District in upper New York. This report was divided into three sections (1. Environmental, 2. Cross-sectional morbidity, and 3. Retrospective cohort mortality), which were subsequently published elsewhere [2-4,6].

Additionally there have been three other mortality studies of GTC workers, all of which were based on the same basic data set.[9-11] The interpretation of the epidemiologic findings of these studies; and the controversy about the mineralogical composition of the talc and its contaminants at this mine has been the subject of numerous publications.[12-23]

Authors of the previous mortality studies differ in their conclusions about the excess risk of lung cancer observed in the GTC workers. The 1980 cohort mortality study published by NIOSH researchers concluded, "exposures to asbestiform tremolite and anthophyllite stand out as the prime suspect etiologic factors associated with the observed increase in bronchogenic cancer and non-malignant respiratory disease among this study cohort."[1] Brown et al., also concluded that "exposures to talcs from the Gouverneur mining area are associated with an increased risk of bronchogenic cancer and non-malignant diseases of the respiratory system."[6] Stille and Tabershaw concluded there were "elevated mortalities but no significant increases in the numbers of deaths from lung cancer, from non-malignant respiratory disease, and from all causes."[9] Lamm concluded that the increased lung cancer risk "is most likely due to risk acquired elsewhere, such as prior employments, or to differences in smoking experience or other behavioral characteristics."[11]

On November 9, 1985, R.T. Vanderbilt, Inc., requested that NIOSH conduct a Health Hazard Evaluation (HHE) to update the 1980 NIOSH study of employees at their Gouverneur Talc Company in Balmat, New York, particularly that portion of the study that dealt with the mortality experience of the cohort. In response to this request NIOSH updated the vital status of the cohort through 1983; and evaluated exposure-response by latency using tenure as a surrogate of exposure.

III. METHODS

Cohort Definition

Since the entire working population is white and ninety five percent male, the study cohort was defined as all white males who worked at least one day at GTC between the beginning of operation in 1947 through 12/31/78. This definition did not include any criteria for a minimum length of employment in order to be consistent with the mortality study published in 1980.[1] The demographic and work history data on the cohort were obtained from R.T. Vanderbilt, Inc., and were originally collected and prepared by Tabershaw Occupational Medical Associates (TOMA)[9] and updated by Lamm and Starr.[10] Data on this tape (referred to as the "DRDS master file") were collected from plant personnel records and include GTC job histories (date of hire; age at hire; type, location and duration of each job held while working at GTC; date of termination) and demographic information.

To assure completeness of the cohort and accuracy of work history information, comparisons were made between the "DRDS master file", Social Security Administration (SSA) quarterly reports (1962-1983), separate lists of employees kept by GTC (one from 1947-1962 and one from 1947-1966), and the master file used in the 1980 study.[1,6] Any differences in job history comparisons were resolved using company personnel records.

Vital status was determined as of 12/31/83 for all white male workers in the cohort. If the vital status could not be determined by the SSA or IRS, then verification was determined by telephone follow-up to next of kin. Death certificates were obtained for all deceased persons in the cohort and compared with name, SSN, and date of birth information in the "DRDS master file" to assure a correct match. The underlying cause of death was coded by a nosologist according to the Eighth Revision of the International Classification of Diseases (ICD).

The person-years analysis consisted of a comparison of age-time-adjusted death rates in the study cohort with the mortality experience of U.S. white males. Standardized mortality ratios (SMR's) were computed by the modified life-table technique described by Monson[24] using the OCMAP computer program.[25] Computation of expected number of deaths from the external population rates were adjusted by the OCMAP program for comparability to the Eighth Revision of the ICD using comparability ratios developed by the National Center for Health Statistics. SMR's were calculated by dividing the observed deaths by expected deaths and multiplying by 100. A statistical test to determine whether the SMR was significantly different from 100 was used, and the observed number of deaths was assumed to have a Poisson distribution.[26]

Person-years (PY) were calculated beginning with initial date of employment and accumulated till death or end of follow-up (12/31/83), whichever occurred first. The PYs for all workers were distributed in 5 year age groups and 5 year calendar time periods, for calculation of expected deaths. PYS also were distributed by tenure and time since first employment, in order to examine risk by these variables.

Tenure was used as a surrogate of exposure, being defined as calendar time spent in all jobs between date of first hire and termination of employment or date of record collection. Latency was defined as time from first employment to time of observation.

IV. RESULTS

There were 710 white males who had worked one day or more between 1947, the beginning of construction of GTC, and 1978. Vital status (alive or dead) was determined for the entire cohort. The cause of death was determined for all but 5 (0.7%) individuals. Follow-up was ascertained through 1983, at which time 161 (27%) members of the cohort were dead.

Table 1 provides descriptive data on the cohort. There were a total of 15,294 PY at risk. The average age at hire was 30, and the average age at death was 56. Almost half of the cohort (322/710), half of the deceased members of the cohort (79/161), and half of the lung cancer cases (8/17) had worked at GTC less than one year.

Table 2 compares the observed number of deaths to the number of deaths expected for this cohort based on U.S. white male mortality rates. The following causes of death had SMRs that were significantly elevated above 100: all causes of death (128), all malignant neoplasms (145), lung cancer (207), and non-malignant respiratory disease (251).

Table 3 provides the distribution of lung cancer deaths by tenure and latency. The lung cancer SMR for the latency group with 20 or more years was 258 (CI 137, 441); over half (8/13) of the lung cancer cases in this latency group occurred in the less than 1 year tenure group where the SMR was 357 (CI 154, 704). Those workers with greater than 20 years latency and with greater than 1 year tenure also demonstrated an increase in risk (SMR, 178), however, the excess was not statistically significant.

In Table 4, all causes, malignant neoplasm, lung cancer, and non-malignant respiratory disease mortality are stratified by workers with less than one year tenure and workers with greater than one-year tenure. After stratification, all cause mortality for workers with

less than one-year tenure was significantly elevated; non-malignant respiratory disease mortality was significantly elevated among workers with greater than one-year tenure. Other increases did not achieve statistical significance.

V. DISCUSSION

This is a small cohort (710 workers), of which 161 (22.7%) are deceased. The SMR analysis (Table 2) indicates a statistically significant excess of lung cancer and non-malignant respiratory disease in this cohort. In a previous update of this cohort[9], which determined vital status as of 12/31/78, ten lung cancer deaths had been identified. This update adds eight new lung cancers to the study. The SMR for lung cancer was uniform across tenure strata and increased with increasing latency (Table 3). There was a statistically significant excess in lung cancer in those with 20 years or more latency and with less than one year employment. Those in this latency group with greater than one year duration also exhibited an increased risk but it was not statistically significant. The increased risk of lung cancer among those with short duration also was observed in the 1980 analysis[1]. There are several possible explanations for this observation. First, cohort members may have been employed in other New York State talc mines and mills where there may have been additional exposures to the same or to similar types of mineral dust. This potential confounding variable is difficult to quantify. Based on limited information [1,27] it is known that as many as half of the lung cancer cases worked in other talc mining operations. In addition, there may have been exposure to other lung carcinogens from employment previous to GTC. Second, some of those in the short duration group may have had very high exposures, especially in the early years of the mining operation. This, too, is impossible to quantify, especially for the oldest exposures. Third, the smoking habits among the employees may have been different from the reference population.

Although several diseases associated with cigarette smoking are nonsignificantly elevated, smoking alone does not account for the excess observed in the cohort. At the time of the morbidity study by Gamble[1], which was conducted in 1975, the smoking patterns among GTC workers were not much different from those of U.S. white males. Among those in the cross-sectional study the distribution was: non-smokers (21%) ex-smokers (31%) and smokers (48%). The distribution, in 1976, among white males 20 years and over in the U.S.[28] was: non-smokers (28.2%), ex-smokers (30%), and smokers (41.2%). For those in the age group, 20-44 years old, which is more comparable to the cross-sectional study group, the smoking prevalence rate for U.S. white males was approximately 47%. Using an adjustment for smoking as suggested by Axelson[29]; even if 100% of the cohort were smokers, the risk for lung cancer would have been increased only by 60% or an SMR of 160.

A combination of these factors, mentioned above, may account for the lack of a positive association between lung cancer risk and duration of employment. It also should be noted that the group with less than one year duration represents half of the person-years of the cohort and although those with longer duration also had an increased risk for lung cancer, the number of workers within each strata, by duration of employment greater than one year, was small and the power to detect a significant risk within these strata was limited.

The excess for nonmalignant respiratory disease was more consistently associated with an occupational exposure at GTC. There was a larger excess risk in those with duration of employment over one year compared to those with less than one year.

To evaluate the consistency of the results of the current analysis with prior research at GTC, SMR's for all causes and for lung cancer were compared between three previous mortality studies of this cohort and an earlier proportionate mortality study of New York talc workers (Table 5). The earliest report was of talc workers with >15 years tenure in the northern part of New York State, presumably in the Gouverneur talc district.[30,31] The talc contained asbestos amphibole and serpentine minerals.[32] The proportionate mortality ratio (PMR) for lung cancer was about 3 times expected.[31]

The remaining SMR studies[1,9,11] involved essentially the same cohort as in this study, i.e. white male employees who ever worked at GTC since it began operations. The results are consistent across studies in that both overall mortality and lung cancer mortality were elevated; the SMR for lung cancer in the 20 or more year latency group was 2.6 to 4.6 times expected. Among employees with greater than 20 years latency, the lung cancer SMR was about 2 times greater for employees with less than one-year tenure compared to those with greater than one-year tenure. However, these differences are based on small numbers.

In conclusion, the results of this updated study support the findings of an excess risk for lung cancer and non-malignant respiratory disease which was observed in these workers by NIOSH researchers in 1980. The recommendations for control of exposure made in the 1980 report remain appropriate.

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VIII. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report are currently available upon request from NIOSH, Hazard Evaluations and Technical Assistance Branch, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), 5285 Port Royal, Springfield, Virginia 22161. Information regarding its availability through NTIS can be obtained from NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. R.T. Vanderbilt Company
2. United Steelworkers of America
3. OSHA Region II
4. NIOSH Boston Region

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

Table 1

Description of Cohort
Gouverneur Talc Company
MHETA 86-012

Age Group	Age at Hire n (%)	Age at Death n (%)	Person-years (PY) by Time Period 1947-59	1960-69	1970-79	1980-83	Total PY
<20	107(15)	0(-)	47	37	41	0	125
20-29	311(44)	5(3)	1050	543	864	212	2669
30-39	184(26)	12(8)	1302	1446	1063	462	4273
40-49	64(9)	31(19)	657	1364	1605	492	4118
50-59	32(4)	52(32)	165	624	1304	642	2735
60-69	11(2)	36(22)	86	150	476	352	1064
70-79	1(<1)	21(13)	12	54	119	72	257
≥80	0(-)	4(3)	5	3	21	24	53
Total	710	161	3324	4221	5493	2256	15294
Average	30 yrs	56 yrs					

Table 2

Cause - Specific Mortality of Cohort, 1947-1983

Gouverneur Talc Company
MHETA 86-012

Cause of Death (ICD - 8)+	Number Observed	Number Expected	SMR	95% CI++
All Causes (1-999)	161	125.5	128**	109-150
Respiratory Tuberculosis (010-019)	3	0.7	419	86-1224
All Malignant Neoplasm (140-209)	36	24.8	145*	102-210
Digestive Organs and Peritoneum (150-159)	8	6.5	167	53-242
Esophagus (150)	1	0.6	167	4-963
Stomach (151)	2	1.2	171	21-616
Liver (155-156)	2	0.4	500	58-1729
Pancreas (157)	2	1.3	154	18-544
Respiratory System (160-163)	18	8.7	207**	123-328
Larynx (161)	1	0.4	250	7-1502
Lung(162-163)	17	8.2	207**	120-331
Prostate (185)	1	1.3	77	2-438
Bladder (188)	1	0.7	143	4-864
Kidney (189)	1	0.6	167	4-865
Brain and CNS (191-192)	1	0.9	111	3-625
Lymphosarcoma and Reticulosarcoma (200)	1	0.6	167	4-969
Hodgkin's Disease (201)	2	0.4	500	62-1857
Leukemia (204-207)	2	1.0	200	23-699
Lymphatic (202-203/820.8)	1	0.6	167	4-911
All Diseases of Circulatory System (390-458)	68	60.7	112	87-142
All Non-Malignant Respiratory Disease (460-519)	17	6.8	250**	146-401
Pneumonia (480-486)	6	2.5	240	90-534
Emphysema (492)	3	1.7	176	37-523
Other Non-Malignant Respiratory (460-479, 487-491, 493-519)	8	2.7	296*	130-594
All Disease of Digestive System (520-577)	8	6.7	119	51-235
External Causes (800-998)	18	16.7	108	64-171
Accidents (800-949)	15	11.2	134	75-221
Suicide (950-959)	3	3.8	79	16-231
All Other	11			

\+ International Classification of Disease, Eighth Revision
++ 95% Confidence Interval for SMR
* $p<0.05$
** $p<0.01$

Table 3

Lung Cancer Mortality by Latency and Tenure
1947-1983

Gouverneur Talc Company
MHETA 86-012

Years since date of hire		Tenure-Years 0-<1	1-9	10-19	20-36	Total
0-<10	O/E	0/.5	1/.7	0/0	0/0	1/1.2
	SMR	--	143	--	--	83
	PY	3612	3274	0	0	6885
10-19	O/E	0/.8	2/.5	1/.7	0/0	3/2.0
	SMR	--	400	167	--	150
	PY	2229	1203	1247	0	4680
20-36	O/E	8/2.2	1/1.2	2/.5	2/1.1	13/5.0
	SMR	364**	83	400	182	260
95%	C.I.	(154,704)	(2,457)	(54,1611)	(21,636)	(137,441)
	PY	1870	821	289	751	3731
Total	O/E	8/3.5	4/2.4	3/1.2	2/1.1	17/8.2
	SMR	229	167	250	182	207**
	PY	7711	5297	1536	751	15294

* p < .05
** p < .01

Mean latency: 22.9 (range: 5.5-34.3)
Mean tenure: 6.3 (range: 0.003-23.5)

Table 4

All Cause, All Malignant Neoplasm, Lung Cancer
and All Respiratory Disease Mortality by Tenure

Gouverneur Talc Company
MHETA 86-012

Cause of Death	Number Observed	Number Expected	SMR	95 C.I.
Workers With Less Than 1 Year Tenure				
All Causes	79	56.0	141**	112-176
All Malignant Neoplasm	15	11.1	135	76-223
Lung Cancer	8	3.6	222	96-438
All Non-Malignant Respiratory Disease	6	3.1	194	72-428
Workers With Greater Than 1 Year Tenure				
All Causes	82	69.5	118	94-147
All Malignant Neoplasm	21	13.8	152	93-230
Lung Cancer	9	4.6	196	89-369
All Non-Malignant Respiratory Disease	11	3.8	289**	145-518

* $p<0.05$
** $p<0.01$

Table 5

Summary: Mortality Studies of New York Talc Workers

Gouverneur Talc Company
MHETA 86-012

Reference	Cohort Eligibility: period of employment	End of Follow-up	Size of Cohort (n)	All Cause Mortality		Lung Cancer Mortality			
						All		>20 yr Latency	
				OBS	RR	OBS	RR	OBS	RR
Kleinfeld[31] 1967	≥15y tenure employed 1940-1969	1969	260	108	--	13	324	--	--
Brown[7] 1980	1/1/47-12/31/59	6/30/75	398	74	121	9	273*	6	462**
Stille[10] 1982	1/1/48-12/31/77	12/12/78	655	113	106	10	157	--	--
Lamm[12] 1988	1947-12/31/77	12/31/78	605	118	141*	12	240*	--	--
This Study	1947-1978	12/31/83	710	161	128**	17	207**	13	258*

* $p < .05$
** $p < .01$
OBS = Observed number of deaths
RR = PMR or SMR

SIMILARITIES IN LUNG CANCER AND RESPIRATORY DISEASE MORTALITY OF VERMONT AND NEW YORK STATE TALC WORKERS

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ABSTRACT

The risks from malignant and non-malignant respiratory deaths of New York State and Vermont State talc workers with at least one year of employment have been compared for both miners and millers. The mortality patterns are similar. In both areas, the talc miners have a 4.5 fold risk of lung cancer, and the talc miners have no increased risk of lung cancer. In both areas, all workers appear to have an increased risk of non-infectious, non-neoplastic respiratory disease (NNRD) mortality, although only the Vermont millers show a statistically significantly elevated risk (7.9 fold). Thus, although the New York talc has been described as asbestiform talc and the Vermont talc as non-asbestiform talc, the mortality patterns of the workers appear to be inconsistent with that classification in that their lung cancer mortality rates are no different and only the Vermont talc millers show a significantly increased NNRD mortality.

INTRODUCTION

Studies of talc miners and millers in the New York and Vermont talc industry include analyses of mortality, morbidity, industrial hygiene, and mineralogy. Mineralogical differences between the two talcs have been highlighted. The upstate New York talc contains an elongated particulate not found in the Vermont talc that is considered by scientists at the National Institute for Occupational Safety and Health (NIOSH) as tremolitic asbestos and by scientists at the Bureau of Mines and at the company that owns the plant as true talc particulates and as prismatic non-asbestiform tremolite. NIOSH has called the New York State talc asbestiform talc and the Vermont talc non-asbestiform talc. Leaving the question of the mineralogical label of these particulates to the mineralogists, we have elected to examine the respiratory health outcomes of the employees at these two talc industries.

MATERIALS

The initial shaft of the New York State talc plant was sunk in 1947. Mining and milling operations started in 1948. The mortality experience (1947 through 1978) of all persons hired at the plant between 1947 and 1977 has been reported.[1] Mortality analysis was restricted to the 705 male employees (all caucasian). None of the 36 women employees had died of a respiratory condition. Sixty percent of the men worked at the plant for at least one year; twenty percent for two months to one year; and twenty percent for less than two months. Mortality analysis was reported separately for the 280 white male employees employed at the talc plant for less than one year and for the 425 white male employees employed for at least one year. That report[1] suggested that prior employment jobs accounted for the lung cancer rate. In-plant job records and prior employment histories on the job applications were analyzed. Employees were classified from the inplant job records as miners (187 worked exclusively in the mine), millers (152 worked exclusively in the mill), and others (34 worked in both the mine and the mill, 11 worked neither in the mine or the mill, and 41 had uninformative records).

The cohort of white male employees of the Vermont talc industry was developed from the records of the Vermont State Health Department's annual radiographic survey of employees of the dusty trades, begun in 1937. Selevan *et al.* of the National Institute for Occupational Safety and Health (NIOSH) defined the Vermont talc study cohort[2] as all white males in the Vermont talc industry on or after January 1, 1940 with at least one year of talc employment prior to January 1, 1970. Individuals who had at least two radiographs in the file and who had worked for any of five talc companies in three geographic areas of Vermont were eligible for the study. Mortality follow-up was continued through 1975 of the 392 men determined to belong to the cohort.

Health Department and company records were scrutinized to determine their job assignments, and each cohort member was classified as a miner after having had one year of exposure in the mine and/or as a miller after having had one year of exposure in the mill. 225 workers were classified as miners; 163 workers were classified as millers (of whom 47 had also been classified as miners); and 51 were not classifiable.

METHODS

This report compares standardized mortality ratios (SMRs,

for malignant and non-malignant respiratory causes of death for miners and millers with at least one year of experience in the Upstate New York talc (said to be asbestiform) industry with those in the Vermont State talc (said to be non-asbestiform) industry. Comparison is reasonable, despite the differences in classification variables between the two studies.

RESULTS

The risks of lung cancer and of non-infectious, non-neoplastic respiratory disease (NNRD) for employees with at least one year in the mines or mills of New York State or Vermont State talc industries are presented, analyzed, and discussed below.

Respiratory Mortality of New York and Vermont Talc Workers

	Observed/Expected Ratios		Standardized Mortality Ratios	
	New York	Vermont	New York	Vermont
Lung Cancer				
Millers	1/1.41	2/1.96	071	102
Miners	5/1.15	5/1.09	460*	435*
Others	0/0.55	0/0.81	---	---
Total	6/3.11	7/3.86	1.92	1.91
NNRD				
Millers	2/0.74	7/0.89	270	787*
Miners	2/0.49	2/0.56	408	357
Others	2/0.38	2/0.34	526	588
Total	6/1.61	11/1.79	373*	615*

* = p<0.05, two-tailed Poisson test

The risk of malignant disease of the lung (lung/respiratory cancer) is not increased for millers but is significantly increased (4.5 fold) in talc miners both in New York (4.60) and in Vermont (4.35). No difference in risk is seen between miners and millers of New York and of Vermont (Figure 1). These data are sufficiently strong to rule out with eighty percent confidence an underlying relative risk for New York miners vs. Vermont miners of 1.7 and with about ninety five percent certainty an underlying risk of greater than 2.0.

The risk of non-malignant respiratory disease (excluding pneumonia and influenza), i.e., NNRD has a significantly increased risk (almost eight-fold) for Vermont talc millers but not for New York talc millers (risk of 2.7, not significant). The risks for NNRD for miners are calculated to be 4.1 and 3.6 (both non-significant) for those from New York and Vermont, respectively (Figure 2).

As for other respiratory system deaths, influenza or pneumonia caused the death of one New York State talc worker (0.9 expected) but no Vermont talc miner (0.7 expected) or miller (0.8 expected). Mesothelioma caused the death of one New York State talc man (15 years after hire which followed 28 years in mining and construction) and of one Vermont talc man.

DISCUSSION

We have attempted to assemble similarly defined cohorts of New York State and Vermont State talc workers in order to compare the respiratory mortality risks of their miners and millers. The exposures of millers generally exceed that of miners by a factor of two to six. Nonetheless, both groups demonstrate a similar excess lung cancer risk only for their millers and not for their miners. The similar lung cancer risks of the two groups of talc workers exposed to the differently described talcs suggest that the elongated particulates seen in the New York State talc have not introduced an increased lung cancer risk. We further observe that the risk of non-infectious, non-neoplastic respiratory death, while apparently increased in all groups, is significantly elevated only among the Vermont millers.

Standardized mortality ratios (SMRs) were calculated for each group based on age-specific, calendar time-specific, cause-specific mortality rates for white males. The New York State study SMRs had been calculated using U.S. rates with death certificates coded according to the eighth revision of the International Classification of Diseases (ICD). The Vermont State study SMRs were first calculated using U.S. rates and then recalculated by its authors using Vermont State rates for non-malignant respiratory disease and respiratory cancer

Figure 1. Respiratory or lung cancer mortality risk for miners and millers of New York State and Vermont State talc.

Figure 2. Non-infectious, non-malignant respiratory disease (NNRD) mortality risks for miners and millers of New York State and Vermont State talc.

COMPARATIVE LUNG MORTALITY RISKS of VERMONT and NEW YORK STATE TALC WORKERS with at least one year experience at Talc Plant

	Vermont		New York		Ever employed New York		< One Year New York	
All Emp >1 yr.	O/E	SMR	O/E	SMR	O/E	SMR	O/E	SMR
All Causes	44/37.15	118	64/49.83	128	118/83.58	141*	54/33.75	160*
All Cancers			15/9.55	157	26/15.7	165*	9/6.15	146
Lung Cancer	6/3.61	163	6/3.11	193	12/5.01	240*	6/1.90	316*
NNRD	11/1.79	615*	6/1.61	372*	6/2.64	227	0/1.03	---
Millers								
All Causes			20/21.74	92	35/30.97	113	15/9.23	163
All Cancers			3/4.23	71	6/5.94	101	3/1.71	175
Lung Cancer	2/1.96	102	1/1.41	71	1/1.92	52	0/.51	---
NNRD	7/.89	787*	2/0.74	270	2/1.02	196	0/.28	---
Miners								
All Causes			31/16.76	185*	50/26.32	190*	19/9.56	199
All Cancers			10/3.23	310*	15/5.00	300*	5/1.77	282
Lung Cancer	5/1.15	435*	5/1.09	460*	9/1.66	543*	4/0.57	701*
NNRD	2/0.56	357	2/0.49	408	2/0.77	260	0/0.28	---
Others								
All Causes			13/11.33	115	33/26.29	126	20/14.96	134
All Cancers			2/2.09	96	5/4.76	105	3/2.67	112
Lung Cancer	0/0.55	---	0/0.61	---	2/1.43	140	2/0.82	244
NNRD	2/0.34	588.0	2/0.38	526	2/0.85	235	0/0.47	---

LUNG CANCER

COHORT DEFINITION

Cohort Variable	NEW YORK	VERMONT
Gender	Male	Male
Race	White	White
Employment Dates	1947-1977	1940-1969
Employment Duration	One Year +	One Year +
Mortality Dates	1947-1978	1940-1975

Cohort Numbers

Miners	152	163
Millers	187	225

NEW YORK VERMONT

Observed/Expected

Millers	1/1.41	2/1.96
Miners	5/1.15	5/1.09
Others	0/0.55	0/0.61

SMR

Millers	71	102
Miners	460	435
Others	---	---

4/7/88

COMPARATIVE LUNG MORTALITY RISKS of VERMONT and NEW YORK STATE TALC WORKERS with at least one year experience at Talc Plant

Ever employed

< one Year

All Emp >1 yr.	Vermont		New York		New York		New York	
LATENCY (Years)	O/E	SMR	O/E	SMR	O/E	SMR	O/E	SMR
0-4			0/0.27	---	0/0.42	---	0/0.15	---
5-9			0/0.31	---	0/0.49	---	0/0.18	---
10-14			1/0.45	224	1/0.69	145.0	0/0.24	---
15-19			2/0.60	331	2/0.98	205.0	0/0.38	---
20-24			3/0.79	378	8/1.29	623*	5/0.50	1000
25-29			0/0.65	---	1/1.09	92.0	1/0.44	227
30+			0/0.04	---	0/0.05	---	0/0.01	---
Total			6/3.11	193	12/5.01	240*	6/1.90	316*
0-9			0/0.58	---	0/0.91	---	0/0.33	---
10-19			3/1.05	285	3/1.67	180	0/0.62	---
20-29			3/1.44	208	9/2.38	378*	6/0.94	638*
30+			0/0.04	---	0/0.05	---	0/0.01	---
Total			6/3.11	193	12/5.01	240*	6/1.90	316*
0-4			0/0.27	---	0/0.42	---	0/0.15	---
5-14			1/0.76	132	1/1.16	85	0/0.42	---
15-24			5/1.39	360*	10/2.27	441*	5/0.88	568*
25+			0/0.69	---	1/1.14	87	1/0.45	222
Total			6/3.11	193	12/5.01	240*	6/1.90	316*

4/7/88

COMPARATIVE LUNG MORTALITY RISKS of VERMONT and NEW YORK STATE TALC WORKERS with at least one year experience at Talc Plant

		Vermont		New York	
		O/E	SMR	O/E	SMR
All Causes	Emp>1	44/37.15	118.0	64/49.83	128
All Cancers	Emp>1			15/9.55	157
Lung Cancer	Emp>1	6/3.61	163	6/3.11	193
NNRD	Emp>1	11/1.79	615	6/1.61	372
Pneumonia/Influ	Emp>1	0/1.89	000	1/0.9	109
All Causes	Millers			20/21.74	92
All Causes	Miners			31/16.76	185
All Causes	Others			13/11.33	115
All Cancers	Millers			3/4.23	71
All Cancers	Miners			10/3.23	310
All Cancers	Others			2/2.09	96
Lung Cancer	Millers	2/1.96	102	1/1.41	71
Lung Cancer	Miners	5/1.15	435	5/1.09	460
Lung Cancer	Others	0/0.55	---	0/0.61	---
NNRD	Millers	7/.89	787	2/0.74	270
NNRD	Miners	2/0.56	357	2/0.49	408
NNRD	Others	2/0.34	588	2/0.38	526
4/7/88	**Bold =**	p <0.05			
Pneumonia/Influ	Millers	0/.83	000		
Pneumonia/Influ	Miners	0/.67	000		
Pneumonia/Influ	Others	0/.39	000		

Standardized Mortality Ratios

	Vermont	New York
Lung Cancer		
Millers	102	71
Miners	435	460
Others	---	---
NNRD		
Millers	787	270
Miners	357	408
Others	588	526

NON-INFECTIOUS, NON-MALIGNANT RESPIRATORY DISEASE

	NEW YORK	VERMONT
Observed/Expected		
Miller	2/0.74	7/0.89
Miners	2/0.49	2/0.56
Others	2/0.38	2/0.34
SMR		
Millers	270	787
Miners	408	357
Others	526	588

with death certificates coded according to the seventh revision of the ICD. This report bases the SMRs on the U.S. rates.

The New York State study reports lung cancer as their measure of malignant respiratory disease and NNRD (non-infectious, non-neoplastic respiratory disease) as their measure of non-malignant respiratory disease. The Vermont State study reports respiratory cancer as their measure of malignant respiratory disease and ONMRD (other non-malignant respiratory disease) as their measure of non-malignant respiratory disease. Both NNRD and ONMRD are terms for total non-malignant respiratory disease, excluding influenza and pneumonia. We have used the labels of lung cancer and NNRD to represent the malignant and non-malignant respiratory disease measures.

Twelve of the thirteen respiratory cancers among the New York State talc workers were lung cancers. The thirteenth case was a man whose five years at the plant included three months as a laborer/oiler in the talc mill and ended with death from mediastinal cancer. Re-analysis of the New York State data as respiratory cancer rather than lung cancer would have reduced the SMR estimates by about 5% but not have altered the comparison between the miners and millers. Both the New York and the Vermont data are compared against U.S. mortality rates.

The Vermont data included persons with experience in both the mine and the mill in each category; the New York data separated them out. There were only 34 such New York workers with experience in both the mine and the mill. Less than 0.1 lung cancer and less than 0.1 NNRD deaths were expected among them, and none were observed. Including this group among the miners and the millers of New York State would not have affected the results.

Studies of both cohorts lack full information on smoking history. Each indicates that most of the lung cancer cases were known to be cigarette smokers, but data on smoking appears to be inadequate for both cohorts. There is no evidence that miners and millers differ in their smoking habits. Thus, it is unlikely that the differences observed in these comparisons could be due to differences in smoking between groups.

The mortality of the experienced employees of the New York and Vermont cohort who worked other than in the mine or the mill for a year were also examined. There were no lung cancer deaths. Each group had two NNRD deaths, yielding non-significant risks of 5.9 for those from Vermont and 5.3 for those from New York.

While the NNRD mortality may be due to dust exposures at the talc plants, the etiology of the lung cancer is less clear. The NIOSH authors[2] concluded that talc dust was unlikely to be the cause of the respiratory cancer, since the risk was seen only in the miners and not seen among the millers, a group with probable higher dust exposure. Radon daughter measurements in the New York mine do not explain the finding. The presence of a particulate in New York dust and not in Vermont talc dust cannot explain the difference.

The CEOH study[1] had supported the hypothesis of risk from prior employments as the explanation for the lung cancer risk of the New York State talc workers, however, that hypothesis has not been examined for the Vermont talc workers. Further study of both cohorts should be undertaken to explain the mortality patterns seen. The small number of cases in either group will probably be a hindrance to a full and clear explanation. Both cohorts should probably be extended to include later employees and the period of follow-up should be brought more current by at least a decade. A four-fold risk of lung cancer seen in two different studies of talc miners (but not millers) cries for an explanation.

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ANALYSIS OF EXCESS LUNG CANCER RISK IN SHORT-TERM EMPLOYEES

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Lamm, S. H. (Consultants in Epidemiology and Occupational Health, Inc., Washington, DC 20007), M. S. Levine, J. A. Starr, and S. L. Tirey. Analysis of excess lung cancer risk in short-term employees. *Am J Epidemiol* 1988;127:1202–9.

An excess of lung cancer found in a cohort of 741 New York State tremolitic talc workers observed from 1947 through 1978 has been shown paradoxically to be concentrated in short-term workers. Review of past work histories suggests that the excess of lung cancer in these short-term workers may be accounted for by prior exposures rather than by exposures at the employment under investigation. This finding has significant implications in view of the developing practice of including short-term workers in occupational cohort studies in contrast to the more traditional practice of excluding short-term workers. The traditional practice was based on the assumption that the inclusion of short-term workers with little exposure, and thus little risk, might dilute an otherwise apparent association between mortality and exposure. This study suggests that in certain instances the inclusion of short-term workers may magnify rather than dilute the estimation of risk, reflecting the presence of confounding variables.

lung diseases; lung neoplasms; occupational diseases; talc

New York tremolitic talc workers have been the subject of numerous epidemiologic studies over the past 50 years. Early reports (1–4) focused on morbidity and mortality from pneumoconiosis and related pulmonary conditions. Excess cancer mortality was reported in 1967 and 1974 by Kleinfeld et al. (5, 6) in a proportional mortality study of 220 New York State talc miners and millers. Among 91 deaths, the only excess cancer mortality was for lung and pleural cancer. This excess was limited to those workers who had been hired prior to 1945 (at which time wet drilling industrial hygiene controls were introduced) and who had died prior to 1960 at age 60 years or greater.

In 1973, Kleinfeld et al. (7) examined 39 workers from an upper New York State talc plant which had begun operations in 1947 and had used only the modern wet drilling techniques. No malignancies, and only one case compatible with pneumoconiosis, were observed among these workers whose only known exposure to commercial talc was at the plant studied. The National Institute for Occupational Safety and Health (NIOSH) subsequently conducted industrial hygiene studies at this talc plant as well as undertaking cross-sectional morbidity and historical mortality studies of its

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Abbreviations: NIOSH, National Institute for Occupational Safety and Health; SMR, standardized mortality ratio.

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workers (8–10). From a cohort mortality study of 398 white males initially hired between January 1, 1947, and December 31, 1959, and followed for their vital status as of June 30, 1975, NIOSH reported finding a statistically significant excess mortality from lung cancer and from nonmalignant respiratory diseases.

An independent cohort mortality study of employees at this same talc plant was performed by Stille and Tabershaw (11). Their cohort study of the 655 white males employed between January 1, 1948, and December 31, 1977, assessed vital status as of December 31, 1978. They reported nonstatistically significant elevations of lung and respiratory cancer mortality in the total cohort and showed a significantly increased risk of respiratory cancers only for employees with any history of prior employment. The authors concluded that this increase was probably due to exposures that had occurred prior to employment at this talc plant.

Due to the conflicting findings with respect to excess mortality from lung cancer in this population of talc workers, a reanalysis of the data gathered by Stille and Tabershaw and by NIOSH has been undertaken.

Materials and methods

Study population

The study population consisted of the cohort of 741 men and women who had ever worked at this talc plant from 1947, when the plant opened and began operations, through December 31, 1977. All of the employees in the study population were white. During this period, 705 men and 36 women had been hired. Mortality follow-up of the 36 women was conducted but not included in the statistical analysis because of the small numbers. A total of 425 men worked at the plant for one year or more; 280 worked for less than one year. The period of observation in the study extended from the date of hire to either the date of death, the date of loss to follow-up, or December 31, 1978, whichever date came first.

The data utilized for this analysis were originally collected by Tabershaw Occupational Medicine Associates as described previously (11). These data were abstracted from employment applications completed at the time of application for hire and from job cards and employment files maintained by the company. Death certificates were obtained by Tabershaw Occupational Medicine Associates and by NIOSH from state health departments. The cause of death was coded by nosologists using the *International Classification of Diseases*, Eighth Revision.

For this reanalysis, additional data on missing dates of birth for 16 workers were obtained from local hospital records. For the remaining 17 whose birth dates were missing from the records, an estimated birth date was developed by G. Block of the National Cancer Institute, using the method by Block et al. (12) based on the year of issuance of the social security number.

Prior employment history

Each prior employment experience indicated on the initial job application at this talc plant was categorized on the basis of its likelihood of association with an increased risk of lung cancer. This categorization was developed by a senior industrial hygienist without knowledge of the individual's vital status or cause of death. The basis for classification was as follows: "Lung cancer risk" jobs included metal mining (primarily lead/zinc mines) (13, 14), steel-making (15), foundry (16), roofing (17), welding (18), construction (19), and paper mill (20). Jobs such as retail sales and restaurant work were clearly classifiable as jobs with "no prior risk." Other employment categories, such as carpentry, electrical work, transportation, military, farming, and engineering, which are not clearly either at risk or free of risk were for this analysis also classified as "no prior risk" employment. Such a classification would tend to bias against finding a difference between the two risk classifications.

The previous analysis by Stille and Tabershaw (11) stratified only on the presence or absence of a prior work history on the job application, while our analysis stratifies on the basis of specific employment information contained in the prior work history.

Individual workers were then classified on the basis of the categorization of their prior employments as ever having had "prior risk" (353, or 50 per cent), as having "no prior risk" (214, or 30 per cent), or as "unclassifiable" (138, or 20 per cent) because their job application gave no indication of their prior work history.

Statistical methods

Observed-versus-expected deaths for all causes and for specific causes of deaths were developed and compared, using National Center for Health Statistics cause-specific death rates for US white males and using the analytic program developed by Monson (21) to calculate the expected numbers. Comparison between the observed and the expected number of deaths was expressed as a standardized mortality ratio (SMR), where SMR equals 100 times the observed deaths divided by the expected number of deaths.

Statistical significance of the difference of a standardized mortality ratio from 100 is presented as a two-tailed p value based on a Poisson distribution.

RESULTS

Mortality for the entire male cohort (table 1) was significantly elevated (SMR = 141) as were the risks of death from all cancers (SMR = 165), from the subclassifications of respiratory cancer (SMR = 246) and of lung cancer (SMR = 240), and from all nonneoplastic respiratory disease (SMR = 236). There was no significant excess mortality from nonrespiratory cancers. The recorded causes of the 10 nonneoplastic respiratory disease deaths were pneumonia (four), pneumoconiosis (two), emphysema (two) and other lung diseases (two). In addition, an electrician at the talc plant died from mesothelioma 15 years after being hired. He had previously worked 20 years in various employments as a miner, a miller, or in construction. Mortality for the 36 females revealed no deaths from lung cancer or other diseases of particular concern.

A similar analysis (table 1) was performed for the 425 men (60 per cent of the cohort) who had at least one year's duration of talc plant employment (experienced workers). The significantly increased mortality from lung cancer noted previously in the total group was no longer evident. The significant excess risk for all nonneoplastic respiratory diseases (SMR = 278) was seen to be restricted to deaths from noninfectious, nonneoplastic respiratory diseases (SMR = 370).

When mortality of the total cohort, of those employed for at least one year (i.e., one year or more), and of those employed for less than one year are compared for all causes, for all respiratory cancers, and for lung cancer (table 2), it becomes apparent that the excess mortality from lung cancer in this cohort is concentrated in those employees who were employed for less than one year. Furthermore, the excess mortality from noninfectious, nonneoplastic respiratory disease is found only in those who were employed for one year or more.

When prior exposure history is added to the analysis (table 3), it can be seen that lung cancer mortality risk also appears to be related to prior occupational exposures. Thus, lung cancer risk is found to be greater in those who had less than one year of employment in the talc plant, and seems to predominate in those who had potential lung cancer risk exposure prior to their talc employment.

In contrast to the findings for lung cancer mortality, mortality from noninfectious, nonneoplastic respiratory disease (table 4) is only demonstrable in those workers with one year or more of employment and, unlike lung cancer mortality, is not concentrated in employees with prior exposure risk.

The 12 cases of lung cancer observed in

TABLE I

Observed and expected numbers of deaths and standardized mortality ratios (SMRs) (1947–1978) among male upstate New York talc plant workers

Cause of death (ICD-8‡)	Deaths among all workers				Deaths among workers employed one year or more			
	Observed	Expected	SMR	95% CI†	Observed	Expected	SMR	95% CI
All deaths	118	83.6	141	117–166	63	49.8	126	97–157
Respiratory tuberculosis (010–019)	3	0.6	493	99–1438	2	0.4	576	65–2063
All cancer (140–209)	26	15.7	165	108–242	15	9.6	157	88–259
Digestive system (150–159)	5	4.2	119	39–278	2	2.5	80	10–288
Respiratory system (160–163)	13	5.3	246	131–420	7	3.3	213	85–438
Lung (162)	12	5.0	240	124–419	6	3.1	193	71–420
Genitourinary system (185–189)	2	1.7	118	14–425	2	1.0	202	24–729
Central nervous system (191)	1	0.6	161	2–898	1	0.4	262	3–1466
Lymphopoietic (200–209)	5	1.8	278	90–648	3	1.1	277	56–812
Other malignancies	0	2.1		0–174	0	1.2		0–308
Benign neoplasms (210–239)	1	0.3	399	5–2228	1	0.2	663	9–3718
Circulatory system (390–458)	52	39.5	132	98–168	30	23.4	129	87–183
All nonneoplastic respiratory disease (460–486)	10	4.2	236	113–435	7	2.5	278	111–572
Pneumonia (080–486)	4	1.6	252	68–644	1	0.9	109	1–605
Noninfectious, nonneoplastic respiratory disease (460–479 and 487–519)	6	2.6	227	83–495	6	1.6	370	135–806
Accidents (E800–949)	9	8.7	104	47–197	2	5.1	39	4–140
Other causes	17	14.6	116	68–186	6	8.8	68	25–149

† CI, confidence interval.

‡ *International Classification of Diseases*, Eighth Revision.

TABLE 2

All cause, respiratory cancer, lung cancer and noninfectious, nonneoplastic respiratory disease mortality risks (1947–1978) by duration of employment among male upstate New York talc plant workers

	Duration of employment					
	Less than one year		One year or more		Total cohort	
	Observed/ Expected	SMR†	Observed/ Expected	SMR	Observed/ Expected	SMR
All causes	55/33.8	163*	63/49.8	126	118/83.6	141*
Respiratory cancer	6/2.0	300*	7/3.3	213	13/5.3	246*
Lung cancer	6/1.9	317*	6/3.1	193	12/5.0	240*
Noninfectious, nonneoplastic respiratory disease	0/1.0		6/1.6	370*	6/2.6	227

* $p < 0.05$, two-tailed test.
† SMR, standardized mortality ratio.

TABLE 3

Lung cancer mortality risks (1947–1978) by duration of employment and prior exposure history among male upstate New York talc plant workers

Work history classification	Duration of employment					
	Less than one year		One year or more		Total cohort	
	Observed/ Expected	SMR†	Observed/ Expected	SMR	Observed/ Expected	SMR
Prior risk‡	3/0.9	333	6/2.0	308*	9/2.9	316*
No prior risk	1/0.4	286	0/0.5		1/0.9	117
Unclassifiable§	2/0.6	313	0/0.7		2/1.3	154
Total cohort	6/1.9	317*	6/3.1	193	12/5.0	240*

* $p < 0.05$, two-tailed test.
† SMR, standardized mortality ratio.
‡ Prior employment in job with lung cancer risk (see text).
§ No prior work history on job application (see text).

the total cohort are reviewed in table 5. Duration of employment of these workers varied from several days to over 17 years, with a mean of 4.7 years (median of 20 months). Ages at time of hire varied from 24 to 57 years, with a mean of 34.8 years (median of 32.5 years).

DISCUSSION

Inclusion of short-term workers in the analysis of occupational cohort studies is generally felt to dilute the measure of association of mortality with the exposure of interest because of minimal exposure duration. To compensate for this perceived difficulty, short-term employees are frequently omitted from the analysis.

We have presented an example of mortality from lung cancer occurring in an occupational cohort of talc workers which demonstrates an *increased* mortality confined precisely to those who are traditionally excluded from analysis, the employees with short-term exposure (less than one year). Risk from occupational exposures is generally expected to increase with duration of employment. Here the risk does not appear to do so. The paradoxical nature of this finding is emphasized by the contrasting fact that mortality from noninfectious, nonneoplastic respiratory disease in this cohort does follow the anticipated pattern of increased incidence with increased duration of employment.

When the lung cancer mortality is analyzed by duration of employment (table 2) and by prior exposure risk categories (table 3), it appears that the lung cancer mortality

TABLE 4

Noninfectious, nonneoplastic respiratory disease mortality risks (1947–1978) by duration of employment and by prior exposure history among male upstate New York talc plant workers

Work history classification	Duration of employment				
	Less than one year	One year or more		Total cohort	
	Observed/ Expected	Observed/ Expected	SMR†	Observed/ Expected	SMR
Prior risk‡	0/0.4	3/0.9	319	3/1.3	224
No prior risk	0/0.1	3/0.3	1200*	3/0.5	666*
Unclassifiable§	0/0.5	0/0.4		0/0.9	154
Total cohort	0/1.0	6/1.6	370*	6/2.6	227

* $p < 0.05$ two-tailed test.
† SMR, standardized mortality ratio.
‡ Prior employment in job with lung cancer risk (see text).
§ No prior work history on job application (see text).

TABLE 5

Characteristics of lung cancer deaths (1947–1978) among male upstate New York talc plant workers

Case no.	Duration of employment	Date of hire	Years of age at hire	Prior risk employment	Date of death
1	8.0 days	1948	57	Unclassifiable§	1970
2	19.0 days	1949	43	Unclassifiable§	1970
3	2.0 months	1948	31	None	1971
4	2.5 months	1948	26	Metal mining	1971
5	3.0 months	1948	24	Metal mining	1970
6	11.0 months	1948	34	Metal mining†	1973
7	2.5 years	1950	30	Metal mining	1974
8	2.8 years	1948	39	Metal mining	1964
9	3.8 years	1949	27	Metal mining	1961
10	12.0 years	1953	37	Paper mill‡	1975
11	16.8 years	1956	45	Metal mining, construction	1973
12	17.5 years	1952	25	Paper mill	1976

† Also 5 months employment at another talc mine.
‡ Also 12 years employment at another talc mine.
§ No prior work history on job application (see text).

is significantly increased for short-term employees (SMR = 317) but not for longer term employees (SMR = 193), and is significantly increased for those with prior risk employment (SMR = 316) but not for those whose prior work history indicates no such employment (SMR = 117).

Several factors might explain these findings, including significant exposures occurring prior to (or subsequent to) employment at this talc plant, greater exposures for those with the short period of employment at this talc plant, differences in smoking habits, or perhaps some other factors that distinguish the short-term employees.

Analysis of prior work histories as discussed above demonstrates that employment in industrial jobs associated with an increased lung cancer risk prior to employment at this talc plant may be significantly related to death from lung cancer. Little information on possible exposures after leaving this employment is available for evaluation.

It is possible that unusual working-conditions existed during the time of employment of the short-term workers, as opposed to that of employees who remained longer at the talc plant, but support of this possibility is not evident. It might be that work-

ers who stayed for a shorter time began with dustier jobs, but the distribution of initial job assignments was no different for those who left within one year than for those who remained employed for at least one year. The lung cancer mortality was found primarily among miners (nine of 12 cases) rather than millers, although measured exposures were greater for the millers. The risk of lung cancer did not appear strongly related to the date of hire. Five of the six deaths from lung cancer in short-term employees occurred in workers who had worked three or fewer months, with two having had, respectively, only eight and 19 days employment at this talc plant (table 5). The presence of unusual working conditions during these short employment time periods thus appears to be an unlikely explanation of our findings.

Variations in other potentially confounding variables in short-term workers, such as cigarette smoking habits, are also possible. Limited anecdotal information on these cases indicates that those who were known to be smokers were considered to be heavy smokers. Additional data collection might assess whether the smoking habit for these workers was greater than for comparison groups and whether the smoking habit of short-term workers differed from those of longer term workers.

Other sociobehavioral or environmental factors that affect subsequent cause and age of mortality may distinguish short-term employees from long-term employees. The "healthy worker effect" is usually applied to the distinction between the ever employed and the never employed or the general population (22). There may also be a "short-time employment effect" or a "very short time employment effect" on mortality patterns of workers. Gilbert (23) found in his Washington State study of nuclear plant employees that the greatest risks for cancer and noncancer mortality were among those employed less than two years. We found half the lung cancer deaths in our study of talc workers to be in those employed less than one year and one-third in those employed less than three months. Shindell et al. (24) found no differences in mortality risk by duration of employment in their study of chemical workers; however, their study was restricted to workers employed for three months or more. Further studies should be done to determine the differential mortality pattern of short-term or very short-term employees. The adverse health, behavior, or work-related practices of persons who remain at a specific company for only a short period of time may differ from the practices of those who remain for a longer period of time or those who were not hired. In this paper, our method has been to determine the vital status of all persons ever employed and then to analyse and assess the results by duration of employment.

Mortality from noninfectious, nonneoplastic respiratory disease was used as a surrogate measure of fibrogenic lung disease in this population. If the talc exposure experienced by workers at this plant is believed to be both fibrogenic and carcinogenic, one would expect a similar exposure-related mortality pattern for both lung cancer deaths and noninfectious, nonneoplastic respiratory disease. However, unlike lung cancer mortality, the mortality risk for noninfectious, nonneoplastic respiratory disease (table 4) is concentrated in those employees who worked more than one year (SMR = 370) and in those whose prior work history did not indicate prior risk (SMR = 666).

Analysis of the mortality risk by duration of employment reveals that the risk from lung cancer in this study decreased with duration of employment while the risk from noninfectious, nonneoplastic respiratory disease increased with duration of employment. This suggests that the sources of these risks are different.

Conclusions

The increase in lung cancer mortality observed in a cohort of talc workers has been shown to be concentrated in short-term employees. This increased lung cancer

risk in short-term workers is most likely due to risk acquired elsewhere, such as prior employments, or to differences in smoking experience or other behavioral characteristics. The inclusion of short-term employees in this occupational epidemiologic study has affected the apparent relation observed between exposure and outcome in a magnifying rather than a diluting manner. The analysis in this study suggests that the lung cancer risk demonstrated in this cohort may reflect risks acquired before this employment rather than during this employment. The assessment of risk by duration of employment can reveal unusual patterns that may indicate confounding variables.

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The Mortality Experience of Upstate New York Talc Workers

W. T. Stille, D.P.H., and Irving R. Tabershaw, M.D.

Deaths for a 31-year period (1948 to 1978) were analyzed in a historical prospective cohort study of 655 white male talc workers. Death rates from all causes, from cancer of the respiratory system, and from nonmalignant respiratory disease were not significantly different from those of the U.S. white male population. However, significant differences for these causes of death were found among workers who had previous occupational histories. An analysis of the latency periods of the observed lung cancer suggests that exposure to an etiologic agent during previous work experience may play a role in the development of lung cancer.

Talc pneumoconiosis was first associated with talc mining and milling by Thorel in 1896[1] and since that time this association has been repeatedly documented in studies from various geographic sites. However, there are a number of contradictory reports regarding disability from talc pneumoconiosis and its effect on working capacity and respiratory function. The contradiction in these reports has been ascribed to the differences in the mineral composition of the various talcs. Kleinfeld et al,[2,3] in a series of reports, confirmed the increased incidence of talc pneumoconiosis and noted that among the talc workers who were 60 to 79 years of age and had 15 or more years of exposure the incidence of lung cancer was four times that among the general population. Their follow-up study repeated these findings but noted that the observed deaths from 1945 to 1959 dropped to approach the expected mortality between 1960 and 1969. The authors attributed this improved mortality experience to better environmental dust control.[3]

Brown and Wagoner,[4] using a similar cohort from the same population base; i.e., talc miners and millers in upstate New York, also found a statistically significant increase in the occurrence of bronchogenic cancer. The average latency for these cancer deaths was 20 years. They noted that data on several variables, particularly cigarette smoking and previous work history, were not available. Thus, from the work of Kleinfeld et al[2,3] and Brown and Wagoner, it appeared that talc mining in upstate New York is associated with an increase in lung cancer. Selevan et al,[5] in studying workers in Vermont talc mines and mills, showed an excess of deaths due to nonmalignant respiratory disease among millers and an excess of lung cancer mortality among miners. The lung cancer rate was similar to that found by Brown and Wagoner in their cohort of New York State workers. Selevan et al concluded, however, that agents other than talc, "either alone or in combination with talc dust, affect mine workers. The possible role of radon daughter exposures for this cancer mortality risk cannot be eliminated."[5]

The present study includes all workers in one talc mine and mill (TMX) in upper New York State who were employed between 1948, when operations began, and Dec 31, 1977.

Materials and Methods

The work force consisted of 744 persons employed between Jan 1, 1948 and Dec 31, 1977. Thirty-five women, primarily employed in office and administrative jobs, were not included because of the small numbers and a lack of exposure to talc. Nearly all employees were white and records indicate that to date all decedents have been white. The vital status of 36 (5.1%) men remained unresolved after Social Security and New York State Motor Vehicle Bureau records were searched. The maximum cohort available for analysis consisted of 708 white men, 113 of whom were known to be dead by Dec. 12, 1978, which was established as the vital status cutoff date.

Demographic data (microfilmed from employment records) consisted of the following: worker identifiers; sex; date of birth, employment and death; cause of death and information on prior employers. Data on cigarette smoking were not available. The occupational history included dates of work, job codes, and work location codes. Records were updated for the dates and causes of death as such information became available. Death certificates were coded according to the eighth revision of the International Classification of Diseases by a trained nosologist. Comparisons of observed deaths by age and year of death with those expected in the U.S. white male population were done by means of the modified life-table methods described by Monson.[6] All standard mortality ratios (SMRs) were computed by this program. Fifty-three workers whose records lacked dates of birth or other significant data had to be

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Table 1 – Observed and Expected Numbers of Deaths and SMRs Among TMX Workers (655 White Males With 11,350 Years at Risk).

Cause of Death ICD,* 8th Revision	Deaths		
	Observed	Expected	SMR
All deaths	113	107	106
Tuberculosis (010-019)†	3	.7	414
All cancer (140-209)	25	20.5	122
Digestive system (150-159)	6	5.7	105
Esophagus (150)	1	.5	216
Stomach (151)	1	1.1	92
Liver (155-156)	2	.4	511
Pancreas (157)	1	1.1	89
Respiratory system (160-163)	11	6.8	163
Lung (162)	10	6.4	157
Prostate (185)	1	1.3	79
Kidney (189)	1	.5	195
Brain (191-192)	1	.7	149
Lymphosarcoma (200)	1	.5	206
Hodgkin's disease (201)	2	.3	631
Leukemia (204-207)	2	.9	229
All lymphopoietic cancer (200-209)	5	2.1	230
All circulatory system (390-458)	48	53.7	89
Myocardial Infarction (410-413)	33	38.3	86
Cerebrovascular disease (430-438)	5	7.1	71
All respiratory disease (460-519)	10	6.1	164
Pneumonia (480-486)	4	2.2	182
Emphysema (492)	2	1.7	121
All digestive system (520-577)	3	5.3	57
External causes of death (800-998)	11	12.6	87
Motor vehicle accidents (810-827)	4	4.3	93
Suicide (950-959)	2	2.8	70

* ICD indicates International Classification of Diseases
† Numbers refer to ICD code

Table 2 – Observed and Expected Numbers of Deaths and SMRs Among Talc Workers With Known Prior Employment Before Work at the TMX (540 White Males With 9,168 Years at Risk).

Cause of Death ICD,* 8th Revision	Deaths		
	Observed	Expected	SMR
All deaths	90	60.6	148*
Tuberculosis (010-019)†	3	.4	680*
All cancer (140-209)	22	11.5	192*
Digestive system (150-159)	6	3.0	201
Esophagus (150)	1	.3	382
Stomach (151)	1	.6	180
Liver (155-156)	2	.2	1,013*
Pancreas (157)	1	.6	164
Respiratory system (160-163)	9	4.0	228‡
Lung (162)	8	3.7	214
Kidney (189)	1	.3	325
Brain (191-192)	1	.5	206
Lymphosarcoma (200)	1	.3	326
Hodgkin's disease (201)	2	.2	849
Leukemia (204-207)	2	.5	391
All lymphopoietic cancer (200-209)	5	1.3	374*
All circulatory system (390-458)	36	28.0	129
Myocardial Infarction (410-413)	27	20.3	133
Cerebrovascular disease (430-438)	3	3.1	97
All respiratory disease (460-519)	9	2.9	307*
Pneumonia (480-486)	3	1.0	274
Emphysema (492)	2	.7	278
All digestive system (520-577)	1	3.5	28
External causes of death (800-998)	11	9.8	112
Motor vehicle accidents (810-827)	4	3.4	119
Suicide (950-959)	2	2.2	92

* Indicates statistical significance at the 1% level
† Numbers in parentheses refer to ICD codes
‡ Indicates statistical significance at the 5% level

dropped from the life-table analyses. Thus, the study cohort consisted of 655 white males, a relatively small sample size and therefore a limitation on the study.

Results

Table 1 shows the numbers of observed and expected deaths in the study cohort of 655 white male talc workers. Although the SMRs are elevated, the numbers of deaths from all causes, from cancer of the respiratory tract and lung from nonmalignant respiratory disease, or from other causes of death are not significantly different from those occurring in the U.S. white male population. Numbers of deaths from circulatory diseases, digestive tract diseases, and accidental and external causes are lower, but not significantly so. The SMR of 106 for all causes of death has 95% confidence limits from 87 to 128, thus the total talc worker population has an SMR within the usual range of variation from the national data. Since people who are chronically ill or disabled are usually unemployable and have higher death rates, healthy working populations typically have SMRs below 100. The SMRs in an occupational group with values over 100 indicate either possible work place hazards or possible confounding with non-occupational exposures.

One such non-occupational exposure is smoking, and it is noted that the SMR of 163 for respiratory cancer in this population is consistent with a smoking effect. While the actual smoking experience of this population is not known, insight into it is gained from knowing the smoking patterns of current TMX workers, many of whom are included in the study cohort. Among 151 workers given a medical examination at TMX in 1979, 69 (46%) were current smokers, 38 (25%) were past smokers and 44 (29%) were nonsmokers. The percentage of current smokers is higher than in the general population, but is consistent with patterns seen in the mining industry.

The SMR for all causes of death, 106, may also reflect in part inclusion in the cohort of everyone ever employed during the study period, regardless of their length of employment. Universal cohort membership generally tends to increase SMRs, since short-term workers often have a greater mortality experience than long-term employees. Most study designs exclude workers with less than one year of working experience. The practice was not followed in

Table 3 – Observed and Expected Numbers of Deaths and SMRs Among Talc Workers With No Known Work Prior to TMX Employment (115 White Males With 2,184 Years of Risk).

Cause of Death ICD, 8th Revision	Deaths Observed	Expected	SMR
All deaths	23	45.9	50*
All cancer (140-209)†	3	9.0	33
Lung (162)	2	2.6	76
Prostate (185)	1	.8	120
All circulatory system (390-458)	12	25.9	46
Myocardial infarction (410-413)	6	18.0	33
Cerebrovascular disease (430-438)	2	4.0	50
All respiratory diseases (460-519)	1	3.2	31
Pneumonia (480-486)	1	1.1	90
All digestive system (520-577)	2	1.8	112

* Indicates statistical significance at the 1% level; note that this SMR is lower than expected with respect to the U.S. national data

† Numbers in parentheses refer to ICD codes

this study in order to maximize cohort size.

The use of the U.S. white male population as the external comparative group does not necessarily describe the TMX mortality experience, since the mortality experience of the U.S. white male population is likely to vary substantially from that of this cohort. For example, the New York State cancer death rate is 199.24 compared to the national average of 174.04, approximately a 13% difference.[7]

Since exposures prior to employment at the TMX could have included carcinogens and other substances hazardous to the lungs, the results have been analyzed to investigate this possibility. Table 2 shows the observed and expected numbers of deaths and the SMRs for all workers whose job histories show prior work before employment at the TMX. Deaths for all causes are significantly increased, as are deaths for a number of cancers and for nonmalignant respiratory diseases. Since the cancers and lung diseases typically have long latencies, the possibility exists that exposures prior to work at the TMX were responsible for at least some of these diseases.

Table 3 shows the observed and expected numbers of deaths for workers with no known employment prior to the TMX. Mortalities for all disease categories do not differ significantly from those for the comparable U.S. population. In fact, the SMRs from all cancers and all respiratory tract diseases (33 and 31, respectively) were among the lowest of all the mortalities. It should be noted that workers whose employment records were devoid of work history data were judged as having had no known prior employment and thus were included in Table 3. If some of these workers did indeed have work experience before employment at the TMX, the effect would be to increase the SMRs. However, even with this possible compromising effect, Table 3 shows a remarkably healthy work force, with most mortalities at 50% or less of those of the comparable U.S. population. As noted earlier, however, the small sample size limits the conclusions that can be drawn from this study.

Five of the 12 lung cancer cases, which are included in Table 5, were substantially older than the median age of

Table 4 – Age at Death and Segments of Work History of Workers at the TMX With Bronchogenic Carcinoma.

Age at Case No./Death, yr	Pre-TMX Employment	Years or Days Employed at the TMX	Post-TMX Employment
1/39	10	4	7
2/49	8	17	6
3/53	8	47 days	27
4/53	13	56 days	23
5/54	12	3	21
6/55	21	3	13
7/59	16	345 days	24
8/62	26	17	1
9/64	25	17 days	21
10/79	39	8 days	22

the entire cohort at age of hire. For those workers with TMX-only employment, 63% were under 25 when hired, contrasted with 35% for those with previous experience. The difference in age at hire between the two cohorts may partially explain the deficit in disease mortality among TMX-only workers and the lung cancer experience of those with other work history.

Discussion

Workers with previous jobs before employment at the TMX were found to have high mortalities, as shown in Table 2. Workers with no known work history before employment at the TMX were found to have much lower mortalities (Table 3). Thus, it would seem that exposures to health hazards occurred in these earlier jobs and that these exposures are causally related to the higher rates of death. Obviously, mines and mining operations are not uniform with respect to the occurrence of health hazards and, as previously stated, Selevan et al[5] have described increased rates of lung cancer in some talc miners exposed to radon daughters. No significant radon daughter exposures occurred at the TMX.[8,9] The low mortalities given in Table 3 are in agreement with the absence of radon daughter and other related hazardous exposures at the TMX. However, mortality studies such as ours lend themselves to various conclusions. Lacking data on smoking and other personal risk factors, we sought to obtain confirmation for our interpretations by an independent analysis of lung cancer latencies.

Data for an analysis of the lung cancer latencies are given in Table 4. For each of the ten cases of lung cancer, the employee's years of occupational history are given as the following: pre-TMX employment (employment was deter-

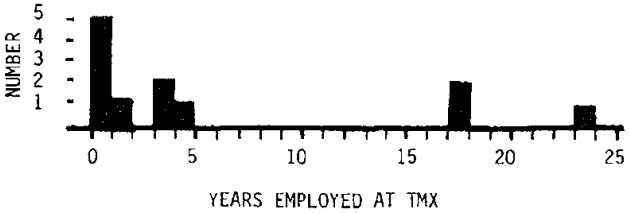

Fig. 1 – Number of lung cancer cases by years of employment at TMX.

Table 5 – Latencies of Bronchogenic Carcinomas in TMX Workers

Latency, *yr	Bronchogenic Carcinomas in TMX Workers Whose Exposure is Hypothesized to Begin	
	On Employment at the TMX	At Age 18, Prior to TMX Employment
<10	1	–
10-14	1	–
15-19	2	–
20-24	5	1
25-29	3	1
30-34	–	1
35-39	–	4
40-44	–	3
45-49	–	1
50-54	–	–
55-59	–	–
≥60	–	1
Total	12	12
Latency	19.9	38.2

* From onset of exposure to diagnosis or death

mined arbitrarily to have begun at age 18); tenure at the TMX; and the period from TMX employment until the diagnosis of lung cancer or death. Although not included in Table 4, two additional persons with lung cancer should be noted. The first was surgically treated for lung cancer at age 47 after 137 days of employment at the TMX. At age 57 he died of pneumonia. His significant occupational periods were 29 years pre-TMX, 137 days of TMX tenure, and zero years post-TMX to the time of diagnosis of lung cancer. The second individual died of lung cancer after the cutoff date. His significant occupational periods were 15 years pre-TMX, 23 years of TMX tenure, and six years post-TMX.

To explore the nature of the dose-response relationship, column 3 in Table 4, which lists numbers of years or days employed at the TMX, is graphically represented in the Figure. The two additional cases of lung cancer just described are included. The clustering of nine of the 12 cases within the first five years of employment at the TMX shows an inverse dose response, i.e., higher risks of lung cancer with less occupational exposure to talc. The lack of a dose response, in terms of years of exposure at the TMX, is in agreement with our findings that workers with "exclusive" TMX employment seem to be at no considerable risk of having lung cancer develop.

Knowledge of the latency period of a disease permits determination of the probable time at which pathological processes began. Thus, the analysis of disease latencies can be useful in attributing or refuting evidence as to when causal exposures occurred. Armenian and Lilienfeld[10] have reviewed the latency periods of a number of cancers. They present evidence that leukemias in different populations and under different conditions have median latency periods and latency variabilities that are quite similar. They also reviewed data that indicate that the intensity of exposure has very little effect on latencies of other neoplasms. Hence, we hypothesize that if occupational talc exposure results in pulmonary exposure to a carcinogen, then the distribution of TMX workers lung cancer latencies should be similar to those reported for lung cancer in other studies. However, if such exposure is not carcinogenic to the lung, then the distribution of TMX lung cancer latencies would be dissimilar to lung cancer latencies reported elsewhere.

To test the hypothesis that carcinogenic exposure began at TMX, the median lung cancer latency of 36.5 years, as calculated by Armenian and Lilienfeld,[10] was compared to the latency period from the onset of TMX employment to the diagnosis of each lung cancer. As can be seen from Column 2 in Table 5, the average latency period of 19.9 years for lung cancer among the TMX workers is almost half the 36.5 years noted above. The Chi Square goodness of fit test provides a quantitative basis for rejecting the hypothesis at the 5% level of statistical significance.

If the occupational talc exposures to the TMX are not carcinogenic, then the question shifts to what other exposures occurred that may have caused the lung cancers. Since each of the subjects with lung cancer included in Table 4 had between eight and 39 years of possible occupational exposure from the time of his 18th birthday to employment at the TMX, this prior period of exposure may be related to subsequent cancers. To test this possibility, we hypothesized that the causal exposure for the lung cancer occurred before employment at the TMX. The data in the last column of Table 5 reveal a much more reasonable relationship to the lung cancers reported by Armenian and Lilienfeld. This second hypothesis, that the causal exposure began before TMX employment, yields an average latency period of 38.2 years, which is only slightly longer than the Armenian and Lilienfeld median of 36.5 years. The Chi Square goodness of fit is almost zero, indicating a very close agreement between the lung cancer worker latency periods and those of talc workers when exposures prior to TMX employment are hypothesized as carcinogenic. Hence, the initiation of cigarette smoking in the late teenage years, World War II exposures, excessive exposures to mineral dust in the past, diet and nutritional status, absence of complete work history, preexisting diseases, and other unknown etiologic agents could contribute to the etiology of the observed lung cancers, while exposures at TMX seem to be noncarcinogenic. It should be noted that nine of the 12 employees with lung cancer worked underground in TMX, which suggests that their other jobs also were likely to have been underground. Review of the death certificates tends to confirm the observation that these men worked in occupations known for their dusty environment. The employment policy of TMX to preferentially hire experienced workers appears to have resulted in the confounding of prior hazardous exposures with employment at TMX.

Summary and Conclusions

A historical prospective mortality study of workers at an upstate New York talc mine demonstrated elevated mortali-

ties but no significant increases in the numbers of deaths from lung cancer, from nonmalignant respiratory disease, and from all causes. However, workers with exposures in other jobs prior to work at the TMX were found to have excessive mortality from lung cancer and from nonmalignant respiratory tract disease. Exposures in jobs held prior to TMX employment also were implicated in an independent analysis of lung cancer latencies.

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August 13, 1982

RECEIVED

AUG 17 1982

TOMA

Irving R. Tabershaw, M.D.
Tabershaw Occupational Medicine Associates
6110 Executive Blvd.
Rockville, MD 20852

Re: The Toxicity of Upstate New York Talc

Dear ~~Dr. Tabershaw~~ Irv:

We have received the enclosed letter from David P. Brown of NIOSH commenting on your article which we published in our June, 1982, issue.

We plan to publish this letter in our Letters to the Editor Department. Would you care to write a response which could be published in the same issue of JOM? If so, could you please provide us with your "reply for publication" within the next 2-3 weeks. Do let us know.

We are also enclosing a copyright release form which should be executed and submitted with any material intended for publication.

Sincerely yours,

Doris

Doris Flournoy
Publisher

DF:hj
encl.

I.R.T.
N. Henry

Letter to the Editor of JOM

THE TOXICITY OF UPSTATE NEW YORK TALC

In a recent issue of the JOM, Tabershaw Occupational Medicine Associates (TOMA) reported the findings from a study entitled, "The Mortality Experience of Upstate New York Talc Workers".[1] The TOMA report concluded that exposures experienced at a particular New York State talc company (identified as TMX) were not carcinogenic and did not result in any increased risk from lung cancer. They suggested that any excess in lung cancer mortality observed in the workers could be attributed to other factors, including prior occupational exposures.

The National Institute for Occupational Safety and Health (NIOSH) had previously conducted a study of mortality among workers at the same talc company. NIOSH concluded, in contrast to the conclusions reached by TOMA, that the possibility of an excess lung cancer risk among workers at "TMX" could not be dismissed, and that occupational exposure to the talc mined in the Upstate New York region is associated with an increased risk in developing lung cancer. In this letter we offer several reasons for the discrepancy between these two studies.

The conclusions reached by NIOSH were based on the finding of a statistically significant, 3-fold increase in both lung cancer mortality and mortality from non-malignant respiratory disease among a cohort of talc workers first employed at the "TMX" mine between 1947-1960.[2] In addition,

mineralogical analyses (performed by both NIOSH and independent laboratories) demonstrated that talcs from the "TMX" mine contain fibrous tremolite and anthophyllite,[3] and that the talc ore from "TMX" was substantially the same as that of other mines in the Gouverneur Talc District of Upstate New York where the "TMX" mine is located and where many of the "TMX" workers were previously employed.[3] These mineralogical analyses are important when interpreting the toxicity of "TMX" talc because previous studies of workers exposed to talc from other Upstate New York mines also found an excess in mortality due to lung cancer and non-malignant respiratory disease,[3,4] and other studies of workers exposed to anthophyllite and tremolite have demonstrated similar findings.[5] Thus, the NIOSH conclusions are not based on the results of the cohort mortality study alone, but also on environmental sampling and on the corroboration of findings at "TMX" with previous reports.

Several problems in the TOMA analysis appear to account for the difference between the TOMA and NIOSH conclusions. First, the TOMA study performed no analysis of mortality by latency interval. Instead, the TOMA study allows workers to enter the cohort as late as December 31, 1977. In the absence of a proper analysis of risk by latency, the possibility arises that a number of recently hired workers are included in the TOMA study group, and that their low rate of cancer mortality may have masked any excess risk that truly existed among workers who had experienced an adequate observation period, ie. who had first been employed prior to 1960.

Second, the distinction made in the TOMA study between previously employed and not previously employed workers overlooks several possibly confounding factors. To address the possible influence of exposures from previous jobs, the TOMA study divided the cohort into those with any known work history prior to employment at "TMX" and those with no known previous work history. This exercise yields a sub-cohort of 540 workers with previous employment and another of 115 workers with no previous employment. When cause-specific mortality of the two subcohorts is examined, the risks associated with the first (N=540) are unusually high for almost every cause, while those of the second (N=115) are unusually low. The TOMA investigators suggest that this difference may reflect hazardous prior exposures, but in fact, it appears to be a consequence of selection biases inherent in the definition of the subcohorts. These selection biases include differences in the length of the follow-up period (i.e. those with previous employment probably have a much longer time since first exposure), and differences in the percentage of more recently hired workers (i.e. there is probably a much higher percentage of more recently hired workers in the group with no previous employment, a difference which exaggerates the healthy worker effect). Furthermore, the size of the population with no previous employment is extremely small (23 total deaths, 3 cancer deaths). Any mortality analysis based on such a small cohort with generally short latency is not likely to be very informative.

Third, the TOMA study does not calculate the relative risk of lung cancer by "dose". Their conclusion that there is ". . . an inverse dose response,

ie., higher risks of lung cancer with less occupational exposure . . ." is supported by an analysis which simply counts the number of observed deaths (and not the expected number of deaths) in each category of years employed. Such an analysis is not very meaningful. The same comment can be made about the TOMA latency analysis which employs the same procedure. In addition, TOMA's conclusions regarding the "negative" effect of dose-response and latency ignore the fact that many "TMX" workers had previous employment in other neighboring talc companies where the talc has been shown to be basically the same as that at "TMX".

In summary, the TOMA report fails to address adequately the question of whether or not there is an increased risk from lung cancer specifically associated with working at the "TMX" facility. In fact, at this time, it is not possible to answer this question based on epidemiologic data alone, because the population available for study is small, the follow-up period is relatively short (long latency diseases associated with employment at this company cannot be adequately addressed), data on smoking are lacking, and previous exposures in other neighboring talc mines and mills represent a confounding factor. In addition, in order to conclude that the talc from "TMX" is <u>not</u> carcinogenic as stated by TOMA would require: 1) A negative study based on a cohort of sufficient size that also has sufficient latency; 2) A demonstration that the talcs from the "TMX" mine are different from other talcs in Upstate New York in their content of tremolite, anthophyllite and other contaminants; or, 3) That other mortality studies of Upstate New

York talc workers incorrectly attributed increased lung cancer mortality to talc exposures. The TOMA study does not adequately address any of these considerations.

Sincerely yours,

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1 Enclosure

DBrown:dm:Rm8403:FOB:Cinti:OH

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TALC-NIOSH DRAFT COMMENTS 6/20/84, 7/3/84, 8-2-84

RESPONSE TO NIOSH COMMENTS ON CEOH REPORT

DATA DIFFERENCES

A detailed comparison of the data in the NIOSH and CEOH reports has been made and reviewed by both Dr. Lamm of CEOH and Mr. Brown of NIOSH. Mr. Brown has reviewed the work histories and has concluded that "the work history of (lung cancer case #3 in CEOH report and lung cancer case A2 in NIOSH's report) as given in the NIOSH Technical Report is apparently in error". There has been no other dispute with regard to work history.

The cancer diagnosis of case #D in CEOH report (not in NIOSH report) listed on the death certificate was "carcinoma lung due to carcinoma liver." Mr. Brown relates that although the hospital report indicates that the final diagnosis was "pneumoconiosis with a lesion in the right upper lobe which spread to the hilum," the report states that "it is difficult to state whether the primary carcinoma is in the lung or in the liver." NIOSH, based on the ICDA-8 nosological rule that cancers not specified as secondary are considered primary except if they occur in lymph nodes or liver, therefore, NIOSH classified the case as lung cancer. The coding rules of ICDA-8 would have classified this case as a lung cancer (not specified as secondary)-162; the coding rules of ICDA-9 would have classified this case as a liver

cancer (not specified as secondary)-155.2.

CEOH did not consider the evidence to be sufficient to classify the case as a primary lung cancer. Rather, CEOH considered in its report that the death certificate's full statement "death was caused by (immediate cause) carcinoma lung due to (or a consequence) of carcinoma liver (due to as a consequence of) pneumoconiosis" indicated that carcinoma lung was a secondary cancer and that carcinoma liver was either a primary or secondary cancer.

Recently (4/24/84), NIOSH informed CEOH that the hospital reported, in addition to the lung findings, that the patient "had a mass in the colon and multiple filling defects of the liver". Unfortunately, an autopsy was not performed. The above information, however, suggests that the case was likely to be a bowel cancer with metastases to the liver and to the lung periphery. Based on all of the above, CEOH classified this death as caused by other than primary carcinoma of the lung.

There is, thus, a dispute as to the appropriate classification of this case. This dispute revolves about both the absence of adequate information on this case and on its death certificate and the slight vagaries in the refinement of the code as peculiarities are identified. One such peculiarity is the classification of cancers not specified as primary, yet indicated (but not specified) as secondary. The rules through the eighth revision have classified these as primary with the exception of liver and lymph nodes. In the ninth revision, code 155.2 (liver cancer, not specified as primary or secondary) was

included. NIOSH reports that it has adjusted to the 7th ICDA revision; CEOH has adjusted to the 9th ICDA revision. Adjustment of the expected numbers has only a minimal, non-detectible effect on the SMR's or relative risks.

ANALYTIC GOALS

Brown et al., (1983) proposes that the TOMA and CEOH analyses should "convincing enough to conclude that R.T. Vanderbilt talc is not carcinogenic." This goal, which NIOSH proposes, is not a reasonable or feasible one, both because it requires the observer to be convincible and because proof of non-carcinogenicity is not an endpoint of epidemiologic studies. Rather the endpoint of an epidemiologic analysis is the assessment of the strength with which a positive association can be demonstrated.

The NIOSH study does demonstrate that there is a statistically significant increased risk of dying from lung cancer for men who have been employees of Gouverneur Talc Company and that this risk peaks twenty plus years after hire. No further statement can be made from the limited analysis presented by NIOSH.

NIOSH reports that less than half its study cohort had even worked one year at the plant, but has not analyzed whether the risk increases with increased duration of employment. In other studies, NIOSH has compared the risks for miners and millers, but here has not. NIOSH has performed no analysis to assess whether the lung cancer risk is related to exposure at the plant or employment at the plant.

TOMA and CEOH have each assessed these qualities in different manners and have basically concluded that while there is an excess risk of lung cancer mortality associated with employment at GTC, available evidence does not indicate that the risk is attributable to exposure to GTC talc.

An associated risk demonstration merely shows that the observed mortality was statistically significantly ($p<.05$) greater for a group than would be expected based only on their age, race, sex, and period of observation. To determine provisionally that an associated risk may be attributable to some specific risk or exposure, it is necessary to demonstrate both that the associated risk can not be explained by or accounted for known factors and that the residual risk behaves in a pattern consistent with being due to that factor or exposure. NIOSH has not adequately examined the data to determine whether the associated risk is attributable to GTC talc dust or particulate exposure, CEOH has, and concludes, within the limits of the study, that the excess risk does not appear to be attributable to exposure to GTC dust or its components.

SPECIFIC CONCERNS

Brown raises a number of specific concerns that can be dealt with.

Exposure Data

The CEOH report quotes the 1977 NIOSH data as an example which NIOSH would accept. That data is consistent with the historical data at the mine, in NIOSH's files, and published in the literature. Kleinfeld in 1973 published 1970 data showing exposures in the mine (excluding primary crushing) to about 2/3 that of the exposure levels in the mill. Kleinfeld (74) has shown historically that exposure levels in mines (ever since wet mining was introduced about 1945) have been markedly lower in the mines than in the mills. GTC has only had wet mining since it opened. While mining practices have of course changed over time, the exposure pattern has been rather consistent.

Subcohort Analysis

The presented analysis has considered both duration of employment and latency in its analysis of the total workforce, and partially for its subcohorts of miners and millers. NIOSH has not performed this type of detailed analysis but opted to use a single latency analysis on its total GTC group. Neither a latency nor a duration analysis were performed in NIOSH's study of Vermont miners and millers. NIOSH asks more of CEOH than of itself. CEOH's tables 8 and 9 indicate that NIOSH's latency findings are dependent on the short-term employees and disappear when duration of employment

greater than one year is considered. CEOH has used a one year cut off in its comparative study, conforming to NIOSH's study of Vermont talc miners and millers where also a one year cut-off was used.

Cause of Death Ascertainment

CEOH has reported its analysis of the lung cancer mortality (ICD-7, numbers 162.1 and 163) among the GTC cohort, what NIOSH calls bronchogenic cancer. Case #C died of mediastial cancer (ICD-7, number 164), which, while classified as respiratory cancer, is not a lung or bronchogenic cancer. Case #D's death certificate read "cancer lung due to cancer liver," which coded in ICD-9 and convert to ICD-7 would be number 155. Later information from NIOSH revealed that the worker had a mass in the colon. Thus, it is most likely that he died of colon cancer metastatic to the lung and the liver (note that the death certificate indicates that the onset of the liver and lung cancers as occurring at the same time one month before death.) NIOSH coded it by ICD-8, as a lung cancer. Interpretation should be based on validated cases, not coding aberrations.

Prior Talc Employment

We have reviewed our coding and classification with NIOSH. NIOSH originally reported that three of their cases had prior talc employment. One of their cases is our case C, who had mediastinal cancer, not lung cancer. The second case has now been reviewed by NIOSH which reports that they were "apparently in error"; and with the third case we concur. Thus, NIOSH and CEOH agree that only one of the lung cancer cases is known to have had prior talc employment, based on the

job application information.

Prior Risk Classification Selection

The classification of the prior employments was made independently by a senior industrial hygienist without knowledge of the vital status or cause of death of the workers. There certainly would be discrepancies between various "experts" as to which jobs or employments. The "a priori" decisions made in this study are detailed in the report on pages A-12 and A-16. Table 9A on page A-17 shows the distribution of workers by prior risk groups and tables 13A and B on page B-7 show the outcome analysis by prior risk groups. The interpretation of these tables is given on page B-6.

Table 10 and 11 in the body of the report are extracted from tables 13A and B in Appendix B. Tables 10 and 11 ralate to those workers who gave a prior work history. As can be seen from table 13A, only 9 of 11 cases are shown in table 10 (Brown misidentifies as table 11) because one case gave no prior employment history on the job application and one had no personal history and was without a job application in his personnel file. Stille and Tabershaw chose to compare the lung cancer risks for those with prior work histories and those without prior work histories. CEOH chose to compare the lung cancer risks of those whose prior work histories showed no employment thought to involve a lung cancer risk and those whose did. No doubt prior employment histories are incomplete. However, we had no reason to believe that there would be on a priori selection bias for or against lung cancer risk, based on completeness of giving prior work

history on the job application.

Validity of Cohort Comparison

The comparison of the mortality experiences of the Vermont talc workers cohort and the experienced GTC workers cohort is among the most valid between study comparisons in epidemiologic analysis. The entry criteria are similar (at least one year employment in either Vermont talc plants or GTC); the periods of employment are similar (1940-69 vs 1947-1977); the periods of observations are similar (1940-79 vs 1947-78); the cause of death classifications were the same; the job classifications were similar; and, additionally, the exposures were quite similar, save the hypothesized presence of asbestos in the GTC talcs. It is precisely because the two groups differ by little other than the hypothesized exposure that the comparison is appropriate. The analysis found no difference in lung cancer risk between the two groups, indicating that there is no apparent increased lung cancer risk associated with the additional hypothesized exposure.

Morbidity Study

A copy of the CEOH report was sent by CEOH to Dr. Gamble in August 1983. CEOH has received no critical response from him.

Study Power and Strength

Brown acknowledges that the findings of the CEOH analysis appear to support the hypothesis that the talc is non-carcinogenic. He claims, however, that the analyses "are inherently deficient in being

able to detect a true risk in an exposed population" because they are "based on assumptions, small numbers, and short latency. This is not so. The analytic assumptions used have been laid out, are reasonable, and can be justified when specified. The numbers may be small, but are larger than other studies upon which etiologic conclusions have been based. The number of workers reported by TOMA and CEOH are almost double that reported by NIOSH. The latencies shown in the study are the data available, which can serve for interpretation within those limits. Even within these limits, one can note that the NIOSH hypothesis would predict rising risk twenty-five years after employment began. CEOH has shown that its analysis had sufficient power to detect a risk twenty-five years after initial exposure that would equal or exceed the risk twenty to twenty-four years after initial exposure. Yet, the data demonstrated the risk at twenty-five plus years latency to be statistically significantly less than that of twenty to twenty-four years latency.

The critical term that NIOSH might have underlined is exposed population. Brown et al have performed no analysis to assess a relationship between lung cancer risk and GTC talc dust exposure. NIOSH has only begun to analyze a relationship between lung cancer risk and GTC employment. We would propose that the data may demonstrate only a selection bias on the part of GTC management for workers who were used to heavy industrial and mining work, jobs that later came to be understood as having a certain risk of lung cancer. NIOSH might, for instance, restrict its analysis to those employees

who remained at least a year and can be reasonably assumed to have had GTC talc dust exposure.

Collateral Evidence

Brown concludes that collateral evidence must be considered in determining the carcinogenic strength (or its absence) of GTC talc dust. He proposes that the critical evidence is that prior studies indicate an increased lung cancer risk among other miners exposed to similar minerals. He does not bring forth as collateral evidence that the studies of other NYS talc miners hired after 1945 (like GTC miners) found no increased lung cancer risk, nor that animal toxicity studies that demonstrate the carcinogenicity of "similar" minerals do not demonstrate carcinogenicity for GTC talc. Finally, the concept that the elongated particulates in GTC talc (non-asbestiform tremolite and non-asbestiform anthophyllite) are "similar" to the asbestiform varieties of these same minerals has long been challenged by mineral scientists both in the company and without, in the government and without. [Strength does not lie in NIOSH's overly broad definitions of mineral fibers.]

The same care that must be given to diagnostic labels for individual medical cases must also be given to mineralogical labels for the individual crystals.

The differences in mineralogical structure may be critically important. Whatever the mineralogic similarities or differences between the crystals found within the talcs at this plant and crystals found elsewhere in the world, we find no evidence in the GTC workers

mortality study of a carcinogenic risk attributable to exposure to the minerals found in the talc at the GTC plant.

NIOSH

TECHNICAL REPORT

OCCUPATIONAL EXPOSURE to TALC CONTAINING ASBESTOS

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

OCCUPATIONAL EXPOSURE TO TALC CONTAINING ASBESTOS

Morbidity, Mortality, and Environmental Studies of Miners and Millers

I. Environmental Study	John M. Dement[1] Ralph D. Zumwalde[1]
II. Cross Sectional Morbidity Study	John F. Gamble[2] William Fellner[2] Michael J. DeMeo[2]
III. Retrospective Cohort Study of Mortality	David P. Brown[1] Joseph K. Wagoner[3]

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DHEW (NIOSH) Publication No. 80-115

ABSTRACT

The National Institute for Occupational Safety and Health (NIOSH) conducted studies of mortality and morbidity patterns and occupational exposures among talc miners and millers in upper New York. The mortality study was based on 398 white male workers who began employment between January 1, 1947 and December 31, 1959, and whose vital status was determined as of June 30, 1975. Observed cause specific mortality for the cohort as compared with that expected based on U.S. white male mortality rates indicated a significant increase in mortality due to bronchogenic cancer, nonmalignant respiratory disease (excluding influenza and pneumonia) and respiratory tuberculosis. The average latency period for bronchogenic cancer was 20 years.

