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Lung Cancer among Industrial Sand Workers Exposed to Crystalline Silica

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In 1997, the International Agency for Research on Cancer determined that crystalline silica was a human carcinogen but noted inconsistencies in the epidemiology. There are few exposure-response analyses. The authors examined lung cancer mortality among 4,626 industrial sand workers, estimating exposure via a job-exposure matrix based on 4,269 industrial hygiene samples collected in 1974–1995. The average length of employment was 9 years, and estimated average exposure was 0.05 mg/m^3 (the National Institute of Occupational Safety and Health Recommended Exposure Limit). Results confirmed excess mortality from silicosis/pneumoconioses (standardized mortality ratio = 18.2, 95% confidence interval: 10.6, 29.1; 17 deaths). The lung cancer standardized mortality ratio was 1.60 (95% confidence interval: 1.31, 1.93; 109 deaths). Limited data suggested that smoking might account for 10–20% of the lung cancer excess. Exposure-response analyses by quartile of cumulative exposure (15-year lag) yielded standardized rate ratios of 1.00, 0.78, 1.51, and 1.57 (p for trend = 0.07). Nested case-control analyses after exclusion of short-term workers, who had high overall morality, yielded odds ratios by quartile of cumulative exposure (15-year lag) of 1.00, 1.35, 1.63, and 2.00 (p for trend = 0.08) and odds ratios by quartile of average exposure of 1.00, 0.92, 1.44, and 2.26 (p = 0.005). These data lend support to the labeling by the International Agency for Research on Cancer of silica as a human carcinogen. There are approximately 2 million US workers exposed to silica; 100,000 are exposed to more than 0.1 mg/m^3. *Am J Epidemiol* 2001;153:695–703.

lung neoplasms; silicon dioxide; silicosis

In the 1980s, there were an estimated 1.7 million US workers exposed to crystalline silica outside of the mining industry (1), of whom approximately 100,000 are exposed to a level two or more times greater than the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit of 0.05 mg/m^3 (2). Exposure occurs in foundries, stonework, sandblasting, and potteries. Besides its well-known relation to silicosis, silica exposure in recent years has been associated with lung cancer, and in 1997, the International Agency for Research on Cancer (IARC) determined that inhaled crystalline silica from occupational sources is a definite (group 1) human carcinogen (3). However, IARC qualified its decision by noting that the evidence was not entirely consistent and that different forms of silica might have different potentials for causing lung cancer. Furthermore, there are few studies with adequate data to analyze exposure-response trends, which can provide the strongest evidence for causality, and some studies with exposure-response data were conducted among miners and may have had confounding exposures from other lung carcinogens such as radon.

We have investigated lung cancer in a cohort mortality study of workers in the industrial sand industry and have estimated past exposures, thereby permitting an exposure-response analysis. Many industrial sand plants processed the sand into silica flour, which is composed of fine particles of crystalline silica and which has been associated with high levels of silicosis in the past (4, 5). The industrial sand industry has not had confounding exposures to other known occupational lung carcinogens such as radon and arsenic, confounders that can affect studies of underground mines exposed to silica. Kidney disease and arthritis, other diseases recently related to silica exposure, are discussed in a separate publication (manuscript in preparation).

MATERIALS AND METHODS

Background on the industry

In 1987, the industrial sand industry employed approximately 2,600 workers in 60 plants in the United States (6). Industrial silica sand is obtained from a variety of sources, from a loose, unconsolidated granular state to hard, highly compacted rocks; the ore form of quartz determines how it will be mined. Hard-rock mining is usually done in an open pit quarry where holes are drilled into the rock layers, filled with explosives, and detonated to break the rock into mov-

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Abbreviations: IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; NDI, National Death Index; SMR, standardized mortality ratio; SRR, standardized rate ratio.

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able pieces. Uncompacted sand is collected by using dredges, hydraulic pumps, scrapers, or clamshells. Trucks are often used to transport the sand to the plant for processing, but pipelines and belt conveyors are also used. At the plant, rocks are crushed to obtain progressively smaller sizes; if the sand is already granular, crushing is usually not necessary. The crushed and granular sand is screened and sized. The screening and sizing operation may be either a wet process or a dry one; dry screening typically has higher dust exposures. Often the sand is milled in rotating ball mills to reduce the sand to a fine powder (silica flour). The final sand products, varying in particle size and quartz content, are bagged or bulk-loaded for shipment. Silica sand has a variety of industrial uses. It is used in sandblasting, fine polishing, glassmaking, and rubber manufacture (where silica powder is used as a dry lubricant); as a filler in plastics and paints; and as a carrier in cosmetics (7). The industrial sand industry has little potential for exposures to other known or suspected lung carcinogens. There is some potential of exposure to diesel exhaust from heavy equipment for quarry workers (11 percent of all workers); however, this exposure would be expected to be minimal because it is outside and not in a confined space.

