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Dose-Response Associations of Silica with Nonmalignant Respiratory Disease and Lung Cancer Mortality in the Diatomaceous Earth Industry

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The potential carcinogenicity of crystalline silica to humans remains a controversial issue. The authors conducted an historical cohort mortality study of 2,342 male workers exposed to crystalline silica, predominantly cristobalite, in a diatomaceous earth mining and processing facility in California. During the years 1942–1994, mortality excesses were detected for nonmalignant respiratory diseases (NMRD) (standardized mortality ratio = 2.01, 95% confidence interval (CI) 1.56–2.55) and lung cancer (standardized mortality ratio = 1.29, 95% CI 1.01–1.61). NMRD mortality rose sharply with cumulative exposure to respirable crystalline silica; allowing for a 15-year latency, the rate ratio for the highest exposure stratum (≥5.0 mg/m^3-years) was 5.35 (95% CI 2.23–12.8). The rate ratio for lung cancer reached 2.15 (95% CI 1.08–4.28) in the highest exposure category. These associations were unlikely to have been confounded by smoking or asbestos exposure. The findings indicate a strong dose-response relation for crystalline silica and NMRD mortality. The lung cancer results, although less convincing, add further support to an etiologic role for crystalline silica. *Am J Epidemiol* 1997;145:680–8.

lung neoplasms; occupational exposure; respiratory tract diseases; silicon dioxide

Silicosis and associated restrictive lung disease are well-established consequences of prolonged intense occupational exposures to crystalline silica (1). Whether crystalline silica is a human lung carcinogen remains a controversial issue. Consistently elevated lung cancer risks have been observed among cohorts composed of silicosis cases from numerous industries (2), although questions have been raised regarding confounding from cigarette smoking and selection biases in some of these cohorts (3). Potential confounding by concurrent exposures to other known and suspected lung carcinogens (e.g., radon in underground mines) has clouded the interpretation of the epidemiologic literature (4). Lung cancer excesses have been reported from epidemiologic studies of workers in settings where confounding exposures to known lung carcinogens are absent or minimal, including the quarry and stone (5, 6), refractory brick (7, 8), and diatomaceous earth (DE) (9, 10) industries. Overall cohort relative risks in these studies have not been large (most are less than 2.0), although some provide indications of dose-response relations, evidenced by greatest excesses among silicotics (8) or among workers with the largest cumulative exposures (5, 7, 9). Dose-response estimation for silicosis, lung cancer, and other diseases has been impeded by a lack of historical quantitative dust exposure data in many studies that have relied on employment duration as dose surrogates.

We report here on an extended follow-up and quantitative dose-response analysis of mortality risks among a cohort of workers in the DE mining and processing industry. DE is derived from the skeletal remains of diatoms that are deposited on ocean and lake beds. After extraction of the mineral, which exists as amorphous (noncrystalline) silica, from open-pit mines, DE is crushed and calcined in kilns to produce the final product consisting of 10–60 percent crystalline silica, principally in the form of cristobalite. DE is marketed commercially as a filtration medium for water, foods, and beverages; as a filler in paints and construction materials; and as a carrier of agricultural chemicals.

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Abbreviations: CI, confidence interval; DE, diatomaceous earth; NDI, National Death Index; NMRD, nonmalignant respiratory disease; SMR, standardized mortality ratio.

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The original study (9) was a mortality follow-up of 2,570 white males employed at either of two California DE plants. Standardized mortality ratios (SMR) of 1.43 and 2.59 were observed for lung cancer and nonmalignant respiratory disease (NMRD), respectively, from comparisons with US white males during 1942–1987. Additionally, relatively strong exposure-response gradients, based on internal cohort analyses, were found for both lung cancer and NMRD, with rate ratios reaching roughly 2.7 among workers with the largest cumulative exposures to crystalline silica. The exposure metric used in those analyses was a semi-quantitative index that represented duration of dust exposure, weighted by exposure intensity differences between jobs and time periods, and the percentages of crystalline silica in the various DE product types. Exposure intensity weights relied on the ratings of occupational hygienists because the dust-monitoring data available for the earlier years of plant operations were judged to be too sparse to support direct quantitation. Since then, we have discovered additional historical exposure data extending farther back in time for the larger of the two plants; these data permitted exposure estimation in quantitative units.

