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Quantitative Exposure-Response for Silica Dust and Lung Cancer in Vermont Granite Workers

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Background *Excess lung cancer mortality among the exposed Vermont granite workers has been reported. These studies were based on job and tenure surrogates, with the potential for misclassification and inability to evaluate quantitative exposure-response.*
Methods *Industrial hygiene data collected from 1924 to 1977 was analyzed in conjunction with mortality data to examine quantitative exposure-response for silica, lung cancer, and other lung diseases. A person-years analysis was undertaken by cumulative exposure group, including lagged and unlagged tabulations. Poisson models were fitted to untransformed and log transformed exposure.*
Results *The results indicated a clear relationship of lung cancer, tuberculosis, pneumoconiosis, non-malignant lung disease, and kidney cancer with cumulative exposure. An exposure to 0.05 mg/m^3 from age 20 to 64 was associated with a lifetime excess risk of lung cancer for white males of 27/1,000.*
Conclusions *The results of this study of workers exposed almost exclusively to silica and no other major occupational confounding exposures indicate a clear exposure-response for lung cancer.* Am. J. Ind. Med. 45:129–138, 2004. *Published 2004 Wiley-Liss, Inc.*†

KEY WORDS: silica; lung cancer; granite; silicosis; tuberculosis; dust exposure

INTRODUCTION

The role of silica in the causation of lung cancer has long been the subject of debate. However, in 1997, further movement towards acceptance of silica as a human carcinogen took place when a working group of the International Agency for Research on Cancer [1997] (IARC) concluded that there was sufficient evidence for the carcinogenicity of inhaled crystalline silica. In doing this, it acknowledged that many studies of silica and mortality from lung cancer suffered from confounding from other exposures. Among those noted as being relatively free from this defect was the study of Vermont granite shed workers [Costello and Graham, 1988]. That study was based on workers who were employed in the Vermont granite industry at some time between 1950 and 1982, and included men who had been exposed to high silica dust concentrations prior to the installation of dust control measures starting around 1940. The findings from the study indicated an overall excess of lung cancer (SMR = 116), as well as excesses in tuberculosis, silicosis, and all lung disease. Shed workers, who received considerably greater exposures than many of their colleagues in the quarry had a lung cancer SMR of 127. In shed workers with 15 or more years since first exposure there was a consistently increasing trend of mortality with tenure (<10, 10–29, and 30+ years), up to a peak of 152.

The Vermont granite cohort study upon which the above results were based has been recently updated. This update included an extended period of follow-up (from 1982 to 1994) and enhanced follow-up procedures. Although the prior study had employed extensive means to identify deaths, and had thereby discovered 558 additional deaths over those identified in an earlier analysis [Davis et al., 1983], the lack of Social Security numbers for the cohort prohibited follow-up using Social Security files. This was not of great consequence for those workers who had remained in the Barre, VT area,

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since their deaths were easily traceable. However, deaths of workers who had migrated to other localities were less easy to determine. As part of the extended follow-up in the later study, death listings from Social Security files stored on CD-ROM were searched manually by last name, enabling further deaths to be identified.

The previous mortality study of this cohort [Costello and Graham, 1988] did not include examination of exposure-response using quantitative assessments of personal exposures to silica dust. Instead, reliance was placed on surrogates such as job and tenure. The lack of quantitative exposure-response was noted in the International Agency for Research on Cancer [1997] review of the 1988 Vermont study [Costello and Graham, 1988]. To remedy this omission, the extended follow-up data for the Vermont cohort has been analyzed in conjunction with exposure data collected between 1924 and 1977 and later summarized by Davis et al. [1983]. These exposure data were linked, after some adaption, with job histories available in the Vermont mortality cohort to provide cumulative respirable silica exposures. The resulting exposures were input to exposure-response analyses for deaths from lung cancer and certain other causes previously found to be associated with exposure to airborne silica; the results are presented here.

MATERIALS AND METHODS

The study was undertaken on granite workers who have been the subject of two previous published analyses. The mortality data were supplemented by respirable silica dust concentration data summarized by time period and job, enabling cumulative exposures to be derived. A person-years analysis was undertaken by cumulative exposure group, including unlagged and lagged tabulations, and Poisson models were fitted to untransformed and log transformed exposure.