Cohort definition

Our study covers 18 plants in 11 different states, chosen because they were part of a trade association and had adequate records. It is based on 5,086 personnel records of former and current workers collected in 1987–1988 at these plants. All of the plants had discarded the records of workers who terminated prior to some specific year, typically in the 1950s or 1960s. Therefore, person-time began at each of these plants no earlier than that specific year. Because personnel records were not sufficiently accurate to determine whether persons who had worked for only a few days had, in fact, been exposed to silica, all workers were required to have worked at least 1 week. A total of 249 workers (5 percent) had worked for less than 1 week. An additional 156 workers (3 percent) had inadequate data for birth date or work history dates to be included, leaving 4,681 subjects who had worked for a week or more available for analysis. Because US referent rates for certain diseases of interest (e.g., silicosis, multiple-cause analyses of other causes) were available only from 1960 onward, we began mortality follow-up in 1960. This decision led to the elimination of another 55 people (13 deaths) who could not be traced through 1960 (i.e., they had died or were lost to follow-up prior to 1960), leaving a final cohort of 4,626. Because only a small number of people were lost by beginning follow-up in 1960, results were virtually unchanged from those without this restriction on the beginning of follow-up.

Analyses for exposure-response trends were conducted on a smaller subcohort with good work history data, i.e., complete data on dates of employment and the type of job performed while employed. Exposure-response analyses were conducted by using a job-exposure matrix in which estimated exposure levels were assigned to workers on the basis of the jobs they held, the plants in which they worked, and the calendar period in which they worked, as discussed below. Information on where 13 percent of the employees worked was lacking; while employment dates were available, personnel records did not provide information on which jobs these workers held (most of these employees were at one plant that had poor records). These were eliminated for exposure-response analyses, leaving 4,027 available for those analyses. However, people who worked in an unknown job for part of their work history were included in exposure-response analyses; the unknown jobs were assigned the mean exposure level for a plantwide worker with a job title such as "general laborer" or "maintenance worker" in the same plant at the same time period. Only 215 of the 4,027 workers (5 percent) in the exposure-response analyses had an unknown job at some point during their work history, and these unknown jobs represented only 2 percent of all jobs held by these workers (workers had a mean of three jobs during their employment). A further subset of the 4,027 workers in the exposure-response analyses, those with at least 6 months employment (n = 3,361), were also analyzed for exposure-response trends.

Exposure data and job-exposure matrix

Quantitative estimates of exposure to respirable silica were estimated for each worker over time by plant and job via a job-exposure matrix, created by using existing exposure data by job and plant. A thorough description of this procedure is available elsewhere (8). Briefly, 4,269 personal samples for respirable silica were available for 1974–1996, either from the Mine Safety Health Administration (available at all 18 plants) or from company data (available at seven of 18 plants) (modeling indicated no significant differences between Mine Safety Health Administration and company data). These samples covered a wide variety of jobs. These data were then restricted to 1974–1988 (1988 was the end of data collection for our study, so work histories ended in that year) and modeled by using general linear models. Predicted values from the model were used to create a job-exposure matrix for the period 1974–1988. In this matrix, we estimated exposure levels for four categories of plants (low, medium, medium-high, and high), three time periods (1974–1979, 1980–1984, and 1985–1988), and 10 job categories. The time periods were chosen by observing when changes in levels appeared to have taken place, and the 10 job categories were based on the main areas where subjects worked and have been used in other surveys (9).

In addition to the silica measurements after 1974, an exposure assessment study using midget impingers was conducted in 19 silica sand plants in 1946. In this study, dust particles smaller than 5 μm in diameter were counted optically and reported in concentrations of million particles per cubic foot. A summary report of this study presented the results of the sampling as mean dust concentrations (n = 125) by job and plant (9), within the same job categories used in the 1974–1988 data described above. These mean impinger-dust concentrations were converted to respirable-mass silica concentrations in $\mu g/m^3$ by multiplying them by the percent of silica (quartz) found by job

in the respirable dust samples from 1974 to 1988 and a conversion factor of 0.1 (10–12). The converted, job-specific medians of the same 10 job categories considered in the 1974–1988 data were used to estimate job-specific exposures in 1946. The silica respirable concentrations were then extrapolated linearly between 1946 and 1974 for each job category. Exposures prior to 1947 were considered to be constant.

