Mortality among workers in the diatomaceous earth industry

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Abstract

A cohort mortality study was conducted among workers from two plants in the diatomaceous earth mining and processing industry in California. Diatomaceous earth consists of the skeletal remains of diatoms. Exposure to amorphous (non-crystalline) and crystalline silica in the form of quartz results from open pit mining and exposure to crystalline silica (principally cristobalite) occurs in the processing of the material. Lung cancer and non-malignant respiratory diseases have been the health outcomes of greatest concern. The main study cohort included 2570 white men (533 Hispanic and 2017 non-Hispanic workers) who were employed for at least 12 months cumulative service in the industry and who had worked for at least one day during the follow up period, 1942-87. Vital status was ascertained for 91% of the cohort and death certificate information was retrieved for 591 of 628 (94%) identified deaths. The all causes combined standardised mortality ratio (SMR) was slightly increased (SMR = 1.12; 628 observed) compared with rates among US white males. The principal contributors to this excess were increased risks from lung cancer (SMR = 1.43; 59 observed) and non-malignant respiratory disease (NMRD) excluding infectious diseases and pneumonia (SMR = 2.59; 56 observed). The excess of lung cancer persisted when local county rates were used for comparison (SMR = 1.59). Internal rate comparisons by Poisson regression analysis were conducted to assess potential dose-response relations for lung cancer and NMRDs. Mortality trends were examined in

relation to duration of employment in dust exposed jobs and with respect to an index of cumulative exposure to crystalline silica. The crystalline silica index was a semiquantitative measure that combined information on duration of exposure, differences in exposure intensity between jobs and calendar periods, the crystalline content of the various product mixes, and the use of respiratory protection devices. Increasing gradients of risk were detected for lung cancer and NMRD with both exposure indices. The relative risk trends for lung cancer and NMRD with crystalline silica exposure lagged 15 years were respectively: 1.00, 1.19, 1.37, and 2.74, and 1.00, 1.13, 1.58, and 2.71. Based on a review of available but limited data on cigarette smoking in the cohort and from application of indirect methods for assessing confounding variables, it seems unlikely that smoking habits could account for all of the association between exposure to dust and lung cancer. The intense and poorly controlled dust exposures encountered before the 1950s were probably the most aetiologically significant contributors to risks from lung cancer and NMRDs. The absence of an excess of lung cancer among workers hired since 1960, and the finding of no deaths attributed to pneumoconiosis as an underlying cause of death among workers hired since 1950 indicate that exposure reductions in the industry during the past 40 years have been successful in reducing excess risks to workers. Further mortality follow up of the cohort and the analysis of radiographic data will be needed to determine conclusively the long term patterns of disease risks in this industry.

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The potential carcinogenicity of crystalline silica has been a topic of considerable interest and debate in recent years.¹⁻³ In 1987 the International Agency for Research on Cancer (IARC)⁴ classified crystalline silica as a probable human carcinogen,

based on a review of epidemiological and experimental evidence. The lung is the principal target site in exposed human populations because inhalation of dust containing crystalline silica is the primary route of exposure. The strongest associations for lung cancer have been found in cohort studies of silicotic patients, which may indicate a dose response relation.⁵⁻¹⁰ Alternatively, it has been suggested that the studies of silicotic patients may be confounded by exposures to other lung carcinogens (for example, radon in underground mines) or increased prevalences of cigarette smoking.³ A recent study from North Carolina showed an excess of lung cancer among silicotic patients who were non-smokers and not exposed to other suspected occupational carcinogens.¹⁰ The potential for confounding by concomitant exposures to other carcinogens exists in studies of underground metal miners,¹¹⁻¹⁴ pottery and ceramics,^{15,16} and foundries¹⁷⁻¹⁹ where excesses of lung cancer have been found. Possible confounding factors in these studies include radon, arsenic, and diesel exhausts in underground mines, fibrous and non-fibrous talc in pottery and ceramics industries, and polycyclic aromatic hydrocarbons and formaldehyde in foundries. There have also been epidemiological studies of risks of lung cancer among occupational cohorts exposed to silica but with low or no potential exposure to other suspected carcinogens. Estimates of relative risk of lung cancer ranging from 1.1 to 2.0 have been reported from studies of workers in the granite and slate²⁰⁻²³ and refractory brick^{24,25} industries.