In the morbidity study current workers (156 male miners and millers) from the same New York talc company were examined. One hundred twenty-one (121) workers were administered the MRC respiratory questionnaire (including smoking and work histories), lung function tests (FEV_1, FVC, expired flow rates), and chest X-rays (PA and lateral). The results are similar for all 121 workers, and for a subset of 93 workers having talc exposure only at the facility under study. Lung function is expressed as percent predicted, with 9,347 coal miners and 1,095 potash miners matched on age, height, and smoking habits providing expected values for the prevalence of symptoms, X-ray findings, and lung function. Cumulative exposure is calculated by estimating the mean exposure level in a current job, times the time spent in that job summated for all jobs.

Findings from the morbidity study included the following: Talc workers with less than 15 years work have a higher prevalence of cough and phlegm than coal and potash miners. Talc workers with more than 15 years work have a higher prevalence of cough, dyspnea, and irregular opacities than potash miners, but less phlegm and dyspnea than coal miners. Pleural thickening and calcification is significantly higher in talc workers than in coal and potash miners, and pleural thickening is significantly higher than in chrysotile asbestos workers in Canada. Mean pulmonary function of the talc workers is reduced compared to coal and potash workers: Reductions in FEV_1 and FVC are associated with the highly correlated variables of years worked, particulate, and fiber exposure. Talc workers with pleural thickening have reduced lung function compared to those workers without pleural thickening.

The industrial hygiene study demonstrated that the major components of the talcs mined and milled are talc, tremolite, anthophyllite, and serpentines with traces of dolomite, calcite, and quartz. These trace metals were found to be present only in very small quantities. Time-weighted average (TWA) exposures to asbestiform amphiboles (anthophyllite and tremolite) were found to be in excess of present U.S. Occupational Safety and Health (OSHA) and Mine Safety and Health Administration (MSHA) occupational exposure standards in many mine and mill operations with more than 90 percent of the total airborne fibers being less than 5-μm in length.

Results of the present study are compared with those of other studies of workers exposed to the same or similar minerals, and it is concluded that exposures to such talcs are associated with an increased risk of developing not only pleural thickening and pleural calcification, but also both bronchogenic cancer and nonmalignant respiratory disease.

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ACKNOWLEDGMENTS

The assistance of the following is acknowledged: Mike Grannan and Eric Kus of NIOSH and Jim Salois of MESA in collection of the industrial hygiene samples; Mike Grannan, Robert Phillips, and Kenneth M. Wallingford in the optical asbestos fiber analyses; Terry Boyle and Dennis Roberts in reduction of the field and laboratory data; Dr. D.R. Bowes of the University of Glasgow in analysis of major elements of talc bulk samples; W.C. McCrone Associates and the Mt. Sinai School of Medicine of the City University of New York in analysis of talc bulk samples.

We wish to thank the staff of the Biometry Section for their help in assembling the necessary data for the mortality study and in preparing the manuscript. The guidance of Richard Lemen was especially helpful.

The time and effort of the field teams that participated in the collection of data for the morbidity study was greatly appreciated.

DEFINITIONS

COUGH	YES to the question, "Do you cough like this on most days for as much as three months each year?"
DYSPNEA	YES to the question, "Do you get short of breath walking with other people your own age on level ground?"
FEF_{25}, FEF_{50}, FEF_{75}	Forced Expiratory Flow (liters/second) at 25 percent, 50 percent and 75 percent of expired FVC.
FEV_1	Forced Expiratory Volume in one second (liters).
FEV percent	$FEV_1/FVC \times 100$.
FVC	Forced Vital Capacity (liters).
HEMOPTYSIS	YES to the question, "Have you ever coughed up blood?"
PHLEGM	YES to the question, "Do you bring up phlegm like this on most days for as much as three months each year?"
SMR	Observed deaths/Expected deaths x 100.
TWA	Eight-hour time weighted average.

INTRODUCTION

The term "talc" in the mineralogical sense denotes a specific rockforming mineral of the sheet silicate category; however, when "talc" is referenced in the industrial or commercial setting, it may represent a varied mixture of minerals with physical properties similar to the mineral talc (1). Minerals commonly found associated with talc include calcite, quartz, diopside, magnesite, serpentines (chrysotile, antigorite, and lizardite), and fibrous and nonfibrous amphiboles (tremolite, anthophyllite, actinolite) (1, 2). The United States produces about 30 percent of the world's talc with New York, California, Vermont, Texas, and Montana accounting for three-fourths of the U.S. production. The work force for both talc mining and milling has been estimated to be about 1,200 in over sixty-five facilities (3).

Largely due to the great variety of minerals commonly associated with talc, few studies have been undertaken which adequately characterize the various minerals to which talc workers are exposed and simultaneously delineate the latent disease manifestations associated with those work environments.

Recognizing the need for additional research with regard to health hazards from industrial talc exposure, the National Institute for Occupational Safety and Health (NIOSH) undertook an industrywide program to study talc mining and milling in two geographic areas, New York and Vermont. This program includes detailed industrial hygiene studies to characterize the various agents to which workers have been exposed, cross-sectional medical surveys to evaluate respiratory impairment, and retrospective cohort studies to evaluate latent disease patterns among workers who have been exposed to talc in the work environment.

The present report restricts itself to that part of the industrywide study concerning an investigation of talcs containing fibrous amphibole minerals as mined and milled in the Gouverneur Talc District in upper New York. This talc mining district located in St. Lawrence County represents a complex association of amphiboles (anthophyllite, tremolite, etc.), talc, quartz, and serpentines (2, 4). Previous studies by Kleinfeld et al. (5, 6) of asbestiform talc miners and millers in this district have demonstrated significantly increased proportional mortality due to both malignant and nonmalignant respiratory diseases. Morbidity studies also have indicated increased symptoms and X-ray and lung function changes consistent with pneumoconiosis (7, 8, 9, 10, 11, 12). More

recently a talc mining company in this district maintained that these studies were not applicable to all talcs in the Gouverneur Talc District. The company stated that talcs extracted from its original mine in the Gouverneur Talc District do not contain asbestiform minerals and that the talcs have been so certified (13). One study, however, at the same operations concluded that asbestiform minerals were contained in the talcs (11). To address this contradiction, the present study restricts itself to that one mine and mill reported by the company to be producing nonasbestiform talc.

DESCRIPTION OF FACILITIES STUDIED

The company under study began talc mining and milling operations in the Gouverneur Talc District of upper New York in 1947. Talcs extracted from this mine are used for a variety of applications including ceramics, pottery, artware, electrical insulators, ceramic tile glaze and flux, paint fillers, in putties, and in spackling compounds.

MINING

In the study mine, underground hard rock mining methods are employed using jackleg drills to make holes for blasting the ore in open stopes. The mine consists of one main shaft 1,250 feet in depth with three main working levels. In 1975, ore was being mined from approximately 6 of the 26 active stopes. Mining follows a typical cycle including: (1) blasting, which is done with gelatin dynamite and ammonium nitrate; (2) dissipation of dusts and gases; (3) removal of ore with some secondary blasting; and (4) drilling of blasting holes for the next shift.

Ore (muck) from the stoping areas is loaded into 2-ton rail cars using either gravity drawpoint or scraper (slusher) loading. Ore from these cars is discharged into a central jaw crusher located at the 700-ft. level although some crushing is also done on the 1,110-ft. level. The crushed ore is loaded into a skip and carried to the mine headframe where a gyratory crusher reduces the ore to approximately 3/4-in. screen size. The ore is then transported by conveyor belt to one of the four wet ore storage bins in the mill. Approximately 40,000 cubic feet per minute (cfm) of mining ventilation is provided. The ore may be inherently moist, and wet drilling is employed. Water sprays are also used for dust suppression at the 700-ft. level crusher. According to company personnel, wet drilling has been practiced since the beginning of these operations.

MILLING

Mill operations include cone crushing first, followed by moisture removal in rotary dryers. The dry ore is further reduced in particle size using a gyratory disc crusher followed by vibratory screening and transportation to one of six dry ore silos. Finely ground products are made from these ores, using either Hardinge pebble mills in closed circuit with Raymond separators or impact crushers in closed circuit with fluid energy mills. The finely ground products are stored in one of several concrete silos and are withdrawn by air slides and pumped to the packaging and shipping areas. Talcs are either

sold in bulk or packaged in 50-lb. valve-type Kraft paper bags. Bag filling is done using pneumatic packing machines.

In the mill, most material transfer points are provided with local exhaust ventilation, and bucket elevators and conveyors are maintained under negative pressure. At the bagging machines, local exhaust ventilation is provided at the filling spout and downdraft ventilation at the bag hopper. For bulk car loading, the telescopic loading spout is provided with a local exhaust ventilation collar.

INDUSTRIAL HYGIENE STUDY

METHODS

In order to evaluate occupational exposure characteristics and levels among workers in this mine and mill and to compare them with those pf previous studies of New York talc operations, a detailed environmental study was undertaken. This study included determinations of time-weighted average (TWA) exposures to respirable dust, free silica, and asbestiform minerals in addition to detailed mineralogical assays of talcs produced at the mine and mill under study. Talc product samples were collected during the study (samples A-F), and additional product samples from the mine and mill being studied were submitted by the company (samples 1-7).

Analyses of collected bulk talc samples were performed by both NIOSH and independent research laboratories. These analyses included X-ray diffraction, optical petrographic microscopy, and electron microscopy. For X-ray diffraction studies, step scanning of diagnostic reflections for the asbestiform minerals and quartz was used (1). Electron diffraction and microchemical analyses of individual fibers were performed by electron microscopy (14, 15). Bulk talc samples were also analyzed for major oxide composition and trace metal contamination. These analyses were performed using spectrophotometry, atomic absorption, and flame photometry (1).

Personal air samples were collected from the breathing zone of miners and millers to determine TWA exposures to respirable dust, free silica, and mineral fibers. Personal samples for respirable dust and free silica were collected at a flow rate of 1.7 liters per minute (lpm) using 37-mm diameter polyvinyl chloride filters (preweighed) preceded by 10-mm nylon cyclone separators. Samples for fiber analysis were collected on open-faced 37-mm diameter Millipore Type AA filters (0.8-μm pore size) at a flow rate of 1.7 lpm. Respirable dust samples were collected for the full work shift periods while fiber samples were changed periodically during the work shift as needed to prevent overloading of filters.

Free silica concentrations were determined using X-ray diffraction as specified in the NIOSH Criteria Document (16). All fiber samples were analyzed using the NIOSH phase contrast counting technique (17). In addition, a representative number of the individual fiber samples was randomly chosen and the samples were analyzed by electron microscopy using selected area electron diffraction and energy dispersive X-ray analysis for

fiber identification. Electron microscopy was also used to determine airborne fiber concentrations and size (diameter and length) distributions (14). Samples for electron microscopic analysis were prepared using methods previous described (15).

In order to compare results of the present industrial hygiene study with historic data for the facility studied, midget impinger samples were also collected for selected jobs in a manner similar to past sampling techniques. Breathing zone impinger samples were collected in ethyl alcohol at a flow rate of 0.1 cubic feet per minute with sampling periods ranging from 15 to 30 minutes. These samples were counted at the end of each work shift using Dunn counting cells and bright field optical microscopy (100x). Two preparations were made for each sample and allowed to stand for 30 minutes prior to counting. Particle counts were made by two experienced counters, and new preparations were made and samples recounted, if counts differed by more than 10 percent.

RESULTS

Product Samples

Results of the X-ray diffraction and petrochemical microscopic analyses of bulk talc product samples collected during the study are shown in Table 1. Talc product samples were found to contain 14 to 48 percent mineral talc, 37 to 59 percent tremolite and 4.5 to 15 percent anthophyllite. All samples were found to contain 10-15 percent serpentines (lizardite and antigorite) and less than 2.6 percent free silica. Calcite and dolomite were also present in trace quantities. Trace metal analyses of talc product samples are shown in Table 2 and major components analyses are shown in Table 3. All trace metals except iron and manganese were essentially absent. Iron and manganese levels were also very low (<0.02 percent). As seen in Table 3, all talcs were found to have a high CaO content which correlates with the observed high tremolite content. Except for traces of calcite, other carbonates were absent or negligible in these talcs as demonstrated by low CO_2 values (18). The Fe and Mn analyses in Table 3 are consistent with the results shown in Table 2, and all major element analyses are in basic agreement with results obtained by Ross et al. (19) and by Dreessen (20) for talcs in the Gouverneur, New York area. Ross et al. (19) also suggested that an additional manganese-rich amphibole, tirodite, may be found in trace quantities in these deposits. While the major element analyses shown in Tables 1, 2, and 3 show 0.12 to 0.22 percent MnO, no manganese-rich amphiboles were detected by the electron microscopy analyses

using selected area electron diffraction and microchemical analysis. Typical electron micrographs of fibers observed in the bulk samples are shown in Figures 1 and 2. Examples of typical electron diffraction patterns and X-ray spectra for the tremolite and anthophyllite fibers observed in these products are also shown in these figures. These analyses have shown that most of the long, thin fibers in these talcs are low iron anthophyllite while tremolite fibers tend to be shorter and have smaller aspect ratios (length/width).

Air Samples

Tabular summaries of TWA exposures by job category for the mine and mill under study are given in Tables 4 and 5, respectively, and more detailed summary statistics concerning these data are given in Appendix I. As shown in Tables 4 and 5, free silica exposures were found to be very low. The highest TWA free silica exposure observed was 0.040-mg/m^3, which is below the 8-hour TWA exposure value of 0.05-mg/m^3 recommended by NIOSH for this material (16). Respirable dust exposures ranged from 0.25 to 2.96-mg/m^3. No respirable dust standard has been determined for the mineral talc or talc containing fibrous tremolite or anthophyllite; however, these concentrations are well below the OSHA limits for nuisance dusts (21).

TWA breathing zone impinger concentrations ranged from 0.5 to 15.8 million particles per cubic foot of air (mppcf) with highest concentrations being observed in the mine. The present OSHA and MSHA standard for "talc" containing less than 1 percent free silica and no asbestos fibers is 20 mppcf (21). Only one of the 32 impinger samples exceeded 20 mppcf. However, since this talc contains asbestiform material this standard is not relevant to these exposures.

TWA exposures to asbestos fibers greater than 5-μm in length exceeded 5 fibers per cc for three of six job categories sampled in the mine and for 6 of 18 job categories sampled in the mill. In addition, 17 of the 24 job categories sampled had TWA exposures exceeding the current OSHA standard of 2.0 fibers less than 5-μm in length/cc. Exposures in excess of the MSHA and OSHA allowable ceiling value of 10 fibers less than 5-μm in length/cc were observed in 9 of 24 job categories sampled.

A summary of TWA airborne fiber concentrations as determined by analytical electron microscopy is given in Table 6. In the mine, concentrations of positively identified fibrous amphiboles (all lengths) ranged from 9.5 to 17.5 fibers/cc whereas concentrations in the mill were somewhat higher ranging from 9.9

to 70.6 fibers/cc. These concentrations represent minimum estimates of true amphibole fiber exposures since many true amphibole fibers may not give identifiable electron diffraction patterns. The concentrations found using electron microscopy are far in excess of those obtained by the optical microscopy as fibers less than 5-μm in length are included in the electron microscopy results, but not in those from optical microscopy.

A summary of airborne fiber types as determined by electron microscopy is shown in Table 7. In the mine, 38 percent of all airborne fibers were anthophyllite, 19 percent were tremolite, and 39 percent were unidentified. In the mill, 45 percent of all fibers were anthophyllite, 12 percent were tremolite, and 38 percent were unidentified. Three percent of the fibers in the mine and 2 percent in the mill gave chrysotile electron diffraction patterns. Approximately 65 percent of the airborne fibers longer than 5-μm in length were identified as anthophyllite while only 7 percent were tremolite. The presence of chrysotile in the air samples is consistent with the results of the NIOSH bulk sample analyses where trace quantities of chrysotile were noted in some samples. All of the chrysotile fibers observed in the air samples were less than 1-μm in length. Nearly all of the serpentine minerals identified in the bulk samples are lizardite.

Results of airborne fiber size determinations (diameter and length) for tremolite and anthophyllite fibers are shown in Tables 8 and 9 with appropriate summary statistics. As expected, tremolite fibers tended to be larger in diameter and shorter in length than anthophyllite fibers. The size distributions for these minerals were similar for the mine and mill. Median fiber diameters of 0.19 and 0.13-μm were observed for tremolite and anthophyllite, respectively. In the mine, median fiber lengths of 1.6-μm for tremolite and 1.5-μm for anthophyllite were observed. Similar lengths were seen in the mill. In the mine and mill, only 3 percent of the tremolite fibers were longer than 5-μm whereas 8-10 percent of the anthophyllite fibers were longer than this length. Median aspect ratios (length to width) of 9.5 and 7.5 were observed for anthophyllite and tremolite, respectively, as shown in Table 10. Only 30 percent of the tremolite fibers had aspect ratios greater than 10 to 1 whereas 48 percent of the anthophyllite fibers had aspect ratios greater than this value. These fiber size characteristics are similar to those observed in other industrial operations processing asbestos fibers (22).

Typical electron photomicrographs of airborne particulates from the mine and mill are shown in Figures 3, 4, and 5. The

asbestiform nature of these fibers may be further demonstrated by observations of their fibril structures.

COMPARISON OF PAST AND PRESENT EXPOSURES

The present studies demonstrate elevated exposures to asbestiform minerals in nearly all mine and mill process operations. Comparisons between present dust (mppcf) and fiber (fibers > 5-μm in length/cc) exposures and historic exposure measurements are shown in Tables 11 and 12, respectively. These data are gathered from a number of sources (11, 23-33).

Trends in dust concentrations as a function of calendar time are difficult to interpret for several reasons. Of primary importance is the relative paucity of data on some operations prior to 1970. Secondly, very few samples were taken in any given year, therefore the representative of these samples is unknown.

To illustrate trends in dust concentrations, average yearly values for mine and mill operations were calculated and are shown in Figures 6 and 7, respectively. Figure 6 shows no consistent trends in dust concentrations when all mine operations are considered. On the other hand, the mine exposures for such operations as drilling, dragline loading, tramming, and mucking show relatively consistent exposure levels over time with only slight deviations. This might be expected since wet drilling has been a routine practice. In addition, ores being mined are relatively wet. Primary crushing and hoist loading operations show a slightly decreasing trend. Controls such as water sprays for dust suppresion at the primary crusher are the most probable explanation for this trend.

A greater trend of decreasing dust concentrations in mill operations is demonstrated in Figure 7 for all mill operations combined. Figure 7 also shows a more pronounced decreasing trend in exposure when the uncontrolled operation of loading bagged talc into box cars is excluded form the calculated yearly averages. Engineering controls for talc milling operations have improved with time.

As shown in Table 12, fiber exposure measurements have only been made since 1970. Results of the 1975 NIOSH survey tend to show a recent reduction in fiber exposure when contrasted with earlier data for most operations.

Radon daughter measurements have been made in the mine under study by the Mining Enforcement and Safety Administration

(MESA). Measurements taken in 1973 and 1976 showed only nil to trace levels (34, 35).

COMPARISON OF EXPOSURE CHARACTERISTICS WITH OTHER TALC MINES AND MILLS IN THE GOUVERNEUR, N.Y. AREA

Throughout the years, a number of different companies have operated talc mining and milling operations in the Gouverneur Talc District. In addition, past health effects studies of workers in these mills have generally considered exposure characteristics between the various operations in this area to be substantially the same. The company under study, however, maintains that ores from various mines in the area are not the same, with some containing asbestos while others do not. The company further maintains that ores from another nearby operation do contain anthophyllite asbestos while ores from the mine and mill which is the subject of the present study do not contain asbestos fibers.

In order to compare airborne exposure characteristics between these two operations, 10 airborne dust samples collected by MESA in the mine and mill acknowledged as containing asbestos were obtained. These samples were analyzed for airborne fiber characteristics using analytical electron microscopy (analytical methods previously described). Results of these studies and comparisons with data from the mine and mill studied by NIOSH and maintained, to be asbestos free by the company, are shown in Table 13.

The data shown in Table 13 demonstrate that exposure characteristics between the two operations are substantially the same. In fact, the airborne dust samples from the mine and mill studied by NIOSH and maintained by the company to be asbestos free were found to contain a higher proportion of positively identified asbestiform amphiboles largely due to a higher tremolite content. All other fiber characteristics, such a median length, diameter, aspect ratio, and proportion < 5-μm in length, were not statistically different at the 0.05 level (36).

REVIEW OF HEALTH EFFECTS FROM EXPOSURE TO TALCS CONTAINING ASBESTIFORM AND ASSOCIATED MINERALS

What are the known health effects of talc? Inhalation by children of large doses of talc have resulted in an inflammatory pulmonary response leading to death in some cases (37, 38). The acute symptoms are initial slight respiratory distress increasing after four to six hours and accompanied by cough, tachycardia, and cyanosis. Autopsy revealed bronchitis and acute bronchiolitis with pulmonary edema, focal atelectasis, and emphysema. Alivisator reported the rapid development of talcosis in eight workers between 16 and 60 months after first exposure in an industrial setting (39). The rapid development and progression was attributed to the high concentration of talc particles less than 50-μm in size as well as the high silicate content. Most of these anecdotal reports have included little characterization of the talcs involved.

RESPIRATORY MORBIDITY STUDIES

Three patterns of infiltration on chest X-ray among those exposed to talc have been described: (1) nodular -- discrete opacities 3-5 mm, similar to silicosis and favoring the mid-lung fields; (2) diffuse -- interstitial fibrosis similar to asbestosis and favoring the lower lung zone; (3) mixed -- both types present (40). This varied type of X-ray pattern has been attributed to the heterogenicity of talc (40). Although changes suggestive of silicosis were observed in some instances, in general X-ray changes were similar to those seen in asbestosis (9, 10, 41).

More than four decades have elapsed since the first epidemiological data were published demonstrating adverse health effects of tremolite talc exposure. In 1933, Dreessen (20) published the results of a chest X-ray study of 57 workers engaged in the mining and milling of talcs containing up to 45 percent tremolite and little free silica. This study showed that all workers with greater than 10 years exposure had increased lung markings ranging from increased fibrosis to what was termed "second stage" pneumoconiosis. Among these 17 workers, no cases of active tuberculosis were observed. Dreessen stated that the observed pneumoconiosis had not led to disability.

The respiratory effects of exposure to talc containing 10 percent "bladed" tremolite in two Georgia talc mines and mills were reported by Dreessen and Dalla Valle in 1935 (42). A total

of 66 workers were given physical examinations and chest X-rays of which 19 were exposed for more than 10 years with only 2 having 20 or more years of exposure. Twenty-two of these workers demonstrated pneumoconiosis with varying severity. Approximately half of the mill workers exposed to an average dust concentration of 300 mppcf were diagnosed as having pneumoconiosis with eight having frank symptoms such as dyspnea, cough, chest pain, rales, and finger clubbing. Examination of nine former talc workers who had been separated from exposure more than 3 years demonstrated pneumoconiosis in all cases with four cases in advanced stages causing these authors to conclude that the lung changes were permanent.

Many of the health effects studies on individuals exposed to talc have been done in New York in the same areas as this study (Table 14). The exposures were generally quite high. These studies indicate that exposed talc workers report increased subjective complaints of dyspnea and cough. Physical findings include diminished breath sounds, rales, rhonchi, wheezing, crepitations, and clubbing. Pulmonary function measures suggest a restrictive disease with reduced transfer capacity (DI_{CO}).

In addition to these findings, radiographic changes in the chest have also been noted, although the findings have not been reported in ILO/UC nomenclature. These include fibrosis and pneumoconiosis, primarily reported as pulmonary infiltrates of grade 0, 1, 2, and 3. The grading of pulmonary infiltrates involves a reticulated appearance in the lower lung fields (grade 1), reticulonodular infiltration involving approximately 50 percent of the total lung area (grade 2), and a more diffuse reticulonodular infiltration involving more than 50 percent of the total lung (grade 3) (10).

Case studies of New York tremolite talc workers were first reported by Porro et al. (43). Fifteen pneumoconiosis deaths in talc workers were studied in addition to five autopsy studies. Thirteen of these deaths were considered to be directly attributable to the pneumoconiosis thus confirming the disabling character of this exposure. These authors concluded that the disabling tissue changes were due to tremolite talc exposure. Some classifications were noted.

Siegal et al. (44, 45) reported a study of roentgenological findings among New York talc workers in addition to an assessment of their exposures. These talcs were described as containing fibrous tremolite and anthophyllite and less than 1 percent free SiO_2. A total of 221 talc workers in three mines and five mills were given chest X-ray examinations. Of the 221

men examined, 32 showed marked fibrosis. Those workers with 10 or more years employment demonstrated an incidence of fibrosis of 29.9 percent whereas those employed for more than 30 years had a fibrosis incidence of 74 percent. This fibrosis was described as disabling and often accompanied by dyspnea, cough, and fatigue. "Talc plaques" were identified in 6.3 percent of the workers examined. These authors described the fibrosis observed as resembling that seen among asbestos workers.

The 32 cases of pneumoconiosis identified by Siegal et al. (44, 45) were followed prospectively by Kleinfeld et al. (46). In the 14 year period after the Siegal study, 19 of the 32 workers died with the ages of death ranging from 48 to 84 years. Four of these 19 deaths were believed to be directly attributable to talc pneumoconiosis. One death due to pleural mesothelioma was reported. Medical examinations of the 13 living workers were performed including a physical examination, chest X-ray, EMG, and peripheral blood studies (Hgb, RBC, WBC, diffferential count). Dyspnea of such severity as to limit ordinary physical activity was found in all workers. Moderate to severe progression of lung X-ray findings were seen in 10 of these workers and "talc plaques" were seen in all but one worker. Six out of 11 demonstrated an abnormal electrocardiogram. Peripheral blood findings were not considered to be of significance. These authors also reported the presence of "asbestos bodies" histologically. Similar findings were reported in a latter study of six pneumoconiosis cases with autopsy studies (41).

A comparative clinical and environmental study of workers exposed to fibrous and nonfibrous talcs in New York was reported by Messite et al. (7). Three talc operations in St. Lawrence County (fibrous ore formations) and one operation in Lewis County (nonfibrous ore formations) were selected for study and a total of 229 workers were given physical examinations and chest X-rays. Among miners, the incidence of pulmonary fibrosis was low for both the St. Lawrence and Lewis County cohorts; however, the mean duration of exposure was only 12.7 and 10.3 years, respectively. Among millers, the incidence of fibrosis was 12.2 percent and 4.3 percent, respectively, for the St. Lawrence and Lewis cohorts. Exposure levels in the plant were described as being similar with all talcs having a low free silica content. These authors concluded that both types of talc were capable of producing pulmonary fibrosis although the tremolite (fibrosis) variety was more pathogenic. In addition, these investigators stated that no cases of fibrosis were found in millers of either talc variety whose average exposure was less than 20 mppcf or whose duration of exposure was less than 10 years.

In a follow-up study, Kleinfeld et al. (8) made additional comparisons, including lung function, between the St. Lawrence and Lewis County, New York, cohorts described above. Thirty workers exposed to fibrous talcs and 13 exposed to nonfibrous talcs were given chest X-ray and pulmonary function tests. Dyspnea was present in 16 of 30 workers in the fibrous talc exposed group and in 6 of 13 in the nonfibrous talc exposed group. Abnormal auscultatory findings (rales, rhonchi, wheezing) were found in 8 of the 30 workers and 6 of the 13 workers exposed to fibrous and nonfibrous talc, respectively. The incidence of pulmonary infiltration as seen in chest films was 13 of 30 for the fibrous group and 3 of 13 for the nonfibrous group. Both groups showed pulmonary function changes with 4 of 13 workers in the group exposed to nonfibrous talc and 14 of 30 workers in the group exposed to fibrous talc showing significantly reduced vital capacity. Exposures to both groups were reported to be considerably in excess of 20 mppcf.

Kleinfeld et al. (12) studied the lung function of 16 tremolite talc workers who ranged from 39 to 69 years of age (mean age 54.8 years). All had been exposed to talc dust in milling operations for 10 or more years and had no previous occupational dust exposures. Clinical examinations of the 16 workers showed 14 had dyspnea on exertion; 10 rales or wheezing; and 6 clubbing of the fingers. Increased pulmonary infiltration was noted in 5 of the 16 workers. The lung function studies showed 7 of the 16 to have reduced vital capacities and one worker was found to have a lung function consistent with restrictive lung disease. The mean duration of exposure for the 16 workers was 20.4 years and the mean weighted average exposure was reported to be 68.9 mppcf. Thirteen of the 16 workers studied gave a positive smoking history (30 cigarettes per day for a minimum of 5 years).

In a subsequent study, Kleinfeld (10) performed similar studies as those described above among a group of 43 tremolite talc workers and 41 unexposed controls of similar age and smoking history. In the talc cohort, 29 had dyspnea versus only 2 in the control population. Eleven talc workers gave a history of chronic cough and 8 talc workers showed finger clubbing whereas no clubbing or cough was noted among controls. Sixteen of 43 talc workers had positive X-ray findings of pulmonary infiltration versus none in controls, and reduced vital capacity was also found in 13 talc workers and one control. These talc workers were reported to have a mean exposure duration of 19 years and weighted average exposure of 62.3 mppcf.

A study of chest X-ray findings and clinical symptoms among miners and millers at the talc mine and mill under study was

reported by Kleinfeld et al. (11). Thirty-nine workers with a mean exposure of 16.2 years (range 11-22 years) were examined in addition to 41 controls who lived in the same geographic area and who were of the same sex and mean age but had no occupational dust exposure. Dyspnea was present in 23.1 percent of the talc workers versus 7.3 percent of the controls, a finding similar to that seen in anthophyllite asbestos workers (47). One worker studied was said to have radiologic findings compatible with pneumoconiosis, whereas no cases were found among controls. The authors suggested that talc containing tremolite and anthophyllite may be less fibrogenic than chrysotile and amosite asbestos at similar exposure levels and exposure duration; however, these authors did not preclude the possible existence of pneumoconiosis among these workers since no lung function studies were conducted.

The importance of sublight microscopic asbestos fibers in asbestosis has recently been reported (48, 49, 50) and brings into question the concept that only fibers greater than 5 microns in length are pathogenic in talcosis (51). In a patient with talc pneumoconiosis, Miller et al., (48) were unable to detect talc by histological techniques using light microscopy. The presence of talc was established by X-ray diffraction and electron microscopy. Most particles were less than 0.5 micron in length, and therefore, below the limit of resolution of the light microscope. The question of the site of early changes in the human lung after exposure to talc has not been very well investigated. Seeler et al. (52), claimed that the earliest change involving the lung parenchyma in two cases of talc pneumoconiosis was a fibrous thickening of the alveolar walls. Kleinfeld et al. (41), noted deposition of ferruginous bodies in the respiratory bronchioles.

The earlier studies of talc workers in the New York area variably reported the presence of pleural plaques and pleural densities (41, 44, 45, 46). The pleura of men exposed to talc are often found on autopsy to have dense fibrosis thickening (41, 48, 52, 53). Pericardial calcification has also been observed (54). Pleural thickening is associated with symptoms and a decreased pulmonary function; pleural plaques are not (55). Pleural thickening may also have a poorer prognosis (56). Pleural thickening and calcifications are a very common radiographic finding in asbestosis and individuals exposed to asbestos, and may be more common than fibrosis (56, 57, 58, 59, 60, 61). The prevalence of pleural changes is higher where there is exposure to anthophyllite (55, 62). Not all pleural changes, however, are necessarily related to asbestos exposure (63).

MORTALITY STUDIES

Although a number of the studies described above have demonstrated the presence of pneumoconiosis among tremolite talc miners in New York, these study designs were insensitive to detection of carcinogenic risks. However, two retrospective proportional mortality studies have demonstrated an increased risk of mortality due to cancer of the lung and pleura among these workers (5, 6). An initial study by Kleinfeld et al. (6) included 220 talc miners and millers employed in 1940 who had 15 or more years exposure between 1940 and 1965. Among this cohort there were 91 deaths of which 10 (11 percent) were due to malignancies of the lung or pleura, whereas only 2.9 (3.2 percent) were expected. In addition, 28 deaths were due to pneumoconiosis or its complications. One of the respiratory cancers was a fibrosarcoma of the pleura.

In a subsequent follow-up study, Kleinfeld et al. (5) extended the period of observation of the previously studied cohort from 1965 to 1969. This updated cohort consisted of 260 workers among which there were 108 deaths. Thirteen of these deaths (12 percent) were due to respiratory cancer, whereas only 4 (3.7 percent) were expected. Twenty-nine deaths were due to pneumoconiosis or its complications. These authors analyzed mortality patterns by 5 year intervals between 1940 and 1969 and concluded that the respiratory cancer risk approached expected values after the period 1960-1964. The validity of this conclusion must be questioned since an analysis of mortality in relation to cancer latency was not undertaken. Indeed, during the additional 9 years of observation, 17 deaths were observed of which 2 (12 percent) were respiratory cancers, observations similar to previous findings. In addition, the limitations of proportional mortality studies in the presence of an elevated pneumoconiosis risk are now well known.

An excess cancer risk has been demonstrated among workers exposed to anthophyllite asbestos (47, 64, 65). Nurminen (65) reported on the mortality experience of anthophyllite asbestos workers in Finland. This study included 1,030 workers who had been employed for 3 months or more from 1936 to 1966 and followed until 1968. Expected cause specific deaths were calculated using Finland national rates for 1951-1964. There were 224 deaths in this cohort whereas 204 were expected. The mean age at death for the cohort was 53.4 years. Twenty-five deaths (12 percent) had asbestosis as an underlying cause, and there was also a highly significant excess risk of respiratory cancer (13 obs. versus 6 exp.; $p<0.01$). No mesotheliomas were

detected. The mean latency between first exposure and death due to asbestosis was 19 years.

One of the most comprehensive studies of mortality and morbidity among anthophyllite asbestos workers was reported by Meurman et al. (47) and Kaviluto et al. (64). A cohort of 1,092 workers who had worked at least 3 months between January 1936 and June 1967 was obtained from two mining operations; one of which produced mainly tremolite talc. For calculation of expected age and cause specific deaths, proportional rates for Finland were used for 1958 which was the median year of death for these workers. In addition, a control group matched for date of birth and sex was chosen from a local population registry. Of the 1,092 employees, 248 deaths were observed. Thirteen deaths due to asbestosis were observed for the cohort and none in the controls. Twenty-one lung cancers were observed in the worker cohort versus 13 in the control group. The most significant cancer risk was observed in those with 10 or more years of exposure. These authors adjusted lung cancer rates for smoking habits and concluded that a nonsmoking asbestos worker has a relative risk of 1.4 whereas the smoking asbestos worker had a relative risk of 17.0. No cases of mesothelioma were reported.

All of the above studies of workers exposed to talc containing fibrous tremolite, fibrous anthophyllite or anthophyllite asbestos have demonstrated an excess risk of both pneumoconiosis and respiratory cancer. Little evidence of an excessive risk of mesothelioma among such exposed workers has yet been demonstrated; however, an excessive incidence of pleural changes including pleural thickening and calcifications has been observed in chest films.

CROSS-SECTIONAL MORBIDITY STUDY

A cross-sectional morbidity study was initiated to examine all presently employed workers in this talc mine and mill. The study was designed to answer the following questions regarding chronic effects of exposure:

1) Is there an increased prevalence of abnormal health effects (e.g., symptoms, decreased pulmonary function) in workers exposed to talc when compared to other industrial populations?

2) If there are detrimental effects of exposure, what are the dose-response relations?

DESCRIPTION OF WORK FORCE

The present work force consists of approximately 156 male millers and miners, 35 of whom had worked at other talc mines. One hundred and twenty-one (78 percent) participated in the study. The average for years of talc exposure is 10.2 years for the study population, and 10.5 years for the nonparticipants. The participation rate among the different work areas is similar.

MATERIALS AND METHODS

A modified Medical Research Council respiratory questionnaire containing questions on total work and smoking history was administered by trained interviewers. Standard PA and lateral chest X-rays were taken and read by three readers using ILO/UC scheme. Flow volume curves from a minimum of five forced respiratory maneuvers were obtained and recorded on magnetic tape using an Ohio 800 rolling seal spirometer. The maximum values from the curves were used for analysis.

Lung function, the prevalence of symptoms and radiographic findings in this population were compared with those from 9,347 coal miners from the second round of the National Coal Study, and 1,095 potash miners examined by NIOSH in the Study of the Effects of Diesel Exhaust in Non-Coal Miners. Individuals in each control population were grouped into similar age (10 year intervals), height (10 cm intervals), smoking (nonsmoker, ex-smoker, and smoker), and years in mining (<15 years, ≤ 15 years) categories. The expected prevalence of symptoms and radiographic findings in coal and potash workers were calculated by using the rates in each category of the comparison populations and multiplying them by the number of individuals in the same categories of the talc population. Predictive

equations reflecting the effects of age and height were calculated for each smoking/years worked category of coal and potash miners. Each talc worker's lung function was then compared to predicted values obtained from the appropriate category in the comparison population. All comparison of talc worker's lung function with expected lung function was summated and multiplied by 100 to give the mean percent predicted lung function. For FEV_1 percent, the difference between observed and expected +100 was used.

Dose was calculated in three ways: (1) Years of exposure is simply the number of years worked at the plant under study; (2) Cumulative exposure was calculated by multiplying (a) present exposure in each job as determined by personal sampling (fibers/cc, mg/m^3) times (b) the time spent in that job (years), and then by summing all the exposure scores. The results for each individual are expressed as fiber-years/cc for cumulative fiber exposure and $mg\text{-}years/m^3$ for respirable particulate exposures. As past environmental exposures are not well defined, and in some jobs exposures were greater in the past than at present (especially in the mill) these estimates of cumulative exposure are lower than actual exposures; (3) The relation of average time spent in each job was examined in workers with and without pleural thickening over the total work history omitting the most recent 10 years.

RESULTS

The age-smoking distribution of the 93 talc workers whose talc exposure was only at the mine and mill being studied is shown in Table 15. Almost half are cigarette smokers with slightly more ex-smokers than nonsmokers. Almost 2/3 of the nonsmokers are less than 30, and over 3/4 of the ex-smokers are 40 years of age or more. Smokers are more evenly distributed in all age groups, although the percentage of smokers is highest in the 30-39 year age group. The distribution is very similar for all 121 workers (Table 15A).

Table 16 shows the distribution of years worked in talc, and cumulative particulate and fiber exposures by age. Except for the group over 60 years old where there are only two individuals, there is a consistent and approximately equal increase in all three exposure parameters with increasing age. A similar relationship of exposure with age is observed for all 121 workers (Table 16).

Tables 17 and 17A summarize the distribution of symptoms and radiographic findings by smoking habits. Smokers have a higher

prevalence of cough, phlegm, hemoptysis and shortness of breath, with symptoms markedly lower among nonsmokers. The differences are also statistically significant for cough and phlegm. Cigarette smoking shows no apparent association with pleural thickening. There are two cases of calcification and four of irregular opacities, but the numbers are too small to analyze for dose-response relations.

Tables 18 and 18A summarize the association of age with symptoms and radiographic findings. Age (and therefore, long-term exposure) shows no discernible association with symptoms. The higher prevalence of cough and phlegm in the 30-39 year age group is probably a reflection of the high proportion of smokers in the category. Likewise, the slightly higher prevalence of dyspnea in the 30-39 and 50+ year age group is also probably due to the relative proportion of smokers and ex-smokers in those ages. Pleural thickening, on the other hand, is not found in the age groups less than 40 (mean of 14 years exposure), and is highest in the 50-59 (mean of 20 years exposure) and greater than 60 year (mean of 28 years exposure) age groups.

In Tables 19 and 19A the prevalence of symptoms and radiographic findings are compared with coal and potash workers controlling for age, height, smoking habits, and years worked. Among the talc workers employed only at the mine and mill under study for less than 15 years, the reported symptom prevalences of cough and phlegm are not significantly higher than those of coal and potash workers.

In the group of workers with more than 15 years experience, there is no statistically significant difference in the prevalence of (a) hemoptysis in talc workers compared to coal and potash workers; (b) cough in talc workers compared to coal workers; and (c) phlegm in talc workers compared to potash workers.

Coal miners with more than 15 years experience have higher prevalence of phlegm and dyspnea than do talc workers, while cough and dyspnea is higher in these talc workers than in the potash workers. These differences are not statistically different.

The prevalence of radiographic abnormalities is less than two percent in all groups with less than 15 years worked. The rates are higher in the greater than 15 year groups, but there are no significant differences in the prevalence of regular opacities between the talc and comparison groups. In the talc workers with no previous talc exposure, pleural calcification is 0

percent in those with less than 15 years worked and 3.4 percent in those with more than 15 years worked (one case), while pleural thickening is 1.6 percent and 31.0 percent respectively. This compares to a rate for pleural thickening of 0.3 percent to 1.6 percent in coal miners and 0.5 percent to 4.4 percent in potash miners. There is no pleural calcification in the potash population, while in coal miners the prevalence is 0 percent for those working less than 15 years and 0.1 percent for those working more than 15 years. In those with more than 15 years experience, the prevalence of irregular opacities is 3.4 percent, 5.3 percent and 0.7 percent in talc, coal, and potash workers respectively (Table 19).

Reported symptom rates increase slightly when all 121 talc workers are considered (Table 19A). In the 82 talc workers with less than 15 years worked, cough and phlegm are higher than potash and coal workers. There is little difference in the prevalence of dyspnea. In the 39 talc workers with more than 15 years experience, reported cough is still higher than in potash workers, but is essentially the same as in coal miners. Phlegm is about the same in talc and potash workers, however, the 26 percent phlegm reported by these talc workers is significantly less than the 46 percent prevalence among coal workers. Dyspnea in these talc workers is 23 percent which is significantly less than the 39 percent in coal workers and greater than the 13 percent in potash workers. Among these talc workers, there is no unusual prevalence of hemoptysis in either category of years worked. There are no differences in the prevalence of radiographic abnormalities in the group who have worked less than 15 years. In those with more than 15 years experience, pleural thickening and pleural calcification are higher in the talc workers than in coal and potash workers; the increased prevalence of pleural thickening is highly statistically significant. Irregular opacities among talc workers are higher than those in coal and potash workers, but the increase is statistically significant only when compared with that in potash workers. The prevalence of rounded opacities is 3 and 2 percent in talc and potash workers respectively, but 15 percent in coal workers.

Table 20 summarizes the relationship between cumulative exposure and pulmonary function among both groups of talc workers employed only at the mine and mill under study. Using predicted values based on coal and potash workers, mean percent-of-predicted FEV_1 and FVC ranged from 92-95 percent. Predicted FEV percent is near 100, and peak flow is above predicted compared to coal workers, but this is not true when

compared to potash workers. Mean flow rates are significantly reduced compared to both coal and potash workers.

Exposure among these talc workers to particulates and to fibers shows a significant association with reduced FEV_1 and FVC. For example, a talc worker in a job with 2 mg/m^3 exposure to respirable particulate will, on the average, experience about a 1 - 1.4 percentage point reduction/year in observed to predicted ratio for FEV_1 and FVC. For an average exposure of 5 fibers/cc, the reduction is about 0.5 - 0.7 percentage points per year. FEV percent and flow rates are not significantly related to exposure, although the percentage point reduction is large for flows at lower lung volumes. The reductions are larger when the comparison group is potash miners. Similar reductions occur if age or years of employment are substituted for fiber or particulate exposure because of their high correlations. These talc workers empirically "age" faster (experience a faster reduction in the FEV_1 and FVC) compared to coal and potash miners.

Table 21 and 21A compare age, smoking habits, and exposure history of talc workers with and without pleural thickening. As previously noted, smoking is not related to pleural thickening. For example, the 50-59 year group with pleural thickening has the lowest mean pack years, and the 40-49 year old group with pleural thickening has fewer average pack years than the 40-49 year old group without pleural thickening. Particulate exposure is slightly lower in the groups with pleural thickening, the average fiber exposure on a yearly basis is the same in the groups with and without pleural thickening. In the 50-59 year age group, those with pleural thickening started working at an earlier age than those without pleural thickening. In the 40-60 year age group, those with pleural thickening have reduced lung function.

Past environmental exposures in each job are not necessarily reflected by present exposure estimates. Exposure information is not available for all jobs and past environmental data were largely collected using impingers rather than filters. For these reasons time worked in different jobs by workers with and without pleural thickening were compared. These data on the 93 talc workers employed only at the mine and mill in this study are summarized in Table 22. There are 9 individuals with pleural thickening and 20 without pleural thickening among those with greater than 15 years employment. Among those with pleural thickening, about 71 percent of their years worked were spent in seven particular jobs, compared to about 17 percent of these same jobs for those without pleural thickening.

To assess the significance of pleural thickening on the health of the individual, symptoms and pulmonary function of all those with pleural thickening in this study are summarized in Table 23.

Controlling for years employment, those with pleural thickening are slightly older than those without pleural thickening. Those with Grade 2 pleural thickening have significantly elevated rates of cough and phlegm, but those with Grade 1 pleural thickening have rates lower than the comparable age group without pleural thickening. The prevalence of hemoptysis and dyspnea increases with increasing grade of pleural thickening, but the increases are not large. Mean ratios of observed to predicted FEV_1 and FVC in Grade 1 pleural thickening is about 10 percentage points below the group without pleural thickening; there is about a 4 percentage point difference between Grade 1 and Grade 2 pleural thickening. Mean FEV_1 percent is reduced only in Grade 2 pleural thickening. Predicted peak flow and FEF_{25} are not related to pleural thickening. Predicted FEF_{50} and FEF_{75} are reduced by about the same proportion as FEV_1 and FVC for those with Grade 1 pleural thickening compared to those with Grade 2.

DISCUSSION

Any cross-sectional epidemiologic study of chronic effects is beset by the problem of selective survival. This study population consists only of workers presently employed. Nonrespondents present a similar problem. For example, if all 35 of the workers who did not participate had had no cough or phlegm, and had participated, the prevalence of cough would have been reduced from 32 percent to 24 percent. Similarly, if all 35 had reported cough and phlegm, the rate would have increased from 32 percent to 49 percent.

Several methodological issues are important in interpreting the data. Even if there had been 100 percent participation instead of 78 percent, the size of the population would still be relatively small to disentangle the effects of age, years worked, and particulate and fiber exposure. In order to evaluate the significance of the health findings, and to adjust for confounding variables of age, height, and smoking habits in estimating dose-response relations, comparison groups of coal miners and potash miners were selected. Although coal mining is a known health hazard, and potash mines using equipment may also present a hazard, using these mine workers as comparison populations can be justified in several ways.

1) The measurement of lung function is not a completely standardized procedure with respect to equipment, training and proficiency of technicians, number of trials, and calculation of the lung measurement. These potential measurement errors are reduced in this study as these procedures were virtually the same in the control and study populations. Comparison with previously published predictive equations (e.g., Kory, Morris) may be misleading. For example, the NIOSH measurement of coal worker lung function tends to be higher than Kory's measurement of healthy, nonexposed populations, and is at least equivalent to Morris's measurements of nonsmoking exposed populations -- two commonly used prediction equations. In addition, prediction equations for different smoking categories are either nonexistent or based on small numbers, thereby making smoking adjustments impossible or of questionable validity. Since one of our primary interests is the effects of exposure to talc on pulmonary function, it is necessary to adjust for age and smoking habits. This is because pulmonary function generally decreases more rapidly in smokers than in ex-smokers and nonsmokers. Comparing smokers with nonsmokers may produce an apparent association of exposure with age, which in fact may be a smoking/age interaction (66). By comparing observed pulmonary function of smokers (ex-smokers, nonsmokers), the analysis of exposure effects is not confounded by the effects of smoking.

2) Talc, coal and potash workers are from mining populations and are likely to be similar with respect to many potentially confounding variables (e.g., physique, socio-economic characteristics, education) that could affect the conclusions, but are not related to the effect of work exposure. Using these mining comparison groups is therefore preferable to comparisons with salaried workers in the same company or even local nonmining populations, for in the comparisons with salaried or other workers there are problems of major discrepancies in physique, pay, education, nutrition and other factors that by themselves could result in differences in health status.

3) Comparing effects of talc exposure with effects from exposure to other substances will not conclusively indicate the nature of the effects of the talc exposure but it will provide relative comparisons; for example, if the health of talc workers is worse than coal miners the differences indicate the toxicity of talc as compared to coal and pinpoint specific health hazards associated with talc. Conversely, effects of talc less toxic than coal do not

necessarily mean there is no risk associated with talc exposure, but only that talc workers are "better off" (e.g., have fewer symptoms, fewer radiographic abnormalities, etc.) than coal workers. If talc workers are healthier than coal miners, they may still be less healthy than if they were not exposed to talc at all. Although less studied than coal, a mortality study of potash miners suggest that exposure to potash does not increase respiratory disease (67). Thus, the medical findings in these talc workers are compared with those in two mining comparison groups -- one that is thought to have little effects on the respiratory system, and one that is known to have a detrimental effect on the respiratory system.

The reported respiratory symptoms in this study group seem high for any healthy population. Most of those with symptoms are either smokers or ex-smokers, and many populations in the dusty trades also report similarily high symptom rates. Specifically, the prevalence of symptoms (except for dyspnea) when contrasted with coal workers is higher in talc workers if length of time worked is less than 15 years, but lower if years worked is greater than 15 years. When compared to potash workers, however, talc workers have higher symptom rates in both groups (except for phlegm and hemoptysis in the greater than 15 years group).

Table 24 compares the prevalence of respiratory symptoms from the talc workers in this study with chrysotile asbestos workers in Canada. Except for the nonsmoking category where asbestos workers report a higher prevalence of symptoms, the results are remarkably similar. When compared to synthetic textile workers, both the asbestos and talc workers generally have a considerably higher prevalence of phlegm and shortness of breath. Anthophyllite asbestos workers cannot be compared directly with talc workers in this study but are included in the table for completeness.

The greatest difference between the coal and potash miners and the talc workers is the highly significant increased prevalence of pleural thickening in the talc workers with greater than 15 years of exposure. In this group, nearly one out of every three talc worker has pleural thickening. Since smoking is not associated with radiographic changes and the same criteria are used, it is possible to compare the prevalence of irregular small opacities, pleural thickening and pleural calcification in chrysotile asbestos workers and the talc workers (Table 25). Grade 1 pneumoconiosis and pleural calcification show no striking dissimilarity between the asbestos and talc workers.

Pleural thickening, on the other hand, is four times higher in the talc workers than in the asbestos workers.

Pleural thickening is a common finding in workers exposed to asbestos. It should be regarded as a significant indicator of exposure and may occur in the presence or absence of fibrosis (57, 58) (Table 26). Pleural calcification occurs later, as it probably develops from the uncalcified pleural plaque (57, 60). In insulation workers it rarely occurred in less than 20 years from onset of exposure (68). Calcification, particularly if bilateral, is very useful in the diagnosis of asbestosis (57, 68), although there are other causes of pleural calcification (e.g., pleurisy, injury following hemothorax, inflammatory conditions that produce pleural effusion and empyema).

Pleural thickening is accompanied by a decrease in lung function, either with or without fibrosis. This was true when measuring FEV_1, FVC, or flow rates as in this and other studies, and for diffusing capacity, total lung capacity, and residual volume in other studies (61, 69, 70).

Except for peak flow and FEV percent, mean percent predicted pulmonary function is significantly reduced in the talc workers when compared to both coal and potash miners. This reduction is thought to be the result of occupational exposure, since adjustments are made for years worked and the known effects of age, height, and smoking habits on pulmonary function.

Despite the association of reduced FEV_1, FVC and flow rates with fiber and particulate exposure and years worked, interpretation of these data are difficult. The cumulative exposure is only an index, not an actual measure of exposure. There is a suggestion from past environmental measurements that exposures in certain jobs, particularly in the mill, have declined over the years. Exposure in the mine appears to be more constant. Analysis of time spent in different jobs by those with and without pleural thickening shows that for the jobs of mine foreman, hoistman, crusher operator, packer, packer serviceman, quality control technician, and shipping and inventory coordinator, those with pleural thickening spent more time in these particular jobs than those without pleural thickening. The time spent in these jobs by those with pleural thickening is 2-5 times greater than the average time spent in all other jobs, and contributes to a majority of the time spent in all jobs. There is, however, no way to adequately determine actual or relative past exposure levels in these jobs.

RETROSPECTIVE COHORT STUDY OF MORTALITY

METHODS

A retrospective cohort study was initiated to determine whether workers who have been employed at this mine and mill have experienced any unusual mortality patterns. This study cohort was defined as all white (those cohort members where racial status was unknown were considered white for purpose of the study, since the majority of this work force is known to be white) males initially employed sometime between January 1, 1947, and December 31, 1959. This cutoff date was selected to allow for a sufficient latent period for any development of chronic disease. An effort was made to determine the vital status of each individual in the cohort as of June 30, 1975, and person-years at risk and duration of employment for the cohort were accumulated until this date.

Vital status was determined through records maintained by Federal and State agencies, including the Social Security Administration, state vital statistics offices, and state motor vehicle registration. For those individuals who could not be located through these sources, U.S. Postal Mail Correction Services and other follow-up searches were used.

For all those who were known to be deceased, death certificates were requested and causes of death were interpreted by a qualified nosologist according to the International Classification of Diseases (ICD Codes) in effect at the time of death and then converted to the 7th Revision of the ICD Codes. A modified life table technique was used to obtain person-years at risk of dying by five-year calendar time periods, by five-year age groups, by duration of employment, and by number of years since initial employment at the talc company. Comparison was made between the observed number of deaths among the study cohort and the number expected for this population using age, calendar time, and cause specific mortality rates of the U.S. white male population. The vital status of 96 percent of the cohort was confirmed (Table 27). Those with an unknown vital status are assumed to be alive as of June 30, 1975 so that the true risk of mortality associated with exposure to talc is not overestimated.

RESULTS

A total of 398 workers meeting the study cohort definition generated 8,733 person-years at risk of dying. Fifty percent of the workers were employed less than one year, while less than 25

percent were employed for 10 years or more. Tables 28 and 29 illustrate the distribution of the study population by duration of employment and by date of initial employment.

Tables 30 and 30A summarize the deaths observed from the study cohort and those expected based on death rates for the U.S. white male population. Although the overall observed mortality is higher than expected, this difference is not statistically significant ($p<0.05$). However, several specific causes of death exhibit increased mortality. The standardized mortality ratio (SMR) (SMR = observed deaths/expected deaths x 100) is significantly elevated for the cause of death category, "all malignant neoplasms", which is partly due to the statistically significant increase in bronchogenic cancer (9 obs. vs. 3.3 exp.; $p<0.05$). Other statistically significant increases for specific causes of death occurred in the categories: "nonmalignant respiratory disease other than influenza, pneumonia, bronchitis, and acute upper respiratory infection" (5 obs. vs. 1.3 exp.; $p<0.05$) and "respiratory T.B." (3.0 obs. vs. 0.49 exp.; $p<0.05$). One death due to mesothelioma was observed.

Table 31 demonstrates the association between bronchogenic cancer and the time interval between the initial date of employment and the date of death (latency). As seen, there is an increasing risk of bronchogenic cancer with increasing latency, a trend consistent with an occupational etiology. In addition, the deaths due to bronchogenic cancer have an average latency of 20 years (Table 32); a period previously observed for a population occupationally exposed to anthophyllite and other minerals (47, 64, 65).

Three additional deaths due to bronchogenic cancer are known to have occurred among study members. However, these deaths occurred shortly after the cutoff date (6/30/75) for analysis and therefore were not included as observed deaths. One individual worked for 17 continuous years at the talc company under study and died at the age of 50. The latency period was 24 years. Another individual who worked for 2 months at the talc company died at the age of 54. The latency period was 27 years. The third lung cancer death was that of a worker employed for 12 years at the company under study and 12 years previously at another New York talc company. He died at the age of 59 and had a latency period of 23 years.

At least three cases of nonmalignant respiratory disease among study cohort members are known to have been reported to the New York State Workmen's Compensation Board. These individuals filed workmen's compensation claims for: (1) pneumoconiosis,

chronic bronchitis; (2) talcosis, pulmonary emphysema, chronic bronchitis; and (3) talcosis, pulmonary fibrosis. These individuals worked at the talc company under study for 18 years, 18 years, and 25 years, respectively.

DISCUSSION

The results of the present study demonstrate an excessive risk of 273 percent due to lung cancer mortality and 385 percent due to nonmalignant respiratory disease among a cohort of talc workers occupationally exposed to both asbestiform tremolite and anthophyllite, but to little free silica. However, several possible confounding factors must be taken into consideration before one can attribute this observed mortality pattern to occupational exposures received at this talc mine and mill.

One such factor that has been shown to be correlated with the causation of lung cancer is cigarette smoking. The smoking patterns are largely unknown for this cohort as is the case with most retrospective studies. However, it has been estimated that in heavy smoking worker population, smoking alone would increase the expected lung cancer mortality risk by no more than 49 percent (71). Thus, cigarette smoking per se is unlikely to account for the increased bronchogenic cancer risk of 273 percent observed among these talc miners and millers.

Another factor to be considered is occupational exposure among cohort members resulting from prior employment. Known prior employment among those in the study who died from malignant and nonmalignant respiratory disease are given in Table 32. Several of these individuals as well as other members of the study cohort worked at other New York State talc companies located in the Gouverneur Talc District. Due to this consideration industrial hygiene analyses were carried out to compare the make-up of talcs in a neighboring mine acknowledged as having asbestiform talc. These comparisons are presented in Table 13.

The analysis of amphibole fiber characteristics between these talc operations showed them to be substantially the same. Thus, while exposure levels in other talc companies may have been higher, all operations involved exposures to asbestiform amphiboles with similar airborne fiber characteristics. All these operations have been shown to have fiber exposures far in excess of established OSHA asbestos standards. Thus, exposures to asbestiform tremolite and anthophyllite stand out as the prime suspected etiologic factors associated with the observed increase in bronchogenic cancer and nonmalignant respiratory disease among this study cohort.

Of interest is the fact that four of nine deaths due to bronchogenic cancer in this cohort were workers employed less than 1 year in the operations under study and only one of these cases is known to have previous exposures to talcs containing asbestiform minerals. Although this cohort is relatively small, it appears plausible that even brief periods of exposure to elevated concentrations of asbestiform minerals may be associated with an increased bronchogenic cancer risk. Such an observation has previously been reported (72).

One death due to mesothelioma is known to have occurred in the study population. This individual worked for 16 years in the talc operation and had 11 years previous employment in construction work. Without full knowledge of this individual's exposure as a construction worker, it is difficult to arrive at any conclusions regarding the etiologic role of talc exposure from this mine and mill for this case. Although previous studies (5, 6, 47, 64, 65) have not shown an association between exposure to asbestiform anthophyllite or tremolite and subsequent development of mesothelioma, a study in Turkey by Baris (73) has demonstrated an increased risk of developing mesothelioma among residents of a particular community exposed to asbestiform tremolite, probably from their drinking water. Therefore, the possible association between exposure to asbestiform tremolite and the risk of developing mesothelioma should be further studied by continued follow-up of these talc workers.

CONCLUSIONS AND RECOMMENDATIONS

An industrial hygiene study, a cross-sectional morbidity study, and a retrospective mortality study were conducted among miners and millers of industrial talcs in upper New York. These talcs were shown to contain fibrous tremolite and anthophyllite as major contaminants. In addition, both present and past worker exposures to these fibers were shown to be far in excess of occupational exposure standards established by the Occupational Safety and Health Administration (OSHA) and the Mining Enforcement and Safety Administration (MESA) (now called Mine Safety and Health Administration MSHA).

The most striking finding of the morbidity study was an increased prevalence of pleural thickening in talc workers with greater than 15 years of exposure, occurring in nearly one out of every three talc workers. Reduced FEV_1, FVC, and flow rates were also observed after adjusting for smoking habits.

The study of mortality among the workers who began employment between 1947 and 1960 demonstrated an increased number of deaths due to bronchogenic cancer. The average latency period for bronchogenic cancer was 20 years.

A thorough review of the available literature demonstrated that findings of the present studies are in agreement with those of other studies of occupational groups exposed to the same or similar minerals or mineral mixtures. This is especially true for occupational exposures to anthophyllite asbestos. These findings make it imperative that workers from the mine and mill studied, herein, be routinely observed using medical surveillance criteria established in the OSHA and MSHA asbestos standard. Furthermore, all provisions of these standards should be followed during the production and subsequent use of these talcs.

Table 1

Results of X-Ray Diffraction and Petrographic Microscopic Analyses of Bulk Talc Samples Collected During Study

Mineral Component	Sample Analysis, % By Weight					
	Product A	Product B	Product C	Product D	Product E	Product F
Talc	31-36	43-48	30-35	33-38	35-40	14
Tremolite	∿40	∿37	∿49	∿43	∿38	∿59
Anthophyllite	∿10	∿4.5	∿5	∿8	10	15
Quartz	2.6	<0.25	<0.25	0.7	0.8	1.1
Calcite	1	<0.5	0	0	<0.5	<1
Dolomite	1	<0.5	<0.5	<0.5	<0.5	<0.5
Serpentines*	10-15	10-15	10-15	10-15	10-15	10

* Includes lizardite and antigorite.

Table 2

Results of Trace Metal Analyses of Bulk Talc Samples Collected During Study*

Product	Date Collected	Trace Metal, PPM**						
		Cr	Co	Fe	Mn	Ni	Zn	Cd
A	11/4/75	3	1	1100	1700	7	20	<1
B	11/4/75	3	<1	1000	840	5	19	<1
C	11/4/75	2	2	880	1000	6	17	<1
D	11/4/75	3	2	970	1300	7	20	<1
E	11/3/75	2	3	1000	1700	5	23	<1
F	11/3/75	3	2	900	1400	5	22	<1

* Trace metals determined by atomic absorption spectroscopy.

** PPM-Parts per million by weight.

Table 3

Results of Major Components Analyses
of Product Talc Samples

Major Components	Sample Analyses, % By Weight*							
	1	2	3	4	5	6	7	Talc Stds**
SiO_2	54.85	54.52	56.11	56.14	52.81	52.47	55.47	61.49
TiO_2	0.04	0.15	0.07	0.03	0.08	0.04	0.07	0.01
Al_2O_3	0.38	0.32	0.13	0.13	0.16	0.11	0.13	1.20
Fe_2O_3	0.10	0.13	0.08	0.11	0.08	0.06	0.11	0.38
FeO	0.04	0.03	0.05	0.03	0.03	0.01	0.03	1.07
MnO	0.21	0.20	0.22	0.15	0.12	0.10	0.12	0.00
MgO	28.40	28.78	29.40	29.56	30.20	30.56	29.10	30.54
CaO	9.02	8.53	7.50	7.40	8.15	8.30	8.25	0.46
Na_2O	0.28	0.44	0.18	0.25	0.38	0.16	0.18	--
K_2O	0.10	0.17	0.10	0.10	0.10	0.10	0.13	--
P_2O_5	0.03	0.03	0.03	0.03	0.03	0.03	0.03	--
H_2O	5.37	5.07	5.00	5.56	6.07	6.67	5.24	5.00
CO_2	1.35	1.15	1.03	0.96	1.30	0.98	0.84	5.00
Total	100.17	99.52	99.90	100.45	99.51	99.59	99.59	

* Samples submitted to NIOSH by Company Analyses performed by Dr. D.R. Bowes, University of Glasgow.

** From talc standard analyses in reference 1.

Table 4

Summary of TWA Exposures
By Job, Mining Operations

Job Title	Fibers fibers >5 μm in length/cc (Optical Microscopy)	Resp.Mass. mg/m^3	Impinger mppcf	Free SiO_2 mg/m^3
Crusher Operator	9.8 (4)	--	--	--
Trammer	5.6 (25)	0.64 (3)	10.1 (3)	0.020 (3)
Scrapper Man	--	1.29 (3)	11.8 (5)	0.012 (3)
Underground Laborer	--	0.58 (1)	--	0.006 (2)
Driller	3.0 (5)	0.98 (3)	0.7 (1)	0.014 (2)
Mucker	--	--	15.8 (1)	--
Cageman	9.5 (5)	0.23 (1)	2.0 (1)	--
Repairman	--	1.14 (1)	--	--
Repairman's Helper	--	0.86 (1)	3.6 (1)	0.000 (1)
Blacksmith	2.6 (3)	--	--	--
Maintenance Mechanic	1.7 (12)	0.42 (1)	1.5 (1)	0.000 (1)

( ) = Number of samples used for calculation of TWA values for each job category. Samples for respirable mass and free SiO_2 were full shift samples.

-- indicates no samples

Table 5

Summary of TWA Exposures
By Job Title

Job Title	Fibers fibers >5 µm in length/cc (Optical Microscopy)	Resp. Mass mg/m^3	Impinger mppcf	Free SiO_2 mg/m^3
Mill Foreman	5.3 (9)	0.58 (2)	2.9 (2)	0.013 (2)
General Laborer	5.6 (5)	1.14 (1)	0.5 (1)	0.014 (1)
Crusher Operator	5.1 (16)	0.85 (2)	2.6 (4)	0.020 (2)
Hardinge Operator	7.9 (14)	1.09 (2)	3.4 (2)	0.012 (1)
Wheeler Operator	8.4 (14)	1.56 (2)	3.1 (2)	0.012 (1)
Packer	5.1 (48)	0.59 (9)	3.6 (6)	0.010 (7)
Packer Serviceman	3.6 (11)	0.42 (2)	2.1 (1)	0.007 (2)
Packhouse Foreman	1.5 (5)	0.25 (2)	--	0.014 (2)
Fork Lift Operator	4.0 (15)	0.35 (3)	1.6 (1)	0.000 (1)
Car Liner	3.4 (4)	0.31 (1)	--	0.000 (1)
Bulk Car Loader	2.0 (3)	0.25 (1)	--	0.016 (1)
Millwright	1.9 (3)	2.37 (2)	--	0.040 (2)
Instrument Repairman	2.8 (6)	0.59 (2)	--	0.000 (1)
Machinist	1.8 (3)	0.40 (1)	--	0.016 (1)
Millwright Helper	4.0 (2)	2.96 (1)	--	0.000 (1)
Sheet Metal Worker	1.7 (3)	0.50 (1)	--	0.013 (1)
Oiler	4.0 (4)	0.72 (1)	--	0.016 (1)
Weldér	1.9 (3)	0.75 (1)	--	

( ) = Number of samples used for calculation of TWA values for each job category. Samples for respirable mass and free SiO_2 were full shift samples.

Table 6

Summary of TWA Amphibole Fiber Exposures
(All Fiber Lengths) in Mining and Milling
Operations As Determined by Analytical Electron Microscopy

Job Title	Asbestos Fiber Conc. fibers/cc*
Mine	
Trammer	17.5 (4)
Driller	9.5 (1)
Cageman	17.5 (1)
Mechanic	16.7 (1)
Mill	
Mill Foreman	25.0 (2)
General Laborer	23.6 (2)
Crusher Operator	12.0 (2)
Hardinge Operator	70.6 (2)
Wheeler Operator	22.9 (2)
Packer	36.0 (2)
Packer Serviceman	11.1 (2)
Packhouse Foreman	14.6 (2)
Fork Lift Operator	36.0 (1)
Machinist	24.9 (1)
Welder	9.9 (1)

*Concentrations shown are only for those giving identifiable electron diffraction patterns and include tremolite and anthophyllite.

( ) Number of samples analyzed by electron microscopy.

Table 7

Summary of Airborne Fiber Types Determined By Analytical Electron Microscopy

Operation	Percent of Airborne Fibers (All Lengths)				
	Positive Amphiboles*		Positive Chrysotile	Non-Asbestos	Not Identified***
	Tremolite**	Anthophyllite**			
All Fibers					
Mine	19	38	3	1	39
Mill	12	45	2	2	38
Fibers > 5 µm in Length (Mine & Mill)	7	65	0	3	25

* Airborne fibers were identified as positive amphiboles by selected area electron diffraction.

** Amphiboles differentiated by energy dispersive microchemical analysis.

*** Electron diffraction patterns are not suffficient for identification; however, many had X-ray spectra identical to tremolite.

Table 8

Summary of Airborne Fiber Diameters for Positive Amphiboles

Operation and Fiber Type	Median Diameter µm	Geo. Std. Deviation	95% Conf. Interval For Median Diameter µm	% ≤ 0.5 µm in Diameter
Mine*				
Tremolite (N=83)	0.19	2.3	0.16-0.23	88
Anthophyllite (N=164)	0.13	2.4	0.12-0.15	93
Mill				
Tremolite (N=160)	0.19	2.4	0.17-0.22	87
Anthophyllite (N=687)	0.13	2.9	0.12-0.14	90

* Results of all samples combined for distribution analysis.

N = Number of individual fibers identified and sized using electron microscopy.

Table 9

Summary of Airborne Fiber Lengths for Positive Amphiboles

Operation and Fiber Type	Median Diameter µm	Geo. Std. Deviation	95% Conf. Interval For Median Diameter µm	% ≤ 0.5 µm in Length
Mine*				
Tremolite (N=83)	1.6	1.8	1.4-1.8	97
Anthophyllite (N=164)	1.5	2.6	1.3-1.7	90-92
Mill*				
Tremolite (N=160)	1.5	1.9	1.4-1.7	97
Anthophyllite (N=687)	1.4	2.9	1.3-1.5	90

* Results of all samples combined for distribution analysis.

N = Number of individual fibers identified and sized by electron microscopy.

Table 10

Aspect Ratios for Positive Amphiboles Determined by Electron Microscopy (All Fiber Lengths)

Aspect Ratio Measurement	Tremolite*		Anthophyllite*	
	Mine	Mill	Mine	Mill
Median Aspect Ratio	7.5	7.5	9.5	9.5
Aspect Ratio				
≤ 5/1	23%	24%	17%	15%
≤ 10/1	70%	70%	52%	52%
≤ 20/1	96%	96%	85%	88%
≤ 50/1	>99%	99%	99%	>99%

* Data shown are for all fiber lengths.

Table 11

Summary of Historic Impinger Dust Measurements in Mine and Mill Operations

Job or Operation	Mean Dust Concentration (mppcf)										Median Yearly Average
	1954	1958	1963	1964	1969	(1) 1970	(2) 1972	(2) 1973	(2) 1975	NIOSH 1975	
Mine											
Drilling	5		5		13	7	4	5	3	12	5
Dragline & Mucking			7			10	8	3	5	12	8
Tramming & Mucking					29	11	10	3	5	10-15	10
Primary Crushing	2	26	23	18	13	48	11	5	18		18
Hoist Loading				70	140	14	18	10	15	2	14
Mill											
Secondary Crushing	12	23	8	10	12	13	3	8	3	3	9
Wheeler Grinding	15	13	5	3	11	19		4	10	3	10
Hardinge Grinding	18	14	4	7		8			10	3	8
Bagging	25	15	5	9	4	8		8	9	4	8
Palletizing	40			25	10	6		8	15	2	10
Bulk Loading						10					35
Loading Bags		109	39	31		62					50
Other											
Millwright								4		4	
Maintenance								12		2	

(1) Values for 1954 - 1970 taken from reference 16.

(2) Calculated from MESA reports, references 33-42.

Table 12

Summary of Historic Fiber Exposure Measurements in Mine and Mill Operations

Job or Operation	Mean Fiber Concentration (fiber > 5μm/cc						
	(1) 1970	(2) 1972	(2) 1973	(2) 1974	(2) 1975	NIOSH 1975	(2) 1976
Mine							
Drilling	8	4	1	1	1	3	24
Dragline & Mucking	16	6	1	2		6	
Tramming & Mucking	22	6	1		3	6	8
Primary Crushing	260	22	5	9	20	10	25
Hoist Loading	29	5	10	13	3	10	12
Mill							
Secondary Crushing	13	5	14	6	9	5	18
Wheeler Grinding	30		14	13	17	8	14
Hardinge Grinding	33			13	10	8	14
Bagging	30		11	15	6	5	14
Palletizing	27		8	15		4	
Bulk Loading	8					2	
Loading Bags						3	
Other							
Millwright			9			2	
Maintenance			14			2-4	38

(1) Taken from reference 16
(2) Calculated from MESA reports, references 33-43

Table 13

Comparison of Airborne Fiber Characteristics in
Study of Mine and Mill
Operations with New York Talc
Operations Acknowledged as Containing
Asbestiform Minerals

Airborne Fiber Characteristic	Asbestiform Mine and Mill	Study Mine and Mill	Statistical Significance
Proportion Positive Amphiboles	0.50	0.58	$p < 0.05$
Proportion Anthophyllite	0.47	0.45	NS
Proportion Tremolite	0.03	0.13	$p < 0.001$
Median Fiber Length			
Anthophyllite	1.61 µm	1.45 µm	NS
Tremolite	*	1.55 µm	--
Median Fiber Diameter			
Anthophyllite	0.16 µm	0.13 µm	NS
Tremolite	*	0.19 µm	--
Median Fiber Aspect Ratio			
Anthophyllite	9.9	9.5	NS
Tremolite	*	7.5	--
% of Fiber $\leq$5 µm in length			
Anthophyllite	92	90-92	NS
Tremolite	*	97	--

* Insufficient number of fibers observed for calculation of size distribution parameters.

NS - Not significantly different at 0.05 level.

TABLE 14

Summary of morbidity studies of workers exposed to tremolite and/or anthophyllite fibers

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
20	Talc containing 45% tremolite and no free silica St. Lawrence CO., New York	57 talc miners & millers, 93% sample of one mine & mill	Miners=4 mppcf Millers=52 mppcf	Bronchitis=5% Dyspnea=0% Normal X-ray=5% Fibrosis=67% Early pneumoconiosis =26% Pneumoconiosis II=2%
42	Steatite talc (70% talc, 10% tremolite, no quartz) Murray County, Georgia	66 talc miners & millers, 30 working at time of survey. 8/11 females working	33 millers=300 mppcf 13 miners=135 mppcf 20 workers=17 mppcf	Pneumoconiosis (Grade) 0 1 2 3 High Exposure 52% 24% 15% 9% Medium Exposure 54% 46% - - Low Exposure 100% - - -
44	Fibrous talc containing tremolite, anthophyllite, 1% free silica St. Lawrence County, N.Y.	221 men at 3 talc mines and 5 talc mills	Mill:crushing milling=46-61 mppcf Mine:drilling= 1350 mppcf Stoping=1290 mppcf Mucking=35 mppcf	Fibrosis Total population= 14.5% 10 years exposure= 29.9% 30 years exposure= 74.% Visceral plaques=6.3% for those 35-75 years old, 4-52 years exposure.

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
74	Tremolite talc of upper New York. Composition of airborne dust from two mines and 4 mills: Talc 15-25% Median 24% Tremolite 15-60% 52.5% Anthophyllite 2-40% 8% Serpentine 1-10% 3% Calcite 2-50% 6% Quartz 0.1-9% 2%	Autopsy specimens of 7 miners and 1 miller.	miners=drilling for 10 months to 27 years. Miller=employed for 6 years.	Lung Ash: Appreciable quantities of talc, tremolite, anthophyllite, quartz only in men engaged in non-talc mining. Characteristic "talc lesion" of multiple irregularity shaped foci of fibrocytic proliferation and macrophages accumulation around medium-sized and smaller blood vessels; bronchioles and smaller bronchi distended and distorted with hypertrophic epithelium.
7	Talc from St. Lawrence County, New York (same location as Siegal, et al.) containing tremolite	82 miners and 156 millers in 2 talc plants, all without previous significant occupational exposure to other dusts.	Pre'46 '46-58 (mppcf) Mine: Drilling 818 3 Mucking 120 4 Mill: Crushing 180 52 Screening 69 37 Milling 92 20 Bagging 151 24	PREVALENCE OF FIBROSIS Miners = 3.6% Millers = 12.2% 20-50 mppcf 10-20 years 18.8% > 20 years 22.2% >50 mppcf 10-20 years 33.3% > 20 years 80.0% NO PLAQUES WERE FOUND

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
41	Talc admixed with tremolite and anthophyllite and a small amount of free silica.	Case histories of six talc miners and millers with pneumoconiosis.	24 years (20-23) talc exposure. Exposure in early years estimated as 150-470 mppcf; in later years as 0-53 mppcf.	Major Findings Clinical: Chronic productive cough, dyspnea, diminished breath sounds, limited chest expansion, diffuse rales, clubbing. X ray: Interstitial infiltration, opaque plate-like densities in region of diaphram; less frequent emphysema and observation of left cardiac border.
8	Fibrous talc, St. Lawrence County, New York	30 talc millers >10 years exposure and no previous occupational dust exposure; 59% smoked >20 cigarettes per day for ≥5 years	Mean duration of exposure= 19.5 years (13-26). Average exposure= 63.1 mppcf, 15 exposed 20-60 mppcf 15 exposed 60-100 mppcf	Dyspnea=53.3%. Abnormal findings (rales, rhonchi, wheezing=26.7%. Pulmonary infiltration (X-ray)=43.3% (4 is grade 1; 7 grade 2; 2 grade 3). Mean % predicted FVC=76.6%, Mean FVC%=.71% Mean % predicted RV/TLC=120.8; Mean % predicted RV=105.2; Mean % predicted TLV=82.1; Mean DL_{CO} = 23.7 cc/mm Hg/min.

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
9	Predominantly talc admixed with tremolite, anthophyllite, serpentine and <5% free silica.	16 Talc millers with >10 years talc exposure and no previous occupational dust exposure. 81% smoked >30 cigarettes/day ≥ 5 years.	7 avg exp= 20-60 mppcf 7 avg exp= 60-120 mppcf 2 avg exp> 120 mppcf	Cough=44%. Exertional dyspnea=88%. Dyspnea at rest= 6%. Lung findings (rales, rhonchi, wheezing) = 63%. Clubbing=38%. Pulmonary Infiltration (x-ray) Grade 1 = 25% Grade 2 = 63% Grade 3 = 12% No platelike densities. % predicted FVC = 72.5% (48-91) 44% were <75%. FEV% = 70% (53-84) 6% were <60%. % predicted RV = 100% (72-153) 6% were >133%. % predicted TLV = 81% (54-103) 31% were <73%. % predicted RV/TLC=121.3% (96-143) 50% were >124%. DL_{CO} 19.2 cc/mm Hg/min (10-38) 38% were <17.7%.

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
10	Talc admixed with tremolite anthophyllite, serpentine, and <5% free silica.	43 talc millers with >10 years exposure and no previous occupational dust exposure; 26 had smoked >30 cigarettes/day for >5 years.	2% avg exp=19 mppcf 49% avg exp= 20-60 mppcf 42% avg exp= 60-120 mppcf 7% avg exp= >120 mppcf	Cough = 33%. Dyspnea = 65%. Lung Crepitations = 28%. Clubbing = 19%. Pulmonary Infiltration (x-ray) Grade 1 = 9% Grade 2 = 23% Grade 3 = 5% % predicted FVC = 80% (30% <75% of pred.) FEV% = 70% (12% had < .60) % predicted RV = 101% (14% >133%) % predicted TLC = 84% (16% <73%) % predicted RV/TLC = 116% (37% >124%) DL_{CO} 24.2 cc/mm Hg/min (19% <17.7)
47	Anthophyllite asbestos, Finland	707 living asbestos workers (including office & forestry workers with no occupational exposure); 110 of these 787 had been engaged in asbestos work for more than 10 years.		

	Cough (%)			Dyspnea(%)
	All	Mod. Exp.	Hvy. Exp.	
Nonsmoker	17%	14%	59%	20%
<15 cigs/day	32%	27%	57%	23%
>15 cigs/day	35%	30%	57%	13%
Total Adjusted for Smoking	27%	23%	58%	20%

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
12	Talc admixed with other silicates (tremolite and anthophyllite) and <5% free silica.	20 workers with >10 years in talc mining and milling, & presence of clinical & x-ray findings compatible with talc pneumoconiosis.	Mean years exposure = 23.1 (11-40) 11 avg. exp=50-100 mppcf 9 avg. exp.>100 mppcf	70% cough. 100% exertional dyspnea. 25% dyspnea at rest. 90% diffuse rales, wheezing, and/or prolonged expiratory phase. 50% minimal to severe clubbing. X-rays 90% interstitial infiltration predominantly in mid-lower lung fields. 25% fine nodulations. 55% obliteration of costophrenic sinus. 70% obliteration of cardiac borders. 25% platelike densities in region of diaphragm. 25% diffuse type of emphysema. 10% bullous emphysema. % Predicted Mean FVC=67% (50% <60% predicted) Mean FEV%=.67 (45% < .70) Mean Peak Flow=76% Mean % Pred. RV=99% (25% >120% pred., 30% < 80% pred.) Mean % Pred. TLC=75% (75% < 80% pred.)

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
64	Anthophyllite, asbestos Finland	252 living workers who had worked between 1936-1967.		Respiratory disease = 44% Normal chest X-ray = 44% Changes in lung parenchyma (X-ray) = 39% Pleural pathology only (X-ray) = 17% Pulmonary and/or pleural pathology =58% Lung pathology excluding pleural lesions (X-ray) = Slight (7%); Moderate (15%); Severe (6%)
75	Anthophyllite asbestos, Finland	116 employed (103 men) & 24 retired (18 men) miners & millers.	TLV for asbestos fibers/cc, > 5µm in length: 33%= 2 yrs exp. 27%= 5-15 yrs exp. 30%=15-25 yrs exp. 7%= 25 yrs exp.	Asbestosis (X-ray) = 27% Mild (49%); Moderate (32%); Marked (19%)
11	Talc with tremolite & anthophyllite as major fibrous components.	39 talc workers exposed >10 years 49% has smoked >20 cigarettes/day for >5 years.	Avg. yrs. exp. 16.2 (11-22) + ++ Mine: Drilling 6 8 Mucking 20 22 Mill: Crushing 15 13 Milling 13 31.5 Bagging 16 30	Cough = 26%; Dyspnea =23%; Grade 1 = 67%; Grade 2 = 11%; Grade 4 = 22%; Lung Crepitations = 5%; Clubbing = 0%. Radiographic findings compatible with pneumoconiosis = 3%.

TABLE 14 (continued)

Reference	Mineral Characteristics	Sample	Exposure	Medical Findings
11			+ mean dust counts (mppcf) over 20 year period ++ fiber count 75 µm/ml in 1970 only	

Table 15

Age-Smoking Composition of Morbidity Study Population Who Had No Previous Occupational Exposure to Talc

	Age					
	20-29	30-39	40-49	50-59	60+	Total
Smoking Status	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Nonsmoker	12 (41)	2 (11)	3 (11)	2 (12)	0 (0)	19 (20)
Ex-smoker	3 (10)	3 (17)	13 (48)	8 (47)	1 (50)	28 (30)
Smoker	14 (48)	13 (72)	11 (41)	7 (41)	1 (50)	46 (49)
Total	29 (31)	18 (19)	27 (29)	17 (18)	2 (2)	93

Cells are column percentages; marginals are percentages of the total.

Table 15A

Age-Smoking Composition of Total Morbidity Study Population
Regardless of Previous Employment

	Age											
	20-29		30-39		40-49		50-59		60+		Total	
Smoking Status	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nonsmoker	16	(46)	3	(13)	4	(11)	3	(13)	0	(0)	26	(21)
Ex-smoker	3	(9)	3	(13)	16	(46)	13	(54)	2	(67)	37	(31)
Smoker	16	(46)	18	(75)	15	(43)	8	(33)	1	(33)	58	(48)
Total	35	(29)	24	(20)	35	(29)	24	(20)	3	(2)	121	

Cells are column percentages; marginals are percentages of the total.

Table 16

Age-Exposure Composition of Morbidity Study Population Who Had No Previous Occupational Exposure to Talc

	Age				
	20-29	30-39	40-49	50-59	60+
Exposure	n=29	n=18	n=27	n=17	n=2
Employment (years)	2.7 (0.3)	5.9 (0.8)	13.9 (1.4)	19.5 (2.0)	28.0 (0)
Particulate Exposure ($mg\text{-}years/m^3$)	2.0 (0.3)	4.6 (1.0)	8.6 (1.3)	11.3 (2.0)	13.7 (11.7)
Fiber Exposure (fiber-years/cc)	10.4 (1.6)	16.7 (3.3)	52.7 (7.6)	68.8 (13.1)	47.4 (41.4)

Standard Error in Parentheses

Table 16A

Age-Exposure Composition of Total Morbidity Study Population Regardless of Previous Employment

	Age				
	20-29	30-39	40-49	50-59	60+
Exposure	n=35	n=24	n=35	n=24	n=3
Employment (years)	3.0 (0.3)	5.8 (0.7)	14.0 (1.2)	19.5 (1.8)	28.3 (0.3)
Particulate Exposure ($mg\text{-}years/m^3$)	2.3 (0.3)	4.3 (0.8)	9.3 (1.3)	12.1 (1.7)	18.0 (8.0)
Fiber Exposure (fiber-years/cc)	12.5 (1.6)	18.3 (2.8)	55.7 (7.7)	72.2 (11.2)	47.2 (23.9)

Standard Error in Parentheses

Table 17

Prevalence (%) of Symptoms and Radiographic Findings by Smoking Habits Among Morbidity Study Population Who Had No Previous Occupational Exposure to Talc

Symptoms/ Radiographic Findings	Nonsmoker n = 19	Ex-smoker n = 28	Smoker n = 46	Total n = 93	p Value
Cough	0	21.4	52.2	32.3	0.0001
Phlegm	10.5	14.3	50.0	31.2	0.0005
Hemoptysis	0	3.6	13.0	7.5	0.12
Dyspnea ($\geq$Grade 2)	0	14.3	19.6	14.0	0.12
Pleural Thickening ($\geq$ Grade 1)	10.5	14.3	8.7	10.8	0.76
Pleural Calcification	5.3	0	0	1.1	0.14
Irregular Opacities	0	0	2.2	1.1	0.60

H_o: There is no difference in rates among the three smoking categories.

Table 17A

Prevalence (%) of Symptoms and Radiographic Findings By Smoking Habits Among The Total Morbidity Study Population Regardless of Previous Employment

Symptoms/ Radiographic Findings	Nonsmoker n = 26	Ex-smoker n = 37	Smoker n = 58	Total n = 121	p Value
Cough	3.9	24.3	53.5	33.9	.0001
Phlegm	19.2	16.2	51.7	33.9	.0004
Hemoptysis	0	8.1	13.8	9.1	.12
Dyspnea (≥Grade 2)	7.7	18.9	19.0	16.5	.40
Pleural Thickening (≥Grade 1)	7.7	18.9	8.6	11.6	.24
Pleural Calcification	3.9	2.7	0	1.7	.37
Irregular Opacities (≥Grade 1)	0	8.1	1.7	3.3	.13

H_O: There is no difference in rates among the three smoking categories.