Follow-up and analytic methods

Follow-up was conducted via the National Death Index (NDI) for the years 1979–1996, the Social Security death tapes, and the Internal Revenue Service. Cause-of-death was obtained from NDI or from death certificates obtained from the states for deaths that occurred prior to 1979 ($n = 333$) (not covered by NDI). Social Security death tapes would be expected to cover about three quarters of the deaths occurring in working populations during the years 1960–1978, the follow-up years not covered by NDI in our study (13); about 6 percent of our cohort was last known alive and was not followed through 1979 and, hence, would be susceptible to underascertainment of deaths during this period. This 6 percent was relatively young, and the number of expected deaths missed among this group would be minimal—probably less than 10, or less than 1 percent of all deaths observed.

We used standard life-table analyses for person-time data to analyze the cause-specific rates for the exposed population versus the US population (14). Follow-up began on January 1, 1960, on the date of first exposure, or on the date when records were first available, whichever was later. Follow-up continued until the date of death for deceased subjects, until December 31, 1996 (the end of the NDI search), or until a subject was last known to be alive if that date was earlier than January 1, 1979. Subjects known to be alive after January 1, 1979 and not found in the NDI to be deceased were assumed to be alive as of December 31, 1996. Life-table analyses for cancers considered unlagged data and data lagged 15 years, a typical minimum induction period for epithelial tumors. In addition to underlying-cause analyses, we also conducted multiple-cause analyses in which cause-specific mortality events were defined as any mention on the death certificate. Such analyses are particularly important for diseases that may be prevalent at death but that are not the underlying cause (e.g., tuberculosis, silicosis) (15).

The data (person-time and observed deaths) were divided into quartiles of cumulative exposure (for each worker, $\sum_{i=1}^{n}$ (level of exposure $\times$ duration of exposure), over all i jobs held) for the purposes of categorical exposure-response analyses. Quartile cutpoints were chose before analysis by using the distribution of cumulative exposure for all decedents, motivated by the desire to obtain approximately equally precise estimates of effect in each quartile. Effects were measured either by indirectly standardized mortality ratios (SMRs) by using the US population as referent or by directly standardized rate ratios (SRRs) using the lowest quartile of the exposed as the referent. Tests for linear trends in SRRs or SMRs with exposure were calculated via methods outlined by Rothman (16) or Breslow and Day (17), respectively. In these tests for trends, the midpoints of the exposure categories were used as scores; for the last category, we used the upper category boundary plus 50 percent of the upper category boundary.

More detailed internal exposure-response analyses were conducted via a nested case-control design analyzed by conditional logistic regression. This allowed for analyses by average exposure (cumulative exposure/duration of exposure) and peak exposure in addition to cumulative exposure. Different lag periods could be considered, as well as different transformation of exposure (e.g., log exposure). In these analyses, 100 controls were chosen randomly per case from among all those who had survived to the same age as the case or later. Controls were matched to cases on race, sex, and date of birth within 5 years. An SAS procedure (PHREG) (18) was used to perform the analysis. Quartiles of exposure in these analyses were chosen on the basis of distribution of exposure among noncases. Tests for exposure-response trend were done via use of a continuous variable for exposure in the model.

Lifetime excess risk of lung cancer was calculated, taking into account competing risk of death from other causes (19). Age-specific male lung cancer mortality rates were taken from the Surveillance, Epidemiology, and End Results data for 1987–1991 (20); we used US 1991 age-specific, all-cause mortality rates.

Data on smoking

Limited data on smoking were available for the cohort. Cross-sectional data on smoking were available from company records for 404 men in the cohort. These data were collected during the years 1978–1989 at four of the largest plants in the study where NIOSH gathered more extensive records pursuant to an exposure survey. We focused our analysis of these data on the 358 men aged 25–64 years for comparison with age-specific US data on smoking. We estimated the impact of smoking differences on lung cancer rates for these men versus the US population, which was our comparison population in our cohort mortality analyses. Using techniques for indirect adjustment outlined by Axelson and Steenland (21), we estimated the lung cancer rate ratio between the cohort and the national population due to smoking differences, under the assumption that the men for whom data on smoking were collected at the four plants were representative of the entire cohort. In these calculations, we assumed that the lung cancer rate ratios for heavy smokers (more than one pack a day), light smokers (one pack a day or less), and former smokers were 20, 10, and 5, respectively. Data for the United States were obtained from the 1987 National Health Survey (22). The expected lung cancer rate ratio between the cohort and the US population due to smoking differences alone is $I_{\text{cohort}}/I_{\text{US}}$, where the lung cancer rates for the cohort (I_{cohort}) and for the United States (I_{US}) are each a weighted average of rates for never smokers (rate = I_0), former smokers (rate = $5I_0$), light smokers (rate = $10I_0$), and heavy smok-