We undertook a historical cohort study of the mortality patterns of workers from two plants in the diatomaceous earth (DE) mining and processing industry. Diatomaceous earth is a mineral derived from the skeletal remains of diatoms that are deposited on marine and lake floors. Exposure to amorphous (non-crystalline) and crystalline silica, in the form of quartz, occurs from open pit mining of DE. Exposure to crystalline silica, predominantly cristobalite, results from DE calcining and handling. Exposures to radon, arsenic, and other occupational carcinogens are either non-existent or minimal in this industry. Concerns about the possibility of an association between lung cancer and silica prompted this study. Risks for silicosis among workers in the DE industry have been reported in the United States²⁶⁻²⁸ and Europe^{29,30} since the 1930s. In 1957 a radiographic survey of workers in five DE plants in California, Nevada, and Oregon conducted by the United States Public Health Service showed a 25% prevalence of silicosis among workers employed for five or more years in the DE industry, and a nearly 50% prevalence in workers employed in areas with the most intense concentrations of cristobalite exposure.³¹

Subsequent radiographic surveys conducted at these plants indicated considerable reductions in silicosis prevalence (roughly 2% overall by 1984) that seemed to have paralleled reductions in levels of dust exposure.^{32,33}

To our knowledge, ours is the first cohort study of mortality patterns among workers in the DE industry ever conducted.

Materials and methods

STUDY SETTING

The study was conducted among the workforces of two DE mining and processing operations in Lompoc, California located roughly 80 km north of Santa Barbara. DE was discovered in the Lompoc area in the late nineteenth century, and mining and milling began at the larger of the two plants in 1902. The second plant began mining in 1946 and milling in 1952.

DE is extracted by open pit or quarry mining. The raw (natural) material, of which the silica content is primarily amorphous, is then crushed and dried and air classified to remove contaminants. The raw material may then be calcined by heating in a kiln at temperatures ranging from 800° to 1000°C. Calcining can be done with or without addition of a flux material, either sodium carbonate or sodium chloride. The raw material contains from trace amounts (<0.1%) to roughly 4% crystalline silica, mainly in the form of quartz from the earth's crust. The percentage of crystalline silica (primarily cristobalite) increases with a combination of time and temperature, particularly in the presence of a flux. Results of industrial hygiene samples taken by the participating companies indicate that cristobalite constitutes about 10%-20% and 20%-25% of the respirable fractions of calcined and flux calcined DE. DE is marketed commercially for use as a filtration aid for water, foods, and beverages, as a filler in construction materials, paints, and insulation, and as a carrier or anticaking agent for agricultural chemicals.

STUDY POPULATION

The study population was enumerated from plant personnel records that seemed to be complete for workers employed since 1942. The cohort was limited to workers who were employed for at least 12 months cumulative service, and had worked for at least one day between 1 January 1942 and 31 December 1987. We identified a total of 2961 workers who met these eligibility criteria. This total included 2674 white men, 37 black men, 242 white women, and eight black women. Review of work records showed that 104 workers (all white men) had possibly experienced previous occupational

exposures to asbestos from earlier employment or from job assignments in small, now defunct DE and asbestos mixing operations. These workers were excluded from the main study cohort. Thus the main study cohort consisted of 2570 white men. Many workers, perhaps 25%–30%, were Mexican Americans. Based on ethnicity inferred from family name, we identified 533 Hispanic and 2037 non-Hispanic white men in the main study cohort. Separate data analyses were conducted for the main cohort of 2570 white men, 37 black men, 242 white women, and 104 white men with past asbestos exposures; there were too few black women and (no deaths among them) for a meaningful analysis.