After publication of the earlier results, Gibbs and Christensen (11) performed an independent exposure assessment to determine the extent of asbestos exposure that may have been underestimated in the plant. Reanalysis of the lung cancer data indicated no confounding by asbestos (12).

The findings presented in this paper are from a 7-year extended mortality follow-up of the cohort. The principal goal was to estimate quantitative dose-response associations for lung cancer and NMRD.

MATERIALS AND METHODS

Cohort enumeration and follow-up

The two DE plants are located in Lompoc, California, approximately 50 miles north of Santa Barbara. DE mining and milling at the larger plant, on which the analyses reported here are based, have operated continuously since 1902. The study cohort and procedures have been described previously (9). Briefly, the original study cohort was defined as workers employed for at least 12 months cumulative service at either plant and employed for at least 1 day between January 1, 1942 and December 31, 1987. The main study cohort from the earlier analysis was composed of 2,037 non-Hispanic and 533 Hispanic white males. The cohort for whom data are presented here differs in two respects from the previously defined main study cohort: 1) In this analysis, workers (n = 317) employed at the smaller plant were excluded because their exposure data were judged to be inadequate for quantitative estimation; and 2) Eighty-nine workers previously excluded from the main study cohort because of job assignments in DE mixing operations involving asbestos exposure were included in the present analysis because quantitation of their asbestos exposures was possible. Thus, the data presented are for 2,342 white males.

Vital status was determined previously for the years 1942–1987 using several data sources, including the National Death Index (NDI), state driver's license bureaus, and a commercial credit bureau (9). Vital status information for the years 1988–1994, inclusive, was determined from an updated NDI search. Workers known to be alive in 1979 who did not match the NDI files were assumed to be alive as of the end of follow-up; this assumption is supported by the previously noted high sensitivity of the NDI for death identification (13). Copies of death certificates, obtained from state vital statistics offices, were coded by a trained nosologist according to the *International Classification of Diseases*, Fifth through Ninth Revisions, codes in effect at the times of death.

Exposure assessment

Detailed job history data were updated through 1994 for workers still employed as of the end of 1987. The methods for estimating quantitative dust exposures are described in detail elsewhere (14) and will be summarized briefly here. Quantitative air monitoring data, including 5,709 measurements made during 1962–1988, were obtained from the company. These data were supplemented with earlier occupational hygiene data for the years 1948–1962 (686 measurements) that were discovered subsequently in the company's archives. All of the pre-1962 data were based on particle counts, whereas nearly half of the post-1962 data were measured as gravimetric quantities of total dust (17 percent) or respirable dust concentrations (32 percent). Conversion of the data from the older units of million particles per cubic foot to modern gravimetric units in milligrams per cubic meter (mg/m^3) was performed by linear regression modeling on companion sampling data for both measurement methods. Job-specific exposures for years before measurement data were available (pre-1948) were estimated by regression modeling extrapolation based on observed temporal changes and knowledge of dates when dust exposure reduction interventions occurred. Arithmetic mean plant-wide exposure estimates across 135 jobs ranged from 3.55 mg/m^3 before 1948 to 0.29 mg/m^3 for 1974 and later. Job- and time-specific estimates were then made for respirable dust and respirable crystalline silica. The respirable crystalline silica estimates incorporated data

on the percentages of crystalline silica in the various product mixes and estimated job-specific fractions of exposure times to these products (9). The estimates of crystalline silica content were 1 percent for uncalcined DE (quartz content of the ore), 10 percent for calcined DE, and 20 percent for flux-calcined DE. The latter two percentages mainly represent cristobalite. The crystalline silica percentages were provided by knowledgeable industry personnel and were based on measured concentrations in bulk product samples rather than on data from measurements of airborne dust, which were not available. Cumulative exposures (mg/m^3-years) were computed as the summed products of job-specific exposure intensities and associated durations in days.