TABLE 1. Description of a cohort of 4,620 industrial sand workers, United States

% White	% male	% deceased	Mean year of birth (SD*)	Mean year last observed (SD)	Mean year first employed (SD)	Mean year last employed (SD)	Mean length of employment (years) (SD)	Mean year of death (SD)	% deceased with known cause of death
96.2	98.9	23.5	1941 (17)	1991 (9)	1967 (12)	1976 (10)	8.8 (10.7)	1984 (8)	95

* SD, standard deviation.

ers (rate = $20I_0$), as follows:

$$I_{\text{cohort}} = I_0(\%\ \text{never}_{\text{cohort}}) + I_0(5)(\%\ \text{former}_{\text{cohort}}) + I_0(10)(\%\ \text{light smoker}_{\text{cohort}}) + I_0(20)(\%\ \text{heavy smoker}_{\text{cohort}}),\ \text{and}$$

$$I_{\text{US}} = I_0(\%\ \text{never}_{\text{US}}) + I_0(5)(\%\ \text{former}_{\text{US}}) + I_0(10)(\%\ \text{light smoker}_{\text{US}}) + I_0(20)(\%\ \text{heavy smoker}_{\text{US}}).$$

RESULTS

Table 1 gives descriptive data on the cohort. The mean length of follow-up was 24 years, and the mean year of first employment was 1967. The mean length of employment was 9 years, with a wide range: 20 percent were employed for less than 6 months, while 31 percent were employed for more than 10 years. Twenty-four percent of the cohort had died, and the cause of death was available for 95 percent of the deceased. If missing causes of death were distributed equally among different causes, then one would expect that cause-specific mortality rates in our cohort would be underestimated by approximately 5 percent. There were 101,177 person-years at risk for the entire cohort (n = 4,021).

Table 2 gives exposure data for the 10 job categories used in the analysis for the period 1974–1996. It is apparent from the table that high exposures were not uncommon in these plants. The adjusted geometric means from the model for plants with high, medium-high, medium, and low exposure in the period 1974–1996 were 41.6, 24.8, 15.4, and 11.1 μg/m^3, respectively. Exposures have dropped considerably over time. The geometric mean exposure in 1974–1979 (based on 1,278 samples) was 51 μg/m^3, dropping to 11.6 μg/m^3 for the period 1985–1988 (based on 680 samples). The median exposure in 1946–1947 was 78 μg/m^3 (based on 125 sample means).

Table 2 also shows the distribution of job categories for workers in their last job for the 4,021 workers in the exposure-response analysis, who had an mean of 3.8 jobs. The most common job category was "other," which included "laborers" (20 percent of cohort), general maintenance (7 percent), and mechanics (6 percent). The second most common category was "administrative," which included managers and clerical staff (8 percent), testers (2 percent), and guards (2 percent). Only 0.6 percent of the cohort had undefined or missing job information for their last job.

Table 3 gives data for selected causes of death for the cohort versus the US population, for both underlying and multiple causes. As expected, there are large excesses for silicosis, unspecified pneumoconiosis (probably silicosis), and tuberculosis (often increased among populations exposed to silica). Lung cancer shows a 60 percent excess. There is a general increase of 20–30 percent in mortality for this cohort from all causes combined, cancer, and heart disease. It is likely that lifestyle characteristics such as smoking account for some of this increase, although exposure to silica is likely to play a role for some specific causes, as discussed below.

Table 4 presents exposure-response analyses for selected causes for the subcohort with good work histories (eliminating 13 percent of the original cohort who worked in unknown jobs only). SMRs for lung cancer show elevations in both the first and fourth quartiles of cumulative exposure. Internal SRR analyses for lung cancer using the lowest quartile as referent show a positive trend in SRRs (p = 0.07) for cumulative exposure lagged 15 years. Silicosis and other unspecified pneumoconioses (probably silicosis in this cohort) as underlying causes show a positive trend in SRRs

TABLE 2. Exposure levels in 1974–1996 by job category in 18 industrial sand plants in the United States

Job category (% of workers in cohort in this category based on last job held)*	No. of samples for 1974–1996 (personal breathing zone)	Geometric mean (μg/m^3 silica) (SD†)	% samples NIOSH† REL† (>50 μg/m^3)
Quarry (11%)	680	9.6 (9.3)	27
Crushing (2%)	282	17.1 (11.1)	42
Wet process (4%)	280	17.7 (11.0)	43
Drying (5%)	427	30.6 (8.7)	54
Screening (2%)	163	44.6 (9.6)	66
Milling (6%)	392	30.2 (10.6)	58
Bagging (7%)	1,142	60.2 (9.9)	69
Loading (7%)	252	28.5 (9.8)	54
Administration (15%)	97	3.5 (6.6)	1
Other (41%)‡	554	21.3 (10.2)	46
Overall	4,269	25.9 (10.9)	51

* Based on cohort of 4,021 workers used for exposure-response analyses.