Cohort and Follow-Up Procedures

Details of the cohort definition and follow-up procedures are provided elsewhere [Costello and Graham, 1988]. Briefly, the cohort included any male employed in the Vermont granite industry from 1950 to 1982 and who was X-rayed at least once by the surveillance program of the Vermont Department of Industrial Hygiene (VDIH). This program has been said to include 98% of all Vermont granite workers [Ashe and Bergstrom, 1964]. Initially, the resulting group of 5,414 workers was followed up for vital status using a variety of methods, including reference to pension funds, matching against state vital records and a VDIH list of deaths, and reference to local information. Lack of Social Security numbers proved a deterrent to the use of more conventional follow-up methods. Similar techniques were applied for the extended follow-up from 1982 to 1994. However, the discovery that death rates for older workers were apparently being severely underestimated led to additional procedures being applied. Among these, a manual search by name of Social Security deaths available on CD-ROM led to the discovery of many more deaths.

Death Certificate Coding

Death certificate coding utilizing the ICD 8th revision was undertaken by a qualified nosologist. A few deaths were inadvertently coded in the 9th revision, and for these the specific causes of death of interest were converted to 8th revision.

Exposure Derivation

Work history information was available for each cohort member, having been collected at the time the worker was X-rayed. This provided start and stop year and job code (unique for each job identified) for each job worked.

The job-time exposure matrix published by Davis et al. [1983] (Table I) formed the basis of the cumulative exposure derivation. This matrix was derived from six environmental surveys undertaken between 1924 and 1977 [Russell et al., 1929; Bloomfield and Waldemar, 1934; Urban, 1939; Hosey et al., 1957; Theriault et al., 1974; Eisen, 1982; Eisen et al., 1984]. As noted by Davis et al. [1983], this period corresponds closely with the years the cohort was employed in the granite industry. Three significant time periods were considered: pre-dust control (<1940), intermediate (1940–1950), and post-dust control (>1950). Dust concentrations for the intermediate period were obtained by averaging the pre- and post-dust control values from Davis et al. [1983]. This three-part breakdown represents a compromise between the views of Davis et al. [1983] and of Graham et al. [2001] as to when and how exposures declined following the introduction of dust controls.

To calculate cumulative exposures, a list of all jobs was compiled from the work histories. These jobs were matched with the job titles available from the job-time exposure matrix; jobs that did not match exactly were linked, after manual inspection, to the generic exposure categories of shed office worker, shed laborer, other shed, other quarry, or quarry office worker, as appropriate. Cumulative exposures were then calculated by summing the products of years in job and dust concentration, taking account of the significant change in exposure level following the introduction of dust control measures. Finally, conversion from mppcf-yr to mg-yr/m^3 was made employing the conversion factor from Davis et al. [1983] of 10 mppcf $= 0.075$ mg/m^3 respirable free silica.

Statistical Analysis

The data were analyzed using the NIOSH LTAS mortality program [Steenland et al., 1990]. This provides

TABLE I. Most Common Work History Jobs and Exposure Assignments*

Work history, job title	Davis et al. [1983], job title	No.	Exposure			Note[a]
			Pre-1940	1940–1950	Post-1950	
Cutter/marker/surfacer	Cutter	1,308	0.37	0.22	0.07	1
Channel bar	Channel bar operator	798	1.07	0.54	0.01	2
Lumper	Lumper	610	0.14	0.09	0.04	
Polisher	Polisher	570	0.12	0.10	0.07	
Sawyer/saw-helper/saw	Sawyer	562	0.05	0.04	0.04	3
Sandblaster	Sandblaster	451	0.06	0.05	0.04	4
Crane	Cranemen	255	0.14	0.09	0.03	5
Boxer	Boxer	247	0.14	0.09	0.03	
Draftsmen/designer	Office worker	179	0.01	0.01	0.01	
Foremen (shed)	Foremen (shed)	170	0.06	0.04	0.01	
Derrick (quarry)	Other quarry	161	0.06	0.04	0.01	6
Maintenance/repairman	Maintenance	121	0.14	0.09	0.03	
Plug drill	Plugdrill operator	113	0.65	0.34	0.02	
		5,545				

*Respirable free silica measurements in mg/m^3. From personal and area measurements compiled from various studies 1924–1977 by Davis.
[a]1, 99% Of these are cutters (based on the examination of a 10% sample of these jobs); 2, includes Leyner bar operator and driller; 3, includes wire, diamond, carbo, gang, and circular saw; 4, includes sandblaster shaper and stencil sandblaster; 5, includes shed derrickmen; 6, includes quarry cranemen.

SMRs and SRRs for all deaths and by cause, overall, by subsets, and by tenure/exposure and latency groups. The reference group was comprised of national death rates from 1940 to 1999. In the current analysis, the exposure data were divided into groups having approximately equal numbers of deaths in each category, but with the cut-points rounded to increments of 0.25 mg-yr/m^3 for ease of description.