Chrysotile asbestos had been used in two small operations in the plant at various times from the 1920s to 1977. Gibbs and Christensen (11) derived quantitative estimates of asbestos exposures (fibers/ml) for all cohort members. These estimates were based on historical exposure-monitoring data for jobs in which asbestos was handled directly, production records, and recorded quantities of asbestos included in various mixed products. Additionally, asbestos exposure levels (of unknown fiber type) were estimated for maintenance workers whose exposures were episodic, such as in kiln relining. The assessment provided asbestos exposure estimates for the years since 1930 (11). To complete the asbestos exposure characterization for all relevant periods of employment, we extrapolated the 1930 job-specific intensity estimates to earlier years of plant operation. Cumulative exposures to asbestos (fibers/ml-years) were derived in similar manner as for the silica exposure indices.

Data analysis

Cause-specific mortality rate comparisons were made against rates for US white males for the years 1942–1994. Standardized mortality ratios and 95 percent confidence intervals were calculated using the National Institute for Occupational Safety and Health life table program (15). Lung cancer mortality rates for white male residents of local counties in southern California (Kern, Santa Barbara, San Luis Obispo, and Ventura counties), obtained from the University of Pittsburgh, in Pittsburgh, Pennsylvania, were used to compute a regionally based standardized mortality ratio for lung cancer. Person-time accumulation for each worker began at the later of January 1, 1942 or the date when 1 year of cumulative service was attained.

Dose-response estimation for lung cancer and nonmalignant respiratory diseases was conducted using Poisson regression modeling (16). These internal analyses involved mortality rate comparisons among subcohorts classified according to cumulative exposures to respirable dust and respirable crystalline silica. Five categories of cumulative exposure were defined such that there was an equal number of deaths from all causes in each category. Rate ratios were estimated treating the lowest cumulative exposure category as the referent. Covariates included: age (<40, 40–44, 45–49, 50–54,...,≥80), calendar year (<1955, 1955–1959, ..., 1985–1989, 1990–1994), duration of follow-up (<10, 10–19, ≥20 years), and Hispanic ethnicity, as a binary variable. Hispanic ethnicity was included as a covariate because of well-documented lower lung cancer risks among Hispanic compared with non-Hispanic white males (17). Cumulative exposure to asbestos (fibers/ml-years) was included as a covariate to assess potential confounding. Asbestos categories were defined as nonexposed (0 cumulative exposure) and two strata containing equal numbers of total deaths. Exposure-response analyses were conducted with cumulative exposures of the silica and asbestos indices lagged by 0 and 15 years to accommodate disease latency effects. Poisson regression modeling was performed using the AMFIT Version 2.0 program of the Epicure statistical package (18).

Evaluation of confounding by cigarette smoking

Data on smoking habits, collected since the early 1960s as part of the company's radiographic screening program, permitted distinctions of ever versus never smoked for 1,171 (50 percent) cohort members. Smoking prevalence was examined in relation to cumulative exposures, and the method described by Axelson (19) was applied to estimate confounding bias in observed rate ratios.

RESULTS

Descriptive characteristics and vital status follow-up data for the cohort are summarized in table 1. Vital

TABLE 1. Descriptive characteristics and vital status ascertainment for the cohort of 2,342 white males, California, 1942–1994

Variable	Median	Range
Year of birth	1927	1881–1966
Age at hire	24.5	15.0–60.5
Year of hire	1952	1908–1986
Duration of employment (years)	5.54	1.00–49.3
Duration of follow-up (years)	29.9	<1–53.0
Vital status as of December 31, 1994	**No.**	**%**
Alive	1,379	58.9
Dead	749	32.0
With certificate	716	95.6*
Without certificate	33	4.4*
Unknown	214	9.1

* Percent of deaths.

status was determined for 91 percent of the cohort, and death certificates were obtained for 716 (96 percent) of 749 deaths that occurred during 1942–1994. The cohort contributed 66,060 person-years of observation. Distributions of cumulative exposures to respirable dust, respirable crystalline silica, and asbestos are presented in table 2.

Mortality comparisons with rates for US white males for causes of death with expected numbers greater than 2.0 are presented in table 3. Observed mortality from all causes combined was nearly identical to expectation (SMR = 1.02), and only a small excess was detected for all cancers (SMR = 1.06). Relative mortality deficits were observed for ischemic heart disease (SMR = 0.82), cerebrovascular disease (SMR = 0.86), diabetes mellitus (SMR = 0.71), and digestive system diseases (SMR = 0.61); this pattern is consistent with a healthy worker effect typically seen in industrial cohorts (20).