† SD, standard deviation; NIOSH, National Institute of Occupational Safety and Health; REL, recommended exposure limit.

‡ Jobs in the "other" category included laborers (20%), maintenance workers (7%), mechanics (6%), welders (1%), construction workers (1%), and other miscellaneous jobs.

TABLE 3. Standardized mortality ratios and 95% confidence intervals for selected causes of death, underlying and multiple-cause analyses in 18 industrial sand plants in the United States

Cause (ICD-9* code)	Observed deaths (underlying cause)	Underlying cause		Observed deaths (multiple causes†)	Multiple causes	
		SMR*	95% CI*		SMR	95% CI
Respiratory tuberculosis (010–012)	5	3.39	1.09, 7.92	16	4.41	2.52, 7.12
Cancer of the lung, trachea, bronchus (162)	109	1.60	1.31, 1.93	114	1.52	1.26, 1.83
Silicosis (502)	11	66.3	33.1, 118.7	NA*		
Pneumoconioses, not specified (500, 503, 505)‡	6	7.77	2.83, 16.90	NA		
Emphysema (492)	7	0.73	0.29, 1.5	29	1.12	0.75, 1.61
Other respiratory disease, including silicosis§ (470–478, 494–519)	NA			207	2.34	2.03, 2.68
Ischemic heart disease (410–414)	330	1.22	1.09, 1.36	474	1.22	1.11, 1.33
All digestive cancers (150–159)	42	0.99	0.72, 1.34	55	0.99	0.74, 1.29
All cancers (140–208)	254	1.28	1.12, 1.44	416	1.33	1.20, 1.46
All causes	1,073	1.23	1.16, 1.31	2,819	1.33	1.28, 1.38

* ICD-9, *International Classification of Diseases*, Ninth Revision; SMR, standardized mortality ratio; CI, confidence interval; NA, not applicable; COPD, chronic obstructive pulmonary disease.

† Any mention on the death certificate.

‡ ICD-9 code 500, coal miner's pneumoconiosis; ICD-9 code 503, other pneumoconiosis; ICD-9 code 505, unspecified pneumoconiosis; all observed deaths in this category were either ICD-9 code 503 or 505.

§ This category consists of pneumoconioses and nonspecific chronic obstructive pulmonary disease (i.e., excluding emphysema or bronchitis, asthma, and pneumonia). This broader category with chronic obstructive pulmonary disease was the only one available for multiple-cause analysis.

with cumulative exposure ($p < 0.00001$). Multiple-cause analyses of respiratory tuberculosis, emphysema, and other nonmalignant respiratory disease (all nonmalignant disease excluding emphysema, bronchitis, asthma, and pneumonia; 20 percent of deaths in this category had silicosis mentioned on the death certificates) also show positive trends in SRRs with increasing exposure. These categories, especially tuberculosis and nonspecific chronic obstructive pulmonary disease, would be expected to be related to increasing silica exposure.

Analysis of the lung cancer mortality data by duration of employment did not show any consistent trend, but did show elevated lung cancer for those with less than 6 months exposure and for those with 10–20 years and 20 or more years exposure. The lung cancer SMRs for less than 6 months; 6 months to 1 year; and 1–2, 2–5, 5–10, 10–20, and 20 or more years were 2.38 (95 percent CI: 1.17, 4.22), 1.67 (95 percent CI: 0.54, 3.90), 2.27 (95 percent CI: 0.91, 4.68), 1.11 (95 percent CI: 0.44, 2.29), 0.84 (95 percent CI: 0.27, 1.96), 1.67 (95 percent CI: 0.99, 2.64), and 1.54 (95 percent CI: 1.05, 2.17), respectively (based on 11, 5, 7, 7, 5, 18, and 32 deaths, respectively).

Analysis of mortality for all causes combined showed an similar increased mortality for short-term workers with less than 6 months duration of employment. The SMRs for all causes for under 6 months, 6 months to 1 year, and 1–2, 2–5, 5–10, 10–20, and 20 or more years employment were 1.47, 1.03, 1.10, 1.17, 1.00, 1.35, and 1.30, respectively, based on 98, 48, 50, 103, 80, 179, and 302 deaths, respectively.