Table 18

Prevalence (%) of Symptoms and Radiographic Findings by Age Among Morbidity Study Population Who Had No Previous Occupational Exposure to Talc

Symptoms/ Radiographic Findings	Age 20-29 n = 29	30-39 n = 18	40-49 n = 27	50-59 n = 17	60+ n = 2	n = 93	p Value
Cough	17.2	55.6	22.2	41.2	100.0	32.3	0.009
Phlegm	20.7	44.4	29.6	29.4	100.0	31.2	0.11
Hemoptysis	6.9	11.1	11.1	0	0	7.5	0.66
Dyspnea (≥ Grade 2)	10.3	16.7	11.1	17.7	50.0	14.0	0.56
Pleural Thickening (≥ Grade 1)	0	0	7.4	41.2	50.0	10.8	0.0001
Pleural Calcification	0	0	0	5.9	0	1.1	0.34
Irregular Opacities (≥ Grade 1)	0	0	0	5.9	0	1.1	0.34

H_o: There is no difference in rates among the five age groups.

Table 18A

Prevalence (%) of Symptoms and Radiographic Findings by Age Among the Total Morbidity Study Population Regardless of Previous Employment

Symptoms/ Radiographic Findings	Age						
	20-29 n = 35	30-39 n = 24	40-49 n = 35	50-59 n = 24	60+ n = 3	Total n = 121	p Value
Cough	17.1	58.3	25.7	37.5	100.0	33.9	.001
Phlegm	22.9	50.0	37.1	25.0	66.7	33.9	.13
Hemoptysis	5.7	12.5	11.4	4.2	33.3	9.1	.42
Dyspnea ($\geq$ Grade 2)	11.4	16.7	11.4	29.2	33.3	16.5	.32
Pleural Thickening ($\geq$ Grade 1)	0	0	5.7	41.7	66.7	11.6	.0001
Pleural Calcification	0	0	0	8.3	0	1.7	.08
Irregular Opacities ($\geq$ Grade 1)	0	0	2.9	12.5	0	3.3	.08

H_o: There is no difference in rates among the 5 age groups

Table 19

Prevalence (%) of Symptoms and Radiographic Findings Among Talc Workers Included in Morbidity Study With No Previous Occupational Exposure to Talc Compared to Coal and Potash Workers Adjusted for Age, Height and Smoking Habits

Symptoms/Radiographic Findings	Years Worked	Talc	Coal	Potash
Cough	< 15 years	31.3	20.9	23.2
	≥ 15 years	34.5	36.7	25.6
Phlegm	< 15 years	34.4	26.0	27.2
	≥ 15 years	24.1	44.6	23.7
Hemoptysis	< 15 years	10.9	6.4	6.4
	≥ 15 years	0.0	9.4	6.7
Dyspnea	< 15 years	12.5	13.3	5.3
	≥ 15 years	17.2	37.9	11.3
Pleural Thickening (Grade 1 and 2)	< 15 years	1.6	0.3	0.5
	≥ 15 years	31.0	1.6*	4.4*
Pleural Calcification**	< 15 years **	0.0	0.0	0.0
	≥ 15 years **	3.4	0.1	0.0
Irregular Opacities (Grade ≥1)	< 15 years**	0.0	0.5	0.0
	≥ 15 years	3.4	5.3	0.7
Regular Opacities (Grade ≥1)	< 15 years**	0.0	1.0	0.0
	≥ 15 years	3.4	13.7	1.1

* $p = < 0.05$ Hypothesis being tested is that there is no difference in rates between the coal and talc populations, or between the potash and talc populations.

** Expected values not large enough for chi square test.

Table 19A

Prevalence (%) of Symptoms and Radiographic Findings Among All Talc Workers Included in Morbidity Study Compared with Coal and Potash Workers Adjusted for Age, Height, and Smoking Habits

Symptoms/Radiographic Findings	Years Worked	Talc	Coal	Potash
Cough	<15	32.9	21.1**	23.3
	≥15	35.9	37.5	26.7
Phlegm	<15	37.8	26.0**	27.4
	≥15	25.6	45.7**	23.7
Hemoptysis	<15	11.0	6.5	6.2
	≥15	5.1	10.4	6.4
Dyspnea	<15	13.4	13.7	5.3
	≥15	23.1	39.2*	13.4
Pleural Thickening (Grade 1 and 2)	<15	1.2	0.3	0.5
	≥15	33.3	1.5****	3.7****
Pleural Calcification	<15++	0	0	0
	≥15++	5.1	0.1	0
Irregular Opacities (Grade ≥1)	<15++	0	0.6	0
	≥15	10.3	5.6	0.4****
Regular Opacities (Grade ≥1)	<15++	0	1.0	0
	≥15	2.6	14.5	1.6

* p = < .05
** p = < .02
*** p = < .005
**** p = < .0005

H_o: There is no difference in rates between the coal and talc populations, or between the potash and talc populations.

\+ N=37 for potash comparisons.
++ Expected values not large enough for chi square test.

Table 20

Dose-Response Relations Among Talc Workers Observed Pulmonary Function As Compared to Pulmonary Function of Coal and Potash Miners, Adjusted For Age, Height, Smoking Habits and Years Worked. (Standrard Error in Parenthesis)

A. Mean Percent Predicted and Pulmonary Function of Talc Workers Compared to Coal and Potash Workers

		Coal	Potash
FEV	a. n = 93	**** 94.0 (1.3)	****94.5 (1.4)
	b. n = 121	**** 93.8 (1.3)	****94.1 (1.3)
FVC	a. n = 93	**** 92.4 (1.2)	****94.7 (1.3)
	b. n = 121	**** 91.9 (1.1)	****94.0 (1.2)
FEV%	a. n = 93	101.3 (0.7)	99.8 (0.7)
	b. n = 121	*101.5 (0.7)	99.9 (0.7)
Peak Flow	c. n = 89	**108.1 (2.8)	99.4 (2.6)
	d. n = 114	***108.5 (2.5)	99.5 (2.3)
FEF_{25}	c. n = 89	* 93.6 (2.8)	****88.8 (2.7)
	d. n = 114	* 94.0 (2.7)	****88.9 (2.6)
FEF_{50}	c. n = 89	**** 85.9 (3.1)	****85.3 (3.2)
	d. n = 114	**** 86.8 (2.9)	****85.6 (2.9)
FEF_{75}	c. n = 89	**** 79.5 (3.1)	****83.7 (3.3)
	d. n = 114	**** 79.9 (2.9)	****83.6 (3.0)

H_O: Mean predicted pulmonary function is not different from 100.

\+ Percent predicted for FEV, FVC, Peak Flow, FEF_{50}, FEF_{75} = $100 \times \frac{\text{observed}}{\text{predicted}}$; For FEV% = 100 + observed-predicted.

Table 20 (continued)

B1. Change in percent predicted pulmonary function per 100 fiber-years/cc

		Coal	Potash
FEV_1	a. n = 93	** - 9.4 (3.2)	**** - 13.7 (3.4)
	b. n = 121	*** - 10.3 (3.0)	**** - 14.4 (3.1)
FVC	a. n = 93	** - 9.6 (3.1)	*** - 12.7 (3.3)
	b. n = 121	**** - 11.6 (2.6)	**** - 14.7 (2.8)
FEV%	a. n = 93	+ 0.2 (1.7)	- 0.7 (1.8)
	b. n = 121	+ 0.8 (1.5)	- 0.05(1.6)
Peak Flow	c. n = 89	+ 2.7 (7.1)	- 2.3 (6.5)
	d. n= 114	+ 0.4 (5.7)	- 4.0 (5.2)
FEF_{25}	c. n = 89	+ 4.8 (6.9)	- 0.3 (6.8)
	d. n = 114	+ 3.0 (6.2)	- 1.5 (5.9)
FEF_{50}	c. n = 89	- 2.5 (7.7)	- 7.6 (7.9)
	d. n = 114	- 5.0 (6.7)	- 9.7 (6.6)
FEF_{75}	c. n = 89	- 9.7 (7.7)	- 13.8 (8.3)
	d. n = 114	-12.0 (6.6)	* - 15.9 (6.9)

B2. Change in percent predicted pulmonary function per 10 mg-particulate-yrs/mg^3

FEV_1	a. n = 93	* - 5.2 (1.9)	*** - 7.5 (2.2)
	b. n = 121	* - 3.8 (1.8)	** - 6.2 (1.9)
FEV	a. n = 93	** - 5.3 (1.9)	** - 6.7 (2.1)
	b. n = 121	*** - 5.5 (1.6)	**** - 7.1 (1.8)
FEV%	a. n = 93	+ 0.2 (1.0)	- 0.6 (1.1)
	b. n = 121	+ 1.2 (0.9)	+ 0.6 (0.9)
Peak Flow	c. n = 89	+ 1.2 (4.2)	+ 0.08(4.0)
	d. n = 114	+ 1.6 (3.3)	- 0.2 (3.1)
FEF_{25}	c. n = 89	- 0.03 (4.1)	- 2.3 (4.2)
	d. n = 114	+ 2.2 (3.6)	- 0.4 (3.6)
FEF_{50}	c. n = 89	- 1.4 (4.6)	- 4.8 (4.9)
	d. n = 114	+ 1.2 (4.0)	- 2.7 (4.0)
FEF_{75}	c. n = 89	- 4.6 (4.6)	- 7.9 (5.1)
	d. n = 114	- 1.8 (3.9)	- 5.1 (4.2)

H_o: Change in pulmonary function is not different from 0.

Table 20 (continued)

* $p = \leq 0.05$

** $p = \leq 0.005$

*** $p = \leq 0.001$

**** $p = \leq 0.0001$

a. For potash comparison, n=91 for FEV, FVC, FEV%

b. For potash comparison, n=119 for FEV, FVC, FEV%

c. For potash comparison, n=87 for Peak Flow, FEF_{25}, FEF_{50}, FEF_{75}.

d. For potash comparison, n=112 for Peak Flow, FEF_{25}, FEF_{50}, FEF_{75}.

Table 21

Comparison of Talc Workers Included in Morbidity Study and Having No Previous Talc Exposure With and Without Pleural Thickening (PT)* By Age, Exposure, and Smoking Habits. (Standard Error in Parentheses) N=93

		Age		
		40-49	50-59	60+
N	No PT	25	10	1
	PT	2	7	1
Age	No PT	44.4 (0.5)	53.1 (0.6)	63.0
	PT	46.5 (0.5)	51.9 (0.6)	51.9
Smoking (pack years)	No PT	27.8 (4.7)	39.0 (8.6)	99.0
	PT	39.0 (23.0)	18.6 (5.2)	44.0
Years Worked	No PT	13.8 (1.4)	16.5 (3.1)	28.0
	PT	14.5 (6.5)	23.7 (0.9)	28.0
Particulate Exposure ($mg\text{-}yrs/m^3$)	No PT	8.7 (1.4)	11.3 (2.6)	25.4
	PT	7.9 (3.9)	11.2 (3.4)	2.0
Fiber Exposure (fibers-yrs/cc)	No PT	52.5 (7.9)	59.5 (16.7)	88.8
	PT	55.9 (41.0)	82.0 (41.0)	6.0
% Predicted FEV				
Coal	No PT	97.9 (2.6)	90.6 (4.7)	84.0
	PT	80.8 (3.2)	77.6 (5.3)	87.3
Potash	No PT	96.3 (2.8)	89.4 (5.0)	--
	PT	77.7 (5.3)	75.4 (5.4)	86.7
% Predicted FVC				
Coal	No PT	95.9 (2.4)	86.7 (4.5)	79.6
	PT	72.9 (7.1)	77.6 (4.4)	82.8
Potash	No PT	96.7 (2.5)	88.3 (4.8)	--
	PT	72.5 (8.7)	77.1 (4.3)	83.2

* Pleural thickening (Grades 1 and 2).

Table 21A

Comparison of All Talc Workers in Morbidity Study With and Without Pleural Thickening (PT)* By Age Exposure and Smoking Habits. (Standard Error in Parentheses) N=121

		Age		
		40-49	50-59	60+
N	No PT	33	14	1
	PT	2	10	2
Age	No PT	44.5 (0.4)	53.3 (0.5)	63.0 (----)
	PT	46.5 (0.5)	52.4 (0.7)	60.5 (0.5)
Smoking (packing years)	No PT	26.8 (4.0)	30.4 (7.2)	99.0 (----)
	PT	39.0 (23.0)	24.6 (6.8)	27.0 (17.0)
Years Worked	No PT	14.0 (1.3)	16.6 (2.6)	28.0 (----)
	PT	14.5 (6.5)	23.5 (1.5)	28.5 (0.5)
Particulate Exposure ($mg\text{-}yrs/m^3$)	No PT	9.4 (1.3)	11.1 (2.2)	25.4 (----)
	PT	7.9 (3.9)	13.5 (2.7)	14.3 (12.4)
Fiber Exposure (fiber-yrs/cc)	No PT	55.6 (8.0)	57.8 (12.8)	88.0 (----)
	PT	55.9 (41.0)	92.4 (18.9)	26.4 (20.4)
% Predicted FEV Coal	No PT	95.5 (3.1)	91.9 (3.8)	84.0 (----)
	PT	80.8 (3.2)	77.8 (5.8)	102.9 (15.6)
Potash	No PT	94.2 (3.3)	90.0 (3.9)	--
	PT	77.7 (5.3)	75.4 (6.0)	98.2 (11.5)
% Predicted FVC Coal	No PT	94.5 (2.6)	87.4 (3.4)	79.6 (----)
	PT	72.9 (7.1)	77.6 (4.7)	89.0 (6.2)
Potash	No PT	95.6 (2.8)	88.3 (3.6)	--
	PT	72.5 (8.7)	77.0 (4.8)	88.0 (4.8)

* Pleural Thickening (Grades 1 and 2)

Table 22

Average Number of Years Worked for Each Individual in Morbidity Study
Having No Previous Talc Exposure With and Without Pleural Thickening and the
Number of These Individuals Working in Selected Jobs Over the Total Work History
Of Those With Greater Than 15 Years Work When 0, 5 and 10 of the Most Recent Years Worked are Omitted.

Selected Jobs Are Those Where the Number of Years Worked Divided by the Number With Pleural Thickening is Equal to or Greater Than One and Greater Than Average Years Worked for Those Without Pleural Thickening.

Average Number of Years Worked/Individual (Number of Individuals Ever on this Job)

	All Years		Omit Most Recent Five Years		Omit Most Recent Ten Years	
	PT	No PT	PT	No PT	PT	No PT
Mine Foreman	19 (1)	7.7 (3)	14.1 (1)	7 (2)	9 (1)	2 (2)
Hoistman	26 (1)	1 (1)	21 (1)	1 (1)	16 (1)	1 (1)
Crusher Operator	24 (1)	8 (2)	20 (1)	6.5 (2)	15 (1)	4 (2)
Packer	14 (2)	14 (2)	9 (2)	12.5 (2)	11 (1)	8.5 (2)
Packer Serviceman	10 (2)	0	7.5 (2)	0	5 (2)	0
Quality Control Technician	16 (1)	4 (2)	16 (1)	1.5 (2)	12 (1)	2 (1)
Shipping & Inventory Coord.	13 (2)	0	16 (1)	0	11 (1)	0
All Other Jobs	5.1 (11)	8.1 (43)	5 (10)	7 (38)	4.6 (9)	5.4 (35)
All Jobs	10.2 (21)	8.0 (53)	9.0 (19)	6.9 (47)	7.4 (17)	5.2 (43)

Note: Numbers for "All Jobs" and All Other Jobs" will exceed number of individuals with (9) and with (20) pleural thickening, since many have held more than one job.

Table 23

Symptom Prevalence, Radiographic Findings and Pulmonary Function By Pleural Thickening (PT) and Years Employment

		PT =0 <15 Years Employment	PT = 0 ≥15 Years Employment	PT = 1* ≥15 Years Employment	PT = 2 ≥15 Years Employment
		n = 81	n = 26**	n = 8	n = 6
Age (Average)		32.9 (1.1)	48.9 (1.0)	50.9 (1.1)	55.2 (2.0)
Symptom Prevalence (95% Confidence Levels in Parentheses)					
Cough		32.1 (22-44)	34.6 (18-55)	12.5 (0-50)	83.3 (40-100)
Phlegm		37.0 (26-49)	23.1 (9-43)	12.5 (0-50)	66.7 (25-95)
Hemoptysis		9.9 (4.5-19)	0 (0-13)	12.5 (0-50)	33.3 (4-75)
Dyspnea (> Grade 2)		13.6 (7-24)	19.2 (7-39)	25.0 (3-65)	33.3 (4-75)
Pleural Calcification		0 (0- 5)	0 (0-13)	25.0 (3-65)	0 (0-45)
Irregular Opacities		0 (0- 5)	3.9 (0-20)	25.0 (3-65)	16.7 (0-60)
Pulmonary Function (Standard Error in Parentheses)					
FEV_1 (% Pred)	Coal	95.5 (1.3)	95.0 (3.4)	83.8 (3.2)	79.1 (11.5)
	Potash	97.5 (1.5)	91.5 (3.5)	80.9 (3.5)	76.5 (11.1)
FVC (% Pred)	Coal	94.4 (1.2)	91.4 (3.1)	80.1 (3.6)	76.4 (7.4)
	Potash	97.9 (1.3)	90.4 (3.1)	79.5 (3.7)	75.8 (7.7)
FEV%		78.1 (0.9)	75.3 (1.3)	76.0 (1.7)	70.2 (4.1)
		n=74			
Peak Flow (% Pred)	Coal	106.1 (2.8)	113.4 (5.5)	113.2 (10.7)	110.6 (17.2)
	Potash	99.5 (2.7)	99.7 (4.5)	99.8 (9.9)	97.2 (16.3)
FEF_{25} (% Pred)	Coal	91.6 (3.0)	98.4 (6.1)	102.6 (10.1)	93.4 (21.1)
	Potash	88.6 (2.9)	89.9 (5.9)	92.9 (9.6)	83.5 (19.3)
FEF_{50} (% Pred)	Coal	86.6 (3.1)	91.1 (7.2)	82.9 (10.0)	76.0 (24.5)
	Potash	87.3 (3.3)	86.2 (7.0)	79.1 (10.7)	70.9 (20.0)
FEF_{75} (% Pred)	Coal	82.6 (3.2)	80.3 (7.0)	65.3 (6.3)	65.5 (22.3)
	Potash	87.4 (3.5)	82.2 (7.5)	65.4 (5.1)	66.7 (19.9)

* One individual has less than 15 years employment; all others with PT ≥ 1 have more than 15 Years employment.

** n=24 for the potash comparisons.

Table 24

Symptom Prevalence (%) of Talc Workers Compared to Asbestos[1] and Synthetic Textile Workers[2] By Age and Smoking Habits

		Nonsmoker	Ex-smoker	Smokers	Total
Winter Cough (3 mos/yr)					
	Ages				
Asbestos Workers	21-35	19	27	49	42
	36-69	35	21	65	56
Talc Workers	20-39	0	33	48	24.4
	40-65	0	21	60	38.3
Anthophyllite Asbestos Workers-heavily exposed greater than 10 years[3]		16.8	--	<15=32.0 >15=35.6	26.6
Phlegm in Winter (3 mos/yr)					
	Ages				
Asbestos Workers	21-35	26	27	43	38
	36-69	40	30	51	47
Synthetic Textile Workers	15-39	6	0	12	10
	40-70	9	5	22	17
Talc Workers	20-39	18	17	45	24
	40-65	20	11	60	37
Breathlessness- Grade 2 or More					
	Ages				
Asbestos Workers	21-25	0	0	13	9
	36-39	22	23	23	23
Synthetic Textile Workers	15-39	6	5	6	6
	40-70	4	7	9	7
Talc Workers	20-39	6	17	14	9
	40-65	0	14	20	17
Anthophyllite Asbestos[3] (dyspnea at rest)		19.8	--	<15=23.0 >15=13.3	19.9

(1) From J.C. McDonald et. al.: Respiratory Symptoms in Chrysotile Asbestos Mine and Mill Workers of Quebec. Arch Env. Health, 24:358, (1972).

(2) J. A. Merchant: Epidemiological Studies of Respiratory Disease Among Cotton Textile Workers, 1970-73. (Rates are calculated from white men working in synthetic wool mills in North Carolina, 1970-71.)

(3) L.O. Meurman, R. Kivilvoto, and M. Hakama: Mortality and Morbidity Among the Working Population of Anthophyllite Asbestos Miners in Finland, Brit. J. Ind. Med., 31:105, 1974.

Table 25

Prevalence of Radiographic Findings in Talc Workers Compared to Asbestos Workers[1] Over 35 Years of Age and After Age Adjustment

	Prevalence (%) of Radiographic Findings		
	Pleural Thickening	Pleural Calcification	Irregular Opacities
Talc Workers with no previous occupational exposure	25.0	3.8	1.9
(n=52)	p<.01	N.S.	N.S.
Asbestos Workers[1]	4.8	2.9	5.6
Talc Workers regardless of previous employment	28.6	7.1	5.7
(n=70)	p<.01	N.S.	N.S.
Asbestos Workers[1]	4.9	3.0	5.8

(1) Data from C.E. Rossiter et.al., (1972). Radiographic Changes in Chrysotile Asbestos Mine and Mill Workers of Quebec, Arch. Env. Health 24:388 (ref. 76).

This study of asbestos workers used the 1968 ILO/UICC classification for pneumoconiosis. There are no differences in the 1968 and 1976 classification for irregular opacities, pleural thickening and pleural calcification.

Table 26 -- Summary of the Prevalence of Pleural Thickening (PT) in Workers Exposed to Asbestos

Reference	Exposure	Prevalence of PT			
56 (1968)	Naval Dockyard; all types of asbesots fibers		Continuous Exposure	Intermittent Exposure	Varied or Insignificant Exposure	% of Cases with 15 Yrs. Since Exposure
		n	42	688	684	
		Extensive PT	5%	1%	<1%	91%
		Limited Plaques of PT	24%	4%	2%	88%
62 (1969)	Former anthophyllite asbestos workers. n=410	Prevalence (%) Of Diffuse PT				
		All	35%			
		No Pulmonary Fibrosis	9%			
		Pulmonary Fibrosis	26%			

Grade Diffuse PT	1	2	3
No pulmonary changes	71%	14%	14%
Grade 1 pulmonary changes	50%	32%	18%
Grade 2 pulmonary changes	21%	58%	21%
Grade 3 pulmonary changes	11%	26%	63%

Reference	Exposure	
63 (1972)	Men & women >40 yrs attending chest clinic in Birmingham (UK) area. n=3868	6% had noncalcified pleural lesions. 1% had pleural calcification, and ∿1/2 of these also had noncalcified pleural lesions.
61 (1972)	10% sample of 3 naval dockyards. n=2442	Extensive noncalcified PT = 0.01% Limited noncalcified PT = 0.01% Pleural abnormalities were more frequent than parenchymal disease.

76 (1972)	2 Chrysotile Asbestos Mines and Mills	PT by Age						
		36-40	41-45	46-50	51-55	56-60	61-65	TOTAL
	n=	1449	1446	1066	867	656	641	11207
	PT >Grade 1	1.4%	2.7%	5.8%	7.2%	7.8%	12.3%	3.8%
	PT ≥Grade in Production Wkrs. at:							
	Thetford Mine	2.8%	4.2%	7.1%	8.0%	7.9%	11.5%	6.4%
	Asbestos	0.7%	1.7%	4.1%	3.6%	4.6%	7.6%	3.2%

Table 26 -- Summary of the Prevalence of Pleural Thickening (PT) in Workers Exposed to Asbestos (continued)

				36-40	41-45	46-50	51-55	56-60	61-65	TOTAL
			In Factory Workers:							
			n =	87	76	66	44	61	64	967
			% in PT	1.1%	2.6%	4.5%	6.8%	4.9%	-----	1.4%

				% PT by Dust Index (dust Level x yrs worked)					
				<10	10-99	100-199	200-399	400-799	800+
			Production Workers:						
			Thetford Mine	2.4%	4.6%	6.5%	5.8%	8.3%	10.5%
			Asbestos	2.9%	2.6%	3.0%	3.0%	4.7%	5.8%
77	(1975)	2 asbestos cement manufacturing plants; primarily chrysotile but some exposure to crocidolite, amosite, silica, talc, mica.	Average age = 45 (21-79)						
			Average dust exposure: 17 yrs (1 month-45 yrs.)	50	50-100	100-200	200-400	400+	TOTAL
			n = 233	233	92	130	245	159	859
			(%)	9%	15%	22%	16%	16%	15%

Table 27

Vital Status of Talc Workers Included in Mortality Study Who Began Employment Between 1947-1960

Known to be alive	308
Known to be deceased	74
Unknown vital status	16
Total	398

Table 28

Study Cohort of Talc Workers Included in Mortality Study According to Length of Employment

Duration of Employment	Number
< 1 month	74
1 month - 6 months	97
6 months - 12 months	31
1 year - 10 years	90
> 10 years	106
Total	398

Table 29

Study Cohort of Talc Workers Included in Mortality Study According to Date of Initial Employment

Date of Initial Employment	Number
1947 - 1949	174
1950 - 1954	156
1955 - 1959	68
Total	398

Table 30

Observed and Expected Deaths According to Major Causes
Among Talc Miners and Millers Included in Mortality Study

Cause of Death	Number	Observed	Expected	SMR
Respiratory T.B.	001-008	3.0	0.49	610*
Malignant Neoplasms	140-205	19.0	10.6	180*
Diseases of the Heart	400-443	27.0	26.5	102
All Non-malignant Respiratory Disease	470-527	8.0	2.9	280*
Accidents	E800-E999	10.0	6.4	156
Other Known Causes	---------	7.0	14.4	---
Total		74.0	61.3	120

* $p < 0.05$

Table 30A

Observed and Expected Deaths According to Specific Cause Among Talc Miners and Millers Included in Mortality Study

Cause of Death	Number	Observed	Expected	SMR
Malignant Neoplasms	140-205	19.0	10.6	180*
Digestive System	150-159	3.0	3.0	100
Respiratory System	160-164	10.0	3.5	290**
Bronchogenic	162-163	9.0	3.3	270*
Lymphatic and Hematopoietic	200-205	4.0	1.2	330
Other Neoplasms	-------	2.0	2.9	69
All Non-malignant Respiratory Disease	470-527	8.0	2.9	280*
Influenza, Pneumonia, Bronchitis and Acute Upper Respiratory Infection	470-502	3.0	1.5	200
Other Non-malignant Respiratory Diseases	510-527	5.0	1.3	380*

* $p < 0.05$

** $p < 0.01$

Table 31

Bronchogenic Cancer Among Talc Miners and Millers Included in Mortality Study According to Interval Since Onset of Employment (Latency)

Interval Since Onset of Employment (years)	Observed	Expected	SMR
<10	0	0.5	---
10-19	3	1.5	200
20-28	6	1.3	460**
Total	9	3.3	270*

** $p < 0.01$

* $p < 0.05$

Table 32

Case Review of Deaths Among Talc Miners and Millers Included in Mortality Study According to Cause of Death and Select Demographic Factors

Case	D.O.B.	Age at Death	App. Length of Emplymt. (Date of Initial Emplymt.)	Latency (Years)	Other previous Emplymt. (Length of Emplymt.)
A. Cancer of Respiratory System					
1	12/04/06	63	1 month (8/10/49)	21	Unknown
2	05/22/17	54	1 month (10/21/48)	23	Coal Supply (7 months) Diamond Drill Other N.Y. State Talc Co.
3	06/08/14	59	1 year (11/08/48)	25	Repairman-Other N.Y. State Talc Co. (5 months) Shaftman-Lead Mine (14 months)
4	03/19/24	46	2 months (11/22/48)	21	Rock Quarries (2 years) Aluminum Plant (4 years) Iron Ore Mine (4 months)
5	06/14/09	55	3 years (07/19/48)	18	Road Building (5 years) Mining (6 years)
6	06/28/07	53	5 years (08/04/54)	6	Foundry (10 years) Other N.Y. State Talc Co. (5-6 years)
7	05/10/20	54	2.5 years (07/12/50)	24	Mucker-Mining (7 years)
8	04/22/891	79	<1 month (12/13/48)	22	Construction (unknown length)
9	01/03/22	39	2.5 years (07/13/49)	12	Mucker-Lead Mine (" ")
10	10/10/11	62	17 years (01/25/56)	18	Unknown
B. Mesothelioma of Lung					
1	02/08/06	62	16 years (12/04/52)	16	Construction (11 years)

Table 32 (continued)

C. Non-malignant Respiratory Disease Other Than Influenza and Pneumonia

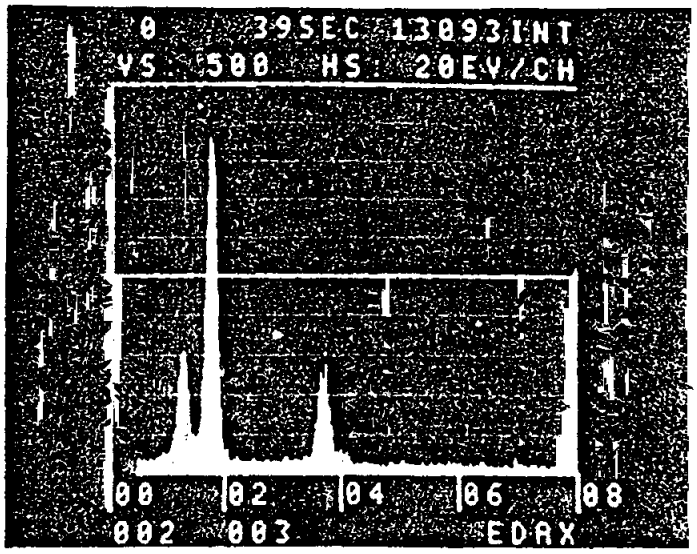
1	08/07/885	75	10 years (11/01/48)	13	Unknown
2	01/07/16	59	<1 month (12/15/48)	27	Unknown
3	09/08/13	58	14 years (06/14/54)	17	Mucker & Driller - Limestone (9 years)
4	03/07/26	49	10 years (04/05/52)	23	Other N.Y. State Talc Co. (5 years)
5	06/20/10	58	1 year (04/17/50)	18	Unknown

D. Respiratory T.B.

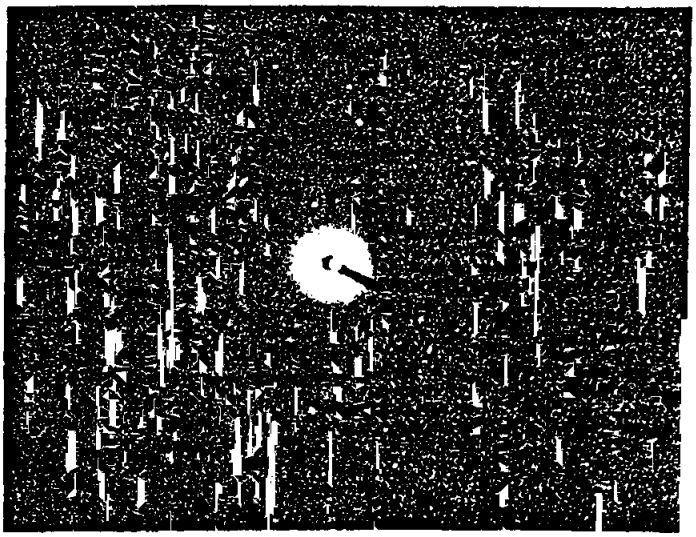
1	12/06/21	49	4 years (06/25/49)	21	Construction (4 months) Miner-Lead Miner (3 mont
2	02/11/09	53	5 months (07/11/49)	12	Miner-Other N.Y. State Talc Co. (16 years) Miner-Lead Mine (unknow length)
3	10/30/29	42	6 years (09/11/54)	17	Unknown

Figure 1. Typical Electron Diffraction Patterns and X-ray Spectra of Tremolite Fibers in Bulk Samples

X-Ray Spectrum



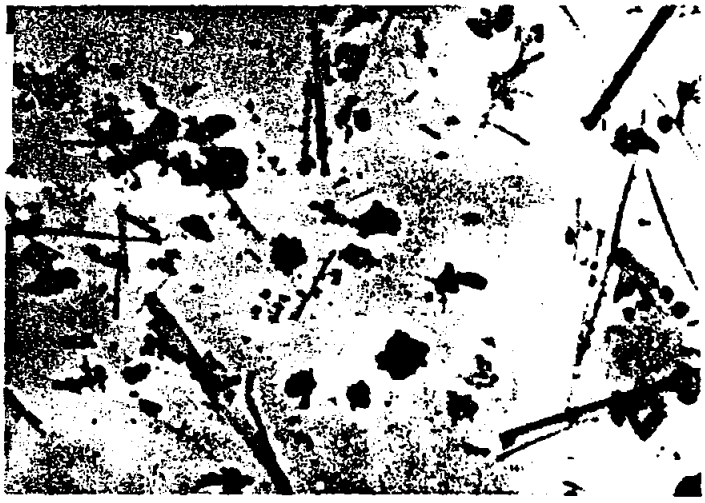
Diffraction Patterns



Electron Photomicrographs

Magnification
10,000 X

1 Micron

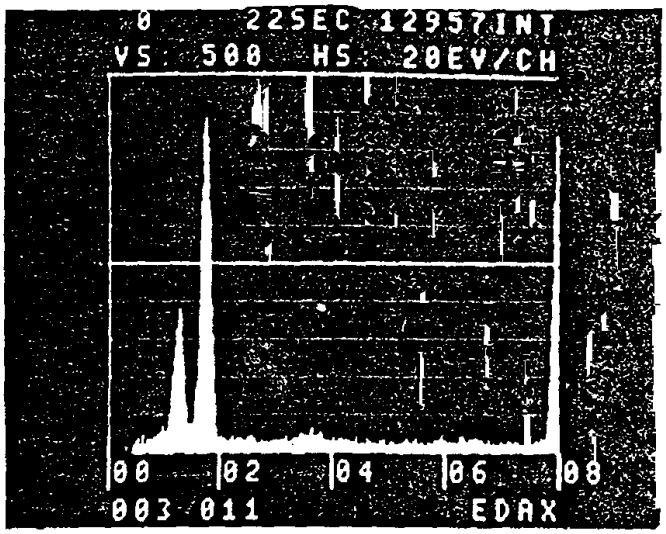


Magnifieation
1,700 X

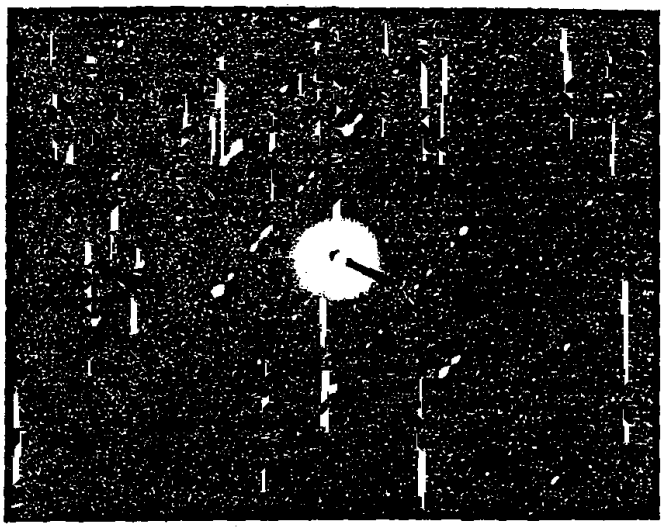
10 Micron

Figure 2. Typical Electron Diffraction Patterns and X-ray Spectra of Anthophyllite Fibers in Bulk Samples

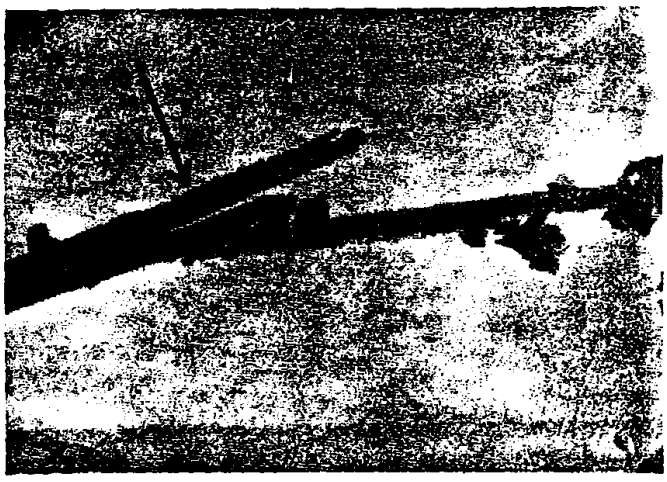
X-ray Spectrum



Diffraction Pattern



Electron Photomicrograph



Magnification
10,000 X 1 Micron

Magnification
5,000 X 1 Micron

MAGNIFICATION 3,000 X
1 MICRON _
10 MICRON _____

Figure 3. Electron Photomicrograph of Airborne Particulates in Mine and Mill

MAGNIFICATION 3,000 X
1 MICRON —
10 MICRON ————————

Figure 4. Electron Photomicrograph of Airborne Particulates in Mine and Mill

NYTAL 300
MAGNIFICATION 3,500 X
(X2.5)

Figure 5. Electron Photomicrograph of Airborne Particulates in Mine and Mill

Figure 6. Mean Yearly Impinger Dust Concentrations for Mine Operations

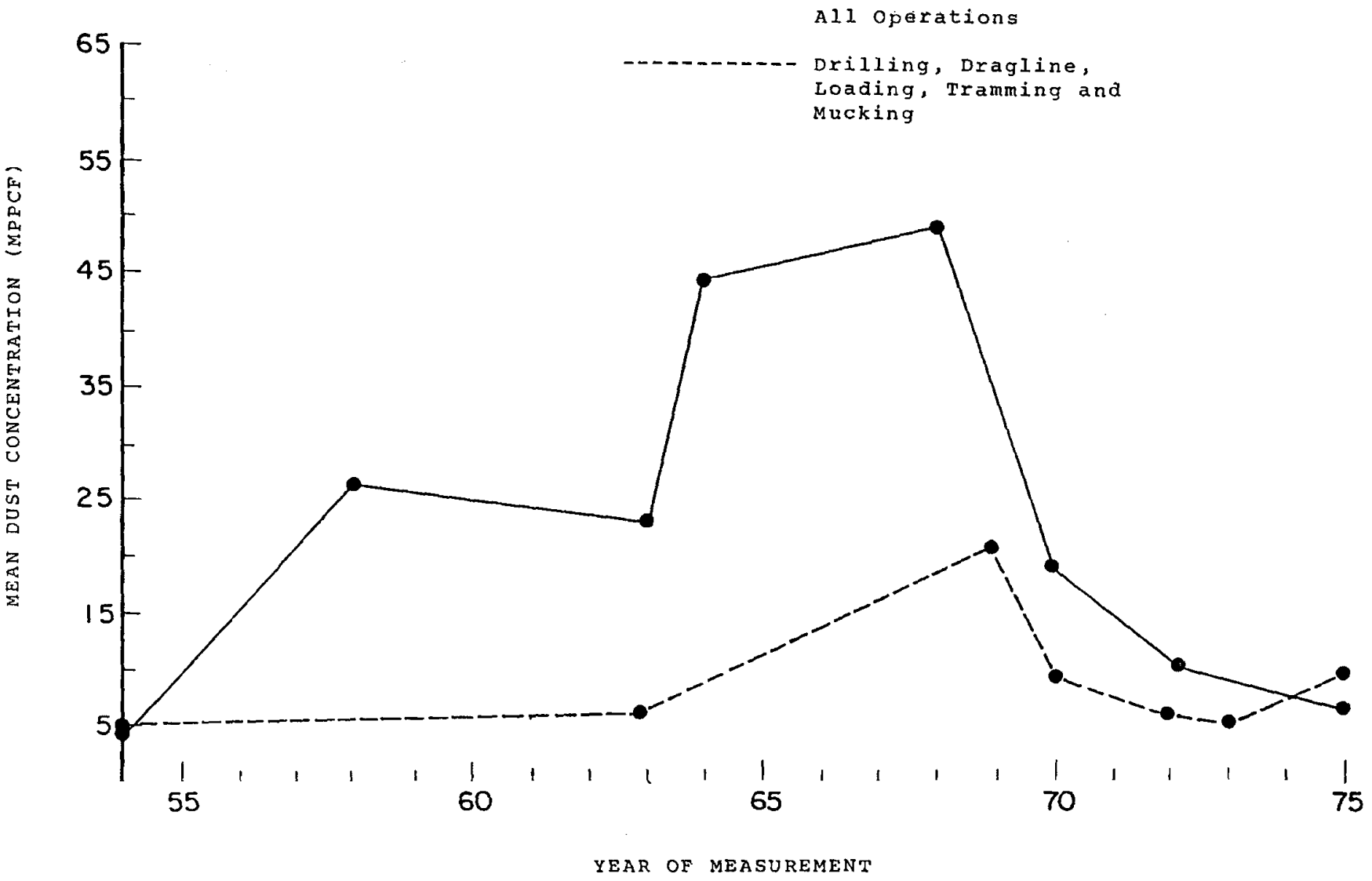
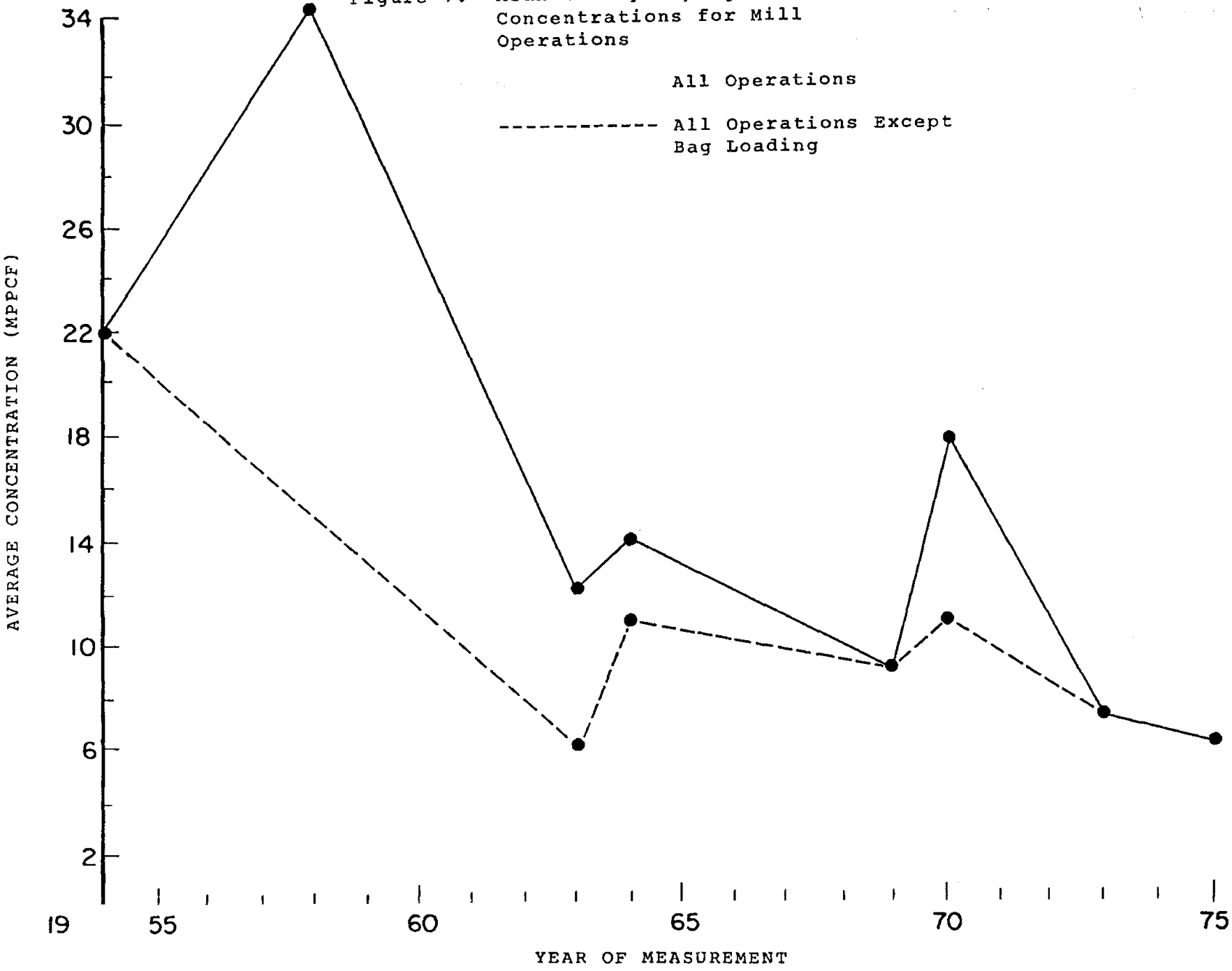


Figure 7. Mean Yearly Impinger Dust Concentrations for Mill Operations



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Appendix. Summary Statistics for NIOSH 1975 Industrial Hygiene Study (Tables A-1 through A-10).

Table A-1

Summary of Fiber Exposures in Mine Operations as Determined by Optical Microscopy

Operation or Job	Fiber >5 μm in Length per cc			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Crusher Operator (4)	7.7 - 14.7	10.3 ± 1.5	9.3	9.8
Trammer (25)	2.3 - 14.6	6.4 ± 0.7	5.1	5.6
Driller (5)	0.9 - 6.8	3.9 ± 1.0	4.6	3.0
Cageman (5)	6.0 - 18.2	10.3 ± 2.1	8.4	9.5
Blacksmith (3)	1.2 - 4.4	3.1 ± 1.0	3.7	2.6
Mechanic (12)	0.2 - 3.9	1.9 ± 0.3	1.9	1.7

( ) Number of samples

SE Standard error

TABLE A-2

Summary of Fiber Exposures in Mill Operations as Determined by Optical Microscopy

Operation or Job	Fiber >5 μm in Length per cc			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Mill Foreman (9)	2.4 - 16.0	5.8 ± 1.4	4.7	5.3
General Laborer (5)	1.5 - 13.2	5.8 ± 2.0	5.5	5.6
Crusher Operator (16)	1.7 - 11.6	5.5 ± 0.9	4.7	5.1
Hardinge Operator (14)	1.7 - 26.8	8.7 ± 1.8	6.4	7.9
Wheeler Operator (14)	2.6 - 29.1	9.9 ± 2.1	6.5	8.4
Packer (48)	0.2 - 21.0	6.9 ± 0.6	6.1	5.1
Packer Serviceman (11)	1.6 - 8.3	4.9 ± 0.7	5.5	3.6
Packhouse Foreman (5)	1.0 - 1.9	1.5 ± 0.2	1.6	1.5
Fork Lift Operator (15)	1.1 - 8.3	4.5 ± 0.5	4.6	4.0
Rail Car Liner (3)	1.3 - 5.6	3.8 ± 1.0	4.1	3.4
Bulk Car Loader (3)	1.6 - 2.4	1.9 ± 0.2	1.8	2.0
Millwright (3)	0.9 - 2.6	1.9 ± 0.5	2.3	1.9
Instrument Repairman (6)	1.2 - 4.0	2.8 ± 0.4	3.0	2.8
Machinist (3)	0.3 - 3.6	1.5 ± 1.1	0.5	1.8
Millwright Helper (2)	0.7 - 8.9	4.8 ± 4.1	4.8	4.0
Sheet Metal Worker (3)	1.2 - 2.2	1.8 ± 0.3	1.9	1.7
Oiler (4)	1.7 - 4.5	3.6 ± 0.7	4.1	4.0
Welder (3)	0.8 - 3.1	1.8 ± 0.7	1.6	1.9

( ) Number of samples

SE Standard error

TABLE A-3

Summary of Amphibole Fiber Exposures in Mine Operations as Determined by Analytical Electron Microscopy

Operation or Job	Amphibole Fiber Concentrations, fibers/cc			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Trammer (4)	8.9 - 22.6	16.2 ± 3.1	16.7	17.5
Driller (1)	9.5 - 9.5	9.5 - ---	9.5	9.5
Cageman (1)	17.5 - 17.5	17.5 - ---	17.5	17.5
Mechanic (1)	16.7 - 16.7	16.7 - ---	16.7	16.7

Concentrations are for positively identified asbestos fibers of all lengths

( ) Number of samples analyzed

SE Standard error

TABLE A-4

Summary of Amphibole Fiber Exposures in Mill Operations as Determined by Analytical Electron Microscopy

Operation or Job	Amphibole Fiber Concentrations, fiber/cc			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Mill Foreman (2)	18.4 - 33.7	26.0 ± 7.7	26.0	25.0
General Laborer (2)	9.0 - 36.6	22.8 ± 13.8	22.8	23.6
Crusher Operator (2)	9.0 - 15.6	12.3 ± 3.3	12.3	12.0
Hardinge Operator (2)	33.6 - 102.7	68.1 ± 34.5	68.1	70.6
Wheeler Operator (2)	18.2 - 25.5	21.9 ± 3.6	21.9	22.9
Packer (2)	31.9 - 41.8	36.8 ± 4.9	36.8	36.0
Packer Serviceman (2)	7.3 - 26.7	17.0 ± 9.7	17.0	11.1
Packhouse Foreman (2)	13.6 - 16.2	14.9 ± 1.3	14.9	14.6
Fork Lift Operator (1)	36.0 - 36.0	36.0 - ----	36.0	36.0
Machinist (1)	24.9 - 24.9	24.9 - ----	24.9	24.9
Welder (1)	9.9 - 9.9	9.9 - ----	9.9	9.9

Concentrations are for positively identified asbestos fibers of all lengths.

( ) Number of samples analyzed

SE Standard error

TABLE A-5

Summary of Respirable Dust Exposures in Mine Operations

Operation or Job	Respirable Dust Concentrations - mg/m^3			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Trammer (3)	0.13 - 0.95	0.64 ± 0.26	0.85	0.64
Scrapper Man (3)	0.58 - 1.72	1.29 ± 0.36	1.57	1.29
Laborer (1)	0.58 - 0.58	0.58 ± ---	0.58	0.58
Driller (3)	0.54 - 1.42	0.99 ± 0.26	1.00	0.98
Cageman (1)	0.23 - 0.23	0.23 ± ---	0.23	0.23
Repairman (1)	1.14 - 1.14	1.14 ± ---	1.14	1.14
Repairman Helper (1)	0.86 - 0.86	0.86 ± ---	0.86	0.86
Mechanic (1)	0.42 - 0.42	0.42 ± ---	0.42	0.42

( ) Number of full shift samples collected

SE Standard Error

TABLE A-6

Summary of Respirable Dust Exposure in Mill Operations

Operation or Job	Respirable Dust Concentrations - mg/m^3			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Mill Foreman (2)	0.52 - 0.64	0.58 ± 0.06	0.58	0.58
General Laborer (1)	1.14 - 1.14	1.14 ± ----	1.14	1.14
Crusher Operator (2)	0.60 - 1.13	0.87 ± 0.27	0.87	0.85
Hardinge Operator (2)	0.65 - 1.56	1.11 ± 0.46	1.11	1.09
Wheeler Operator (2)	0.45 - 2.73	1.59 ± 1.14	1.59	1.56
Packer (2)	0.39 - 0.95	0.59 ± 0.07	0.50	0.59
Packer Serviceman (2)	0.40 - 0.44	0.42 ± 0.02	0.42	0.42
Packhouse Foreman (2)	0.22 - 0.28	0.25 ± 0.03	0.25	0.25
Fork Lift Operator (3)	0.23 - 0.44	0.35 ± 0.06	0.37	0.35
Car Liner (1)	0.31 - 0.31	0.31 ± ---	0.31	0.31
Bulk Car Loader (1)	0.25 - 0.25	0.25 ± ---	0.25	0.25
Millwright (2)	0.16 - 4.64	2.41 ± 2.24	2.40	2.37
Instrument Repairman (2)	0.58 - 0.59	0.59 ± 0.01	0.59	0.59
Machinist (1)	0.40 - 0.40	0.40 ± ---	0.40	0.40
Millwright Helper (1)	2.95 - 2.95	2.95 ± ---	2.95	2.95
Sheet Metal Worker (1)	0.50 - 0.50	0.50 ± ---	0.50	0.50
Oiler (1)	0.72 - 0.72	0.72 ± ---	0.72	0.72
Welder (1)	0.75 - 0.75	0.75 ± ---	0.75	0.75

( ) Number of samples (all full shift samples)

SE Standard Error

TABLE A-7

Summary of Respirable Free Silica Exposures in Mine Operations

Operation or Job	Respirable Free SiO_2 Concentrations - mg/m_3			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Trammer (3)	0.012 - 0.025	0.020 ± 0.004	0.024	0.020
Scrapper Man (3)	0.012 - 0.012	0.012 ± 0.000	0.012	0.012
Laborer (2)	0.000 - 0.012	0.006 ± 0.006	0.006	0.006
Driller (2)	0.000 - 0.024	0.014 ± 0.007	0.014	0.014
Repairman's Helper (1)	0.000 - 0.000	0.000 - -----	0.000	0.000
Mechanic (1)	0.000 - 0.000	0.000 - -----	0.000	0.000

( ) Number of full shift samples collected

SE Standard error

TABLE A-8

Summary of Respirable Free Silica Exposures in Mill Operations

Operation or Job	Respirable Free SiO_2 Concentrations - mg/m^3			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Mill Foreman (2)	0.013 - 0.014	0.014 - 0.000	0.014	0.013
General Laborer (1)	0.014 - 0.014	0.014 - -----	0.014	0.014
Crusher Operator (2)	0.012 - 0.028	0.020 ± 0.008	0.020	0.020
Hardinge Operator (1)	0.012 - 0.012	0.012 - -----	0.012	0.012
Wheeler Operator (1)	0.012 - 0.012	0.012 - -----	0.012	0.012
Packer (7)	0.000 - 0.015	0.019 ± 0.002	0.013	0.010
Packer Serviceman (2)	0.000 - 0.013	0.007 ± 0.006	0.007	0.007
Packhouse Foreman (2)	0.013 - 0.016	0.015 ± 0.001	0.015	0.014
Fork Lift Operator (1)	0.000 - 0.000	0.000 - -----	0.000	0.000
Car Liner (1)	0.000 - 0.000	0.000 - -----	0.000	0.000
Bulk Car Loader	0.016 - 0.016	0.016 - -----	0.016	0.016

( ) Number of full shift samples collected

SE Standard error

TABLE A-9

Summary of Airborne Dust Concentrations in Mine Operations as Determined by Midget Impinger/Optical Microscopy Techniques

Operation or Job	Impinger Dust Concentrations, mppcf			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Trammer (3)	6.0 - 12.7	10.4 ± 2.2	12.4	10.1
Scapper Man (5)	3.8 - 24.5	14.0 ± 4.2	18.4	11.8
Driller (1)	11.7 - 11.7	11.7 - ----	11.7	11.7
Mucker (1)	15.8 - 15.8	15.8 - ----	15.8	15.8
Cageman (1)	2.0 - 2.0	2.0 - ----	2.0	2.0
Repairman Helper (1)	3.6 - 3.6	3.6 - ----	3.6	3.6
Mechanic	1.5 - 1.5	1.5 - ----	1.5	1.5

( ) Number of individual samples

SE Standard error

mppcf Millions of particles per cubic foot of air

TABLE A-10

Summary of Airborne Dust Concentrations in Mill Operations Determined by Midget Impinger/Optical Microscopy Techniques

Operation or Job	Impinger Dust Concentrations, mppcf			
	Range of Individual Samples	Mean (± SE) of Individual Samples	Median of Individual Samples	Time-Weighted Average
Mill Foreman (2)	1.8 - 3.9	2.9 ± 1.1	2.9	2.9
General Laborer (1)	0.5 - 0.5	0.5 - ---	0.5	0.5
Crusher Operator (4)	1.2 - 3.5	2.6 ± 0.5	2.8	2.6
Hardinge Operator (2)	2.9 - 3.9	3.4 + 0.5	3.4	3.4
Wheeler Operator (2)	2.5 - 3.6	3.1 ± 0.5	3.1	3.1
Packer (6)	2.0 - 6.4	3.6 ± 0.6	3.3	3.6
Packer Serviceman(1)	2.1 - 2.1	2.1 - ---	2.1	2.1
Fork Lift Operator(1)	1.6 - 1.6	1.6 - ---	1.6	1.6

( ) Number of individual samples

SE Standard error

mppcf = Millions of particles per cubic foot

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date November 22, 1985

From John Gamble

Subject Critique of NIOSH position on Vanderbilt talc as an asbestiform mineral increasing the risk of lung cancer in exposed workers

To Director, DRDS
Thru: Chief, Epidemiology Branch _____

I have addressed the NIOSH position in the OSHA hearings as they relate to New York talc and the asbestos standard. This position is based on the NIOSH study of Vanderbilt talc workers (2). Two related issues are in question:

1) Does the talc contain asbestos? The answer is relevant to the second question because studies of anthophyllite asbestos workers and the occurrence of pleural changes suggestive of asbestos exposure are used as supporting evidence for the conclusion that New York talc is a carcinogen. Neither in my view is correct as the anthophyllite study itself is not conclusive, and pleural changes have also been observed in talc workers where there is no known exposure to asbestos. There is substantial support for a negative answer to this question.

   The answer to this question in part depends on the definition used. If the NIOSH definition of an aspect ratio greater than 3:1 is used, then there are asbestiform particles in the talc. If a mineralogical definition is used, and if the complete regulatory definition of fibrous habit is applied, then Vanderbilt talc does not contain asbestos. It contains the nonasbestos varieties of tremolite and anthophyllite.

   While this question about the nature of the tremolite and anthophyllite in Vanderbilt talc is important and has been used to support the conclusion of excess cancer risk, the answer to the second question must stand on its own.

2) Is there an excess risk of lung cancer? We don't know from the NIOSH study because there is possible confounding from smoking, a high proportion of the lung cancer cases have short exposure times, and there is potential confounding from other exposures. Animal and other epidemiology studies also provide no support for the conclusion that Vanderbilt talc increases the risk of lung cancer.

Since there is no clear answer yet, NIOSH should not pronounce the talc as guilty, but should re-evaluate the mortality study and the position taken on tremolite asbestos in talc. In the rest of this discussion I will discuss the NIOSH position and interpretations presented at the OSHA hearings,(1) the argument for and against the issues of asbestos in the talc, and the health risk of lung cancer due to talc exposure.

NIOSH made the following recommendations at the 1984 OSHA hearings to promulgate a new standard for asbestos:

> "NIOSH recommends a revised asbestos standard. It is our conclusion that there is no safe concentration of exposure to asbestos [p.4]"
>
> This position is "consistent with" the CPSC report that "all major fiber types studied (i.e. chrysotile, amosite, crocidolite) appear to be capable of causing lung cancer, and all except anthophyllite, pleural mesothelioma in humans."[p.4]
>
> It is also consistent with the joint NIOSH/OSHA report (which "continue to be NIOSH policy today") and which state that "...there is no scientific basis for differentiating between asbestos fiber types for regulatory purposes." [p.4]
>
> Asbestos for regulatory purposes according to the joint NIOSH/OSHA committee and NIOSH "is defined to be chrysotile, crocidolite, and fibrous cummingtonite-grunerite including amosite, fibrous tremolite, fibrous actinolite, and fibrous anthophyllite. The fibrosity of the above minerals is ascertained on a microscopic level with fibers defined to be particles with an aspect ratio of 3 to 1 or larger." [p.2]

In the review of the biological effects of asbestos in humans, NIOSH has a section on "exposure to asbestiform minerals other than commercially mined asbestos". [p.18] The immediate concern in this section is with the studies relating to talcs in the Gouveneur Talc district of upper New York state. [p.19] The NIOSH industrial hygiene, morbidity, and mortality study of Vanderbilt talc workers has been reported in a NIOSH technical report(2) and published elsewhere.(3,4,5) The NIOSH testimony to OSHA concludes that: [p.19-20].

> "Talcs in this area...have been shown to contain tremolite and anthophyllite, resulting in elevated miner and miller exposure to these fibers."
>
> "...10 respiratory cancers were observed, but only 3.5 were expected. Excess mortality was also observed for non-malignant respiratory diseases."
>
> "Talc workers with greater than 15 years employment were found to have an increased prevalence of pleural abnormalities...FEV_1 and FVC reductions demonstrated significant association with particulate and fiber exposure".

A subsequent mortality study by Stille and Tabershaw(14) of the same cohort was also described. This study did not show any increased risk from lung cancer to the workers". This conclusion was discounted because:

a) There was "no analysis of mortality by latency interval";
b) "confounding factors were overlooked with regard to those previously employed or those that were not"; and
c) the study did not calculate the relative risk of lung cancer by dose.

I would add that criticisms (b) and (c) apply to the NIOSH study as well, and neither study has controlled for smoking.

Two of the conclusions derived from the NIOSH studies of Vanderbilt talc (2-5) have been contested as follows:

1) "It is recommended that exposures to these and similar 'talcs' be treated as any other asbestos exposure and subject to all provisions of the asbestos standard."(3) It is the contention of the company(10,11), OSHA(12), BOM(15), and NIOSH(7) that Gouveneur talc does not meet the mineralogical definition of asbestos.

2) "Exposure to talcs from the Gouveneur mining area are associated with an increased risk of bronchogenic cancer."(5) The association of lung cancer and "asbestos" exposure in the New York talc workers has not been confirmed in 2 other studies of these same workers(9,19), and so the company contends there is no increased risk of lung cancer from New York talc.

It is important that an attempt be made to resolve these two issues. The arguments pro and con are briefly summarized, and suggest that the company may be correct in their contention that New York talc is not "asbestiform" and that New York talc is not causally associated with increased risk of lung cancer. Since NIOSH authors published these original conclusions, NIOSH should correct them if they are incorrect. Before NIOSH makes any conclusions about health risk the mortality study should be updated and analyzed by latency and exposure and controlled for smoking and other exposures.

Issue #1: Does New York talc contain asbestos? (This section was written by John Jankovic)

If the talc is <u>not</u> asbestiform then NIOSH needs to say so, since we are the ones contending that it is.(1-8) The following comments provide insight into why the issue of the composition of the New York talc needs to be re-evaluated. It also points up the problems with the NIOSH definition of asbestos in mining and in the evaluation of exposure among the secondary users of ores. (See 10 also).

In April 1980 the NIOSH-OSHA Asbestos Work Group released a report (81-103) which defined asbestos to be

> ...chrysotile, crocidolite, and fibrous cummingtonite-grunerite including amosite, fibrous tremolite, fibrous actinolite, and fibrous anthophyllite. The fibrosity of the above minerals is ascertained on a microscopic level with fibers defined to be particles with an aspect ratio of 3 to 1 or larger.

The first sentence of the quote is sufficiently accurate mineralogically to be unambiguous in terms of which minerals and mineral habits should be considered for regulation as asbestos, i.e. only the fibrous habits. The second sentence, taken in context with the first or by itself, presents a problem in interpretation. I believe the work groups' intention was to delineate the size parameters of the fibrous minerals which should be included in performing a microscopic fiber count, not that mineral fibrosity was to be determined microscopically on the basis of a 3 to 1 aspect ratio. Proof that the former rather than the latter definition was intended, can be found in the same document.

> ...the condition of fibers in nature as a result of crystal growth is the only criteria for distinguishing asbestos from other silicates...Most properties mentioned above can only be measured on bulk samples (macroscopic properties of the parent minerals).

Thus it is clear that the intent of the work group was to direct attention towards the regulation of the six commercially exploited minerals of fibrous habit: chrysotile, cummingtonite-grunerite asbestos, anthophyllite asbestos, tremolite asbestos, actinolite asbestos and crocidolite.

Unfortunately, many have apparently interpreted the definition of asbestos to include any particle with a length three times its width regardless of the habit of the particle's parent rock.

With this definition of asbestos in mind, I reviewed the industrial hygiene study contained in NIOSH's Technical Report titled Occupational Exposure to Talc Containing Asbestos (80-115). (Ref 2) The report contains no physical or mineralogical description of the parent minerals. In the absence of information indicating that the parent minerals occur in a fibrous habit, it is not scientifically correct to classify elongate particles as fibrous (asbestiform) on the basis of morphological characteristics observed in electron photomicrographs. If information about the crystal habit of the deposit is available, then it should be included in the report; and if, as the company contends, the deposit is massive rather than fibrous, all terminology and references to asbestos or fibers should be removed from the report.

Issue #2: Whatever the conclusion on Issue #1, the question remains: Does exposure to New York talc pose an increased risk for lung cancer?

The arguments for (1-3, 5-8) and against this question are presented below and summarized in Table 1. The issue about asbestos in the talc is important in this regard because circular reasoning may have been used to assume a causal association between exposure to New York talc and lung cancer. However, the issue of risk of lung cancer from Vanderbilt talc should stand on its own.

Dement and Brown[7] list 4 criteria suggested by Hill[30] to be used in determining causation: strength of association, temporal relationships, biological plausibility, and consistency. Biological gradient (dose-response) and coherence are part of Hill's rules of evidence and have been added to assist in evaluation of the nature of the association. A second thought process necessary in applying these criteria is to assess the adequacy of the studies: e.g. control for confounders (other exposures and smoking).

While the arguments are briefly presented in Table 1, conclusions on each criteria will be presented:

1) Strength of Association: The strength of an association can vary because of the proportion of exposed workers with adequate latency in the total cohort. Thus the NIOSH study (2,3) shows an SMR for lung cancer of 270 (employed 1947-1959), the TOMA study[14] an SMR of 157 (employed 1948-1979). Additionally, association is possible because of confounding from smoking (not controlled in any study of New York talc) and other exposures. For example the TOMA[14] SMR for Talc workers with "known prior employment" was 214 and the SMR for "talc workers with no known work" was 76.

   Strength of Association by itself only rarely can provide a conclusive answer about whether an association is causative. It cannot in this instance. The moderately strong association observed in the NIOSH study is suggestive but certainly not conclusive because "the population available for study is small, the follow-up period is relatively short..., data on smoking are lacking, and previous exposures in other neighboring talc mines and mills represent a confounding factor."[6] Potential non-Vanderbilt employment increasing the risk of lung cancer.[19] includes working in lead mines, iron mines, aluminum pot rooms, aluminumum mines, construction, zinc mines, paper mills, and other talc mines.

2) Temporality: For a chemical agent to cause lung cancer, exposure to the agent must precede the onset of disease. The presence of a latency gradient (as demonstrated in the NIOSH study) is consistent with an asbestos etiology.

3) Biological Gradient: Is there an exposure-effect relationship within the population at risk? If the answer is yes, there is a strong argument for causation. Even though we are considering whether an agent is a carcinogen, and many consider the prudent policy is to assume no threshold, a causative association for asbestos and lung cancer is still expected to show a dose-response relationship under control for latency. A dose-response analysis was not done by either NIOSH[2,5] or TOMA[14]. Lamm and Starr in an update of there analysis presented to OSHA[20] a partial tenure by latency analysis:

Gross Tenure

	<1 year		≥ 1 year	
Latency	O/E	SMR	O/E	SMR
<10 yrs	0/.33	-	0/.58	-
10-19	0/.62	-	3/1.05	286
≥20	6/.89	674	2/1.48	135

The expected numbers in each cell are so small it is not possible to positively identify a biological gradient; certainly no dose-response association is substantiated. Finding four of ten deaths in the NIOSH study and 6 of 11 in the Lamm and Starr study with less than one year tenure suggests there is unlikely to be a dose-response association. NIOSH should not be too definitive about causation in the light of small numbers.

NIOSH also argues that "brief periods of exposure to elevated concentrations of asbestiform minerals may be associated with an increased bronchogenic cancer risk".[3] This assumption was based on a group of workers in a New Jersey amosite asbestos factory employed for short periods from 1940-44, and were generally not career asbestos workers. The transformed data by latent period for these workers is taken from Walker[38] and shows an apparent decline in risk after 20 years latency; the overall risk still appears high when latency is greater than 10 years. The similarity of SMR's between these two cohorts is tenuous, as expected numbers are quite small.

	Latent Period					
	5-9		10-19		20-29	
	Exp	SMR	Exp	SMR	Exp	SMR
Amosite	1.68	119	0	564	9.21	463
<10						
Vanderbilt	0.5	—	1.5	200	1.3	460

The other point in this argument is that the short-term workers would have exposure to elevated concentrations. Table 2 shows that even if the highest measured particulate ("fiber") exposure for the job held by a worker dying of lung cancer is used to estimate cumulative exposure, 6 of 11 had estimated cumulative exposures of less than 14 fiber-years (f-y), and only 2 had exposures over 100 f-y. Over 1/2 (55%) of the workers in the study population were millers, while at most 2/11 (18%) of the cases were millers. The mill appears to have higher dust levels than the mine. The lung cancer cases with long tenure appear to have jobs with similar exposure to cases with low tenure; they certainly have much higher cumulative exposure. There thus does not appear to be any suggestion from the environmental data and work histories that the short-term workers who developed lung cancer had elevated exposures.

The credibility of the dose-response argument is not sufficient to label Vanderbilt talc a carcinogen one way or the other. In fact a dose-response analysis under control for smoking has not been done, and no dose-response analysis other than greater or less than 1 year tenure as the exposure variable has been done.

4) Biological Plausiblity and 5) Consistency:

These 2 criteria are linked together as they rest on similar assertions, i.e.,

a) Vanderbilt talc contains anthophyllite asbestos (and contains tremolite and anthophyllite similar to other New York talcs).

b) If there is an increased risk of lung cancer among anthophyllite asbestos workers (and other New York talc workers), then

c) It is plausible that there should be increased risk in Vanderbilt talc workers.

Lets examine each assertion in turn:

1) a) Comparison with Finnish anthophyllite asbestos workers:

The Finnish anthophyllite is asbestos, while the anthophyllite in the talc is nonasbestiform. Since the Finnish workers are mining and milling asbestos, the "fiber" exposure is likely to be greater. Worker employment began at least a decade before talc workers which could affect both exposure and latency. The exposure is both quantitatively and qualitatively different.

b) Comparison with other New York talc workers: All New York talc studies except 2[4,18] were of other New York talc operations, and refer to populations with a substantial portion of their employment prior to the opening of the Vanderbilt operation, and prior to the introduction of wet drilling. Exposures were apparently much higher prior to 1946 (see Table 1, section 5). There is at least some variability in New York talcs, and none of the talc are well characterized in the medical reports. The significance of this variability is unclear. It should be possible to examine the mineralogy however. Exposures appear to be at least quantitatively different.

The effects of smoking may have been less in the older studies than more recent ones. The per capita consumption of cigarettes from 1925 to 1950 increased steadily from 1,285 to 3,522 cigarettes/person. A peak of 4,336 was reached in 1963 with a slow decline in per capita consumption for the next 15 years totalling about 3,965 cigarettes per person in 1978. The increasing use of filter-tip cigarettes starting about 1953 could offset the increasing per capita consumption.[47]

In short the very high talc exposures in the other New York talc studies and the unknown roles of smoking makes this comparison problematic.

2) Assuming for the sake of argument that the comparisons of anthophyllite asbestos and other New York talc studies with Vanderbilt are credible, is there an increased risk?

a) Finland: There were excess deaths due to lung cancer and asbestosis among miners and millers compared to controls (controls had excess cardiovascular deaths compared to exposed). There was, however, no control on smoking ("unusually common in Finland") and no dose-response analysis. The authors say "...it is too early to draw any far-reaching conclusions on the association of malignancy and anthophyllite exposure in Finland".(23)

"There was a three-fold excess of dyspnea and a two-fold excess of cough...for asbestos workers compared with the controls after adjustment for smoking".(23) There were more heavy smokers among asbestos workers. These are non-specific effects often seen in mining populations, and potentially confounded with dust and smoking.

A radiological survey in Finland of 431 former anthophyllite workers(30) with tenure ranging from 3 months to over 20 years had prevalences of 28% small opacities, 14% pleural changes without opacities, and 28% with both pleural and pulmonary changes. Of the 174 cases with pulmonary changes on the x-ray, 7% were rounded opacities, 7% were combined rounded and irregular, and 85% irregular opacities. Diffuse pleural thickening was higher in those with opacities than those without (about 70% diffuse pleural thickening among workers with opacities). The prevalence may be particularly high in this group as mean latency was about 20 years.

Vanderbilt talc workers(17) with 11-22 years exposure had an excess prevalence of cough and dyspnea of a similar magnitute to the Finnish anthophyllite asbestos workers.(23) The prevalence of small opacities was a much lower 3%. Gamble et al.(4) also showed an excess cough and dyspnea but reduced radiographic findings (2% small opacities, 1% pleural calcification, and 11% pleural thickening) among Vanderbilt workers compared to the Finnish asbestos workers. However when controlling for smoking the following prevalences were observed:

		Finnish Anthophyllite Workers(23)	Vanderbilt Workers(4)
Cough	Nonsmokers	17%	0%
	Smokers	33%	52%
Dyspnea	Nonsmokers	20%	0%
	Smokers	18%	20%

Thus the Finnish nonsmokers had about 20% more cough and dyspnea, while the Vanderbilt talc workers who smoke had twice the prevalence of cough and the same prevalence of dyspnea as the anthophyllite workers suggesting a smoking effect rather than a dust effect.

The comparisons of the radiographic findings of the Finnish anthophyllite workers[23] and Vanderbilt talc workers with 15 or more years exposure also show differences:

		≥ 15 years tenure		
	Finnish Anthophyllite %	New York Talc Workers %	Coal %	Potash %
Rounded Opacities	3.2	3.4	13.7	1.1
Irregular Opacities	36.3	3.4	5.3	0.7
Pleural Thickening	16	31.0	1.6	4.4
Pleural Calcification	33	3.4	0.1	0

These results show that Vanderbilt talc workers with 15 or more years exposure had a similar prevalence of rounded opacities, 1/10 the prevalence of irregular opacities and pleural calcification, and twice the prevalence of pleural thickening of former anthophyllite asbestos workers.

While there are not sufficient data on the demographic and exposure characteristics of the anthophyllite workers to adequately make these comparisons, the difference are highly suggestive and do not lend credence to the idea that the radiographic response is similar in these 2 groups. When the talc workers with 15 or more years tenure were compared to coal and potash mining populations under control for age, smoking, and tenure the only statistically significant difference was in the prevalence of pleural thickening. The pleural changes are not necessarily specific for asbestos, however, as a similar prevalence of pleural changes was observed among Vanderbilt talc and other talc workers in Montana, Texas, and North Carolina.[21,22]

The question remains unanswered: Are the differences in radiological findings between Vanderbilt and Finnish anthophyllite workers due to differences in exposure intensity, qualitative differences in the dust, difference in methodology, or what?

b) New York State talcs: There are several morbidity studies (31-37) and 2 mortality studies[25,26] of other New York talc workers. The 2 mortality studies are of the same

cohort, and the results are similar. The morbidity studies are difficult to evaluate for radiographic findings because the classification systems used are not the same. The prevalences of fibrotic infiltrations in the older studies is higher than the prevalence of pneumoconiosis seen in the Vanderbilt studies. There is no particular note of pleural thickening or calcification in these earlier studies, but it is not clear they were looked for specifically. It is <u>not</u> obvious therefore that there is, in fact, a consistent pattern of pleural changes among other New York talc workers, or whether there is a similar pattern of pneumoconiosis.

The mortality study[25,25] of New York State talc workers suffers from defects similar to the NIOSH study: small numbers (12 lung cancer deaths), and no smoking data. This is a high exposure group with 15 or more years tenure, 15 or more years latency and high dust exposure due to dry drilling. There was 1 peritoneal mesothelioma, as there was in the NIOSH study. An approximate 4-fold excess of cancer of the lung and pleura occurred during the years 1945-1959, but was close to expected for the years 1960-69. The latter period correlates with reduced dust (but still high "fiber" counts) after 1945.

On the issue of lung cancer the cited studies suffer from basically the same defects as the NIOSH study. They do not, therefore, provide support either for or against Vanderbilt talc as a causative agent of lung cancer. If it is to be used as supporting evidence the similarity of the constituents should be documented, smoking controlled for, and a dose-response analysis performed of the other NY talc workers.

Does the occurrence of a case of mesothelioma suggest increased risk as the presence of asbestos? Some comparative rates are summarized below:

	Number of cases of mesothelioma	Total Deaths	PMR %
Nonasbestiform mineral workers			
Vanderbilt Talc (2)	1	74	0.14
Other New York Talc (24)	1	108	0.09
Homestake Mine (14)	2	861	0.002
Asbestos Workers			
Anthophyllite Asbestos (22)	0	216	0
Tremolite-Actinolite (Vermiculite, 39)	2	161	1.2
Chrysotile miners and millers in Quebec (40)	7	3749	0.19
Asbestos Insulators - NY (40)	3	46	6.5
Asbestos Insulators (NY-NJ) (40)	32	421	7.6
Insulation Construction Workers (40)	23	446	5.2
General Population (40)			
USA - 1969			.03
Canada - 1970			.03

McDonald[42] also showed elevated risks among workers in the construction industry (including building trades, painter, sheet-rock spackling and building demolitions). Risk appears to be about 2 times expected.

Between 1953 and 1969 85 cases of mesothelioma were reported to the Finnish cancer registry. Asbestos exposures was probable in 11% of the cases, possible in 34% and no exposure in 55%. Occupational exposure to anthophyllite asbestos is high in Finland, yet the occurrence of mesothelioma is low.[43]. There were 0 cases in the cohort mortality study of anthophyllite asbestos workers.[22] The rates in New York talc workers was low compared to insulation workers and vermiculite workers, but similar to Canadian chrysotile miners and millers. No worker exposed to the nonasbestiform amphibole cummington-grunerite had mesothelioma.

The case with mesothelioma in the Vanderbilt cohort had worked in mines and construction for 28 years before working at Vanderbilt, where he was employed for 15 years in the mine. Latent period was 17 years.[19] Latency for 2 series of workers exposed to crocidolite was 20 and 24 years[44]. The latency for mesothelioma is usually very long (35-39 years for pleural and about 45 years for peritoneal mesothelioma.[46] The proportion dying of mesothelioma among workers exposed to crocidolite is quite high (~20%). It is not clear that the case with mesothelioma occurring at Vanderbilt talc was due to the talc because of: short latency and possible other asbestos exposure (28 years in construction). If the anthophyllite in the talc is to be compared to anthophyllite asbestos one would not expect any cases.

c) Coherence: This criteria is also concerned about plausiblity, and relates to the reasonableness in biologic terms. If asbestos causes tumors in animals, does Vanderbilt talc produce a similar response. There is some evidence it does not (Table 1).

Smith[27,28] has shown that injection of tremolitic talc from New York state into the pleural of hamsters produced no mesotheliomas. Similar injection of tremolitic talc from the western United States, tremolite asbestos and chrysotile produced mesotheliomas.

Stanton et al [45] implanted particles in the pleura of rats and tabulated the incidence of malignant mesenchymal neoplasms and examined the correlation with particle dimensions. They found the best correlation (~0.8) was with fibers measuring 0.25 μm or less in diameters and 8μm or more in length. A lower correlation was observed for thicker (up to 1.5 μm diameter) and shorter (4 μm or more in length) particles. Seven talc sample (including Vanderbilt talc) showed either no tumors or low tumor incidence (5-7%) that was not distinguishable from controls. Two samples of tremolite asbestos showed 100% tumor probability.

These studies show that long, thin asbestos fibers produce tumors in animals, but talcs and nonasbestiform tremolite from New York talc do not. Thus the coherence criteria does not support the idea of Vanderbilt increasing the risk of mesothelioma.

Summary

What then can we conclude about the carcinogenicity of Vanderbilt talc? What is needed is a population of adequate size and long enough latency[8]. In addition a dose by latency analysis should be done (but will still suffer from small size). Smoking is a known confounder for lung cancer, and has not yet been investigated in a case-control type mode. Other occupational exposures (both before and after Vanderbilt employment) have not been investigated. While analysis for these confounders may still not allow for a clear-cut answer, if there is a clear preponderance of smoking or other exposures that could explain the elevated lung cancer risk, then we may be able to better address the question of risk. The worst that can happen is to be in the same situation we are in now-unsure about the carcinogenicity of the talc. Until there are more conclusive or documented supporting arguments NIOSH should not conclude that Vanderbilt talc is asbestos, and that it increases the risk of lung cancer.

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Table 1

Is New York Talc responsible for excess lung cancer?

Arguments: Yes	No
1) <u>Strength of Association</u> "Strong associations were observed between exposure to New York talc and increased mortality due to lung cancer..."(7) "Statistically significant, three-fold increase in...lung cancer mortality...(6) Significant increase in bronchogenic cancer (9 obs vs 3.3 exp. $p < .05$, SMR = 270)	This is a moderate association(19) There is potential confounding from smoking and other exposures, and there could be a spurious association due to small expected number of lung cancer deaths.

Table 1 (con't)

Yes	No
2. Temporal Relationships Lung cancer was "observed more frequently among those who had satisfied a minimum latency period of 20 years than in those with briefer latency periods." Interval Time Onset of Employment: <10 years: OBS 0, EXP 0.5, SMR -; 10-19: OBS 3, EXP 1.5, SMR 200; 20-28: OBS 6, EXP 1.3, SMR 460 (p<.01)	This argument by itself is not conclusive. Expected numbers are low.
3. Biological Gradient "The conclusion reached in the TOMA study that there is '...an inverse dose response, i.e., higher risks of lung cancer with less occupational exposure...' is supported by an analysis which simply counts the number of observed deaths (and not the expected number of deaths) in each category of years employed. Such an analysis is not very meaningful".(6)	NIOSH has done no dose-response analysis. Lamm and Starr(20) presented an SMR analysis of workers with less than 1 year and 1 year or more employment at GTC: (gross tenure): <1 yr.: O/E 6/1.9, SMR 317* ≥ 1 yr.: O/E 5/3.1, SMR 161 Total: O/E 11/5, SMR 220 Lung Ca Of the 6 cases with less than a years tenure, 5 had worked in the mine: 2 for 2 months, 3 months, and 11 months. A carpenter had worked 8 days.

Table 1 (cont'd)

	Yes	No
4.	Biological Plausibility "The findings are biologically plausible in that..." a) "anthophyllite fibers were unequivocally identified in the dust to which workers were exposed..."(7) "Mineralogic analyses...demonstrated that talcs from the TMX mine contain fibrous/ tremolite.(6) McCrone and Mt. Sinai School of Medicine found 5-15% anthophyllite fibers by weight(7) and anthophyllite was identified as an important fiber contaminant in a previous report.(18). Since asbestos causes lung cancer, the strong association of excess risk of lung cancer and presence of asbestos for the talc suggest the association is causative.	This is contested: See discussion of issue #1 Talc from the Vanderbilt mine contains non-fibrous, nonasbestiform tremolite and anthophyllite(15,13,17)
	b) "...and the increased prevalence of pleural disease is a marker of exposure to asbestos fibers"(7)	Increased prevalence of pleural changes have also been observed in other talc workers with no known asbestos exposure, and the prevalence of pleural changes show no apparent difference between talc exposed populations.(21,22)
	c)"and is consistent with the findings in published epidemiologic studies of anthophyllite miners and millers"(7) in Finland such as ref. 23, 24. (See also consistency criteria for other NY talc studies(25,27).	Mortality study(23): The RR of lung cancer was 17 for asbestos workers who smoke, and 1.4 for non-smoking asbestos workers (21 lung cancer deaths);"...even though one half of the workers with exposure lasting 20 years or more died from lung cancer, it is too early to draw any far-reaching conclusions on the association of malignancy and anthophyllite asbestos exposure in Finland." 35 of 248 cases had asbestosis; only 8 of the 35 had lung cancer at the time of death, less than the 1/2 reported in other mortality studies of asbestos workers.(23) In a cohort mortality study(24) of other New York talc workers lung cancer SMR for males and females was 2.23 (n=13) and 0 (n=0) respectively. Asbestosis was 20/0 and 5/0; respiratory disease 27/8.9 and 7/1.2. There was no

Table 1 (con't)

Yes	No
5. Consistency "...results of the NIOSH studies are consistent with the large body of published epidemiologic data concerning respiratory effects of New York talc exposures."(7)	Talcs within the Gouveneur mining district are quite varied. Earlier studies are of these different mines, and dust levels were quite a bit higher than at Vanderbilt, at least prior to 1946.(25) Since the talc has not been well characterized, there was no control on smoking, and exposure was quite high, the relevance of the earlier studies is not clear. They do show that at high exposure levels there is increased pneumoconiosis. The effects on morbidity (PFT, symptoms) are nonspecific and cannot be necessarily attributed to asbestiform particles even if present. Radiographic findings are characteristic of dust exposure, but are not a clear cut response to asbestos.
Ref. 26: PMR for lung and pleura cancer was 11/3.2 (344) and inc. in 60-79 year age group (15+ yrs exposure prior to 1965).	Average increase of 14.6 years exposure prior to wet driller (1946) when mine dust counts dropped 90 times and mill average 5 times. No smoking information. Talc not described (but said to contain tremolite and anthophyllite asbestos.(25)
Ref. 25: (Added 5 yr follow-up to Ref. 26) PMR for Resp Cancer = 12/3.7 (324).	No dose-response or latency analysis; Excluded all with <15 yrs exposure.
Ref. 27: (Vanderbilt): 39 men with >10 years exposure; 3-fold excess dyspnea compared to local controls and 2-fold excess cough; 1/39 with pneumoconiosis; compared to 35 talc workers at a different plant: 13-fold excess of pneumoconiosis, 1.6 fold excess cough, 2.5 fold excess dyspnea, 4.5 fold excess lung crepidations among comparative (non Vanderbilt) talc workers.	Low exposures compared to pre 1946 exposures in(25) and (26); prescence of pneumoconiosis unlikely"

Table 1 (con't)

Yes	No
6. Coherence	Intrapleural injections of chrysotile, amosite, anthophyllite asbestos, asbestiform tremolite, and crocidilite produce pleural adhesions and "mesothelioma in hamsters, while Vanderbilt talc produced very little fibrosis and no mesothelioma.(28,29) Implants of tremolite asbestos in the pleura of rats produced neoplasms while talc implants did not show any detectable increases above controls.(45)

Table 2

Estimated Exposure of Lung Cancer Cases, identified at Vanderbilt Talc (from Ref. 19)

Case	Job Location/title	Date of Hire	Years Exposure	x Avg (high) fiber/cc	= fiber-years
1	Mine/Mucker	1948	.21	5.6 (14.6)	1.2 (3.1)
2	Mine/blacksmith and welder	1948	2.8	2.6 (4.4)	7.3 (12.3)
3	Mine/mucker	1948	0.2	5.6 (14.6)	1.1 (2.9)
4	Mine/mucker	1948	0.9	5.6 (14.6)	5.0 (13.1)
5	Mine/blacksmith	1948	0.25	2.6 (14.4)	0.7 (1.1)
6	Carpenter	1948	0.02		
7	Mine/mucker, Eimco	1949	3.8	5.6 (14.6)	21.3 (55.5)
8	Mill/machinist	1949	0.03	1.8 (3.6)	.05 (.11)
9	Mine/mucker, driller	1950	2.5	4.3 (10.7)	10.8 (26.8)
10	Mill/variety of jobs	1952	17.5	7.9 (26.8)	138.3 (469)
11	Mine/mucker, Eimco scraper	1956	16.8	5.6 (14.6)	94.1 (245.3)

Calculated cumulative fiber-year exposure estimated by multiplying average "fiber" exposure for job (from Tables A-1 and A-2 in Ref. 2) times years spent in that job. For Example:

Case 1: Tenure as a mucker in the mine was 0.2 years.