VITAL STATUS ASCERTAINMENT AND DETERMINATION OF CAUSE OF DEATH

Information on vital status for the years 1942–87 for workers not employed as of the end date of follow up was taken from various sources, including Social Security Administration death tapes, a similar system for deaths in California,³⁴ the National Death Index (NDI), which provides a computerized list of deaths in the United States since 1979, state drivers' licence bureau, and commercial credit bureaux. The Social Security Administration has in past years provided information on vital status, but had ceased to offer this service by the time this study was started. Survival until 1988 was assumed for workers known to be alive in 1979, but who did not match the NDI data base, because the NDI has been shown to provide virtually complete mortality coverage.³⁵ Workers with unknown vital status contributed person time only up to the dates last known alive. Copies of death certificates were obtained from state vital statistics offices and were coded by a trained nosologist according to the International Classification of Diseases (ICD) codes in effect at the times when deaths occurred. Codes for the fifth to the ninth revisions of the ICD were used.

For the main study cohort, vital status as of 31 December 1987 was found for 2347 of 2570 (91.3%) workers, and death certificates were retrieved for 591 of 628 (94.1%) identified deaths. The percentage of the vital status found for black men was 94.2%, white women 91.3%, and asbestos exposed white men 94.2%. Death certificates were retrieved for all 46 deaths among these latter three groups.

Table 1 shows some descriptive characteristics of the main study cohort of 2570 white men. On average, workers were hired at the age of 27 in 1956. The mean duration of employment was 8.8 years, and the mean duration of follow up was 23.8 years. Collectively, the main study cohort accumulated 59 349 person years of observation. The total per-

Table 1 Descriptive characteristics of the study cohort of 2570 white men

Variable	Mean (SD)	Median	Range
Year of birth	1929 (17.2)	1928	1881–1966
Age at hire (y)	26.6 (8.0)	24.2	15–60
Year first employed	1956 (14.2)	1953	1908–86
Duration of employment (y)	8.8 (9.9)	4.0	1–46.5
Duration of follow up (y)	23.8 (13.8)	24.5	< 1–64.5

son years for the smaller cohorts were 362 for black men, 4461 for white women and 2339 for white men exposed to asbestos.

ASSESSMENT OF EXPOSURE

Data on work history, including job assignments, leaves of absence, and dates of job changes, were abstracted from personnel records. Data on industrial hygiene monitoring for dust measurements were reviewed but were judged to be too incomplete for quantitative reconstruction of workers' cumulative exposures. Results for dust sampling since the 1950s were available for one company and since the 1960s for the other larger company. Much of the data, however, represent air sampling results that do not reflect air concentrations actually experienced by workers, and little or no personal sampling data were available for most job assignments. Converting data collected with impingers, the method used until the late 1970s, which are expressed in units of millions of particles per cubic foot (mppcf), to gravimetric units (mg/m³) obtained by current sampling techniques would have added further uncertainty to the assessment.³⁶

We constructed two indices of cumulative exposure. The first was the duration in jobs with potential for dust exposure; time spent in jobs with no or minimal potential for dust exposure were discounted in this index. The second was a semiquantitative estimate of cumulative exposure to crystalline silica. There were too few workers (129) in the main study cohort who were exposed only to amorphous silica for separate analyses of the effects of amorphous and crystalline silica.

The crystalline silica index was derived by assigning weights to each job to reflect different intensities of exposure between jobs and over time, the relative amounts of the natural, calcined, and flux calcined material produced during different time periods, and estimates of the percentages of crystalline silica in the respirable fractions of the three product types. Also, we included a factor representing the assumed effectiveness of use of respirators at different times. Intensity of exposure

was weighted after consultation with knowledgeable industry personnel and by review of historical documents indicating process and engineering changes that had occurred in the plants. Jobs were ranked by potential exposure as none, low, moderate, and high, with corresponding weights assigned as 0, 1, 3, and 6. These relative weights were assumed to reflect different intensities of exposure to dust that remained constant over time.