As in the earlier analysis (9), we excluded pneumonia and infectious diseases from the NMRD category in order to focus on the conditions most plausibly associated with occupational dust exposure. The NMRD category included 27 deaths with underlying causes indicative of pneumoconiosis or silicosis listed as: "silicosis" (7), "diatomaceous earth pneumoconiosis" (5), "silicosis and asbestosis" (1), "pneumoconiosis" not otherwise specified (9), "pulmonary fibrosis" (4), and "idiopathic pulmonary fibrosis" (1). There were no deaths from silicotuberculosis. Other NMRD deaths were attributed to emphysema (14), asthma (3), chronic bronchitis (3), pneumonitis (4), and chronic obstructive pulmonary disease, not otherwise specified (16). There was a prominent mortality excess of NMRD (SMR = 2.01) and a smaller excess for lung cancer (SMR = 1.29). The lung cancer SMR increased to 1.44 (95 percent CI 1.14–1.80) in comparison with local county rates. Mortality from other cancers was largely unremarkable, although excesses based on small numbers were detected for cancers of the larynx (SMR = 1.73, four observed) and brain and central nervous system (SMR = 1.38, seven observed).

The largest NMRD mortality excesses occurred among workers hired between 1920 and 1939 (table 4). The NMRD elevations among workers hired since 1960 suggest a persistent risk, although the corresponding standardized mortality ratios are based on very small observed numbers. In contrast, the excesses of lung cancer were apparently limited to workers hired before 1960. Age at death was generally unrelated to an excess of either NMRD or lung cancer.

As shown in table 5, there were consistently strong NMRD mortality gradients with respect to the dust exposure indices. The association with cumulative exposure to respirable crystalline silica was stronger than with the less-specific respirable dust index, irrespective of lag interval. The most pronounced trend was seen for respirable crystalline silica, lagged 15 years; the rate ratio for the highest exposure stratum (≥5.0 mg/m^3-years) compared with the lowest exposure category (<0.5 mg/m^3-year) reached 5.35 (95 percent CI 2.23–12.8). The trend slopes were unchanged when adjustments were made for cumulative exposure to asbestos.

Dose-response trends for lung cancer (table 6) were considerably weaker than those detected for NMRD. Despite the absence of consistent monotonically increasing gradients, there is evidence for a positive dose-response relation for lung cancer, particularly with cumulative exposure to respirable crystalline silica. The rate ratio for the ≥5.0 mg/m^3-year stratum was 2.15 (95 percent CI 1.08–4.28). As with the NMRD findings, control for asbestos exposure did not alter the dose-response slopes. The results for pleural and peritoneal mesothelioma, often regarded as sentinels for asbestos exposure, did not suggest an asbestos hazard. We observed one death due to pleural cancer, probably a mesothelioma, compared with 0.68 expected, and there were no deaths from peritoneal mesothelioma.

A possible synergistic effect of crystalline silica and asbestos exposure on lung cancer risk was of interest, particularly in view of some suggestive findings from a previous analysis of this cohort (12). Rate ratios for

TABLE 2. Distributions of cumulative exposures to respirable dust, respirable crystalline silica, and asbestos

		Percentile						
	Mean (SD)*	0	10	25	50	75	90	100
Respirable dust†	7.31 (12.00)	0	0.54	1.46	3.58	8.33	16.69	168.84
Respirable crystalline silica†	2.16 (3.51)	0	0.13	0.37	1.06	2.48	5.14	62.52
Asbestos‡	1.44 (4.44)	0	0	0	0.05	1.36	3.68	97.55

* SD, standard deviation.
† Milligrams per cubic meter × years (mg/m^3–years).
‡ Fibers per milliliter × years (f/ml–years).