Average TWA exposure for mucker was 5.6 fibers/cc (highest values was 14.6)

Since there were no value for mucker, the average value for trammer was used.

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June 28, 1982

Mr. Konrad C. Rieger
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Dear Mr. Rieger,

Enclosed are my comments on the Critiques of the NIOSH study. I did not prepare anything on the Conclusions or Abstract since this would have been repetitive. I have also enclosed several "papers" I believe relevant and which I refer to in my comments. I fear the Toma study suffers from small size of the cohort in the same way as the NIOSH report. McDonald has a comment as to most all epidemiology studies looking at low exposure groups. While at this time I think there is evidence that exposure to talc at high enough levels will cause pleura and pulmonary fibrosis, the available data regarding carcinogenesis is not that convincing. Whether fibers as well as non-fibrous particles play a role is unknown, though the latter do appear to play an etiologic role in fibrosis. To say that the causative agent is "asbestos" in the true meaning of that word does not seem supported, though I am not qualified to pass judgment on the mineralogical identifications.

If there are queries regarding these comments, please do not hesitate to make them.

Cordially yours,

George W. Wright, M. D.

Comments regarding the Critique of "Review of Health Effects, etc."

On balance, the majority of the specific points raised in the critique seem tenable. I derived the impression that they were aimed primarily at the NIOSH contention that any excess of biological events is related to the presence of "asbestos" fibers. Given the almost missionary zeal of NIOSH and others with regard to asbestos exposure, it is probably understandable that they as well as some other more careful scientists would gravitate to the view that fibers they believe are identified as "asbestiform" present in some of the talc deposits and products must be the cause of the biological effects observed. As a non-mineralogist, I cannot judge the merits or dispute whether or not "asbestos fibers" have been or are now present in talc. I can understand the importance of the controversy since the term "asbestos" has such wide-spread adverse connotations. Nevertheless, it appears that fibers of some kind are present and these along with other particles must be considered as possible etiologic agents.

Several points seem to me worth mentioning. First, in the milieu of true asbestos exposure, it is assumed that the bulk of those particles having the shape of a fiber are in fact asbestos. The regulators are interested in the concentration of these fiber-shaped particles that are of a size to be respirable. They are not interested in the mineralogical definition of asbestos since all the fibers have been and are assumed to be asbestos in a clear-cut, known exposure to asbestos production or use. To carry this attitude into another setting (talc) could be an important and serious error or misconception. I believe it is proper, at least for clarity of thinking, to require better criteria than simple size and shape of particles if the term "asbestos" is to be used in an operation other than true asbestos.

The second point is of a biological nature. There is strong evidence that durable particles of diverse chemical make-up but having a "fiber" shape are biologically active if they are thinner than 1.5 micrometers and longer than 10 micrometers. All durable fibers in this size range regardless of their chemical or physical characteristics are suspect of being fibrogenic and carcinogenic until shown to be free of this effect.

assume that durable, non-asbestos (mineralogically defined) fibers in this size range are inert would seem to me to be unreasonable. In a setting where non-asbestos fibers of this size range are present and adverse biological effects have been shown to occur requires some specific evidence that such fibers are actually innocent.

The above comment brings me to the third point. In the talc setting, as well as in the true asbestos exposure setting, respirable particles other than fibers are always present. The possibility that these may be responsible, alone or in combination with fibers or other agents, must be strongly considered for any demonstrated biological effects of the total exposure. This is a point which I believe you quite correctly raised with me. Kleinfeldt, Porro, and also Gamble, have suggested this possibility. The latter did so because of the thickened pleura seen in Montana talc workers. J. C. Wagner, et al, have clearly demonstrated severe pulmonary fibrosis (pneumoconiosis) produced in rats exposed via inhalation to Italian talc, reported to be free of asbestiform materials. I would have thought the possibility, if not probability, that the pneumoconiosis (talcosis) and pleura thickening seen in talc exposed persons was not caused by asbestiform fibers but actually by the non-fiber particles would have been discussed in detail by NIOSH in their literature review.

A fourth point. To ascribe the biological effects of talc to fibers should take into consideration the dose of these fibers. This is especially true if the analogy of true asbestos exposure is to be utilized. While the actual fiber levels of talc exposure over the past years cannot be determined accurately, on the basis of known exposures in asbestos workers the former (talc) must have been far lower than the latter, especially those fibers thinner than 1.5 and longer than 10 micrometers. To use the analogy of true asbestos exposure would require evidence of levels of pertinent size fibers in the talc exposures that have equaled or exceeded those where biological effects of true asbestos have been observed. Of course, the effects may be due to a combined fiber and non-fiber influence. In any event, none of this was discussed in the NIOSH health effects review even though the authors must have been fully aware of the critical influence of "dose".

In the critique, the issue of prior exposure to potentially harmful dusts was raised as a possible explanation for thickening of the pleura, pulmonary fibrosis, and for the modest excess of bronchogenic cancer reported by some. While such possibilities do exist, there are certain requirements that must be met. The actual length and specific nature of the exposure, the age over which exposure occurred and the lapse time must be known. This is rarely available. There is considerable knowledge about other agents to which workers are exposed. Silicosis may develop (especially in exposures 30 or more years ago) in miners of other materials. Actually, to my knowledge, virtually all mines - and especially St. Joe Minerals Zinc Mine - have operated since 1940-45 at levels of silica that do not cause silicosis. Moreover, the radiographic appearance of silicosis is clearly different from the diffuse, interstitial fibrosis of talcosis and no radiographic evidence of thickened pleura develops. Neither iron or zinc mining, or exposure to silica, has been shown to be carcinogenic. A British iron mine where radon daughters were very high is an exception. To allege prior exposure as the cause of the biological effects reported in the talc populations is in my judgment very weak and would require far more specific data and validation than is available.

The point was raised in the critique (p.16) that excess of bronchogenic cancer occurred in the 60-79 year age group rather than 40-59 for asbestos-exposed workers. This may be explained by dose relationships. In some animal models, it has been shown that higher dose accelerates the onset of cancer occurrence. I believe higher cumulative doses of fibers occurred in the asbestos exposed populations. I am enclosing the Wagner study in which he reports fibrogenesis in rats and also another study regarding human experience that has some value with respect to whether or not talc might cause mesothelioma.

Comments regarding the Critique: "Cross Sectional Morbidity Study".

I agree in substance with the points raised in this section but would like to make some comments about them.

The choice of a control population must address the question to which the research study is directed. If the question is, "are there evidences of altered health (morbidity) arising out of exposure to talc"?, it is nonsense to compare the exposed population to another population exposed to another kind of dust. This is particularly inappropriate when serious alterations are known to have occurred as a result of such other dust exposure, as is the case with coal and asbestos The control group responsive to the question is one that is age and smoking matched but without known occupational exposure to dust, gases or fumes. Such populations are available though the matching with regard to cigarette smoking may not be exact. Even better is the use of an age-matched, etc. group living in the same community. A comparison of the findings in a group of talc-exposed to groups exposed to other dusts does have validity of a specific kind if properly done. The question being looked at is vastly different however. The question in that case has nothing to do with whether or not a specific dust cloud is or is not hazardous to health. Instead, the question being addressed is one of comparative severity of health effects. It has nothing to do with etiology. To conclude that since the health effects of two different dusts are similar, the etiologic agent must be the same, simply makes no scientific sense.

Further, as you have noted, a comparison of health effects of different dusts requires the evidence that other confounding influences such as cigarette smoking, personal hygiene, living conditions, etc. are held constant. No evidence is presented in this study that these variables were in fact adjusted for. We are asked to believe that cigarette smoking as to quantity, intensity, (coalworkers cannot smoke underground; hence the intensity pattern may differ from talc workers) tar, etc. content were the same. What is the evidence for it? I have the impression that the authors of this study took the easy way out. They already had data for coal and potash workers and did not want to do

they should have compared talc workers to the data available from the general public, etc.

I would emphasize the author's own self-criticism regarding structuring cumulative exposures (see lines 18 to 21). The use of current measurements in retrospective estimates of cumulative exposure over the past years flies in the face of all that is known about efforts to control dust currently and in the past.

Comments regarding the Critique of: "Retrospective Cohort of Mortality"

I have no disagreement with the points made in this critique except to raise a question about the Toma study referred to in comments regarding line 24. As indicated earlier to you, I did not see in this study the age spread of those with and without prior occupational exposure. I suspect the age of the latter is substantially less and hence the actual number of cancers of the lung that will develop at an age comparable to the group having prior exposure is unknown at present.

I would like to make some additional comments regarding the NIOSH study. Some of these points have been raised by you.

The size of the cohort under study is small by any standards. This is especially so if one removes the approximately 200 who worked less than a year. In fact, only 100 worked for 10 or more years. Several constraints are imposed by these small numbers. First, lacking reasonable knowledge of employment elsewhere, either before or after, casts great doubt on ascribing their health experience to the employment at this particular operation. Second, if you remove those having worked for less than one year, the cases of bronchogenic cancer drop to 4 and only one occurred in those employed 10 or more years. These numbers are really too small to be useful and should not be considered in a scientifically competent study. Third, if an "asbestiform material" is to be blamed as the agent, it would appear to be far more carcinogenic than true exposure to chrysotile asbestos since McDonald found no excess of bronchogenic cancer at levels of asbestos exposure considerably higher than that reported by NIOSH. McDonald found no evidence of excess bronchogenic cancer in a large population (1904 persons) exposed for 20 or more years to chrysotile at about 20/f/cc. Using the E-M rather than Light Microscope, as was done by NIOSH, this would estimate at about 1600-2000 f/cc. The talc "fiber" exposure using the E-M scope, as reported by NIOSH in Tables 6 and 7, was a small fraction of this level. They quote Seidman, et al, (72) as showing an elevated risk after short exposures. First, Seidman, et al, did not know total lifetime exposures. Second, though reported as brief, the exposures were very severe - as attested by the large number of asbestos fibers found in the lung tissue and by what was known about that particular "wartime"

One further point. Pulmonary fibrosis appears to develop at lower levels of asbestos fiber exposure than does excess bronchogenic cancer. If the cancers in the talc exposure were truly related to asbestos, I would have expected more radiographic evidence of fibrosis than was demonstrated in this study.

As to the deaths said to be due to NERD, one is at a complete loss to know how to evaluate them since actual causes of death are not given. Also, the total occupational histories are unknown. Given the chance for erroneous diagnosis on death certificates, large numbers in the cohort are essential. This is especially true in regions where workmen's compensation claims are an important custom.

To summarize this section, I do not believe the NIOSH report would pass peer review in its present state in any of the scientifically discriminating Journals.

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October 4, 1982
WCC 3254

Mr. Allen Harvey
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Dear Mr. Harvey:

In line with your request, I have reviewed the critique of the NIOSH technical report, "Occupational Exposure to Talc Containing Asbestos," DHEW (NIOSH) Publication No. 80-115, dated February, 1980. In connection with this review I have again read the major reports to which the authors refer, and have also reviewed the report from Tabershaw Occupational Medical Associates (TOMA) published in 1982, and the NIOSH criticism of that study. The last will be the subject of a separate letter.

While limiting my comments to the material above, with emphasis on the Vanderbilt critique, I have attempted to relate my review to what appear to be the principal questions at issue:

1. Which, if any, commercially-developed talc deposits in the United States contain fibrous minerals which should be called asbestiform minerals or asbestos?
2. In the mining and processing of talc from these deposits, are there airborne concentrations of asbestiform minerals sufficient to be hazardous to health?
3. Does the mineral talc exist in a fibrous form, and if so, how should this be defined? Is there any justification for calling such particles asbestiform?
4. Can talc, in the mineralogic or in the commercial sense, produce chronic health effects in the absence of asbestiform components?
5. Does the morbidity experience in the GTC mine and mill in New York differ from that in other New York talc operations, or from talc operations in Vermont, Montana, Texas, and North Carolina?
6. Is there an excess of deaths from non-malignant respirtaory disease (specifically pneumoconiosis) or excess lung cancer in individuals whose occupational exposures have been confined to those at the GTC mine and mill in New York?

The evidence bearing on the foregoing questions falls in several categories. Although these are not all equally developed in the NIOSH Technical report and will not all be discussed in detail in this review, they are listed as a guide to orderly consideration of the questions at issue. The categories are as follows:

2. Characterization of the shape, diameter, and lengths of particulates obtained from source materials, products, and samples of airborne dust for comparison with commercial asbestos known to be hazardous to health.
3. Measurements of the airborne concentrations of talc, silica, and fibrous particulates to which workers have been exposed.
4. Studies of morbidity, in which symptoms, signs, radiographic findings, and pulmonary function are compared with controls and comparisons are made between groups from different talc-mining areas.
5. Epidemiologic studies of mortality, with comparisons of groups from different talc-mining areas.
6. Studies of the pathologic findings in individuals with exposures in various talc-mining areas.
7. Studies in experimental animals.

The NIOSH Technical Report under review concentrates on a study of a single operation in St. Lawrence County, New York, but draws upon a heterogeneous mass of published literature. It unequivocally concludes that there are biologically significant amounts of asbestiform minerals in the deposit, the product, and airborne dust. The talc is referred to as containing asbestos, and it is stated that this has produced an excess of lung cancer and radiographic abnormalities in the workers. The results are contrasted with those in Vermont talc workers who are described as having been exposed only to "non-asbestiform" talc. The R. T. Vanderbilt critique, and the report of a study of workers at the same plant by TOMA, conclude that the NIOSH conclusions are not supported by the data. NIOSH in turn has prepared a rebuttal to the TOMA criticism which supports its original conclusions.

I agree with the basic thesis of the Vanderbilt critique, although there are a number of areas where I would modify the tone or delete criticisms which are either not of major importance or which appear argumentative. In addition to a literature review, there are three principal sections in the NIOSH technical report describing new studies: one dealing with environmental aspects, one covering a study of morbidity, and one reporting an historical prospective study of mortality. Of the three, the section on morbidity is most carefully written and supplies more information for independent review. The section on environmental studies suffers from a lack of mineralogic expertise and a consequent inconsistency in strict definitions and criteria for mineral and fiber identification. The mortality study has a tone of advocacy rather than scientific inquiry.

This report will use the Vanderbilt critique as a primary frame of reference in reviewing the topic. This will be done, section by section.

Abstract (pp ii - iv). I agree in general with the Vanderbilt critique of the abstract. The latter was carelessly written in view of the areas of disagreement. I would not have belabored a few of the points, such a metal carcinogenesis. I think it important to emphasize the fact that there were pleural changes in Montana, Texas and North Carolina similar to those in New York workers, contrary to the last sentence on page iv of the NIOSH report, "...exposures to such talcs are associated with an increased risk of

contradiction between the first line of the abstract, which describes the study as one of "talc miners and millers in upper New York", and the last sentence on page 2 of the introduction, which describes it as a study of "one mine and mill". A third very important point is the false statement on page iv (lines 5-9) that the time-weighted average (TWA) exposures to asbestiform minerals (anthophyllite and tremolite) were found to be in excess of present U.S. Occupational Safety and Health (OSHA) and Mine Safety and Health Administration (MSHA) occupational exposure standards. As will be pointed out under discussion of Industrial Hygiene, this misrepresents the facts.

Introduction (pp 1-2). I defer to the mineralogists for comments on the critique re lines 5 and 16. The comment in the critique re line 18 regarding delineation of "latent disease manifestations" is a statement of the obvious and could well have been omitted from the critique. The error in the original NIOSH statement was the assumption that there had to be "latent disease manifestations" associated with the work environments. The comments regarding line 25 are too detailed to apply to an introductory statement as to study design. Again, it is proper to criticize the expression "latent disease patterns" which has no scientific meaning. The comments on line 31 are entirely appropriate.

Page 2. Line 1. I have no comment. Line 6. Again, I leave the detailed mineralogic controversy to the mineralogists. I would not have included the last sentence regarding malignancy. Kleinfeld et al did mention this fact, but if they were correct in stating that the longest period of employment or elapsed time observed was 22 years, it was really a bit soon to make any statement regarding a population of 39 workers.

I again would like to call attention to the last sentence on page 2, which defines the scope of the study to be reported: "the present study restricts itself to that one mine and mill reported by the company to be producting nonasbestiform talc". This contradicts page ii of the abstract and the statement in paragraph 2 or the letter from Jay Beaumont (signing for David Brown) to Dr. Tabershaw on December 29, 1981, which states "The TOMA study attempts to assess the association between the risk from mortality and employment (or exposure) specifically at the R.T. Vanderbilt plant, whereas, the NIOSH mortality study concluded that one can only assess the association between mortality and exposure to talc in the area of Upstate New York".

Description of facilities studied. No critique available.

Industrial Hygiene Study (pp 5-10). The Vanderbilt critique of this section is excellent. I agree with its criticism of the confused and unscientific use of words like fiber, fibrous, asbestiform and asbestos. The most disturbing feature of the section, however, was the way dust concentrations based on phase contrast light microscopy and scanning electron microscopy (SEM) were handled in the New York study. Counts based on the former technique were reported as though the elongated particles in question were unequivocally fibers. For example, on page 7, line 30, it is stated, "TWA exposures to asbestos fibers greater than 5 um in length exceeded 5 fibers per cc for three of six job categories sampled in the mine and for 6 of

The authors certainly must have known that the foregoing was unjustified. Instudies of Vermont talc operations (Boundy et al, 1979), co-authored by Dement and published a year earlier, parallel counts by light microscopy and SEM had resulted in great reductions of so-called fiber counts. Whereas by light microscopy 9 of 15 counts had been reported as exceeding 2 fibers/cc longer than 5 um, the SEM counts ranged from 0 to 0.8 fibers/cc longer than 5 um. The authors attributed these lower counts to the ability of SEM examination to eliminate rolled talc particles and talc shards. It is strange that this possibility was not mentioned in the New York study, where table 6 lists airborne concentrations for all lengths of "positively identified fibrous amphiboles" as ranging from 9.5 to 70.6 fibers/cc by SEM, with only a minor caveat in the text stating these counts were far in excess of those obtained by light microscopy because of the inclusion of short fibers. From tables 8, 9 and 13, however, one can estimate how few of the particles seen by SEM could have been detected by optical microscopy and how very few of these could have been over 5 um in length. Fibers counted by SEM had median diameters of 0.13 and 0.19 um. (By light microscopy, counting below a diameter of 0.5 um is uncertain.) Median lengths were 1.4 to 1.6 um with over 90% shorter than 5 um. The data presented do not permit translation of the SEM figures into concentrations relevant to commercial asbestos standards, since these are limited to particles greater in diameter than 0.3 or 0.4 um and longer than 5 um. It should be pointed out, however, that the Vermont SEM "fiber" counts were very low, even though the length constraint was not applied.

It is highly improper for NIOSH to present SEM fiber data in this way and to imply any relationship of such concentrations to the OSHA standards for commercial asbestos. The latter were derived by NIOSH and OSHA from epidemiologic studies based on phase contrast light microscopy in situations where the dusts were known to have been largely commercial asbestos. Entirely different and much higher standards would have to by formulated for SEM fiber counts.

For the foregoing reasons, I support the critique relating to page 3 and amplification of the subject in the critique of page 8. Your reviewers caught the errors on lines 34 and 37, page 7, and in table 9, columns 2 and 4.

I have no comment on the critique re page 9 and 10.

Section on review of health effects. In my opinion, the critique of this section is for the most part correct. The literature review adds to the confusion regarding the health effects of talc and the various minerals, fibrous or otherwise, which may be present in commercial talc.

The section lumps studies which antedated modern methods for mineral identification and particle characterization, and uses terms like "asbestos", "asbestiform", "tremolite", and "anthophyllite" indiscriminantly. It therefore provides no literature base applicable to the report's title: "Occupational exposure to talc containing asbestos", or to the heading of the section: "Review of health effects from exposure to talc containing asbestiform and associated minerals". There is no need to belabor the point

This uncritical review does not help in solving the questions. A review of the page-by-page critique follows:

Page 11 -- The first paragraph of the critique correctly calls attention to the misleading title and the inappropriateness of many of the references. I was unable to find the source of the statement about "prior accusation of New York State talc being the only industrial talc contaminated with asbestiform minerals".

The second paragraph is a valid criticism. Massive inhalation of talc by children is utterly irrelevant.

The subsequent criticisms are accurate, but criticism of the small number of positive cases must be tempered by the relatively few talc workers (10 or 57) and slate workers (13 of 79) who had been employed for over 15 years. The dust exposures were of course extraordinarily high.

Page 12 and table 14 -- Table 14 is incorrectly captioned, since, for many of the groups included, there is no evidence in the reports that there were any fibers involved. I have not reviewed all the papers in detail in the interest of time, but consider most of the questions raised by the critique to be appropriate.

Page 13 -- I agree with most of the comment about the Kleinfeld, Messite, and Tabershaw report (reference 46). The statement about mesothelioma in the critique, however, is a little misleading. The authors did not attribute this tumor to tremolitic talc; in fact, at the time of the report in 1955, the association between commercial asbestos and mesothelioma was not known. The cause of death was obtained from one of the listed sources, not all three.

It is not necessary to be too defensive about mesothelioma and its diagnosis; certainly diagnosis without a complete autopsy is uncertain, but overdiagnosis prior to 1955 was unlikely. More importantly, other exposures to commercial asbestos would have to be ruled out. It is also important to remember that 15 to 20% of mesothelioma cases cannot be shown to have any known association with asbestos exposures. Therefore, one case cannot be given much weight.

Page 14 -- no comment.

Page 15, line 8 -- Although the point is not relevant to the main issues at stake, it is improper to criticize the report's statement that the findings of dyspnea were similar to the ones observed in anthophyllite asbestos workers in reference 47. It is literally true that the prevalence of dyspnea in the study by Kleinfeld et al (reference 11) and that found by Meurman et al (reference 47) were nearly identical, and both took smoking into account. The first study showed 23.1% in talc workers and 7.3% in controls, the second, 19.9% and 6.1%. The relative ratios were thus 3.16 to 1 and 3.26 to 1.

Page 15, line 16 -- The criticism of the paragraph on short sub-light microscopic fibers (incidentally, the word "[illegible]

studies very selectively. Reference 48 is of course inadequate in terms of its exposure history and description of lung particles.

I would omit the third paragraph on the second page of the Vanderbilt criticism of line 16, which reads "In order to substantiate their belief that particles below 5 um in diameter have been considered most harmful, a 1938 reference was cited". This refers to diameter, not length, and this point is not at issue. Sayers' report in 1938 was a general discussion of "Harmful Dusts" and correctly stated that particles under 5 um in diameter were in the respirable range and therefore more harmful than larger particles. The next two paragraphs of the critique also should be omitted as argumentative and non-contributory.

The remaining comments on page 15 are acceptable in my opinion.

Page 16 -- There were no comments in the ritique on this page, which continued a discussion of the Finnish experience with anthophyllite asbestos. I cannot agree that this is totally irrelevant to the main thesis if it could be demonstrated that appreciable numbers of anthophyllite fibers in the size ranges found in Finland occurred in talcs. The important fact is that this has not been demonstrated.

Mortality Studies

Page 16 -- Although NIOSH was uncritical when summarizing the Kleinfeld studies, I think it is improper and unwise to criticize the actual studies severely. Studies of proportionate mortality have their weaknesses, but ratios of 3 or 4 between observed and expected percentages can rarely if ever be explained by differences in smoking pattern or prior employment status. The high proportion of deaths due to pneumoconiosis (30.7%) in the 1967 report (reference 6), and 26.9% in the 1974 report (reference 5) would have had the effect of lowering the proportion of observed deaths due to cancer. The explanation for the majority of lung and pleural cancers having occurred in the 60-69 year age group rather than the younger ages as seen in asbestos workers and Finnish workers exposed to anthophyllite asbestos could be the one suggested by Kleinfeld et al, i.e. that the carcinogenic potential of talc and accompanying minerals is less than the other substances named and manifested by a longer latent period. This, coupled with evidence for very high dust concentrations prior to wet drilling, would suggest a weaker carcinogenic potential for talc-associated exposures, but not lack of any effect at all.

Although the excess of gastrointestinal tract cancers was not significantly elevated in Kleinfeld's study, there was a slight excess. It should be remembered that in commercial asbestos workers, the excess from cancers of these sites is relatively modest, in the order of a two to three-fold increase.

In my opinion, the NIOSH report was justified in its questioning any conclusions about the number of cancers in the 1960-1964 period. It is incorrect to draw conclusions about the two lung cancer deaths out of 17 total deaths in this period.

Page 17 -- The critique's statements about tremolite talc are thoroughly justified.

In conclusion, I agree with the overall appraisal of this section ; it appears to create confusion deliberately. This is reminiscent of the infamous Homestake mine study.

Cross-sectional morbidity study (pp 19-27, 55-74). The most serious deficiencies in this portion of the NIOSH report are the failure to mention the study of talc workers in Montana, Texas, North Caroline and Vermont, and the attempt to make dose-response relationships based on "fiber/cc-years" of exposure.

For the most part, this section is an exercise in overinterpretation of a relatively small data base. Comparisions with coal miners and potash workers is an interesting exercise, particularly if the studies were done by similarly trained teams using similar criteria and equipment. One is right in handling any comparisions cautiously, in view of many variables, including geographic and weather differences. No mention has been made of ethnicity and the lower normal pulmonary function of blacks.

Since pleural thickening was the most striking radiographic finding, more attention should have been paid to a description fo what was seen. Grade 1 pleural thickening is defined as being thickening up to 5 mm thick and not exceeding one half of the projection of one lateral chest wall. At this level, there are considerable variations between readers, as thickening can be simulated in postero-anterior films by fat or muscle shadows. Since talc workers and asbestos workers are reputed to have this radiographic change, any readers in any epidemiologic study bearing on this point should not be aware of the work history. Control films of non-exposed workers should be included. Nevertheless, I am not prepared to discount that there is excess pleural thickening in the eseveral populations of talc workers, since the differences reported were of considerable magnitude.

Page 19 -- As stated before, the comparisons with coal and potash workers are not completely unwarranted, but those with chrysotile and anthophyllite asbestos workers, etc., as well as those with synthetic textile mill workers, are unjustifiable in view of differing criteria and techniques. Tables 24 and 25 should never have been published.

Page 20 -- These comments are valid except I would not claim that the difference between 3.3% and 1.1% of irregular opacities was significant, based as it was on 4 and 1 cases respectively. It is imperative to show the numbers of individuals with unilateral and bilateral thickening as well as any that had grade 2 or grade 3 thickening. The comments re page 21 are excellent, as are those on page 23. With respect to page 25, I wouldn't overplay minor criticisms of the handling of the pulmonary function data, which shows little of major concern. The comments re page 26 are acceptable. The comment regarding line 6 on page 27, while true, is non-contributory, since there is no reason to believe that conditions similar to those in Czechoslovakia exist in localized areas of [illegible]

In my opinion, table 26, with its limited literature review of pleural thickening in workers exposed to "asbestos," is another example of jumping the gun from talc to fibrous particulates, to asbestisform minerals, to asbestos.

Retrospective cohort study of mortality, pages 29-32, 76-81. The Vanderbilt critique of this portion of the NIOSH report is well-prepared and almost entirely correct. NIOSH has not followed guidelines that have been recommended by OSHA for occupational epidemiologic studies, so evaluation is difficult. For example, tests used for statistical evaluation are not specified. Insufficient information is given on many points, so that independent analyses are impossible. One wonders what tables were prepared by the authors and discarded because they did not support predetermined positions. There are several questions involved in interpreting the New York study. First, was there truly an excess risk on lung cancer and non-malignant respiratory disease? If so, was this attributable to exposures during employment at the GTC mine and mill? If the latter was so, was this due to exposure to asbestiform minerals?

With respect to the first question, the fact that there were 10 observed deaths form lung cancer with 3.3 observed is fairly strong evidence of an increased risk; i.e., 2.73 times expected or an excess 173%. If the NIOSH group had proceeded from this poing with the wisdom of those who drafted the report of the Vermont study, they would have provided useful information.

The relationship to employment at the GTC mine is clearly not established by the study. The large proportion of the lung cancer cases with very brief employment periods is very important. It cannot be glibly explained by the extreme carcinogenic potential of something to which workers were exposed at GTC. This has not been a characteristic even of commercial asbestos.

The significance of brief employment seems more likely to be that it has created opportunities for employment in other jobs -- at least 3 cancer cases had talc employment prior to GTC and one had been in construction work. However, there were also prolonged opportunities for significant exposures after leaving GTC; i.e. 29, 23, 22, 22, 20, 20, 13, and 10 years for 8 of the 10 cancer deaths. Only two deaths from lung cancer occurred in men who were still employed, despite the fact that 9 of the 10 deaths occurred at pre-retirement ages. This is not consistent with an in-house hazard unless turnover was extraordinarily high.

The contribution of smoking to the excess lung cancers is hard to estimate. The authors are correct in stating that a true SMR of 273 cannot be explained by smoking unless smoking patters were widely disparate. While blue-collar workers tend to smoke more than average, and there is information to support a heavy smoking pattern in New York State, it is not likely to explain the observed difference. The fact that there was an upward trend in cancer mortality with increased years since joining, beginning work at TMX, does not disprove the smoking contribution, as a population with an excess smoking pattern will also tend to show an increase of lung cancer with increasing cumulative pack-years and age.

As was pointed out in the discussion of industrial hygiene data, it is highly improper for the authors to state, as they did on page 31, that "All these operations have been shown to have fiber exposures far in excess of established OSHA asbestos standards." This is a falsehood, after one considers the SEM data and the Vermont comparison of light and SEM counts in talc operations.

Review of the Vanderbilt critique line by line follows:

I have no quarrel with the overall appraisal but would cross out a paragraph here and there for the sake of brevity. The comparison between Vermont and New York studies is excellent. With respect to page 29, line 3 comment, I have no quarrel. Regarding line 31, while the use of New York rates would have been an illuminating exercise, it should not be made a critical issue. It is doubtful that this would have improved the study, because of the domination of New York State rates by urban areas. Their use in Upper New York State is not likely to be appropriate. The situation in Vermont is different. Line 39, I agree.

Page 30, line 8, you are so right--these statements show a peculiar preoccupation with anthophyllite, in choosing 3 references from Finland for this simple point of a 20 year "latency." The 20 year average latency is an argument against an association between GTC employment and lung cancer, since most asbestos-related lung cancers occur much later. The 20 year "latency" supports the TOMA contention that pre-GTC exposures were most important. Line 19--mentioning the death from mesothelioma at this point without comment is unobjectionable. I am more concerned with the way it was handled on page 32. Page 30, line 20--I think that the comment of "increasing risk of bronchogenic carcinoma with increasing latency" is an improper way of stating the actual observation which was that there appeared to be a greater risk of bronchogenic carcinoma with increasing interval since the start of employment at GTC. While this was true, the same pattern would be found for cancer associated with confounding variables, i.e. a heavier smoking pattern, and exposures prior to or subsequent to employment at GTC. Line 24 -- I would leave out the Liddell comment. With respect to the TOMA paper, it would be better to say that the data "suggest" rather than "indicate." Line 29--I would omit reference to the 3 additional deaths.

Page 31, line 17--the cigarette issue is overplayed; it is important, but almost certainly not enough to explain the difference observed. I would emphasize, however, the importance of the Gamble data on smoking in New York. The figure of 49% as an increased risk factor reports the excess that was described as probable in the uranium miner study, where cigarette smoking histories were available. To overstress the cigarette issue is nevertheless unwise, in my opinion. Line 22--this is true for all occupational epidemiologic studies, and one often has to make the assumption that there was no important difference between this population and controls. Lines 32, 24, and 38--I agree.

Page 32, line 1--it would have been more honest, as the critique implies, to have actually emphasized how extremely short (less than one month) several

continued to work at the mine and mill for many years did not approach a much higher rate. In fact, they did not.

The reference cited by NIOSH regarding short exposures is one by Seidman relating to workers heavily exposed to amosite in an asbestos factory, where even brief exposures were extraordinarily high. Even here, the excess risk for those employed less than one year is not convincingly shown, and there was correction of death certificates to arrive at "best estimate" diagnoses rather than "death certificate diagnoses." There was no gradient in incidence when those who worked less than 1 month, 1 month, 2 months, and 3-5 months. A slight gradient appeared in the 6-11 month group, and a marked upswing with one year or more.

Page 32, line 10--NIOSH handled the one diagnosed case of pleural mesothelioma in a biased way. It should have pointed out that a latency period of 16 years would have been very short for asbestos-related mesothelioma, where cases commonly occur much later. It should also have been pointed out that exposures during a prior 11 years in the construction industry would have been a much more plausible explanation, since asbestos exposures are common in construction work and the time from exposure to disease would have been in the expected range.

The NIOSH comments about Baris' work in Turkey are entirely irrelevant.

Conclusions and Recommendations. I completely concur with the critique regarding this section, which sums up, without qualifications, the dubious studies and reports of the literature that have made up this long, confused, and tedious Technical Report. There are so many examples of bias in the report that calling them to attention makes one sound contentious and tendentious. I would like to close with a list of questions that I feel should be addressed to the NIOSH authors, in the spirit of trying to get at the truth:

1. Why were fiber concentrations in New York, based on phase contrast light microscopy, reported without qualification, when it had been shown by electron microscopy in Vermont that the former method included rolled talc and shards?

2. Why did the New York report not include detailed information on the diameter and length distribution of the so-called tremolite and anthophyllite fibers to permit proper characterization and comparison with light microscopic data?

3. Why, in the face of the foregoing ambiguities, did the New York report continue to state that OSHA standards for asbestos had been exceeded?

4. Why was the point not made that there is no way of relating fiber counts by SEM with OSHA standards or NIOSH recommendations?

5. Why were the data on morbidity, especially those relating to pleural thickening, presented and discussed with no reference to [illegible]

6. Why were not the recommendations of the guidelines for epidemiologic studies, prepared in 1979 under the auspices of the Interagency Regulatory Liason Group, followed more closely?

7. Why, if the basis for the study was to determine whether or not there were health problems associated with the TMX mine and mill, as stated in the introduction, did the focus eventually shift to whether or not there were health problems in upper New York State mines and mills?

8. Why were employees' entrance criteria different for the Vermont and New York studies, i.e. one or more years employment for the former, but no minimum time for the latter?

9. Why were not separate analyses made of mine and mill employees in New York, when this had been found important in Vermont?

10. Why was the fact that the average time from first employment to death from lung cancer was 20 years treated as an argument in favor of an association between such employment and the cancer, when in fact it was an argument against such an association and in favor of smoking or prior employment being of major importance?

11. Why was the literature regarding the pathogenic potential of short fibers, particularly those below the light microscopic diameter range, so selectively presented, with no mention of the numerous negative animal studies?

12. Why was there no attempt to clarify the populations included in the various reports by Kleinfeld and others, to guide the reader as to which studies involved the same populations and which involved different types of exposure?

13. Why was there such limited and selective presentation of data in the mortality study, in contrast with the morbidity study, so that it is impossible to make independent analyses?

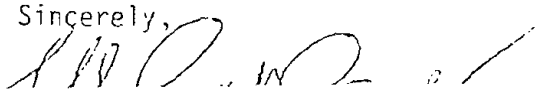
14. Why was there no mention of the studies in animals by William Smith or Fairleigh Dickinson, published in 1979?

15. Why, with the emphasis on anthophyllite asbestos, did the reports on the Finnish experience not point out the remarkable fact that despite extensive pleural changes, these anthophyllite asbestos-exposed individuals showed no excess of mesothelioma?

I apologize for being so long-winded. The subject seems to be conducive to this failing.

I send my very best wishes.

Sincerely,



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April 21, 1987
WCC 4554

Mr. Konrad C. Rieger
R.T. Vanderbilt Company, Inc.
30 Winfield Street
Norwalk, Connecticut 06855

Dear Konrad:

I have reviewed the questions that you gave me on February 5, 1987. The answers to most of them are fairly straightforward.

Question 1. Would occupational health be better served if OSHA used mineralogically correct asbestos definitions and descriptions?

The answer is yes! Regulations and control measures aimed at protecting health must rest on a factual base. The essence of this is definition of what is harmful and how much is harmful. There are always situations where gaps in knowledge and reliance on uncertain or expensive analytic methods make decisions difficult. While these encourage expedient and simplistic action, they should be faced up to honestly. If OSHA believes that miscellaneous mineral cleavage fragments should be regulated, it should say so and not call them asbestos particles.

Question 2. Do you feel that OSHA intended nonasbestiform minerals to be regulated more stringently than asbestos?

I am certain they did not. From 1969 through 1972 I was on an advisory committee of the Bureau of Occupational Health (later NIOSH) and was involved in reviewing the first NIOSH Criteria Document recommending a standard for Occupational Exposure to Asbestos. This was published in 1972 and set the stage for the first OSHA regulations promulgated in 1972. These standards were primarily concerned with protecting workers involved in mining, milling, processing, or using commercial asbestos. Nonasbestiform particles did not seriously complicate evaluations of environments where there were large numbers of unquestionable fibers.

Question 4 (no question 3). Did you interpret previous asbestos standards and proposed rules by OSHA to intentionally include the nonasbestiform varieties of tremolite, anthophyllite, and actinolite?

It never entered my mind that these regulations and proposals covered nonasbestiform particles, which by definition would not be included in an asbestos standard. The omission of qualifiers for tremolite, anthophyllite, and actinolite in 1972 [illegible]

1984 proposed rule change first appeared (Fed Reg 49, p 14122, April 10, 1984). I was astonished when this position was later reversed.

Question 5. In their assessment of tremolite and anthophyllite, June 20, 1986, do you feel that OSHA applied appropriate criteria to support their conclusion?

The entire section on this subject on pages 22630-22631 reveals a stubborn refusal to look at the evidence. The conclusion was: "OSHA therefore finds that there is insufficient evidence upon which to state with any degree of certainty that exposure to some forms of fibrous tremolite or anthophyllite is safe." This embodies two fallacies common throughout the document. First, use of the word "fibrous", when what was meant was "particles with length-to-width ratios greater than 3 to 1". Second, the apparent insistence on proving a negative before abandoning a standard. This point will be covered more fully later in a discussion of risk assessment.

I think it inexcusable not to deal honestly with the problems of the RTV study by Brown, Dement and Wagoner, i.e. dominant effect of short-exposure workers, probable importance of pre- and post-RTV exposures, failure to separate miners and millers, incorrect description of so-called fiber exposures, and inappropriate comparisons with Vermont studies. Findings in the Gamble et al study of radiographic findings and pulmonary function were again misrepresented, using comparisons with potash and coal miners and ignoring similarities to effects in other talc mines without tremolite exposures.

Throughout the section, imprecision in language causes confusion. For example, on page 22630, the document refers to "... the minerals tremolite and anthophyllite, which may be found in amorphous, fibrous, or asbestiform habits". I am not sure what is meant by amorphous in this context, but there is no mention of where the real problem lies, which is discriminating between cleavage fragments and real fibers, whether asbestiform or not. For some reason, they treat "fibrous" and "asbestiform" as mutually exclusive. All fibers are not asbestiform, but some are. All asbestiform particles are fibrous. When the term fibers is used indiscriminately to apply to all particles with aspect ratios of at least 3 to 1, communication becomes impossible.

Nowhere in the section is there any effort to compare the effects of nonasbestiform vs. asbestiform tremolite, anthophyllite and actinolite, after proper definition of terms.

Question 6. Has OSHA adequately considered all the studies cited in their list of references to ensure that their findings and interpretations are based on the best available evidence?

No.

Question 7. Has OSHA supported its findings (by substantial

The answer to this is definitely no. There has been no attempt by OSHA to assemble and review evidence in lower animals and man based upon clear definitions of what is meant by asbestiform and non-asbestiform, or by fibrous and non-fibrous.

Of even more fundamental concern is the misuse of quantitative risk assessments. On page 22647 of the June 20, 1986 OSHA document, the statement is made that "the health evidence for asbestos-related disease is far more convincing, due to the quality and number of human studies available, than the health effects data for any other hazardous substance". Further on, Dr. Nicholism responds affirmatively to a question, relating to asbestos, that "there really is a much more complete data base for conducting risk assessment and making estimates (of risk) than you would have for any other substance". These statements make the serious error of treating asbestos as a single substance, similar to benzene or carbon tetrachloride. This is not true, since there are six types of commercial asbestos with quite different properties, which come in many diameters, lengths and length-width ratios. Thus there is no way of making a quantitative risk estimate for a substance called asbestos. As Langer pointed out in his letter to the Envrionmental Protection Agency (April 18, 1986), criticizing EPA's proposed rules on asbestos, "There are clear differences in attack rates and attributable risks for the different fiber types". It is grossly improper to use the experience of amosite-exposed insulation workers to predict the health of school children exposed to chrysotile. It is equally improper to use such estimates for workers exposed to any form of anthophyllite or tremolite, and it is scientifically and legally indefensible to apply them to individuals exposed to nonasbestiform tremolite or anthophyllite.

Question 8. Has OSHA documented well designed and conducted studies of relevant human populations(p 22632) to suggest that family contacts of workers and persons living near tremolite, anthophyllite and actinolite mines (nonasbestiform vs. asbestiform) show a definite association between exposure to tremolite, anthophyllite, and actinolite, and an increased incidence of lung cancer, pleural and peritoneal mesothelioma, gastrointestinal cancer, and asbestos? (p 22755).

I know of no studies that show an increased risk of disease in family contacts of workers exposed to tremolite or actinolite nor in persons living near tremolite or actinolite mines. There have been studies in Finland showning pleural changes in individuals living in anthophyllite asbestos mining areas, but without evidence of mesotheliomas. This anthophyllite was unequivocally asbestiform.

Question 9. Has OSHA documented well designed and well conducted studies of relevant human populations to suggest that exposures to tremolite, anthophyllite, and actinolite have also been associated with an increased incidence of esophageal, kidney, laryngeal, pharyngeal and

Question 10. Since OSHA described "asbestosis" as "pulmonary fibrosis caused by the accumulation of asbestos fibers in the lung" and considered the diagnosis of asbestosis as being based on a "history of exposure to asbestos" (22755), would you consider the term "asbestosis" appropriate if the exposure is to nonasbestiform amphiboles?

Of course not; asbestosis can't be caused by any dust that is not asbestos.

Question 11. OSHA believes that the animals studies can provide valuable qualitative information on asbestos-related disease. For example, the animal studies show that all commercial asbestos types can cause cancer and pulmonary fibrosis (22632).

This is essentially true, but it is irrelevant to the argument as to whether or not nonasbestiform minerals should be treated like asbestiform minerals. Nonasbestiform tremolite, anthophyllite, and actinolite are not forms of commercial asbestos.

Question 12. Do you consider the conclusions of the NIOSH mortality study published in the NIOSH technical report, "Occupational Exposure to Talc Containing Asbestos" by Brown, Dement and Wagoner, strong, plausible and coherent?

I commented at length on this report two years ago and time has strengthened my earlier opinion. It is an uncritical and incoherent summary in which the authors appear to be principally concerned with reinforcing preconceived opinions. Leaving aside the complete failure to discriminate between nonasbestiform and asbestiform amphiboles, it uses terms like "fibrous" and "fibers" as though they were facts. There is no mention in the summary of the lack of correlation with length of employment -- indeed, the fact that so many cases occurred in those with brief employment is used as an argument for a high potency carcinogen which for some strange reason had less effect on those who worked longer. The reference used to support the likelihood of cancer from brief exposures to asbestos (in this case amosite) was by Seidman et al. They did not point out that the short period evidence was relatively weak, while very high cancer risks occurred as employment periods increased. This was quite different from the RTV-NY study. Also, the paper devoted a paragraph to speculation about the possibility of the single case of mesothelioma being possibly related to tremolitic talc, ignoring the fact that the 16 years since hire was quite short for mesothelioma, but highly consistent with asbestos exposures during 11 prior years of construction work.

Question 13. Would you comment on the strength and shortcomings of the Stille and Tabershaw study as discussed in the F.R. Notice? (FR Vol 48, No 215, Friday, November 4, 1983).

The criticisms of the Stille-Tabershaw study made by Brown et al and reported on page 51110 of the F.R. of November

There is criticism of comparing those with no pre-TMX employment with those who had had such employment because of low latency followup period intervals being more likely in those with no pre-TMX employment. However, the facts presented in the tables do not support this criticism.

Pre TMX exp	No.	Person-years	Mean PY per person	Deaths	Death per person	Deat per PY
Known	540	9,168	17.0	90	0.17	9.8
None known	115	2,184	19.0	23	0.2	10.6

In other words, those without known pre-TMX employment were not observed for only brief periods nor did they have the mortality pattern of a younger group of workers.

On page 51119, the criticism was made that "Brown et al pointed out that Stille and Tabershaw's conclusions had not adequately acknowledged that many study facility workers had been employed by neighboring talc companies with exposures similar to those of the study facility". This would seem to invalidate the original argument of Brown et al that they were reporting mortality attributable to the Vanderbilt operation. Now they have shifted to all upper NY mines. Brown et al never responded to the important criticism that they had not separated mill and mine employees, whereas Stille and Tabershaw had shown that only one TMX miller developed lung cancer, analogous to the Vermont findings. The double-standard was so apparent that it was unpardonable for OSHA to ignore it.

Question 14. Do you consider the Lamm study important enough to be considered in OSHA's review of "Taconite and Anthophyllite"?

Lamm's study, "Absence of lung cancer risk from exposure to tremolitic talc", dated February 14, 1986, is a valuable addition to the literature. It provides an independent analysis of the TMX data base in a way which permits direct comparison of New York and Vermont results and it is responsive to some of the criticisms made by Brown et al in 1984. I found its arguments cogent and convincing.

Question 15. How would you compare the mortality findings of the Vermont study with NIOSH "Occupational Exposure to Talc Containing Asbestos"? What conclusions do you reach from such a review?

There appears to be no significant difference in the health effects on workers in Vermont, where NIOSH says there are no hazardous contaminants in the talc, and in the New York mine and mill in which they claim that tremolite fibers cause lung cancer. In both instances there appear to be risks of non-malignant respiratory disease if large amounts of talc are inhaled, but no evidence of a significant lung

Question 16. What comments and suggestions do you have in reviewing the internal NIOSH memo?

The memorandum from John Gable to Robert Glenn (Director Divison of Respiratory Disease Services) on November 1985 was an excellent critique of the NIOSH position. Robert Glenn's more recent memorandum (June 25, 1986) to Richard Lemen (NIOSH's Director of OSDTT) is equally important in presenting well-reasoned and updated criticism of OHSA for its inclusion of nonasbestiform tremolite, anthophyllite and actinolite in an asbestos standard. It is incredible to me that the well-reasoned opinions of these highly qualified NIOSH scientists were disregarded.

Question 17. Do you consider the comparision (morbidity findings) of tremolitic talc miners with coal, potash and asbestos workers of greater significnace than the comparison with other mining and milling cohorts involving talcs of different mineralogy and morphology?

If one is considering the effects of talc, then non-talc miners and millers are appropriate for comparison. If one is considering the effect of tremolite and anthophyllite, whether fibrous or non-fibrous, then other talc workers with no exposures to tremolite or anthophyllite are more appropriate.

Question 18. Do you agree with OSHA (based on your replies to the previous questions) in its decision to regulate the nonasbestiform varieties of tremolite, anthophyllite and actinolite under the Asbestos Standard?

I certainly do not. These minerals should only be included in their asbestiform habit, with aspect ratios no less than 5:1 and preferably 10:1.

In conclusion, I hope I have made my opinions known without too much equivocation. I can provide more documentation if and when it is needed.

Sincerely,

W. Clark Cooper, M.D.

WCC:bs

Mp R.C. Kriger

November 28, 1977

A Review of

"Mortality Patterns Among Miners and Millers Occupationally Exposed to Asbestiform Talc" (draft 11/1/77)

by

Joan Gustafson Haworth
Charles T. Haworth

Like previous studies of potential occupational health hazards in the Talc industry, this study relies on statistical inference to establish a relationship between exposures to Talc and the mortality of former workers. The basic technique used in this paper is to compare the actual mortality pattern of workers who were initially employed at the mine between 1947 and 1959 with the mortality pattern of the total white male population. The report states that this technique found several causes of death to be more frequent than would have been predicted from that found in the total population. On the basis of this finding the paper arrives at the conclusion that "exposure to such talcs are associated with an increased risk of both bronchogenic cancer and non-malignant respiratory diseases." (page 1).

Sample and Population Problems

The findings of causation in this retrospective cohort study rest upon the miners and the white, male population being similar in all factors except their exposure to talc. If, for instance, the talc miners are heavier smokers than their cohorts then the smoking factor could be contributing to the respiratory death rates instead of the miners' exposure to talc. From the MESA Technical Assistance Health Evaluation we can get information about the smoking habits of the talc workforce. Looking at the 40 or older age groups, in order to match the mortality study's age group of miners hired between 1947 and 1959, we note that only 5 of the 46 miners (11%) were classified as non-smokers. The smoking rate of this group of talc miners is clearly higher than the rate among all white males. This suggests that the study's conclusion attributing the higher respiratory death rate to talc mining is not the only conclusion consistent with this data. An alternative hypothesis which this study does not disprove is that the miners' heavy smoking pattern is, in fact the cause of the increased respiratory causes of death.

In order to counter this potential problem the study cited another work, saying, "However, it has been estimated that

in a heavy smoking worker population, smoking by itself would increase the expected lung cancer mortality risk by no more than 49%" (page 6). It would be better to use mortality expectations based on a heavy smoking population similar to the talc miners. In the absence of a comparision the proposed base figures could have been applied to the core of the study's data analysis as presented in Table 4 of the report. If smoking increases the risk of lung cancer by as much as 49% then an adjustment in the table could be made to increase the expected deaths and a consequent lowering of the SMR. It would certainly have been helpful in reaching conclusions in this study to have seen the effect this smoking adjustment has on the significance of the various respiratory cancer death rates. It seems likely that even using the author's suggested percentage as an adjustment, despite its broad base, would have changed the statistical significance of the SMR for some of the mortality categories.

However, smoking is not the only factor which could be causing the higher level of deaths among the talc worker population. If the talc miners' life style or geographic location or other characteristics affecting respiratory death rates were different than the total white males used as this study's base, these differences could also contribute to the apparent differences in respiratory death rates which the study cites. Possible factors which should certainly be controlled for before the study is used include the New York State climate, the extent

and intensity of alcoholic consumption among miners since prevalence of serious respiratory conditions is higher for heavy users of alcohol, as well as the other occupations and places of employment of the talc miners before and after their employment at a specific talc mine. These factors may reduce or increase the difference in respiratory death rates between the two groups but they should definitely be considered. For example, it would have been possible at least to compare these talc workers to a population, age and time adjusted, of blue collar workers living and working in the Northeast U.S. Such an analysis would come much closer to comparing similar population groups and therefore, would allow a better identification of the effects on specific death rates, if any, of this type of talc mining.

Specification Problems

In addition to the failure to use the proper base population another basic problem of causation is present. In the technique used in the mortality study an individual who comes to a talc mine for a period of time, even as little as part of 1 month, and moves on to work at other jobs--such as lead mining or diamond drilling in this sample--may finally die of lung cancer. It is assumed in this study that the brief employment in a talc mine twenty years ago is the cause of the cancer.

Conclusion

The technique of comparing the mortality patterns of a sample of workers in an occupation with a similar population outside that occupation is an appropriate method to identify the effect of the occupation on disease specific mortality rates. Unfortunately, this study has serious errors of omission and commission which invalidate any results obtained. The wrong set of people were included in the population base and the specification of the people to be included in the sample leads to erroneous conclusions. Hence, the findings of this study, in its draft form, cannot be regarded as useful in determining the effect of Talc mining on workers health.

Charles Haworth PhM. 1 of 6

July 5, 1980

Comments on NIOSH Technical Report "Occupational Exposure to Talc Containing Asbestos", dated February, 1980

The conclusions of this study are based largely upon statistical inference. Through the use of cross-sectional morbidity and mortality comparisons, the authors have attempted to analyze the chronic effects of talc exposure upon worker's health. The following comments cover points in the report which are bothersome and/or incomplete to an outside reviewer. These points would need further clarification before I could make a final evaluation of the validity of their findings. The mortality study is particularly flawed. It is built upon a questionable technique with erroneous and misleading comparisons being made. Most of the specific comments are directed to the mortality study.

General Comments

Parts of this report have two characteristics that this reviewer found surprising in a study what would normally be expected to be objective. First, especially in the mortality study, the author seemed determined to find his result. When alternative hypotheses were equally consistent with the data they were dismissed. Data anomolies were also ignored or not commented upon.

The second characteristic, again found especially in the mortality study, is the failure of the author to include the data and information that would allow a reviewer to analyze the results for himself. The morbidity study, by contrast, provided extensive data.

Potential Measurement Error

Measurement error refers to the problems associated with collecting information about appropriate variables. There is discussion on pages 19-20 of the report about methods used to develop key health indices. The indicators were collected through a questionnaire, physical examinations, laboratory tests, and x-rays. Measurement errors could affect the data in several ways and hence, affect the study's conclusions. Either adjustments for such errors or sufficient information for the reviewer to make appropriate adjustments should have been included.

The questionnaire results are particularly sensitive to measurement error. The subjects of the questionnaire have great discretion in interpreting their own symptoms. As long as the subjects have no incentive to bias their interpretation, the discretion does not introduce measurement bias. However, it is possible that recent public discussion over "black lung" and other occupational related illnesses has made the subjects aware that a potential exists for some form of compensation if they are affected by talc. Con-

sequently, the data developed from workers' response is potentially biased. Any tests performed using this data must be viewed with caution and compared, for consistency with tests from other data.

Cohort Study of Mortality Methodological Problem

Underlying a longitudinal study is the implicit assumption that the past is the predictor for the future. But if there has been a shift in some key parameter that was present in the past and is no longer present, this implicit assumption does not hold true. On page 23 the report notes that "past environmental exposures in each job are not necessarily reflected by present exposure estimates". To the extent that these past high exposures were responsible for any present problem, the study will overstate the importance of current exposure. In addition, if the relationships are nonlinear or have a threshold effect, such as a certain level of accumulation before morbidity occurs, it is possible that the conditions 15 years ago are so different that the longitudinal study is inappropriate.

Appropriate Comparison

The mortality statistical study attempts to compare what actually happened (mortality patterns of past and present talc workers) with a benchmark. In this case the benchmark was age corrected mortality rates of the U.S. white

associated with an increased risk of developing not only pleural thickening and pleural calcification, but also both bronchogenic cancer and non-malignant respiratory diseases. (page IV of abstract).

There are serious questions about this technique and the comparisons made. For example, the data on present talc workers indicate a larger percentage of heavy cigarette smokers than found in the general white male population. Since there is a well known correlation between cigarette smoking and lung cancer we would predict this group of talc miners to have a higher lung cancer mortality rate than the general male population. This problem is mentioned in the report and then passed over by the use of an estimate that "...smoking alone would increase the expected lung cancer mortality rate by no more than 49 percent." Using the data found in Table 30 we can see how this estimated 49% increase could affect their findings on expected and observed causes of death.

Major Cause	Observed	Expected	SMR
Malignant Neoplasm			
Respiratory System	10.0	3.5	290**
Bronchogenic	9.0	3.3	270*

*p 0.05
**p 0.01

Page 31 of the report notes that "thus, cigarette smoking

and millers".

Suppose however, that the expected value was increased by the 49% cited as the maximum smoking connected increase. The table would then read:

Major Cause	Observed	Expected	SMR	
Respiratory	10.0	5.2	192	(significance unknown)
Bronchogenic	9.0	4.9	184	

This one adjustment to the benchmark data did significantly reduce the"increased chance of risk". Of course, actual data instead of the maximum should be used but it is clear that this effect cannot be lightly discarded. Instead, adjustments must actually be made for smoking before conclusions should be reached.

There are several other questions concerning the use of the total white male population as the reference group. Certain parts of the country have higher lung cancer rates than others (even after adjusting for occupational mixes). It would help the reader if NIOSH had provided more information about alternative reference groups instead of presenting only one. This is equally true for the other non-malignant respiratory ills shown. My judgment is that upstate New York would have more respiratory ills than the southwest. However, that is just speculation. More discussion and data by NIOSH should be given to allow the reader the opportunity to evaluate alternative benchmarks

Observed Data

Not only is there a question about the appropriate reference group, there are also very serious questions about the procedure used in measuring the frequency of deaths. Every worker employed at some point in time at the facility and who had died, was assigned a cause of death. Reviewing the list of individuals on page 80-81, one is struck by the fact that most of the deceased were engaged in occupations either before or after employment at the talc facility, which had some potential health problem. For example, all of the eight victims of respiratory system cancer whose work experience was known, had been engaged in other types of mining and/or construction. This is important from two viewpoints.

1) Should the benchmark be all white males when these miners have been employed in other industries with potential health hazards?
2) Could the other employment experience have led to the same results without the talc mining experience?

This problem can perhaps be seen more clearly in an example. One of the victims had worked at a rock quarry, aluminum plant and iron ore mine, in addition to the talc mine. If NIOSH were conducting a similar study of these other industries, they would have also assigned the death to those

against four industries with the result that other industries would also show higher than predicted frequency of mortality. Given their methodology it is possible for every industry in the U.S. to be above average risk.

Clearly, some more thought needs to go into such evidence before one would draw conclusions from it.

Significance Level

Mortality, like many other events involving humans, has a random element. The technique used in statistical studies is to determine whether the observed frequency of a mortality source differs from the expected frequency by more than one could reasonably expect to occur by chance.

In this report, the chance of this difference occuring by chance is shown as an estimate indicating a probability. For example, ($p<.05$) indicates that there is less than 5 chances in one hundred that the difference between observed and expected could occur by chance. Again no information is provided on the statistical test nor the results. This makes it difficult for a reader to determine whether a factor such as acknowledged smoking could change the results. Also, if certain statistical tests, e.g. chi square, were used there are restrictions on their use with small samples which are not always recognized. Since the report does not indicate which test was used, it is very difficult to evaluate the statistical findings.

Summary

I've concentrated my discussion on the mortality study since that study is the bottom line of potential health hazards. To put it mildly, the study has methodological weaknesses. What is most bothersome is that the report draws conclusions (as shown in the abstract) upon such a shaky foundation. It does not present the data and facts necessary for an intelligent review of either the conclusions or the methodology.

United States Department of the Interior

JUL 7 1982

GEOLOGICAL SURVEY
RESTON, VA. 22092

June 29, 1982

Dr. C. S. Thompson
Manager-Research and Development
R. T. Vanderbilt Company, Inc.
30 Winfield St.
Norwalk, CT 06855

Dear Dr. Thompson:

At your request, I read the NIOSH technical report of February 1980 (DHEW-NIOSH publication No. 80-115) titled "Occupational exposure to talc containing asbestos." The authors of this document classify oblong silicate mineral particles having a length to width ratio of 3:1 or greater as asbestos - regardless of the overall size of the mineral fragments. The number of "asbestos fibers", so defined, found in air samples collected at several work sites of a talc mining and milling industry varied from 9.5 to 70.6 "fibers" per cubic centimeter (Table 6). If these were truly asbestos fibers such concentrations could present a moderate to severe health hazard to those enduring long exposures. However, the average length and diameter of these "fibers" (Table 8, 9) is 1.5 μm and 0.16 μm, respectively. Over 90 percent of the "fibers" counted were less than 5 μm long (mislabeled <0.5 μm in Table 9). There is no epidemiological evidence in man nor evidence from animal experiments that such short mineral fragments at these concentrations cause a measurable increase in disease.

A similar misidentification of asbestos fiber has been made in the Environmental Protection Agency document EPA-450/3-81-006, "Assessment and control of chrysotile asbestos emissions from unpaved roads" (May, 1981). In this document, it is stated (p. B-11, lines 13-14) that the average fiber length (asbestos) is approximately 1.0 μm and average diameter is approxiamtely 0.06. In both the NIOSH and the EPA studies mentioned above, positive identification of the particle type was generally not made. The designation "asbestos" was usually made only on the basis of particle shape.

A significant number of airborne mineral particles from most crushed, blasted, or milled rock will fit the shape criteria used in these EPA and NIOSH reports to define asbestos. If these documents become a basis for national regulatory policy then most mining operations can be considered to present a possible asbestos health hazard. The implications to all industries involved with mining and milling or the utilization of rock products, is apparent.

Sincerely,

Mac Ross
USGS

R.T. Vanderbilt Company, Inc.
INDUSTRIAL MINERALS AND CHEMICALS

30 WINFIELD STREET, NORWALK, CONNECTICUT 06855 • (203) 853-1400
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April 25, 1988

Mr. David Brown
Epidemiologist
NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
4676 Columbia Parkway
Cincinnati, OH 45226

Dear Mr. Brown:

At our recent meeting in Atlanta, you raised several questions which, upon reflection, I would like to further comment upon.

1. The most critical point involved a request to explain the diffraction patterns, x-ray spectra and photomicrographs exhibited in the 1980 Technical Report. These exhibits are clearly suggestive of asbestiform tremolite and anthophyllite. I have copied and commented directly on pages 82, 83 and 84. Basically, there are a series of problems reflected here. Photos of some true asbestiform fibers are shown but none are identified. Instead, it is inferred these particles are tremolite or anthophyllite by selecting particles for x-ray diffraction and SAED patterns which are either cleavage fragments or a talc fiber confused as anthophyllite. Talc may present the same x-ray spectra as anthophyllite due to the same 2 to 1 silica/magnesium ratio and overlapping range. Talc fibers also reflect a similar 5.3 angstrom spacing on SAED patterns.

To support these comments I have also attached photomicrographs taken after our meeting to demonstrate how talc fibers can be identified by refractive index oil (use of Becke Line). I have also enclosed an analysis report prepared for us by Dunn Geoscience Corp and an internal line by line critique of the IH section of the Technical Report. In our experience, the "fibers" referred to as tremolite and/or anthophyllite turn out to be talc or transitional. Although others could better explain the mineralogical and analytical complexities inherent in this dust population, I hope the attached helps clarify the basic problem for you. A letter from Dan Crane (OSHA's Salt Lake City lab) to Greg Piacitelli is also attached. We feel Mr. Crane presents a reasonable description of our talcs composition as well. Please feel free to share this information with whomever you wish. Hopefully a meeting can be arranged to address these and other points in detail when our dust analysis project is ready for OSHA submission.

Of course, the next question which invariably arises is the health effect of talc fibers. After all (so the popular theory goes), if some of them are asbestiform wouldn't they be carcinogens? Our response to that question includes the following: (a) talc is not listed as a regulated asbestos mineral (b) these fibers were present in animal studies which yielded no tumor development while regulated asbestos minerals did (c) even among asbestiform minerals characteristics vary (e.g. surface charge, hardness, etc.) and the carcinogenic potential among regulated asbestos differs (e.g. chrysotile vs. crocidolite). Hence, some evidence would be necessary to show a carcinogenic association to fibrous talc (d) efforts to quantify the presence of these particles in air samples reflects particle per cc ranges magnitudes below any existing standard - their presence is of academic interest only.

2. A question was raised as to why we said dust exposures in other area talc operations were asbestiform while ours was not. At the time the statement was made, it was believed that ores previously processed from certain area mines (e.g. the Freeman mine, the 2 1/2 and 3 1/2 mine, etc.) contained very fibrous material and some of that fiber was believed to be amphibole (suspect anthophyllite asbestos but never confirmed). Besides these fibers, past talc mining operations frequently mined material with a high fibrous talc content (significantly higher than that mined by GTC). The Dunn Report reflects considerable data on one such deposit (referenced at mine #3). A good comparison between that deposit and the ore mined and milled at our operation can be seen on pages 16 and 17 in that report. Our mineralogist provided a sample of this material to John Dement but no mention of it was made in the Technical Report.

Regardless of the exact "fiber" content, it is clear past talc mining posed significantly different airborne particulate exposures than those encountered at our mine and mill. It is clear the concentration of dust was significantly higher as well. If you reference the last paragraph of page 31 in the NIOSH Technical Report (attached), the importance of this point should be apparent.

As for why particle characteristics in other operations appeared the same as ours, there is a perfectly plausible explanation. As noted at the meeting, Dr. Dement did not collect the comparison samples. Instead, samples MSHA had collected were characterized. While I expect there is nothing wrong in doing this we cannot tell from the Technical Report if these samples were collected at a mill

processing ores from the mines I have referenced. If we had dates for the samples, records might be available to reflect exactly what ore grades were being processed at the time. Ores from these high fiber mines were routinely processed but ores more typical of our own were routinely processed as well (in fact, more often processed). Hence, to say the two talc dust populations are the same, (without ore specific information) is misleading and is likely incorrect.

I hope the above clarifies my comments of April 20th. Please feel free to phone if I can assist in anyway.

Very truly yours,

R. T. VANDERBILT COMPANY, INC.

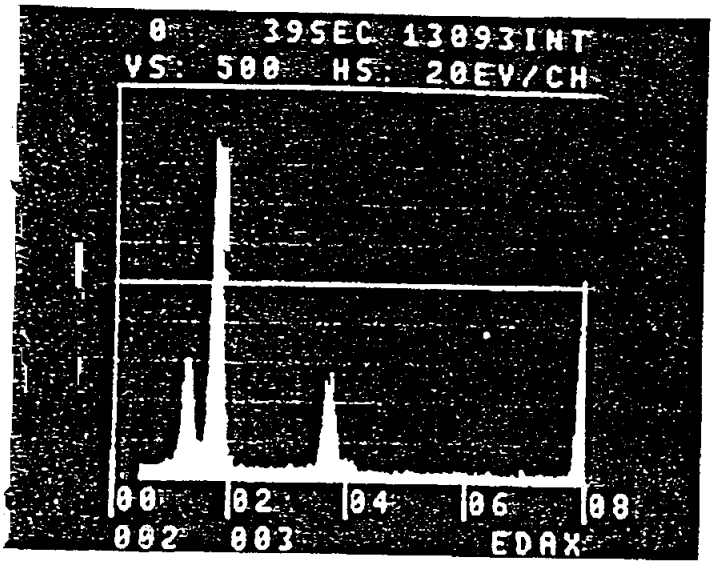
John W. Kelse
Corporate Industrial Hygienist
Manager, Occupational Health & Safety

JWK/sk
attachment

cc: Ms. Diane Porter, CDC
Mr. Robert Glenn, DRDS

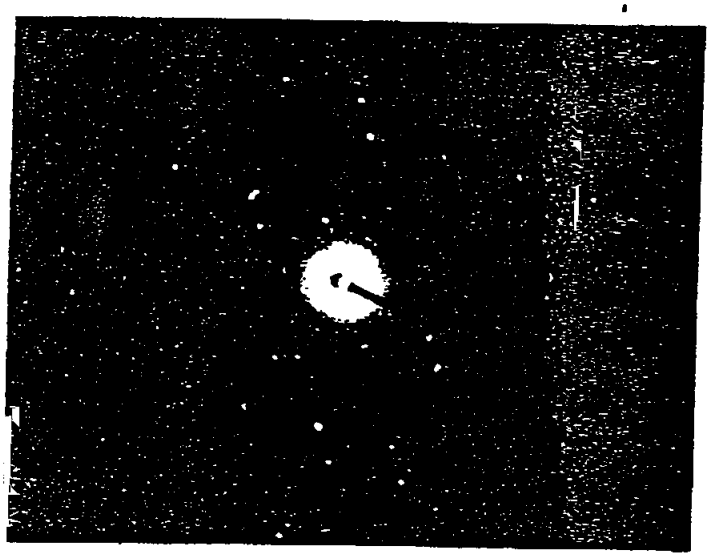
Figure 1. Typical Electron Diffraction Patterns and X-ray Spectra of Tremolite Fibers in Bulk Samples

X-Ray Spectrum



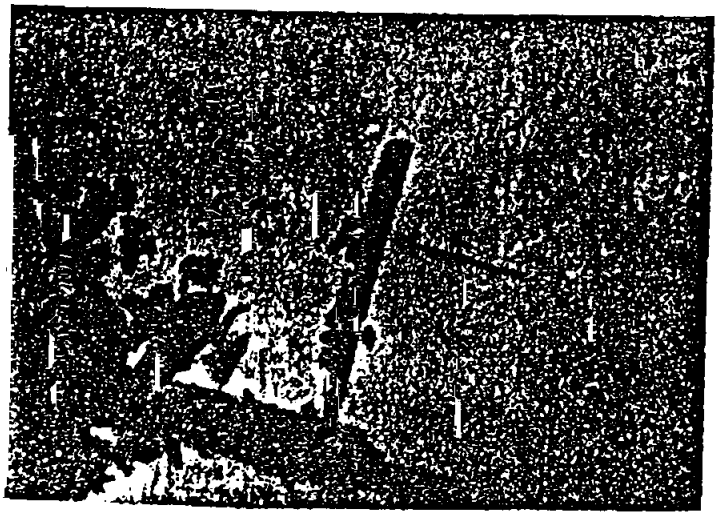
- Demonstrates presence of tremolite. Does not demonstrate growth habit (asbestiform or not)

Diffraction Patterns



- No measurements are shown. It is assumed this is the cleavage fragment at bottom left

Electron Photomicrographs



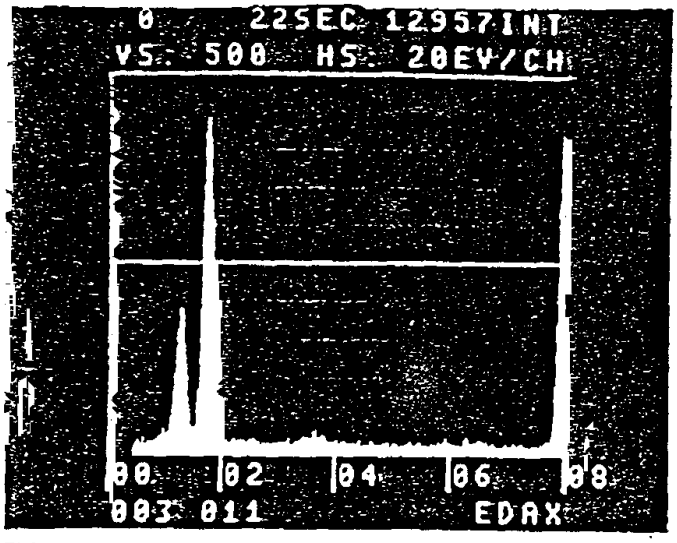
- This is an obvious cleavage fragment. Note the terminations, note the absence of fibrils.

- There are many obvious fibers here. Why was the cleavage fragment on the left selected for the x-ray spectrum and diffraction pattern: Note the "fibers" are not identified - why - because they are likely talc not tremolite as suggested in the figure.

Figure 2. Typical Electron Diffraction Patterns and X-ray Spectra of Anthophyllite Fibers in Bulk Samples

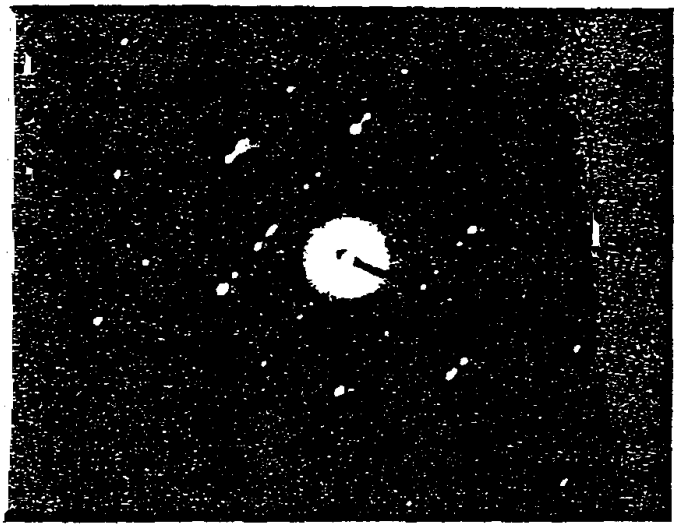
- We expect you are trying to demonstrate the presence of asbestiform anthophyllite here. This is not demonstrated for the reasons noted below.

X-ray Spectrum



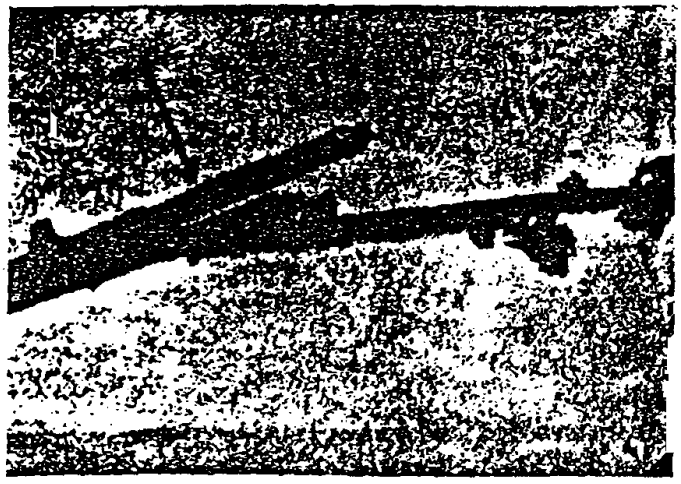
This spectrum could be anthophyllite or talc. Both Mg/SiO_2 ratios are essentially 1 to 2. This spectrum is within the variations of composition for both minerals. Ratio range for anthophyllite is 56 to 27.9, range for talc is 62 to 31.7. I could be anthophyllite but x-ray would not reflect habit (asbestiform or not).

Diffraction Pattern



- No measurements show again. Note the repeat 5.3 angstrom spacing however. This is also common to talc fibers. You could better make the distinction with optics and index oil.

Electron Photomicrograph



Magnification 10,000 X 1 Micron

These could be cleavage fragments (resolution is not good enough to tell). This could also be talc fiber your x-ray spectrum and diffraction pattern wouldn't tell you.

Magnification 5,000 X 1 Micron

- These more clearly appear to be cleavage. Note how few of these approach 20 to 1 (longer ones tend to be in 15 to 1 range).

• Notice how nothing in this photomicrograph is identified. There does seem to be considerably more true fiber here than we are used to seeing so we wonder how common this is (how many fields were searched to find this?) Regardless, several asbestiform fibers are apparent (see my A and B). From what we are told in the preceedin pages, we are to presume these particles are asbestiform tremolite or asbestiform anthophyllite. However, as every analysis we have ever undertaken demonstrates, these greatly elongated - asbestiform and nonasbestiform particles - are talc fibers (most commonly) or transitional particles (talc evolving from anthophyllite). To demonstrate, please see the simple use of the Becke line in my photomicrographs (next page).

MAGNIFICATION 3,000 X
1 MICRON —
10 MICRON ————————

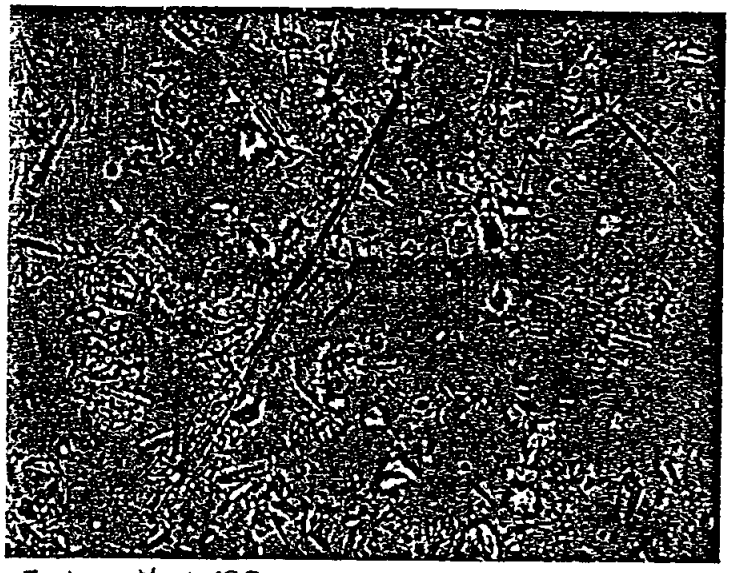
Figure 3. Electron Photomicrograph of Airborne Particulates in Mine and Mill

BECKE LINE

Photomicrographs of NYTAL 300 Field from a Bulk Sample

In index oil 1.592 (upper limit for low iron talc)
at 244 x magnification. Each division = 1.71 um

#1 NYTAL 300 244 X



Index oil 1.592 Div 1.71 um

Photo #1: Note the obvious asbestiform fiber in the center (extremel high aspect ratio, curvature, splayed ends Etc.)

#2

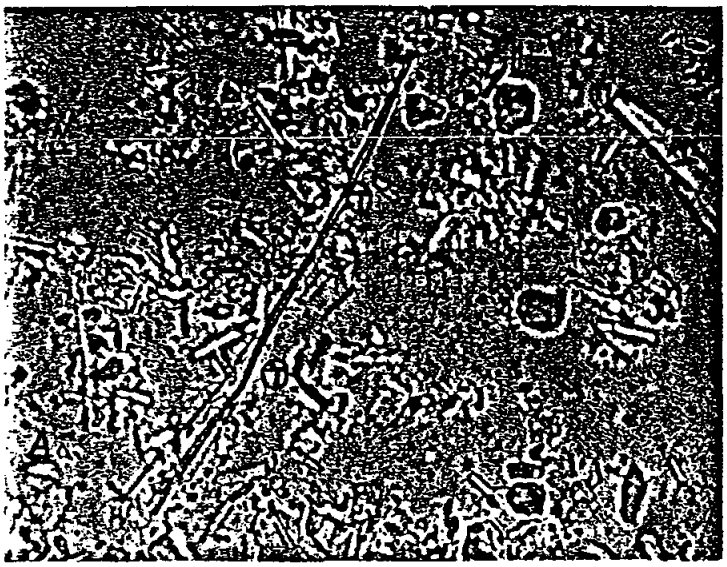


Photo #2: Here, we have slightly lowered the microscope to note the direction of the Becke Line (away = below the retractive index, toward = above the index). Note particles labeled Ⓣ show light outside the particle while particles labeled A are brighter inside the particle. Ⓣ is therefore talc fiber (notice these are the more fibrous particles) while A's are likely amphiboles (those noted are cleavage).

Animal Studies

Specific To RTV Talc

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Chronic Effects of Dietary Exposure to Amosite Asbestos and Tremolite in F344 Rats

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Carcinogenesis bioassays of blocky (nonfibrous) tremolite and amosite asbestos alone or in combination with the intestinal carcinogen 1,2-dimethylhydrazine dihydrochloride (DMH) were conducted with male and female Fischer 344 rats. The minerals were administered at a concentration of 1% in pelleted diet for the entire lifetime of the rats starting with the dams of the test animals. One group of amosite rats also received chrysotile asbestos via gavage during lactation. Group sizes varied from 100 to 250 animals.

The offspring from mothers exposed to tremolite or amosite asbestos were smaller at weaning than those from untreated mothers and remained smaller throughout their life. The administration of dimethylhydrazine (DMH) did not affect body weight gain, either in amosite-exposed or nonexposed animals. Survival was comparable in the tremolite and control groups. The amosite-exposed rats showed enhanced survival compared to the untreated controls. DMH exposure reduced survival by approximately one year, although the amosite plus DMH groups survived slightly better than the DMH alone groups.

No toxicity or increase in neoplasia was observed in the tremolite-exposed rats compared to the controls. Significant increases ($p < 0.05$) in the rates of C-cell carcinomas of the thyroid and monocytic (mononuclear cell) leukemia in male rats were observed in amosite-exposed groups. However, the biological significance of the C-cell carcinomas in relation to amosite asbestos exposure is discounted because of a lack of significance when C-cell adenomas and carcinomas were combined and the positive effect was not observed in the amosite plus preweaning gavage group. The biological significance of an increased incidence of mononuclear cell leukemia is questionable, because of a lack of statistical significance in the amosite group when evaluated using life table analysis, lack of significance when compared to the tremolite control group, and the fact that no toxic or neoplastic lesions were observed in the target organs, i.e., gastrointestinal tract and mesothelium.

DMH caused a high rate of (62–74%) of intestinal neoplasia in amosite and nonamosite-exposed groups. Neither an enhanced carcinogenic nor protective effect was demonstrated by exposure to amosite asbestos.

Introduction

In November 1973 the National Institute of Environmental Health Sciences and the Environmental Protection Agency cosponsored a symposium on the possible biological effects of ingested asbestos. (*1*). This conference concluded that a paucity of definitive data existed concerning the effects of ingested asbestos and that specific research was needed.

A subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs was established to review existing data and to prepare a draft research protocol that would be responsive to the possible public health implication of ingested asbestos. This protocol was widely distributed for comment within and outside the government and a public meeting of the subcommittee was held on February 11, 1975. On the basis of the comments received, a revised final protocol was developed which called for the use of long-

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term animal toxicology studies to evaluate the ingestion of several minerals for carcinogenic effect. As a result, the National Toxicology Program has investigated the carcinogenic potential of the ingestion of chrysotile asbestos in hamsters and rats, amosite asbestos in hamsters and rats, crocidolite asbestos in rats and tremolite in rats. All of the studies were to encompass the lifetime of the animal, including exposure of the dams from which the test animals were derived.

Crystalline tremolite (not actually in asbestos fiber) was chosen for this study because up to 20 years ago it was a common contaminant of talc which was used in foods and pharmaceuticals. The grinding of tremolite in preparation for its intended use may result in the production of fibers which have the morphology of asbestos minerals. Stanton et al. (2), in reviewing intrapleural mineral deposition studies, speculated that the asbestos mineral hazard question may be directly related to fiber size in contrast to chemical composition. Therefore, the study of crystalline tremolite was deemed appropriate because of its past widespread exposure and the fact that it assumes fiber characteristics when ground in the processing of talc.

This report represents the results of those studies undertaken to determine the effects of tremolite or amosite asbestos in the diet fed to Fischer 344 rats. In addition, the study was designed to determine if the feeding of amosite asbestos modified the response of a known intestinal carcinogen, 1,2-dimethlhydrazine dihydrochloride (DMH). Reports on chrysotile and crocidolite asbestos will be reported later.

Table 1. Fiber characteristics of amosite asbestos.

Fiber characteristics	
Surface area, m^2/g	4.13
Density, g/cm^3	3.35 ± 0.026 SD
Measurements, transmission electron microscopy	
Fiber count/g	0.3466×10^{10}
Median length (μm)	4.37
Range of length, μm	0.85 – 995
Median diameter, μm	0.72
Range of diameter, μm	0.064 – 12.4
Median fiber aspect ratio (*l*/*d*)	6.4248

Table 2. Chemical-instrumental analysis of amosite asbestos.

	Content, wt-%
Al_2O_3	0.42
CaO	0.48
FeO	34.61
Fe_2O_3	2.24
MgO	6.22
K_2O	0.30
SiO_2	50.36
Na_2O	0.03
MnO	2.66
Cr_2O_3	0.03
NiO	0.01
CO_2	0.88
H_2O-	0.15
H_2O+	2.30
Benzene extracted organics	0.021

Materials and Methods

Test Materials

Asbestos is a general term applied to certain natural silicates when they appear in a fibrous

Table 3. Particle size distribution of amosite asbestos by particle number: SEM.

	Length interval, μm						
	0–1.99	2–3.99	4–5.99	6–7.99	8–9.99	10–19.99	20–39.99
Amosite mean width, μm	0.28	0.38	0.45	0.45	0.48	0.52	0.51
Amosite particles per interval	57	126	88	78	52	181	184
Total amosite particles, %	5.6	12.3	8.6	7.6	5.1	17.7	18.0
Cumulative % amosite	5.6	17.9	26.5	34.1	39.2	56.9	74.9
Amosite, vol-%[a]	–	0.1	0.3	0.4	0.4	2.4	5.0
Cumulative volume-% amosite	–	0.1	0.4	0.8	1.2	3.6	8.6
Number of other particles	11	8	1	0	1	1	0
Amosite particles per length interval by aspect ratio, %							
1:1–2.9:1	12	0	0	0	0	0	0
3:1–4.9:1	34	10	6	5	2	0	0
5:1–9.9:1	43	52	23	14	4	1	1
10:1–19.9:1	11	34	52	38	40	21	1
20:1–49.9:1	0	4	18	41	54	64	30
50:1–99.9:1	0	0	1	2	0	12	55
100:1–199:1	0	0	0	0	0	2	12
200:1–499:1	0	4	0	0	0	0	1
>500:1	0	0	0	0	0	0	0

[a]Calculated from particle number data, assuming rectangular cross section with third dimension equal to ½ measured width.

form. Amosite is a fibrous member of the amphibole mineral group, its chemical structure is $(Fe^{2+}Mg)_7Si_8O_{22}(OH)_2$. Mineral and fiber characteristics of amosite are shown in Tables 1–3.

The amosite sample identified as S-33 was purchased by the Bureau of Mines from the Atlas Asbestos Company, Montreal, Quebec, Canada. This material is from a mine in the area known as Penge, in the Transvaal, Republic of South Africa. Not a proper mineral name, amosite is a term used to describe the material from asbestos mines in South Africa. To develop homogeneity of the sample the amosite was processed by a single pass through an air jet mill.