Measures of dust control, including the installation of ventilating baghouses and air filter units on quarry equipment, conversion from hand to unit loading of trucks and trains, and the substitution of burlap packing with paper sacks, have been implemented in the industry over the years. Dates when changes were made were found from historical plant documents. For example, the United States Public Health Service study showed that the percentage of dust concentrations in excess of 5 mppcf decreased from 62% to 21% from 1954 to 1956.³¹ In an attempt to reflect temporal changes in dust exposure, we divided work history dates into five periods: before 1944, 1944–53, 1954–63, 1964–73, and 1974–87, and assigned corresponding relative exposure weightings of 12, 6, 2, 1.5, and 1 to the work history data. Use of a respirator has been required for workers in all moderately and heavily exposed jobs since the mid-1950s, although enforcement of this practice has increased gradually over time. The following weights, reflecting the absence of respiratory protection, were assigned to jobs ranked as moderately or heavily exposed: 1.0 for employment periods before 1954, 0.8 for 1954–63, 0.5 for 1964–73, and 0.2 for 1974–87. The amount of crystalline silica in the various types of product was estimated by combining data on plant production by type of product with estimates of the percentage of crystalline silica in the respirable fractions of the dust. The percentage of crystalline content in the natural dust was estimated to be 1% at both plants. Content of crystalline silica in calcined and flux calcined DE varied by plant; the estimated percentages were 10% and 20% at one plant, and 20% and 25% at the other. An index of exposure to cumulative crystalline silica was thus computed as the summed product of the times spent in different industry jobs and the corresponding weights for differences in exposure intensity by job and time period, respiratory protection, and percentage of crystalline silica in the materials handled.

DATA ANALYSIS

Cause specific mortality patterns were initially examined by calculation of standardised mortality ratios (SMRs), comparing observed deaths in the cohort with expected numbers based on rates in the United States population for 1942–87, by race and

sex. A microcomputer version of the Occupational Cohort Mortality Analysis Program' (OCMAP) from the University of Pittsburgh,³⁷ supplemented by cause specific rates from the National Institute for Occupational Safety and Health (NIOSH) life table program,³⁸ was used to compute expected values and SMRs. Cause specific rates are available from these programmes on a quinquennial basis by age and calendar year. Person time accumulation for each worker was started at either 1 January 1942 or the date when one year of cumulative employment was reached. Site specific cancer mortalities for 1950–87 by age, race, and sex for local Southern California counties (Kern, Santa Barbara, San Luis Obispo, and Ventura Counties) were obtained from the University of Pittsburgh, and thus permitted an assessment of the effect of regional variation on SMR results. Analyses of SMRs were conducted separately for the main study cohort of 2570 white men, 37 black men, 242 white women, and 104 white men exposed to asbestos.

Exposure response relations were examined by means of internal rate comparisons with Poisson regression modelling.³⁹ These analyses were restricted to the main study cohort because of small numbers in the other groups. Relative risks (RRs), adjusted for age, calendar year, duration of follow up, and ethnicity (Hispanic *v* non-Hispanic), were estimated for increasing duration of exposure to dust and the cumulative crystalline silica exposure index. Hispanic ethnicity was included as a covariate in the analysis because Mexican Americans typically have lower risks for lung cancer than non-Hispanic white men.^{40,41} Values of RR are expressed in relation to rates in the lowest exposure category. Person years and deaths were tabulated by age (< 45, 45–49, ..., 75–79, ≥ 80), calendar year (< 1955, 1955–59, ..., 1980–84, 1985–87), duration of follow up (< 10, 10–19, ≥ 20 years), and by categories of exposure, with a FoxPro version 2.0 program⁴² written by one of us (NJH). Quantitative exposure variables were calculated as person-year weighted averages of cumulative exposure within each cell of the table for use in the regression modelling. The accuracy of the person-year program was verified by close agreement with data generated from the OCMAP program. The exposure categories for duration of employment in dust exposed jobs were set at < 5, 5–9, 10–19, and ≥ 20 years. Boundaries of the exposure categories for the crystalline silica index were found by multiplying the cohort's mean annual exposure value by 5, 10, and 20 to provide a rough correspondence between the analyses with respect to the two exposure indices. The exposure categories for crystalline silica were thus < 50, 50–99, 100–199, and ≥ 200 units. Analyses were conducted allowing for disease

latency, which involved lagging exposures by the estimated latency interval;⁴³ lag widths of 0, 5, 10, and 15 years were incorporated. Poisson regression models were run with the EGRET statistical package.⁴⁴