Model fitting was undertaken using Poisson regression using Proc Genmod of SAS® following the methods described by Breslow and Day [1987]. In the former models, output from the LTAS program, consisting of observed deaths and person-years by age group, 5 year period, and exposure group were used as the input to the model [Breslow and Day, 1987]. In addition, we employed the Poisson model incorporating external standard rates instead of internal coefficients. In both cases, the cumulative exposures were first averaged within each exposure category, and the effect of exposure then examined using untransformed and log transformed values based on those means. The same models were fitted after allowing for a 15 year lag in cumulative exposures.

Lifetime (i.e., up to age 85) excess risks adjusted for competing causes were computed following the approach described by Gail [1975] for various intensities of dust concentration and assuming a 45 year working lifetime's exposure to silica dust from age 20 to 64. The background rates were based on 1992 vital statistics (national or state).

RESULTS

Tenure Duration

The findings on tenure duration will be presented elsewhere (Graham and Costello, personal communication). In summary, the reanalysis showed that the overall lung cancer SMR was 117, with deaths from tuberculosis, diseases of the respiratory system, and pneumoconiosis all clearly elevated. For shed workers, the lung cancer SMR was 130, as compared with 72 for the quarry workers. A breakdown by tenure for those with 15 years since first exposure showed an almost identical trend to that noted in 1988, from 76 to 153 (<10 years compared to 30+ years). The greatest excess in lung cancer mortality (SMR = 170) was seen in shed workers with 30+ years of exposure and 40+ years since first exposure—also compatible with the previous study. Overall, the findings confirmed those from the earlier study, showing increases in statistical significance, but no major deviations.

Dust Exposures

There were 203 unique job and department title combinations found in the work histories. Of these, 61 occurred only once, and 80 occurred 2–10 times. Some of the job titles were synonyms (e.g., channel bar and leyner bar), while others reflected similar work locations and exposures (e.g., electrician and welder). A few also reflected coding errors, i.e., the obviously wrong assignment of a job to a department

(channel bar to shed, for instance). After summarization into job groups having similar work, 13 titles accounted for 75% of the 7,428 work history record entries (Table I). The most frequent job reported was cutter/marker/surfacer (a shed job), with 1,308 work history entries reported, followed by channel bar operator (a quarry job) with 798 entries. Each of the summarized job titles was matched with the job titles in the job-exposure matrix given by Davis et al. [1983]. Nearly all of the 13 most frequently reported job groups could be linked directly with specific jobs in the exposure matrix. The two exceptions were: draftsmen/designer, which was assigned the shed office worker job-exposure level, and quarry derrick man, which was assigned to the other quarry exposure group. Apart from the jobs listed in Table I, the following other shed jobs (and their synonyms) could be linked directly with exposure data: toolgrinder, grouter, shed laborer, contour planer, and blacksmith. For the quarry, the jackhammer workers could be likewise linked directly with an exposure level. Together, these job titles accounted for another 343 work history entries, bringing the number of titles accounted for up to 79%. The remainder of the jobs were linked to the generic exposure categories. In nearly every case the assignment posed no difficulties, since the match was obvious. The only exceptions to this rule occurred for a few jobs for which historical reports indicated alternative, more specific assignments.

A distribution of the cumulative exposure levels for each worker derived by linkage of the work histories and the exposure levels as output from the LTAS mortality program is shown in Figure 1; the summary statistics are given in Table II. The mean cumulative exposure was 2.1 mg-yr/m^3 with an s.d. of 3.8 mg-yr/m^3. As can be seen, the distribution was strongly skewed, the median being 0.74 mg-yr/m^3, with 10% of the distribution above 6.4 mg-yr/m^3. The mean tenure was 20.2 years, with 80% of the range falling between 1 and 43 years. The average intensity of exposure (i.e., the silica dust concentration, obtained by dividing each person's cumulative exposure by their total tenure) was 0.08 mg/m^3, with 10% being greater than 0.21 mg/m^3. The eight groups formed by subdividing the range of cumulative exposure having roughly equal numbers of deaths from lung cancer are shown in Table III. Also shown are the mean cumulative exposure, mean tenure, and mean dust concentration (obtained by dividing the cumulative exposure by the duration of employment for each individual) for each range. As can be seen, cumulative exposure increases as both tenure and dust concentration increase, with the initial increases being more dependent on tenure, and the later increases depending more on dust level. Evaluation of the correlation coefficients confirmed these observations (Pearson correlation coefficients = 0.87 for dust concentration and 0.55 for tenure).

