

FILE NAME: RT Vanderbilt (RTV)

DATE: 2002 May 6

DOC#: RTV006

DOCUMENT DESCRIPTION: Journal Article - Mortality Among Workers
at a Talc Mining and Milling Facility

Mortality among Workers at a Talc Mining and Milling Facility

YASUSHI HONDA^{1*}, COLLEEN BEALL², ELIZABETH DELZELL², KENT OESTENSTAD³, ILENE BRILL² and ROBERT MATTHEWS²

¹Environmental Health Sciences Program, Institute of Health and Sport Sciences, University of Tsukuba, Tsukuba 305-8574, Japan; ²Department of Epidemiology, University of Alabama at Birmingham School of Public Health, Birmingham, AL 35294-0022, USA; ³Department of Environmental Health Sciences, University of Alabama at Birmingham School of Public Health, Birmingham, AL 35294-0022, USA

Received 15 August 2001; in final form 6 May 2002

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/m³-days for all exposed employees, 739 mg/m³-days for mine workers and 683 mg/m³-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

*Author to whom correspondence should be addressed.
Tel/fax: +81-298-53-2627; e-mail: honda@taiiku.tsukuba.ac.jp

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 concen-

tration 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/m³ 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 18048 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*	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		

*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), whereas 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)

^aRR for each category of years since hire and years worked adjusting for age (<35, 35–54, 55–64, 65+) and calendar year (1960–69, 1970–79, 1980–89).

^bReferent 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 (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 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)

^aRR for mill workers compared with all other employees, adjusting for age, calendar period and employment in mines.

^bRR 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/m³-days for all exposed subjects combined, 739 mg/m³-days for men ever employed in mines and 683 mg/m³-days for men ever employed in mills (Table 6). Among exposed decedents, the median estimated cumulative respirable dust exposure was 520 mg/m³-days for all decedents combined, 347 mg/m³-days for men with lung cancer, 376 mg/m³-days for men with ischemic heart disease, 888 mg/m³-days for men with any form of NMRD as the underlying cause of death, 1199 mg/m³-days for men with other

NMRD as the underlying or a contributing cause and 3759 mg/m³-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/m³ for all subjects, 0.9 mg/m³ for all decedents, and 0.9 mg/m³ 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/m³ 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)	30	100	1199
Pulmonary fibrosis decedents ^b (11.8)	17	100	3759

^aNon-malignant respiratory disease as the underlying cause of death.

^bNon-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	

^aTertiles are based on the cumulative exposure distribution of cases in the cause of death category.

^bAge 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.

^cReferent category for the RR.

^ddf, 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/m³-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 28

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 $<2 \text{ mg/m}^3$.

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 $\geq 800 \text{ mg/m}^3\text{-yr}$, 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.

Acknowledgements—This study was supported by a research contract with the R.T. Vanderbilt Co. Inc.