TABLE 3. Standardized mortality ratios for selected causes of death, 1942–1994

Cause of death	Observed	Expected*	SMR†	95% CI†
All deaths	749	737	1.02	0.94–1.09
All cancers	181	171	1.06	0.91–1.22
MN,† buccal cavity, pharynx	4	4.62	0.87	0.24–2.22
MN, esophagus	1	4.22	0.24	0.01–1.32
MN, stomach	7	6.83	1.03	0.41–2.11
MN, intestines, except rectum	14	15.5	0.90	0.49–1.52
MN, rectum	3	3.97	0.76	0.16–2.21
MN, liver	4	3.97	1.01	0.27–2.58
MN, pancreas	10	8.66	1.15	0.55–2.12
MN, larynx	4	2.32	1.73	0.47–4.42
MN, trachea, lung, bronchus	77	59.9	1.29	1.01–1.61
MN, prostate	11	12.6	0.88	0.44–1.57
MN, kidney	3	4.31	0.70	0.14–2.04
MN, bladder	2	4.46	0.45	0.05–1.62
MN, skin	2	3.53	0.57	0.07–2.05
MN, brain and nervous system	7	5.06	1.38	0.56–2.85
Leukemia and aleukemia	5	6.47	0.77	0.25–1.81
Other hematologic malignancies	5	5.88	0.85	0.28–1.99
Diabetes mellitus	8	11.3	0.71	0.31–1.40
Ischemic heart disease	191	232	0.82	0.71–0.95
Cerebrovascular disease	34	39.5	0.86	0.60–1.20
Digestive diseases	21	34.6	0.61	0.38–1.93
Genitourinary diseases	10	9.47	1.06	0.51–1.94
Respiratory diseases	91	50.9	1.79	1.44–2.20
Pneumonia	22	16.5	1.33	0.83–2.01
Emphysema	14	8.56	1.64	0.89–2.75
Respiratory diseases except pneumonia, infections	67	33.4	2.01	1.56–2.55
Nervous system diseases	7	8.63	0.81	0.33–1.67
Accidents	50	45.7	1.10	0.81–1.44

* Based on rates for US white males, 1942–1994.
† SMR, standardized mortality ratio; CI, confidence interval; MN, malignant neoplasms.

joint strata of crystalline silica and asbestos cumulative exposures, each lagged 15 years, are presented in table 7. At each level of cumulative asbestos exposure, lung cancer risk was only elevated in the highest crystalline silica stratum. In comparison, lung cancer mortality was inversely associated with asbestos exposure among the lowest crystalline silica stratum. The similarity of rate ratios in the highest crystalline silica stratum across levels of asbestos exposure (bottom row) does not indicate a synergistic effect.

The distribution of cigarette smoking prevalence, based on data for 50 percent of the cohort, across increasing categories of cumulative exposure to respirable dust lagged 15 years, was 0.64, 0.81, 0.84, 0.84, and 0.84. A similar distribution was detected with respect to cumulative exposure to crystalline silica lagged 15 years: 0.63, 0.82, 0.80, 0.86, and 0.83. We applied the method of Axelson (19) to estimate smoking-adjusted effect estimates. Based on the observed smoking distributions and assuming a 20-fold increase risk for lung cancer among smokers compared with nonsmokers, the rate ratios for lung cancer in the highest exposure strata of respirable dust and crystalline silica, each lagged 15 years, would be decreased to 1.59 and 1.67, respectively. Assuming a 20-fold increased risk for NMRD related to smoking, the corresponding revised rate ratios for NMRD mortality would be 2.62 and 4.15.

DISCUSSION

Extended follow-up of this cohort and the discovery of additional exposure data permitted more precise quantitation of dose-response relations than was possible previously (9). There are, however, certain limitations of our study that deserve comment. Vital status could not be ascertained for 9 percent of the cohort, which may have caused inflated standardized mortality ratios for the cohort as a whole because person-year accumulation was truncated for unknowns at the dates that they were last known to be alive. However, the internal analyses of dose-response trends for NMRD and lung cancer may have been biased slightly downward by incomplete vital status tracing because vital status was more complete for workers hired since 1960 (98 percent) than for those hired in earlier years (87 percent), when exposures and disease risks were highest.