The temolite sample used in this study was obtained from a single lense from the Governeur Talc Company, Governeur, NY. This 1200-lb lense was taken from the 500 ft level, American vein, No. 4 footwall stope, lower portion of the footwall bedding. The lense was crushed in a Denver Jaw Crusher and then to minus 14 mesh in a roll crusher. This material was then wheeler-milled at 204°C and bagged in 50-lb Kraft bags. The final particle size was nominal minus 325 mesh. To develop homogeneity of the sample, approximately 960 lb tremolite was blended in a 10 ft^3 V-type blender. Mineral and fiber characteristics of tremolite are shown in Tables 4 and 5.

After final blending the samples were weighed to 25 ± 0.5 lb and placed in fiberboard drums. These drums were shipped to a special warehouse at Research Triangle Park, NC. Each drum received a color marking unique to the mineral type. Homogeneity of the samples was verified by fluorescent X-ray spectrography for samples collected from six randomly selected drums. No significant differences were detected.

The homogeneity of the samples and the physical and chemical properties of the materials were characterized by the Bureau of Mines, U.S. Department of the Interior (Supt. of Documents No. I 28.23:8452) and by the Fine Particle Laboratories, Illinois Institute of Technology Research In-

Table 4. Fiber characteristics and chemical-instrumental analysis of tremolite.

Fiber characteristics	
Surface area, m^2/g	5.2 ± 0.5
Density, g/cm^3	2.91 ± 0.01 SD
Analyses, wt-%	
Al_2O_3	1.57
CaO	11.26
Fe_2O_3	0.27
MgO	26.71
K_2O	0.18
SiO_2	54.00
Na_2O	0.80
TiO_2	0.03
MnO	0.05
Li_2O	0.02
SnO	0.01
SrO	0.03
Bi_2O_3	0.01
CO_2	0.78
H_2O^-	0.24
H_2O^+	3.73
Benzene-extracted organics	0.003

Table 5. Particle size distribution for tremolite by particle number: SEM.

	Length interval, μm										
	0–0.99	1–1.99	2–2.99	3–3.99	4–4.99	5–5.99	6–6.99	7–7.99	8–8.99	9–9.99	>10
Mean width, μm	0.48	0.88	0.97	1.51	2.05	2.19	2.79	3.29	2.96	3.13	5.22
Number of particles per interval	59	291	194	106	53	40	31	19	9	13	58
% of all particles per interval	6.8	33.4	22.3	12.2	6.1	4.6	3.6	2.2	1.0	1.4	6.4
Cumulative % of all particles	6.8	40.2	62.5	74.7	80.8	85.4	89.0	91.2	92.2	93.6	100
Tremolite particles per interval	34	197	128	83	38	27	23	15	9	12	49
% of tremolite particles	5.5	32.0	20.8	13.5	6.2	4.4	3.7	2.4	1.5	2.0	8.0
Cumulative % tremolite	5.5	37.5	58.3	71.8	78.0	82.4	86.1	88.5	9.0	92.0	100
Talc-serpentine particles per interval	9	72	53	19	11	9	8	4	0	1	7
Other particles per interval	16	22	10	4	2	4	0	0	0	0	2
Tremolite particles per length interval, by aspect ratio, %[a,b]											
1:1–2.9:1	100	92	75	67	76	67	65	66	67	30	35
3:1–4.9:1	0	8	22	29	18	30	30	20	22	35	37
5:1–9.9:1	0	0	3	4	6	3	5	7	11	35	18
10:1–19:1	0	0	0	0	0	0	0	7	0	0	4
20:1–49:1	0	0	0	0	0	0	0	0	0	0	4
50:1–99:1	0	0	0	0	0	0	0	0	0	0	0
100:1–199:1	0	0	0	0	0	0	0	0	0	0	2

[a]Data for aspect ratio obtained from a second set of measurements.
[b]Total particles = 871, total tremolite = 615, total talc-serpentine = 193, and total other = 63.

stitute, Chicago, IL (Special Report and Addendum on project L6085, contract N01-ES-5-3157). Copies of these reports are available upon request from the National Toxicology Program.

Test Diets

The feed used was NIH-31 open formula rodent diet prepared by Zeigler Brothers, Inc., Gardner, PA. Tremolite or amosite asbestos was incorporated to a level of 1% by weight into the test diet. All feed was pelleted with a Sprout-Waldron pelleter; the pellets were of oval configuration, 3/8 in. by 3/4 in. in size. Pelleted feed was packaged in 25-lb aliquots in standard paper feedbags which were color coded to minimize the occurrence of feeding errors at the test laboratory.

Each lot of blended feed was analyzed for tremolite or amosite asbestos concentrations, pesticide contamination and nutrient content.

*1% Chrysotile (Medium Range) Gavage.** The required amount of chrysotile (medium range), a gray powder with lumps, was weighed on a Mettler balance and placed in a beaker. Sterile water (for injection) was added to obtain the desired concentration and the suspension was then mixed in a magnetic stirrer for a short period of time. The suspension was administered by gavage, at a dose level of 0.47 mg/g of body weight, to the amosite and preweaning gavage (PWG) animals from birth to weaning (21 days).

Source and Specifications of Test Animals

Parental Generation (F_0). Weanling Fischer 344 (caesarean-derived) rats, which were barrier sustained and specific pathogen-free, were purchased from Charles River Breeding Laboratories, Inc., Wilmington, MA. These animals constituted the F_0 generation.

On arrival, animals were taken directly to the quarantine area and acclimated to laboratory conditions for approximately 2 weeks. At 24 hr after the animals arrived, eight animals of each sex were selected, sacrificed, and pathogen burden was determined for each animal. Pathogens examined for included ectoparasites, intestinal parasites, and bacteria. Serological tests were conducted for viruses. After approximately 2 months of quarantine the rats, both males and females, were randomized and divided into test groups by a computerized randomization process and placed on the appropriate designated diets.

*Animals were to receive 1% amosite, but were inadvertently gavaged with 1% chrysotile.

After at least 7 days exposure to the appropriate diets, the rats were placed in breeding cages (one male to two females). During the breeding period, the rats continued to be fed the designated diets; 20 days later (on the average), females were separated and housed individually in polycarbonate cages (Hazleton Systems, Aberdeen, MD). Males were removed from the breeding cages and re-housed two per cage.

Filial Generation (F_1). The F_0 females were allowed to deliver their F_1 litters naturally, and these were reduced to no more than eight pups (four/sex if possible) per litter. At birth, the litters from the F_0 dams within the control and treated groups were assigned randomly to the corresponding lifetime feeding phase groups such that birth dates were equally distributed. All pups assigned to the amosite and preweaning gavage (PWG) groups were exposed to the PWG phase of the study to assure exposure to asbestos from birth to weaning.

At 21 days after birth, the pups were weaned and given a temporary number, then selected, using a random number table, to be placed in their respective groups for the lifetime feeding study. Litters in which only one sex was present were excluded from those animals to be selected. The extra weanlings were discarded.

At 8 weeks of age, 1,2-dimethylhydrazine dihydrochloride (DMH) was administered by gavage to a control group and an amosite group every 14 days for a total of five doses. Males received 7.5 mg/kg, and females 15.0 mg/kg, based on a previous pilot study (*3*) which showed that these doses produced an approximate incidence of 15% intestinal neoplasia. Concentrations of DMH in the dosing solutions were determined within one hour prior to dosing and following dosing. The results of these determinations showed that the proper concentration of DMH was present in the dosing solution and had not deteriorated during dosing.

Animal Maintenance

The control and mineral exposed rats were placed in separate rooms with monitored temperature and humidity, and a controlled light cycle (12 hr light/12 hr dark). Temperature was maintained at 74 ± 4°F and humidity at 50% ± 10%. The rats were housed three per cage in polycarbonate cages covered with nonwoven polyester filter sheets and stored on Enviro-racks. Racks and filters were changed approximately once every 2 weeks. Cages and bedding were replaced twice per week. Control and treated diets and tap water

via automatic waterers were available *ad libitum*. Two water samples were collected and submitted for asbestos analysis. Stainless steel feed containers were changed once every 2 weeks.

The incoming air in the animal rooms was filtered to remove particulate matter. Ten to fifteen changes of room air per hour were provided. Prior to initiation of the study, air samples were collected and analyzed for baseline asbestos determinations. Additional samplings were collected approximately every 6 months for analysis to assure personnel safety.

Other measures used for personnel protection included the wearing of fully protective disposable suits, gloves, boots and bouffant caps and the use of a dust/mist respirator mask. Personnel leaving the animal rooms were required to take showers. In addition, physical examinations, including pulmonary function tests and chest radiographs, were conducted at the initiation of the study, yearly thereafter, and at the end of the study.

Clinical Examinations and Pathology

Observations and Records. All animals were observed twice daily for moribund condition and mortality. Recorded weekly were individual body weights; signs of toxicity or pharmacologic effects; incidence, size and location of palpable tissue masses or nodules; and food consumption per cage.

Sacrifice and Gross Pathology. Animals were sacrificed when exhibiting any one of these conditions: palpable masses within the abdominal cavity (excluding retained testes); masses protruding from the rectum; rectal discharge of bright red fluid (an indication of the presence of a bleeding colonic or rectal neoplasm); large ulcerated masses in the area of the ears or on side of face (Zymbal gland tumors); large subcutaneous masses which have been ulcerated or infected; masses which interfere with breathing and eating or which severely hamper locomotion; huge tissue masses (>10 cm); central nervous system signs accompanied by weight loss (head tilt, circling incoordination, ataxia, paralysis); severe weight loss or emaciation; or comatose or very weak.

When the remaining animals of either the control and DMH or the corresponding amosite and DMH group of either sex was reduced to 10% of those starting the study, both groups within that sex were killed. When survival or untreated control or amosite or amosite and PWG group of either sex reached 10%, all remaining animals of these groups within that sex were killed. The tremolite-exposed groups were handled similarly. Animals were killed by exsanguination under sodium pentobarbital anesthesia (Nembutal, Abbott Laboratories, Inc., North Chicago, IL, or Diabutal, Diamond Laboratories Inc., Des Moines, IO). Final body weights were recorded and necropsies performed which included these additional procedures: blood smears taken from animals sacrificed *in extremis* or terminally sacrificed, touch preparations made from any enlarged spleen or lymphoid organ.

Since the gastrointestinal tract was considered as the target organ prior to the study, it was handled in a manner slightly different from that in standard rodent lifetime bioassays. Prior to placement in fixative, the entire esophagus was opened and examined. The stomach and cecum were opened and pinned with the exterior surface adjacent to paper; 2-cm lengths of duodenum and ileum and two portions of jejunum were placed unopened in fixative. The remaining small intestine was opened and washed gently with saline and the mucosal surface was then examined carefully using transillumination on a radiograph viewing box. Suspect lesions were processed separately and identified individually as to location. Likewise, the entire colon with anus was opened, examined, and placed on cardboard (serosal surface down) prior to fixation. The size and location of masses were recorded. Masses greater than 1 mm in diameter were removed as separate specimens for processing. After fixation and prior to embedding, the colon was "carpet-rolled" starting at the proximal end, with the mucosal surface inward.

All tissues were fixed in 10% neutral buffered formalin, sectioned, and stained with hematoxylin and eosin. Tissues/organs examined microscopically were: tissue masses, the above-mentioned portions of gastrointestinal tract, mesenteric, celiac, iliocolonic, renal, iliac, mandibular, cervical, pancreatic and bronchial lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow (sternum), nasal cavity with turbinates, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate, testes/epididymus, ovaries/uterus, brain, pituitary gland, eyes and spinal cord.

Data Recording and Statistical Methods

The individual animal pathology data on this experiment were recorded in the computerized

carcinogenesis bioassay data system. The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, and individual pathologic results.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (*4*). Animals were statistically censored as of the time that they died of other than natural causes or were missing; animals dying from natural causes were not statistically censored. Differences in survival were evaluated by Cox's (*5*) life table method.

The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., leukemia), the denominators consist of the numbers of animals necropsied.

For the statistical analyses of tumor incidence data, two methods of adjusting for intercurrent mortality were employed. Each used the classical methods of combining contingency tables developed by Mantel and Haenszel (*6*). The first method of analysis assumed that all tumors of a given type were fatal; i.e., they caused the death of the animal, either directly or indirectly. According to this approach, the proportions of tumor-bearing animals in the treated and control groups were compared at each point in time at which an animal died with a particular tumor. The denominators of these proportions were the total number of animals at risk in each group. These results were then combined by the Mantel-Haenszel methods to obtain an overall probability (p) value. This method of adjusting for intercurrent mortality is Cox's life table method (*5*).

The second method of analysis assumed that all tumors of a give type were "incidental"; i.e., they were merely observed at autopsy in animal dying of an unrelated cause. According to this approach, the proportions of male and female rats found to have tumors in treated and control groups were compared in each of five time intervals: 0-60 weeks, 61-86 weeks, 87-112 weeks, 113-126 weeks and beyond 126 weeks. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result (*7*). For comparisons involving groups receiving DMH (which showed markedly reduced survival), somewhat shorter time intervals were utilized for the incidental tumor test: 0-52 weeks, 53-78 weeks, 79-92 weeks, 93-116 weeks (males), 93-102 weeks (females), beyond 116 weeks (males) and beyond 102 weeks (females).

In addition to these tests, one other set of statistical analyses was carried out for each primary tumor: the Fisher exact test based on the overall proportion of tumor-bearing animals (*8*). All reported p values are one-sided. Except where noted, the three alternative analyses gave similar results.

Results

Establishment of Test Groups

The experiment was designed to evaluate the effects of orally ingested tremolite or amosite asbestos during the entire life of the animal, starting from the time the rats were able to eat solid food. For this reason, the mated female rats had been on the test diets for approximately 12 weeks when the first litters were born. To minimize the chance that the mothers would reject or cannibalize their young, the litters were not handled during lactation, except for the group receiving asbestos via preweaning gavage.

Litter size and survivability of offspring were unaffected by the presence of amosite in the diets. The average number of live fetuses born to tremolite-exposed dams was 7.6 versus 7.8 for the control groups. The average number of live fetuses born to amosite-exposed dams was 8.5 versus 7.7 for the control groups. Significant mortality was induced in those pups which received the preweaning asbestos gavage (PWG). The average size of the litters in this group was 3.4 at weaning compared to 7.5 in the non-PWG amosite group. The average weight at birth of the tremolite-exposed pups was 4.7 g versus 4.8 g for the controls. The average weight at birth of the amosite-exposed pups was 4.7 g versus 4.8 g for the controls. The tremolite-exposed offspring were slightly smaller at weaning, 22.8 g versus 26.3 g (control). The amosite-exposed offspring were also slightly smaller at weaning, 23.2 g versus 27.4 g (control).

A summary of groups, number of animals and diets for the filial (F_1) animals is presented in Table 6.

Table 6. Summary of distribution and diets: a lifetime feeding study of tremolite or amosite asbestos in rats.

Test group	No. of animals		% of diet	DMH, mg/kg[a]	
	Male	Female		Male	Female
Control	118	118	0		
Tremolite	250	250	1		
Control	117	117	0	–	–
DMH	125	125	0	7.5	15.0
Amosite	250	250	1	–	–
Amosite + DMH	175	175	1	7.5	15.0
Amosite + PWG[b]	100	100	1	–	–

[a]Gavage with 1,2-dimethylhydrazine dihydrochloride.
[b]Animal was inadvertently gavaged during preweaning with intermediate (medium)-range chrysotile instead of amosite.

Clinical Signs

The incidence of clinical signs occurred at essentially comparable frequencies throughout the study groups except those that received DMH (see below). No distinct signs of compound effect were noted in any of the tremolite- or amosite-treated animals during the first 52 weeks of study. As the study proceeded, the incidence of clinical signs increased among all the groups. At intervals where there were a large number of moribund sacrificed animals in any one particular group, the clinical signs most frequently observed were supportive of the conditions for moribund sacrifice previously outlined in the Methods section. A comparison of clinical signs observed during the same selected intervals among all the groups revealed a larger number of palpable abdominal masses, tissue masses, and central nervous system signs, a well as red discharge and protruding masses from the rectum in the DMH and amosite and DMH groups. These findings were presumably due to the administration of DMH since they were not clinically observed with any frequency in any of the tremolite- or amosite-treated groups.

Body Weight and Food Consumption

Mean body weights were analyzed at selected intervals: birth, 3, 8, 11, 15, 24, 33, and 60 weeks for the males, and birth, 3, 8, 11, 16, 27, 48 and 60 weeks for the females by the method of Rao (*9*). The data revealed a 13% depressed mean body weight gain at weaning in both sexes of the tremolite groups and 15% in the amosite groups compared to the controls. The depressed weight gain in the tremolite- and amosite-exposed rats was more apparent at 8 weeks of age (tremolite:33% for males and 17% for females; amosite: 37% for males and 25% for females). Weight gain then paralleled the controls (except for DMH-exposed rats) for the remainder of the study but the mineral-exposed rats remained smaller throughout the study. Both male and female DMH-exposed groups gained less than their respective controls.

In the tremolite-exposed males and females, the average weekly food consumption was 97% that of the untreated controls. In the DMH, amosite, amosite and DMH, and amosite and PWG males, the mean weekly food consumption was 102%, 102%, 105%, and 107%, respectively, compared to the untreated control group and 98%, 101%, 105%, and 108% that of the untreated control for comparable groups of females.

Survival

Survival data of intervals prior to the final sacrifice of a group are summarized in Table 7. There were no significant differences in survival between the tremolite-exposed and control groups. Survival of males and females was approximately equal until 112 weeks, after which the females tended to live longer. When compared to the survival rates of the untreated control group, the amosite male survival at 118 weeks was higher, while amosite and PWG male survival was somewhat less. In female rats, the amosite group survival was better than the untreated controls, while the amosite and PWG group was about the same. The survival of both groups of DMH-exposed rats was considerably less than the untreated controls. The amosite plus DMH group was comparable to the DMH alone group.

Pathology

There were no apparent treatment related neoplasms in the digestive tract of the tremolite, amosite, or amosite PWG groups (Tables 8 and 9). Also, no specific type was increased, either at a particular location (e.g., cecum) or in the stomach, small or large intestine as a whole. In addition, the incidences of non-neoplastic diseases of the gastrointestinal tract such as enteritis, diverticulitis, ulceration or inflammation in general were comparable in the control and tremolite- or amosite-exposed rate (Tables 10 and 11).

There were no organs/tissues in the tremolite-exposed rats which showed an increased rate of neoplasia compared to the control groups. Organs which showed an increase in neoplasms in the amosite or amosite PWG groups compared to the control group were the thyroid and hematopoeitic system. The results are as follows.

Thyroid. Table 12 summarizes the incidence

Table 7. Survival of F344 rats in lifetime oral asbestos study at various time points.

Group	Age, weeks	Males		Females	
		No. alive/ total no.	Survival, %	No. alive/ total no.	Survival, %
Control	106	98/118	83	97/118	82
	120	70/118	59	71/118	60
	146	6/118	5	20/118	17
	148	–	–	14/118	12
Tremolite	106	206/250	82	207/247	84
	120	150/250	60	144/247	58
	146	36/250	14	33/246	13
	148	–	–	22/246	9
Control	106	95/117	81	92/117	79
	118	71/117	61	62/117	53
	142	7/117	6	20/116	17
	146	–	–	10/116	9
DMH	106	27/125	22	15/125	12
	118	16/125	13	–	–
	142	–	–	–	–
	146	–	–	–	–
1% Amosite	106	221/250	88	202/246	82
	118	117/250	71	162/246	66
	142	35/249	14	43/245	18
	146	–	–	28/245	11
1% Amosite + DMH	106	46/175	26	32/174	18
	118	26/175	15	–	–
	142	–	–	–	–
	146	–	–	–	–
1% Amosite + PWG	106	77/100	77	86/100	86
	118	52/100	52	56/100	56
	142	6/100	6	15/100	15
	146	–	–	9/100	9

of thyroid C-cell proliferative lesions. A significantly increased incidence of C-cell carcinoma was found in amosite-treated male rats ($p < 0.05$). This effect was not observed in amosite PWG male rats. Furthermore, the overall incidence of C-cell tumors (adenomas and/or carcinomas) was comparable between control and treated groups. C-cell hyperplasia was equivocally increased in amosite and amosite PWG female groups.

Hematopoietic System. A significantly increased incidence of mononuclear cell leukemia occurred in amosite ($p < 0.05$) and amosite PWG ($p < 0.01$) male rats (Table 13). However, neither group was significant when compared to the tremolite control group (39%). This increased incidence was not observed in amosite-exposed females.

Miscellaneous Neoplasms

Occasionally a somewhat higher or lower rate of commonly occurring neoplasms were observed in amosite treated groups. A statistically significant ($p < 0.05$) decrease in the rate of neoplasia was observed in the pancreas (Islet cell adenoma), adrenal medulla (pheochromacytoma), thyroid (follicular cell carcinoma) and preputial gland in at least one group of amosite-exposed rats compared to the controls. Similar observations were not observed in the tremolite-exposed groups.

Nonneoplastic Findings

A plethora of incidental lesions of aging Fischer 344 rats was found in all groups. Statistical analyses showed no obvious correlation between the incidence of specific lesion types and the type of treatment. Nonneoplastic lesions that were observed in more than 5% of the rats in any of the experimental groups are as follows: skin: epidermal inclusion cyst; lung: chronic inflammation (peribronchiolar and perivascular lymphoid cuffing); spleen: fibrosis, hemosiderosis, extramedullary hematopoeisis, lymphoid atrophy; lymph

Table 8. Number of tremolite-exposed F344 rats with primary epithelial neoplasms of the alimentary tract.

	Males[a]		Females[a]	
	Control	Tremolite	Control	Tremolite
Animals examined	118	250	118	250
Total alimentary	8(7)	12(5)	3(3)	7(3)
Oral/pharynx				
Papilloma	1(1)	1(0)	0(0)	1(0)
Carcinoma	3(3)	1(0)	2(2)	5(2)
Esophagus				
Total gastrointestinal	4(3)	9(3)	1(1)	1(0)
Total stomach	3(3)	2(1)	0(0)	0(0)
Nonglandular				
Papilloma	2(2)	1(0)		
Carcinoma	1(1)	1(0)		
Glandular				
Polyp				
Carcinoma				
Total small intestine	0(0)	3(1)	0(0)	0(0)
Polyp		1(0)	1(1)	
Adca in polyp[b]				
Carcinoma		2(1)		
Total large intestine	1(1)	4(2)	0(0)	0(0)
Cecum				
Polyp		1(0)		
Adca in polyp[b]				
Carcinoma				
Colon				
Polyp	1(1)	1(0)		
Adca in polyp[b]				
Carcinoma		2(1)		

[a]Values in parentheses are percentages.
[b]Adenocarcinoma arising in adenomatous polyp.

nodes (various): lymphoid or reticulum cell hyperplasia, lymph-angiectasis, hemorrhage, pigmentation, chronic inflammation; heart: chronic inflammation; liver: degeneration, necrosis, fatty metamorphosis, toxic hepatitis (associated with leukemia), granuloma, angiectasis, pigmentation, focal cellular change; bile duct (extrahepatic): chronic inflammation, mucosal hyperplasia, cysts, fibrosis; pancreas (exocrine): atrophy, hyperplasia, ectopia; pancreas (endocrine): hyperplasia; kidney: chronic progressive nephropathy, cysts, pigmentation; pituitary gland: cysts, angiectasis, hyperplasia; adrenal (cortex): fatty metamorphosis, hyperplasia; adrenal (medulla): hyperplasia; thyroid: follicular cysts, C-cell hyperplasia; parathyroid: hyperplasia; testes: seminiferous degeneration, interstitial cell hyperplasia; prostate: abscess, chronic inflammation, glandular hyperplasia; seminal vesicles: cysts; ovary: follicular and parovarian cysts; uterus: hydrometra, endometrial cyst; mammary gland: cystic ducts, glandular hyperplasia, galactocele; mesentery: chronic inflammation; eye: cataract, hemorrhage, inflammation, retinal degeneration; zymbal gland: cystic ducts; bone: osteopetrosis, exostoses, marrow hyperplasia. Alimentary tract nonneoplastic lesions are noted in Tables 10 and 11.

1, 2-Dimethylhydrazine Dihydrochloride-Treated Groups

Two groups of male and female rats were exposed to 1, 2-dimethylhydrazine dihydrochloride (DMH) by gavage at levels of 7.5 mg/kg for males and 15.0 mg/kg for females, biweekly for a total of five doses. One group served as a positive carcinogen control and the other received amosite from weaning throughout life.

Exposure of rats to DMH or DMH with amosite was associated with a dramatically increased incidence of neoplasms of the intestinal tract, Zymbal's gland, and liver of male and female rats, and kidney in female rats. It is also noteworthy that survival in the DMH groups was shortened due to the presence of these neoplasms.

Table 9 summarizes the numbers of rats with primary epithelial neoplasms in the gastrointestinal tract by specific site and classification. Intestinal neoplasms, particularly the adenomatous polyps, were often multiple within a given animal.

Table 9. Number of amosite-exposed F344 rats with primary epithelial neoplasms of the gastrointestinal tract.

	Untreated control[a]		Amosite[a]		Amosite PWG[a]	
	M	F	M	F	M	F
Animals examined	117	117	249	250	100	100
Total gastrointestinal	4(4)	2(2)	7(3)	4(2)	3(3)	3(3)
Total stomach	1(1)	1(1)	2(1)	1(0)	0(0)	0(0)
Total small intestine	3(3)	0(0)	2(1)	3(1)	1(1)	1(1)
Duodenum						
Carcinoma			1(0)		1(1)	
Adca in polyp[b]						
Adenomatous polyp						
Jejunum						
Carcinoma	2(2)			1(0)		1(1)
Adca in polyp[b]			1(0)			
Adenomatous polyp				2(1)		
Ileum						
Carcinoma						
Adca in polyp[b]						
Adenomatous polyp	1(1)					
Total large intestine	0(0)	1(1)	3(1)	0(0)	2(2)	2(2)
Cecum						
Carcinoma						
Adca in polyp[b]						
Adenomatous polyp					1(1)	
Total colon	0(0)	1(1)	3(1)	0(0)	1(1)	2(2)
Ascending colon						
Carcinoma			1(0)			
Adca in polyp[b]						
Adenomatous polyp						
Transverse colon						
Carcinoma						1(1)
Adca in polyp[b]						
Adenomatous polyp						
Descending colon						
Carcinoma						
Adca in polyp[b]					1(1)	
Adenomatous polyp		1(1)	2(1)			1(1)

[a]Values in parentheses are percentages.
[b]Adenocarcinoma arising in adenomatous polyp.

The incidence of gastrointestinal neoplasia was dramatically increased with DMH treatment. However, the incidence appeared to be essentially comparable between groups receiving DMH alone and those receiving DMH with amosite. Furthermore, the number of animals with tumors either in the small intestine or in the large intestine was also essentially comparable between DMH alone and DMH with amosite. There was no difference in the time to tumor between the groups.

Evaluation of the incidence of the three categories of intestinal neoplasia (carcinoma, adenocarcinoma arising in an adenomatous polyp, and adenomatous polyp) by site (Table 14) reveals an increased incidence of duodenal carcinoma ($p < 0.05$) in the DMH with amosite-treated females, compared to female rats receiving DMH alone. In the jejunum, however, this incidence is reversed, with more carcinomas occurring in the female group receiving DMH alone.

In the large intestine the frequency of carcinoma arising in an adenomatous polyp and adenomatous polyps was greatest in the descending colon. In the cecum, the incidence of carcinoma was less in the DMH with amosite-treated group than those treated with DMH alone, in male rats. This effect was not observed in the female group. The appearance of carcinomas in the ascending colon was somewhat greater in DMH with amosite-treated males than in males receiving DMH alone. Adenocarcinoma arising in adenomatous polyp occurred more frequently in the transverse colon of male and female rats receiving DMH with amosite compared to rats receiving DMH alone.

Kidney Neoplasms

Almost without exception, the renal masses associated with DMH treatment were malignant

Table 10. Incidence of nonneoplastic lesions in the alimentary tract of F344 rats exposed to 1% tremolite in the diet.[a]

	Males[b]		Females[b]	
	Control	Tremolite	Control	Tremolite
Animals examined	118	250	118	250
Palate/tongue				
Inflammation	0(0)	0(0)	0(0)	4(2)
Necrosis	0(0)	0(0)	0(0)	1(0)
Hyperkeratosis	0(0)	1(0)	0(0)	2(1)
Acanthosis	1(1)	3(1)	1(1)	1(0)
Esophagus				
Inflammation	1(1)	0(0)	0(0)	1(0)
Necrosis	2(2)	1(0)	0(0)	0(0)
Hyperkeratosis	9(8)	18(7)	3(3)	4(2)
Acanthosis	1(1)	0(0)	0(0)	1(0)
Stomach-nonglandular				
Mineralization	13(11)	5(2)	4(3)	2(1)
Inflammation, chronic	19(16)	29(12)	25(21)	38(15)
Ulceration	10(8)	17(7)	9(8)	11(4)
Necrosis	20(17)	46(18)	17(4)	31(12)
Hyperplasia	3(3)	1(0)	0(0)	2(1)
Hyperkeratosis	18(15)	34(14)	15(13)	29(12)
Acanthosis	26(22)	54(22)	23(19)	45(18)
Stomach-glandular				
Hyperplasia	7(6)	1(0)	3(3)	0(0)
Small intestine				
Inflammation	0(0)	2(1)	0(0)	1(0)
Necrosis	2(2)	0(0)	1(1)	3(1)
Ulceration	0(0)	1(0)	0(0)	0(0)
Colon				
Parasitism	5(4)	32(13)	5(4)	3(1)
Inflammation	0(0)	5(2)	3(3)	0(0)
Necrosis	0(0)	3(1)	1(1)	1(0)
Hyperplasia	0(0)	1(0)	0(0)	1(0)
Cecum				
Parasitism	9(8)	2(1)	2(2)	1(0)
Inflammation	1(1)	2(1)	4(4)	1(0)
Necrosis	1(1)	4(2)	1(1)	3(1)
Hyperplasia	0(0)	0(0)	0(0)	1(0)
Rectum				
Necrosis	0(0)	1(0)	0(0)	0(0)
Anus (no lesions)				

[a]Incidence of nonneoplastic lesions that occur with a frequency of 1% or more in at least one group.
[b]Values in parentheses are percentages.

mesenchymal or mixed malignant tumors. Purely mesenchymal growths were classified according to their morphology (i. e., fibrosarcoma, undifferentiated sarcoma). Those having epithelial elements or epithelial-like elements were classified as mixed malignant tumors. In early stages, these neoplasms appeared as interstitial sclerosing growths near the inner cortex. Collagen formation was accompanied by proliferating, basophilic, primitive-appearing cells. Epithelial elements consisted of glands, ductlike structures or poorly differentiated solid tubules. The growths were often massive but rarely metastasized.

Table 15 summarizes the incidence of kidney tumors in control and DMH-treated groups. The high incidence of renal neoplasms was confined almost exclusively to treated female rats receiving either DMH alone or DMH with amosite ($p < 0.01$). The incidence rates for the two treated female groups was the same. Renal neoplasms occurred infrequently in male rats.

Zymbal Gland Neoplasms

Carcinoma was the most commonly observed neoplasm in Zymbal's gland. These neoplasms were composed of proliferating eosinophilic to basophilic squamous epithelial cells which formed thick fingers of tissue, masses of keratin and nests of sequestered cells. Some had sebaceous features with formation of sebum. Infiltration of adjacent tissues was not uncommon; however, metastases were rare. Table 16 summarizes the number of control and DMH-treated rats with Zymbal's gland neoplasms.

Table 11. Incidence of nonneoplastic lesions in the alimentary tract of F344 rats exposed to amosite asbestos.[a]

	Control[b]		Amosite[b]		Amosite PWG[b,c]	
	M	F	M	F	M	F
Tongue, number examined	117	117	249	250	100	100
Esophagus, number examined	115	117	249	246	100	100
Hyperkeratosis	12(10)	7(6)	4(2)	7(3)	12(12)	6(6)
Stomach, nonglandular, number examined	117	117	249	250	100	100
Mineralization	9(8)	3(3)	2(1)	2(1)	1(1)	0(0)
Inflammation, chronic	21(18)	21(18)	56(22)	60(24)	17(17)	18(18)
Ulceration	13(11)	4(3)	25(10)	30(12)	7(7)	10(10)
Necrosis	23(20)	13(11)	41(16)	37(15)	15(15)	11(11)
Hyperkeratosis	22(19)	24(21)	41(16)	56(22)	16(16)	17(17)
Acanthosis	31(26)	26(22)	62(25)	72(29)	21(21)	23(23)
Muscle degeneration	8(7)	2(2)	3(1)	3(1)	0(0)	0(0)
Stomach, glandular, number examined	117	117	249	250	100	100
Hyperplasia	6(5)	2(2)	0(0)	1(0)	0(0)	0(0)
Duodenum, number examined	117	117	249	249	100	100
Jejunum, number examined	117	117	249	249	100	100
Ileum, number examined	117	117	249	249	100	100
Colon, number examined	117	117	249	250	100	100
Parasitism	4(3)	2(2)	17(7)	6(2)	4(4)	8(8)
Cecum, number examined	117	117	249	250	100	100
Rectum, number examined	117	117	249	250	100	100
Anus, number examined	117	117	249	250	100	100

[a]Incidence of nonneoplastic lesions that occur with a frequency of 1% or more in at least one group.
[b]Values in parentheses are percentages.
[c]PWG = preweaning gavage.

Table 12. Number of F344 rats with thyroid C-cell proliferative lesions.

	Control[a]		Amosite[a]		Amosite PWG[a]	
	M	F	M	F	M	F
Animals examined	117	116	246	247	100	100
Total C-cell tumors	27(23)	24(21)	76(31)	65(26)	25(25)	29(29)
C-cell adenoma	16(14)	14(12)	26(11)	37(15)	11(11)	15(15)
C-cell carcinoma	11(9)	10(9)	50*(20)	29(12)	14(14)	14(14)
C-cell hyperplasia	21(18)	22(19)	58(24)	71(29)	23(23)	26(26)

[a]Values in parentheses are percentages.
*$p < 0.05$ vs. controls (incidental tumor and Fisher exact tests).

Table 13. Number of amosite-exposed F344 rats with mononuclear leukemia.

	Untreated control		Amosite		Amosite PWG	
	M	F	M	F	M	F
Animals examined	117	117	249	250	100	100
Mononuclear cell leukemia[a]	38(32)	40(34)	106*(42)	82(33)	49†(49)	34(34)

[a]Values in parentheses are percentages.
*$p < 0.05$ vs. controls (incidental tumor and Fisher's exact test).
†$p < 0.01$ vs. controls.

Approximately one quarter of all rats receiving DMH alone or DMH with amosite developed Zymbal's gland neoplasms ($p < 0.01$), while in control animals the occurrence was low (1–3%). The incidence appeared essentially comparable between the two DMH-treated groups.

Liver Neoplasms

The classification of hepatocellular proliferative lesions was based on the ILAR Monograph (*10*). Table 17 summarizes the number of control or DMH-treated rats with neoplastic nodules or hepatocellular carcinoma.

Table 14. Number of DMH-exposed F344 rats with primary epithelial neoplasms of the gastrointestinal tract.

	Untreated control[a]		DMH positive control[a]		DMH with amosite[a]	
	M	F	M	F	M	F
Animals examined	117	117	125	124	173	175
Total gastrointestinal	4(4)	2(2)	92(74)	77(62)	118(68)	114(65)
Total stomach	1(1)	1(1)	3(2)	4(3)	2(1)	1(1)
Total small intestine	3(3)	0(0)	18(14)	14(11)	19(11)	24(14)
Duodenum						
Carcinoma	0(0)	0(0)	11(9)	3(2)	13(8)	19(11)
Adca in polyp[b]						
Adenomatous polyp						
Jejunum						
Carcinoma	2(2)	0(0)	2(1)	11(9)	3(2)	2(1)
Adca in polyp[b]					1(1)	
Adenomatous polyp			1(1)			
Ileum						
Carcinoma			2(1)			
Adca in polyp[b]						1(1)
Adenomatous polyp	1(1)					
Total large intestine	0(0)	1(1)	81(65)	70(56)	110(64)	101(58)
Cecum						
Carcinoma			16(13)	7(6)	6(3)	6(3)
Adca in polyp[b]						
Adenomatous polyp					2(1)	
Total colon						
Ascending colon						
Carcinoma			10(8)	10(8)	20(12)	14(8)
Adca in polyp[b]			2(1)	4(3)	3(2)	7(4)
Adenomatous polyp			5(4)	7(6)	5(3)	8(5)
Transverse colon						
Carcinoma			1(1)		2(1)	2(1)
Adca in polyp[b]			8(6)	9(7)	21(12)	20(11)
Adenomatous polyp	8(6)	6(5)	22(13)	22(13)		
Descending colon						
Carcinoma				(1)	3(2)	2(1)
Adca in polyp[b]			20(16)	15(12)	25(14)	22(13)
Adenomatous polyp		1(1)	34(27)	27(22)	40(23)	31(18)
Colon (other)[c]						
Carcinoma				4(3)	2(1)	2(1)
Adca in polyp[b]						
Adenomatous polyp			1(1)	1(1)		1(1)

[a]Values in parentheses are percentages.
[b]Adenocarcinoma arising in adenomatous polyp.
[c]Colon (other) = site not identified.

Table 15. Number of DMH-exposed F344 rats with primary renal neoplasms.

	Untreated control		DMH positive control		DMH with amosite	
	M	F	M	F	M	F
Animals examined	117	117	125	124	173	175
Total renal tumors[a]	0(0)	1(1)	3(2)	49(32)*	4(2)	56(32)*

[a]Values in parentheses are percentages.
*$p = < 0.01$.

A significantly increased incidence of neoplastic nodules and/or hepatocellular carcinomas occurred in groups receiving DMH alone and in groups receiving DMH plus amosite. Generally, females had a higher incidence ($p < 0.01$) than males ($p < 0.05$).

Miscellaneous Neoplasms

In several instances, DMH treatment with or without amosite led to statistically significant decreased incidences of certain spontaneous neoplasms, particularly of the endocrine system.

Table 16. Number of DMH-exposed F344 rats with Zymbal gland neoplasms.

	Untreated control		DMH positive control		DMH with amosite	
	M	F	M	F	M	F
Animals examined	117	117	125	124	173	175
Zymbal gland neoplasms[a]	1(1)	4(3)	33(26)*	34(27)*	55(32)*	39(22)*

[a]Values in parentheses are percentages.
*$p < 0.01$ vs. controls.

Table 17. Number of DMH-exposed F344 rats with hepatocellular neoplasms.

	Untreated control		DMH positive control		DMH with amosite	
	M	F	M	F	M	F
Animals examined	117	117	125	124	173	175
Neoplastic nodules[a]	9(8)	4(3)	18(14)*	29(23)*	27(15)*	32(18)*
Hepatocellular carcinoma[a]	1(1)	1(1)	9(7)*	10(8)*	7(4)†	8(5)‡

[a]Values in parentheses are percentages.
*$p < 0.05$ vs. controls.
†$p < 0.05$ vs. controls (incidental tumor and life table analysis).
‡$p < 0.05$ vs. controls (life table analysis only).

These included a reduced number of subcutaneous fibromas, pituitary adenomas in females, adrenal pheochromocytomas, pancreatic acinar cell adenomas and islet cell adenoma in males, mammary tumors, and interstitial cell tumors in male rats. However, many animals in these two groups died at an early age compared to the untreated controls.

Discussion

Tremolite (*11*) or amosite asbestos (*12*) was administered at a level of 1% in the diet to male and female F344 rats for their lifetime, including exposure of their dams to the test material. While the tremolite used in this study is considered crystalline or nonfibrous in its natural form, a small amount assumes a fibrous character during the crushing and milling process. However, the milling process used in the preparation of the tremolite for this study was identical to what is done in the commercial setting.

Starting at birth, one of three groups of neonate rats from amosite-exposed mothers were given chrysotile asbestos (instead of amosite) by gavage until weaning at which time they were given the 1% amosite diet. For all intents and purposes this group of rats should be regarded as being exposed to amosite asbestos for their lifetime. Two groups (control and amosite exposed) of weanling rats were exposed to five biweekly doses of 1,2-dimethylhydrazine dihydrochloride (DMH), a known intestinal carcinogen, to test the promotor or cocarcinogenic effects of DMH and amosite asbestos.

The clinicopathologic results in this study showed that the ingestion of tremolite or amosite asbestos did not adversely affect the fertility of the mothers or litter size of the F_1 bioassay animals. The average weight of the offspring at birth from mothers exposed to either mineral was comparable to the offspring of nonexposed mothers. However, the weight of the exposed offspring at weaning was slightly less than the control rats. The cause of the decreases in weight during lactation is not known. The differences in body weight gain became more apparant between weaning and 8 weeks of age. While the tremolite- and amosite asbestos-exposed rats paralleled the control animals in weight gain, they remained smaller throughout their life. The mean body weight of the male rats exposed to the chrysotile preweaning gavage (PWG) and subsequently to amosite asbestos was slightly higher than the amosite alone rats. This may be related to the mortality induced in the neonates by the PWG technique which would allow the remaining pups more milk during lactation. Exposure to DMH caused a small reduction in body weight gain in female but not in male rats.

No clinical signs were observed which could be attributed to the ingestion of either mineral. Starting at 9 months of age, the DMH-exposed rats showed signs attributable to DMH-related neoplasia, but no difference was noted between the DMH and DMH plus amosite groups.

The ingestion of either tremolite or amosite in the diet for the life of the rats did not adversely affect their survival. In fact, survival of female rats exposed to amosite or amosite plus chrysotile PWG was slightly better up to 112 weeks than the controls. Similarly, the survival of male rats exposed to amosite was slightly better than the untreated controls, although the amosite plus chrysotile PWG group showed slightly less survivability.

The most plausible explanation for the increased survival of the amosite exposed rats is their lower weight throughout the study. Yu et al. (*13*) have shown that rats of lower body weight caused by restricted caloric intake lived longer than rats that were allowed to eat an unlimited amount of food.

The survival of the rats (control and amosite) in this study compares favorably with other NTP bioassays (*14*). At 106 weeks of age (age at end of typical 2-yr bioassay) the percentage of male rats alive in this study was: untreated tremolite control, 83%; untreated amosite control, 81%; tremolite, 82%; amosite, 88%; and amosite plus PWG, 77%. The percentage of female rats alive at this time was: tremolite control, 82%; amosite control, 79%; tremolite, 84%; amosite, 82%; and amosite plus PWG, 86%. Haseman (*14*) in reviewing the 25 most recent NTP feeding studies found an average of 66% of control males and 73% of control females alive at 112 weeks of age.

The survival of control groups of males and females was similar at 106 weeks. In most 2-yr studies involving rats, more females generally survive to the end of the study than do males. However, the longer survival of female rats (control and tremolite or amosite exposed) was clearly demonstrated after 142 weeks.

The ingestion of either tremolite or amosite asbestos over the lifetime of these rats did not cause a biologically significant increase of neoplasms at any anatomic site when compared to the concurrent controls. The gastrointestinal tract was considered a potential target organ based on epidemiological studies in humans (*15*). The overall incidence of intestinal neoplasms in the control (male 4 and female 2%) and two amosite asbestos groups (male 3 and female 2%; male 4 and female 3%) was low, and there was no significant ($p < 0.05$) difference between the treated and control groups. Similar observations were noted in the tremolite groups and their respective controls. In addition, nonneoplastic lesions of the gastrointestinal tract were not increased. In summary, amosite asbestos did not cause any adverse affects in the gastrointestinal tract of either male or female F344 rats.

Rats exposed to DMH showed a high incidence (60–70%) of neoplasia of the gastrointestinal tract, primarily in the large intestine. This high rate of intestinal neoplasia was unexpected because a pilot study (*3*) using the same dosing regimen of DMH would have predicted an incidence of 15 ± 5% in this study. In a previous NTP bioassay, hamsters exposed to DMH and chrysotile asbestos also failed to develop the desired rate of intestinal tumors based on a similar pilot study (*28*). Apparently the neoplastic dose response to DMH is relatively steep and duplication of low rates of intestinal neoplasia are difficult to reproduce.

Because of the high background rate of DMH-induced neoplasia, it is not possible to determine with accuracy if amosite had a cocarcinogenic or additive effect in this study. Female rats exposed to DMH and amosite had a higher incidence (11% versus 2%) of neoplasia of the duodenum than the DMH controls. Conversely, they had a lower incidence (9% versus 1%) of neoplasms of the jejunum; thus the total number of animals with neoplasms of the small intestine was comparable. A similar situation was observed in the large intestine of male rats. The rats exposed to DMH alone had a higher incidence (13% versus 3%) of carcinoma of the cecum but a lower incidence (13% versus 26%) of neoplasms of the transverse colon.

The morphologic appearance of the neoplasms induced by DMH were comparable to those described previously in rats exposed to hydrazine compounds (*16*). In addition, the few intestinal neoplasms which occurred in the control and tremolite- or amosite (no DMH)-exposed rats were of the same morphologic types to those induced by DMH. The neoplasms observed in the kidney, liver and Zymbal's gland of DMH-exposed rats were consistent with those reported for these types of intestinal carcinogens (*17*).

A significantly ($p < 0.05$) increased incidence of C-cell carcinomas of the thyroid occurred in amosite-treated male rats. This effect was not observed in the amosite PWG male rats and the overall incidence of total benign and malignant C-cell tumors was comparable between control and treated groups. Therefore, this is not considered to be a treatment-related effect.

The incidence of mononuclear cell leukemia (synonyms—monocytic leukemia, Fisher rat leukemia) was elevated in amosite (42%) and amosite PWG (49%) male rats compared to the concurrent control group (32%). However, the rates were not significant when compared to the tremolite male control group (39%). This increased inci-

dence was not observed in treated female rats. Coleman et al. (*18*) reported an incidence of nearly 30% in male F344 rats within the age group of 24–40 months. In 2-yr-old F344 rats, Goodman et al. (*19*) reported 12% of males and nearly 10% of females had lymphoma/leukemia, a much lower incidence than in these studies. It is apparent from this study and above cited studies that the incidence of leukemia increases rapidly after 2 years of age. In view of considerable variation in the incidence of such disorders, the fact that the amosite-exposed male rats survived longer than their concurrent controls and lack of significance when compared to the tremolite control group, it is doubtful that the increase in the rate of leukemia is treatment related. More importantly, an increased incidence of neoplasia was not observed in target organs (GI tract and mesothelium). Even though it is known that certain types of asbestos are absorbed through the GI tract (*20,21*), it is difficult to envision how oral asbestos could cause an increase in leukemia without causing an increase of tumors in the proposed target tissues.

In summary, these effects represent only a modulation of neoplasms which occur in concurrent control groups and are known to occur in historical control rats of this strain. No uncommon or unique neoplasms were observed in any of the tremolite- or amosite-treated groups. In addition, the biological importance of the neoplasms in the absence of target organ neoplasia is questionable.

A large variety of nonneoplastic lesions, primarily lesions of aging, were observed in all groups. There was no obvious correlation between treatment and specific lesions. Therefore, tremolite or amosite at the level of 1% in the diet did not appear to cause any overt toxicity.

Studies on the effects of chronic ingestion of tremolite are not available. However, Stanton et al. (*2*) showed that the intrapleural inoculation of fibrous tremolite (two types) caused a high incidence of pleural sarcoma in Osborne-Mendel rats. In contrast, intrapleural studies of tremolite talc failed to show a carcinogenic response in hamsters (*22*). The tremolite used in the NTP study is a nonfibrous type and more closely resembles that used by Smith (*22*) than Stanton et al. (*2*).

Other studies involving the long-term ingestion of asbestos are few. Donham et al. (*23*) reported equivocal results in F344 rats which were fed a diet containing 10% chrysotile for their lifetime. While they did not observe a statistically significant ($p < 0.05$) increase in the number of tumors in exposed animals, the authors believed that there was a trend toward increased colon lesions in general, evidence of penetration of asbestos into the colonic mucosa, possible cytotoxicity to colonic tissues and suggested a possible relationship to peritoneal mesothelioma. Another equivocal study is that reported by Gibel et al. (*24*), who described an increase in malignant tumors in the lung, kidney, liver and reticuloendothelial system but no increase in intestinal neoplasia in Wistar rats fed asbestos filter material (20 mg/day) for a period of 8–14 months. Cunningham et al. (*25*) reported two studies in Wistar male rats using 1% chrysotile in the diet: one study of 24 months and one of 30 months. These authors concluded that trace amounts of ingested asbestos can penetrate the walls of the gastrointestinal tract, but evidence of carcinogenicity was inconclusive. Negative results were reported by Gross et al. (*26*), who fed rats a diet containing 5% chrysotile asbestos for a period of 21 months with no evidence of intestinal neoplasia.

Corollary studies to this investigation were conducted in Syrian golden hamsters (*27, 28*). The exposure regimen was similar in that male and female hamsters were exposed to 1% amosite asbestos (same source as the subject study) and short-range or intermediate-range chrysotile asbestos in their diet for their natural life-span. There was no adverse effect on body weight gain or survival, and no asbestos-related neoplasms were observed.

Another oral asbestos study in hamsters was reported by Smith et al. (*29*). They exposed groups of 30 male and female hamsters via drinking water for lifetime to amosite asbestos, mine tailings, beach rock or Lake Superior drinking water. They did not observe adverse effects on body weight or survival time in any of the groups. A peritoneal mesothelioma, one pulmonary carcinoma, and two early squamous cell carcinomas of the nonglandular stomach were found in the hamsters exposed to amosite but the incidence was not statistically significant ($p < 0.05$). They concluded that the study was essentially negative. A subsequent study in rats using similar materials also failed to elicit a carcinogenic response (*30*).

Except for the studies of Donham et al. (*23*), Smith et al. (*29*) and the NTP (*11, 12, 27, 28*), the other studies were conducted with relatively small numbers of animals. Also some were conducted for an insufficient period of time to adequately test the carcinogenic potential of ingested asbestos.

A long-term study of amosite asbestos designed to determine the promotor potential of asbestos

was reported by Ward et al. (*31*). They exposed 6-week-old male F344 rats three times per week for 10 weeks to 1 mg amosite asbestos in saline via gavage. Once per week during this same period, half of the rats received subcutaneous injections of 7.4 mg/kg azoxymethane (AOM), a known intestinal carcinogen in animals which produces effects similar to DMH. The rats were allowed to live out their lifespan or untl 94–95 weeks of age at which time they were killed. The authors reported an intestinal tumor incidence of 66.7% in AOM alone, 77.1% for amosite plus AOM and 32.6% for amosite alone. The authors concluded that while amosite did not significantly add to the incidence of AOM-induced intestinal neoplasia, amosite alone caused a relatively high rate of intestinal neoplasia. However, there was no untreated control group to compare to the treated groups. These results should also be viewed with some suspicion because the authors also reported a 14% incidence of Zymbal gland tumors in the rats exposed to amosite alone. The historical rate of Zymbal gland tumors in the Bioassay Program is 0.34%, indicating that this is a relatively rare tumor (*19*). However, AOM is known to induce Zymbal gland tumors with a sngle dose of 5.1 mg/kg in male F344 rats producing a 14% incidence of tumors in this organ (*17*); in this study 5.1 mg/kg AOM also caused a 24% incidence of intestinal neoplasia. A possible explanation for the incidence of Zymbal gland tumors in the amosite groups would be that they were inadvertently exposed to AOM. If this occurred, these rats would also be expected to show a high incidence of intestinal neoplasms.

Conclusions

Under the conditions of this lifetime bioassay, tremolite or amosite asbestos was not toxic, did not affect survival, and was not carcinogenic when ingested at a level of 1% in the diet by male and female Fischer 344 rats. While there were significant ($p > 0.05$) increases in the rate of C-cell carcinomas of the thyroid in male, and monocytic (mononuclear cell) leukemia in male rats exposed to amosite asbestos compared to untreated controls, their biological significance is questionable because of a lack of response in the concurrent amosite and preweaning gavage group or control group of the corollary study, nonaffect when all neoplasms of that organ are analyzed, lack of significance when examined using life table analysis or the absence of neoplasia in target organs. The cocarcinogenic studies using 1,2-dimethylhydrazine dihydrochloride (DMH) were considered flawed because of the high rate of intestinal carcinogenesis in both the DMH and amosite asbestos and DMH alone groups.

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The research described in this paper has been peer and administratively reviewed by the U.S. Environmental Protection Agency and approved for presentation and publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals [1,2]

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ABSTRACT—In 72 experiments, durable minerals in the form of particles on respirable size and of wide chemical and structural varieties, were implanted in the pleurae of outbred female Osborne-Mendel rats for periods of more than 1 year. The incidence of induced malignant mesenchymal neoplasms correlated well with the dimensional distribution of the particles. The probability of pleural sarcoma correlated best with the number of fibers that measured 0.25 μm or less in diameter and more than 8 μm in length, but relatively high correlations were also noted with fibers in other size categories having diameters up to 1.5 μm and lengths greater than 4 μm. Morphologic observations indicated that short fibers and large-diameter fibers were inactivated by phagocytosis and that negligible phagocytosis of long, thin fibers occurred. The wide variety of compounds used in these experiments suggested that the carcinogenicity of fibers depended on dimension and durability rather than on physicochemical properties.—JNCI 1981; 67:965-975.

Work in several laboratories has indicated that diverse varieties of minerals are carcinogenic when applied directly to the pleura of the rat or hamster in the form of microscopic fibers, i.e., particles with dimensional aspect ratios of 3:1 or greater (*1-9*). The same minerals are much less carcinogenic when applied at equal weight and size in nonfibrous form. Further, preliminary experiments indicate that carcinogenicity correlates best with increasing numbers of fibers having both diameters of 0.25 μm or less and lengths of more than 8 μm and that the correlation diminishes with fibers of greater diameter or lesser length. Consequently, a reasonable conclusion is that the long, thin, fibrous structure is critical to the carcinogenicity of these minerals. Studies on fibrous samples within very narrow dimensional ranges would be valuable in the establishment of this hypothesis, but these ideal samples are not available. Consequently, we are faced with the correlation of carcinogenicity with fiber samples of widely mixed dimension. The purpose of this report is to correlate our best estimate of fibrous dimension with carcinogenicity for all those minerals that we have studied that are both durable and within the size range of respirable particles. This involves 72 experiments with minerals of wide chemical and structural variety. Of special interest are the data on the amphibole asbestoses: amosite, tremolite, and crocidolite, though estimates of the dimensions of the asbestoses are especially liable to error. Chrysotile, although as carcinogenic as the amphiboles at comparable dimensions, could not be included since it has proved difficult to be measured with any degree of precision.

MATERIALS AND METHODS

None of the methods were appreciably different from those described in earlier papers (*4, 6, 9-11*). Consequently, only modifications of methods are detailed here. A standard 40-mg dose of particles uniformly dispersed in hardened gelatin was applied by open thoracotomy directly to the left pleural surface of 12- to 20-week-old, outbred female Osborne-Mendel rats. In each experiment, 30-50 rats were treated and followed for 2 years, at which time the survivors were killed. All rats were necropsied and all lesions examined histologically. A positive response was the occurrence of pleural sarcomas that resembled the mesenchymal mesotheliomas of man, developing after the 1st year (*12*). Three types of controls were considered: untreated rats, rats that received thoracotomies but no pleural implant, and rats with pleural implants of nonfibrous material. There were two types of spontaneous tumors that could cause confusion: the fibrosarcomas of left mammary glands and the subcutaneous fibrosarcomas induced by suture material. Vigilance and early surgical removal accounted for most mammary tumors; the use

ABBREVIATIONS USED: alumin = aluminum oxide; attapul = attapulgite(s); crocid = crocidolite(s); dawson = dawsonite(s); halloy = halloysite(s); UICC = International Union Against Cancer; wollaston = wollastonite(s).

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[2] The guidelines for the care and use of laboratory animals were followed as set forth by the Committee on Revision of the Guide for Laboratory Animal Facilities; by the Guide for the Care and Use of Laboratory Animal Resources, the National Research Council; and by the National Institutes of Health.

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of synthetic, biodegradable, polyglycolic acid sutures largely eliminated suture sarcomas. An equivocal diagnosis for the origin of a tumor was necessary in less than 1% of the tumors. The probability of pleural sarcoma in each experiment was calculated by an actuarial life table method that accounts for early deaths without pleural sarcoma and provides a good means of making quantitative comparisons of one experiment with another. Details of this method are given in (*13, 14*).

The fibrous materials used in these experiments were mostly commercial products that were submitted by the manufacturers from an interest in their potential carcinogenicity. Consequently, they were used as received and were not especially refined except in our efforts to separate particles by size. None of the preparations appeared overtly contaminated by other materials when examined in the electron microscope. A few of the small-fibered subfractions of the fibrous materials were obtained by ball milling in a steel ball mill and consequently were contaminated with fragments of steel. In general, subfractions were obtained by simple gravimetric methods in aqueous media to separate fibers of different dimensions. These maneuvers included sedimentation, centrifugation, and filtration, which in some instances were also responsible for the reduction of the size of the particles but did not otherwise alter the particles physically or chemically. Eleven chemically and structurally different groups of fibers were available for study, and samples studied are listed in text-figure 1 and table 1. Six major groups of particles had multiple dimensional ranges; these include: crocidolites: (samples crocid 1-13), glasses (glass 1-22), aluminum oxide whiskers (alumin 1-8), talcs (talc 1-7), dawsonites (dawson 1-7), and wollastonites (wollaston 1-4). Seven additional types of particles had only one or two dimensional ranges. These were the amphibole asbestoses tremolite (tremolite 1, 2) and amosite, the clays attapulgite (attapul 1, 2) and halloysite (halloy 1, 2), crystals of silicon carbide and potassium titanate (titanate 1, 2), and nickel titanate (titanate 3). All of these materials have been described elsewhere (*4, 6, 10, 11, 15-18*), but the following information is pertinent.

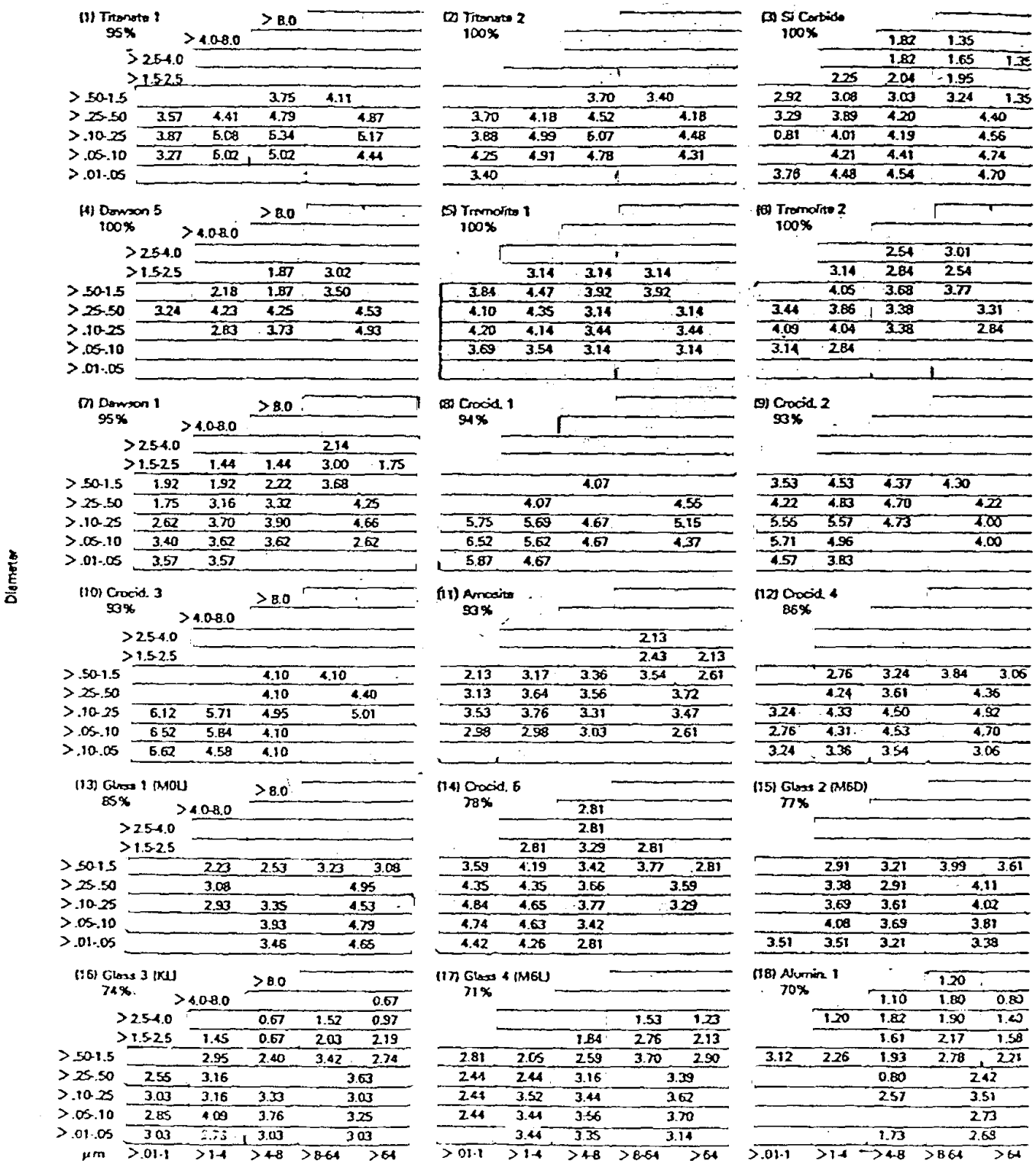
Crocidolite (crocid 1-13).—These 13 samples of South African crocidolite (an amphibole asbestos) were from four different sources. Samples crocid 1, 3, and 9 were prepared in our laboratory from a single sample of hand-cobbed, unmilled ore. The ore sample was hand milled without exposure to any metallic materials and reduced to the approximate size of commercial crocidolite. Samples crocid 6, 7, 8, 11, 12, and 13 were all prepared in our laboratory by various milling, sedimentation, and flotation methods from a single lot of standard UICC crocidolite designated crocid 5. Differences in dimension were the result of different milling times. Crocid 5, the original UICC sample, has been characterized in (*19, 20-23*). Samples crocid 4 and 10 were specimens prepared in a commercial laboratory from a single separate sample of South African crocidolite and separated by centrifugation to obtain mutually exclusive size ranges from the same sample (*24*). The remaining sample, crocid 2, was obtained from Dr. J. C. Wagner (Medical Research Council Pneumoconiosis Unit, Penarth, Wales) as representative of the material used by him in his original experiments (*25*). It was our impression that any mechanical manipulation of these samples could both reduce the size of the particles by fragmentation and effectively increase the size of the particles by clumping. For this reason, probably the dimensional measurements on crocidolite are the least representative of all the fibers measured.

Glass (glass 1-22).—The first 18 of the 22 glasses were borosilicate glasses that have been previously reported and can be recognized from those publications by their letter designations (*4, 10*). Glasses 12, 14, 15, and 18 were preparations of typical large-diametered insulation glass fibers that were coated with a phenol-formaldehyde binder. In the early experiments, glass 18 was used as a control and also served as a vehicle for the implants. Glasses 19 and 20 were preparations of large-diametered fibrous glass that was leached to remove all elements except SiO_2. These two glasses were exceptionally fragile and contained many irregular fragments. Glasses 21 and 22 were large-diametered extruded fibers with a microcrystalline aluminum oxide content greater than 80% (glass 21) and with a microcrystalline zirconium oxide content greater than 90% (glass 22).

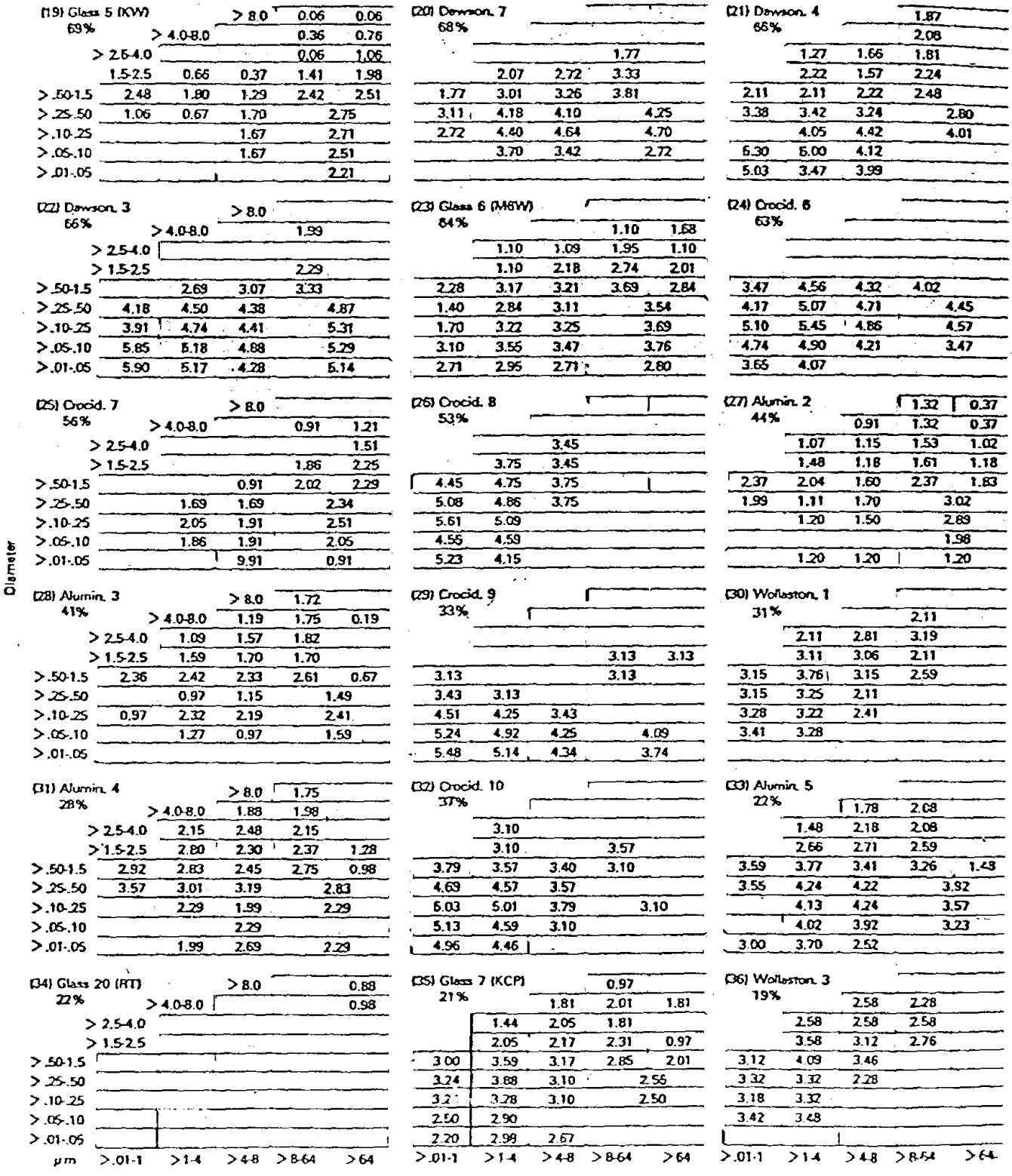
Aluminum oxide (alumin 1-8).—The 8 samples of aluminum oxide were all crystalline sapphire whiskers prepared by General Technologies Corporation, Reston, Va., or by Thermokinetics Fiber Incorporated, Nutley, N.J. (*15-18, 26*). All of the samples were processed and selected for dimensional ranges. Of the samples, 3 were exceptionally noteworthy. Sample alumin 8 was nonfibrous, sample alumin 3 was exceptionally fine but tended to cluster in nonfibrous balls, and sample alumin 4 contained whiskers of aluminum nitride as well as aluminum oxide.

Talcs (talc 1-7).—All seven talcs were refined raw materials for commercial products. Each was from a separate and diverse source and selected to include all extreme ranges of dimension. Platelike structure was consistent and was considered in the calculation of the volume (*15-18*).

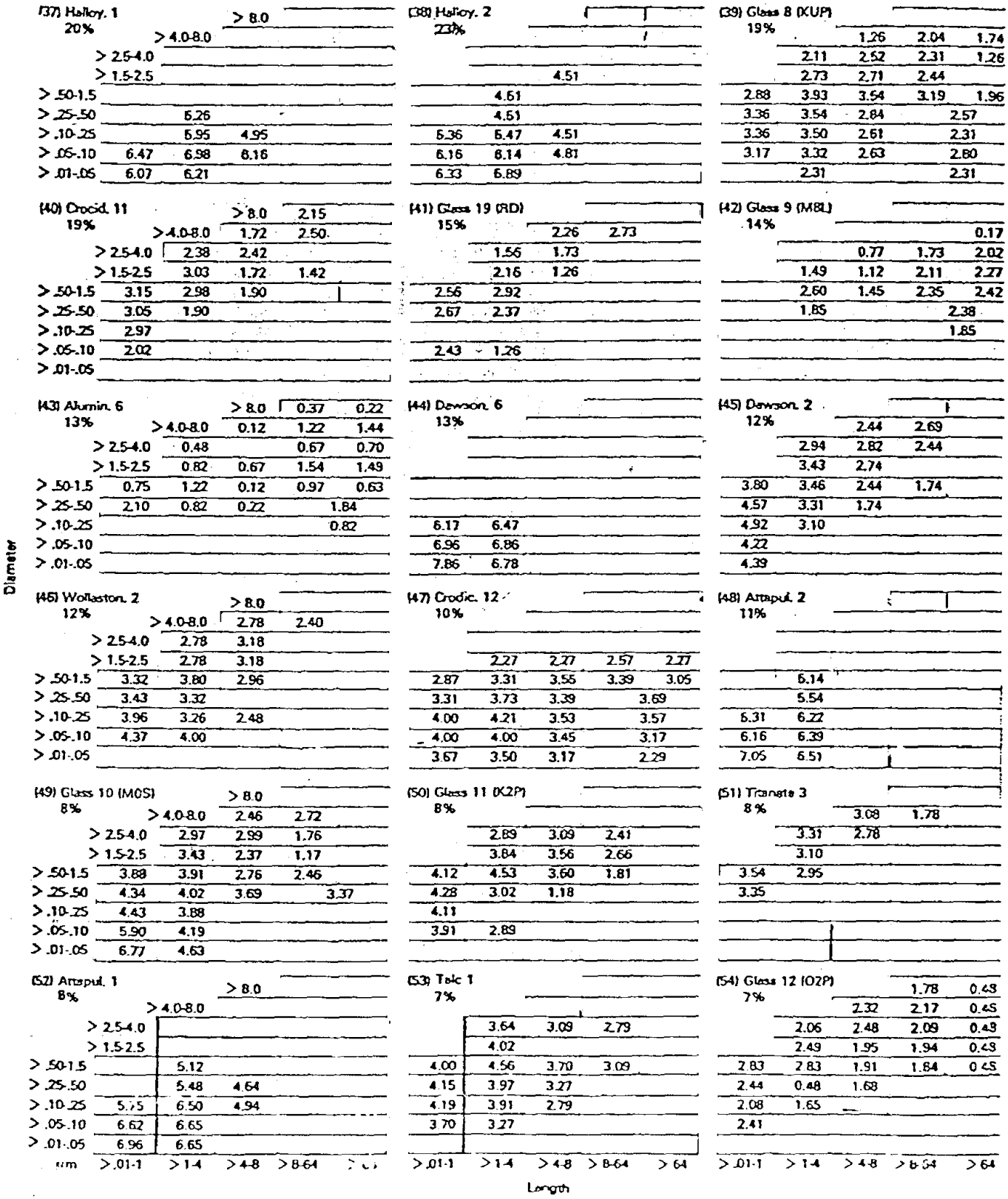
Dawsonite (dawson 1-7).—The 7 dawsonite samples (crystalline dehydroxy sodium aluminum carbonate $[NaAl(OH)_2CO_3]$ were from several sources. The characteristics and synthesis of dawsonite can be found in (*27, 28*). Samples dawson 2 and 3 were synthetic crystals prepared by a commercial company (for dawson 2) and by the Bureau of Mines, U.S. Department of Interior (for dawson 3). Sample dawson 4 was a natural crystalline dawsonite from the Olduvai Gorge, Tanzania. The remaining 4 samples (dawson 1, 5, 6, and 7) were synthetic crystals from a second commercial company. These 4 samples were especially crystallized and sorted to achieve narrow ranges of size.



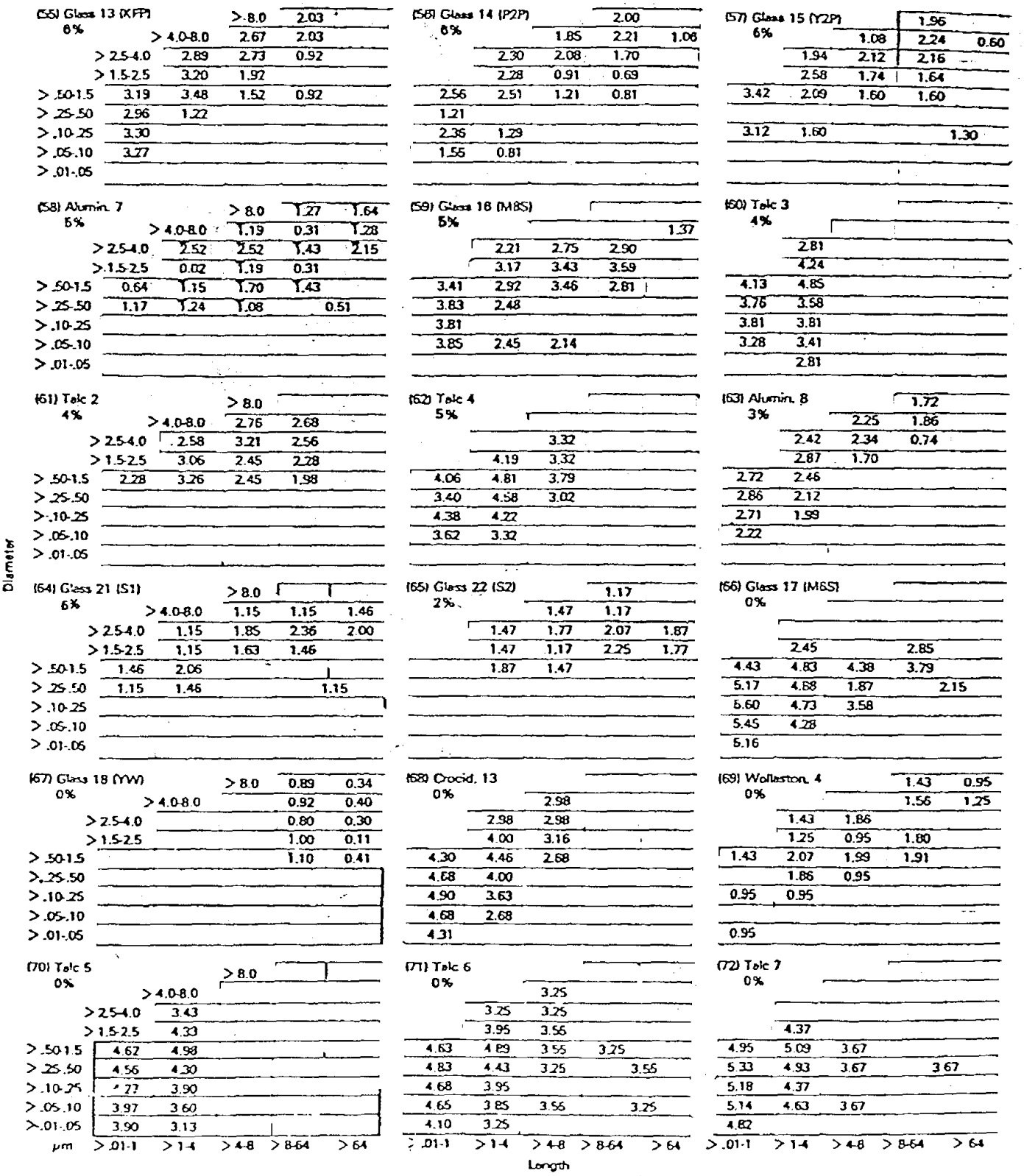
TEXT-FIGURE 1. Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.



TEXT-FIGURE 1 *(continued).*—Fiber distribution by co[illegible] log of the number of particles per microgram in each of 34 dimensional categories.



TEXT-FIGURE 1 (*continued*).—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.



TEXT-FIGURE 1 *(continued).*—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.

TABLE 1.—*Summary of 72 experiments with different fibrous materials*

Expt No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤0.25 μm × >8 μm	Expt No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤0.25 μm × >8 μm
1	Titanate 1	21/29	95±4.7	4.94	37	Halloy 1	4/25	20±9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23±9.3	0
3	Si carbide	17/26	100	5.15	39	Glass 8	3/26	19±10.3	3.01
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19±8.5	0
5	Tremolite 1	22/28	100	3.14	41	Glass 19	2/28	15±9.0	0
6	Tremolite 2	21/28	100	2.84	42	Glass 9	2/28	14±9.4	1.84
7	Dawson 1	20/25	95±4.8	4.66	43	Alumin 6	2/28	13±8.8	0.82
8	Crocid 1	18/27	94±6.0	5.21	44	Dawson 6	3/30	13±6.9	0
9	Crocid 2	17/24	93±6.5	4.30	45	Dawson 2	2/27	12±7.9	0
10	Crocid 3	15/23	93±6.9	5.01	46	Wollaston 2	2/25	12±8.0	0
11	Amosite	14/25	93±7.1	3.53	47	Crocid 12	2/27	10±7.0	3.73
12	Crocid 4	15/24	86±9.0	5.13	48	Attapul 2	2/29	11±7.5	0
13	Glass 1	9/17	85±13.2	5.16	49	Glass 10	2/27	8±5.6	0
14	Crocid 5	14/29	78±10.8	3.29	50	Glass 11	1/27	8±5.5	0
15	Glass 2	12/31	77±16.6	4.29	51	Titanate 3	1/28	8±8.0	0
16	Glass 3	20/29	74±8.5	3.59	52	Attapul 1	2/29	8±5.3	0
17	Glass 4	18/29	71±9.1	4.02	53	Talc 1	1/26	7±6.9	0
18	Alumin 1	15/24	70±10.2	3.63	54	Glass 12	1/25	7±5.4	0
19	Glass 5	16/25	69±9.6	3.00	55	Glass 13	1/27	6±5.7	0
20	Dawson 7	16/30	68±9.8	4.71	56	Glass 14	1/25	6±5.5	0
21	Dawson 4	11/26	66±12.2	4.01	57	Glass 15	1/24	6±5.9	1.30
22	Dawson 3	9/24	66±13.4	5.73	58	Alumin 7	1/25	5±5.1	0
23	Glass 6	7/22	64±17.7	4.01	59	Glass 16	1/29	5±4.4	0
24	Crocid 6	9/27	63±13.9	4.60	60	Talc 3	1/29	4±4.3	0
25	Crocid 7	11/26	56±11.7	2.65	61	Talc 2	1/30	4±3.8	0
26	Crocid 8	8/25	53±12.9	0	62	Talc 4	1/29	5±4.9	0
27	Alumin 2	8/27	44±11.7	2.95	63	Alumin 8	1/28	3±3.4	0
28	Alumin 3	9/27	41±10.5	2.47	64	Glass 21	2/47	6±4.4	0
29	Crocid 9	8/27	33±9.8	4.25	65	Glass 22	1/45	2±2.3	0
30	Wollaston 1	5/20	31±12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28±12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	37±13.5	3.09	68	Crocid 13	0/29,	0	0
33	Alumin 5	4/22	22±9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22±10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21±8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19±10.5	0	72	Talc 7	0/29	0	0

RTV talc

They represent an excellent size distribution for comparison.

Wollastonite (wollaston 1-4).—Wollastonite is a naturally occurring crystalline fiber of monocalcium silicate (*15-18*). Four separate samples of this substitute for asbestos were received from the same Canadian mine. These were graded commercially according to size by the designation A, B, D, and F. It was apparent at low-power magnification that only grade F was completely fibrous and that these fibers were relatively large.

Tremolite (tremolite 1, 2).—The second type of amphibole asbestos studied was tremolite, a material that has a close affinity to the talcs. Both of these samples were from the same lot of asbestos and were in the optimal range of size for carcinogenesis. Comparison of these fibers indicated that they were distinctly smaller in diameter than the tremolite fibers used by Smith et al. (*29*).

Amosite.—The third amphibole asbestos studied was a single sample of South African amosite from the UICC standard reference samples. No efforts were made to alter this as received, and descriptions of this sample as published should apply (*19, 21, 22*).

Attapulgite (attapul 1-2).—Of the natural fibers, the clay attapulgite was of particular interest because of its use in many household items that generate respirable dust. Two different samples of this complex hydrated magnesium silicate were obtained from sources in Attapulgus, Decatur County, Georgia. Both samples were considerably refined, and by electron microscopy they were seen to be composed entirely of short fibers of consistently small diameter (*30*). These refined clays were considered by the U.S. Bureau of Mines to be 90% or greater in purity, with the remaining 10% being quartz.

Halloysite (halloy 1-2).—Halloysite is a natural fibrous hydrated aluminum silicate, which is respirable and of minute size. The 2 samples were obtained from Dr. Walter Parham, who recovered them from the raw water supply of Hong Kong. On examination these samples were seen to have a tendency for clumping in water. In an effort to disperse the minute fibers, the second sample was sonicated and treated with sodium

hexametaphosphate. Clumping persisted in this second sample, and little different was seen between the 2 samples.

Silicon carbide (si carbide).—One metallic crystalline whisker other than alumin was prepared by the General Technologies Corporation. Silicon carbide was a single sample, which was of exceptionally fine, uniform dimension.

Potassium octatitanate (titanate 1–3).—In addition to the synthetic crystals of dawsonite, aluminum oxide, and silicon carbide, 2 samples of fibrous crystalline potassium octatitanate (titanate 1 and 2) were tested. These were obtained from two different suppliers but they represent a single source. Because of the potential carcinogenicity of metallic nickel, the control for these 2 samples was nonfibrous, finely ground nickel titanate (titanate 3).

The 72 experiments represent all of the experiments done in a single dose range and with durable minerals and particles in the respirable range. Additional controls outside of these limits are mentioned in "Results."

Fiber measurements.—An aliquot of each of the 72 experimental mineral samples was placed on a Formvar-covered, slotted grid with an opening measuring 1×2 mm. This grid was air dried and first examined under the light microscope. If the fibers appeared satisfactorily distributed, a photomontage of the entire grid was made at a final magnification of ×3,000. The slotted grid was then placed in a Siemens electron microscope, Elmiskop 1-A, and the entire grid was scanned at low magnification. From this scan, an area that seemed to represent a typical distribution of particles in the specimen was selected for counting. At a final magnification of about ×5,000–100,000, a second photomontage was made of that section of the grid selected to include particles typical of the sample. This selected area, which generally measured about 350×150 μm, was then located on the lower magnification montage of the grid and examined to determine whether the area chosen was truly representative of the entire grid. Finally, all fibers in the area were counted and measured individually. For the diameters, a comparative scale at the final magnification was used to measure magnified diameters that measured less than 1 mm. In most cases, the selected area counted included at least 1,000 fibers, but the actual number varied with the overall size of the particles.

Subsequently, with the aid of the IBM system 370 computer, assuming the fibers to be of cylindrical shape and using the density of the material, we were able to estimate the weight of the counted samples and the number of particles of a given dimension in the 40-mg dose administered. For the purpose of calculation, particles were grouped into 34 dimensional ranges as indicated in text-figure 1, and the number of particles per microgram in each category was calculated. Duplicate counts on the montages were done on most samples and were surprisingly similar, as were counts on different areas of the same montage. However, when studies of repeat samples from the original fibers were made, considerable variation in counts occurred. Clearly, the method is subject to several errors; calibration of the electron microscope, deviation of particles from the assumed cylindrical shape, and sampling errors, especially where large particles are concerned, represent the major problems. Nevertheless, the estimates are probably valid to within one order of magnitude. Consequently, the counts are reported as the common log with the characteristic of the log representing the probable limit of accuracy (text-fig. 1).

RESULTS

Controls have been discussed in previous publications (*4, 6, 9–11*), but they were approached here in a slightly different way. In addition to untreated controls we studied rats in which open thoracotomy was performed and a noncarcinogenic material was either applied to the pleura or implanted in the lung. These 3 groups (table 2) were rats from numerous experiments that were of the same species, sex, and age and that were housed in the same quarters. The incidence of clearly apparent pleural neoplasms in untreated, aged outbred Osborne-Mendel female rats was essentially nonexistent. However, a few pleomorphic sarcomas that might be confused with pleural tumors occurred in the left thorax of both treated and, to a lesser degree, untreated controls. Although these tumors involved the thickness of the chest wall, in most cases the tumors appeared to be derived either from mammary gland fibroadenoma or from suture granuloma in the subcutaneous tissues. But there remained a few tumors for which no definite origin could be determined and which were histologically comparable with pleural sarcomas. In both the experimental groups and the control groups these questionable tumors were counted as pleural sarcomas. These essentially confusing tumors observed in the controls need to be taken into account in the assessment of the carcinogenicity of the experimental materials. The incidence of pleural sar-

TABLE 2.—*Incidence of pleural sarcomas in outbred female Osborne-Mendel control rats*

Time, wk	Untreated[a]	Noncarcinogenic pulmonary implants[a]	Noncarcinogenic pleural implants[a]	Combined controls[a]
12–52	1/113	0/49	0/47	1/209
53–65	0/15	2/26	1/72	3/113
66–78	0/26	4/50	3/64	7/140
79–91	0/68	1/70	2/85	3/223
92–104	0/26	1/72	[illegible]	11/392
105–120	0/98	1/162	—/136	2/296
121–130	1/66	0/3		1/69
131–143	0/27			0/27
144–156	0/27			0/27
156	1/22			1/22
Total	3/488	9/432	17/598	29/1,518
Percent	0.6	2.1	2.8	1.9

[a] No. dead with pleural sarcomas/No. dead without pleural sarcomas.

comas in all 3 control groups combined, calculated by the life table method (*13*), was 7.7±4.2%. Comparison of this incidence with the pleural sarcoma incidence in the 72 individual experiments showed that the incidence of pleural sarcomas in a particular experimental group was significantly greater than that in the combined control group only if it exceeded 30% (*see* expts 1-29 in table 1).