Modified Life Table Analysis

A person-years analysis was undertaken to examine exposure-response between standard mortality ratios and extent of cumulative exposure. Mortality from malignancy of the trachea, bronchus, and lung is shown in Table IV and rises almost consistently with exposure level, from an SMR of 0.77 in the lowest exposure group to 1.70 in the penultimate exposure group (3.0–6.0 mg-yr/m^3). The elevations in the SMR for the penultimate two exposure groups are statistically significant ($P < 0.05$ and $P < 0.01$). The SMR for the final exposure group, although elevated over that for the initial exposure groups, is distinctly lower than that

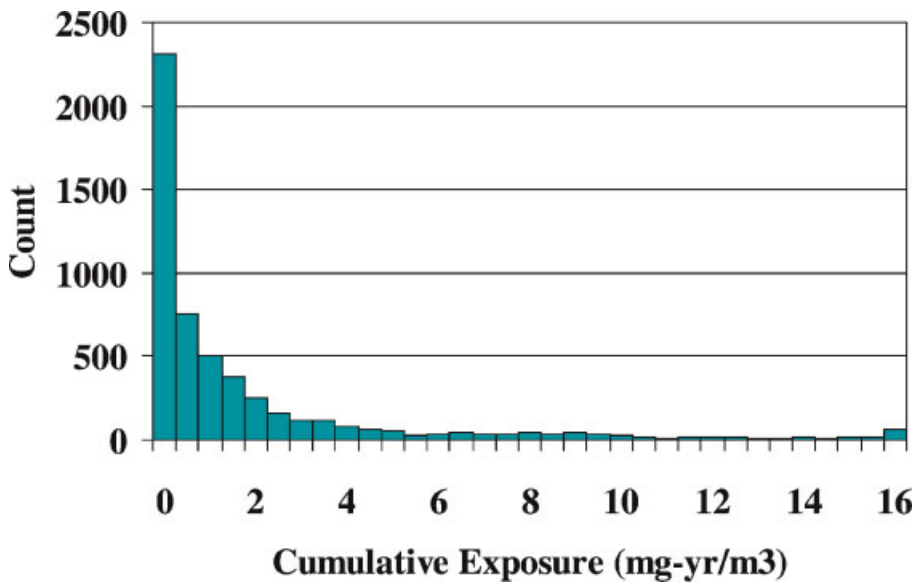

FIGURE 1. Distribution of cumulative exposure to respirable free silica. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

TABLE II. Summary Statistics on Respirable Free Silica Exposure Variables

	Cumulative exposure (mg-yr/m^3)	Tenure (yr)	Dust concentration (mg/m^3)
Mean	2.1	20.2	0.08
Standard deviation	3.8	15.3	0.10
Median	0.72	18	0.045
Lower decile	0.02	1	0.01
Upper decile	6.4	43	0.21

for the previous exposure group. There was an overall excess mortality for this cause of death group (SMR = 1.17, $P < 0.05$). SRR statistics reveal a similar trend to that seen in the SMRs. A trend test for directly standardized SRRs proposed by Rothman [1986] for the full exposure range showed a nonsignificant trend of lung cancer with cumulative exposure. If, however, workers in the highest exposure group are removed from the analysis, the trend becomes highly statistically significant (slope = 0.00022, s.e. = 0.00004, chi-square = 35, $P < 0.001$).

The mortality indices for other causes of death of interest are shown in Table V. Mortality from respiratory tuberculosis and pneumoconiosis showed dramatic increases with exposure level. From an SMR of 0.73 for the lowest exposure group, there was a consistent rise to a high of 34.0 for the greatest exposure group. There was a significant overall elevated SMR, while most of the elevations in the higher exposure groups also demonstrated statistical significance ($P < 0.01$ for most).

Pneumoconiosis mortality followed a similar pattern to that for respiratory tuberculosis, although the overall excess was less, and the trend with exposure was not so consistent. A significant excess was seen overall, and also in all of the higher exposure groups ($P < 0.05$ or stronger).

Deaths from diseases of the respiratory system, including pneumoconiosis but not tuberculosis, also trended higher with exposure, from a low of 0.89 in the lowest exposure group, to 2.53 in the highest exposure group. Overall mortality from this cause group was significantly high, while significant elevations were found in most of the higher exposure groups ($P < 0.05$ or stronger).