TABLE 4. Nonmalignant respiratory disease and lung cancer mortality comparisons with US white males, by year of hire, year of death, and age at death, 1942–1994

	NMRD*			Lung cancer		
	No. of deaths	SMR*	95% CI*	No. of deaths	SMR	95% CI
Year of hire						
<1920	0	0		3	20.8	4.29–60.8
1920–1929	9	3.01	1.37–5.71	5	1.52	0.49–3.55
1930–1939	17	3.97	2.31–6.35	8	1.29	0.56–2.55
1940–1949	29	1.73	1.16–2.49	37	1.28	0.90–1.76
1950–1959	7	0.93	0.37–1.92	21	1.27	0.79–1.95
1960–1969	3	1.98	0.41–5.82	3	0.72	0.14–2.11
≥1970	2	8.14	0.99–29.4	0	0	
Year of death						
<1950	0	0		0	0	
1950–1959	4	3.29	0.90–8.42	6	2.54	0.93–5.54
1960–1969	7	2.01	0.81–4.14	9	1.37	0.62–2.60
1970–1979	19	2.69	1.62–4.20	24	1.68	1.07–2.50
1980–1989	31	2.41	1.63–3.41	26	1.14	0.74–1.66
1990–1994	6	0.69	0.25–1.50	12	0.87	0.45–1.53
Age at death (years)						
<40	0	0		0	0	
40–49	4	2.31	0.63–5.90	4	0.80	0.22–2.06
50–59	14	2.90	1.58–4.87	24	1.59	1.02–2.37
60–69	13	1.12	0.60–1.92	26	1.09	0.71–1.60
70–79	30	2.69	1.82–3.84	22	1.64	1.03–2.48
≥80	6	1.47	0.54–3.20	1	0.39	0.01–2.19

* NMRD, nonmalignant respiratory disease; SMR, standardized mortality ratio, based on rates for US white males, 1942–1994; CI, confidence interval.

The validity of our dose-response estimates is largely dependent on the quality and completeness of exposure data. Available data on dust monitoring spanned the years 1948–1988, with the majority of measurements made since the early 1960s. Consequently, extrapolation models were necessitated to estimate exposure concentrations for earlier years (14). Uncertainties in the conversion factors for dust particle counts to gravimetric units, the respirable fractions of dust concentrations, and the relative amounts of crystalline silica in the dust are other potential sources of measurement error. Nonetheless, exposure assessment was performed in a blinded manner with regard to health outcome, thus virtually ensuring that there was nondifferential misclassification, which ordinarily, although not always (21), will result in attenuated dose-response relations. Exposure to asbestos could be documented from personnel records for workers assigned to two small, dust-mixing operations during 1952–1977; however, asbestos exposures may also have been experienced by workers who had temporary, yet unrecorded, assignments in those departments, as well as episodically by maintenance workers involved in lagging and kiln relining (11). Therefore, misclassification of asbestos exposure may have hindered our ability to control for asbestos as a potential confounder (22).

Mortality from NMRD continued to be excessive in this cohort and bore a strong relation to cumulative dust exposure. Silicosis has been documented as a hazard in this facility since the 1930s (23), with declining prevalence noted subsequent to dust exposure reductions (24). The dose-response trends observed for NMRD mortality undoubtedly reflect the association with silicosis and its sequelae. We have obtained historical chest radiographs for the majority of the cohort and are currently undertaking a more explicit assessment of silicosis time trends and dose-response relations. Obstructive diseases included in the NMRD grouping have been associated with silica exposures among metal miners (25, 26) and pottery workers (27). Our findings for NMRD indicating strong, monotonically increasing exposure-response associations with crystalline silica are consistent with other studies of cohorts exposed to silica. The rate ratio of 5.35 that we observed for the highest cumulative exposure category of respirable crystalline silica, lagged 15 years, is in line with relative risk estimates of 2.4–8.9 found in the most heavily exposed segments of US crushed stone industry workers (6), Italian refractory brick workers (7), South African gold miners (25), and US gold miners (28). However, direct quantitative comparisons of exposure-response gradients across these studies are complicated by differences in the catego-

TABLE 5. Nonmalignant respiratory disease mortality trends by cumulative exposure to respirable dust and cumulative exposure to respirable crystalline silica, 1942–1994