EVALUATION OF POTENTIAL CONFOUNDING BY SMOKING

The possibility of workers' smoking habits being a confounding factor was examined indirectly by inspection of mortality risks for other smoking related diseases,⁴⁵ and by hypothetical estimation of the extent of confounding required to produce spurious observed excesses with the method of Axelson.⁴⁶ The relative risk due to confounding (RR_c) is estimated from the independent relative risk associated with smoking (RR_s) and the proportions of smokers in the reference (P_{s-ref}) and exposed groups (P_{s-exp}). This formulation can be expressed as⁴⁷:

$$RR_c = [(P_{s-exp})(RR_s - 1) + 1] / [(P_{s-ref})(RR_s - 1) + 1]$$

An observed estimate of RR will be due solely to confounding when it is equal to RR_c .⁴⁸ Solving the above expression for P_{s-exp} , for assumed fixed values of RR_s and P_{s-ref} , indicates the proportion of smokers in the exposed group needed for the observed RR to be an artifact of confounding.

Information on cigarette smoking has been obtained since the early 1960s as part of the industry's medical surveillance programme. Data that permitted a distinction between ever and never smokers were available for 1113 members of the main study cohort. The smoking data did not

include detailed information on amount smoked or duration of smoking. Thus we regarded the smoking data as insufficiently complete or detailed for purposes of direct statistical adjustment. It was possible, however, to examine the correlations between smoking and exposure level and to estimate the extent to which the observed risk gradients might have been biased.

Results

MAIN STUDY COHORT

Table 2 shows that mortality from all causes combined was slightly increased compared with United States rates ($SMR = 1.12$), with the largest excess due to the category of non-malignant respiratory diseases ($SMR = 2.27$). An SMR of 2.59 (56 observed) was found for the non-malignant respiratory diseases (NMRD) excluding pneumonia and infectious diseases. Among the deaths in this group, the death certificates listed five deaths with silicosis, five with diatomaceous earth pneumoconiosis, and seven with pneumoconiosis as underlying cause (there were no deaths from asbestosis). Excesses found for renal diseases were based on small numbers, but may be noteworthy in view of earlier evidence of a nephrotoxic potential of crystalline silica.⁴⁹ The mortality deficit for ischaemic heart disease ($SMR = 0.85$) is consistent with the healthy worker effect.⁵⁰

Table 3 shows site specific cancer $SMRs$. The most important finding was the excess of lung cancer ($SMR = 1.43$; 59 observed). The other findings for site specific cancers were largely unremarkable. The lung cancer excess persisted when rates in the

Table 2 Observed and expected deaths and standardised mortality ratios ($SMRs$) for major causes of death categories: 2570 white men, 1942-87

Cause of death	Obs	Exp*	SMR	(95% CI)†
All causes	628	563	1.12	(1.03-1.21)
All cancers	132	121	1.09	(0.91-1.29)
Diabetes mellitus	8	7.89	1.01	(0.44-2.00)
Ischaemic heart disease	159	187	0.85	(0.72-0.99)
Cerebrovascular disease	30	30.9	0.97	(0.66-1.39)
Digestive disease	21	28.5	0.74	(0.46-1.13)
Genitourinary diseases:	10	7.06	1.42	(0.68-2.61)
Glomerulonephritis				
Renal failure	2	0.63	3.17	(0.38-11.5)
Chronic nephritis	4	3.31	1.21	(0.33-3.10)
Non-malignant respiratory disease:	77	34.0	2.27	(1.79-2.83)
Acute upper respiratory tract infections	1	0.23	4.35	(0.11-24.3)
Influenza	1	0.60	1.66	(0.04-9.23)
Pneumonia	19	11.5	1.65	(0.99-2.58)
Chronic bronchitis	1	1.45	0.69	(0.02-3.85)
Emphysema	12	6.69	1.80	(0.93-3.14)
Asthma	2	1.02	1.96	(0.24-7.08)
NMRD except pneumonia and infectious diseases‡	56	21.6	2.59	(1.96-3.36)
Nervous system diseases	5	5.81	0.86	(0.28-2.01)
Accidents	51	42.4	1.20	(0.90-1.58)