Deaths from malignancy of the kidney rose with increasing exposure level, although the trend flattened towards the middle of the exposure range, and as with lung cancer, declined in the greatest exposure group. The SMR in the penultimate exposure group showed a statistically significant elevation (SMR = 3.1, $P < 0.05$).

Mortality from all causes also showed an exposure-response relationship, rising from 0.71 in the lowest exposure group to 1.35 in the highest exposure group. Although there was no significant overall excess, the SMRs in the last three exposure groups all were elevated ($P < 0.05$ or stronger).

Poisson Models

Models were fitted to deaths from lung cancer using both untransformed and log transformed cumulative exposure. Models were first fitted with terms for age group and decade, and then using standard rates. The effect of deleting the final exposure group from the analysis was examined, and unlagged and 15 year lagged exposure models fitted.

The first part of Table VI provides a summary of findings for the exposure coefficient for the unlagged models. Inclusion of the last exposure group in the untransformed exposure models led to coefficients small in magnitude, with lack of statistical significance. For the log transformed models, the coefficient for models including the last exposure group was about half that for models excluding that group, but retained statistical significance ($P < 0.010$). Models eliminating the highest exposure group all had highly significant coefficients in comparison ($P < 0.005$ for all). Within this group there was little difference between models based on the transformed

TABLE III. Distribution of Cumulative Exposures to Respirable Free Silica and Average Tenure and Dust Concentration Within Each Exposure Range

		Average		
Exposure range	Number of miners	Cumulative exposure (mg-yr/m^3)	Tenure (yr)	Dust concentration (mg/m^3)
0-	1,748	0.08	5.7	0.023
0.25-	556	0.37	17.5	0.038
0.5-	760	0.73	17.3	0.054
1.0-	509	1.24	24.7	0.065
1.5-	375	1.73	30.3	0.069
2.0-	428	2.42	33.2	0.085
3.0-	374	3.86	36.4	0.116
5.0-	658	10.57	37.9	0.290

TABLE IV. Mortality Statistics for Malignancy of Trachea, Bronchus, and Lung by Respirable Free Silica Exposure Group*

	SMR for each cumulative exposure level (mg-yr/m^3)								
Exposure level	0-	0.25-	0.5-	1.0-	1.5-	2.0-	3.0-	6.0-	All
Observed deaths	29	15	28	22	22	26	29	30	201
Expected deaths	37.8	16.8	20.8	17.3	16.5	17.6	17.1	25.8	179.2
SMR	0.77	0.98	1.26	1.25	1.33	1.47[a]	1.70[b]	1.16	1.17[a]
SRR	1.00	0.91	1.28	1.32	1.32	1.38[a]	1.76[a]	0.86	1.30[b]

*Time since first exposure = 15 years or more.
[a]One-sided $P < 0.05$.
[b]One-sided $P < 0.01$.

versus untransformed exposure, and between those using internal versus external adjustment for age and decade. However, the log transformed models had marginally greater statistical significance.

Use of 15 year lagged exposures generally led to weaker relationships than those found for the unlagged exposures. However, the model with the dust coefficient having the greatest statistical significance was found in this group (for the untransformed exposure using external rates and omitting the final exposure group). Table VII shows excess risk predictions for the latter model. (Excess risk predictions are shown for this model not only because it was the best among those examined here, but because it permits comparison with a recent risk assessment silica exposure in the diatomaceous industry employing models using untransformed exposure with a similar lag period.) The results show that at a 45 year exposure to 0.05 mg/m^3 of silica dust, the excess risk is about 27/1,000 workers.

DISCUSSION

This mortality analysis of Vermont granite workers has shown a clear relationship between exposure to silica and the development of lung cancer. The results have been consistent, in that they emerged using both indirect surrogates of exposure, such as tenure and job, and also using a quantitative index of exposure. Strong relationships of silica exposure with other disease outcomes known to be caused by, or to occur more frequently with, silica exposure, such as silicosis or tuberculosis were also detected. The latter findings validate the derived cumulative exposure estimates, and thus strengthen the view that silica exposure can lead to lung cancer.