Cumulative exposure (mg/m³-years*)	Respirable dust						Cumulative exposure (mg/m³-years*)	Respirable crystalline silica					
	Exposure lag (years)							Exposure lag (years)					
	0			15				0			15		
	Deaths	RR*	95% CI*	Deaths	RR	95% CI		Deaths	RR	95% CI	Deaths	RR	95% CI
<1.9	10	1.00		13	1.00		<0.5	7	1.00		10	1.00	
1.9–<4.0	8	0.94	0.37–2.40	9	1.26	0.51–3.15	0.5–<1.1	8	1.52	0.55–4.20	9	2.04	0.77–5.45
4.0–<7.4	9	1.18	0.47–2.98	8	1.25	0.48–3.25	1.1–<2.1	10	1.98	0.75–5.22	8	1.96	0.71–5.43
7.4–<18.3	14	1.37	0.59–3.20	11	1.31	0.53–3.24	2.1–<5.0	12	2.34	0.91–6.00	13	3.17	1.25–8.05
≥18.3	26	2.63	1.16–5.94	26	3.39	1.49–7.70	≥5.0	30	4.79	2.01–11.9	27	5.35	2.23–12.8
Trend slope†		1.02	1.00–1.03		1.02	1.01–1.03			1.08	1.03–1.13		1.08	1.03–1.14
Trend slope adjusted for asbestos exposure (f/ml-years*)		1.02	1.00–1.03		1.02	1.00–1.03			1.08	1.02–1.14		1.08	1.03–1.14

*mg/m³-years, milligrams per cubic meter × years; RR, rate ratio, adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic); CI, confidence interval; f/ml-years, fibers per milliliter × years.

† Rate ratio per mg/m³-years, adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic).

TABLE 6. Lung cancer mortality trends by cumulative exposure to respirable dust and cumulative exposure to respirable crystalline silica, 1942–1994

Cumulative exposure (mg/m³-years*)	Respirable dust						Cumulative exposure (mg/m³- years*)	Respirable crystalline silica					
	Exposure lag (years)							Exposure lag (years)					
	0			15				0			15		
	Deaths	RR*	95% CI*	Deaths	RR	95% CI		Deaths	RR	95% CI	Deaths	RR	95% CI
<1.9	15	1.00		18	1.00		<0.5	17	1.00		22	1.00	
1.9–<4.0	13	1.01	0.48–2.13	14	1.31	0.62–2.76	0.5–<1.1	14	1.07	0.53–2.18	12	0.96	0.47–1.98
4.0–<7.4	11	0.99	0.45–2.19	15	1.64	0.78–3.47	1.1–<2.1	7	0.55	0.23–1.32	9	0.77	0.35–1.72
7.4–<18.3	20	1.50	0.75–2.99	14	1.43	0.66–3.12	2.1–<5.0	15	1.19	0.59–2.41	14	1.26	0.62–2.57
≥18.3	18	1.67	0.77–3.63	16	2.05	0.92–4.56	≥5.0	24	2.11	1.07–4.11	20	2.15	1.08–4.28
Trend slope†		1.01	1.00–1.03		1.01	1.00–1.03			1.06	1.01–1.11		1.05	0.99–1.11
Trend slope adjusted for asbestos exposure (f/ml × years*)		1.01	1.00–1.03		1.01	1.00–1.03			1.06	1.01–1.11		1.05	0.99–1.11

*mg/m³-years, milligrams per cubic meter × years; RR, rate ratio, adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic); CI, confidence interval; f/ml-years, fibers per milliliter × years.

† Rate ratio per mg/m³-years, adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic).

TABLE 7. Lung cancer mortality by cumulative exposures to respirable crystalline silica and asbestos, each lagged 15 years, 1942–1994

Respirable crystalline silica (mg/m³–years*)	Asbestos (f/ml × years*)								
	0			>0–1.20			>1.20		
	Deaths	RR*	95% CI*	Deaths	RR	95% CI	Deaths	RR	95% CI
<0.5	18	1.00†		3	0.88	0.25–3.14	1	0.57	0.07–4.46
0.5–<1.1	5	0.73	0.26–2.01	4	1.27	0.42–3.86	3	0.93	0.26–3.28
1.1–<2.1	5	0.73	0.26–2.03	3	1.19	0.34–4.16	1	0.33	0.04–2.53
2.1–<5.0	6	1.00	0.38–2.62	2	0.75	0.17–3.32	6	1.90	0.71–5.05
≥5.0	13	2.03	0.93–4.45	4	2.09	0.68–6.47	3	1.77	0.50–6.22

* mg/m³–years, milligrams per cubic meter-years; f/ml × years, fibers per milliliter-years; RR, rate ratio, adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic); CI, confidence interval.
† Reference category.

rization of NMRD and the exposure metrics used for analysis (e.g., mg/m^3-years in our study and particle-days in the US gold miners study (28)).