In regard to the controls, some negative experiments with intrapleural implants not used as controls should be mentioned. These experiments included intrapleural implants that did not conform to the type of materials under consideration because the particles were either nondurable (cotton lint, gypsum, and carrageenan), were of greater than respirable size (steel shavings, steel wool, vermiculite, polyurethane, tungsten carbide, and infusorial earth), or were exclusively nonfibrous (polyacrylic nitrile, antigorite, silicon dusts, and several glasses). None of these experiments had an incidence of pleural sarcoma that was significantly greater than the 7.7% incidence of the combined control group.

From the summarization of the 72 experiments in table 1 and text-figure 1, even cursory examination of the fiber distribution suggested that particles in the relatively thin- and long-dimensional categories were associated with higher tumor probabilities. This observation was confirmed by the statistical correlation and regression techniques that were used in previous papers (*4, 9, 10*). The logit transformation (*13*) was applied to the estimated tumor probabilities (p) according to the formula: Logit$=\ln [p/(1-p)]$, where ln denotes the natural logarithm. The 34 dimensional categories indicated in text-figure 1 were arbitrarily grouped into 11 larger categories, and the simple correlation coefficients of the logit of tumor probability with the common logarithms of numbers of particles per microgram in each of these categories was calculated (*see* table 3). The maximum correlation coefficient, 0.80, was with particles equal to or less than 0.25 μm in diameter and greater than 8 μm in length. There was no correlation with particles equal to or less than 4 μm in length or with particles greater than 1.5 μm in diameter, but relatively good correlations were noted with log numbers of fibers in categories greater than 4 μm in length and up to 1.5 μm in diameter, with correlation coefficients of 0.45-0.80.

The possibility of the existence of relationships between the particle size distributions and tumor probabilities, which are not disclosed by the simple correlation coefficients in table 3, was explored by multiple regression methods. These methods were used to find the best-fitting function of the form: logit$=a+b_1 x_1 + \ldots + b_k x_k$, where $x_1, \ldots, x_k$ represent the common logs of numbers of the particles per microgram in the size categories of table 3, and $a, b_1, \ldots, b_k$ are the regression coefficients to be estimated. The analysis indicated that the addition of further dimensional categories to the category with diameter equal to or less than 0.25 μm and with length greater than 8 μm did not significantly improve the explanation of the variation in tumor probability. The regression equation for the single variable (x) representing the common log of number of particles per microgram with diameters equal to or less than 0.25 μm and lengths greater than 8 μm was:

$$\ln[p/(1-p)] = \underset{(0.24)}{-2.62} + \underset{(0.0834)}{0.9305}x.$$

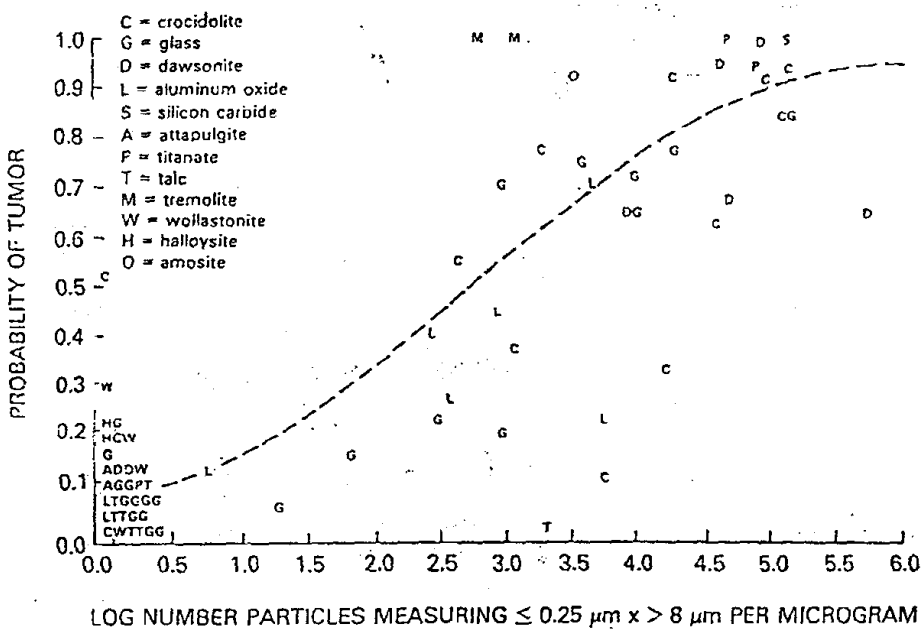
The *numbers in parentheses* beneath the regression coefficients are their estimated standard deviations. The relationship expressed by the above equation is highly significant ($P<0.0001$). The estimated regression curve is illustrated in text-figure 2.

The fact that the use of additional dimensional categories did not significantly improve the fit of the regression equation does not indicate lack of carcinogenicity in other categories. The regression of logit of tumor probability on common log of numbers of particles in other categories with a diameter up to 1.5 μm and a length greater than 4 μm would also indicate a highly significant relationship. The difficulty here is that the numbers of particles in adjacent size categories were highly correlated. Better definition of the critical range of carcinogenicity would require more narrowly defined samples (i.e., particles in a narrower dimensional range). What is perhaps more likely than the existence of a narrow range of sizes within which particles are carcinogenic and outside of which they are not is that the probability of tumor falls as particle diameter increases and length decreases.

Of the 72 experiments, 7 had tumor incidences that deviated markedly from those predicted by the estimated regression line. These were: experiments 5 (tremolite 1), 6 (tremolite 2), 26 (crocid 8), 29 (crocid 9), 33 (alumin 5), 47 (crocid 12), and 71 (talc 6) (*see* table 1 and text-fig. 2). For the first 3 of these experiments the observed responses were higher than the predicted responses, but the high responses can in part be explained by the fact that there were substantial numbers of fibers in size categories adjacent to the category used in the regression equation. For the remaining 4 experiments, the observed response was substantially lower than the expected response; although no apparent explanation existed for these deviations, they were possibly due to inaccuracies in the assessment of functional particle size. In preparations of amphibole asbestoses (which included the crocidolites and tremolites), we observed that both

TABLE 3.—*Correlation coefficients of logit of tumor probability with common logarithm of number of particles per microgram in different dimensional ranges*

Fiber diameter μm	Fiber length, μm		
	≤4	>4-8	>8
>4	—	-0.28	-0.30
>1.5-4	-0.45	-0.24	0.13
>0.25-1.5	0.01	0.45	0.68
≤0.25	0.20	0.63	0.80



TEXT-FIGURE 2.—Regression curve relating probability of tumor to logarithm of number of particles per μg with diameter ≤0.25 μm and length >8 μm.

clumping and fragmentation of the particles were greater than those in the other minerals, and estimates of particle size distribution in duplicate samples varied most for amphibole asbestoses.

DISCUSSION

The results show that a wide variety of compounds that seem to have only dimension and durability in common are carcinogenic for the pleura of the rat. Our conclusions regarding those dimensional categories that correlate strongly with probability of pleural tumor remain essentially the same as in previous studies, namely, that probability of pleural sarcoma correlates best with fibers that measure ≤0.25 μm×>8 μm, but that relatively high correlations were also observed with fibers in other categories having a diameter up to 1.5 μm and a length greater than 4 μm. A more refined estimate of critical carcinogenic dimension may be possible if the parameters of the experiments were changed. A different animals species, lower dose, more precise means of fiber measurement, more accurate volumetric calculations, and samples with narrower dimensional ranges all might be determining factors in better assessment of the particle dimensions critical to carcinogenicity. However, we should keep in mind two points: *a*) the dimensional limits are probably far from absolute, and *b*) we are dealing with cancer in the rat and thus extrapolation to man may not be precise.

It is clear from the histologic studies of these experiments and of previous studies that our data offer an explanation more for the lack of carcinogenicity of short fibers and thick fibers than for the carcinogenicity of long, thin fibers. Sections of preneoplastic pleural lesions show avid phagocytosis of both short fibers and large-diameter fibers but negligible phagocytosis of long, thin fibers. Consequently, in these experiments we may simply be measuring the efficiency of phagocytosis. Doubtless, we have little real knowledge of the way that long, thin fibers can cause cancer, but as Rous (*31*) once said, "Since what we think largely determines what we do, it is well that we think something." In the spirit of this quote, it might be profitable to consider potential mechanisms of cancer production by long, thin fibers. Of first importance are those hypotheses in which the progenitor of the cancer cell is not directly affected by the fiber. The long latent period would suggest that a generalized alteration either in local milieu or systemic environment might be at fault. In this regard, the abundant collagen in the preneoplastic pleural scars should be noted. Consideration of a relationship between this phenomenon and "solid-state" carcinogenesis is attractive, though the reduction of plastic sheets to small particles tends to reduce carcinogenesis. Mechanisms of solid-state carcinogenesis have been thoroughly reviewed by Brand (*32*), and little more need be added.

Any hypothesis concerning fibers must take into account the fact that both short fibers and thick fibers are less carcinogenic than fine, long fibers. Since dose was fixed in weight, but was different in dimension for all experiments, one might consider the surface area as a possible factor. If this were the case then fibers from the same pool that were modified only by shortening should be equal in tumor-producing capacity. Clearly, this is not true in the following experiments: 13 (glass 1, MOL) vs. experiment 49 [glass 10, MOS *see* (*4*, *10*)],

and in experiment 24 (crocid 6) and experiment 25 (crocid 7) vs. experiment 40 (crocid 11), experiment 47 (crocid 12), and experiment 68 (crocid 13). However, in these examples the phagocytosis variable cannot be ruled out.

A provocative explanation relates to the ability of fine, long fibers to penetrate cells without killing them. That this can occur is evident from in vitro studies (*33*). However, simple penetration of cells by mycelia of fine dimension (a notable aspect of contamination of cell cultures by fungi) rarely produces transformation of cell cultures and thus is unlikely to produce cancer. However, mineral fibers differ from fungi in their rigidity as well as chemical content, and one easily could conceive of physical differences between the mineral fibers and mycelia that might be critical.

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August 1, 1984

Dr. C. S. Thompson
R. T. Vanderbilt Company
30 Winfield Street
Norwalk, Connecticut 06855

Dear Dr. ~~Thompson~~ Slim:

In response to your request, the following is a list of the sample numbers published by Stanton et al (1981)* and the information about the samples of wollastonite, talc and tremolite that I have found by going through Stanton's mineral collection and notes. In some cases the information is incomplete.

Sample #	Tumor Probability (%)	Sample Description
Wollastonite 1	30	Wollastonite A rec'd. from Dr. Mangan 1/16/79
Wollastonite 2	12	Wollastonite B rec'd. from J. J. Mangan 1/16/79
Wollastonite 3	11	Wollastonite D rec'd. from J. J. Mangan 1/16/79
Wollastonite 4	0	Wollastonite F rec'd. from J. J. Mangan 1/16/79
Talc 1	7	Cyclo-Sorb.
Talc 2	4	J. and J. Baby Talc
Talc 3	4	Mistron Frost
Talc 4	3	Cyclo-Fil
Talc 5	0	Mistron Vapor
Talc 6	0	Nytal 300
Talc 7	0	Asbestine
Tremolite 1	100	Tremolite from California
Tremolite 2	100	Tremolite from California

Sincerely yours,

Ann G. Wylie

*Mearl F. Stanton, Maxwell Layard, Andrew Tegeris, Eliza Miller, Margaret May, Elizabeth Morgan and Alroy Smith, "Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals", Journal of the National Cancer Institute, Vol. 67, No. 5, 1981, p. 965-975.

AFFIDAVIT OF ANN G. WYLIE

Ann G. Wylie, having been duly sworn, deposes and states as follows:

1. In 1972, I received a PhD in economic geology from Columbia University.

2. I am currently an associate professor of geology at the University of Maryland, and acting associate dean for research in the University's Graduate School.

3. I am also a member of the United States Department of Education Task Force on Asbestos, and I have worked as a consultant to the United States Bureau of Mines in matters that deal with asbestos. Much of my research effort during the past ten years has been directed toward the study of asbestos.

4. On July 5, 1984, I appeared at a public hearing on asbestos regulation held by the Occupational Safety and Health Administration (OSHA). At that time, I explained the mineralogical characteristics of asbestos and asbestos fibers, and answered various questions posed by parties to that hearing.

5. I understand that, during OSHA's hearing, several individuals claimed that tremolitic talc poses a health hazard. I also understand that Dr. Mearl F. Stanton's research on fibrous substances has been cited as evidence of the health hazard posed by tremolitic talc.

6. I have reviewed the notes that Dr. Mearl F. Stanton used to prepare his paper entitled "Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals" (Journal of the National Cancer Institute, Vol. 67, No. 5, 1981, pp. 965-975). From that review, I determined that the seven talc samples Dr. Stanton discussed in his paper actually consisted of the following commercial products:

Dr. Stanton's Sample Designation	Tumor Probability as Found By Dr. Stanton	Commercial Product
Talc 1	7%	Cyclo-Sorb
Talc 2	4%	Johnson & Johnson Baby Talc
Talc 3	4%	Mistron Frost
Talc 4	3%	Cyclo-Fil
Talc 5	0%	Mistron Vaper
Talc 6	0%	Nytal 300
Talc 7	0%	Asbestine

5. The samples designated Talc 1 - Talc 5 are marketed as pure talcs. The samples designated Talc 6 and Talc 7, Nytal 300 and Asbestine, are or were marketed as tremolitic talcs. These products usually contain approximately 30-50% nonasbestiform tremolite by weight, and small quantities of nonasbestiform anthophyllite and fibrous talc. Thus, for the two tremolitic

talc samples tested, Dr. Stanton found a 0% probability of tumors in his experiments.

Ann G. Wylie

Subscribed and sworn to before me this 1st day of November, 1984.

Notary Public

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Attorneys for Defendant, R. T. Vanderbilt Company, Inc.

Plaintiff(s), BONNIE PARKER, Individually and as Executrix of the Estate of PETER HIRSCH vs. Defendant(s), Carborundum Corporation, et al.	SUPERIOR COURT OF NEW JERSEY MIDDLESEX COUNTY LAW DIVISION DOCKET NO. MID-L-2706-03 CIVIL ACTION **AFFIDAVIT OF ANN G. WYLIE, Ph.D.**

STATE OF MARYLAND

SS:

COUNTY OF PRINCE GEORGE

I, Ann G. Wylie, of full age, being duly sworn according to law, upon my oath depose and say:

1. I am a Professor of Geology and currently Interim Dean of the Graduate School and have been involved with the study of the mineralogy of talc for many years and am fully familiar with the facts of the within matter.

2. I am fully familiar with the sources of talc analyzed in Dr. Stanton's 1981 study.

3. Prior to his death, and while conducting the study at issue, Dr. Stanton was employed by the National Cancer Institute and worked out of his lab, which was located at Bethesda, Maryland.

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4. Sometime after his death, the National Cancer Institute contacted the University of Maryland in the early 1980s and indicated that they wanted the University to take possession of Dr. Stanton's samples in their entirety and their documentation.

5. At this tim e, I was chosen to receive the records as I was working with the Bureau of Mines.

6. Upon review of the records, I noticed that some of the records regarding the 1981 study were incomplete.

7. As a result, I telephoned the National Cancer Institute and spoke with an employee who indicated that some of the missing records might be in the possession of Dr. Stanton's wife at the family home or in the archives at the National Cancer Institute.

8. After spe aking to Mrs. Stanton, I learned that Dr. Stanton did maintain some records in his home.

9. I then made arrangements with Mrs. Stanton to review and pick up the records from the attic.

10. I also reviewed Dr. Stanton's records at the National Cancer Institute.

11. At that point, I had all available records that Dr. Stanton retained regarding the 1981 study.

12. My purpose of the record review was to identify the sources of the various samples because to a mineralogist, the origin of a sample is an important part of its identity.

13. Some time after I had possession of these records, I was requested to provide the information I had regarding the origin of some of the samples used in the 1981 study by Dr. Thompson, an employee of R.T. Vanderbilt.

14. Dr. Stanton's published paper showed that Talc 6 had 0% tumor probability when implanted in the lin ng of the lungs of lab rats. Dr. Stanton's notes indicated that Talc 6 was NYTAL 300.

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15. Dr. Stanton's published paper showed that Talc 7 had 0% tumor probability when implanted in the lin ng of the lungs of lab rats. Dr. Stanton's notes indicated that Talc 7 was Asbestine.

16. Dr. Stanton's mineral collection included mineral samples of Talc 6 and Talc 7.

17. I personally viewed the sample Talc 6 with the aid of a microscope. After viewing this sample, I determined that it was consistent with the talc that R.T. Vanderbilt was currently mining in the New York Mine. It has a distinctive mineralogy which is unique to this district.

18. I am stil in retention of this sample.

19. I have review it recently and my opinion has not changed.

20. The bottle containing Talc 7 is currently empty. However, Dr. Stanton's notes identified it as Asbestine.

21. While my August 1, 1984, letter stated that in some cases information was incomplete, this statement relates only to the total number of samples. After reviewing all of the notes and samples I believed some may have been missing. However, the information with regard to Talc 6 and Talc 7 which was listed in the August 1, 1984 letter is complete.

22. This Affidavit is made in support of Defendant(s), Hirsch v. R. T. Vanderbilt Company, Inc.'s, further brief as to the admissibility of documents identifying the sources of these samples.

Ann G. Wylie

ANN G. WYLIE, PhD
Professor of Geology and
Interim Dean of the Graduate School

Sworn and subscribed to before me
this 24 day of June, 2005.

Janet P. Turnbull

Notary Public for Maryland

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A Reanalysis of the Stanton *et al.* Pleural Sarcoma Data

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An analysis of the Stanton *et al.* (1981, *J. Natl. Cancer Inst.* 67, 965–975) data reconfirms number of index particles as the primary dimensional predictor of tumor incidence. Fitting separate intercepts and/or slopes to each mineral type results in substantial significant improvement in fit, indicating the importance of mineral type. This contrasts with the "Stanton hypothesis," which states that dimensional properties alone determine carcinogenesis. Log mean aspect ratio is not as good a predictor of tumor incidence as the number of index particles; among those samples that did not have index particles, log mean aspect ratio is not a significant predictor of tumor incidence.

INTRODUCTION

Stanton *et al.* (1981) report the results of 72 experiments wherein fibrous minerals were surgically inserted in the pleurae of rats and the rats were observed for the incidence of pleural sarcoma. Specific methods and materials used by these researchers can be found in their paper and references therein. The key finding of their research was that the ability of mineral particles to cause tumors is mostly a function of the dimensional properties of the particles, rather than physicochemical properties; this is sometimes called the "Stanton hypothesis." The present paper reanalyzes the Stanton *et al.* data and makes two claims. First, in disagreement with the Stanton hypothesis, the Stanton *et al.* data contain evidence that mineral type is an important determinant of carcinogenicity in addition to the important effect of particle dimensions. Second, in agreement with the Stanton *et al.* results, the number of index particles is superior to other dimensional properties of particles (such as log mean aspect ratio) as a predictor of tumor; the other dimensional properties may derive what predictive power they have from their correlation with the number of index particles.

Interest in the Stanton *et al.* data has been reinvigorated recently as OSHA has proposed new rules on occupational exposure to nonasbestiform tremolite, anthophyllite, and actinolite, and the Stanton *et al.* data figure prominently in the OSHA document (OSHA 1990).

BACKGROUND

Our concern here is the statistical analysis of the Stanton *et al.* data and the ways in which it can be improved. For each mineral sample, 30 to 50 (N_i) rats were surgically treated and followed for 2 years. Rats surviving more than 1 year were used to estimate the probability of tumor. Since some rats died due to other causes, a life table method was used to estimate the probability of tumor $\hat{p}_i$, for i from 1 to 72. The technique as described in Stanton *et al.* (1977) is also known as

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the Kaplan–Meier product limit estimate of survival (or mortality) (Kaplan and Meier, 1958).

In addition to tumor data, Stanton *et al.* collected dimensional data for each mineral type. They then used these dimensional data to predict tumor incidence via regression analysis. The dependent variable in their regressions was the logit of tumor incidence: $\text{logit}(p) = \ln(p/(1-p))$. The independent variables in the regressions were the common logs of the number of particles in dimensional categories. In particular, particles longer than 8 μm and narrower than 0.25 μm are called index particles, and the (common log of the) number of index particles in 1 μg is singled out as a predictor of tumor. An earlier paper (Stanton *et al.*, 1977) reports using weighted regression, with weights equal to the estimated standard errors of the tumor probability estimates.

Several other authors have analyzed all or parts of the data in Stanton *et al.* (1981). Bertrand and Pezerat (1980) analyzed the fibrous glass data in Stanton *et al.* (1977). These authors also used regression of the logit of tumor probability on dimensional characteristics. However, instead of the common log of particle counts in dimensional categories, these authors used total count of particles, average particle length, average particle diameter, and log average particle aspect ratio for independent variables. Bertrand and Pezerat did their regressions with and without weighting, but when they did use weights, they used weights inversely proportional to the square of the standard error of the tumor probability estimates. They concluded that the log of the average aspect ratio was a good predictor of tumor incidence, corresponding to an assumption that all particles contribute to carcinogenicity, with some dimensional classes more active than others.

Bonneau *et al.* (1986) reanalyzed the data in Stanton *et al.* (1981). They used regression of the logit of tumor incidence probability on the log of average aspect ratio, with weights equal to the estimated standard errors of the tumor probability estimates. These authors analyzed crocidolite, dawsonite, alumina, and glass separately and presented separate regression equations. Thus, their analysis was similar in methodology to the original analysis in Stanton *et al.* (1981), but analyzed some minerals separately and used log mean aspect ratio as a predictor instead of dimensional counts. They concluded that log mean aspect ratio was a good predictor of tumor incidence and that mineral type was also important in predicting tumor incidence.

Wylie *et al.* (1987) presented a critique of the work in Stanton *et al.* (1981). Their effort included reanalyzing some of the crocidolite samples used in Stanton *et al.* to verify their dimensional characteristics. They found that the log of the number of index particles is reasonably stable, varying by about 0.5 from trial to trial. This supports the claim that the log of the number of index particles is measuring a real characteristic of the material. They criticized the use of 0 ($=\log(1)$) for the index number when the observed count of index particles was zero (corresponding to $-\infty = \log(0)$) and the use of all the data when there is an apparent gap in the predicting covariate between materials with and without index particles. They reanalyze the data which did have index particles.

We have two major criticisms of these analyses, plus some quibbles. The first serious criticism is that the least squares regression used in all these analyses is

not appropriate. Instead, we should use logistic regression. Logistic regression is specifically designed for the statistical structure of binomial counts (of tumors) and provides more efficient estimates than linear regression. None of the weighting schemes used is equivalent to logistic regression. See under the Methods section.

Besides giving efficient estimates, logistic regression avoids some problems that arise in the least squares regression approach. For example, the logit of 0 or 1 is infinite, yet many materials had no tumors, and some materials had 100% tumors. These materials would dominate the linear regression, but in fact, they have little information about the slope. For example, Fig. 1 of Bertrand and Pezerat (1980) shows a curve which closely fits the points near 0 and 1 tumor probability, but misses most of the points in the middle.

Another advantage of logistic regression is that we have an absolute measure of goodness of fit—the deviance. A large deviance indicates model lack of fit, and we may calibrate the deviance by comparing it to a chi-square random variable. Therefore, we can determine when there is significant lack of fit in a model.

The second criticism is that Stanton *et al.* (1981) and Wylie *et al.* (1987) did not allow for separate models by mineral type. We shall show (in agreement with Bonneau *et al.* 1986) that mineral type is an important predictor of carcinogenicity and needs to be included.

The log of the number of index particles is criticized in Wylie *et al.* (1987) because some materials exhibit no index particles. Moreover, the use of log(1) instead of log(0) when there are no index particles (as was done in Stanton *et al.* (1981)) is criticized as arbitrary. We agree that the use of log(1) is arbitrary, but feel that using log(1) is preferable to deleting all those materials from the analysis (as was done in Wylie *et al.*). Adding a constant to counts before taking logs is called "starting the count" by Tukey (1977), who suggested adding 1/6. Both Tukey (1977) and Mosteller and Tukey (1977) have discussions on how to choose the constant, and note that many values have been suggested including 1/6, 1/4, 1/3, 1/2, and 1. For the Stanton *et al.* data, the choice hardly matters.

METHODS

Suppose that y_i is a binomial count of tumors in N_i test animals. The observed fraction of animals having tumor is thus y_i/N_i. The true probability of tumor is p_i, and we assume that

$$\text{logit}(p_i) = a + bx_i,$$

where x_i is a known covariate such as index number or log mean aspect ratio. Logistic regression fits the parameters a and b to the data via maximum likelihood based on the binomial assumptions. More generally, we may use more than one predicting variable for the logit of p, in analogy with multiple regression. See McCullagh and Nelder (1983) for a detailed discussion of logistic regression. Many standard statistical software packages have facilities for fitting logistic regression. This paper uses the GLIM package (Payne 1986).

In order to use logistic regression, we need the sample size N_i, tumor count y_i,

and covariates for each experiment. We may obtain the log particle counts by dimensional category from Stanton *et al.* (1981). We then transform these log counts into covariates. The covariates examined in this study include:

- The common log of the number of particles per microgram with length greater than 8 μm and diameter less than 0.25 μm (index particles), as in Stanton *et al.* (1981);
- The log of the number of *nonindex* particles per microgram greater than 4 μm in length and less than 1.5 μm in diameter;
- The fractions of particles in these dimensional groups;
- The log of the mean particle aspect ratio, as in Bertrand and Pezerat (1980) and Bonneau *et al.* (1986);
- The log of total particle count per microgram;
- The log of the product of mean aspect ratio and total particle count;
- The 90th, 95th, and 99th percentiles of log aspect ratio;
- The 1000th and 10,000th largest log aspect ratio per microgram.

To compute aspect ratios, we used the length and diameter values given in Bertrand and Pezerat (1980). In this paper, we abbreviate the log of the number of index particles by lnip and the fraction of index particles (i.e., the fraction of particles that are index particles) by fip.

For each experiment, logistic regression needs the number of animals with tumor and the number of animals on test. The Stanton *et al.* data do not have this form; we do know the number of animals with tumor d_i, and we know the number of animals originally put on test N_i, but some animals are lost from the study due to nontumor mortality. These lost animals are not on test for the full time period. We may compute an "effective sample size" by using the estimated tumor probability $\hat{p}_i$ and the standard error of the estimate s_i (see Kaplan and Meier 1958):

$$N_{Ei} = \frac{\hat{p}_i(1 - \hat{p}_i)}{s_i^2}. \tag{1}$$

The largest possible value for the effective sample size in N_i, which occurs if all tumor deaths precede all nontumor deaths. The smallest possible value for the effective sample size is $d_i/\hat{p}_i$, which occurs if all nontumor deaths precede all tumor deaths.

For example, consider the noncarcinogenic pleural implant control rats described in Table 2 of Stanton *et al.* (1981). There were 568 rats which survived 52 weeks. In the second year, 16 died with tumor, 250 were lost due to nontumor mortality, and 37 survived the second year. The estimated probability of tumor is $\hat{p}_{\text{control}} = 0.0414$, with a standard error of $s_{\text{control}} = 0.01028$. This gives an effective sample size of 375.5, or 66% of the starting sample size N_i.

We computed an effective sample size for the Stanton *et al.* data in the following way. All groups with $\hat{p}_i = 1$ (estimated tumor probability 100%) were given an effective sample size equal to d_i, the number of animals observed with tumor. All groups with $\hat{p}_i = 0$ (estimated tumor probability 0%) were given an effective sample size equal to 0.661 N_i, using the analogy that noncarcinogenic or low

carcinogenic materials will lose about the same fraction of animals to nontumor death as was observed in the noncarcinogenic pleural implant control rats. All groups with $0 < \hat{p}_i < 1$ were given an effective sample size computed according to Eq. (1) using the $\hat{p}_i$ and s_i values from Table 1 of Stanton *et al.* (1981). If the computed effective sample size was smaller than the lower bound value, the lower bound value was used as the effective sample size.

Table 1 of Stanton *et al.* (1981) contains a few questionable numbers. Wylie *et al.* (1987) correct the estimated tumor probability for crocidolite 10, giving a corrected value of 0.26. We have used the new value. The common log of the number of index particles per micrograms for experiments 1 and 5 do not match the data as given in Fig. 1 of Stanton *et al.* (1981). We have used values computed from Fig. 1. Finally, 16 of the 72 experiments (numbers 8, 9, 10, 11, 12, 13, 14, 15, 23, 30, 32, 35, 60, 63, 64, 65) had lower bounds for effective sample size which exceeded the effective sample size computed from Eq. (1) by 2 or more. We have chosen to use the lower bound in these cases because, (1) the computation of the lower bound depends on d_i and $\hat{p}_i$, which are more likely to be accurately computed than $\hat{p}_i$ and s_i; and (2) most of the flagged experiments have a $\hat{p}_i$ value near 1 or 0, and a small s_i value, making the computation of effective sample size more sensitive to roundoff error.

In our analysis, we will compute *P*-values to assess the statistical significance of various predictors. The *P*-value for adding a predictor to a model is the probability that adding a worthless predictor to the model results in an improvement in model fit as great as or greater than what we observed for our given predictor. (Even random noise can explain *some* variation in the data.) A small *P*-value thus means that it is unlikely that a worthless predictor could have made an improvement in model fit as great as what we observed. Predictors with *P*-values less than 0.05 or 0.01 are usually referred to as statistically significant, though these cutoffs have little basis other than tradition.

RESULTS

Analysis revealed that none of the alternative predicting variables alone was nearly as good as lnip, the original proposal in Stanton *et al.* (1981), though some variables could be used in conjunction with lnip to polish the fit. Type of material was also important, and separate curves need to be fit for each material.

The logistic regression fit using lnip gives the results found in Table 1. These coefficients are close to those given in Stanton *et al.*, although the standard errors here are smaller. We note that lnip is highly statistically significant and that the deviance shows considerable remaining lack of fit.

TABLE 1
COEFFICIENTS (SE) FOR LNIP

Intercept	−2.516	(0.1253)
lnip	0.8287	(0.0395)
Deviance	315.8	
Degrees of freedom	70	

Allowing a separate intercept for each material significantly improves the fit of the model (reduction in deviance = 122.7 with 11 degrees of freedom, P-value effectively zero). The coefficients for this model are shown in Table 2. This model has a deviance of 193 with 59 degrees of freedom, showing that there is still significant lack of fit remaining. Notice the large intercepts and standard errors for tremolite asbestos and silicon carbide. Both have small sample sizes (2 and 1), and all three points have 100% tumor incidence. Thus, while we know that the intercepts should be large, we have almost no information about just how large they should be. Amosite is much more accurately estimated, even though it has only one observation, because its response (93%) lies closer to the middle and is thus more informative.

We may interpret differences in the intercepts as differences in log odds ratios. For example, compare glass and talc. Their difference of intercepts is about 1.8, and exp (1.8) is about 6. Thus the odds ratio of tumor for glass is about six times the odds ratio for talc, when comparing talcs and glasses with the same lnip. When there is a 50–50 chance of tumor for glass (odds ratio 1), there will be a 1 in 7 chance of tumor for talc (odds ratio 1/6). On the other hand, the difference of intercepts for talc and wollastonite is about 2.75, and exp (2.75) is 15.6. Thus when wollastonite has a 50–50 chance of tumor (odds ratio 1), there will be a 1 in 16.6 chance of tumor for talc (odds ratio 1/15.6).

Allowing a separate lnip slope for each material produces a further significant improvement in fit (reduction in deviance = 26.8 with 6 degrees of freedom, P-value 0.00016). The coefficients for this model are shown in Table 3, along with the deviances by material. Slopes could not be estimated for wollastonite, amosite, attapulgite, halloysite, and silicon carbide because either the sample sizes were too small or the covariate lnip only took one value (typically zero).

All the mineral types fit the separate logistic models using lnip tolerably well with the exception of crocidolite and dawsonite, which fit badly. Glass (P-value

TABLE 2
COEFFICIENTS FOR SEPARATE INTERCEPTS MODEL

Material	Intercept	SE
Crocidolite	−2.498	0.2336
Glass	−2.664	0.1671
Aluminum oxide	−2.749	0.2350
Talc	−4.457	0.5324
Dawsonite	−2.221	0.2971
Wollastonite	−1.705	0.3438
Tremolite asbestos	7.353	12.67
Amosite	−0.119	1.050
Attapulgite	−2.303	0.5244
Halloysite	−1.299	0.3761
Silicon carbide	5.621	18.32
Potassium octatitanate	−1.265	0.4714
Covariate	**Coefficient**	**SE**
lnip	0.7821	0.0496

TABLE 3
COEFFICIENTS (SE) FOR SEPARATE LINES MODEL

Material	Intercept	Slope	Deviance	*df*
Crocidolite	−1.605 (0.3244)	0.5245 (0.08665)	79.64	11
Glass	−3.143 (0.2488)	0.9927 (0.08639)	36.43	20
Aluminum oxide	−2.765 (0.4804)	0.7883 (0.1662)	13.03	6
Talc	−3.409 (0.5082)	−2.567 (14.87)	3.179	5
Dawsonite	−1.885 (0.4545)	0.6914 (0.1097)	23.05	5
Wollastonite	−1.705 (0.3438)	[a] [a]	8.18	3
Tremolite asbestos	9.683 (107.3)	0.05423 (32.97)	0.00	0
Amosite	2.639 (1.035)	[a] [a]	0.00	0
Attapulgite	−2.303 (0.5244)	[a] [a]	0.15	1
Halloysite	−1.299 (0.3761)	[a] [a]	0.05	1
Silicon carbide	9.649 (18.32)	[a] [a]	0.00	0
Potassium octatitanate	−2.412 (1.008)	1.225 (0.2861)	2.06	1

[a] Indicates not estimable.

for lack of fit = 0.02), aluminum oxide (0.04), and wollastonite (0.04) are marginal fits. The dawsonite fit involves two samples with low tumor rates and low lnip and five samples with high tumor rates and high lnip. Thus, the fit to lnip is significant. However, within the high lnip group, the tumor rates differ considerably, and the differences between these rates are not related to lnip. This leads to the lack of fit. For crocidolite, there is a significant relationship between tumor rates and lnip, but there are several wild deviations from the relationship, where samples with low lnip have high tumor rates, and samples with high lnip have low tumor rates.

An alternative to producing separate curves for each material is to add additional covariates to the separate intercepts model. The log of the number of nonindex particles less than 1.5 μm in diameter and more than 4 μm in length did not improve the fit (*P*-value nearly 1). Adding the log of mean aspect ratio did significantly improve the fit (reduction in deviance 12.4, *P*-value 0.0004). However, adding the fraction of index particles (fip) improved the fit much more (new deviance 163.1, *P*-value for inclusion of fip nearly 0), and log mean aspect ratio is not significant if both lnip and fip are in the model (*P*-value 0.62). None of the other variables could significantly improve the prediction of a model which included lnip and fip. This improvement obtained by adding fip to the model is significant, even after compensating for a search over many possible predictors and groups of predictors. Moreover, this model with two covariates has a slightly better fit than the model fitting lnip separately to each material. The coefficients for the two covariate model are given in Table 4. Again, crocidolite fits this model poorly, and several other materials have marginal fits.

We may also add additional variables to the separate lines model. Additional covariates are significant for crocidolite, glass, and dawsonite; sizable improvements in fit occur for crocidolite and dawsonite. However, these additional covariate fits have few degrees of freedom, and we worry that we may have overfit the data. For this reason, we do not advocate the additional covariate fits separately by mineral type.

TABLE 4
COEFFICIENTS FOR TWO COVARIATE MODEL

Material	Intercept	SE	Deviance	df[a]
Crocidolite	−2.121	0.237	82.82	12
Glass	−2.692	0.170	36.25	21
Aluminum oxide	−2.970	0.252	5.13	7
Talc	−4.159	0.524	9.44	6
Dawsonite	−2.360	0.309	14.11	6
Wollastonite	−1.705	0.344	8.18	3
Tremolite asbestos	7.831	12.70	0.00	1
Amosite	0.187	1.051	0	0
Attapulgite	−2.303	0.524	0.15	1
Halloysite	−1.299	0.376	0.05	1
Silicon carbide	5.004	18.32	0	0
Potassium octatitanate	−1.072	0.448	7.18	2
Covariate	**Coefficient**	**SE**		
lnip	0.611	0.058		
fip	3.556	0.678		

[a] Degrees of freedom by mineral type are not adjusted for the covariates and are thus slightly too large.

The log mean aspect ratio is a significant predictor of tumor incidence by itself (*P*-value near zero), but the deviance of 538.7 shows that it does not fit the data nearly as well as lnip (which had a deviance of 315.8). Adding log mean aspect ratio to the model containing separate intercepts and lnip does make a significant reduction in the deviance, but adding log mean aspect ratio does not make a significant reduction in deviance when fip is also in the model (*P*-value 0.62). Adding lnip to a model with log mean aspect ratio (with or without separate intercepts) significantly improves the fit (*P*-values near zero). The preceding two statements are true if we restrict ourselves just to samples that have index particles. Among those materials with no index particles, log mean aspect ratio is not a significant predictor of tumor probability (*P*-value 0.24 for common intercept, 0.97 for separate intercepts). These results suggest that the predictive power that log mean aspect ratio does possess is mostly a function of its correlation with lnip. That is, the data indicate that log mean aspect ratio does not contain significant information about tumor incidence above and beyond what is in lnip.

Log nonindex particle count in dimension categories with length greater than 4 μm and diameter less than 1.5 μm is not a significant predictor after allowing for lnip and separate materials intercepts (*P*-value nearly 1). The log total count with length greater than 4 μm and diameter less than 1.5 μm is a significant predictor, but this count includes the index particles and is probably deriving its predictive power from the index counts.

Table 5 summarizes the models and their deviances.

DISCUSSION

This work has verified the claim in Stanton *et al.* (1981) that the number of index

TABLE 5
SUMMARY OF MODELS FIT

Variables in model	Deviance	*df*
Constant	986.5	71
Aspect ratio	538.7	70
lnip	315.8	70
lnip + aspect	309.8	69
Type + lnip (separate intercepts)	193.1	59
Type + lnip · type (separate lines)	166.3	53
Type + lnip + fip (two covariates)	163.1	58
Type + lnip + fip + aspect	162.8	57

particles was the best dimensional predictor of tumor incidence; at least we could not find any better predictors. However, significant improvements in fit can be accomplished by allowing separate curves for the different materials types, and by including additional covariates, particularly fip. Thus, using a single criterion (such as number of index particles) for all material types may badly overestimate the tumor potential of some types and badly underestimate the tumor potential of other types. The type of particle is important.

The models estimated in this work reinforce the idea that the probability of tumor is related to the count (or fraction) of very long, very thin particles. The numbers or distributions of particles outside the index class did not seem to have any significant predictive power. It remains possible that nonindex particles contribute to carcinogenicity, but the Stanton data are not sufficiently precise to establish such a connection.

We have established that dimensional properties are not the sole determinants of carcinogenicity. We have not, however, found prediction models which are themselves completely satisfactory. In particular, crocidolite is poorly fit by all models considered, and fits for several other materials are marginal. All of the prediction models are dependent on the material samples used in the original Stanton *et al.* experiment. The models can only predict carcinogenicity for the same materials as in the experiment, processed in the same fashion. We cannot necessarily extrapolate these prediction models to other samples of the same materials, possibly processed in other ways. To do this, we would need to know how representative the Stanton *et al.* samples were of other samples of the same materials, and how much variability there is within the populations.

We have produced four models of varying complexity. The simplest model uses lnip as a covariate and has a common intercept for all mineral types. This model does not fit adequately. The next model uses lnip as a covariate and separate intercepts for each material type. This should be the smallest model considered. The last two models are rather different but of comparable complexity and goodness of fit. The model of separate lines for each material using lnip and the two covariate model both significantly improve over the single slope model. We favor the two covariate model because it fits slightly more simple, it fits slightly better, and it permits the construction of smoothly varying tumor probability estimates

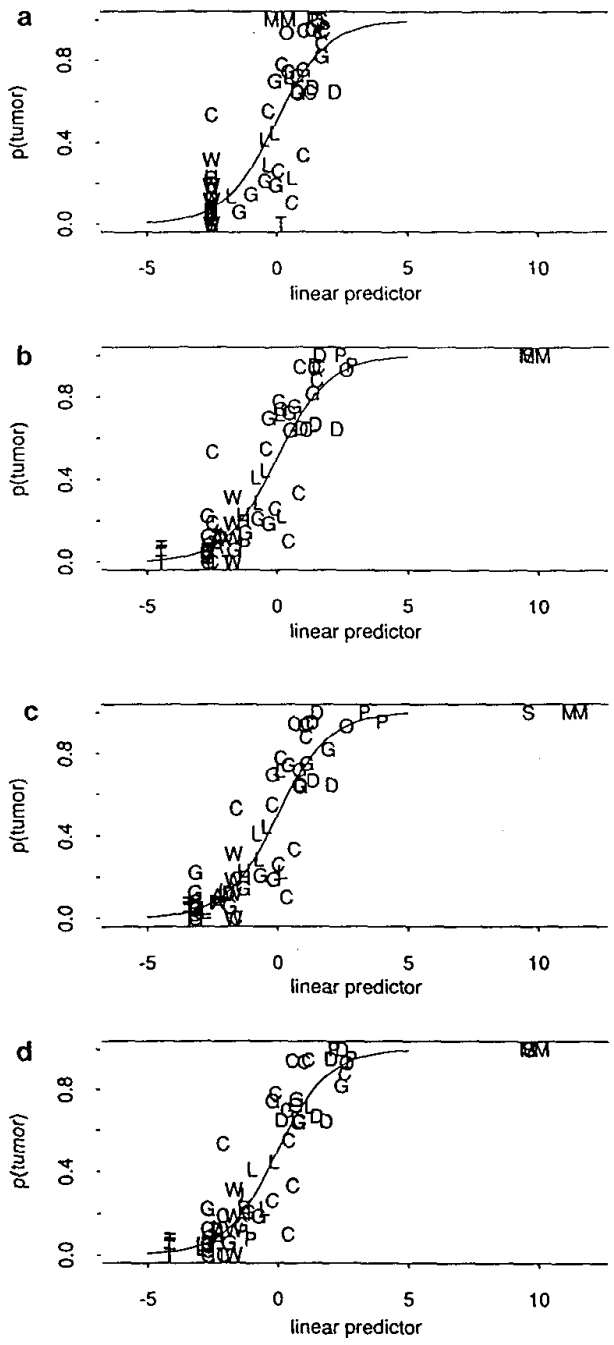

FIG. 1. Observed tumor incidence versus linear predictor for four logistic regression fits. (a) Lnip model; (b) separate intercepts model; (c) separate lines model; (d) two covariates model.

for all material types (though we need to worry about extrapolating beyond the range of predictors in the experiment).

We illustrate the fit of the four models in Fig. 1. The four panels of Fig. 1 plot the observed incidence of tumor against the linear predictor in the logistic regression for the models using (a) lnip, (b) separate intercepts and lnip, (c) separate lines, and (d) separate intercepts, lnip, and fip. (The linear predictor is the sum of the intercept and the linear combination of the covariates.) The letters in each panel indicate the type of material and are the same as in Stanton *et al.* (1981): C, crocidolite, G, glass, D, dawsonite, L, aluminum oxide, S, silicon carbide, A, attapulgite, P, titanate, T, talc, M, tremolite, W, wollastonite, H, halloysite, and O, amosite. This view emphasizes the overall quality of the fit. There is a clear improvement in fit as you advance through the panels.

Table 3 lists the coefficient of lnip for talc as -2.567 (14.87). This negative coefficient has a very large standard error and is not significantly different from zero. The negative coefficient arises from the single talc sample that had index particles but had no tumors; it is not evidence that talc reduces tumor incidence.

We have criticized the methods of others and should, in fairness, state that the current work is not without weaknesses. In particular, the computation of effective sample size seems the weakest link of this analysis. Access to the actual dates of tumor and nontumor deaths (for example, as shown in Stanton *et al.* (1977)) would allow a more reliable computation of effective sample size.

We also conjecture that improvements in the fit can be achieved by modelling the two-dimensional distribution (length by diameter) of particles for a given material and computing a smoothed estimate of the number of particles in the index class. This modelling could be done via poisson regression (McCullagh and Nelder, 1983) on the actual counts in the various dimensional classes, provided that data were available. Assuming the modelling is adequate, the resulting counts of index particles per microgram should be more accurate than the observed counts used here. This method should also eliminate some zero counts and provide some estimates between 0 and 2.5, two criticisms of lnip found in Wylie *et al.* (1987).

Finally, we note in agreement with other authors that the crocidolite data are not well fit by the model. Stanton *et al.* (1981) suggested that this may be a result of the difficulty in counting the crocidolite particles, particularly from preparation to preparation. It is possible to incorporate this type of error into the prediction model by using an "errors in variables" model which assumes that the observed lnip is equal to the true lnip plus an error. The variability of this error is estimated simultaneously with the logistic parameters. We have not attempted this analysis.

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BIOLOGIC TESTS OF TREMOLITE IN HAMSTERS

William E. Smith, Doras D. Hubert

Health Research Institute, Farleigh Dickinson University, Madison, New Jersey 07940.

Harold J. Sobel, Eugene Marquet

Veterans Administration Hospital, East Orange, New Jersey 07019, and College of Medicine and Dentistry, Newark, New Jersey.

Some years ago, we began to test specially prepared samples of minerals for carcinogenicity and fibrogenicity by intrapleural injection into hamsters. In these tests, we found that we could get tumors resembling mesotheliomas by injecting preparations of chrysotile asbestos fibers, provided that we used large enough doses, and provided that we used preparations with large numbers of fibers longer than 20 μm (Smith, 1974; Smith and Hubert, 1974). From experiments with glass fibers, we learned that not only the length, but also the diameter of fibers was important, tumors resulting in hamsters after the injection of fibers 0.75 μm in diameter, but not with fibers 5 μm in diameter (Smith and Hubert, 1974).

Our long-fiber preparations of chrysotile induced extensive, fibrous pleural adhesions, and the occasional tumors came later; whereas our short fiber preparations did not. A question then arose as to whether the tumors were a non-specific result of mesothelial cells becoming trapped in fibrous pleural adhesions where their oxygen supply could be impaired, and malignant change might occur, according to Warburg's theory of carcinogenesis (Warburg, 1956).

TABLE 1. Tests of Samples of Tremolite by Intrapleural injection in Hamsters (Suspension of all samples except 72N were autoclaved before injection.)

Sample Number	Tumors/survivors[1] Dose: 25 mg			Tumors/survivors[1] Dose: 10 mg		
	350 days	500 days	600 days	350 days	500 days	600 days
14	0/35	0/27	0/20			
275	0/31	0/15	0/3[2]	0/34	0/14	0/6[3]
31	2/28	4/9	6/5	1/41	1/19	1/11
72	3/20	5/6	5/1	0/13	1/6	3/2
72N	4/22	9/10	11/2	0/25	0/19	6/9

[1]Numerator = cumulative number of hamsters with tumors related to treatment. Denominator = number survivors

[2]2 additional animals survive

[3]6 additional animals survive

Reprinted from DUSTS and DISEASE
Published by Pathotox Publishers, 1979

To explore that question we attempted to induce fibrosis by injecting talc, since talc had occasionally been used in surgery in attempts to induce adhesions of pleural surfaces for the treatment of pneumothorax. We bought a commercially available industrial talc, and injected that into the pleural space of hamsters. This material induced very little fibrosis, and no tumors.

The sample of industrial talc that we had used was obtained from a distributor, Whittaker, Clark & Daniels, Inc., in New York City under their label "#13 Talc", which is described by them as a fibrous talc from New York State. It became our sample FD-14, whose physical and chemical characteristics have been previously described, along with results of our biologic tests of it (Smith, 1974). It was found to contain 50% tremolite, 35% talc, 10% antigorite and 5% chlorite.

Since then, we have carried out intrapleural tests in hamsters with 3 different samples of tremolite specially prepared by various milling and separation techniques. Biologic responses to these samples have differed, as shown in Table 1.

The top line in Table 1 is data from our previously published tests of tremolitic talc (FD-14). It was tested only at our highest dose level (25 mg), and, as shown, no tumors resulted. The other samples (275, 31 and 72) listed in Table 1 are the preparations made from tremolitic ores. Sample 275 was isolated from a sample of tremolite taken from a tremolitic talc ore body similar to those from which FD-14 was produced. Sample 31 was prepared from a sample of tremolite taken from a deposit of tremolitic talc in the western United States. Sample 72 was prepared from a specimen of asbestiform tremolite.

As shown, no tumors related to treatment were found in animals injected with sample 275 at either the 25 mg or 10 mg dose level. A few animals treated with that sample are still living; however, from comparison with the other samples, it appears to be non-carcinogenic. (Animals surviving at time of presentation of this paper were subsequently necropsied. no tumors were found in them).

In contrast, tumors related to treatment were found in some animals injected with samples 31 and 72 at the 25 mg dose level, and less often, at the 10 mg dose level. The first tumor was found 184 days after injection, and most of the tumors by a year or longer after starting the tests. To compare the carcinogenicity of these samples, one must therefore bear in mind the number of animals that survived long into the period of the experiments. The number of survivors at various times, and the cumulative number of animals with tumors related to treatment are shown in Table 1. We conclude that sample 31 is less carcinogenic than sample 72. As shown, at the 10 mg dose, only a single tumor arose in response to sample 31, despite the relative number of animals that survived into late periods of the experiment. Pleural fibrosis was extensive in animals treated with sample 72, less so with 31, and very slight with 275 and FD-14. The fibrogenicity of these samples thus paralleled their carcinogenicity.

For intrapleural injection, our routine procedure has been to suspend mineral samples in saline, and sterilize the suspensions by autoclaving, before injection. In the present work, we injected one group of hamsters with a suspension of sample 72, autoclaved in our usual manner, and we injected another group of hamsters with a suspension of sample 72 that had not been autoclaved. Table 1 shows that more tumors occurred in the group given material that had not been autoclaved, but this may not be significant because the number of survivors in these 2 groups are so different.

When the samples are compared microscopically, morphologic differences can be seen. Figure 1 shows scanning electron micrographs of each sample at x 1250. Comparative measurements of fiber size distributions in those samples are not yet

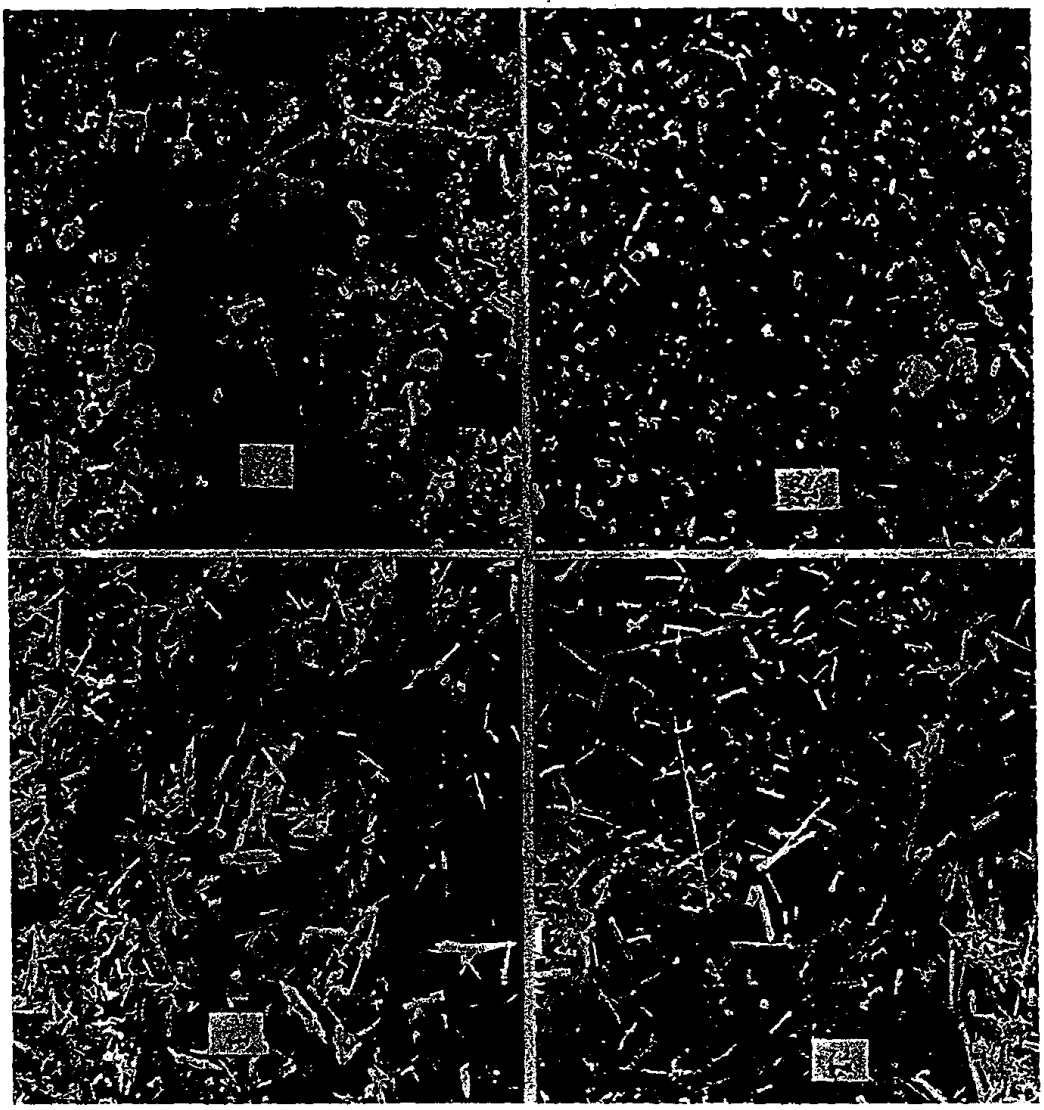

FIGURE 1. Scanning electron micrographs of samples FD-14 (upper left), 275 (upper right), 31 (lower left) and 72 (lower right). Scale on micrographs = 5 μm. Original magnification x1250.

available, but differences can be visualized from Figure 1, in which each micrograph bears a 5 μm scale.

The sample that induced most tumors (Number 72) is seen to contain numerous long, thin fibers with parallel sides. Average diameter of these fibers has been calculated as 0.4μm. By reference to the 5 μm scale on the micrograph, it can be seen that many of these fibers are longer than 20 μm.

The less carcinogenic sample (Number 31) also shows many long, thin particles. Average diameter is 0.5 μm. Some of these particles appear to have parallel sides, but others, although elongated, appear to be rather roughly shaped, resembling acicular fragments rather than crystalline fibers.

Sample 275, which induced no tumors, shows the paucity of long, thin particles so evident in samples 31 and 72. The average diameter of particles in 275 is 0.4 μm. In sample 31, as in 275, some of the elongated particles appear to be fibrous-shaped with parallel sides, but others are rather roughly shaped acicular fragments.

The other sample that proved non-carcinogenic, FD-14, shows long fibers, some thin and some thick, and many platy or amorphous particles. Recall that it contains about 35 % talc. measurements of only the fibrous-shaped particles by optical microscopy at x1000 were earlier reported to show an average diameter of 1.6 μm (Smith, 1974). Measurements of fibrous-shaped particles in the presently available scanning electron micrographs at x1250 show an average diameter of 1 μm.

The negative results with FD-14 may be explained by its lesser content of tremolite, which was 50%, although a relatively low content of tremolite would not explain the negative results with 275. X-ray diffraction studies of 275, 31 and 72 show their tremolite content to be, respectively, about 95%, 90% and 95%.

To what can we attribute the positive results with 72 and 31? Since they contain at least 5% of material other than tremolite, we cannot be sure that their activity is due wholly, or even in part, to tremolite. If we assume that their activity is due to tremolite, then the experiments indicate that appropriately high doses of long, thin particles of tremolite induced tumors, whereas high doses of shorter particles did not. This would, of course, be consistent with previous findings by ourselves and others with other materials, such as chrysotile and glass fibers.

From the point of view of industrial hygiene, it is noteworthy that the experiments show clear-cut, dose-related responses to both preparations that induced tumors. In addition, for estimation of biologic activity of materials containing tremolite, the experiments show that consideration must be given, not merely to the amount of tremolite, but also to other factors, such as the morphologic characteristics of the mineral. Factors of host susceptibility must also be considered. Most tumors in these experiments were diagnosed as mesotheliomas, of which some were examined by electron microscopy and found to contain Type C virus particles (Sobel *et al.*, 1978). Observation of virus particles in the cells of these tumors suggests further work to learn whether a virus is involved in the causation of mesotheliomas.

ACKNOWLEDGMENTS

This work was supported by a grant from Institute of Occupational and Environmental Health (Montreal) and a grant from R.T. Vanderbilt Company. Preparations of tremolitic ores used in these experiments were provided by Dr. James P. Leineweber, Johns-Manville Corporation, Denver, Colorado, and Dr. Allan M. Harvey, R.T. Vanderbilt Company, East Norwalk, Connecticut.

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Johnson & Johnson

New Brunswick, N.J.
May 25, 1972

Subject: CHARACTERIZATION OF TREMOLITE-TALC FD-14
(DR. W. SMITH, FAIRLEIGH DICKINSON UNIVERSITY)

Dr. A. J. Goudie

Figures 1-9 are Scanning Electron Microscope photographs (Appendix A has the experimental procedures used) of Tremolite-Talc FD-14. The photographs show the diversity of particle shapes and sizes in this material. Since FD-14 contains, besides talc; tremolite and serpentine (antigorite), figures 10 through 15 are photographs for comparison of tremolite and serpentine (mainly, antigorite) standards.

Figures 16 through 19 are general views of FD-14 taken on an Electron Microscope by McCrone Associates (Appendix B contains McCrone's experimental procedure, as well as, their detailed results). With Electron Microscopy, one is also able to diffract the electron beam off of the surface of a particle or particles under examination. This method, called Selected Area Electron Diffraction (SAED), results in a diffraction pattern which many times is unique enough to identify the particle under examination. For example, Figure 20 has been identified as antigorite from its electron diffraction pattern (Figure 21). The particle or particles in Figure 22 may also be antigorite from its electron diffraction pattern (Figure 23). Figures 24 and 26 are identified from their respective diffraction patterns (Figures 25 and 27) as tremolite. From morphology and SAED, FD-14 has been found to contain talc, antigorite (serpentine), tremolite and chlorite. No chrysotile has been detected.

A rough mineralogical breakdown of FD-14 has been done from the Electron Microscope results, however, one is not looking at the total material as received but at the separated fines below 5 μ. in size. McCrone Associates reports, based upon particle counting, the following distribution in FD-14;

50% Fibrous Tremolite
10% Antigorite
35% Talc of which about 75% is platy and 25% rolled or fibrous
2-5% Chlorite

Another form of microscopy that has been used to characterize FD-14, is Optical Microscopy. Optical microscopic examination of minerals, referred to as petrographic analysis, results in the following percent mineral breakdown based upon number of particles.

50-60% Amphibole (Tremolite) occurring as broad lath shaped to long prismatic and acicular shaped crystals.

15-20% Platy talc

20-30% Fibrous talc and talc shards

1% Carbonate mineral

X-Ray Diffraction

Using the technique of x-ray diffractometry, the following minerals were identified in the FD-14 sample at estimated levels of concentration:

Major: tremolite, talc
Minor: serpentine (antigorite), anthophyllite
Trace: quartz

Quantitative analysis of the tremolite yielded a value of 57% ± 2% by weight (Appendix C).

Size Analysis of FD-14

Particle size analysis (Appendix D) has been carried out on FD-14 using the Andreason Sedimentation Method resulting in a medium particle size of 8.5 μ. Fiber diameter analysis at 2,000X magnification (Appendix D) results in the following distribution:

1 μ.	20%
1-2 μ.	36%
2-4 μ.	32%
4-6 μ.	8%
6-8 μ.	2%
10 μ.	2%

Elemental Analysis

Emission Spectrographic Analysis of FD-14 (see Appendix E) reveals the following semi-quantitative elemental analysis:

10%	Magnesium, Silicon
0.1-1.0%	Aluminum, Calcium
0.01-0.1%	Phosphorus, Iron, Manganese

Quantitative analysis by Atomic Absorption Spectroscopy for the following elements have been done.

Manganese	-	0.17%
Chromium	-	0.003%
Nickel	-	None Found
Cobalt	-	None Found

F. Robert Rolle

F. Robert Rolle, Ph.D.

ab

cc: Dr. G. Hildick-Smith
Dr. G. H. Lord
Dr. W. Nashed
to
Talc File
Dr. T. H. Shelley
to
Dr. E. R. L. Gaughran
Dr. W. E. Smith
Central File

SMITH FD-14

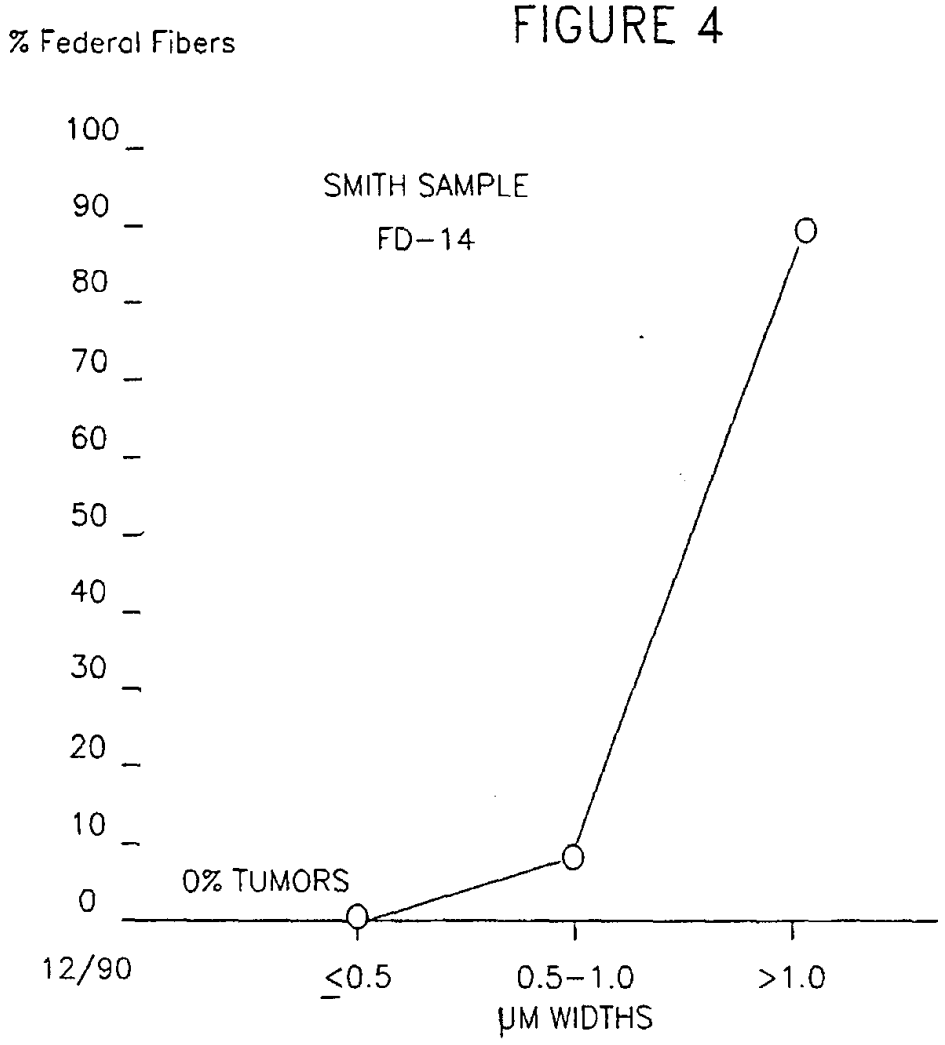
Process used to obtain particle width and length distribution data:

1. None of the four tremolite samples used in this hamster intrapleural injections study (Ref. 4) were sized by length and width in sufficient detail for this dimensional comparison. In addition, only sample FD-14 was available for further analysis. This analysis was conducted by the R. J. Lee Group (Project #RDH003165).

2. FD-14 was an off-the-shelf sample of New York State tremolitic talc obtained from a distributor of this product. This sample contained approximately 50% tremolite with the remainder predominantly talc. Accordingly, the sample analysis required the identification and sizing of all tremolite particles in this sample. The sample was examined by scanning electron microscopy (computer controlled) at a magnification of 2000X. Energy dispersive spectrometry x-ray analysis was conducted at 200,000X. 500 particles were characterized of which 64 were tremolite "federal fibers".

3. The reported widths of all federal fiber tremolite was then compared to determine the width distribution by percent. The aspect ratio distribution and weight distribution of all federal fiber tremolite in this sample was obtained as well.

FIGURE 4



WILLIAM SMITH EXPERIMENTS (REFERENCE 4)

Dr. William Smith conducted hamster pleural injection studies of four tremolite samples of differing morphology. A 10 milligram and 25 milligram dose was singularly injected into animals in each group. These four samples were designated as FD-14, FD-275, FD-31 and FD-72. Sample FD-14 is an off-the-shelf sample of New York State tremolite talc provided by a distributor of this product (40-60% tremolite). Sample FD-275 was a respirable sized concentrate (95%+) of the tremolite in FD-14. Samples FD-72 and FD-31 were provided by Johns Manville Corporation and described as fibrous and/or asbestiform in nature. The exact origin of these latter two samples remain unclear. Of these samples, only FD-14 was available for further analysis. Tumors were observed for samples FD-31 and FD-72 but were not observed for FD-14 and FD-275.

INTER-OFFICE MEMORANDUM

If you need additional info. please let me know. K.C.R. 1-3 1979

Date: May 2, 1978

To: Mr. A. M. Harvey

From: K. C. Rieger

Subject: Characterization of CPS 275-1 and FD-14 Samples

(1) Origin:

CPS 275-1 was a hand picked sample of our typical sugary tremolite. The sample was hand picked to avoid contamination of associated minerals.

FD-14 is #13 talc from Whittaker, Clark & Daniels, Inc. This is a 3X product produced by former International Talc Company. A similar grade produced today would be a NYTAL 200 produced by R. T. Vanderbilt.

(2) Preparation:

CPS 275-1 was jaw crushed and bicoed. 500 g. of this material were wet ball milled for 18 hours, suspended in 10 liters of water and allowed to sediment for 2 hours.

Aliquot samples were taken at increasing depth and run through a 10 μm microsieve to determine the +10 μm/-10 μm interface. The solution was siphoned off to just about the interface.

The resulting -10 μm suspension was run through a Buchner funnel, oven dried and bicoed to obtain the final product. The procedure was repeated twice.

The preparation of this tremolite was geared to obtain respirable size fractions.

This sample was submitted to William Smith, M.D. on March 31, 1976, by A. M. Harvey.

A similar ore type was submitted to NIEHS in much larger quantity (1200 lbs.?). This material, however, had different particle size distribution.

Sample 275-1 could be characterized as being a tremolite hand picked from a tremolitic talc ore similar to that FD-14 was produced.

3X from International
N-200 R.T. Vanderbilt Company, Inc

#13 TALC — MAGNESIUM SILICATE

Source: New York

Color: White

Brightness: 88½

Description: #13 Talc is a fibrous talc.

Uses: Paint, caulking compounds, oil cloth, putty.

Physical Constants:

Tapped Bulk:	
20 grams—500 times	= 23 c.c.
Apparent Density	= 54.4 lbs./cu. ft.
Loose Bulk:	
20 grams	= 51.9 c.c.
Apparent Density	= 24.1 lbs./cu. ft.
Specific Gravity	= 2.72
True Density	= 22.66 lbs./gal.
	= .0441 gal./lb.
Reflectance:	
Green Stim. Filter	= 88½
Oil Absorp. (rub-out)	= 28
Sieve Fineness:	
Thru 200 mesh	= 99.82%
Thru 325 mesh	= 98.43%
pH	= 9.30
Slip	Poor

Chemical Composition:

Silica	SiO_2	62.49%
Magnesium Oxide	MgO	26.08
Calcium Oxide	CaO	5.10
Aluminum & Ferric Oxides	Al_2O_3 & Fe_2O_3	1.23
Manganous Oxide	MnO	0.44
Loss on Ignition		5.21

Comments: Widely used as ingredient in exterior house paints because of durability characteristics of fibrous Talcs.

Tel: 207 244-7527

21 November 1986

William E. Smith, M.D.
P.O. Box 1067
Southwest Harbor, Maine 04679

Donna E. Foliart, M.D.
Environmental Health Associates, Inc.
520 Third Street Suite 208
Oakland, Calif. 94607

Dear Dr. Foliart:

This is in response to your letter of the 11th and our phone conversations.

My laboratory (Health Research Institute at Fairleigh Dickinson University) closed and I retired in 1983. From my recollection and material that I have, I can offer the following.

Experiments described in the paper that you cite ("Biologic Tests of Tremolite in Hamsters" by myself et al, pp 335-9 in DUSTS AND DISEASE, 1979) were carried out with four preparations of minerals identified by us as Samples 14, 275, 31 and 72.

As stated in that paper, Sample 14 was a commercial product said to be a "fibrous talc" from New York State. Details of our biologic tests of that sample were presented in enclosed copy of an earlier paper (Smith, W.E. "Experimental Studies On Biological Effects Of Tremolite Talc On Hamsters" pp 43-8 in Proceedings of the Symposium on Talc, Information Circular 8639. U.S. Bureau of Mines. 1974).

Sample 275 was provided to us by Dr. Allan M. Harvey, R.T. Vanderbilt Company, East Norwalk, Conn. He advised that it had been prepared in his laboratory from a tremolitic talc ore body in New York State. Dr. Harvey could no doubt give you detailed information as to its origin, preparation and characterization.

Samples 31 and 72 were provided to us by Dr. James Leineweber, Johns-Manville Corp., Denver, Col. As stated in our above paper in DUSTS AND DISEASE, he advised that 31 was prepared in his laboratory from a deposit of tremolitic talc in the western United States and that 72 was prepared in his lab from a specimen of asbestiform tremolite. Dr. Leineweber is now dead, but others at Manville, possibly Dr. Paul Kotin, may have access to records re origin, preparation and characterization of those samples, which were identified as JM sample numbers 4368-31-1 and 4173-72-1.

My laboratory at Fairleigh Dickinson was set up for biologic rather than mineralogic work, but, to get some comparison of particle shapes and sizes under the same conditions, we took each of the above four samples to a nearby commercial laboratory in New Jersey (StructureProbe, Inc) and they made scanning electron micrographs at X1250.

Representative areas of those micrographs were reproduced in our paper in DUSTS AND DISEASE to compare the four samples in a single plate. The particles can be seen more clearly in the enclosed print of the larger photo submitted for that plate.

The representative areas were selected from assemblies of all of the SEMs. I could send you prints of the assembled SEMs for each of the four samples if you care to have them.

As can be seen in the micrographs, most of the fiber-shaped particles in Sample 72 have fairly smooth parallel sides whereas most fiber-shaped particles, notably the thicker ones, in Sample 31 tend to have rougher sides and, I believe, might be called acicular or cleavage fragments.

I am not a mineralogist, but I believe this suggests that most of the fiber-shaped particles in 72 had crystallized in nature as fibers whereas most of the fiber-shaped particles in 31 resulted from milling.

After presentation of our paper in DUSTS AND DISEASE, we used the assembled X1250 SEMs to make measurements of fiber-shaped particles in them. From those measurements we calculated that percent of fiber-shaped particles 10 μm or longer and 1 μm or less in diameter was zero for Sample 275, 1.5% for Sample 31, 7.4% for Sample 72 and 6.2% for Sample 14.

Although <u>percentage</u> of long thin fiber-shaped particles was found to be about the same in Sample 72, which proved highly carcinogenic, as in Sample 14, which proved non-carcinogenic, inspection of the micrographs indicates that <u>number</u> of long thin fiber-shaped particles was much greater in Sample 72, less in Sample 31 (which was less carcinogenic than 72), still less in Sample 14 and least in Sample 275 (which proved non-carcinogenic).

Carcinogenicity of the four samples as measured by intrapleural injection in hamsters would thus appear to correlate with content of fiber-shaped particles 10 μm or longer and 1 μm or less in diameter. Tremolite content reported to us by others was 50% for Sample 14 and 90 - 95% for Samples 275, 31 and 72.

Above cited measurements made in our laboratory were made on particles with aspect ratios 3;1 or greater without regard to whether sides were parallel or rough. From records in Dr. Leineweber's laboratory, Johns-Manville may be able to provide additional information. Perhaps you or I could inquire re data on number and mass of particles in different sizes and shapes in Samples 31 and 72 which were JM sample numbers 4368-31-1 and 4173-72-1.

Some mineralogic studies of our samples have been made in Dr. William Campbell's laboratory at U.S. Bureau of Mines. His associate, Dr. Ann Wylie, whom I believe you know, could provide and discuss those studies.

Enclosed please find reprint of our paper "Dimensions Of Fibres In Relation to Biological Activity" by myself at al, pp 357 - 360 in BIOLOGICAL EFFECTS OF MINERAL FIBRES, vol. 1. IARC 1980.

I understand that you have copies of papers on tremolite by Mearl Stanton and by J. C. Wagner. Enclosed is copy of a recent paper by J.M.G. Davis et al titled "Inhalation Studies On The Effects Of Tremolite And Brucite Dust In Rats" Carcinogenesis 6: 667 - 674, 1985.

Trusting that the above may be of interest,

Sincerely,

Enclosures

...rgh Dickinson University
Rutherford Campus Teaneck-Hackensack Campus Florham-Madison Campus
Madison, New Jersey 07940
201-377-4700

12 May 1978

Mr. Konrad C. Rieger
Minerals, Ceramics & Paper Department
Research & Development Division
R.T. Vanderbilt Company, Inc.
30 Winfield Street
Norwalk, Conn. 06855

Dear Konrad:

As you requested, herewith 20 grams of our sample FD-14. This was supplied to us from Whittaker, Clark & Daniels, Inc., NYC, on 4 May 1965 under their label "#13 TALC." We subsequently used it for intrapleural injection into hamsters that were followed in life-span tests reported in 1973 in our paper at the Bureau of Mines Symposium on Talc.

This was the sample from which we furnished an aliquot to Johnson & Johnson and on which they carried out physical and chemical characterization studies described in their report of 25 May 1972, copy of which you have.

A few months ago, I sent an aliquot of this sample to Dr. William Campbell at Bureau of Mines. A few weeks ago, he told me by phone that he had not yet carried out any studies of it, but planned to do some physical and chemical characterizations. He said he would acquaint me with results when available.

With best regards,

Sincerely,

Bill

William E. Smith, M.D.
Director
Health Research Institute

WES/elc

cc: Dr. A. Harvey

AM. IND. HYG. ASSOC. J. 54(5):239–252 (1993)

THE IMPORTANCE OF WIDTH IN ASBESTOS FIBER CARCINOGENICITY AND ITS IMPLICATIONS FOR PUBLIC POLICY

A. G. Wylie[a*]
K. F. Bailey[b]
J. W. Kelse[c]
R. J. Lee[d]

[a]Laboratory for Mineral Deposits Research, Department of Geology, University of Maryland, College Park, MD 20742; [b]Vulcan Materials Company, Birmingham, AL 35209; [c]R.T. Vanderbilt Company, Inc., Norwalk, CT 06855; [d]RJ Lee Group, Inc., Monroeville, PA 15146.

Evidence from human epidemiology, experimental animal implantation and inoculation studies, and lung burden studies shows that fibers with widths greater than 1 μm are not implicated in the occurrence of lung cancer or mesothelioma. Furthermore, it is generally believed that certain fibers thinner than a few tenths of a micrometer must be abundant in a fiber population in order for them to be a causative agent for mesothelioma. These conclusions are fully consistent with the mineralogical characteristics of asbestos fibers, which, as fibrils, have widths of less than 1 μm and, as bundles, easily dissagregate into fibrils. Furthermore, the biological behavior of various habits of tremolite shows a clear dose-response relationship and provides evidence for a threshold between fiber width and tumor experience in animals. Public policy in regulating mineral fibers should incorporate this knowledge by altering the existing federal asbestos fiber definitions to reflect it.

Width and length of fibers are both important parameters in determining the carcinogenic potential of asbestos and other specific fibrous materials. Most investigators who have examined this subject agree that there exists a minimum length and maximum width below which and above which fibers are not related to tumor induction. Although fiber dimension is linked to the pathogenic effects of asbestos and certain other fibrous materials, it is also recognized that fiber characteristics other than dimension (i.e., durability, harshness, surface chemistry, surface area or activity, etc.) likely play an important role in the pathogenetic process. Whatever fiber characteristics contribute to the pathogenicity of asbestos, however, it is important to ensure that size parameters used for regulatory purposes reflect those most closely associated with asbestos and known carcinogenic effects.

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Although it is common to see the dimensions of asbestos fibers discussed in terms of a ratio of length to width, or aspect ratio, the use of such a dimensionless parameter results in the loss of information about the size of fibers and, therefore, is of little use in the discussion of fiber carcinogenicity or exposure. While asbestos fiber length is recognized in federal regulatory policy, width is ignored entirely. It is the purpose of this paper to examine the relationship between asbestos fiber width and fiber carcinogenicity, to suggest how this parameter might be used to identify other potentially harmful mineral fibers and to enhance the specificity of existing asbestos regulations.

The National Institute for Occupational Safety and Health (NIOSH) has established the definitions and analytical methods for asbestos used to one degree or another by all asbestos regulatory bodies in the United States. Under the NIOSH scheme, asbestos is simply defined as any fiber of chrysotile, crocidolite, amosite, anthophyllite, tremolite, or actinolite. A "fiber" is defined as a particle with a length to width ratio (aspect ratio) of at least 3:1 and a length of 5 μm or more as determined by the phase-contrast optical microscope (PCM) at a magnification of 450X–500X.[1–2] In this paper a "NIOSH fiber" refers to any particle with these dimensional parameters as determined by any accepted analytical technique.

PREVIOUS WORK

Mesothelioma and Fiber Width

Several investigators have examined the question of what particle sizes are most likely associated with the induction of mesothelioma. Merle Stanton first proposed that a distinct relationship exists between the shape or dimensions of durable fibers and mesothelial tumors in rats.[3] Stanton and co-workers concluded from these experiments that populations with abundant fibers longer than 8 μm and narrower

TABLE I. Bulk and Airborne Particles—Cleavage Fragments

Mineral and Reference	*Instrumentation*	*Length Restriction*	*Percent less than stated widths or mean width (μm)*
Wollastonite			
a. Bulk Samples			
[75] New York	TEM	None	90%<2.3; 50%<1.1 10%<0.62
Tremolite			
a. Bulk Samples			
[78] New York	SEM	> 5 μm	9%<1.0; 0%<0.5
b. Airborne			
[58] New York	SEM	> 5 μm	0%<0.25
Cummingtonite			
a. Airborne			
[61] S. Dakota	SEM	> 5 μm	22%<1.0; 7%<0.5; 0%<0.25
[70] S. Dakota	SEM	> 5 μm	11%<1.0; 2%<0.5
Actinolite			
a. Airborne			
[75] Virginia	SEM	> 5 μm	15%<1.0; 0.5%<0.5 0%<0.25
Grunerite and Actinolite			
a. Airborne			
[61] Minnesota	SEM	> 5 μm	1% <1; 0%<0.25
Antigorite			
a. Airborne			
[74] Vermont	TEM 400X	> 5 μm	22%<1.0; 2%<0.5
[74] Vermont	TEM 20KX	> 5 μm	37%<1.0; 10%<0.5
Riebeckite			
a. Bulk Samples			
[75] California	SEM	> 5 μm	27%<1.0; 5%<0.5

than 0.25 μm were most closely linked to pleural tumor response irrespective of fiber type.[4] Most other researchers who use the animal model support the position that only narrow fibers are capable of inducing tumors.[5-7]

Evidence for the importance of narrow fibers in regard to mesothelioma also comes from human experience. Timbrell and co-workers observed that the differences in the incidence of mesothelioma among two groups of asbestos miners in South Africa noted by Harington is most likely related to width.[8,9] In the northwestern Cape, where miners experienced elevated mesothelioma, the mean fiber diameter for crocidolite is 0.073 μm. In the Transvaal crocidolite and Transvaal amosite regions, mean diameters of 0.212 μm and 0.243 μm, respectively, were noted and mesotheliomas are rare. Among vermiculite miners and millers in Libby, Montana who were exposed to tremolite-asbestos, mesothelioma was elevated.[10,11] Studies by Atkinson and co-workers on bulk samples from the Libby vermiculite mine show that 87% of tremolite fibers longer than 5 μm have widths equal to or less than 1 μm and 54% have widths less than or equal to 0.5 μm.[12] The high incidence of mesothelioma in Turkey has been attributed to fibers of asbestiform (wooly) erionite that are on the order of 0.1 μm in width.[13-15] In contrast, no evidence of mesothelioma has been found in mining environments where NIOSH fibers produced by cleavage of massive amphiboles are abundant.[16-20] In these mining environments 78% or more of the 5 μm long particles have widths greater than 1.0 μm while 93% or more have widths greater than 0.5 μm. Few, if any, show widths below 0.25 μm (Table I).

Some have suggested that the carcinogenic potential of mineral fibers extends to those with widths as large as 2 μm, and there is some evidence from animal experimentation to support this position. For example, Pott et al. have induced tumors in Wistar rats by intraperitoneal injection with basalt and ceramic fibers with median diameters close to or in a few cases greater than 1 μm.[21,22] Hesterberg et al. report tumors in Syrian hamsters after inhalation of refractory ceramic fibers with an average diameter of 0.95 μm.[23] However, the effect of the wide fibers in these studies is most evident when the fibers are very long (up to 50 μm) or when a significant number of narrow fibers are part of the population, a fact that may not be evident from reporting mean or median widths of the population. Many populations of shorter fibers (still longer than 5 μm) with widths predominantly greater than 0.5 μm, such as wollastonite, gypsum, and certain fibrous glasses, have been shown to produce no significant tumor responses after instillation in animals.[22,24,25] Furthermore, the tumor potential of wide fibers has not been demonstrated by inhalation experiments, in part, at least, because such fibers deposit in the conductive airways in the head and lung and do not reach the lung alveoli.[26]

An opportunity to examine in humans the carcinogenic potential of a naturally occurring population of relatively wide mineral fiber is provided by the experience of anthophyllite-asbestos miners and millers in Paakkila, Finland. Anthophyllite-asbestos from this locality has a mean width of approximately 0.6 μm, and in the fiber population, widths less than 0.1 μm are quite rare.[27] In his study of lung tissue

from four individuals exposed to Paakkila anthophyllite-asbestos. Timbrell reports one fiber of 4 μm in width, some fibers between 2 and 4 μm and more than 50% of the fibers with widths less than 0.7 μm. In fact, Timbrell has shown that the distribution of amphibole fiber widths in lung tissue closely resembles the distribution of fiber widths in air.[28] Among the occupational cohort of miners and millers exposed to Paakkila anthophyllite-asbestos, asbestosis is common and the incidence of lung cancer is elevated, primarily in smokers.[29] However, the incidence of mesothelioma is not elevated.[27] The fact that Paakkila anthophyllite-asbestos will induce malignant tumors in animals after intraperitoneal inoculation[22] and inhalation[30] demonstrates that it has a detectable carcinogenic potential in animals under certain experimental conditions. However, the human experience tells us that either because of aerodynamic characteristics and/or the body's defenses, a population of durable fibers with the dimensions of Paakkila anthophyllite-asbestos does not represent the same occupational or environmental mesothelioma risk as other types of asbestos. The best explanation for these observations, in conformity with the Stanton hypothesis, is that the most abundant fibers of Paakkila anthophyllite-asbestos are by and large too wide and the thin fibers are too scarce for the population to induce mesothelioma even with the high exposures associated with this occupational setting.

Lung Cancer and Fiber Width

There are fewer data on the relationship between fiber width and lung cancer than there are for fiber width and mesothelioma. However, studies of human populations exposed to asbestos and animal inhalation studies involving asbestos consistently show an association between asbestos exposure and lung cancer as well as between mesothelioma and asbestos exposure.[8–11,29] In contrast, exposures to the nonasbestiform analogs of asbestos minerals (cleavage fragments) have not shown an elevated lung cancer risk in man.[16,18–20] Lippmann has reviewed the literature in this area and concludes that lung cancer is associated with fibers with widths between 0.3 and 0.8 μm (and length $>$ 10 μm).[31] His conclusions rest in part on the work of Timbrell who has shown that lung retention is greatest for fibers with these widths and lengths.[32] Such dimensions are consistent with those commonly associated with asbestos fibers but not for common cleavage fragments (see Tables I and III). Thinner fibers migrate to the pleura and peritoneum. Thicker fibers are usually rare in an airborne population of asbestos, and when present, disaggregate into thinner fibrils.

Lung Burden Studies in Asbestos-Related Diseases and Fiber Width

During the past 15 years, there have been a significant number of lung burden studies of persons occupationally exposed to asbestos who have developed asbestos-related diseases. Numerous investigators have published information on the sizes of asbestos fibers found in these persons and only rarely are fibers with widths greater than 1.0 μm detected (See Table II). In fact, most asbestos fibers found in lung tissue have widths less than a few tenths of a micrometer. The data are summarized in Table II. While there may be a gradual transition in the carcinogenic potential of fibers from greater to lesser as fiber width increases, as suggested by Pott, wide fibers are not implicated in mesothelioma in humans because they appear to be incapable of translocating to pleural regions, and they are not found in the lungs of people who have developed this disease.[33]

Fibers longer than 5 μm with widths greater than 1 μm are not often found in lung tissue of asbestos miners, millers, and fabricators for several reasons. First, wider fibers contain more mass than narrow fibers of the same length and are thus less likely to become airborne. Wider fibers are also likely to be intercepted in the upper respiratory tract before they reach the lung. Work by numerous investigators has shown that the penetrability of airborne fibers into the peripheral rat lung drops sharply with an aerodynamic diameter above two, which corresponds to a diameter of approximately 0.67 μm.[5] Pott and co-workers assert that fibers with a diameter range of 1–5 μm cannot be tested for carcinogenicity by inhalation because they deposit in the upper respiratory tract and do not reach the lung.[21]

There are also two very important mineralogical reasons why wide fibers of asbestos are rare in lung tissue. First, populations of asbestos fibers of all types are composed of fibers that are less than 1 μm in width, and, therefore, wide fibers are simply not readily available for inhalation (Table III). Second, asbestos fibers wider than 1 μm are composed of bundles of fibrils that readily split longitudinally into individual fibers of much smaller width. Even if wider fibers were inhaled, because of the fibrillar structure of asbestos, the fibers disaggregate. Cook and co-workers demonstrated the effectiveness of this process in their animal intratracheal instillation experiments with ferroactinolite-asbestos.[34] In these experiments they showed that the number of fibers found in lung tissue increased following cessation of exposure and that the increase was due to longitudinal splitting of fiber bundles. Other natural fibers that have been shown to exhibit a significant carcinogenic potency such as asbestiform (wooly) erionite are also characterized by very narrow widths and the ability to split longitudinally. The fibrillar structure is the hallmark of asbestiform fibers.[35] All asbestos minerals that have been implicated as carcinogens in humans exhibit this unique habit of crystal growth structure.