Previous mortality analyses of this particular cohort relied upon indirect measures of exposure such as job and tenure [Costello and Graham, 1988; Graham et al., 2001] In particular, work in sheds was equated with higher exposures, while work in the quarry was felt to lead to lower exposures. Overall, the results confirmed this, as long duration of work in the sheds was found to lead to the highest standardized mortality ratio. The exposures employed in this study were derived from an existing job exposure matrix [Davis et al., 1983], which itself had been compiled from data from various industrial hygiene studies [Bloomfield and Waldemar, 1934; Urban, 1939; Hosey et al., 1957; Theriault et al., 1974; Eisen, 1982; Rothman, 1986]. In general, they confirm the view that shed work was more dusty than quarry work. However, this is really only true for the post-dust control period (1950 onwards). During this time, dust concentrations were estimated to be about 3–9 mmpcf (0.02–0.07 mg/m^3) for most jobs in the sheds, while quarry workers had levels lower than 3 mmpcf (0.02 mg/m^3). In the pre-dust control period, the assumption that shed workers had the higher exposures does not appear to be borne out by the dust

TABLE V. Standard Mortality Ratios for Various Causes of Death by Respirable Free Silica Exposure Group*

	SMR for each cumulative exposure level (mg-yr/m^3)								
Exposure level	0-	0.25-	0.5-	1.0-	1.5-	2.0-	3.0-	6.0-	All
Respiratory tuberculosis	0.73	0.00	0.95	4.40[a]	2.73	10.52[b]	13.77[b]	34.01[b]	12.88[b]
Diseases of the respiratory system	0.89	0.98	0.95	1.02	1.63[b]	1.57[a]	1.22	2.53[b]	1.41[b]
Pneumoconiosis	1.04	1.69[a]	1.20	1.34	2.16[b]	1.94[a]	1.70[a]	5.37[b]	2.10[b]
Malignancy of the kidney	0.31	0.76	1.84	2.36	1.71	2.39	3.12[a]	0.50	1.37
All causes	0.71	0.91	0.94	1.10	1.03	1.21[b]	1.12[a]	1.35[b]	1.03

*Time since first exposure = 15 years or more.
[a]One-sided $P < 0.05$.
[b]One-sided $P < 0.01$.

TABLE VI. Mortality Statistics for Malignancy of Trachea, Bronchus, and Lung by Respirable Free Silica Exposure Group*

	SMR for each cumulative exposure level (mg-yr/m^3)								
Exposure level	0-	0.25-	0.5-	1.0-	1.5-	2.0-	3.0-	6.0-	All
Observed deaths	35	18	32	22	17	27	23	27	201
Expected deaths	45.0	17.9	22.5	18.0	13.8	14.4	14.0	24.2	169.7
SMR	0.78	1.01	1.42[a]	1.22	1.23	1.88[b]	1.64[a]	1.12	1.18[b]
SRR	1.00	1.24	2.14[a]	1.93	1.68	2.60[b]	1.90[a]	1.18	1.93[b]

*Exposure lagged by 15 years.
[a]One-sided $P < 0.05$.
[b]One-sided $P < 0.01$.

exposure assessment made by Davis et al. [1983]. Here, three of the five listed quarry jobs had exposure intensities that were 2–3 times higher than the greatest dust concentration for shed jobs. Overall, this indicates that use of department (i.e., shed vs. quarry) as a surrogate indicator for exposure could lead to major misclassification for the pre-dust control period. Accordingly, the quantitative exposure variable employed in the present analysis should provide a more valid indication of exposure-response than past approaches used for this cohort.

It is important to note that the cumulative exposures employed in this analysis are truly a reflection of both time spent in the industry and intensity of exposure. The correlation analysis shows that both average exposure intensity and tenure were substantial contributors to the index, with dust concentration possibly making the greater contribution (correlation coefficient = 0.87 for dust concentration vs. 0.55 for tenure). As a result, it cannot be said that cumulative exposure is mainly an indicator of tenure, a possibility that has been raised as a potential defect by Finkelstein [1995].

Although Vermont granite workers have been the subject of many industrial hygiene and medical surveys, only one study has related mortality outcomes to measured exposure. This was the study by Davis et al. [1983], which used the same basic job exposure matrix employed here as input to a proportional mortality study. The results from this study showed evidence of greatly increased mortality from tuberculosis and silicosis, but only a minor elevation for lung cancer. When the mortality results were tabulated by exposure level, clear gradients in percentage of tuberculosis and silicosis deaths occurred with exposure level, but were not seen for lung cancer or any other cause of death. It seems likely that the small size of the cohort and the limited latency period (26 years maximum) may have restricted the ability of the study to identify any lung cancer associated risks.