* Based on rates for United States white males.

† 95% confidence interval for SMR .

‡ Includes 17 deaths due to pneumoconiosis (no asbestosis).

Table 3 Observed and expected deaths and standardised mortality ratios (SMRs) for site specific cancers: 2570 white men 1942-87

Cause of death	Obs	Exp*	SMR	(95% CI)
All sites combined	132	121	1.09	(0.91, 1.29)
Buccal cavity and pharynx	3	3.62	0.83	(0.17, 2.42)
Oesophagus	0	2.89	0	(0, 1.28)
Stomach	5	5.39	0.93	(0.30, 2.16)
Colon	13	10.9	1.19	(0.64, 2.04)
Rectum	1	3.18	0.32	(0, 1.76)
Liver	3	2.79	1.08	(0.62, 8.76)
Pancreas	7	6.30	1.11	(0.45, 2.29)
Larynx	2	1.74	1.15	(0.14, 4.15)
Lung	59	41.4	1.43	(1.09, 1.84)
Prostate	6	7.30	0.82	(0.30, 1.79)
Kidney	2	3.07	0.65	(0.08, 2.35)
Bladder	2	3.14	0.64	(0.08, 2.30)
Skin	2	2.54	0.79	(0.10, 2.85)
Brain and CNS	6	3.93	1.53	(0.56, 3.33)
Lymphosarcoma and reticulosarcoma	0	2.17	0	(0, 1.70)
Hodgkin's disease	1	1.33	0.75	(0.02, 4.19)
Leukaemia	1	4.77	0.21	(0.01, 1.17)
Other haematological malignancies	2	3.39	0.59	(0.07, 2.13)

* Based on rates for United States white males.

local counties rather than national rates were used for comparison (SMR = 1.59). Relative to United States rates, the largest relative lung cancer excesses were found for workers hired before 1930 and during the 1950-59 decade of death (table 4). The high SMR (2.10) found for <10 years since first employment was based on only three deaths; the SMR of 1.50 among workers ≥ 30 years since first employment was based on a much larger number of deaths (33), and is consistent with an exposure effect requiring a long induction time. The corresponding patterns for NMRD mortality (table 4) were irregular and not readily interpretable.

Table 5 shows the gradients of RRs for lung cancer with respect to duration of employment in dust exposed jobs based on internal comparisons with Poisson regression modelling. The regression coefficient (slope) in the quantitative analyses may be interpreted roughly as the proportional increase in risk associated with a unit (one year) increase of exposure. Increasing trends were detected for all assumed latency (exposure lagging) intervals. The strongest gradient occurred when a 15 year latency was assumed; compared with the reference category of workers with less than five years of exposure, the RR reached 2.88 (95% confidence

Table 4 Lung cancer and non-malignant respiratory disease (NMRD) * mortality by year of hire, year of death, years since first employment, age at death: 2570 white men, 1942-87