Short-term workers are known to have high excess mortality, often for reasons unrelated to occupational exposures (23, 24). We therefore reanalyzed the data restricted to those with 6 or more months employment ($n = 3{,}361$). SMR results for these analyses are shown in table 5. While high SMRs for the lowest quartile are now somewhat reduced, they are still elevated. The U-shaped curve of SMRs from table 4 is still apparent, although less marked.

Results of nested case-control analyses of lung cancer for those with more than 6 months employment are shown in table 6. The results for cumulative exposure generally parallel those in table 5. Average exposure (defined as cumulative exposure divided by duration of exposure) showed somewhat more pronounced trends than did cumulative exposure. There was a twofold excess risk for those in the highest quartile with either exposure. Log transformation of exposure variables did not improve the fit of the model. Neither duration of exposure nor lagged duration of exposure showed a significant relation to lung cancer risk. Inclusion

TABLE 4. Exposure-response analyses: standardized mortality ratios (observed deaths) and standardized rate ratios (observed deaths) by quartile of cumulative exposure to respirable silica for selected causes (n = 4,027)* in 18 industrial sand plants in the United States

Cause of death	Quartile of cumulative exposure to respirable silica (mg/m³-years)				
	>0–0.10 (SD†)	>0.10–0.51 (SD)	>0.51–1.28 (SD)	>1.28 (SD)	p value for trend
SMR† (US referent)					
Lung cancer	1.82 (22)	1.24 (19)	1.13 (17)	2.25 (27)	0.17
Lung cancer, 15-year lag‡	1.63 (17)	1.28 (21)	1.61 (20)	2.38 (16)	0.11
Silicosis and unspecified pneumoconiosis	8.3 (1)	10.1 (2)	19.6 (4)	36.7 (7)	0.03
Other respiratory disease, including silicosis§	1.44 (22)	2.40 (47)	2.17 (41)	3.59 (54)	0.0005
Emphysema§	0.87 (3)	0.35 (2)	1.47 (8)	2.10 (11)	0.0005
Respiratory, TB†, multiple cause§	2.06 (1)	1.34 (1)	4.70 (3)	9.03 95)	0.03
SRR† (internal referent)					
Lung cancer	1.00 (22)	0.75 (19)	0.61 (17)	1.50 (27)	0.66
Lung cancer, 15-year lag‡	1.00 (17)	0.78 (21)	1.51 (20)	1.57 (16)	0.07
Silicosis and unspecified pneumoconiosis	1.00 (1)	1.22 (2)	2.91 (4)	7.39 (7)	<0.00001
Other respiratory disease, including silicosis§	1.00 (22)	1.63 (47)	1.45 (41)	2.40 (54)	0.02
Emphysema§	1.00 (3)	0.48 (2)	1.68 (8)	2.50 (11)	0.009
Respiratory TB, multiple cause§	1.00 (1)	0.18 (1)	1.42 (3)	3.37 (5)	0.01

* Analyses based on 4,027 subjects with good detailed work histories; excludes 13% of the total cohort who worked in undefined jobs. SMRs are indirectly standardized rate ratios using the US population as the referent, while SRRs are directly standardized rate ratios using the low exposed group as the referent.

† SD, standard deviation; SMR, standardized mortality ratio; TB, tuberculosis; SRR, standardized rate ratio.

‡ 11 lung cancers were "lagged out" and were not included in this analysis, vs. 8.47 expected.

§ Based on multiple-cause analysis (any mention on death certificate).

of a dichotomous variable for the state in which the plant was located, dichotomized based on state lung cancer rates, had little effect on results.

Review of the death certificates of lung cancer cases found mention of silicosis on only two of 109 death certificates, less than the approximately four instances of joint occurrence expected (43 of 1,073 deaths had silicosis mentioned on the death certificates). This analysis is limited because mortality data underestimate silicosis and because of the small numbers involved.

Assuming a mean exposure level of 0.05 mg/m^3, exposure at the NIOSH Recommended Exposure Limit from ages 20–65 years, and results for the best model in the nested case-control study (average exposure), the lifetime excess lung cancer risk through age 75 for a male would be 1.3 percent (95 percent CI: 0.4, 2.4). With the model for cumulative exposure lagged 15 years, the estimated lifetime excess lung cancer risk was similar (1.4 percent, 95 percent CI: –0.3, 3.8), although confidence intervals were wider. For comparison, the background lung cancer lifetime risk by age 75 years for a US male not exposed to silica is 5.3 percent (smokers and nonsmokers combined). The Occupational Safety and Health Administration generally seeks to regulate levels so that lifetime excess risk does not excess 1 in 1,000.