Smoking is always an issue in cohort mortality studies involving lung diseases. However, although smoking is repeatedly raised by skeptics as a potential confounder of occupational exposure, there is evidence that it has limited capacity to cause confounding [Asp, 1984; Blair et al., 1985; Siemiatycki et al., 1988]. Wong [2000] has noted that the use of quantitative exposures tends to minimize any possible effects of confounding. In this study, the prior analysis used department and tenure as the indicators of exposure. Had exposure intensities been consistently higher in all shed jobs compared to all quarry jobs, it is conceivable that different levels of smoking facilitated by indoors versus outdoors activities may have led to confounding. However, marked gradients of exposure existed not just between sheds and quarries but also within both locations. Therefore, for confounding to occur, smoking would have to have been corre-

TABLE VII. Exposure-Response Coefficients of Respirable Free Silica From Poisson Models on Lung Cancer Using Untransformed and Log Transformed Data, Internal and External Adjustment for Age and Decade, and Including or Excluding the Final Exposure Group

	Internal adjustment		Adjusted using external rates	
Including last exposure range	**Untransformed**	**Log transformed**	**Untransformed**	**Transformed**
Unlagged models				
Yes	0.016 (0.46)[a]	0.13 (0.0058)	0.017 (0.37)	0.11 (0.0077)
No	0.19 (0.0026)	0.18 (0.0012)	0.18 (0.0016)	0.18 (0.0009)
Lagged models (15 year)				
Yes	0.012 (0.61)[a]	0.097 (0.010)	0.017 (0.40)	0.090 (0.007)
No	0.19 (0.0030)	0.13 (0.0025)	0.19 (0.0008)	0.14 (0.0009)

[a]Exposure regression coefficient and associated *P*-value from Proc Genmod of SAS®.

lated with exposure intensity both within the sheds and within the quarries. Since it is hard to envisage such a scenario, it seems unlikely that major confounding of dust exposure with smoking occurred in this study.

Examination of causes of death apart from lung cancer that are typically associated with smoking (e.g., NMRD, emphysema, heart disease, and cancers of the larynx, bladder, and esophagus) [Steenland et al., 1984] provides little evidence that smoking was more prevalent amongst the shed workers (i.e., those tending to have the higher dust exposures). For the non-malignant diseases (bronchitis, emphysema, and ischemic heart disease), mortality was distinctly greater among the quarry workers compared to the shed workers (421, 206, and 178 for quarry workers vs. 136, 107, and 87 for shed workers), whereas, if smoking were greater in the sheds the opposite would be true. Laryngeal and bladder cancers were found to be elevated in the shed workers (141 and 150 shed compared to 0 and 83 quarry), although esophageal cancer was not (69 shed and 68 quarry). However, for shed workers employed 1940 and after, and for whom the lung cancer rate was significantly elevated, none of the corresponding SMRs for bronchitis, emphysema, ischemic heart disease, or laryngeal, bladder, and esophageal cancer showed significant elevations (150, 62, 76, 69, 113, and 54, respectively). Hence, the argument that the tenure-related trend of lung cancer mortality in workers hired after 1940 is due to excess smoking in that group does not appear to have any foundation.

The apparent reduction in lung cancer mortality in the highest cumulative exposure group is puzzling. Such a drop is not seen for tuberculosis, neither for pneumoconiosis or diseases of the respiratory system. Initially we thought that workers with the highest exposures may have received short but very intense exposures, leading to acute or accelerated silicosis and then premature mortality from these and related causes (i.e., they may have not lived long enough to develop lung cancer). However, the average age at death, although lower, was not appreciably different to those for the lower exposure groups. We do know that this group is distinctive in entering the cohort with substantial exposures—83% had worked for 20 years or more in the high dust levels prevalent prior to controls. They were, therefore, a highly selected healthy worker group. A further reason may be that in the days when tuberculosis and silicosis were the main health concerns in these workers, lung cancer may have been obscured in this group as a cause of death in some cases.

Because of the reservations we had about the final exposure group, we chose to fit exposure-response models with and without it. We did this, not only for the above reasons, but because the last exposure group is so heavily influential that it dominates the model fitting. When all data are included, the model using all of the data implies lack of exposure-response. This is clearly contradictory to the findings for the SRRs, which indicate almost monotonically and statistically significantly increasing risks of lung cancer with rising silica exposure up until that last group. Hence, we feel that the model fitted to all of the data is not truly representative of the underlying pattern in the results. Use of curvi-linear (e.g., quadratic) models does not seem appropriate, since they would imply a downturn in exposure-response with increasing exposure, which seems inconsistent with reasonable concepts of etiologic cause and effect.