Variable	Lung cancer			NMRD		
	Obs	SMR†	(95% CI)	Obs	SMR†	(95% CI)
Year of hire:						
< 1930	8	2.63	(1.12-5.15)	8	3.27	(1.41-6.45)
1930-39	8	1.72	(0.74-3.39)	12	4.18	(2.16-7.30)
1940-49	27	1.32	(0.87-1.92)	24	2.21	(1.41-3.28)
1950-59	14	1.33	(0.72-2.23)	8	1.79	(0.77-3.52)
1960-69	2	0.82	(0.10-2.96)	3	3.53	(0.73-10.3)
1970-86	0	0	(0-16.4)	1	10.2	(0.26-57.0)
Year of death:						
1942-49	0	0	(0-10.9)	2	9.50	(1.15-34.3)
1950-59	6	2.96	(1.09-6.45)	2	1.99	(0.24-7.18)
1960-69	7	1.04	(0.42-2.15)	7	1.97	(0.79-4.06)
1970-79	24	1.65	(1.05-2.45)	21	2.90	(1.79-4.43)
1980-87	22	1.24	(0.78-1.88)	24	2.50	(1.60-3.72)
Years since first employment:						
< 10	3	2.10	(0.43-6.14)	3	4.21	(0.85-12.1)
10-19	6	1.08	(0.40-2.36)	3	1.28	(0.26-3.73)
20-29	17	1.39	(0.81-2.23)	16	2.90	(1.66-4.71)
≥ 30	33	1.50	(1.02-2.09)	34	2.61	(1.81-3.65)
Age at death:						
< 40	0	0	(0-6.09)	2	4.73	(0.53-15.8)
40-49	5	1.22	(0.40-2.85)	2	1.66	(0.20-5.99)
50-59	22	1.72	(1.08-2.60)	13	3.09	(1.64-5.28)
60-69	19	1.21	(0.73-1.89)	12	1.52	(0.78-2.65)
≥ 70	13	1.58	(0.84-2.71)	27	3.45	(2.27-5.02)

* Excludes infectious diseases and pneumonia.

† Based on rates for United States white males.

Table 5 Trends of lung cancer mortality by duration of employment in dust exposed jobs and latency interval: 2570 white men

Duration of employment (y)	Latency interval (y)							
	0		5		10		15	
	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)
< 5 (reference)	24	1.00 (—)	27	1.00 (—)	28	1.00 (—)	31	1.00 (—)
5–9	10	1.67 (0.79–3.51)	8	1.24 (0.56–2.75)	10	1.56 (0.75–3.25)	9	1.29 (0.60–2.76)
10–19	11	1.85 (0.88–3.88)	12	1.72 (0.86–3.47)	12	1.67 (0.83–3.35)	13	2.00 (1.01–3.95)
≥ 20	14	2.30 (1.18–4.51)	12	2.29 (1.13–4.62)	9	2.58 (1.17–5.66)	6	2.88 (1.13–7.33)
Trend: Slope† (SE)		0.033 (0.012)		0.037 (0.014)		0.044 (0.015)		0.048 (0.018)

* Relative risk, adjusted for age, calendar year, duration of follow up, ethnicity (Hispanic *v* non-Hispanic).

† Proportional increase in risk per year of exposure.

interval (95% CI 1.13–7.33) among workers exposed for ≥ 20 years. Trends in RRs or cumulative exposure to crystalline silica were strong but did not increase with latency interval (table 6). The most consistent gradient was found when exposures were lagged by 15 years.

The trends in mortality from NMRD with duration of employment in dust exposed jobs (table 7) were weaker and less consistent than the lung cancer gradients. Monotonically increasing risk gradients were found for NMRD with respect to the cumulative crystalline silica index (table 8).

ASSESSMENT OF POTENTIAL CONFOUNDING BY SMOKING

A relatively straightforward, albeit crude, approach to evaluate the potential for confounding by smoking is to inspect the patterns of risk for diseases related to smoking other than those of primary interest.⁴⁵ With the exception of emphysema, which

was included in the NMRD category, there were no overall excesses of cancers of the oral cavity, pancreas, larynx, kidney, or bladder, which are the major diseases related to smoking other than lung cancer (table 3). The deficit of ischaemic heart disease is more likely an indicator of the healthy worker effect than an absence of excessive smoking in the cohort.