Data on smoking collected on 346 men aged 25–64 years employed at four plants during the years 1978–1989 are shown in table 7. The most common year of data collection (the mode) was 1987. Table 7 also presents the data for the cohort collected in 1987 and the comparable data for US males in 1987. Use of calendar time- and age-specific data to compare smoking habits between the cohort and the US population is important for a time when smoking habits were changing, as they were in the United States during the 1980s. It is clear that the cohort, especially the younger workers, smoked somewhat more than did the comparable US population. However, differences were not dramatic. We used the 1987 data for the cohort and the United States and applied an indirect adjustment to estimate the effects of smoking differences between the cohort and the United States on expected lung cancer rate ratios. Under the assumption that the smoking differences seen in table 7 are representative of the entire cohort, one would expect a lung cancer rate ratio for the cohort versus the United States of 1.18 based on the data for men aged 25–44 years and a lung cancer rate ratio of 1.09 based on the data for men aged 45–64 years.

We also considered the effect of smoking differences within our cohort to see whether they might account for our positive internal exposure-response trends. Categorical analyses of workers aged 25–64 years for smoking status (never, current, former) by four cumulative exposure categories (those used in table 6), controlling for age category, showed little association between smoking status and cumulative exposure (p = 0.25). A regression of cumulative exposure (continuous variable) on smoking status controlling for age found that neither current (p = 0.37) nor former smokers (p = 0.28) had significantly higher cumulative dose than did never smokers. We also divided our sample of workers with data on smoking into two categories of cumu-

TABLE 5. Exposure-response analyses: lung cancer standardized mortality ratios (observed deaths) by quartile of cumulative exposure to respirable silica in a cohort with 6 or more months employment (n = 3,361)* at 18 industrial sand plants in the United States

	Quartile of cumulative exposure to respirable silica (mg/m³-years)												p value for trend
	>0–0.10			>0.10–0.51			>0.51–1.28			>1.28			
	SMR	95% CI†	(Deaths)	SMR	95% CI	(Deaths)	SMR	95% CI	(Deaths)	SMR	95% CI	(Deaths)	
Cumulative exposure‡	1.55	0.86, 2.71	(12)	1.24	0.75, 1.94	(19)	1.13	0.66, 1.81	(17)	2.25	1.48, 3.27	(27)	0.06
Cumulative exposure, 5-year lag§	1.40	0.67, 2.57	(10)	1.28	0.79, 1.96	(21)	1.61	0.98, 2.49	(20)	2.38	1.36, 3.87	(16)	0.06

* Standardized mortality ratios (SMRs) are indirectly standardized using the US population as the referent. This cohort of 3,361 is a subset of the 4,027 workers in table 4.
† CI, confidence interval.
‡ The SMR for lung cancer (unlagged) in this analysis for all exposed groups combined is 1.48 (95% CI: 1.19, 1.81).
§ Eight lung cancers were "lagged out" and were not included in this analysis, vs. 7.46 expected.

lative exposure (<0.59 and ≥0.59 mg/m³-years) and applied an Axelson-type adjustment. We found that the high-exposure group would be expected to have a lung cancer rate ratio of 1.04 compared with the low-exposure group for those aged 45 years and above because of smoking differences. The corresponding rate ratio for those under age 45 years was 1.10.

DISCUSSION

This cohort is valuable for studying silica exposure and lung cancer because 1) it was unlikely to have had significant exposure to other occupational lung carcinogens, which can occur with silica-exposed workers (e.g., miners, foundry workers), 2) it is reasonably large (109 lung cancer deaths), and 3) it has industrial hygiene sampling data over time, which enabled us to estimate historical levels of silica exposure by job, plant, and calendar time. These exposure estimates enabled us to conduct exposure-response analyses.

Such analyses are less subject to confounding by smoking than are simple comparisons of lung cancer rates in exposed workers versus the general population because workers with a high exposure may be compared with those with a low exposure who are more likely to share similar smoking and other lifestyle habits. Exposure-response trends, or the lack of them, also provide valuable evidence with which to draw conclusions about whether the agent in question truly causes the disease in question.

Weaknesses in our study include 1) the availability of only limited data on smoking, restricted to about 10 percent of the cohort, gathered in the 1980s, and 2) the lack of historic industrial hygiene data for the period 1947–1974, which required use of linear extrapolation between these time points.

We had no gold standard to confirm the validity of our estimates of historical exposure. However, partial confirmation was provided by the significant positive exposure-response trends observed for mortality from diseases known to be caused solely or partly by silica, i.e., silicosis, unspecified pneumoconiosis, tuberculosis, and other nonmalignant respiratory disease.