In summary, human epidemiology, experimental animal studies, and the information on size distributions of fibers found in human lung tissue strongly suggest that fibers wider than 1 μm are not likely to be a significant factor in the production of mesothelioma or lung cancer in man. To test the hypothesis that 1 μm is a reasonable upper limit for critical width, we have examined data from tremolite-asbestos and nonasbestiform tremolite. This analysis will show that a clear dose-response relationship and evidence for a threshold exist between the abundance of fibers less than 1 μm in width and carcinogenic response. While fibers wider than 1 μm that are actually fiber bundles might also be important in

producing a carcinogenic response they are usually uncommon in terms of fiber number in an airborne asbestos population. We have therefore neglected these bundles in analyzing fiber abundance data although it may be inappropriate to ignore them for regulatory purposes.

MATERIALS AND METHODS

Tremolite occurs naturally as a gangue and as a component of ore at a number of mines producing industrial talc, vermiculite, play sand, marble, crushed stone, and chrysotile-asbestos. Health risks associated with tremolite have been the source of considerable debate in both the scientific community and regulatory arena for many years.[36–38] Tremolite, in its massive and most common habit, when crushed, forms elongated cleavage fragments that are similar in size and shape to cleavage fragments of other common amphiboles. In this form, there are no epidemiological studies that clearly implicate tremolite as the cause of mesothelioma or lung cancer in man despite its prevalence in some mining environments.[36] In its rare asbestiform habit, on the other hand, it appears to be the cause of both mesothelioma and lung cancer in man.[10,11,39] In animals, mesothelioma has been observed after exposure to tremolite asbestos.[4,40,41] One animal inhalation study involving tremolite asbestos showed elevated lung tumors as well as mesothelioma.[42] There is a modern source of commercial tremolite-asbestos in Korea, and in the past tremolite-asbestos has been mined locally in Europe, Asia, and North America. Tremolite-asbestos possesses the characteristics that distinguish the more commercially important amphibole-asbestos types (crocidolite, amosite, anthophyllite-asbestos) including flexibility, thin fibrils, and a fibrillar structure.[35] Therefore, tremolite is an ideal mineral to study because it occurs naturally in the full range of amphibole habits, its asbestiform variety is known to cause mesothelioma and lung cancer in both man and animals, it is widely distributed, and it is known to occur in a number of important industrial mineral products.

TABLE II. Fibers in Lung Tissue of Humans Exposed to Asbestos

Mineral and Reference	*Instrumentation*	*Length Restriction*	*Percent less than stated widths or mean width (μm)*
Amphibole and Chrysotile			
[76] lung parenchyma	TEM	None	mean = 0.13; range: 0.05–0.32
[76] parietal pleura	TEM	None	mean = 0.06; range: 0.03–0.09
Amphibole			
[76]	TEM	>4 μm	100%<1.0; 63%<0.25
[73] pleura	TEM	None	mean width = 0.15 ± 0.07
[73] parenchyma	TEM	None	mean width = 0.19 ± 0.21
[73] node	TEM	None	mean width = 0.21 ± 0.12
Crocidolite			
[28] mining	TEM	None	100%<1.0
[68]	TEM	None	mean widths = 0.13, 0.09, 0.14, 0.15
[52] lung parenchyma	TEM	>4 μm	96%<0.375
[55] shipyard and construction	TEM	>1 μm	25%<0.07; 75%<0.16
[47]	TEM	None	100%<0.12 ± 0.10
Amosite			
[28] mining	TEM	None	>95%<1
[68]	TEM	None	mean widths = 0.27, 0.24, 0.35, 0.20
[52] lung parenchyma	TEM	>4 μm	66%<0.375
[55] shipyard and construction	TEM	>1 μm	25%<0.09; 75%<0.29
[55] shipyard and construction	TEM	>4 μm	74%<0.31
[47] shipyard and construction	TEM	None	100%<0.43 ± 0.29

A number of well-characterized samples of nonasbestiform tremolite and tremolite-asbestos have been used in animal experimentation and made available to us for study. The importance of these samples is that they represent a range in naturally occurring mineral habit that has not been evaluated for any other mineral. The tremolites include samples with numerous fibers of a fibrillar or asbestiform habit, samples in which only part of the tremolite is fibrillar, and samples lacking tremolite particles of a fibrillar habit altogether (nonasbestiform). We have examined the tumor response of these samples (established through animal experimentation by independent researchers) as a function of the dose of fibers longer than 5 μm with widths less than and greater than 1 μm. Only tremolite particles with a length to width ratio of 3:1 or greater (NIOSH fibers) were included.

Davis and co-workers have recently released the results of injection experiments that used six samples of tremolite: California tremolite-asbestos from Jamestown; Korean

TABLE II. Continued

Mineral and Reference	Instrumentation	Length Restriction	Percent less than stated widths or mean width (μm)
Chrysotile			
[54] referent	TEM	>5 μm	mean width = 0.15 ± 0.18
[54] environmental	TEM	>5 μm	mean width = 0.13 ± 0.25
[54] occupational	TEM	>5 μm	mean width = 0.13 ± 0.16
[53] textile plant	TEM	>5 μm	mean width = 0.10 ± 0.02
[53] mine	TEM	>5 μm	mean width = 0.07 ± 0.01
[68]	TEM	None	mean widths = 0.07, 0.07, 0.07, 0.07, 0.04, 0.11
[76]	TEM	>4 μm	100%<0.25
[55] shipyard and construction	TEM	>1 μm	25%<0.03; 75%<0.06
[47]	TEM	None	100%<0.07 ± 0.02
[73]	TEM	None	mean width 0.09 ± 0.15
			mean width 0.07 ± 0.06
			mean width 0.08 ± 0.06
Anthophyllite			
[28]	TEM	None	80%<1
[55]	TEM	>1 μm	25%<0.17; 75%<0.44
[65]	TEM	None	50%<0.67
Tremolite			
[57]	TEM	None	100%<1.0; 80%<0.5
[54] referent	TEM	>5 μm	mean width = 0.66 ± 0.48
[54] environmental	TEM	>5 μm	mean width = 0.62 ± 0.74
[54] occupational	TEM	>5 μm	mean width = 0.30 ± 0.25
[53] textile plant	TEM	>5 μm	mean width = 0.35 ± 0.04
[53] mine	TEM	>5 μm	mean width = 0.32 ± 0.02
[68]	TEM	None	mean widths = 0.24, 0.31
[55] shipyard and construction	TEM	>1 μm	25%<0.23; 75%<0.57
Actinolite			
[55]	TEM	>1 μm	25%<0.15; 75%<0.37

tremolite-asbestos; tremolite-asbestos from a laboratory in Swansea; fibrous Italian tremolite (Ala de Stura); tremolite from Carr Brae, Dornie, Scotland; and tremolite from Shinness, Scotland.[40] In this paper, these samples are identified as tremolite A, B, C, E, F, and G, respectively. Tremolite A, B, and C are composed primarily of tremolite-asbestos. Fiber bundles, curved flexible fibers, and small fibril widths are evident from optical microscopic examination of the samples. Tremolite E (Italian) consists of very long, highly unusual, single, needle-like crystals, with limited flexibility. Many of these fibers are twinned and in subsequent analysis, an asbestos subpopulation was reported.[43] Sample F (Dornie) is composed primarily of tremolite cleavage fragments. However, a small portion of the sample contains fiber bundles of tremolite-asbestos. Tremolite G (Shinness) was obtained by crushing large prismatic crystals, and it is composed entirely of cleavage fragments. Davis and co-workers packed the samples into cylinders of Timbrell dust dispensers and airborne dusts were generated. They collected the respirable fraction of these dusts and administered it to rats by using the intraperitoneal injection technique. Measurements of width and length for the fibers in the populations were collected by scanning electron microscopy after deposition on 0.2 μm pore-size polycarbonate filters. Davis and co-workers provide dimensional data for approximately 450 particles from each sample. The dose in terms of number of particles per milligram of dust was obtained directly from the data of Davis and co-workers.[40]

In earlier work Stanton reported the results of 72 rat pleural implantation experiments involving approximately 30 different inorganic materials.[4] Among these materials, one tremolite-asbestos sample was implanted on two different occasions. The sample comes from California, but its exact origin is unknown. Like tremolite A, B, and C, this tremolite possesses all the characteristics of commercial asbestos. In this paper it is referred to as tremolite D. Another Stanton sample identified as Talc 6 is a commercial tremolitic talc from the state of New York identified from Stanton's laboratory notes as Nytal 300. This sample contains 40–50% tremolite cleavage fragments. It is referred to as tremolite H in this paper.

Stanton and co-workers did not provide adequate dimensional data to evaluate width satisfactorily, and it was necessary to re-examine both tremolite D and H. Samples of tremolite-asbestos 1 and 2 (tremolite D) and of Talc 6 (tremolite H) were obtained from the National Cancer Institute and prepared for analysis by gentle sonication in distilled water and filtration on a polycarbonate filter. Portions of the filters were mounted on a polished SEM stub and carbon coated. For Talc 6, the filters were scanned at 5000X and the chemical composition of particles longer than 4 μm was established by energy dispersive spectroscopy (EDS). The particles were identified as tremolite or "other" from their chemical spectra, and their dimensions were measured and recorded. For tremolite D, the samples were photographed at 5000X. All particles in the photograph with lengths longer than 4 μm were measured. From each population 100–150 particles were measured.

Stanton provided estimates of the number of particles longer than 4 μm in a microgram.[4] From our measurements of tremolite-asbestos D, we determined that 74% of the particles longer than 4 μm met the definition of a NIOSH fiber. We also determined that 99% of the NIOSH fibers of tremolite had widths less than or equal to 1.5 μm, 88% had widths less than or equal to 1.0 μm, and 52% had widths less than or equal to 0.5 μm. From these data we calculated the number of NIOSH fibers per total dose and the number of fibers within each of the width categories.

From Talc 6 (tremolite H), we used the number of particles per microgram longer than 4 μm provided by Stanton. From our analysis, we determined that 30% of those particles longer than 4 μm were NIOSH fibers of tremolite. Of these, 9% had widths less than or equal to 1.5 μm, 9% had widths less than or equal to 1.0 μm and 0% had widths less than or equal to 0.5 μm. As was the case for tremolite D, we calculated the number of tremolite NIOSH fibers per total dose and the number within each of the width categories.

Smith and co-workers reported the results of intrapleural injection of four tremolite samples into Syrian hamsters.[44] Only limited information on the size distributions of these samples was published, but one sample, FD-14, was available for additional analysis. Sample FD-14 was an off-the-shelf sample of tremolitic talc from the state of New York that contained approximately 50% nonasbestiform tremolite. The samples were examined by SEM at 2000X and the particles were identified as tremolite based on their chemical composition. Five hundred tremolite particles were measured of which 64 met the definition of a NIOSH fiber. Data regarding the number of tremolite NIOSH fibers in a microgram were not available for this sample. Interestingly, very long fibers of the mineral talc that have narrow widths and a fibrillar structure occur in this sample. This sample is referred to as tremolite I in this paper.

TABLE III. Bulk and Airborne Particles—Asbestos and Other Fibers

Mineral and Reference	*Instrumentation*	*Length Restriction*	*Percent less than stated widths or mean width (μm)*
Crocidolite			
Cape Province			
a. Bulk Samples			
[50]	SEM	>5 μm	98%<1.0; 85%<0.5
[56] UICC	TEM	None	>99%<1.0; >90%<0.5
[63] UICC	TEM	None	mean width = 0.23 ± 0.06
[64]	TEM	>2 μm	99%<1.0; 99%<0.5
[22] UICC	TEM	None	median width = 0.20
[60]	SEM	None	mean width = 0.35 (2S.D. = 0.78 – 0.16)
[60]	TEM	None	mean width = 0.12 (2S.D. = 0.31 – 0.05)
b. Airborne			
[69]	TEM	None	98%<0.4
[69]	TEM	>5 μm	90%<0.3
[52]	TEM	>4 μm	88%<0.375
[45]	TEM	>5 μm	98%<1.0; 82%<0.5
[46] UICC	TEM	>0.25 μm	99%<1.0; 88%<0.5
[9]	TEM	None	99%<0.5
Crocidolite			
Transvaal			
a. Bulk Samples			
[64]	TEM	>2 μm	89%<1.0; 65%<0.5
Crocidolite			
Australia			
a. Bulk Samples			
[64]	TEM	>2 μm	100%<1.0; 99%<0.5
Crocidolite			
Bolivia			
a. Bulk Samples			
[64]	TEM	>2 μm	85%<1.0; 60%<0.5
Amosite			
Transvaal			
a. Bulk Samples			
[50]	SEM	>5 μm	91%<1.0; 50%<0.5
[56] UICC	TEM	None	98%<1.0; 80%<0.5
[72] UICC		>5 μm	92%<1.0; 72%<0.5
[63] UICC	TEM	None	mean width = 0.47 ± 0.17
[60]	SEM	None	mean width = 0.55 (2S.D. = 1.29 – 0.23)
[60]	TEM	None	mean width = 0.35 (2S.D. = 1.22 – 0.10)

RESULTS

There are several ways to examine the width data. First, the correlation between tumor incidence and the dose of NIOSH

TABLE III. Continued

Mineral and Reference	*Instrumentation*	*Length Restriction*	*Percent less than stated widths or mean width (μm)*
b. Airborne			
[69]	TEM	None	95%<0.4
[69]	TEM	>5 μm	45%<0.3
[52]	TEM	>4 μm	66%<0.375
[62]	PCM	>5 μm	99.4%<1; 94.2%<0.5
[61]	SEM	None	95%<1.0; 80%<0.5
[9] (inc. croc.)	TEM	None	95%<1.0; 70%<0.5
Chrysotile Quebec			
a. Bulk Samples			
[50]	SEM	>5 μm	99%<1.0; 94%<0.5
[63] UICC	TEM	None	mean width = 0.17 ± 0.03
[22] UICC	TEM	None	median width = 0.15
[67]	PCM	82% >5 μm	81%<1.0
b. Airborne			
[69]	TEM	None	98%<0.4
[69]	TEM	>5 μm	61%<0.3
Chrysotile California			
a. Bulk Samples			
[50]	SEM	>5 μm	99%<1.0; 94%<0.5
[50]	TEM	>5 μm	100%<1.0; 98%<0.5
Chrysotile Rhodesia			
a. Bulk Samples			
[63] UICC	TEM	None	mean width = 0.16 ± 0.04
Chrysotile Vermont			
b. Airborne			
[74]	TEM 400X	>5 μm	63%<1.0
[74]	TEM 20KX	>5 μm	90%<1.0; 71%<0.5
Anthophyllite Finland			
a. Bulk Samples			
[56] UICC	TEM	None	90%<1.0; 60%<0.5
[22] UICC	TEM	None	median width = 0.61
b. Airborne			
[51]	TEM	None	70%<1.0; 40%<0.5

fibers wider than 1 μm is illustrated in Figure 1. It is clear that the dose of wide fibers (>1 μm) shows no relationship to the likelihood of producing tumors. It is important to note that the number of wide (>1 μm) NIOSH fibers in the dose of tremolite in the cleavage fragment samples (G, F, and H) is comparable to that in the tremolite asbestos samples. Thus, the argument that more tumors might have been observed if there had been more wide NIOSH fibers in these samples is not supported. In contrast, the correlation between tumor incidence and the number of NIOSH fibers per total dose administered with widths less than or equal to 1 μm is shown in Figure 2. This figure shows a dose-response relationship in the form of an s-shaped curve suggesting a threshold and a rapid increase in tumor incidence as the number of these thin (<1 μm) fibers increases. The curve in Figure 2 is derived from a least-squares linear regression of the form:

$$\text{logit} = m(\log \text{ of total dose} \leq 1\ \mu m) + b$$

where

$$\text{logit} = \ln\left(\frac{\%\ \text{tumor}}{1 - \%\ \text{tumor}}\right)$$

The equation for the curve in Figure 2 is shown below and is highly significant ($R^2 = 0.84$, $p<0.005$):

$$\text{logit} = 3.04(\log \text{ total dose } <1\ \mu m) - 6.25$$

A straight linear regression of the form below is also highly significant ($R^2 = 0.90$, $p<0.005$). In the data in Figure 2, this equation is:

$$\%\ \text{Tumor} = 49.3(\log \text{ total dose } \leq 1\ \mu m) - 54.6$$

Another way to illustrate the importance of width relative to tumor response is to characterize the samples in terms of the percentage of NIOSH fibers that have widths of less than 1 μm. It has been shown in most cases that up to 30% of ordinary cleavage fragments of amphibole longer than 5 μm have widths less than 1 μm, and more than 90% of asbestos fibers have widths less than 1 μm (all asbestos fibrils will be less than 1 μm). (See Tables I and III.) Therefore, the proportion of a fiber population with small widths is a measure of the asbestos-like nature of the population or of the abundance of the asbestiform components in a sample. Figure 3 shows the correlation between tumor incidence and the percentage of the tremolite NIOSH fiber population that has widths less than 1.0 μm. By

TABLE III. Continued

Mineral and Reference	Instrumentation	Length Restriction	Percent less than stated widths or mean width (μm)
Actinolite-asbestos			
a. Bulk Samples			
[34] Minnesota	TEM	None	mean width = 0.41 50%<0.24
[75] South Africa	SEM	>5 µm	96%<1.0; 70%<0.5
[49]	TEM	None	90%<0.33; 50%<0.06
[75]	SEM	>5 µm	98%<1.0; 90%<0.5
[22] Fed. Rep. Ger.	TEM	None	median width = 0.17
Tremolite-asbestos			
a. Bulk Samples			
[12] Montana	TEM	>5 µm	87%<1.0; 54%<0.5
[77] Montana	TEM	None	81%<0.6; 67%<0.4
[77] Metsovo	TEM	None	96%<0.6; 85%<0.4; 64%<0.2
b. Airborne			
[66] Korea	TEM	>0.4 µm	99%<1.0; 90%<0.5
[11] Montana	TEM	>5 µm	for w >0.45: 98%<1.24; 93%<0.88; 68%<0.62
Tremolite-asbestos and tremolite			
a. Bulk Samples			
[12] S. Carolina	TEM	>5 µm	81%<1.0; 48%<0.5
[75] India	SEM	>5 µm	61%<1.0; 34%<0.5
Asbestos, mineral ID not specified			
b. Airborne			
[59]	TEM	None	80%<0.43
Wooly Erionite			
a. Bulk Samples			
[22] Turkey	TEM	None	median width = 0.38
[22] Oregon	TEM	None	median width = 0.21
[71] Oregon	TEM	None	width range = 0.01–0.13 mean width = 0.03
Nemalite			
a. Bulk Samples			
[22]	TEM	None	mean width = 0.06

this measure an increase in tumor incidence is again observed as the proportion of tremolite fibers <1.0 μm in width increases in the population. The curve in Figure 3 is derived from a least-squares linear regression of the form:

$$\text{logit} = m(\%\ \text{fibers} \leq 1\ \mu\text{m}) + b$$

The equation for the curve in Figure 3 is shown below and is highly significant ($R^2 = 0.85$, $p < 0.005$):

$$\text{logit} = 0.008(\%\ \text{fibers} \leq 1\ \mu\text{m}) - 4.6$$

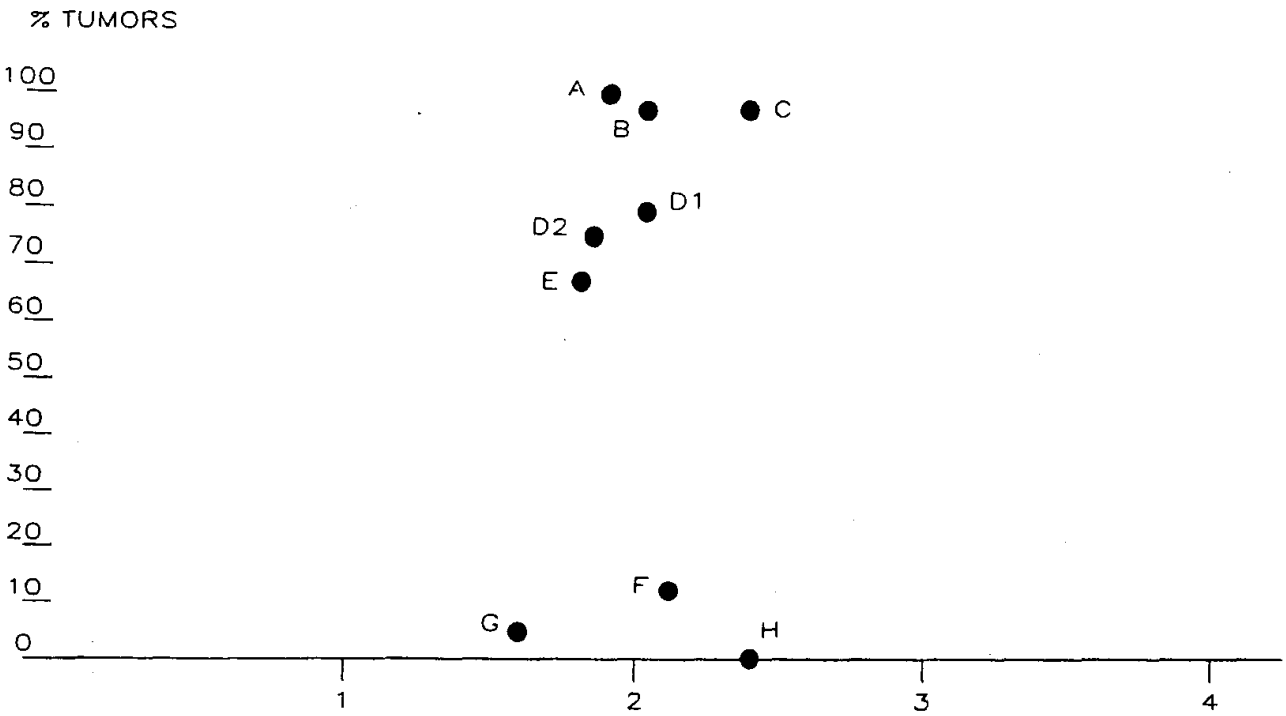
A straight linear regression of the data using the equation below is also highly significant ($R^2 = 0.93$, $p < 0.005$):

$$\%\ \text{Tumors} = 1.2(\%\ \text{fibers} \leq 1\ \mu\text{m}) - 14.4$$

DISCUSSION

Figures 1 and 2 contrast the pleural and peritoneal tumor response (mesothelioma) produced by wide and thin tremolite NIOSH fibers. For wide NIOSH fibers alone, there is no regular dose-response relationship, whereas for thin fibers, the s-shaped curve indicates a strong relationship between dose and carcinogenicity. Furthermore, as illustrated by Figure 3, as the proportion of tremolite NIOSH fibers with widths greater than 1 μm increases, the tumor incidence produced by the sample decreases. Complicating this somewhat simple picture is the fact that as the width of fibers increases, the number of fibers per microgram must decrease. Hence, the number of wide fibers will always be less than the number of narrow fibers in samples of equal weight. Notwithstanding this reality, however, is the observation that without thin fibers, tremolite NIOSH fiber populations are not associated with the induction of pleural or peritoneal tumors in animals. It is also made clear in these figures that characterization of populations of nonasbestiform tremolite by the NIOSH aspect ratio criterion for fibers produces an index that shows no relationship to mesothelioma risk.

The tremolite samples can be divided into three groups based on their carcinogenic potential: those without significant response, those with intermediate responses, and those that produce tumors in almost all the experimental animals. Criteria for a "significant" response varies according to the experimental animal, the level of total dose, the method and location of sample introduction of the fibers, latency, and experience of controls. Davis and co-workers indicate that by intraperitoneal injection, tumor responses in less than 10% of the animals are insignificant. For Stanton and



A: Addison–Davis California Tremolite Asbestos
B: Addison–Davis Korean Tremolite Asbestos
C: Addison–Davis Swansea Tremolite Asbestos
D1: Stanton Tremolite Asbestos 1
D2: Stanton Tremolite Asbestos 2
E: Addison–Davis Italian Tremolite Asbestos/Cleavage Fragments
F: Addison–Davis Dornie Tremolite Cleavage Fragments/ Asbestos
G: Addison–Davis Shinness Tremolite Cleavage Fragments
H: Stanton Talc 6 Tremolite (Non–asbestiform)

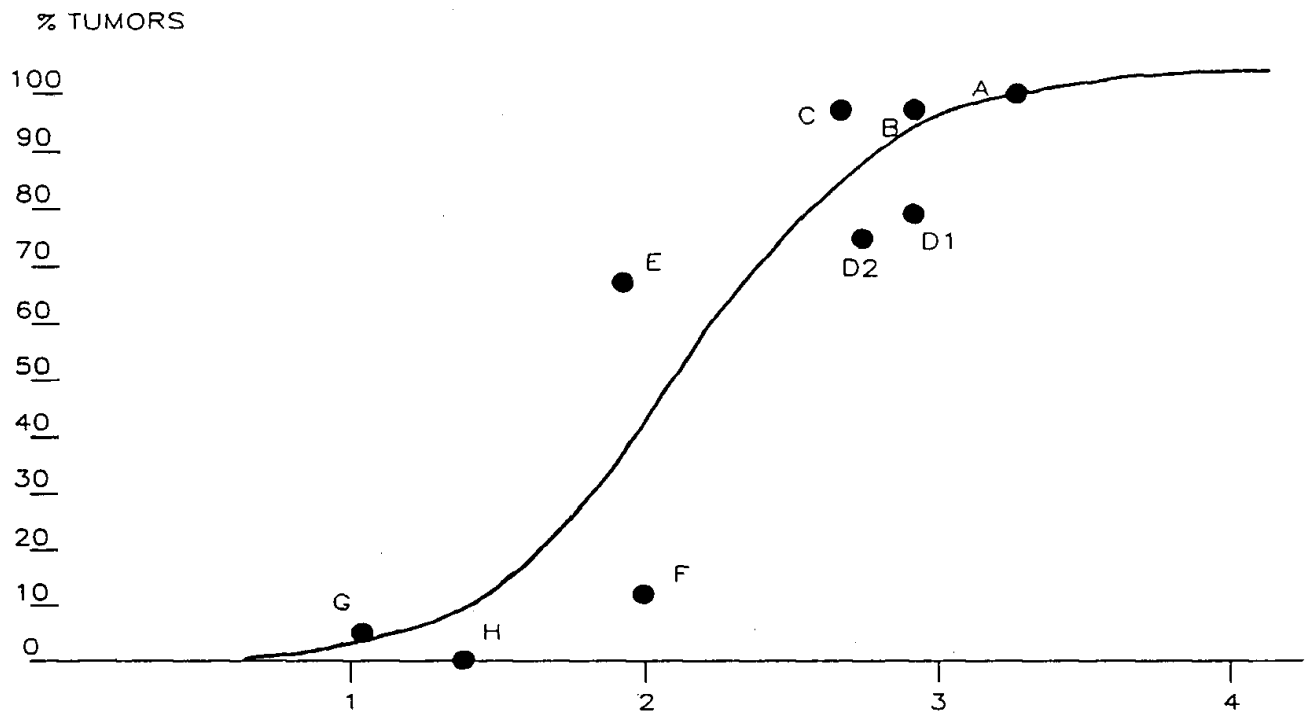
Figure 1. Percentage of tumors observed in experimental animals after exposure to tremolite as a function of the total dose of tremolite (number of fibers) equal to or longer than 5 μm, wider than 1 μm, and with an aspect ratio equal to or greater than 3

co-workers, 30% tumors were necessary for a significant response by pleural implantation.

Samples G, H, and I fall into the first category. Two of these samples are tremolitic talc from the state of New York (H and I). The high proportion of wide tremolite fibers in these samples is a clear indicator that the tremolite is nonasbestiform.

Samples E and F produced intermediate tumor responses in the animals. However, while sample E produced a high proportion of tumors, the mean survival time of the animals was almost twice that of the animals injected with tremolite A, B, and C, leading Davis and co-workers to conclude that tremolite E represented one-fortieth the hazard of tremolite C, a relationship not evident from the total tumor response. The intermediate responses might be expected from these two samples based on their mineralogical characteristics. Sample E contains a large proportion of highly unusual mineral fibers that lack a recognizable fibrillar structure. Other researchers, employing higher resolution electron microscopic techniques, report an asbestos subpopulation in this sample.[43] The long latency observed in the animals injected with this material might reflect a slow disaggregation of twinned or possibly asbestiform fibers. This hypothesis is further supported by the fact that the number of fibers per microgram, whether defined as total NIOSH fibers or as NIOSH fibers with widths less than 1 μm, in sample E is less than in sample F. The inverse correlation between dose and response could be explained by sample alteration in vivo as well as by several other mechanisms resulting from differences in surface properties. A comparison between the width distribution of the sample and the width distribution of the fibers found in the lung is necessary to evaluate the hypothesis that disaggregation occurs in vivo.

Sample F contains a small proportion of asbestiform fibers. The limited response of the animals to this material is most likely due to a low dose of asbestos. Davis and co-workers characterize this sample as unlikely to be carcinogenic to man given the marginal biological response observed in what is generally regarded as the most sensitive animal tumor induction technique (intraperitoneal



A: Addison–Davis California Tremolite Asbestos
B: Addison–Davis Korean Tremolite Asbestos
C: Addison–Davis Swansea Tremolite Asbestos
D1: Stanton Tremolite Asbestos 1
D2: Stanton Tremolite Asbestos 2
E: Addison–Davis Italian Tremolite Asbestos/Cleavage Fragments
F: Addison–Davis Dornie Tremolite Cleavage Fragments/ Asbestos
G: Addison–Davis Shinness Tremolite Cleavage Fragments
H: Stanton Talc 6 Tremolite (Non–asbestiform)

Figure 2. Percentage of tumors observed in experimental animals after exposure to tremolite as a function of the total dose of tremolite (number of fibers) equal to or longer than 5 μm, less than or equal to 1 μm wide, and with an aspect ratio equal to or greater than 3

injection).[40] Tumors have been induced with this test through the introduction of substances as benign as saline solution.[22]

Tremolite-asbestos samples A, B, and C produced pleural tumor incidences in excess of 95% with very short latency periods. While tremolite-asbestos samples D1 and D2 produced 75% and 79% tumor incidences, respectively, Stanton considered this response equivalent to a 100% tumor probability.

Because the tremolite studies did not involve inhalation exposures in either man or animals, they do not directly test carcinogenic potential relative to lung cancer. However, human epidemiology, lung burden data, and animal experimentation previously discussed support the hypothesis that as the number of asbestos and certain other fibers with widths below 1 μm (and 5 μm or longer) increases, the risk of both lung cancer and mesothelioma increases as well. Therefore, to the extent mesothelioma tumor experience observed in these tremolite animal studies is consistent with both fiber-size observations and biological response reported elsewhere, reasonable assumptions about lung cancer can be made with respect to the tremolite samples discussed here. It has already been established that excess lung cancer and mesothelioma are not evident in human populations exposed only to amphibole cleavage fragments but they are evident for human populations exposed to tremolite asbestos.

CONCLUSIONS

Combining tremolite samples that have been administered in different ways and to different animal groups such as we have done may appear to overlook important distinctions among these approaches. Despite this simplification, the data show a systematic relationship between dose based on width and mesothelioma tumor response in animals. It should also be noted that by using only the Addison and Davis data, the relationship of tumor response to fiber width remains strong. Furthermore, the fact that asbestos, with its unique dimensions, is known to cause lung cancer and pneumoconiosis suggests that width is related to respiratory

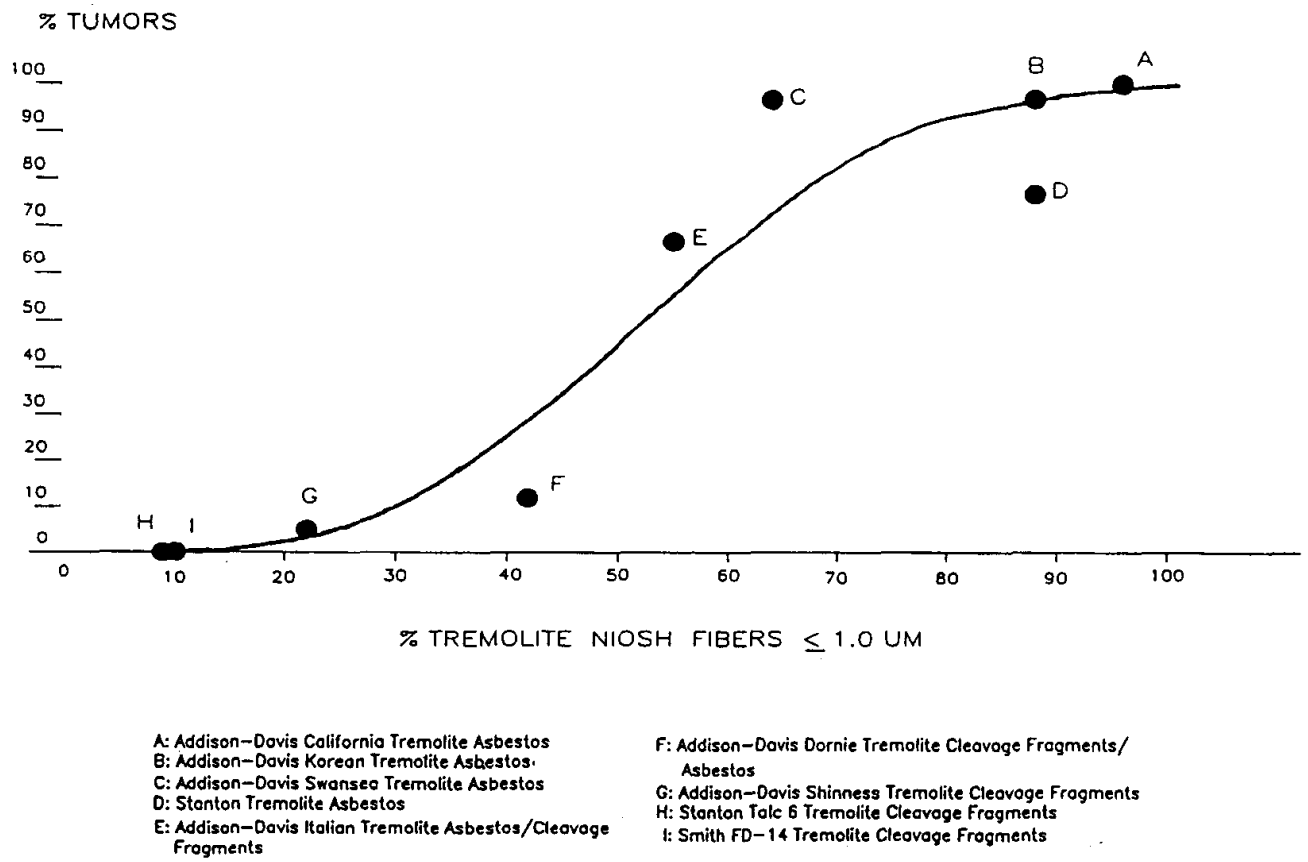


Figure 3. Percentage of tumors observed in experimental animals after exposure to tremolite as a function of the percentage of tremolite equal or longer than 5 μm with an aspect ratio equal to or greater than 3 that have widths less than or equal to 1 μm.

diseases other than mesothelioma. It seems clear that width is an extremely important variable that to date has been overlooked in regulatory policy. While fibers from a tenth to 200 μm long have been found in human lung tissue, it is the narrow width of these fibers that has given them access. A fiber 15 μm long and 5 μm wide meets the NIOSH criteria for a fiber, but such a particle is highly unlikely to cause disease in humans because it cannot gain access to a human lung. Not only is width a useful indicator of mesothelioma tumor induction, but a dose-response with a threshold is indicated as well.

We propose that NIOSH fiber size parameters used in the quantification of asbestos be modified to include only particles longer than 5 μm with widths less than 1 μm and that the use of the aspect ratio criterion be abandoned. Furthermore, in monitoring airborne asbestos particles or in determining the weight percentage of asbestos in bulk mineral samples, all 5 μm or longer particles that exhibit a fibrillar structure should be included as possible asbestos regardless of width. The potential of fiber bundles to disaggregate, in the air or in vivo, appears to be one of the most hazardous aspects of asbestos. The observation of fiber bundles should be included as part of the asbestos identification procedure. Electron and/or polarized light microscopy of the bundles would be necessary to determine the mineral composition.

Regulatory policy should also recognize that there exists a natural background of mineral particles that are longer than 5 μm and have widths less than 1 μm, which are not asbestos and which, from all evidence, are not associated with any carcinogenic risk. Nonasbestiform amphiboles, pyroxenes, feldspar alumino-silicates, and even phyllosilicates may form elongated fragments when they are crushed, and some will be of this size. However, *populations* of these elongated mineral fragments are easily distinguished from *populations* of asbestiform mineral fibers and vice versa. By establishing thresholds and meaningful definitions, asbestos regulations will not be extended to harmless rock fragments unnecessarily. While we may advocate asbestos regulation based on specific widths, we fully recognize that the scientific basis for regulation comes from populations of mineral fibers and that if asbestos is present in a population of mineral particles, the full range of its dimensions will also be present. It must be stressed that our recommendations have been derived from data and literature references on minerals whose asbestiform variety is known to be carcinogenic. Given the broad range and complexity of physio-chemical properties typically associated with mineral dusts, it is not reasonable to assume similarly sized particles of different minerals will act the same way once in the human lung. Therefore, the authors do not advocate the untested application of dimensional

observations addressed in this paper to all elongated particles. Rather, their application should be restricted to asbestos until such time that their relevance to other materials can be empirically demonstrated.

It is clear, however, that dimensional parameters can be effectively applied to distinguish asbestos dust populations and other fibrous dust exposures from common cleavage fragment dust exposures. This distinction appears to be both dose and risk dependent as well. It is also reasonable to conclude that all fiber populations of similar width, length, and crystal morphology as asbestos should be viewed with caution and perhaps given deference with respect to biological testing.

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XRD RING-RETURN

November 28, 1990

Mr. John Kelse
Vanderbilt

Re: RJ Lee Group Project No.: RDH003165

Dear Mr. Kelse:

Enclosed are the results obtained from our analysis of sample FD-14 (RJ Lee Sample No. 92399). The sample was examined by scanning electron microscopy and x-ray diffraction in order to determine the nature of the tremolite component.

For x-ray diffraction analysis, a portion of the sample was mixed with 10% CaF_2 as an internal standard. A bulk x-ray mount was prepared and examined on a Philips Diffractometer using monochromatized copper radiation at 40kV and 35ma.

For SEM analysis a portion of the sample was placed in a beaker containing acetone and agitated ultrasonically for ten minutes. The material was deposited on a 47 mm diameter 0.2µm-pore size polycarbonate filter. A portion of the filter was removed and redeposited onto another filter. This was done to achieve the proper sample loading for SEM analysis. After deposition, each filter was examined with an optical light microscope for uniformity of loading and proper areal concentration. One cm^2 portion of the filter was mounted face up on a polished carbon planchette SEM stub. The sample stub was then coated with a thin layer of carbon by evaporative deposition under vacuum.

Automated scanning electron microscopy, referred to as computer controlled scanning electron microscopy (CCSEM) provides simultaneous measurement of individual particle size, shape and elemental composition, in a very short time span. CCSEM combines three analytical tools under computer contrbl: 1) scanning electron microscopy (SEM), 2) energy dispersive spectrometry X ray analyzer (EDS), and 3) a digital scan generator (DSG) for image processing.

For this study, the backscattered electron mode, which is sensitive to differences in atomic number, was used to determine when the beam is on a particle. As the computer moves the electron beam across the image, the image intensity at each point is compared with a threshold level. This comparison is used to determine whether the electron beam is "on" a particle (above threshold) or "off" a particle (below threshold). If the signal is below the threshold level, the computer selects a coordinate and directs the beam to the new point. The distance between these "off points" is specified so that all particles larger than a selected size will be detected. Once a coordinate is reached where the signal is above the threshold level, the computer switches to a subroutine that drives the beam across the particle in a preset pattern to determine the dimensions and shape of the detected feature. For each feature, the minimum, maximum, and average diameters are stored, along with the centroid location. The centroid of each particle is compared with those of previously detected particles to prevent double counting.

For this study, a total of 500 particles were analyzed by CCSEM. The particle size range ran from a minimum length of 0.2 µm to a maximum of 100 µm.

CCSEM classifies each particle as a particle type based on its elemental chemistry. This is accomplished by collection of characteristic X rays which are fluoresced by the electron beam on the particle. The X ray spectrum from each particle is processed to obtain relative concentrations for 19 elements. Particle-by-particle X ray spectrum data was transferred to and stored in a personal computer (PC). Using the elemental composition and shape factor, each particle is assigned a defined mineral type. The aspect ratio is calculated next, using the stored maximum, minimum, and average diameters. The volume of each particle, computed from the projected area measurements, is multiplied by the particle density to obtain the particle's mass.

Manual scanning electron microscopy (MSEM) was performed using a JEOL T-300 scanning electron microscope (SEM) equipped with a Tracor Northern energy dispersive spectrometry X ray analyzer (EDS). During the manual SEM analysis, the samples were scanned in the TV mode at a magnification of 2000X. All EDSs were taken at 200,000X. Federal Fibers were defined as particles that were >5μm in length and having an aspect ratio >3:1. Fiber identification was made using morphology and elemental composition. The EDS system was used to collect characteristic X ray spectra for each fiber. Fiber dimensions (length and width in micrometers) were measured from the SEM viewing screen. For the manual SEM analysis, a known amount of sample was deposited on a filter, a known area of the filter was scanned and the mass of all tremolite "federal fibers" on the area scanned was determined. This allows the calculation of the weight percent tremolite fibers on the sample.

The CCSEM data indicates 36.1% tremolite of which 10.9% is greater than 3:1 (i.e. 3.95% of the bulk sample consists of tremolite with an aspect ratio greater than 3:1). CCSEM also found:

Calcite	1.7
Diopside	4.7
Serpentine/Anthophyllite/Talc	55.2
Quartz	1.2
Mixed silicates	1.3

Of the tremolites which the CCSEM run found that has aspect ratios greater than 3:1 and were longer than 5 micron, none were greater than 10:1.

The federal fibers tremolite content calculated from the MSEM run was 4.18%. This value is in excellent agreement with the 3.95% from the CCSEM. Figure 1 shows the weight distribution of the 64 tremolite fibers measured during the MSEM run. six of these 64 tremolite fibers had widths less than one micron. This is 9% of the total Federal Fiber tremolites (this amount to 2.8% by weight). Two of the 64 Federal Fiber tremolites had aspect ratios greater than 10:1. This is 3.1% of the total Federal Fiber tremolites.

XRD confirms the presence of talc, anthophyllite, tremolite, serpentine, diopside and quartz (figure 2). A mass of 12.9% serpentine is determined from the XRD.

The magnesium silicate component of the sample consists of serpentine, talc and anthophyllite. A total of 7.15% of the sample was identified by CCSEM as having a magnesium silicate composition and an aspect ratio greater than 3:1. This value probably corresponds closely to the anthophyllite percentage in the sample. Further work is necessary to more completely quantify this amphibole component of the sample.

These results are submitted pursuant to RJ Lee Group's current terms and conditions of sale, including the company's standard warranty and limitation of liability provisions and no responsibility or liability is assumed for the manner in which the results are used or interpreted. Unless notified in writing to return the samples covered by this report, RJ Lee Group will store the samples for a period of ninety (90) days before discarding. A shipping and handling fee will be assessed for the return of any samples.

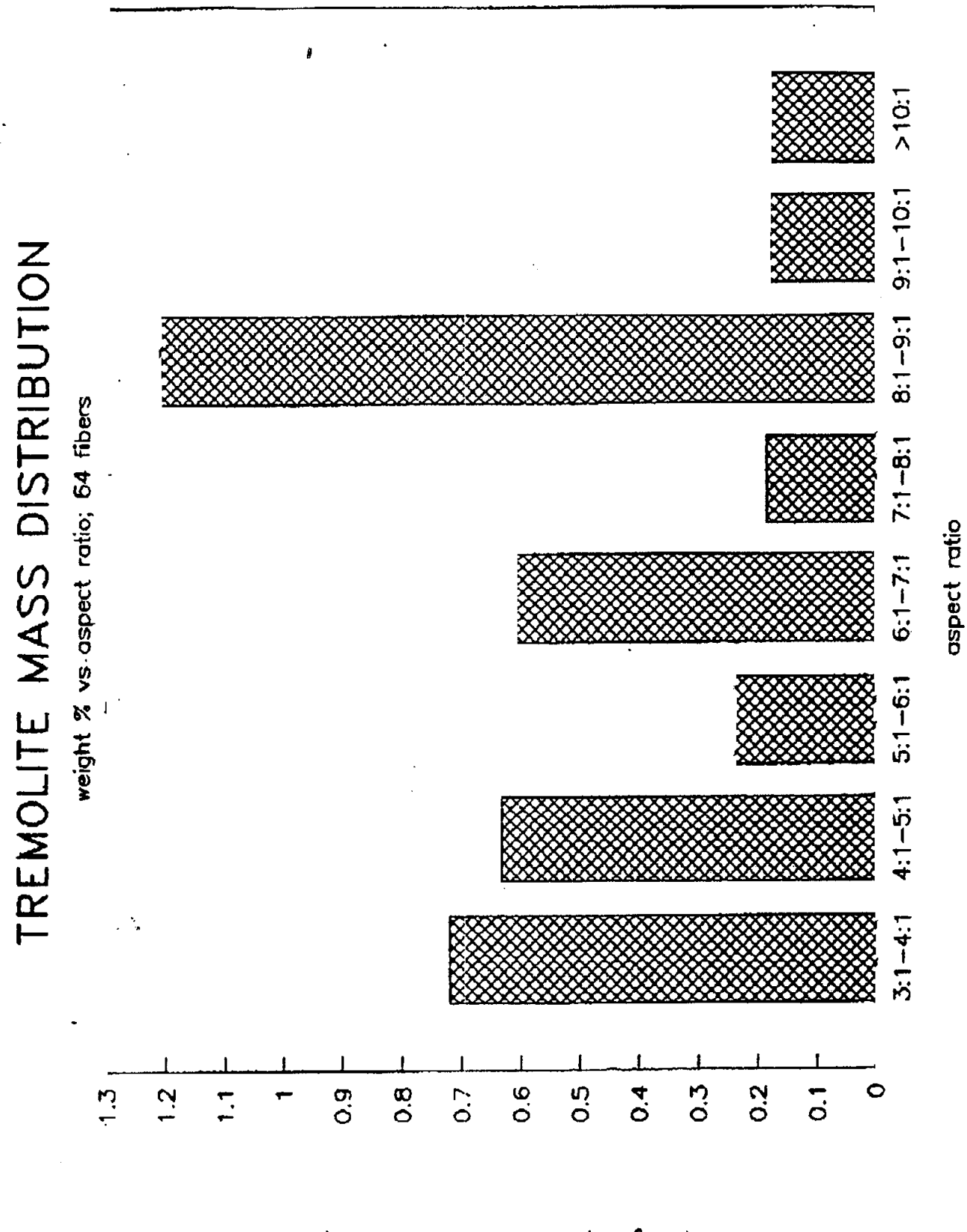
If you have any questions please do not hesitate to call.

Sincerely,

Gary A. Cooke

Gary A. Cooke
Manager, Analytical Chemistry

GAC/ljm
Enclosure


TREMOLITE MASS DISTRIBUTION
weight % vs aspect ratio; 64 fibers
weight percent in bulk sample
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3:1–4:1
4:1–5:1
5:1–6:1
6:1–7:1
7:1–8:1
8:1–9:1
9:1–10:1
>10:1
aspect ratio

Cell Studies

Specific to RTV Talc

TOXICOLOGY AND APPLIED PHARMACOLOGY 147, 000–000 (1997)
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Mineralogical Features Associated with Cytotoxic and Proliferative Effects of Fibrous Talc and Asbestos on Rodent Tracheal Epithelial and Pleural Mesothelial Cells

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Mineralogical Features Associated with Cytotoxic and Proliferative Effects of Fibrous Talc and Asbestos on Rodent Tracheal Epithelial and Pleural Mesothelial Cells. Wylie, A. G., Skinner, H. C. W., Marsh, J., Snyder, H., Garzione, C., Hodkinson, D., Winters, R. and Mossman, B. T. (1997). *Toxicol. Appl. Pharmacol.* 147, 000–000.

Inhalation of asbestos fibers causes cell damage and increases in cell proliferation in various cell types of the lung and pleura *in vivo*. By using a colony-forming efficiency (CFE) assay, the cytotoxicity and proliferative potential of three mineral samples containing various proportions of fibrous talc were compared to NIEHS samples of crocidolite and chrysotile asbestos in cell types giving rise to tracheobronchial carcinomas, i.e., hamster tracheal epithelial (HTE) cells, and mesotheliomas, i.e., rat pleural mesothelial (RPM) cells. Characterization of mineralogical composition, surface area, and size distributions as well as proportions of fibers in all mineral samples allowed examination of data by various dose parameters including equal weight concentrations, numbers of fibers >5 μm in length, and equivalent surface areas. Exposure to samples of asbestos caused increased numbers of colonies of HTE cells, an indication of proliferative potential, but fibrous talc did not. RPMs did not exhibit increased CFE in response to either asbestos or talc samples. Decreased numbers of colonies, an indication of cytotoxicity, were observed in both cell types and were more striking at lower weight concentrations of asbestos in comparison to talc samples. However, all samples of fibrous minerals produced comparable dose–response effects when dose was measured as numbers of fibers greater than 5 μm or surface area. The unique proliferative response of HTE cells to asbestos could not be explained by differences in fiber dimensions or surface areas, indicating an important role of mineralogical composition rather than size of fibers. © 1997 Academic Press

Occupational exposures to mineral fibers such as asbestos are associated with the development of pulmonary and pleural disease (Mossman and Gee, 1989; Mossman *et al.*, 1990; Guthrie and Mossman, 1993). Although various types of asbestos are biologically active in a number of *in vivo* and *in vitro* bioassays, the properties of fibers important in reactivity with cells and tissues are unclear (Guthrie and Mossman, 1993; Mossman and Begin, 1989). It is generally agreed that length and width or aspect ratio are important variables for predicting the carcinogenicity and fibrogenicity of durable fibers (Davis *et al.*, 1986; Stanton *et al.*, 1981). However, the mineralogical composition and structural features of fibers and particles may also play a role in pathogenicity (Oehlert, 1991; Wylie *et al.*, 1987; Skinner *et al.*, 1988; Wylie *et al.*, 1993). These properties govern surface properties as well as durability of fibers in the lungs and pleura, factors that may be critical in the development of lung cancer and mesothelioma. (Mossman and Gee, 1989; Mossman *et al.*, 1990; Guthrie and Mossman, 1993; Health Effects Institute, 1991).

Asbestos types, in contrast to a number of other fibrous and nonfibrous nonpathogenic materials, cause both cell proliferation and cytotoxicity in a dose-related fashion in several cell types (reviewed in Health Effects Institute, 1991). These biological responses may reflect the disease potential of various fiber types, as cell injury and hyperplasia are early events in rodent inhalation models of asbestosis and carcinogenesis (Mossman and Gee, 1989; Mossman *et al.*, 1990; Guthrie and Mossman, 1993; Health Effects Institute, 1991). In this study, we compared the cytotoxicity and proliferative potential of three New York talc samples to crocidolite and chrysotile asbestos in cell types affected in asbestos-induced tumors, i.e., hamster tracheal epithelial (HTE) cells, which can give rise to tracheobronchial neoplasms, and rat pleural mesothelial (RPM) cells, cells affected in the development of mesothelioma. In studies here, we used an established colony-forming efficiency (CFE) assay that documents both increases in cell proliferation and cell survival, as measured by increases in numbers of colonies, at low concentrations of minerals, and growth inhibition, as indicated by decreases in colony formation or size at high concentration of minerals, to compare responses to well-characterized samples of asbestos and fibrous talc in HTE and RPM cells. An additional advantage of this bioassay is that it employs cells from the lung and pleura and measures responses

0041-008X/97 $25.00

to minerals over a 7-day time period of exposure as opposed to shorter time frames used (<24 hr) in most other *in vitro* assays in the literature (reviewed in Health Effects Institute, 1991. In the CFE assay, nonfibrous particles such as glass beads are proliferative or cytotoxic to HTE cells at ≥100-fold concentrations when compared to asbestos at equal weight concentrations (Mossman and Sesko, 1990; Marsh *et al.*, 1994; Timblin *et al.*, 1995).

The three talc samples used here differ somewhat in their mineralogy, both in the types of minerals and in their relative abundances. However, all three contain varying proportions of fibrous talc which is similar dimensionally and morphologically to asbestos. We thus hypothesized that factors other than length and width of fibers would govern the reactivity of minerals in the *in vitro* assays used here. The experiments were undertaken to explore the questions: (1) Do fibrous talc and asbestos fibers cause similar biological responses in epithelial and mesothelial cells? (2) Is reactivity to mineral samples dose related? and (3) Are responses in various cell types related only to numbers and sizes of fibers in each preparation or does mineralogy, including chemical composition, surface properties, and mineral structure, play a role?

METHODS

Sources of Mineral Samples

Three samples from the New York State Gouverneur Mining District, FD14, S157, and CPS183, and two asbestos samples, NIEHS chrysotile (Plastibest 20) and NIEHS crocidolite, were used in this study. The asbestos samples are essentially monomineralic and have been studied in detail (Campbell *et al.*, 1980). The general geology and mineralogy of the Gouverneur District are described by Engle (1962) and Ross *et al.* (1968). FD14 is a commercial talc, S157 was once produced from this district as a fiber talc product, and CPS183 is a laboratory separated concentrate of fibrous talc. Fibrous talc is a general term that includes fibers composed entirely of the mineral talc as well as fibers that are composed of both talc and amphibole (probably anthophyllite) intergrown on a submicrometer scale (Stemple and Brindley, 1960; Virta, 1985). The index of refraction of the fibers increases as the amphibole component increases (Veblen and Wylie, 1993). Fibrous talc is present in trace amounts in many commercial talc deposits, but it is a major component of most talc products from the Gouverneur Talc District. All samples were characterized by scanning electron microscopy (SEM), optical microscopy (OM), and x-ray diffraction (XRD); CPS183 and NIEHS crocidolite were also studied by TEM as this technique is more sensitive for the detection of smaller, thinner particles.

Characterization of Minerals

The samples were studied by XRD and SEM at Yale University in order to establish the overall mineralogy, mineral abundances, and the number of fibers per microgram. They were examined by OM at the Laboratory for Mineral Deposits Research, University of Maryland, in order to determine the mineralogy, mineral abundances, and number of fibers per microgram of the samples, and by transmission electron microscopy (TEM) at AMA Laboratories, Beltsville, Maryland (under the direction of the Laboratory for Mineral Deposits Research) for the purpose of determining the detailed size distribution of fibrous talc and especially to examine the content of fibers 0.1 μm in width and smaller. The protocols followed in each laboratory are described below. For purposes of this paper, "particles" refers to particles of all aspect ratios. "Fiber" refers to particles that have an aspect ratio (length/width) of at least five and to bundles of such fibers. "Fibers" (unless otherwise specified) include true mineral fibers (very high aspect ratio particles whose shapes were attained during mineral formation) as well as elongated cleavage fragments (shape produced during comminution).

X-ray diffraction. Samples mixed with an internal standard and spun to minimize preferred orientation were analyzed by using a SCITAG Pad V automated diffractometer. Identification of minerals was based on comparison of the X-ray pattern with standard patterns.

Optical microscopy. A known weight of sample was dispersed in water and then passed through a 22-gauge needle 8× and sonicated 4 min before mounting on slides. A drop of immersion oil n_D = 1.598 was placed over the dried sample. For all samples except chrysotile (N = 2 mixtures), at least five separate mixtures were prepared from each sample and at least two slides were made from each mixture. One-hundred fibers were counted from each slide. All fibers longer than 5 μm and all particles that appeared to be composed of bundles of fibers were categorized by length and width and by index of refraction according to the following characteristics: all indices of refraction greater than 1.598 (amphibole), index of refraction parallel to elongation greater than 1.598 and index of refraction perpendicular to elongation less than 1.598 (fibers composed of talc and a significant amount of amphibole, and referred to as talc/amphibole), or all indices of refraction less than 1.598 (fibers dominated by the mineral talc). The number of fiber per microgram was calculated by assuming that particle distributions were representative and directly proportional to the area of the filter.

Scanning electron microscopy. A known weight of sample was dispersed in water, passed through a 22-gauge syringe needle 8×, and deposited onto a 0.45-μm cellulose filter. Replicate preparations were made for each sample and analyzed independently to test for homogeneity. The filters were examined with a JEOL JXA 8600 SEM equipped with EDXA. Particles that were at least 1 μm in length and 0.12 μm in width could be detected. Mineral identification was automated by predetermining the relative percentages of Na, Ca, K, Mg, Al, Si, Mn, and Fe in mineral standards and comparing them to the elemental compositions determined on the sample particles (Petruk and Skinner, 1997). The number of particles per microgram of sample was calculated by assuming that the particle distributions were representative and directly proportional to the area of the filter.

Transmission electron microscopy. A known weight of sample was dispersed in water, flushed with a 22-gauge syringe needle 8×, and then sonicated for 4 min. The solutions were then diluted and filtered through a 0.22-μm cellulose acetate filter. The samples were analyzed on a JEOL 100 CX II electron microscope at 19,000× magnification. Over 300 fibers from each sample were measured.

Surface area measurements. All five samples were tested for single point N_2-BET surface areas by J. W. Anderson of R. T. Vanderbilt Corporation. The tests were repeated 4× for each sample. Data were expressed as square millimeters per gram of sample.

Cell culture and addition of fibers to bioassay. A HTE cell line previously isolated and characterized by Mossman *et al.* (1980) was maintained at passages from 38 to 50 and cultured routinely in Ham's F12 medium (Gibco, Grand Island, NY) containing penicillin and streptomycin (both at 100 U/ml) and 10% newborn calf serum (Gibco). This cell line is diploid and possesses features, i.e., mucin secretion and cilia, of differentiated epithelial cells. Primary cultures of RPM cells were isolated by scraping the parietal pleural of two weanling male Fischer 344 rats (Janssen *et al.*, 1994) and were maintained for up to eight passages in Ham's F12–DMEM containing antibiotics (as above), 10% fetal calf serum (Gibco), hydrocortisone (100 ng/ml), insulin (2.5 μg/ml), transferrin (2.5 μg/ml), and selenium (2.5 ng/ml).

Mineral samples presterilized in a dry oven overnight at 130°C were added to Hanks' balanced salt solution (HBSS) before titration 8× through a 22-gauge syringe needle and addition to cultures in 2% serum-containing medium.

A CFE assay was also used as a sensitive test for cytotoxicity and cell proliferation (Mossman and Sesko, 1990, Marsh *et al.*, 1994; Timblin *et al.*, 1995). HTE (400 cells/60 mm dish) and RPM (2000/60 mm dish) were plated for 24 hr before addition of dust suspension medium containing 2% serum as described

TABLE 1
Characterization of Talc and Asbestos Samples

Sample	Mineralogy (% of sample)
	Mineral composition
FD14	Talc (37), tremolite (35), serpentine (15), other (<2), unknown (12)[a]
S157	Talc (60), tremolite (12), unknown (21), other (4), anthophyllite (3), quartz (1)
CPS183	Talc (50), quartz (12), unknown (28), tremolite (4), other (4), anthophyllite (3)
NIEHS crocidolite	Riebeckite (100)
NIEHS chrysotile	Chrysotile (100)
	Mineralogy of fibers >5 μm
FD14	Talc (62), amphibole (24),[b] talc/amphibole (14)
S157	Talc (84), amphibole (11), talc/amphibole (5)
CPS183	Talc (99), amphibole (1), talc/amphibole (<1)
NIEHS crocidolite	Crocidolite (100)
NIEHS chrysotile	Chrysotile (100)

Sample	Surface area (mm^2/gm)	Fibers/μg	Fibers ≥ 5 μm/μg
	Surface area and fibers/μg[c]		
FD14	6.2 ± 0.2[d]	2.5×10^3	0.8×10^3
S157	4.9 ± 0.2	1.1×10^4	4.8×10^3
CPS183	4.9 ± 0.4	1.1×10^4	9.2×10^3
NIEHS crocidolite	10.3 ± 1.3	5.3×10^5	3.8×10^5
NIEHS chrysotile	25.4 ± 0.5	5.3×10^4	3.4×10^4

[a] Primarily magnesium silicates (talc and talc/amphibole) with SEM/EDXA spectra too low for conclusive identification.

[b] The most abundant amphibole is tremolite. A very small amount of anthophyllite may be included.

[c] Data are based on SEM measurements. Chrysotile values are low due to its poor visibility on the SEM. Standard error of measurement is estimated to be 20%.

[d] Mean ± standard error of measurement of four individual measurements per group.

above. Minerals were then added, and untreated and mineral-exposed cultures were maintained for 7 days before examination. At this time, plates were rinsed in HBSS and fixed in methanol and stained with 10% Giemsa stain, and total colonies greater than 50 cells per plate were counted by using a blind code (Mossman and Sesko, 1990; Marsh *et al.*, 1994; Timblin *et al.*, 1995). Duplicate experiments were performed for each bioassay with $N = 3$–4 dishes per group per experiment. Statistical analyses of all data were performed by using analysis of variance and trend analysis.

RESULTS

Mineralogy

The overall mineralogical composition, the mineral composition of the fibers, the number of fibers per microgram, and the surface area measurement of the samples used in our studies are given in Table 1. FD14 is composed of platy talc, true mineral fibers of talc and talc/amphibole, cleavage fragments of tremolite, platy serpentine (chrysotile absent), and trace amounts of other minerals. Fibers make up approximately 11% of the particles identified by SEM. They are mostly talc followed by amphibole cleavage fragments and talc/amphibole. S157 is composed of platy talc, true mineral fibers of talc and talc/amphibole, tremolite and anthophyllite cleavage fragments, and quartz. Fibers make up about 37% of the particles, and they are mostly talc with smaller amounts of amphibole cleavage fragments and talc/amphibole. CPS183 is composed of true mineral fibers of talc and a very small amount of talc/amphibole, cleavage fragments of tremolite and anthophyllite, and quartz. Fifty-nine percent of the particles are fibers, and they are almost all fibers of talc. The three talc samples represent a range in the amount of fiber present (both in portion of sample and in number of fibers/μg) and in the mineralogy of the fibrous portion, primarily in the content of amphibole both as a separate phase and as a component of fibrous talc. NIEHS crocidolite and NIEHS chrysotile are essentially monomineralic populations of true mineral fibers of riebeckite and chrysotile, respectively. The very small widths result in many more fibers per microgram than are found in the talc samples.

Surface Area

The specific surface areas (mm^2/g) of talc samples are smaller than asbestos samples and roughly comparable to each other. The larger surface area of FD14 compared to the other talc samples is probably due to the presence of more abundant small platy talc particles that have two almost equivalent dimensions and one that is very much smaller, producing a large surface area/mass ratio. The greater surface area of chrysotile with respect to crocidolite can be attributed to its lower density and small fibril width and perhaps in part to the straw-like structure of the chrysotile fibers if N_2 penetrates the hollow center of the chrysotile tubes. Since the surface reactivity of different minerals affects the surface adsorption of N_2, some of the variation among samples may be related to mineralogy as well.

Size Distributions of Fibers in Mineral Preparations

Figure 1 shows the frequency of length and width for all fibers in units of fibers/microgram and the frequency of width for only those fibers greater than or equal to 5 μm in length as established by SEM and OM. The abundance of narrow crocidolite fibers accounts for the fact that the NIEHS crocidolite contains more fibers per microgram than any other sample (Table 1). CPS183 and S157 are very similar in many respects. They are composed of similar numbers of fibers per microgram, but there are slightly more longer fibers and fewer long, wide fibers in CPS183. FD14 contains the smallest number of fibers per microgram and the highest proportion of the widest fibers. In general, talc fibers are narrower than amphibole cleavage fragments and the differences in the sizes of the fibers among the talc samples in part reflect the differences in the abundance of amphibole cleavage fragments vs fibrous talc. As

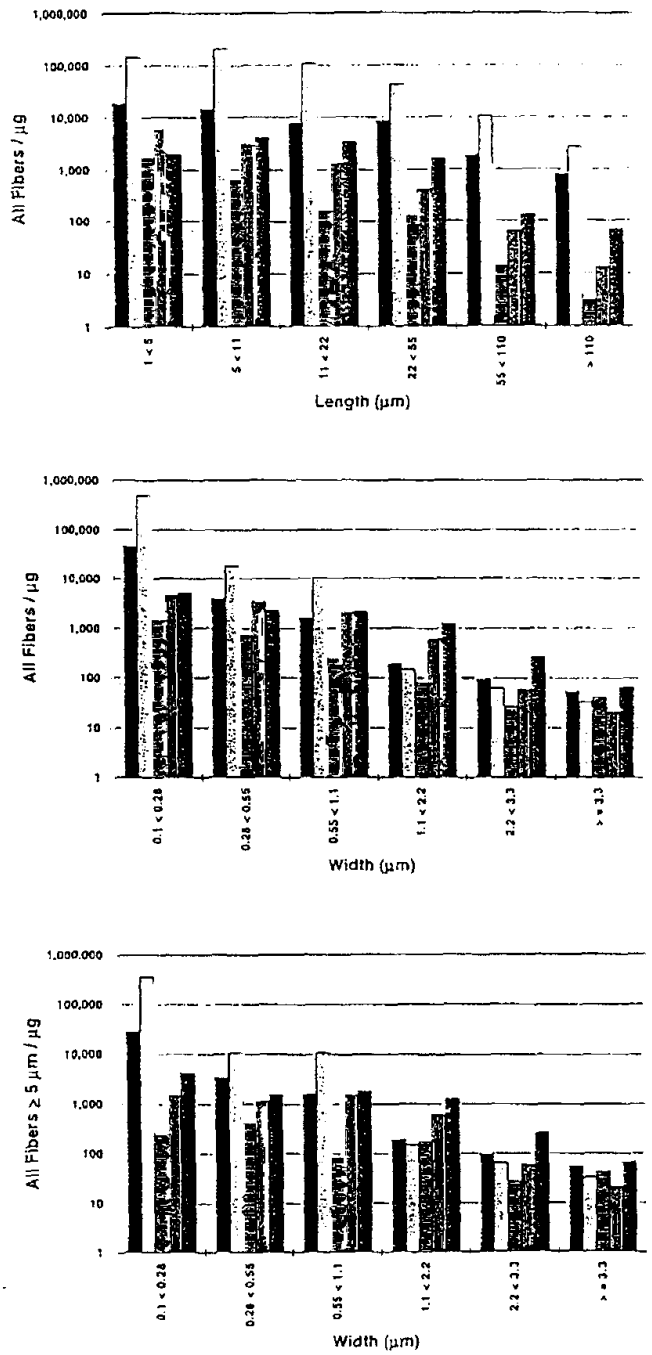

FIG. 1. The frequencies of length and width in units of fibers per microgram are shown for the three talc samples and two NIEHS asbestos samples. Also shown is the frequency of width (fibers/µg) for those fibers longer than 5 µm. (■) Chrysotile; (□) crocidolite; (▩) FD14; (▥) S157; (▨) CPS183.

the amphibole content increases from CPS183 to S157 to FD14, the total fiber content goes down, and, on average, the fibers decrease in length and increase in width. No distinction between the size distributions of talc and talc/amphibole fibers were documented.

T2 Table 2 gives the percentage of fibers in length–width categories for CPS183 and NIEHS crocidolite asbestos as measured by TEM. These data enable a direct comparison between the dimensions of fibrous talc and crocidolite that is not restricted by the 0.1-µm width limit in the SEM data. These two true mineral fiber populations are quite similar, differing most notably in the higher proportion of wide (>0.5 µm) fibers and slightly lower proportion of long (>20 µm) fibers in fibrous talc.

CFE Assays

F3 Combined data from duplicate experiments with HTE and RPM cells are presented in Figs. 2 and 3, respectively. CFE data are expressed as a ratio of the number of colonies in mineral-exposed cultures in comparison to control colonies × 100 at various concentrations of minerals on a weight basis ($\mu g/cm^2$) as is typically found in the literature (Mossman *et al.*, 1990; Health Effects Institute, 1991). In HTE cells, both asbestos types showed an elevated number of colonies ($p < 0.05$) at lowest concentrations indicating increased cell proliferation and/or survival in response to asbestos fibers and confirming earlier studies (Mossman and Sesko, 1990; Marsh *et al.*, 1994). Significant decreases ($P < 0.05$) in CFE, an indication of toxicity or growth inhibition, were observed at concentrations of asbestos of 0.5 $\mu g/cm^2$ and greater. In contrast, RPM cells did not exhibit proliferative effects in response to either asbestos type, but statistically significant ($p < 0.05$) decreases in CFE were observed at concentrations of asbestos fibers greater than 0.05 $\mu g/cm^2$. In both cell types, the talc samples were less cytotoxic than asbestos. CPS183 was the most toxic talc sample, followed by S157 and FD14. In contrast to the other mineral samples, S157 and FD14 did not exhibit significant linear trends in cytotoxicity with increasing dosages in HTE cells.

F4-F5 Figures 4 and 5 show the same cellular response data as Figs. 2 and 3, but dose is calculated based on the number of

TABLE 2

Percentage of Fibers by Length and Width (µm) as Determined by Transmission Electron Microscopy

Length	Width: 0.01–0.1	>0.1–0.25	>0.25–0.5	>0.5–1.0	>1.0
CPS183					
<1	2.9	1.6	—	—	—
>1–2	4.1	14.1	0.5	—	—
>2–5	2.5	22.0	6.8	1.6	—
>5–10	0.9	9.8	4.3	4.5	0.5
>10–20	0.5	7.3	3.2	2.3	2.5
>20–50	0.2	1.8	2.7	1.4	2.0
>50–100	—	—	—	—	0.2
		NIEHS crocidolite			
<1	0.3	0.3	—	—	—
>1–2	1.1	9.5	0.3	—	—
>2–5	4.6	31.6	2.9	—	—
>5–10	1.4	18.1	3.7	0.6	—
>10–20	1.1	10.7	3.2	0.3	—
>20–50	0.6	2.9	1.4	1.1	—
>50–100	—	1.7	1.4	0.6	—

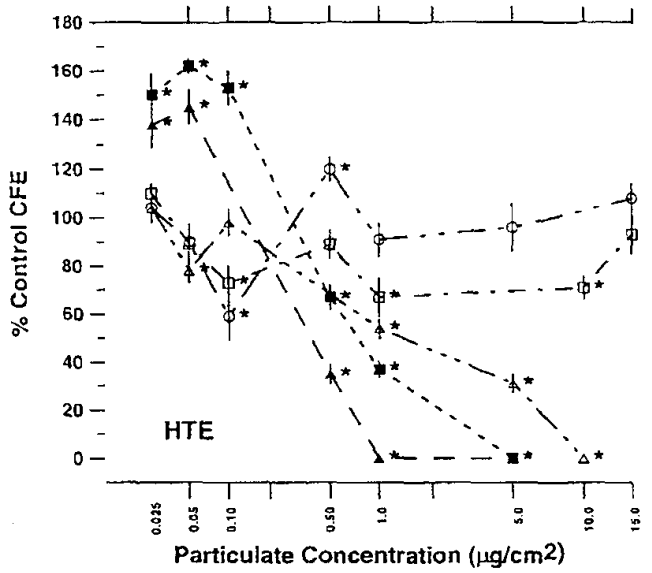

FIG. 2. Colony-forming efficiency (CFE) of HTE cells at various weight concentrations of samples. Standard error in CFE is indicated on symbol. *$p <$ 0.05 in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

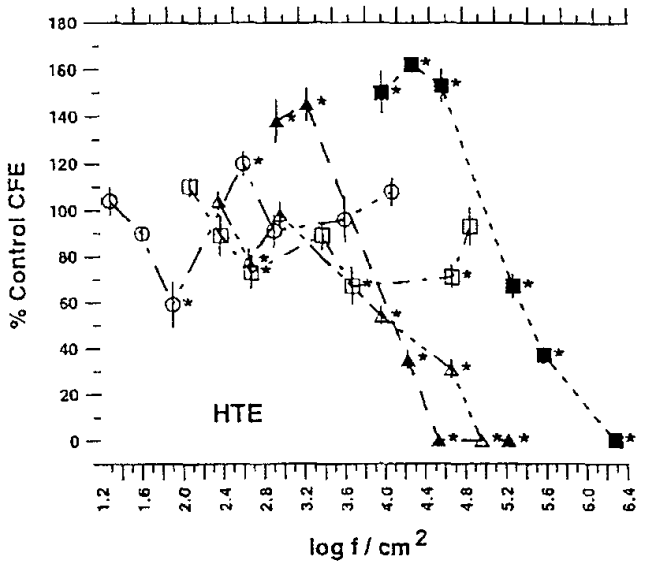

FIG. 4. Colony-forming efficiency (CFE) assays in HTE cells expressed as a function of fibers ≥5 μm in length per cm² (f/cm²). The symbol width is equal to or greater than estimated error. The standard error in CFE is indicated on the symbols. *$p < 0.05$ in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

fibers greater than or equal to 5 μm/cm² (fibers/cm²) rather than total sample weight per square centimeter. The data are taken from the SEM characterizations, but the comparisons would be the same if OM or TEM data were used. Doses of total sample per square centimeter administered to the cultures covered such a wide range that there were equivalent doses of fibers per square centimeter in almost all length/width categories for all samples. Therefore, even though crocidolite and chrysotile contained many more fibers per microgram than the talc samples, the same number of fibers per centimeter were administered in low doses of asbestos and high doses of talc (μg/cm²).

As shown in Fig. 4, the enhanced responses of HTE cells to asbestos appear to be a function of mineralogy and not fiber

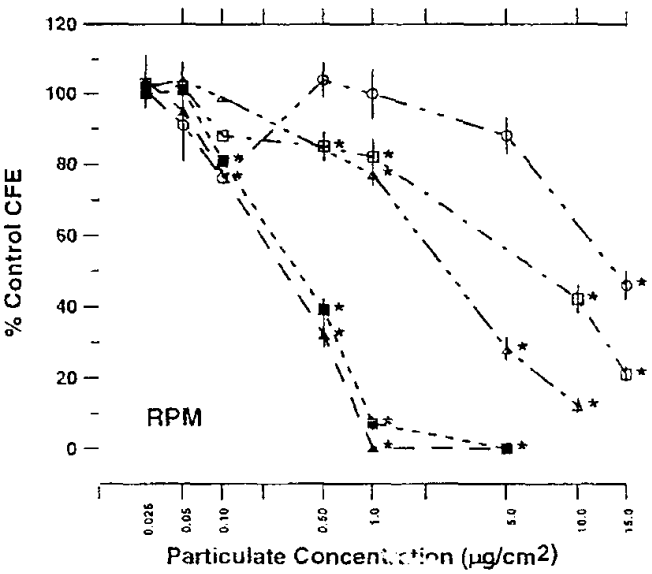

FIG. 3. Colony-forming efficiency (CFE) of RPM cells at various weight concentrations of samples. The standard error in CFE is indicated on the symbols. *$p < 0.05$ in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

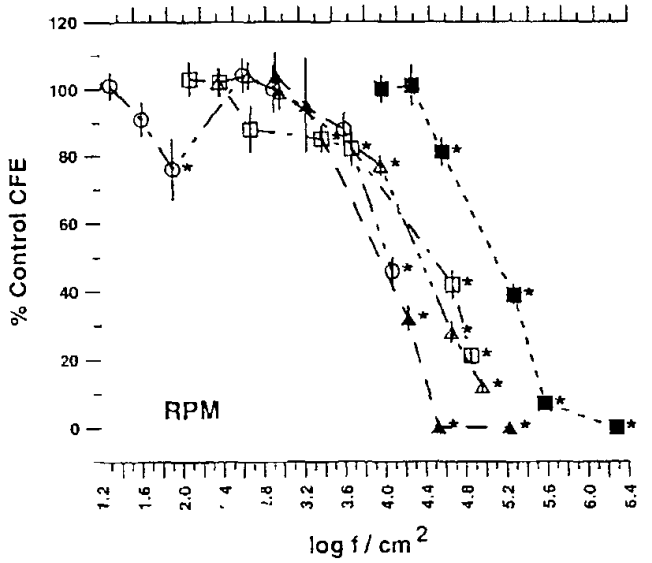

FIG. 5. Colony-forming efficiency (CFE) assays in RPM cells expressed as a function of fibers ≥5 μm in length and length:width ≥ 5:1 per cm² (f/cm²). The symbol width is equal to or greater than estimated error. The standard error in CFE is indicated on the symbols. *$p < 0.05$ in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

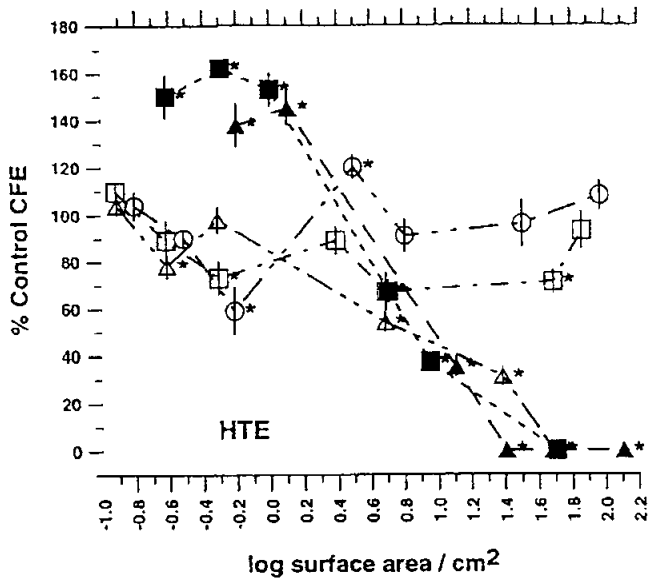

FIG. 6. Colony-forming efficiency (CFE) assays in HTE cells expressed as a function of surface areas of mineral samples (mm^2/cm^2). The symbol width is equal to or greater than one standard error. The standard error in CFE is indicated on the symbols. *$p < 0.05$ in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

concentration. The same concentrations of fibers greater than 5 μm of chrysotile and crocidolite that cause proliferation in HTE cells result in no effects when comparable concentrations of FD14 fibers are used, insignificant cytotoxicity with S157 fibers, and significant cytotoxicity with CPS183 fibers. It therefore seems likely that characteristics of the samples that are related to their mineralogy contribute to proliferation and/or cell growth inhibition.

As shown in Fig. 5, the response of RPM cells appears to be independent of the mineralogy of the samples. Neglecting the slight cytotoxic response of FD14 at low concentrations, the minimum concentrations of fibers per square centimeter necessary to cause significant decreases in CFE is between 10^3 and 10^4 fibers per square centimeter for all samples. In changing the size definition of a fiber (e.g., >8, ≤0.25 μm; >20 μm, all widths; all lengths, w < 0.28 μm), we found that the effective dose changed but the relationships among the samples did not (data not shown).

F6-F7

Figures 6 and 7 show CFE data in HTE and RPM cells, respectively, as a function of surface area. It is evident that surface area per se cannot explain cellular responses to minerals in HTE or RPM cells. Despite the fact that crocidolite and chrysotile have much larger surface areas per microgram, the range in the amount of sample administered resulted in similar doses between the asbestos and talc samples.

DISCUSSION

Asbestos is a term applied to a group of minerals that possess similar physical properties because of their habit of growth. However, different types of asbestos differ in their mineralogy and fiber size, which in turn may vary in preparations obtained from different geographic locations and sometimes even from the same locality (Guthrie and Mossman, 1993). The two most widely studied types of asbestos are the serpentine mineral chrysotile ($Mg_3Si_2O_5(OH)_4$), the most common type of asbestos in the Northern hemisphere and in commercial usage historically, and the asbestiform variety of the amphibole riebeckite, crocidolite ($Na_2Fe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH)_2$), a high-iron-containing asbestos mined in parts of South Africa and Western Australia. Although crocidolite is implicated as more potent in the induction of mesothelioma, both chrysotile and crocidolite are linked occupationally to the development of lung cancer and asbestosis (Mossman and Gee, 1989; Mossman *et al.*, 1990, 1996; Guthrie and Mossman, 1993; Health Effects Institute, 1991).

How asbestos causes lung disease is uncertain, but acute toxicity, measured by a variety of techniques which have detected increases in membrane permeability, necrosis, release of oxygen-free radicals, exfoliation, and cell death (reviewed in Mossman and Begin, 1989) has been observed in a variety of cells exposed to high concentrations of fibers. At lower concentrations, both crocidolite and chrysotile asbestos cause cell proliferation in HTE cells and organ cultures, phenomena not observed with various synthetic fibers or nonfibrous analogs of asbestos (Marsh and Mossman, 1988; Woodworth *et al.*, 1983). These biological responses to asbestos may be important in the induction of neoplasms as cell injury may cause exfoliation and compensatory hyperplasia of surrounding cell types which are more sensitive to genetic damage. As suggested by Ames and Gold (1990), mitogenesis may facilitate mutagenesis and contribute to tumor development. In addition, cell proliferation is

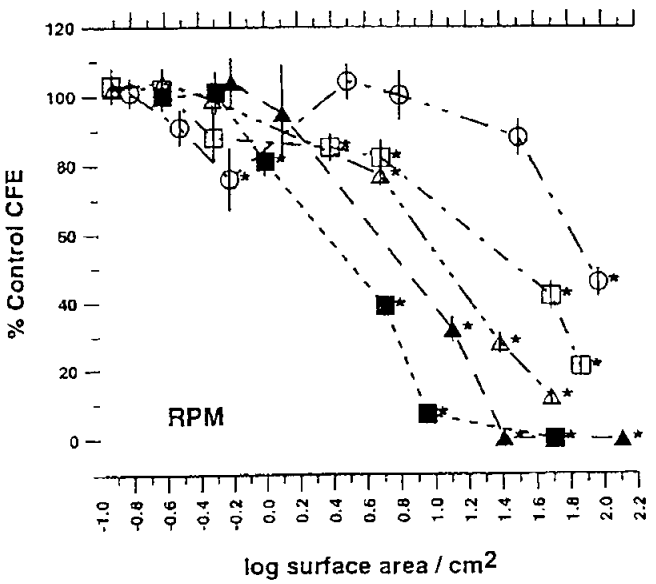

FIG. 7. Colony-forming efficiency (CFE) assays in RPM cells expressed as a function of surface areas of mineral samples (mm^2/cm^2). The symbol width is equal to or greater than one standard error. The standard error in CFE is indicated on the symbols. *$p < 0.05$ in comparison to untreated controls. (▲) Chrysotile; (■) crocidolite; (○) FD14; (□) S157; (△) CPS183.

an important component of tumor promotion and progression, and asbestos is a documented tumor promoter in epithelial cells of the respiratory tract (reviewed in Mossman *et al.*, 1990, 1996; Health Effects Institute, 1991).

Our results with asbestos samples are interesting in that HTE cells are unique in exhibiting increased CFE, in comparison to untreated and talc-exposed cells. Moreover, both cell types were more sensitive to the cytotoxic effects of equal weight dose amounts of asbestos in comparison to talc. The lack of response of RPM cells to the proliferative effects of asbestos may reflect the fact that single cells, as opposed to confluent monolayers (Marsh and Mossman, 1988; Woodworth *et al.*, 1983), were exposed to fibers here. For example, when added to confluent, growth-arrested RPM cells, crocidolite causes cell proliferation as measured by dual fluorescence techniques with an antibody to 5-bromodeoxyuridine (BrdU) and the DNA dye YOYO (Goldberg *et al.*, 1997). Moreover, increased numbers of both pleural mesothelial and bronchial epithelial cells incorporating BrdU are observed after inhalation of NIEHS crocidolite or chrysotile by rats (BeruBe *et al.*, 1996). As suggested by Gerwin *et al.* (1987), mesothelial cells may require growth factors, either produced endogenously or produced by other cell types, for proliferative responses to asbestos, and the small numbers of cells used in the CFE bioassay may not be sufficient for amounts of cytokines needed here.

Our experiments also show that fibrous talc does not cause proliferation of HTE cells or cytotoxicity equivalent to asbestos in either cell type despite the fact that talc samples contain durable mineral fibers with dimensions similar to asbestos. These results are consistent with the findings of Stanton *et al.* (1981) who found no significant increases in pleural sarcomas in rats after implantation of materials containing fibrous talc. Moreover, Smith and colleagues report no sarcomas in hamsters after implantation of FD14 (1979), and other rodent studies in which talcs of various types have been administered by inhalation of injection also have not shown an increased incidence of mesotheliomas or carcinomas (Stenback and Rowland, 1978; Wehner *et al.*, 1977). Epidemiological studies also indicate that talc in a number of occupational settings is less pathogenic than asbestos in the development of lung cancer, and the reports indicating excess lung cancer mortality may underestimate smoking habits, an important confounder, and exposure to commercial asbestos (reviewed in IARC, 1987a,b; Ross *et al.*, 1993). In essence, data have not proven that talc is a human carcinogen as small numbers of cohorts have been studied, smoking histories are poorly documented, and workers were often exposed to other dusts, including asbestos, that may cause lung disease.