Of the two approaches: modeling with or without the final exposure group, we feel that the latter is more valid. First, the data for group with greatest exposure are the weakest, since in that group the exposure estimates are the poorest, there is the great likelihood for cohort selection effects, and competing causes and misdiagnosis are likely. Second, findings from the lower exposure groups comprise 85% of the total deaths, i.e., represent the great majority of the data and are very consistent internally, showing significant excesses rising linearly with increasing exposure. Third, exposure levels of most interest today—those around current compliance and recommended exposure limits (45 years at 0.05 mg/m^3 for instance = 2.25 mg-yr/m^3)—fall within the linear range of the findings within the lower exposure groups, implying that predicted risks for those exposures are more properly estimated from the model without the highest exposure group. Lastly, as noted below the findings obtained omitting the final exposure group are much more consistent with risk estimates obtained in other studies than those from the model using all of the data.

This study has employed industrial hygiene data collected on six occasions between 1924 and 1977. This interval covers the time when exposures were known to be high because of lack of controls, and the period after imposition of controls. No extrapolation of consequence was required in deriving the exposure estimates; only the interpolation between 1940 and 1950 was necessary. Overall, therefore, the exposures employed in this study are superior in quality to those used in most other occupational exposure-response studies. Their primary defect is that they are not company specific. While this was considered desirable, it was not found to be possible with the existing data now available.

In common with certain other published mortality studies [Miller and Jacobsen, 1985; Kuempel et al., 1995], this investigation was based on a cohort derived from worker participation in a medical survey. Accordingly, the work history records derive from worker reports and not from company records. They are, therefore, are truncated at date of last medical examination. Any further work completed after that date is not included in the exposure calculations, resulting in the exposures being underestimates to varying degrees. Data do not exist for us to estimate the degree of underestimation, and the subsequent upwards bias in the exposure-response coefficients. It should be noted, however, that this bias acts in the opposite direction to the attenuation that naturally arises from errors and variability intrinsic to the

work histories, the measured sample data, and the extrapolation process.

The findings reported here are similar but slightly lower than those published on industrial sand workers [Hughes et al., 2001]. There, cumulative exposures of 1.8—4.5 mg-yr/m^3 were associated with a relative risk lung cancer of 2.15 compared to those with exposures <0.70 mg-yr/m^3. This compares to our SRRs of 1.38 and 1.76 for 2.0–3.0 and 3.0–6.0 mg-yr/m^3 compared to <0.25 mg-yr/m^3.

The excess lifetime risks predicted from this study are similar to those published in a recent article examining risk of lung cancer in diatomaceous workers [Rice et al., 2000]. In that study, 45 years of exposure to silica dust at 0.05 mg/m^3 led to a predicted risk of 19 lung cancer cases per thousand. This compares to the 27/1,000 estimated from the present study. The estimates of lifetime excess risk from the best fitting model shown in Table VIII are at the lower end of the range for all models with significant exposure coefficients. The predicted excess risks from the models employing the log-transformed exposure were the greatest, and amounted to 93 per 1,000 at 0.05 mg/m^3 for the 15 year lagged model with external adjustment and omitting the final exposure group. These estimates are fairly similar to 75 year lifetime risks estimated for a silica dust concentration of 0.05 mg/m^3 among industrial sand workers [Steenland and Sanderson, 2001], where they amounted to 140 per 1,000 for a model with 15 year lagged exposures. In the log models in this study, the principle source of the excess risk lay in the increase attributable to silica exposure versus no exposure, as opposed to the much smaller increase associated with increasing silica dust concentration. In contrast, when comparing relative risks attributable to exposure level among workers exposed to silica dust, the relative risks between the lowest and highest concentration levels for the untransformed and log-transformed models were very similar (approx. 1.5).

TABLE VIII. Predicted Excess Risks for Lung Cancer for White Males Following 45 Years Exposure to Silica Dust at Various Concentrations*

Respirable free silica dust level (mg/m^3)	Estimated	Upper 95% CL	Lower 95% CL
0.01	5	2	8
0.02	10	4	16
0.03	15	6	26
0.04	21	8	36
0.05	27	10	48
0.06	34	13	60
0.07	41	15	74
0.08	48	17	89
0.09	56	20	105
0.1	64	22	123

*Model based on untransformed exposure, 15 years lag, omitting last exposure group, and external adjustment. (Estimated risks per 1,000 workers.)

The results of this study of workers exposed almost exclusively to rock dust containing silica and no other major occupational confounding exposures indicate the presence of clear exposure-response for lung cancer and silica exposure. Predictions from the study suggest that the present NIOSH REL (and also the OSHA PEL) might not be fully protective against the development of lung cancer among workers exposed for a full working lifetime.

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