The overall lung cancer excess relative to national (SMR = 1.29) or local (SMR = 1.44) mortality rates is similar to those reported for other cohorts exposed to silica (4), but slightly reduced from the standardized mortality ratios (1.43 and 1.59 compared with national and local rates, respectively) that we observed previously for 1942–1987 (9). The decreased standardized mortality ratios may be partly due to more complete vital status tracing for the extended follow-up interval. We detected reasonably strong, but not monotonically increasing, dose-response trends for lung cancer. Excess risk was predominantly concentrated in the highest cumulative exposure stratum of either respirable dust or respirable crystalline silica. The choice of exposure category boundaries, made somewhat arbitrarily, was not the sole explanation for the shape of the dose-response trends; similar relative risk gradients were found when we varied the number and location of exposure boundaries. The trends for the two dust-exposure metrics were not appreciably different, although the rate ratio per mg/m^3-year of crystalline silica (1.05–1.06) was slightly greater than the corresponding trend for respirable dust, ignoring the crystalline component (rate ratio = 1.01). In contrast, the association with NMRD risk was considerably stronger with the crystalline silica metric than with respirable dust. These findings indicate that crystalline silica was more important etiologically than other dust components (e.g., amorphous silica), particularly in the case of NMRD.

We found no evidence that asbestos exposure in the DE industry confounded the observed associations for NMRD and lung cancer. Statistical adjustment for asbestos exposure had no influence on the dose-response trends for NMRD and lung cancer. Moreover, we did not observe an independent association of asbestos with lung cancer risk. The occurrence of only one death from pleural mesothelioma and one death attributed jointly to silicosis and asbestosis further indicates the absence of an important asbestos hazard in this plant. The amount of asbestos used in filtration products was quantitatively very small compared with calcined DE. Therefore, even when considering exposures to maintenance workers, asbestos levels were probably too low to have posed a substantial lung cancer risk in this cohort.

It is very unlikely that confounding by cigarette smoking was the sole or predominant explanation for the observed associations with NMRD and lung cancer. Our ability to assess potential confounding by smoking was limited by incomplete, crude data. The slightly lower prevalence of smoking in the subset of workers with the lowest cumulative dust exposures suggests the possibility of confounded internal comparisons. However, the patterns of smoking prevalence and rate ratios for lung cancer (and NMRD) mortality with respect to dust exposure were dissimilar. In particular, smoking prevalence was very similar in the two highest exposure strata of respirable crystalline silica lagged 15 years (0.86 vs. 0.83), contrasted with a marked difference in lung cancer rate ratios (1.26 vs. 2.15).

The lung cancer results for our cohort are generally consistent with those from a considerably smaller cohort of Icelandic workers (10). Compared with national incidence rates, the Icelandic cohort experienced a 14 percent overall excess, whereas a standardized incidence ratio of 2.34 was noted for workers employed for 5 years or longer. The epidemiologic evidence from other studies concerning silica and lung cancer has been mixed, as exemplified by quantitative dose-response estimation from two studies of gold miners. Hnizdo and Sluis-Cremer (29) detected a positive dose-response association of respirable dust counts with lung cancer among South African gold miners, although confounding by radon exposure could not be discounted. In contrast, lung

cancer was apparently not dose-related in a cohort of South Dakota gold miners (28), despite a past history of very intense silica exposures revealed by pronounced NMRD risks.

Our findings for NMRD strongly indicate an etiologic role of crystalline silica. Additionally, our dose-response analyses provide support for the hypothesis that crystalline silica is a human lung carcinogen, albeit not an overwhelmingly potent carcinogen. Comparisons of the lung cancer results in this cohort with findings from most other studies may not be fully appropriate because cristobalite is the principal source of crystalline silica in the DE industry, whereas quartz is the main silica polymorph in most other settings. Possible differences in carcinogenic potential among the various polymorphs would complicate interpretations of the epidemiologic literature. Inasmuch as occupational exposures to crystalline silica are widespread throughout the world, a clear resolution of carcinogenic potential(s) will have significant implications for worker protection policies.

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