We found a 60 percent excess of lung cancer overall in the exposed cohort compared with the US population (SMR = 1.60, 95 percent CI: 1.31, 1.93). The cohort experienced high mortality for all causes combined (SMR = 1.23, 95 percent CI: 1.16, 1.31), in part due to elevations in causes related to silica exposure, but probably also partly due to nonoccupational reasons. We found increased smoking in our sample of workers from four plants in the 1980s. However, the amount of increased smoking, compared with the smoking habits of the US population, would have been expected to cause an excess lung cancer mortality on the order of 10–20 percent. Lung cancer rate ratios on the order of 1.10–1.20 due to smoking differences between workers and the general population are what one would expect based on both empirical data (25, 26) and theoretical data (21). Such increased rate ratios due to confounding by smoking can only partially explain the observed 60 percent excess lung cancer rate found in the workers exposed

TABLE 6. Odds ratios and 95% confidence intervals for a nested case-control study of lung cancer among workers with more than 6 months employment† in 18 industrial sand plants in the United States

	Quartile of cumulative exposure to respirable silica (mg/m³-years)											
	0–0.18		>0.18–0.59			>0.59–1.23			>1.23			*p* value for trend*
	OR‡	(Deaths)	OR	95% CI‡	(Deaths)	OR	95% CI	(Deaths)	OR	95% CI	(Deaths)	
Cumulative exposure	1.00	(16)	1.28	0.65, 2.51	(20)	0.73	0.36, 1.49	(12)	1.70	0.88, 3.25	(27)	0.04
Cumulative exposure (15-year lag)	1.00	(20)	1.35	0.72, 2.54	(21)	1.63	0.83, 3.18	(18)	2.00	1.00, 4.01	(16)	0.08
	Quartile of average exposure to silica (mg/m³)											
	0–0.023		>0.023–0.046			>0.046–0.065			>0.065			
	OR†	(Deaths)	OR	95% CI	(Deaths)	OR	95% CI	(Deaths)	OR	95% CI	(Deaths)	
Average exposure	1.0	(15)	0.92	0.42, 2.00	(12)	1.44	0.72, 2.86	(20)	2.26	1.17, 4.38	(28)	0.003

* Trends assessed by a continuous exposure variable.
† Nested within the cohort with good detailed work history and 6 months or more employment (n = 3,361). Cutpoints defined by quartiles of exposure (either cumulative or average) among controls.
‡ OR, odds ratio; CI, confidence interval.

TABLE 7. Data on smoking collected in a cohort of 346 men aged 25–64 years at four industrial sand plants in the United States during 1978–1989

	Ages 25–44 years (n = 180)	Ages 25–44 years, 1987 (n = 74)	Ages 25–44 years, United States, 1989	Ages 44–65 years (n = 166)	Ages 44–65 years, 1987 (n = 73)	Ages 44–65 years, United States, 1987
% never smokers (n = 78)	24	27	42	21	25	26
% current smokers (n = 143)	50	45	36	32	34	34
<1 pack/day (n = 90)	33	29	23	16	14	20
>1 pack/day (n = 58)	17	15	13	17	20	14
% former smokers (n = 125)	26	28	22	46	41	40

to silica. Similarly, the relatively small smoking differences we found between high- and low-exposure groups, assuming that they are representative of the entire cohort, would be unlikely to explain much of our positive exposure-response trends.

Increased lung cancer risk due to increased smoking could also result from effect modification if the lung cancer rate due to smoking and silica together was markedly extremely high compared with that for nonsmokers exposed to silica (21). There are only limited data to date on this point, with inference limited by the number of nonsmoker lung cancers as usual; however, what data do exist do not suggest effect modification by smoking (27).

We also noted that there was an increased all-cause mortality for short-term workers with less than 6 months of employment, which may have reflected nonoccupational lifestyle factors. Elimination of these persons (27 percent of the cohort) reduced, but did not eliminate, the overall lung cancer excess (SMR for lung cancer = 1.49, 95 percent CI: 1.17, 1.87).

Positive exposure-response trends were found for lung cancer with cumulative silica exposure lagged 15 years and with average silica exposure. Most of the literature on silica has focused on cumulative exposure, but there has been one report in the literature of workers exposed to silica in which average exposure, but not cumulative exposure, predicted lung cancer risk (28). In our data, the correlation between average and cumulative silica exposures was 0.45. In contrast to cumulative and average exposures, we found no significant positive trend for lung cancer with duration of exposure, which is a component of cumulative exposure but ignores the level or intensity of exposure.

Exposure-response trends were not always monotonic; workers with the lowest exposures included short-term workers who had relatively high lung cancer rates and high overall mortality rates. Trends for cumulative exposure were stronger and more consistent when those with less than 6 months employment were eliminated.

In conclusion, our findings tend to support the 1997 judgment by IARC that crystalline silica is a lung carcinogen.

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