REFERENCES

- Blair A, Stewart WF, Stewart PA *et al.* (1995) A philosophy for dealing with hypothesized uncontrolled confounding in epidemiological investigations. *Med Lav*; 86: 106–10.
- Brown DP, Wagoner JK. (1978) Occupational exposure to talc containing asbestos: III. Retrospective cohort study of mortality, US DHEW (NIOSH) Publication no. 80-115. Cincinnati, OH: National Institute for Occupational Safety and Health. pp. 23–33.
- Brown DP, Kaplan SD, Zumwalde RD, Kaplowitz M, Archer VE. (1986) A retrospective study of underground gold mine workers. In Goldsmith DF, Winn DM, Shy CM, editors. *Silica, silicosis and cancer: controversy in occupational medicine*. Philadelphia: Praeger Press. pp. 335–50.
- Brown DP, Sanderson W, Fine LJ. (1990) NIOSH health hazard evaluation report no. 90. Cincinnati, OH: National Institute for Occupational Safety and Health. pp. 390–2065.
- Callas PW, Pastides H, Hosmer DW. (1990) Empirical comparisons of proportional hazards, Poisson, and logistic regression modeling of occupational cohort data. *Am J Ind Med*; 33: 33–47.
- Cooper WC, Wong O, Trent LS, Harris F. (1992) An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med*; 34: 1173–80.
- Davis JMG, Addison J, McIntosh G, Miller G, Niven K. (1991) Variations in the carcinogenicity of tremolite dust samples of differing morphology. In Landrigan PJ, Kazemi H, editors. *The third wave of asbestos disease*. New York: New York Academy of Sciences. Vol. 643, pp. 473–90.
- Gamble JF. (1993) A nested case-control study of lung cancer among New York talc workers. *Int Arch Occup Environ Health*; 64: 449–56.
- Goodman M, Morgan RW, Ray R, Malloy CD, Zhao K. (1999) Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control*; 10: 453–65.
- Higgins TTT, Glassman JH, Ohs MS, Cornell RG. (1983) Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol*; 118: 710–9.
- Kelse JW, Thompson CS. (1985) The regulatory and mineralogical definitions of asbestos and their impact on amphibole dust analysis. *Am Ind Hyg Assoc J*; 50: 613–22.
- Lamm SH, Levine MS, Starr JA, Tirey SL. (1988) Analysis of excess lung cancer risk in short-term employees. *Am J Epidemiol*; 127: 1202–9.
- Marsh G, Youk AO, Stone RA, Sefcik S, Alcorn C. (1998) OCMAP-Plus: a program for the comprehensive analysis of occupational cohort data. *J Occup Environ Med*; 40: 351–62.
- McConnell EE, Rutter HA, Ulland BM, Moore JA. (1983) Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. *Environ Health Perspect*; 53: 27–44.
- McDonald JC, Gibbs GW, Liddell FDK, McDonald AD. (1978) Mortality after long exposure to cummingtonite-grunerite. *Am Rev Respir Dis*; 118: 271–7.
- Oestensstad K, Honda Y, Delzell E, Brill I. (2002) Assessment of historical exposures to talc at a mining and milling facility. *Ann Occup Hyg*; 46: 587–96.
- Pott F, Huth F, Friedrichs KF. (1974) Tumorigenic effect of fibrous dusts in experimental animals. *Environ Health Perspect*; 9: 313–5.
- Rubino GF, Scansetti G, Piolatto G, Romano C. (1976) Mortality study of talc miners and millers. *J Occup Med*; 18: 186–93.
- Rubino GF, Scansetti G, Piolatto G, Gay G. (1979) Mortality and morbidity among talc miners and millers in Italy. In Lemen R, Dement JM, editors. *Dust and disease*. Park Forest South, IL: Pathotox Publishers. pp. 379–88.
- Seidman H, Selikoff IJ, Gelb SK. (1986) Mortality experience of amosite asbestos factory workers: dose-response relationship 5 to 40 years after onset and short-term work exposure. *Am J Ind Med*; 10: 479–514.
- Smith WE, Hubert DD, Sobel HJ, Marquet E. (1979) Biologic tests of tremolite in hamsters. In Lemen R, Dement JM, editors. *Dust and disease*. Park Forest South, IL: Pathotox Publishers. pp. 335–9.
- Stanton MF, Layard M, Tegeris A *et al.* (1981) Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J Natl Cancer Inst*; 67: 965–75.
- Stille WT, Tabershaw IR. (1982) The mortality experience of upstate New York talc workers. *J Occup Med*; 24: 480–4.
- Straif K, Keil U, Taeger D, Holthenrich D, Sun Y, Bungers M. (2000) Exposure to nitrosamines, carbon black, asbestos, and talc and mortality from stomach, lung, and laryngeal cancer in a cohort of rubber workers. *Am J Epidemiol*; 152: 297–306.
- US Bureau of the Census. (1972) County and city data book. Washington, DC: US Government Printing Office.
- US Department of Labor. (2000) Background information regarding the analysis of industrial talcs. Salt Lake City, UT:

- Occupational Safety and Health Administration Salt Lake Technical Center.
- Wagner JC, Berry G. (1969) Mesothelioma in rats following inoculation with asbestos. *Br J Cancer*; 23: 567–81.
- Wergelund E, Anderson A, Baerheim A. (1990) Morbidity and mortality in talc-exposed workers. *Am J Ind Med*; 17: 505–13.
- Wild P, Leodolter K, Refregier M, Schmidt H, Zidek T, Haidinger G. (2002) A cohort mortality and nested case-control study of French and Austrian talc workers. *Occup Environ Med*; 59: 98–105.
- Wylie AG, Virta RL, Russek E. (1985) Characterizing and discriminating airborne amphibole cleavage fragments and amosite fibers: implications for the NIOSH method. *Am Ind Hyg Assoc J*; 46: 197–201.
- Wylie AG, Bailey KF, Kelse JW, Lee RJ. (1993) The importance of width in asbestos fiber carcinogenicity and its implications for public policy. *Am Ind Hyg Assoc J*; 54: 239–52.
- Wylie AG, Skinner HCW, Marsh J *et al.* (1997) Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. *Toxicol Appl Pharmacol*; 147: 143–50.