Increases in cytotoxicity over time with CPS183, as opposed to the other talc samples, in both cell types also suggest the importance of mineralogic differences as the size distributions of CPS183 and S157 are similar. Since CPS183 fibers are mainly talc, while S157 contains more talc/amphibole and amphibole, mineralogical variability may affect the responses of cells to cytotoxic effects of talc. Nonfibrous particles such as quartz may also play a role in cytotoxicity of the talc samples since CPS183 higher number of quartz particles, a mineral known to be cytolytic (Mossman and Begin, 1989).

Data presented here lend increased uncertainty to the concept that long thin fibers [length >8 μm, width <0.25 μm, i.e., the Stanton hypothesis (Stanton *et al.*, 1981)] are the predominant factors predicting tumorigenicity and fibrogenicity (Mossman *et al.*, 1990; Health Effects Institute, 1991). In his elegant and comprehensive studies, Stanton and colleagues implanted two samples of fibrous talc (No. 6 and No. 7 samples) into rats. One of us (AW) examined talc No. 6 and found it to be similar in mineralogy, size distribution, and morphology to FD14, and little is known about No. 7 except that it was obtained from the Gouverneur District. Neither talc produced significant excesses in pleural sarcomas despite the fact that the dose of fibers >8 μm in length and <0.25 μm in width in sample No. 6 was large enough to predict a tumor probability of >50%.

In summary, intrapleural injection studies in rats, epidemiologic investigations, and our *in vitro* work with fibrous talc here suggest caution in generalizing that durable fibers >5 μm or with aspect ratios approximating Stanton criteria are always more bioreactive and pathogenic. Our work is significant in that it supports reanalysis of the Stanton data by Wylie *et al.* (1987) and others (Oehlert, 1991; Nolan and Langer, 1993) and provides data implicating the importance of mineral type, rather than fiber length per se, in determining cellular outcomes associated with pathogenicity of mineral dusts.

ACKNOWLEDGMENTS

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AN EVALUATION OF THE EPIDEMIOLOGICAL EVIDENCE CONCERNING "TALC" AND MALIGNANCY IN HUMANS WITH SPECIFIC ATTENTION TO "TALC" AS PRODUCED BY THE GOUVERNEUR TALC COMPANY [A SUBSIDIARY OF THE R.T. VANDERBILT COMPANY INC] AT ITS MINES IN NEW YORK STATE.

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QUALIFICATIONS AND EXPERIENCE.

I received a Baccalaureate [BSc] degree in Geology and Chemistry at the University of London, England in 1966, a Master of Science [MSc] degree in Geological Sciences [Dean's Honours List] at McGill University in 1969 and a Doctor of Philosophy degree [PhD] in Epidemiology [Dean's honours List] at McGill University, Montreal, Canada in 1972. I am a Licentiate of the Royal Society of Chemistry [LRSC] and a Registered Occupational Hygienist [ROH] through the Canadian Registration Board of Occupational Hygienists. I have worked in the occupational and environmental health fields for more than 40 years. My curriculum vitae and list of publications are attached [APPENDIX A].

BACKGROUND.

The R.T. Vanderbilt Company Inc., through the Environmental Sciences Laboratory, Brooklyn College of the City University of New York, have requested that I undertake a review of the various epidemiological studies of workers employed by the Gouverneur Talc Company in New York State to determine if they support or otherwise the designation of talc from this deposit as a carcinogen. The following is my report on this matter.

DEFINITIONS

The "Draft Background Document" for "Talc Asbestiform and Non-Asbestiform" is not clear in its definition of "Talc Asbestiform". The summary statement on page iii and v refer to: "Talc containing asbestiform fibers". Does this mean talc containing asbestos fibres or talc containing non-asbestos asbestiform fibres, both or talc containing elongated particles with aspect ratios exceeding 3:1, but with diameters less than about 3-4 micrometres? On page 5, the document notes "Natural talc deposits and commercial talc products are found to contain serpentines (chrysotile, antigorite and lizardite) and fibrous and non-fibrous amphiboles [Rohl et al 1976]. This form is also known as asbestiform talc, talc [containing asbestos] or talc containing asbestiform fibres."

If this is the definition being adopted by NTP, and if the term fibrous amphiboles in this definition refers to

amphibole asbestos, then, it is not clear why a separate nomination would be needed for talcs containing asbestos as the asbestos minerals have already been classified as carcinogenic. The presence of asbestos fibres in a talc does not render the mineral talc carcinogenic, but the mixture, dependant on the asbestos fibre type, fibre dimensions and percentage may increase cancer risk.

On the other hand, the "Draft Background Document" cites studies of GTC miners and millers in support of the nomination. Because of this, it must be assumed the author of the "Draft Background Document", RG1 and RG2 consider that these workers are exposed to "talc asbestiform". This presents a definition problem because there is expert mineralogical opinion that GTC workers are not exposed to asbestos although they may be exposed to cleavage fragments meeting the OSHA definition of a fiber, talc fibers and transitional fibers. I will leave this technical issue to those who have studied the ore, product and airborne dusts and in this submission, the term "GTC talc" will refer to the mixture of minerals produced as "talc" by the Gouverneur Talc Company from its New York Deposit and include all its components. When the unqualified term "talc" is used, it refers to the minerals and mineral habits present in a particular talc.

CRITERIA TO DECIDE WHETHER GTC TALC IS CARCINOGENIC

According to the background document, listing a substance as a "known human carcinogen" requires that there is sufficient evidence from studies in humans, "which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer". The criteria for listing a substance as "Reasonably anticipated to be a human carcinogen" is "There is limited evidence of carcinogenicity from studies in humans, which indicates causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded" or there is sufficient evidence of carcinogenicity from studies in experimental animals.

The report of the Carcinogens review group RG1 concluded that talc containing asbestiform fibers is known to be a human carcinogen and RG2 concluded that talc containing asbestiform fibers is reasonably anticipated to be a human carcinogen. Both conclusions are based largely on studies of talc miners and millers and "asbestos" exposure is mentioned.

In order to correctly interpret the results of the GTC worker studies, it is important that any pre-conceived notion that asbestos may be present and must be responsible for any increased respiratory cancer risks be set aside. The evidence for or against classifying talc as produced by GTC as a carcinogen should rest on the evidence from the studies of talc workers and determine if the exposures are causally associated with increased risks of respiratory cancer or that a causal interpretation is credible. The experimental data are part of this evaluation. Experimental data will not be discussed in this report, but must be considered in relation to plausibility. Some of the criteria which are often used in deciding on causality in epidemiological studies are listed in APPENDIX B.

LUNG CANCER RISKS IN GTC WORKERS.

The first study to include some GTC workers was a proportional mortality ratio [PMR] study of miners and millers in New York State who had had 15 or more years of exposure to talc dust in 1940 or between 1940 and 1965 [Kleinfeld et al 1997]. Follow-up began in 1940 which was, seven years before GTC began production. It is evident that the number of GTC workers included in this cohort would have been very limited. The study indicated a high PMR from lung cancer, but this needs to be interpreted with considerable caution as 30% of deaths in the cohort were due to pneumoconiosis or complications, a cause of death not common in the referent US general population. It was also based on the US proportional mortality for only one year. The role of smoking was not assessed and the characterization of the dusts to which the workers were exposed was general with no reference to mineral habit. All cases of lung cancer had initial exposure before 1945 when wet drilling was introduced, but "there was no evidence to indicate that there was a direct relationship between duration of exposure prior to the onset of wet drilling and the occurrence of pulmonary carcinoma". In retrospect, this is perhaps the first indication that the lung cancer risk may not be exposure related.

Brown et al [1980] reported on the NIOSH study. This study has been well critiqued [eg: Gamble 1985] and there is little value in revisiting this cohort of 398 workers as the study has now been updated and superseded by more recent information. For the record, the study did not examine exposure-response or take smoking into consideration.

Stille & Tabershaw [1982] studied 744 men employed January 1 1948 through December 31 1977. After exclusions for lack of information, 655 white male talc workers were available for analysis. The mortality from lung cancer compared to US white males was not statistically significantly increased [SMR = 157 Observed = 10] in men who worked at the plant [assumed to be GTC] but was statistically significantly greater [SMR=214 observed 8] in men who worked elsewhere before joining the plant. Incidentally, most of the criticisms levelled at this report by IARC and noted the "Background Document, page 20", also apply to the original NIOSH study in 1980 and Vermont study by Selevan et al [1979] as none of these studies took account of smoking or involved an examination of exposure-response.

Lamm et al [1988] reported on what appears to be essentially the same cohort as studied by Stille and Tabershaw [1982]. They found that 425 had worked for GTC for more than one year and 280 for less than one year. They categorized each job on the pre-employment history by likelihood of increasing lung cancer risk. The overall mortality from respiratory cancer was elevated [SMR = 240], but as reported by Stille & Tabershaw [1982], the lung cancer mortality was concentrated in men employed for 1 year or less [SMR=317] and concentrated in those who had worked in jobs carrying a lung cancer risk before joining GTC [SMR=316]. The respiratory cancer risk was lower in persons with longer duration of employment. Importantly they noted that there were no differences in the initial jobs assignments at GTC for workers who left within 1 year and those who stayed. This observation does not support the hypothesis put forward by Brown et al [1980] that the excess lung cancer risk is due to short high exposures encountered by short-term workers. This study did not have smoking information available.

In 1990, Brown et al [1990] expanded the original NIOSH cohort definition, increasing the cohort size to 710 white males employed at any time between 1947 and 1978, and updated the vital status to December 1983. The overall SMR for lung cancer was still elevated [SMR 207] compared to the experience of US males. However, the authors found that the SMR for workers with 20 or more years of latency and less than 1 year tenure was 357 [CI: 154, 704], while those workers with more than 20 years of latency and more than

1 year of tenure had an SMR = 178 which was not statistically significant; ie could have occurred by chance. Again, detailed smoking histories were not available. This difference in risk between the short term and long term employees would not be the pattern anticipated if the lung cancer excess were related to the GTC exposures unless the short-term workers had higher talc exposures than longer term workers. The study by Lamm et al [1988] did not suggest that this was a likely scenario. Again an exposure response study was not undertaken. This report was not cited in the Background Document.

The reason for the excess lung cancer reported by Kleinfeld et al [1967] and Brown et al [1980] was not known in 1986 when IARC [1987] deliberated on talc. It was probably inferred because the studies involved talc miners and millers and minerals such as "tremolite and anthophyllite [asbestiform and nonasbestiform habits] were mentioned. In fact, there had been no exposure-response studies and smoking had not been taken into account. The results of the larger NIOSH study [Brown et al 1988] or the results of studies discussed in the following paragraphs were not available to them.

Four years after the IARC [1987] review of Talc, the interpretation of the data were still being debated [Morgan & Reger 1990]. However by that time, it was known that:

> There was an increased mortality from lung cancer in GTC cohort members. This was observed by all researchers, but this should not be surprising as they were studying the same or overlapping cohorts.
>
> The excess mortality from lung cancer was greater in the workers employed for less than 1 year than in those employed for more than 1 year.
>
> The excess did not seem to be due to different initial job assignments for workers with short and long term employment.
>
> The excess lung cancer mortality seemed to be explained in part by prior employment in other "cancer risk" industries.

Since 1990, two studies have become available which are extremely important in understanding the epidemiological studies and are the only ones available which provide information on which to determine whether or not the excess lung cancer in GTC workers is associated with exposure to GTC talc.

The first study is the nested case-control study reported by Gamble [1993]. The 22 cases selected for study were those dying with lung cancer in the NIOSH update cohort of 710 white males studied by Brown et al [1990]. There were 3 controls per case, matched as closely as possible for date of birth and date of hire. Controls had to survive the case. Work history information was obtained from GTC files and tobacco use and additional work history information was obtained from the cases and controls or from relatives and friends. Smoking status was obtained for all cases and controls. A panel of epidemiologists and occupational hygienists classified the non-talc jobs held by the cases and controls as to the risk of lung cancer associated with them on a scale of probable [score 3], possible [score 1], or none [score 0]. The composite score was developed for each man by multiplying the score for each job by the time spent in that job and summing the results over all jobs. The total scores were broken into 4 categories and estimates of the odds ratios for each category were then used to determine if this index of work at other than GTC jobs increased the risk of lung cancer. The author analyzed the data with and without non-GTC talc experience and took latency into account. The important findings were as follows:

- In an analysis to determine lung cancer risk in relation to smoking, the odds ratio in smokers was 5.71 when the odds ratio for ex-smokers and no-smokers was set at 1.00. This risk was 6.55 in persons smoking more than >40 cigarette/day smokers. There were no no-smoking lung cancer cases. It is evident that smoking has the potential to play an important role in the lung cancer experience of these workers.

- All workers had had non-GTC jobs. However, there was no increasing trend in the odds ratios for the risk of lung cancer with the "non-talc employment" indices. This indicates that workers were not dying of lung cancer as a result of working elsewhere. It is unfortunate that the author did not also carry out this analysis with a 20 year latency, to determine whether the most relevant employment in non-GTC jobs was associated with an increased lung cancer risk as this was suggested by previous research. For this reason the possibility that work elsewhere contributed to the lung cancer risk cannot be totally excluded.

- When only smokers were analyzed, the case control studies showed that the odds ratios for lung cancer risk by tenure at GTC with and without a 20 year latency showed no increasing trend and odds ratios remained below 1.00 as tenure increased. In fact the results consistently suggest that the risk of lung cancer decreased significantly with tenure at the plant. This pattern did not change in any important way when non-GTC talc exposure were added. This is not consistent with exposures at the plant being responsible for the apparently increased risk of lung cancer in the cohort unless tenure does not reflect exposure.

- The decreasing pattern of risk with increasing tenure would occur if the risk of the short tenure workers was elevated [for whatever reason]. The fact that it was increased was suggested in previous studies. In this regard it is important to note that Gamble did analyze the data excluding men with less than 20 years latency and less than both 1 year of tenure and men with less than 3 months of tenure. In the latter case, 11 lung cancer cases were removed. The case-control analysis restricting the analysis to smokers and setting the odds ratio for the 3 months - 5 years of employment at 1.0 showed that workers employed 15-34 years with more than 20 years since first employment had an odds ratio of 0.73.

The use of tenure as a surrogate for exposure has limitations. First, if there are non-exposed workers, tenure assumes exposure. Second, if there are large variations of exposure over time, tenure would not reflect these and this could affect the tenure-response relationship observed. Further the numbers become small [9 cases] when the short term workers are excluded. In spite of these limitations, the absence of an increasing trend of lung cancer risk with increasing tenure after a latency of 20 years and after eliminating short term workers is not supportive of a GTC employment etiology.

The question now remains as to whether the dust exposure of workers in the GTC mine and/or mill are associated in any way for the increased risk of lung cancer. The second study attempts to answer this question [Delzell et al 1995]. It is unfortunate that this study has not been published. However, it was reviewed by 4 reviewers and their collective comments are available [Boehleke 1994].

In this study, individual cumulative respirable dust exposures were estimated for all GTC cohort members. These estimates were based on a job-exposure matrix. This consisted of an average respirable dust concentration in each work area and calendar year for the period 1948 through 1989. Historical dust

concentrations exposures in various work areas by time periods were rated by a knowledgable panel of GTC employees. Special dust sampling surveys were conducted and paired respirable dust and dust count samples collected and used to convert historical dust count data to gravimetric respirable dust concentrations.

Baseline dust concentrations were based on the results of the special survey and a NIOSH survey. Past dust concentrations were then estimated by weighting baseline concentrations by the scores developed for the various time periods. These estimated past concentrations were then validated against historical dust measurements. It appears that a carefully considered approach was used to obtain respirable GTC talc exposure estimates which could be used to develop individual exposures for use in evaluating exposure-response.

The cohort consisted of 818 white men who worked for at least 1 day at the GTC from 1948 through 1989 and who had known birth and employment dates. The follow-up period was January 1 1948 through December 31 1989. There were 46 men with no work history who had a median duration of employment of 0.19 year. Their exclusion would not impact the risks of longer term workers. Twenty eight percent of the cohort were deceased. Causes of death were available for 222 [98%] of the 225 deaths. It should be noted that 344 [42%] of workers worked for <1yr and 521 for <5 years.

Compared to US white men, the cohort had an SMR from all causes of 141 [95% CI=123-161]. Excess mortality was observed for several causes of death including circulatory diseases, non-malignant respiratory diseases and cancer [SMR = 154, 115-200, observed = 54]. The cancer excess was mainly due to lung cancer [SMR 254, 173-361 observed = 31]. This finding of an overall excess of lung cancer is similar to that of earlier investigators. The use of local rates did not change the results.

For lung cancer, 22 of the 31 deaths occurred in men with less than 5 years of employment. The SMR did not rise with increasing length of employment within any category of years since hire. However, a statistically significant excess was present for the group of workers with less than 5 yrs of employment and more than 20 years since hire. For workers with more than 5 years of employment with 20+ years since hire there was a non statistically significant increased risk of lung cancer [SMR = 215, 86-442, observed = 7]. Thus, in the 20+ years since hire workers, the SMR of those employed for a short period exceeded that of the longer term workers. This argues against a GTC work related factor being responsible for the observed increased risk of lung cancer.

The overall excess of lung cancer was concentrated in men employed in the underground mine [SMR = 440, 262-695, Observed = 18]. In fact the excess lung cancer mortality was in men who were only employed in the mine [SMR = 473, 280-747, Observed =18].

In contrast, there was only a small non-significant increase in lung cancer mortality in mill workers [SMR = 139, 56-287, observed = 7], a group with similar exposures to the underground workers. Such an increased risk might be explained by smoking [but this cannot be determined as smoking data were not available]. NMRD was in excess in millers [SMR = 321] and in underground miners [SMR = 349]. If talc were responsible for the excess lung cancer, one would have expected the same pattern of mortality of lung cancer mortality in both the millers as well as miners.

Lung cancer mortality was also increased among men who were <u>exclusively</u> employed in unexposed jobs [SMR= 443, 87-1264, Observed = 3]. This again, on small numbers, argues against a GTC talc etiology for the lung cancer excess.

When exposure-response was examined, there was an inverse relationship between lung cancer mortality and estimated cumulative dust exposure. The relative risk [RR] was 0.66 [CI: 0.32-1.4] for men with cumulative exposures greater than or equal to the median exposure versus those below the median value. Analyses by quartiles also suggested an inverse association. When men with less than one year of GTC employment were excluded, the RR for the same comparison was 0.62 [CI: 0.22-1.8].

All 7 subjects who had reportedly died with pneumoconiosis or interstitial lung disease had cumulative exposures above the cohort's median value. This suggests that the cumulative index of exposure is relating sensibly to mortality from pneumoconiosis, but that there is no evidence that the cumulative exposure to GTC talc relates sensibly to the lung cancer risk observed in this industry.

Two deaths from mesothelioma were reported. The one mesothelioma case had only 15 years between hire and death. In the Quebec chrysotile miners and millers there was not a single case with less than 20 years from first exposure to death. The other mesothelioma case had worked for several years on the construction of another talc mine before his GTC employment. At GTC he worked as a draftsman during mill construction in 1948-49 and worked outdoors. After leaving GTC he worked in removing, installing and maintaining oil heating systems where the possibility of asbestos exposure cannot be excluded. Thus, neither case is likely linked to GTC employment.

In addition to examining the relationship between cumulative respirable dust exposure and lung cancer mortality [not done in any other study], this cohort was larger than the original and updated NIOSH studies; the follow-up period was longer by 7 years than the most recent NIOSH study; analyses were performed using national, regional and local rates; internal comparisons were done and a major effort was undertaken to ensure that the cohort was complete using IRS 941 records. Unfortunately, tobacco consumption was not taken into account and is a weakness in hat we do not know whether the persons with low cumulative exposures smoked more than those with high cumulative exposures. I think this is unlikely, based on my experience with other industries, but we do not know.

While the authors note that the use of an inappropriate index of exposure is another potential weakness, it would reasonably be expected that a higher respirable dust exposure would mean a higher exposure to any pertinent carcinogenic constituent of the GTC talc if there were any, so while at most, reducing the slope of an exposure-response relationship, it would be highly unlikely to reverse it. It is unfortunate that Delzell et al did not gather smoking or non-GTC employment information and carry out a nested case-control study to determine if they offer a possible explanation for the decreasing risk of lung cancer with increasing cumulative GTC talc dust exposure.

INFORMATION FROM OTHER STUDIES

There are other studies, some of which were not evaluated by IARC which are pertinent to the issue of respiratory cancer risks associated with talc.

Rubino et al [1976] followed 1514 miners and 478 millers in Italy. They separated the miners and millers because they considered the mine air dust to include certain amounts of inhalable silica. The talc was reasonably well characterised with no amphibole or chrysotile asbestos detected "in any amount in rocks and in inclusions". Rubino et al examined the risk of lung cancer in relation to 3 categories of cumulative exposure levels and showed no increasing risk with either level of latency. They also did not find any

increased risk in miners compared to millers. The study used an external comparison population in the area and also internal comparisons. IARC expressed concerns about their comparison group. In a later paper [Rubino et al 1979] expected deaths were recalculated using Italian white male rates, which would have eliminated this concern. There was still a deficit of lung cancer in the miners and millers and no increase in risk with increasing cumulative exposure to "talc". This study does not support an increased lung cancer risk associated with their talc which contained quartz, muscovite, chlorite, garnet, carbonates [calcite and magnesite]. Talc or other fibers were not mentioned as present or absent.

Wergeland et al [1990] conducted a small study of 94 talc miners and 295 talc millers in Norway. Their talc was described as "non-asbestiform" talc with low quartz content. However, the talc contained trace amounts of tremolite and anthophyllite. Fibres were reported to have been detected near the "detection limit for optical microscopy" and low fiber content confirmed by electron microscopy. It is not known whether these were asbestos fibers or talc fibers. The main minerals in the talc deposit are talc and magnesite. In addition the ore contains magnetite, chromite, chlorite and antigorite with adjacent rocks containing serpentine, mica, feldspar, calcite and the amphiboles, hornblende and tremolite. Fibers, identified as tremolite, anthophyllite and talc were particles fulfilling the fiber definition of having a length: diameter ratio greater than 3:1. Smoking information was available. The numbers in the mine were too few to meaningfully interpret, but in the mill there was no excess incidence of lung cancer.

Selevan et al [1979] carried out a mortality study of what was described as "non-asbestiform" talc in Vermont. Quantitative estimates of "talc" exposure were not made, so the talc exposure-response relationships were not examined. It was of interest that there was a significant increase in respiratory cancer mortality in the miners but not in millers. It is perhaps relevant that if "talc" were responsible for the increased risk of lung cancer, then one would have expected to see the excess in both the millers and miners.

COMMENT

There seems to be little doubt that the overall lung cancer risk in the various GTC cohorts is elevated. On the other hand, virtually all the epidemiological evidence points away from the lung cancer increase being related to the GTC talc exposure. The excess lung cancer in the GTC cohort is present in miners but not in millers. Tenure and cumulative exposure, trend in a direction contrary to that expected if there were a link with GTC talc exposure. This trend holds when short term workers are excluded. One can only speculate on reasons for the high overall mortality and mortality from lung cancer. Smoking seems one likely candidate, but seems unlikely to explain some of the very high SMR's observed for underground miners. Miners encounter minerals which may entail exposures which are diluted with other dusts in the mill, so the exposure of miners is probably different from millers qualitatively. One possibility which has not been evaluated is whether workers were migrants. If this were the case, neither US or local rates would be appropriate and might provide spuriously increased SMRs.

CONCLUSION

1. NTP needs to carefully define what is meant by "Talc Asbestiform".

2. The reason for the overall excess lung cancer in cohorts of GTC workers is still not known. However, it is clear that a statistically significant excess of lung cancer is present in underground miners but not in millers. The lung cancer risk does not increase with increasing tenure or cumulative exposure to respirable GTC talc dust.

3. The evidence does not establish a link between GTC talc exposure and mesothelioma.

4. Collectively the currently available epidemiological studies of GTC workers do not support a causal relationship between GTC talc and respiratory cancer.

5. The currently available epidemiological studies of GTC workers do not support the premise that a causal relationship between GTC and respiratory cancer is credible.

6. In the absence of firm human data establishing a link between GTC talc exposure and respiratory cancer, biologic plausibility depends on an evaluation of the experimental data relating to GTC talc and its constituents. This has not been evaluated in this report.

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11-29-2000

Submission to the NTP regarding the 10th ROC Nominations: solicitations of Public Comment- "Talc Containing Asbestiform Fibers"

Brian Boehlecke MD, MSPH

These comments are based on my review of the results of medical surveillance examinations performed every 2 years on workers at the Gouverneur Talc Company. I enclose comments relevant to this solicitation which were previously submitted to the OSHA Docket H-033-d in 1990 as well as an update including the results of the examinations conducted in 2000.

I have continued to serve as an advisor to the Corporate Manager of Occupational Safety and Health of the R.T. Vanderbilt Company since the submission of comments to OSHA in 1990. I have thereby personally reviewed the chest radiographs of the workers at Gouverneur Talc company taken during each subsequent round of medical surveillance examinations.

In 2000, I reviewed the chest radiographs of 115 workers with exposure to the talc mined and milled at Gouverneur Talc Company. Findings were as follows.

Ten workers had findings which could be related to occupational exposure to talc. Six had definite pleural plaques and 2 had possible pleural plaques, all of which had been present on previous examinations and did not show progression. The length of time from first exposure to talc at Gouverneur Talc Company ranged from 21 to 35 years.

One man had possible irregular opacities (ILO Classification of profusion of 1/0) which had shown no change since 1994. He has had 31 years of exposure.

No evidence of lesions consistent with a malignancy was observed by myself or by the radiologist who performed the clinical readings of these films.

One man had a radiograph finding consistent with new pleural plaques. He had 26 years of exposure. Further medical evaluation of these findings by the worker's private physician has been performed. I have not seen the results of this evaluation but have been informed that nothing of clinical significance was found.

My interpretation of these findings is that the workers exposed to talc mined and milled at the Gouverneur Talc Company do have a risk for development of benign focal pleural thickening (pleural plaques) as has been demonstrated to exist for exposure to talc which has no associated "asbestiform fibers". The risk of development of plaques has been demonstrated to be related to the latency since first exposure and the men in this workforce with plaques have all had over 20 years since first exposure.

Only one man had any evidence of increased interstitial markings which could be consistent with a pneumoconiosis. These markings have not increased in profusion in the past 6 years despite continued exposure.

The medical surveillance results from workers at Gouverneur Talc Company available to me at this time continue to support the conclusion submitted to the OSHA docket in the 1990, i.e. the data do not indicate that the workers exposed to the talc at this facility are at risk for developing asbestos related pneumoconiosis. They do appear at risk for developing conditions shown to develop in workers exposed to talc not containing asbestos. With current occupational exposure levels, essentially no progression of pneumoconiosis related to cumulative exposure appears to have occurred in the men in this workforce for whom I have had serial radiographs to review.

April 23, 1990

Submission to OSHA Docket H-033-d
from BRIAN BOEHLECKE, M.D., M.S.P.H.

These comments are based on the results of my review of medical examinations performed on workers at the Gouverneur Talc Company (GTC) as part of the company's medical surveillance program and on my interpretation of pertinent medical literature.

In 1985 I reviewed the chest radiographs of 203 current workers at GTC who had been examined in 1984. I also tabulated the interpretations of the radiographs taken in 1982 which had been read previously by 2 other NIOSH certified "B" readers. Abnormalities were considered to be definitely present when at least 2 of the three readings agreed on the presence of the condition. For all workers whose 1982/1984 radiograph(s) showed an abnormality which might be consistent with a pneumoconiosis, I later reviewed all radiographs in the worker's file to determine when the abnormality was first detectable. The Company also abstracted each worker's occupational history from his employment application to determine whether any exposure to talc or other minerals may have occurred prior to hire at GTC. Results of the review of previous radiographs and work history are given in Table 1.

Parenchymal Opacities

There were 3 workers whose 1982/1984 radiograph(s) showed parenchymal changes consistent with pneumoconiosis (irregular linear opacities).

All 3 men with parenchymal opacities had had 10 or more years of occupational exposure to N.Y. State talc at other facilities before working at GTC. In all cases radiographic abnormalities were first detectable within 3 years of starting at GTC. For worker #110 the parenchymal opacities were definitely present on a film taken 3 years after hire (category 1/0) and were probably present on his initial radiograph at GTC which I interpreted as category 0/1. For workers #131 and #2002 the opacities were present on the first film taken after hire at GTC.

One additional worker had a question of parenchymal opacities on his 1984 film but the 1982 film was read as negative by both readers. Review of his 1978 film upon hire at GTC showed the same questionable appearance of opacities which had not changed on subsequent films. He is not shown on Table 1.

Localized Pleural Thickening (Plaques)

The consensus radiographic review identified seven other cases with only localized pleural thickening (plaques). Unlike cases with parenchymal changes, only one of these 7 men had reported previous occupational exposure to N.Y. State talc. The pleural changes were present on his film at the time of hiring at GTC. The onset of recognizable pleural thickening ranged from 7 to 23 years after hire in the men without previous exposure to talc.

One additional case of possible pleural thickening was reviewed although there was no consensus on the 1982/1984 films. By viewing previous films I concluded he probably did have a pleural plaque on his hemidiaphragm which was first detectable 20 years after hiring at GTC. He had 13 years of occupational exposure to N.Y. State Talc prior to working at GTC but is not shown on Table I since there was not a consensus about the findings.

Follow-up

I have continued to review the radiographs of the workers at GTC on subsequent rounds of medical surveillance examinations done each 2 years. None of the men with abnormalities described above have shown significant radiographic progression since the 1984 examination.

In early April 1990 I reviewed the current radiographs of 55 men who have worked 15 or more years at GTC in jobs with potential exposure to talc and who had no other reported occupational exposure to talc. Four of these men (7.3%) had definite pleural plaques and 2 (3.6%) had probable pleural plaques. None had definite parenchymal opacities consistent with a pneumoconiosis. The years of exposure were 16, 25, 31, and 40 for the men with definite plaques and 20 and 24 for those with probable plaques.

Interpretation

My interpretation of these observations is as follows:

1. The parenchymal opacities detected to date appear to be associated with exposures prior to working at GTC. They were detectable within 3 years or less of beginning work at GTC which would be a very short latency unless exposures were very high. This seems unlikely since employees without prior exposure have not demonstrated similar onset. All three men had had 10 or more years of previous exposure which would be sufficient time for the onset of a pneumoconiosis which would become clinically manifest thereafter.

2. There is no evidence from these data that additional cases of parenchymal pneumonconiosis are developing in the GTC workforce under current conditions or that significant progression of previously detected cases is occurring.

3. The medical surveillance examinations should be continued to monitor the workforce for possible new cases or progression of established cases.

4. Some men appear to have developed pleural plaques in association with occupational exposure at GTC without recognized exposure to other N.Y. State talc. This is evidenced by the review of the 1982/1984 radiographs and those of the current workers with 15 or more years work at GTC.

Discussion

The finding of an association between plaques and occupational exposure to this talc does not necessarily imply that the talc must be contaminated with asbestos. In some population surveys, only a minority of persons with pleural plaques had recognizable exposure to asbestos (1-3). Occupational exposures to other talcs which were not associated with any asbestiform minerals have also been associated with a prevalence of pleural plaques higher than that found in a control population. Importantly, the prevalence of plaques in the workers exposed to these nonamphibole containing talcs was similar to that found at GTC.(4).

Moreover, the finding of pleural plaques does not by itself imply that the work environment carries the same risk for other adverse health effects associated with exposure to asbestos. Pleural plaques are not premalignant lesions and are generally not considered to be markers of an increased risk for malignancy beyond that which would have been associated with a given exposure in the absence of the development of plaques (5-7). Workers with occupational exposure to asbestos and radiographically detected pleural plaques have not been shown to have an increased risk of developing bronchogenic carcinoma relative to that of workers with similar exposure to asbestos but no plaques (8). Also, plaques are not uniformly associated with pulmonary parenchymal fibrosis (5). Even on careful pathologic examination, only a minority of persons with pleural plaques showed interstitial fibrosis; the proportion with fibrosis was not different from that in matched controls without plaques (9). Therefore, the presence of plaques alone does not necessarily imply the presence of the risks which are associated with exposure to asbestos.

Nevertheless, the risk of development of a parenchymal pneumoconiosis ("talcosis") has long been recognized to be associated with over exposure to airborne talc. I believe that the Gouverneur Talc Company recognizes this risk and has informed its employees and customers of it.

Previous studies of N.Y. State talc miners showed that excess non-malignant respiratory disease occurred in association with the very high dust levels present before modern dust control methods were implemented. The presence of parenchymal opacities on chest

radiographs taken shortly after hire at GTC in men with prior exposure to talc is consistent with this observation. However, the radiographic reviews described here suggest that the risk is much less for workers exposed to current conditions at GTC.

Conclusion

Current employees at Gouverneur Talc Company do not appear to have the same risk for pneumoconiosis as was present for men with exposure to the much dustier work environments of the past. Adequate medical surveillance and dust control are still vital to the health of the workforce and are continuing. Characterization of the radiographic findings in GTC workers as indicative of "asbestos related diseases" (OSHA proposed rule page 4947, paragraph 8) with the implication of the presence of excessive risk of adverse health effects under current conditions is not supported by the data presented here.

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Table 1

Workers with abnormalities consistent with penumoconiosis in 1982/1984

	Worker #	Radiographic Abnormality in 1982/1984	Years* of talc exposure prior to hire at GTC	Years from hire at GTC to first evidence of the radiographic abnormality
1.	110	parenchymal,pleural	10-12	0-3
2.	131	parenchymal,pleural	12-14	1
3.	2002	parenchymal,pleural	10-12 +10 chemical co	2
4.	392	pleural only	none	7
5.	263	pleural only	none	20
6.	56	pleural only	none	12
7.	231	pleural only	none	12
8.	85	pleural only	none	20
9.	111	pleural only	none	23
10.	1655	pleural only	13-15	0

*The range of years is given because the exact portion of the years worked for the first and last years of previous employment was not available.

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TESTIMONY REFERENCES

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AN EPIDEMIOLOGICAL–INDUSTRIAL HYGIENE STUDY OF TALC WORKERS

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Abstract—Two-hundred and ninety-nine (299) miners and millers exposed to talc from Montana, Texas and North Carolina were examined in a cross-sectional study of respiratory systems, lung function and chest X-rays. Work histories were taken from personnel records. Personal respirable dust samples were collected for all jobs. Cumulative exposure was calculated by summing the products of the estimated exposure for each job and the length of time worked in that job. The average time worked was 7, 6, and 10 yr and the average exposure (cumulative exposure/total time worked) was 1.2, 2.6, and 0.3 mg m^{-3} in Montana, Texas, and North Carolina respectively. Free silica content of bulk samples was low (below the limit of detection in Montana, 1.5% in North Carolina, and 2.2% in Texas). No fibres were observed under the light microscope. Under the transmission electron microscope, tremolite and antigorite fibres (0.5–3 μm length) were observed on the Texas talc, acicular particles (aspect ratios 5–100 to 1 and some diameters less than 0.1 μm) in North Carolina talc, and no fibres in the Montana talc. The differences in age-corrected symptom prevalences (cough, phlegm, and dyspnea) between regions, when compared by both smoking categories and exposure groups were not statistically significant. None of the symptoms showed any consistent association with years worked or cumulative exposure. Symptom prevalence was not elevated compared with blue collar workers and potash miners. There were two cases (less than 1%) of grade 1 small rounded opacities. The prevalence of bilateral pleural thickening among workers 40 yr or older was 7, 15, and 14% in Montana, Texas, and North Carolina and 0, 0, and 10% in those less than 40 yr of age. No non-smoker had bilateral pleural thickening and there was a slight tendency for the prevalence to increase with exposure. Workers with bilateral pleural thickening had lung function 10–20% below workers with no pleural thickening. They had also worked twice as long (13 yr) and an average of 13 yr between beginning exposure to talc and the time of the X-ray. The prevalence of bilateral pleural thickening was elevated in workers 40 yr or older compared with blue collar workers and potash miners. There also were no demonstrated differences in prevalence when the subjects in this study were compared with workers exposed to New York talc which contains tremolite and anthophyllite. For the entire study population no association of reduced lung function with exposure was demonstrated. After adjustments for age, height, and smoking, FEV_1 and FVC were not detectably different compared with potash miners and blue collar workers; however, flow rates at low lung volumes were reduced 4–19%. There was little difference among these three populations in age coefficients for FEV_1, FVC, and flow rates by smoking category. Predicted pulmonary function of the study population was elevated compared with New York talc workers.

There were no significant increases in symptoms or pneumoconiosis among the study group of talc workers nor significant reductions in lung function; however, the average amount of time worked by the study group was short. Bilateral pleural thickening was significantly increased and was associated with decreased pulmonary function. The prognostic significance of the pleural thickening awaits prospective evaluation.

INTRODUCTION

TALC is a mineral with a wide variety of uses in paint, paper, ceramics, cosmetics, roofing products, textile material, rubber, lubricants, corrosion proofing compositions, fire extinguishing powders, cereal polishing, water filtration, insecticides, to name a few. Pure talc is a hydrated magnesium silicate, but the talc found in nature has a quite variable chemical composition. The mineral contaminant in talc of most concern is

asbestos. Such contaminated talc can produce a clinical condition resembling that seen on exposure to asbestos. The hazard from exposure to 'pure' talc free of asbestos contamination is less well documented. The purpose of this study was to ascertain the effects on the respiratory system (symptoms, lung function, radiographic) of exposure to talc dust thought to contain no asbestos.

Talc workers in seven mines and eight mills in Montana, Texas and North Carolina were studied in this cross-sectional study. The mines in Montana and Texas were typical open pit operations, while the underground mine in North Carolina employed square set timbers and stopes. In each mine examined, typical mucking techniques were employed. ANFO (ammonium nitrate and fuel oil) was the most common type of explosive used.

Following extraction of the ore, the talc was hand sorted to remove extraneous material, as in Montana, or went directly from the mine to the primary crusher. Froth flotation and heavy metal separation techniques were not used in any facility examined. Following initial crushing, the talc might be calcined, as in the case of ceramic grade talcs, before being ground using dry grinding methods into the final product. Once the talc was ground to the appropriate mesh size, it was sterilized as in the case of pharmaceutical grade talc and then shipped in bags or bulk.

The specific questions being addressed in this paper are: (1) What is the prevalence of symptoms and abnormal radiographic findings by exposure categories within each region? What is the association of exposure with reduced lung function? (2) After adjustment for confounding variables, how does the study population compare with other mining and non-mining populations in the prevalence of symptoms, abnormal radiographic findings and mean lung function?

METHODS

The study of population consisted of workers who mined and milled talc from three regions of the United States: Montana, Texas and North Carolina. Although several different companies may be involved, the results for each region were combined and analysed. Since there were no demonstrated differences among the regions by age, smoking and exposure groups, the combined results of all regions are presented in this paper. Over 90% of the workers participated in the study.

The industrial hygiene portion of the study took place in every facility in which the morbidity data were collected. Personal respirable breathing zone samples were collected utilizing a Model G MSA* pump and a 10 mm nylon cyclone. These samples were analysed for respirable dust and percent quartz and cristobalite. The quartz and cristobalite analysis was done by X-ray diffraction (NIOSH, 1977). Time weighted averages (TWA) were obtained for each job classification at each facility. General area dust samples were collected on open face cellulose acetate filters and were analysed by atomic absorption for iron, manganese, calcium, aluminium, zinc and nickel (NIOSH, 1977).

From each ore body airborne dust samples were collected on open face cellulose acetate filters and analysed by phase contrast microscopy for the presence of fibres

* Mention of brand names does not constitute endorsement by the USPHS.

(NIOSH). Analysis for fibrous tremolite and anthophyllite was done on bulk and airborne dust samples utilizing analytical electron microscopy (NIOSH, undated). Bulk samples from each ore body were analysed for calcite and dolomite by X-ray diffraction (NIOSH, 1977).

All workers were administered either a Spanish or English version of the British Medical Research Council respiratory questionnaire by trained interviewers. Non-talc work histories were obtained in the interviews; work experiences at the talc facility were obtained from company records. Standard postero-anterior chest radiograms were read by three 'B' readers using the ILO U/C 1971 scheme. The films were read independently without knowledge of age, occupation or smoking history. The median of the three readings (i.e. the middle number) was used for analysis. Flow volume curves from a minimum of five forced expiratory manoeuvres were obtained and recorded on magnetic tape using an Ohio 800* rolling seal spirometer. Values from the maximum envelope were used for analysis. Sputums were collected on workers ≥ 35 yr of age. Personal environmental samples were collected on day shift workers and were used to estimate talc dust exposure for each job. This estimate was then used to calculate cumulative talc dust exposure by multiplying job exposure by time and adding the results. The association of lung function and exposure (cumulative exposure and years worked) was analysed by multiple regression. Years worked was divided into < 5, 5–9, and ≥ 10 yr worked categories for analysis of symptoms and pleural thickening. Cumulative exposure was the estimate of total exposure to respirable particulate over all years employed and was divided into low (< 2 mg m^{-3} × years), medium (2–6 mg m^{-3} × years) and high (> 6 mg m^{-3} × years) exposure groups for analysis of symptoms and pleural thickening. Differences by region and department (classified according to whether the majority of work was done in the mine, mill, crayon plant or other) were also estimated.

The prevalences of selected symptoms and pleural thickening were compared with mining and non-mining populations after indirect adjustment for smoking and using the age distribution of all populations (Fleiss, 1973). Prediction equations were calculated for each smoking category of the comparison populations. The observed lung function of each worker from the study population was compared with the predicted of the appropriate smoking category of the comparison population. The percent predicted lung function from all smoking categories and regions were then combined. Female prediction equations were available for only the blue collar comparison populations. Percent predicted lung function comparisons with the mining populations are therefore for males only.

RESULTS

Environmental results

Respirable dust exposure was highest in Texas and lowest in North Carolina, and mill dust levels were higher than mine dust levels in all regions (Table 1).

Montana talc had the lowest concentrations of trace metals of the three regions examined. Concentrations were slightly higher in North Carolina. Texas talc differed

* Mention of brand names does not constitute endorsement by the USPHS.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE TALC WORKER POPULATIONS BY REGION

		Montana	Texas	North Carolina
n		177	71	51
Age	(SD)	34.9 (11.5)	38.0 (13.7)	43.1 (12.6)
Height (cm)	(SD)	175.5 (8.8)	173.0 (6.9)	172.5 (8.3)
Years worked	(SD)	6.6 (6.3)	5.5 (5.7)	10.1 (8.6)
Cumulative exposure [(mg m^{-3}) × years]	(SD)	5.9 (7.6)	11.3 (45.1)	3.0 (4.8)
Average exposure (mg m^{-3})	(SD)	1.21 (0.94)	2.64 (7.12)	0.28 (0.33)
Geometric mean of current respirable dust samples (mg m^{-3})	(GSD)	0.86 (0.77)	1.08 (0.72)	0.21 (0.86)
Mine (95% CI)		0.66 (0.85–1.41)	0.45 (0.18–0.75)	0.14 (0.07–0.31)
Mill (95% CI)		1.1 (0.47–0.92)	1.56 (0.96–2.54)	0.26 (0.13–0.51)
Non-smokers	(%)	33	20	21
Ex-smokers	(%)	21	27	17
pack years	(SD)	15.7 (17.9)	13.3 (20.7)	18.2 (16.5)
cigarettes/day	(SD)	23.0 (15.0)	12.0 (14.0)	21.4 (15.7)
Smokers	(%)	45	54	62
pack years	(SD)	17.9 (16.9)	14.3 (19.7)	23.7 (21.8)
cigarettes/day	(SD)	20.4 (11.0)	14.5 (11.1)	20.4 (10.0)

most significantly from the other regions by its extremely large concentration of calcium, as indicated by a much larger percentage of dolomite (13 compared with 3 and 1%) and a slightly larger percentage of calcite (1 compared with <1 and 0%) than the other two regions. Silica content of bulk samples of Montana talc was below the limit of detection ($<0.8\%$), 1.45% in North Carolina and 2.23% in Texas. Respirable dust samples revealed the silica content in Montana and North Carolina to be generally below the limit of detection (0.04 mg m^{-3}). The Texas talc had slightly higher levels of respirable silica (0.09 mg m^{-3}) (Table 2).

No fibres were detected in any of the regions by light microscopy utilizing phase contrast techniques. Analysis of bulk samples from each region utilizing analytical transmission electron microscopy revealed no fibres in any samples of Montana talc. Two fibrous minerals were identified in the Texas talc: tremolite and antigorite. Antigorite, a serpentine mineral, was the main constituent. The fibres of both minerals ranged from 0.5 to 3.0 μm in dia. and 4 to 30 μm in length. The morphology of the North Carolina talc was identified as acicular. The acicular particles had aspect ratios ranging from 5–1 to 100–1, with some dia. <0.1 μm, and may have resulted from mechanical destruction of talc plates.

Demographic characteristics

All Texas talc workers were male, while about 20% of the Montana and North Carolina workers were female. The North Carolina population had the highest proportion of smokers (62%) and lowest proportion of ex-smokers (17%). The highest proportion of non-smokers (33%) and lowest proportion of smokers (46%) were in Montana. Pack years ranged from 13 to 24 and cigarettes smoked/day from 12 to 23 in the three regions. Montana workers were on average 8 yr younger, 3 cm taller, had worked 3.5 yr less and had 2.9 mg m^{-3} yr more cumulative exposure than the workers

TABLE 2.

mg m^{-3}	
Iron	
LOD	
Manga	
LOD	
Calciur	
LOD	
Alumin	
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Zinc	
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Nickel	
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* LOD =

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Symptoms and radiograp

Tables 3–6 summariz
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The overall prevalenc
age. Overall, smokers had
no apparent association

The overall prevalenc
regions and smoking cate
total population. There
(Table 5).

LATIONS BY REGION

	North Carolina
	51
	43.1 (12.6)
	172.5 (8.3)
	10.1 (8.6)
	3.0 (4.8)
)	0.28 (0.33)
)	0.21 (0.86)
'5)	0.14 (0.07–0.31)
54)	0.26 (0.13–0.51)
	21
	17
)	18.2 (16.5)
)	21.4 (15.7)
	62
)	23.7 (21.8)
)	20.4 (10.0)

TABLE 2. METAL AND MINERAL COMPOSITION OF BULK SAMPLES BY REGION

	Montana	Texas	North Carolina
mg m^{-3}			
Iron	0.05	0.5	0.05
LOD*	0.01	0.1	0.02
Manganese	<0.01	<0.08	<0.02
LOD	0.01	0.08	0.02
Calcium	0.05	8.0	0.05
LOD	0.03	0.2	0.02
Aluminium	0.2	0.4	0.2
LOD	0.1	0.2	0.04
Zinc	<0.01	0.03	<0.02
LOD	0.01	0.08	0.02
Nickel	<0.01	<0.08	<0.02
LOD	0.01	0.08	0.02
Percent			
Calcite	<1	1	0
(range)	(0–0.8)	(0–3)	0
Dolomite	1	13	3
(range)	(0–3)	(7–20)	(1–4)

* LOD = Limit of Detection.

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of smokers (46%) were in
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e exposure than the workers

in North Carolina. Mean values for these parameters in Texas were not demonstrably different from those for Montana and North Carolina. Average exposure (cumulative exposure divided by years worked) was less in North Carolina than in the other two regions (Table 1).

There was one case each in Texas and Montana of grade 1 small rounded opacities. This number is too small to analyse further. There were no other radiographic interpretations of pneumoconiosis. Cytology on sputums collected from workers 35 yr of age or older were read as follows: 20% unsatisfactory, 60% normal cytology or regular metaplastic cells, 20% atypical.

Symptoms and radiography (internal comparisons)

Tables 3–6 summarize the prevalence of cough, phlegm, shortness of breath and pleural thickening by age, smoking and exposure. Regions were combined for presentation of these results as there were generally no statistically significant differences among the regions. If differences were observed they are noted in the text.

The overall prevalence of cough was 19%. The prevalence tended to increase with age and smoking (only the difference between non-smokers and smokers was significant). There was no apparent association with either exposure variable (Table 3).

The overall prevalence of phlegm was 23%. There was no consistent increase with age. Overall, smokers had a higher prevalence of phlegm than non-smokers. There was no apparent association with exposure (Table 4).

The overall prevalence of dyspnea was 5%. Prevalence increased with age in all regions and smoking categories, but the increase with age was significant for only the total population. There was no apparent association with smoking or exposure (Table 5).

TABLE 3. PREVALENCE (%) OF COUGH* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE (ALL REGIONS COMBINED)

	Age		
	<40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	7 (2–16)	15 (5–32)	10 (5–20)
Ex-smoker	7 (1–21)	19 (9–34)	13 (6–24)
Smoker	26 (18–35)	30 (18–45)	27 (20–35)
Total	21 (15–29)	23 (15–32)	19
Years worked			
<5			19 (14–25)
5–9			19 (10–31)
≥10			21 (10–36)
Cumulative exposure			
Low			14 (8–23)
Medium			25 (17–35)
High			16 (9–26)

Summary: (i) No demonstration difference among regions by age, smoking or exposure. (ii) Tendency to increase with age except among smokers. (iii) Higher prevalence in smokers. (iv) No demonstrated association with exposure.

* Cough = Answering yes to the question: 'Do you usually cough on most days for as much as 3 months each year?'

TABLE 4. PREVALENCE (%) OF PHLEGM* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age		
	<40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	12 (5–24)	7 (1–22)	11 (5–20)†
Ex-smoker	13 (5–29)	27 (14–43)	21 (12–33)
Smoker	33 (24–43)	26 (15–40)	31 (24–39)†
Total	23 (16–30)	22 (15–31)	23
Years worked			
<5			19 (14–25)
5–9			16 (8–26)
≥10			25 (14–39)
Cumulative exposure			
Low			13 (7–21)
Medium			24 (16–34)
High			19 (11–30)

Summary: (i) No demonstrated difference among regions by age, smoking or exposure. (ii) Smokers had highest prevalence. (iii) No demonstrated association with age or exposure.

* Phlegm = Answering yes to the question 'Do you usually bring up phlegm from your chest for as much as 3 months each year?'

†95% CI do not overlap.

WORKERS BY AGE, SMOKING
NED)

	Total % (95% CI)
32)	10 (5–20)
34)	13 (6–24)
45)	27 (20–35)
32)	19
	19 (14–25)
	19 (10–31)
	21 (10–36)
	14 (8–23)
	25 (17–35)
	16 (9–26)

regions by age, smoking or among smokers. (iii) Higher ion with exposure.
isually cough on most days for

ALL TALC WORKERS BY AGE,
E

≥40 (95% CI)	Total % (95% CI)
(1–22)	11 (5–20)†
(14–43)	21 (12–33)
(15–40)	31 (24–39)†
(15–31)	23
	19 (14–25)
	16 (8–26)
	25 (14–39)
	13 (7–21)
	24 (16–34)
	19 (11–30)

ong regions by age, smoking or No demonstrated association with

you usually bring up phlegm from

TABLE 5. PREVALENCE OF DYSPNEA* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age <40 % (95% CI)	Age ≥40 % (95% CI)	Total % (95% CI)
Non-smoker	4 (1–13)	11 (3–27)	6 (2–14)
Ex-smoker	3 (0–16)	16 (1–18)	10 (4–20)
Smoker	1 (0–5)	6 (0–13)	3 (1–7)
Total	2 (0–5)†	10 (5–18)†	5
Years worked			
<5			6 (3–10)
5–9			0 (0–6)
≥10			8 (2–20)
Cumulative exposure			
Low			5 (2–11)
Medium			3 (1–8)
High			7 (2–14)

Summary: (i) No demonstration differences among regions by age, smoking or exposure. (ii) Increased prevalence with increased age. (iii) No demonstrated association with smoking or exposure.

* Dyspnea = Answering yes to the question: 'Do you get short of breath walking with people your own age on level ground?'

† 95% CI do not overlap.

TABLE 6. PREVALENCE OF BILATERAL PLEURAL THICKENING AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age <40 % (95% CI)	Age ≥40 % (95% CI)	Total % (95% CI)
Non-smoker	0 (0–7)	0 (0–11)	0 (0–6)
Ex-smoker	6 (0–24)	3 (0–15)	4 (0–14)
Smoker	2 (0–7)*	22 (11–36)*	9 (5–15)
Total	2 (0–6)	11 (5–18)	5
Years worked			
<5			2 (0–5)‡
5–9			3 (0–10)*
≥10			23 (12–38)*‡
Cumulative exposure			
Low			4 (1–10)†
Medium			5 (1–12)
High			8 (3–17)†

Summary: (i) No demonstrated differences among regions by age, smoking or exposure, except medium cumulative exposure group in North Carolina had higher prevalence than in Montana. (ii) Tendency to increase with age (significant among smokers). (iii) No bilateral pleural thickening among non-smokers. (iv) Increasing prevalence with increasing years worked. (v) No demonstrated association with cumulative exposure.

*‡ 95% Confidence intervals do not overlap.

† 1 with extent 2 pleural thickening.

The prevalence of pleural thickening was 4, 13 and 18% in Montana, Texas and North Carolina respectively, and was significantly less in Montana after adjustment for age or years worked. The number of those with unilateral pleural thickening was one of six, five of nine, and three of nine in the three regions. There were no radiographic interpretations of pleural calcification.

The overall prevalence of bilateral thickening was 5%. The prevalence among the medium exposure group was 30% in North Carolina and 0% in Montana. There were no other demonstrable regional differences. Prevalence increased with age, but only among smokers. Prevalence was highest among smokers, and no non-smokers had bilateral pleural thickening, but none of the differences were significant. The prevalence was greater (23%) in the group working 10 yr or more, compared with 2.5% in those working less than 10 yr, but was about the same in the low, medium and high cumulative exposure groups (Table 6).

Table 7 compares workers with and without pleural thickening. Those with any pleural thickening were about 10 yr older than those without. Workers with bilateral pleural thickening on average weighed more (11–15 kg), had worked longer (6 yr) and had higher average and cumulative exposures than those with unilateral or no pleural thickening. All pulmonary function values of those with bilateral pleural thickening

TABLE 7. COMPARISON OF WORKERS WITH AND WITHOUT PLEURAL THICKENING (REGIONS COMBINED)

	No PT	Unilateral	Bilateral
n	255	9	15
Frequency (95% CI)			
Cough (%)	18 (14–23)	22 (4–56)	33 (14–63)
Phlegm (%)	18 (14–23)	22 (4–56)	33 (14–63)
Dyspnea (≥Grade 2)	5 (3–8)	11 (0–44)	7 (0–30)
Obliteration of costophrenic angle			
Unilateral	2 (0–5)	11 (0–44)	13 (2–37)
Bilateral	<1 (0–1)	0 (0–29)	0 (0–19)
*Means (SE)			
Age	36.4 (0.8)	46.7 (3.4)	47.7 (2.2)
Height (cm)	174.0 (0.5)	170.1 (2.1)	175.3 (2.0)
Weight (kg)	76.6 (0.8)	80.5 (4.9)	91.9 (4.3)
Years worked	6.7 (0.4)	6.9 (2.2)	13.4 (2.3)
Cumulative exposure [(mg m^{-3}) × years)]	5.1 (0.4)	2.4 (0.7)	34.1 24.6)
Average exposure (mg m^{-3})	1.1 (0.1)	0.9 (0.3)	3.2 (2.5)
'Latency' years	—	4.50 (1.4)	13.1 (2.3)
†$FEV_1/FVC \times 100$	77.10 (0.7)	80.20 (2.7)	72.50 (2.2)
†FEV_1 (L)	3.56 (0.05)	3.47 (0.19)	3.08 (0.16)
†FVC (L)	4.61 (0.06)	4.29 (0.22)	4.19 (0.18)
†Peak flow (L s^{-1})	8.37 (0.15)	7.62 (0.56)	7.02 (0.45)
FEF_{50}	4.10 (0.13)	4.19 (0.49)	3.30 (0.40)
FEF_{75}	1.40 (0.06)	1.43 (0.21)	1.24 (0.18)

* Lung function least square means adjusted for differences in sex, age, height, weight and smoking status.

† Pleural thickening is a significant variable in the linear regression model.

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Symptoms and radiograp

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TABLE 8

n	
Age (SD)	
Height (cm) (SD)	
Years worked (SD)	
Non-smokers (%)	
Ex-smokers (%)	
Mean pack years (SD)	
Mean cigarettes day (SD)	
Smokers (%)	
Mean pack years (SD)	
Mean cigarettes day (SD)	
Current dust levels (mg m^{-3})	
Fibres >5 μm cc^{-1}	

NA = Not Available.
* Personal samples of respirabl
† Personal samples of total dus
‡ Unpublished data from Marti

were reduced compared with those without pleural thickening. Those with unilateral pleural thickening generally had intermediate lung function values. The prevalences of cough and phlegm were not statistically significant and were not adjusted for age and smoking.

Symptoms and radiography (external comparisons)

Table 8 summarizes the characteristics of the comparison populations. The potash mines were part of the MSHA/NIOSH epidemiological–industrial hygiene study of metal and non-metal underground miners (ATTFIELD, 1979; SUTTON *et al.*, 1979). White male miners from six potash mines were used for comparison. All of the potash mines used diesel engines and had high dust exposures. The New York talc miners and millers were exposed to tremolite and anthophyllite (GAMBLE *et al.*, 1979a; DEMENT and ZUMWALDE, 1979; DEMENT *et al.*, 1980). The blue collar comparison population was part of a NIOSH blue collar control study and included male and female workers from North Carolina in such industries as electronics, synthetic textiles, bakeries and bottling plants (PETERSEN, personal communication). The workers in the comparison populations had generally worked longer in their current industry than had the Montana and Texas talc populations. The mining populations generally were heavier smokers than the study populations and the blue collar workers. The mining comparison groups had occupational exposures in the form of diesel fumes and 'potash' (primarily sylvite, a mixture of KCl and NaCl, and langbeinite or $K_2Mg_2(SO_4)_3$) and talc containing asbestiform fibres.

Table 9 summarizes the age and smoking adjusted prevalence of cough, phlegm, dyspnea and pleural thickening of the study and comparison populations. There was no demonstrated difference in the prevalence of cough between the study population and the potash or blue collar workers. New York talc workers had an elevated

TABLE 8. CHARACTERISTICS OF COMPARISON POPULATIONS

	New York talc	Blue collar‡ Male	Blue collar‡ Female	Potash
n	121	843	597	875
Age (SD)	39 (12)	38 (14)	40 (13)	41 (13)
Height (cm) (SD)	176 (6)	173 (7)	162 (6)	176 (6)
Years worked (SD)	11 (9)	12 (12)	11 (10)	16 (13)
Non-smokers (%)	21	25	49	20
Ex-smokers (%)	31	23	10	28
Mean pack years (SD)	26 (28)	21 (23)	9 (10)	23 (20)
Mean cigarettes/day (SD)	28 (19)	23 (15)	16 (12)	25 (14)
Smokers (%)	48	54	42	52
Mean pack years (SD)	26 (17)	23 (19)	17 (13)	28 (23)
Mean cigarettes/day (SD)	27 (11)	23 (11)	19 (9)	25 (12)
Current dust levels (mg m^{-3})	*0.77 (Mine) *0.87 (Mill)	NA	NA	†3.45
Fibres > 5 μm cc^{-1}	*5.40 (Mine) *4.80 (Mill)	NA	NA	NA

NA = Not Available.
* Personal samples of respirable dust and light microscope fibre counts from DEMENT *et al.* (1980).
† Personal samples of total dust from ATTFIELD (1979) and SUTTON *et al.* (1979).
‡ Unpublished data from Martin Petersen

TABLE 9. COMPARATIVE RATES OF COUGH, PHLEGM, DYSPNEA AND BILATERAL PLEURAL THICKENING AMONG ALL TALC WORKERS COMPARED WITH NEW YORK TALC WORKERS, BLUE COLLAR WORKERS AND POTASH MINERS (INDIRECTLY ADJUSTED FOR AGE AND SMOKING)

	Study population (combined) % (95% CI)	Comparison group: New York talc % (95% CI)	Potash miners % (95% CI)	Blue collar workers % (95% CI)
Cough	20.3 (16–25)	36.1 (28–45)	24.1 (20–27)	16.7 (14–20)
Phlegm	20.3 (16–25)	35.5 (27–45)	29.5 (27–34)	17.3 (14–21)
Dyspnea	5.8 (4–10)	12.3 (7–19)	8.4 (6–11)	7.5 (6–10)
Bilateral pleural thickening	6.3 (3–9)	7.9 (4–15)	0.2 (0–0.5)	0.4 (0–1)

Summary: (i) Cough: Study population less than New York talc, no different from potash and blue collar. (ii) Phlegm: Study population less than New York talc and potash, no different from blue collar workers. (iii) Dyspnea: No difference among study and comparison populations. (iv) Bilateral Pleural Thickening: Study population and New York talc workers greater than potash and blue collar workers. (Difference indicated by non-overlap of confidence intervals)

prevalence of cough compared with other populations. There was no apparent difference in the prevalence of phlegm among the study population and blue collar workers, and the prevalence in both these populations was less than the potash and New York populations. There were no demonstrated differences in the prevalence of dyspnea among the study and comparison populations. The prevalence of bilateral pleural thickening was higher in both talc (study and New York) populations compared with the potash and blue collar populations.

Pulmonary function

Table 10 summarizes the results of multiple regression models of pulmonary function with the predictor variables race, sex, age, height, smoking status. Region, department, years worked and cumulative exposure were tested for association with lung function. Age and height were significant for all parameters. Race, department, years worked and cumulative exposure were not significant for any of the lung function tests. Sex was not significant for FEF_{50} and FEF_{75}. FVC was reduced in Texas compared with Montana and North Carolina. The effect of smoking was generally as expected.

Table 11 summarizes the mean percent predicted pulmonary function of the study population compared with potash, blue collar workers (male and female) and New York talc workers. Flow rates (peak flow, FEF_{50}, FEF_{75}) of the talc workers were reduced compared with the potash and blue collar workers, but there were no significant differences in FEV_1 and FVC. Compared with New York talc workers, all pulmonary function parameters were elevated except percent predicted peak flow.

TABLE 10. SUMMARY OF M
ADJUSTED FOR

Department	
Years exposure	
Cumulative exposure	
Region	
Montana	3.
Texas	3.
North Carolina	3.
Smoking status	
Non-smokers	3.
Ex-smokers	3.
Smokers	3.

* Regression model: Lung status) + β_6 (region) + β_7 (depar
NS = $P > 0.05$.
† $P < 0.05 > 0.01$.
‡ $P < 0.01$.
Summary: (i) Age and height
(ii) No exposure variable was
Cumulative exposure was signifi
(height) + β_4 (weight) + β_5 (smo

Comparison of age coeffic
the four populations. The
effect of age than did the

Interpretation of the d
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examining ex-workers in t

The reasons for using
population is ideal, and seve
affect the morbidity of a stu
measured include region, so
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it is unlikely that all the com
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The length of the study
development of occupationa

IPV - Z*

RAL THICKENING AMONG
WORKERS AND POTASH

iners CI)	Blue collar workers % (95% CI)
7)	16.7 (14–20)
4)	17.3 (14–21)
1)	7.5 (6–10)
.5)	0.4 (0–1)

ent from potash and blue different from blue collar ions. (iv) Bilateral Pleural h and blue collar workers.

TABLE 10. SUMMARY OF MULTIPLE REGRESSION MODEL* FOR LUNG FUNCTION AND SELECTED MEANS ADJUSTED FOR SEX, AGE, HEIGHT, SMOKING STATUS, REGION AND EXPOSURE

	Lung function parameter				
	FEV_1	FVC	Peak flow	FEF_{50}	FEF_{75}
Department	NS	NS	NS	NS	NS
Years exposure	NS	NS	NS	NS	NS
Cumulative exposure	NS	NS	NS	NS	NS
Region	NS	†	NS	NS	NS
Montana	3.58 (0.06)	4.65 (0.06)	8.51 (0.16)	4.07 (0.13)	1.41 (0.06)
Texas	3.51 (0.10)	4.39 (0.11)	8.46 (0.27)	4.63 (0.23)	1.48 (0.10)
North Carolina	3.71 (0.10)	4.62 (0.11)	7.87 (0.28)	4.48 (0.24)	1.55 (0.11)
Smoking status	†	NS	‡	†	†
Non-smokers	3.71 (0.08)	4.62 (0.09)	8.31 (0.23)	4.55 (0.19)	1.63 (0.09)
Ex-smokers	3.58 (0.09)	4.51 (0.10)	8.60 (0.25)	4.52 (0.21)	1.44 (0.10)
Smokers	3.51 (0.07)	4.53 (0.08)	7.93 (0.20)	4.12 (0.17)	1.37 (0.08)

* Regression model: Lung function $= \alpha + \beta_1$ (race) $+ \beta_2$ (sex) $+ \beta_3$ (age) $+ \beta_4$ (height) $+ \beta_5$ (smoking status) $+ \beta_6$ (region) $+ \beta_7$ (department) $+ \beta_8$ (years exposure) $+ \beta_9$ (cumulative exposure).

NS $= P > 0.05$.

† $P < 0.05 > 0.01$.

‡ $P < 0.01$.

Summary: (i) Age and height were always significant; sex was significant for FEV_1, FVC and Peak Flow. (ii) No exposure variable was significant. Region was significant for FVC (Texas was reduced). (iii) Cumulative exposure was significant for FVC ($P = 0.02$) in model lung function $= \alpha + \beta_1$ (sex) $+ \beta_2$ (age) $+ \beta_3$ (height) $+ \beta_4$ (weight) $+ \beta_5$ (smoking status) $+ \beta_6$ (cumulative exposure) $\beta_6 = -4(4)$.

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w York) populations

Comparison of age coefficients by smoking categories showed little difference among the four populations. The New York and blue collar populations showed a greater effect of age than did the study and potash populations (Table 12).

DISCUSSION

Interpretation of the data from this study has the inherent problems of all cross-sectional prevalence studies. The workers examined in this study comprise only those currently working. While there are few studies that have examined ex-workers to determine the effects of selection, significant disease has been observed among older ex-hemp workers (BOUHUYS *et al.*, 1969) and progressive massive fibrosis among ex-workers in two silica flour mills (BANKS *et al.*, 1981). In both of these studies there was significant disease among the currently employed workers. The consequences of not examining ex-workers in this study are unknown.

The reasons for using several comparison populations are that no comparison population is ideal, and several may help in interpretation of the data. Factors that may affect the morbidity of a study population (in addition to work exposure) but are not measured include region, socio-economic status and type of employment (for example, mining). These may affect morbidity by selection of particular kinds of individuals, but it is unlikely that all the comparison populations will have biases in the same direction relative to the study population (although the biases in the study group still cannot be estimated).

The length of the study group's working history is a relatively short time for the development of occupationally related symptoms, radiographic changes and impaired

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TABLE 11. MEAN PERCENT PREDICTED PULMONARY FUNCTION OF ALL TALC WORKERS COMPARED WITH POTASH MINERS AND BLUE COLLAR WORKERS AND ADJUSTED FOR AGE, HEIGHT AND SMOKING*

Percent predicted pulmonary function (SE)	New York talc (males only) $n=119$	Potash miners (males only) $n=251$	Blue collar workers (males and females) $n=292$
FEV_1	106.3 (1.3)‡	98.9 (1.0)	99.7 (1.0)
FVC	105.7 (1.1)‡	99.6 (0.8)	101.0 (0.8)
Peak Flow	95.2 (1.1)	93.2 (1.0)†	97.9 (1.0)
FEF_{50}	161.1 (39.8)	95.6 (2.1)†	94.1 (2.0)†
FEF_{75}	130.5 (4.7)‡	88.2 (3.1)†	84.5 (2.4)†

* Percent predicted pulmonary function = Σ(observed/expected) × 100.
† = >2 SE less than 100.
‡ = >2 SE greater than 100.
Summary: (i) FEV_1 and FVC were not demonstrably different from comparison potash and blue collar populations, but elevated compared with New York talc values. (ii) FEF_{50} and FEF_{75} reduced compared with potash and blue collar populations, but elevated compared with New York populations.

TABLE 12. AGE COEFFICIENTS OF MALE STUDY AND COMPARISON POPULATIONS (WITH SE)

	Study population	New York talc	Potash	Blue collar
FEV_1 (ml)				
Non-smokers	−24 (5)	−52 (9)	−28 (3)	−30 (3)
Ex-smokers	−35 (5)	−36 (11)	−32 (3)	−36 (3)
Smokers	−41 (5)	−54 (6)	−40 (2)	−39 (2)
FVC (ml)				
Non-smokers	−6 (5)	−55 (12)	−23 (3)	−24 (3)
Ex-smokers	−32 (6)	−42 (13)	−26 (4)	−25 (3)
Smokers	−27 (6)	−50 (8)	−32 (3)	−25 (2)
FEF_{50} (ml s^{-1})				
Non-smokers	−51 (11)	−66 (29)	−36 (7)	−43 (6)
Ex-smokers	−49 (15)	−21 (24)	−44 (8)	−58 (8)
Smokers	−73 (11)	−80 (14)	−63 (5)	−71 (5)
FEF_{75} (ml s^{-1})				
Non-smokers	−43 (7)	−40 (11)	−32 (4)	−38 (4)
Ex-smokers	−2 (10)	−22 (7)	−28 (3)	−40 (3)
Smokers	−44 (5)	−38 (5)	−41 (2)	−50 (2)
n				
Non-smokers	67	25	178	207
Ex-smokers	56	36	244	193
Smokers	128	58	451	442

lung function that might be caused by exposure to a mineral dust. Significant changes in FEV_1 and FVC due to exposure to respiratory irritants (such as cigarette smoke, for example) may not become noticeable until after 20–30 yr of smoking. Essentially the same time interval may be required for the development of pneumoconiosis (CHERNIACK and MCCARTHY, 1979). The mean ages of the study populations were

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was to adversely affect F
effect because of the sho
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no environmental surveill
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estimates and could obscu
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highly correlated. This wa
worked and cumulative
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In this report, both in
comparisons were made w
a 'non-exposed' blue collar
comparisons supported e
dyspnea there was no do
external comparison. For
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compared with both non-
For pulmonary functio
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thought to be less subject to
The two methods were con
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detectable differences in FE
were reduced in the study p
but the age coefficients did
Flow rates at low lun
compared with two of the co
while FEF_{75} was between 80
measuring changes occurring
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that changes in the lung funct
of the small airways (BECKL
FEF_{50} and FEF_{75} are of int
changes in the small airways
they become evident in more
(such as the ability of FEF_{50} a
non-smokers) are compatible
airways, there are no availabl
of these reductions is only sug
rates at low lung volumes is
population is not convincing.
Peak flow was reduced in

around 40, and mean exposure to talc dust was less than 10 yr. Therefore, if talc dust was to adversely affect FEV_1 and FVC, the lung function results might not reflect that effect because of the short exposure times.

Estimating past exposure was a problem in this as in other studies where there was no environmental surveillance. Although dust levels were assumed not to have changed substantially with time, past exposures were probably higher than the calculated estimates and could obscure a true dose–response relation if it existed. Years worked is an exact time period, but it may be a less accurate measure of overall exposure than the calculated estimate of cumulative exposure. Often, years worked and exposure are highly correlated. This was not as true for Texas, but there was an association of years worked and cumulative exposure in Montana and North Carolina. Age was also correlated with exposure (years worked and cumulative exposure).

In this report, both internal comparisons (dose–response relations) and external comparisons were made with another talc population, another mining population and a 'non-exposed' blue collar population. For symptoms and pleural thickening the two comparisons supported each other. That is, for symptoms of cough, phlegm and dyspnea there was no dose–response relationship and no excess prevalence in the external comparison. For bilateral pleural thickening there was a dose–response relationship (association with years worked) and the prevalence was increased, compared with both non-talc populations.

For pulmonary function there was also substantial agreement in the internal and external comparisons. Mean percent predicted pulmonary function after adjustment for age, height and smoking, and the age coefficients by smoking status taken from prediction equations were used for the external comparisons. Age coefficients are thought to be less subject to bias than predicted values (HANCOCK and ATTFIELD, 1980). The two methods were consistent in showing a tendency for the study population to have an elevated pulmonary function compared with New York talc workers, with no detectable differences in FEV_1 and FVC in the other comparisons. Mean flow rates were reduced in the study population compared with potash and blue collar workers, but the age coefficients did not reflect this deficiency.

Flow rates at low lung volumes (FEF_{50} and FEF_{75}) were slightly reduced compared with two of the control populations. FEF_{50} was better than 90% predicted, while FEF_{75} was between 80 and 90%. Air flow at low lung volumes is considered to be measuring changes occurring primarily in the small airways (HYATT *et al.*, 1979; MEAD, 1979). A current hypothesis of the pathophysiology of chronic air flow obstruction is that changes in the lung function seen in disease such as emphysema start in the region of the small airways (BECKLAKE and PERMUTT, 1979; MACKLEM, 1972). Tests such as FEF_{50} and FEF_{75} are of interest, because it is difficult to detect pathophysiological changes in the small airways that may be occurring for unknown time periods before they become evident in more routine tests such as FEF_1 and FVC. While existing data (such as the ability of FEF_{50} and FEF_{75} to detect differences in the young smokers and non-smokers) are compatible with the idea that air flow obstruction begins in the small airways, there are no available prospective data to prove it. Therefore, the significance of these reductions is only suggestive. Thus, the prognostic significance of reduced flow rates at low lung volumes is not proven and the evidence for reductions in the study population is not convincing.

Peak flow was reduced in the study population compared with potash and New

F ALL TALC WORKERS
ND ADJUSTED FOR AGE.

Blue collar workers (males and females) $n=292$
99.7 (1.0)
101.0 (0.8)
97.9 (1.0)
94.1 (2.0)†
84.5 (2.4)†

:d) × 100.

it from comparison potash
talc values. (ii) FEF_{50} and
ns, but elevated compared

POPULATIONS (WITH SE)

otash	Blue collar
28	−30 (3)
32	−36 (3)
40 (2)	−39 (2)
23 (3)	−24 (3)
26 (4)	−25 (3)
32 (3)	−25 (2)
36 (7)	−43 (6)
44 (8)	−58 (8)
63 (5)	−71 (5)
32 (4)	−38 (4)
28 (3)	−40 (3)
41 (2)	−50 (2)
178	207
244	193
451	442

eral dust. Significant changes
s (such as cigarette smoke, for
r of smoking. Essentially the
lopment of pneumoconiosis
f the study populations were

York talc workers but was no different from blue collar workers. Peak flow is most sensitive to changes in large airways, but is also most subject to technician differences and subject effort. The prognostic significance of reduced peak flow is also not known.

The most important finding in this study was the increased prevalence of pleural thickening. Asbestos (particularly anthophyllite) from either occupational or community exposure is believed to cause an increased prevalence of pleural thickening (SARGENT *et al.*, 1977) and in some instances, pleural changes have been more common than parenchymal changes (HURWITZ, 1961). Talc contaminated with asbestos (tremolite and anthophyllite) seen under the light and electron microscope has also been associated with an increased prevalence of pleural thickening (GAMBLE *et al.*, 1979b). But studies of workers exposed to talc without significant asbestos content have reported higher prevalence of pneumoconiosis than pleural changes (RUBINO *et al.*, 1977; DELAUDE, 1977; MESSITE *et al.*, 1959; FINE *et al.*, 1976; WEGMAN *et al.*, unpublished) and excessive mortality due to non-malignant respiratory disease (SELEVAN *et al.*, 1979). Radiographic evidence from these Vermont talc millers showed pneumoconiosis on 9 of 11 available chest roentgenograms. Although exposures were high, the talc was free of asbestos and free silica (BOUNDY *et al.*, 1979). Pneumoconiosis, however, was not significant in this study. Pleural abnormalities (unspecified) were found in 9% of Vermont talc workers (WEGMAN *et al.*, unpublished), compared with 9% with small irregular opacities and 12% with small rounded opacities. This is in contrast to this study where pleural thickening was observed in 9% of the population, but less than 1% had any signs of pneumoconiosis.

Pleural thickening is generally considered to take many years to develop. In a study of a Swedish population, mean latency for the development of bilateral pleural plaques after first exposure to asbestos was estimated at about 30 yr, which was consistent with other studies. Pleural plaques were rare before age 40 (HILLERDAHL, 1978). However, OCHS and SMITH (1976) reported on at least one case where as little a time interval of 1 yr was necessary for the appearance of bilateral pleural thickening in an individual without occupational asbestos exposure. In the study reported here, latency (time between first known talc exposure and date of the study) was 13 yr for workers with bilateral thickening and 4.5 yr in those with unilateral pleural thickening, a much shorter time than generally associated with pleural thickening from asbestos exposure. North Carolina also had an increased prevalence in workers less than 40 yr of age.

The association of pleural thickening and asbestos exposure may vary considerably in different populations. In a Swedish study about 1% of the men over 40 and less than 0.1% of men less than 40 had bilateral pleural plaques (HILLERDAHL, 1978). Almost 80% were current ex-smokers and had had some exposure to asbestos. Fibrosis was rare (4% of those with pleural thickening). Another community type study in Birmingham, England (BTTA and MRCPU, 1972) found that about 7% of those attending chest clinics had pleural plaques (10% of these were calcified). Unilateral obliteration of the costophrenic angle (not considered to be caused by asbestos) was observed in 36% of those with pleural plaques and there was a definite history of asbestos exposure in no more than 11% of the cases. Much of the pleural thickening was considered to be due to pleural disease (e.g., emphysema, severe chest wall injury, pleurisy). In the study of talc workers reported here, there was no apparent difference between those with and without pleural thickening in the exposure to asbestos or in chest disease.

In these two community studies the association of pleural thickening and asbestos exposure was quite different. The association of pleural thickening with asbestos may be coincidental, as the prevalence of pleural thickening is quite different in asbestos exposed workers. For example, prevalences of 17.5 and 35% have been reported in asbestos manufacturing plants and shipyard joiners (WEISS and THEODOS, 1978; FLETCHER, 1971). Two other studies of shipyard and dockyard workers reported prevalences of pleural thickening of around 5% (FLETCHER, 1972; reported in WEISS and THEODOS, 1978). It is possible that factors other than asbestos may account for these differences (e.g., age distribution, method of reading X-rays, oblique X-rays in addition to PA, different exposures and exposure times, smoking habits, readers, etc). Some of these factors could possibly account for the differences between study and comparison populations seen in this study.

Exposure to other dusts have also been associated with pleural abnormalities. SMITH (1952) reported finding a pleural calcification among 302 men making mica insulators, 6.3% among miners and millers of tremolitic talc, but zero among 261 asbestos workers. The common feature of exposure of all four groups was said to be exposure to talc/or mica.

No asbestos was seen in the NIOSH samples of Montana and North Carolina talc. MCCRONE (1975) analysed two samples from North Carolina and found 0.1–5% tremolite–actinolite by polarized light microscopy in one of the samples. Tremolite and actinolite have been reported in the Murphy talc deposits although the quantities were small (VAN HORN, 1948). GREXA and PARMENTIER (1979) report 0–5% anthophyllite in 'North Carolina' talc and no asbestos in Montana talc. Seven samples from Montana revealed no asbestos (MCCRONE, 1975) and antigorite was observed in some of the Texas samples (MCCRONE, 1975). While analysis of the talc from these three regions revealed little or no asbestos, the presence of asbestos as an impurity often occurs. It is not known whether very low levels of exposure to asbestos for short periods of time is sufficient to cause pleural thickening.

Thus, while pleural thickening is generally considered to be a signpost of asbestos exposure (SARGENT *et al.*, 1977), the possibility of other agents causing pleural thickening should be considered. The conclusion of MEURMAN (1966) that factors other than asbestos were either contributory or the sole cause of calcified plaques seems applicable to pleural thickening. The results of this study suggest that talc itself may produce pleural changes.

The clinical significance of pleural thickening, pleural plaques and pleural calcification as a result of asbestos exposure remains unclear, but is of concern because the pleural changes were considered to represent a significant exposure to asbestos and may be related to mesothelioma. However, there may be no association of mesotheliomas and pleural plaques even in the presence of asbestos, as no mesotheliomas associated with anthophyllite asbestos exposure have been observed in Finland (MEURMAN *et al.*, 1974). The suggestion that talc is carconogenic (BLEJER and ARLON, 1973) may be due to asbestos contamination of the talc. The characteristics of talc have been poorly reported in the past. Talc free of asbestos contamination does not appear to increase the risk of cancer, and mesothelioma has not been associated with talc exposure (KLEINFELD *et al.*, 1974; RUBINO *et al.*, 1976; WAGNER *et al.*, 1977; RCBTA and MRCPU, 1979; SELEVAN *et al.*, 1979). Risk of cancer in this study cannot be determined. Among those with bilateral pleural thickening, lung function was

significantly reduced. The prognostic significance of these observations is unknown and deserves prospective evaluation.

CONCLUSIONS

In this cross-sectional study of 299 talc workers from Montana, Texas and North Carolina, there was no demonstrated association of symptoms (cough, phlegm, dyspnea) or reduced lung function with exposure. The prevalence of symptoms was not elevated and there was no demonstrable reduction in FEV_1 and FVC compared with the control populations. Thus, both internal and external comparisons were consistent in confirming the lack of association between morbidity and exposure variables. While there were no demonstrated differences in the symptom prevalences among the three talc regions (despite differences in exposure and talc composition), there were differences in the prevalence of cough and phlegm between the study population and the workers exposed to talc containing tremolite and anthophyllite.

The only significant effect observed in this study was related to the increased prevalence of bilateral pleural thickening. The excess was considerable in relation to the non-talc comparison populations, but the dose–response relationship was somewhat confounded with age. The comparable results among the talc populations, the lack of a consistent association of pleural thickening with asbestos exposure, and the lack of parenchymal changes in the talc exposed workers suggest talc as an etiological agent in the development of bilateral pleural thickening. While those with bilateral pleural thickening had reductions in lung function and a possible increase in symptoms, the long-term significance is unclear.

At least two warnings must be acknowledged. The mean number of years worked is relatively short. Therefore, more time may be needed to see exposure effects. The suggestion of reduced flow rates at low lung volumes supports this caution, as they may be early indicators of airways disease. The association of talc exposure with bilateral pleural thickening was relatively weak. However, latency was shorter than is commonly found in other studies and the excess is considerable compared with non-talc populations. A prospective study is necessary to answer the questions concerning prognostic significance.

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DISCUSSION*

J. C. MCDONALD: In addition to the pleural thickening you observed, was there any evidence of pleural calcification?

J. A. MERCHANT: May I answer that? I reviewed all the films with pleural thickening and there were no cases at all of pleural calcification. Most of the pleural thickening was grade 1, but there was one case where the thickening was considered grade 2. Two of the cases of pleural thickening were extent 2; the remainder extent 1.

J. WILLEMS: Do you have full information on the size-distribution of your talc dust particles?

Dr DEMENT: We do have some information that is not presented in this report. Of course, the respirable dust sampling attempted to simulate those particles which have the possibility of deep lung penetration. In general, the Montana talc had by far the largest particle size with much larger plates. In North Carolina there is a combination of the platy and acicular particles which were identified by electron diffraction and microchemical analysis as being talc with a rather unusual morphology.

S. F. MCCULLAGH: In this study (and several others) use is made of the standard respiratory questionnaire. Among other questions, workmen are asked if they get more short of breath walking on the level than other men of their own age. I have asked this question of thousands of workmen in Australia and at least half answer, 'Gee, Doc, I wouldn't know'. In the present study were the men forced to a decision, do you have a 'don't know' category or are American workers a great deal more intelligent than Australians?

Dr DEMENT: We try to administer the same questions to both our exposed and non-exposed populations and hope the level of intelligence is similar and better. The questionnaires are difficult to answer off-the-cuff, but we employ trained interviewers who are familiar with answering the questions and try to seek the answer in a polite manner. Very seldom does a worker answer, 'I don't know'. A very high percentage answer 'Yes' or 'No' and, if the answer is equivocal, the question is repeated with the admonition to answer 'Yes' or 'No'.

M. JACOBSEN: May I comment on Dr McCullagh's question. Whilst it is true that there are often ambiguous answers and strict protocols have to be used in order to maintain properly recorded answers useful for epidemiological studies, there is evidence from our studies that, if this is done rigorously and conscientiously, then the data obtained may be used sensibly for epidemiological purposes. Coal miners who have been asked these questions are no more or less intelligent than Dr McCullagh's patients. Their responses indicate very clearly that their mortality risk, particularly to the respiratory diseases, can be related to those responses to the questions particularly those relating to breathlessness and to cough and phlegm.

M. L. NEWHOUSE: I am surprised at the high prevalence of pleural thickening that you report. In a survey of 30–40 pharmaceutical workers exposed to a carefully specified, non-fibrous talc, we observed no more than one or two pleural thickenings.

* The paper was presented, and questions taken, by Dr J. M. DEMENT.

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Dr DEMENT: There are several possible reasons for the difference. I think the possibility of contamination cannot be ruled out until we look at the talc composition in these facilities over a number of years. The possibility that pockets of fibre contamination exist in these operations also cannot be excluded.

F. D. K. LIDDELL: Tables 3–5 present the prevalence of cough, of phlegm and of dyspnea by years worked and by cumulative exposure, but for all three States combined. On the other hand, Table 1 reveals important associations between age, duration of employment and dust concentration in the three States. To what extent are the 'negative' findings of Tables 3–5 a masking of positive associations, within at least one State, by the interactions shown in Table 1?

Dr DEMENT: All the regions analysed were looked at separately. Admittedly the numbers were small within each region, but the only really significant finding in each of the regions was the pleural thickening.

J. C. GILSON: I would like to make two comments. The first concerns the recording of pleural thickening. The classification does provide a means of measuring the extent of this as well as the width, and I think it is important to make use of this information in order to deal with the kind of question that Dr Newhouse has raised.

My second point relates to the respiratory questionnaire. This questionnaire, as many of you know, was originally started here in S Wales by my colleague Dr Fletcher and, of course, it was applied to coal miners. Now coal miners do, by virtue of their job, have to walk together often underground under very adverse conditions. Also, in this particular area, the coal mines are in relatively steep valleys so miners were constantly walking with their colleagues. I have always thought the questions were particularly applicable in these circumstances and that they might well be inapplicable where people were walking on the level. If we had originally had coal mines in Norfolk this particular questionnaire would never have been developed.

J. C. MCDONALD: In our studies of Quebec asbestos workers, we found a very much higher prevalence of pleural thickening in one region than in the other, even allowing for exposure and other factors. This suggested to us that there might be something other than the asbestos involved, but we found no evidence for this. The same went for calcification.