Another indirect method of confounding assessment, described by Axelson,⁴⁶ is to compute the extent of smoking prevalence in the cohort and its relation to exposure level that would be required for the observed excess to be spuriously due to confounding. To illustrate the method we computed the smoking prevalences according to cumulative exposure to crystalline silica, assuming a 15 year latency, that would have been required to cause all RR values to equal 1.0 (that is, to eliminate completely the risk gradient). In these calculations it was assumed that smoking alone increases risk of

Table 6 Trends of lung cancer mortality by estimated cumulative exposure to crystalline silica and latency interval: 2570 white men

Cumulative exposure*	Latency interval (y)							
	0		5		10		15	
	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)
< 50 (reference)	19	1.00 (—)	20	1.00 (—)	22	1.00 (—)	23	1.00 (—)
50–99	6	0.76 (0.30–1.90)	6	0.78 (0.31–1.94)	6	0.79 (0.32–1.98)	8	1.19 (0.52–2.73)
100–199	11	1.48 (0.69–3.15)	11	1.51 (0.71–3.22)	12	1.65 (0.80–3.44)	9	1.37 (0.61–3.06)
≥ 200	23	2.87 (1.47–5.64)	22	2.81 (1.43–5.53)	19	2.40 (1.21–4.77)	19	2.74 (1.38–5.46)
Trend: Slope‡ (SE)		0.027 (0.009)		0.026 (0.009)		0.024 (0.009)		0.026 (0.009)

* Exposure intensity score x years.

† Relative risk, adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic *v* non-Hispanic).

‡ Proportional increase in risk per year of exposure at cohort's mean annual exposure (10).

Table 7 Trends of non-malignant respiratory disease (NMRD) mortality by duration of employment in dust exposed jobs and latency interval: 2570 white men

Duration of employment (y)	Latency interval (y)							
	0		5		10		15	
	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)
< 5 (reference)	23	1.00 (—)	24	1.00 (—)	24	1.00 (—)	26	1.00 (—)
5–9	12	2.01 (0.99–4.05)	11	1.92 (0.93–3.96)	11	2.03 (0.97–4.22)	11	1.80 (0.87–3.74)
10–19	13	2.06 (1.02–4.16)	13	1.97 (0.97–3.96)	15	2.19 (1.11–4.30)	13	1.89 (0.94–3.80)
≥ 20	8	1.17 (0.52–2.64)	8	1.32 (0.58–3.00)	6	1.29 (0.51–3.26)	6	1.82 (0.71–4.66)
Trend: Slope† (SE)		0.008 (0.014)		0.013 (0.014)		0.017 (0.015)		0.025 (0.017)

* Relative risk, adjusted for age, calendar year, duration of follow up, ethnicity (Hispanic v non-Hispanic).

† Proportional increase in risk per year of exposure.

Table 8 Trends of non-malignant respiratory disease (NMRD) mortality by estimated cumulative exposure to crystalline silica and latency interval: 2570 white men

Cumulative exposure level*	Latency interval (y)							
	0		5		10		15	
	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)	No of deaths	RR† (95% CI)
< 50 (reference)	14	1.00 (—)	15	1.00 (—)	16	1.00 (—)	19	1.00 (—)
50–99	7	1.29 (0.52–3.22)	7	1.32 (0.53–3.26)	7	1.42 (0.57–3.55)	6	1.13 (0.44–2.93)
100–199	12	2.19 (1.00–4.79)	11	2.03 (0.91–4.51)	10	1.94 (0.85–4.44)	9	1.58 (0.69–3.63)
≥ 200	23	2.91 (1.41–6.00)	23	2.92 (1.42–5.99)	23	3.06 (1.49–6.30)	22	2.71 (1.35–5.46)
Trend: Slope (SE)		0.020 (0.008)		0.021 (0.008)		0.021 (0.008)		0.020 (0.008)

* Exposure intensity x years.

† Relative risk, adjusted for age, calendar year, duration of follow up, ethnicity (Hispanic v non-Hispanic).

‡ Proportional increase in risk per year of exposure at cohort's mean annual exposure (10).

lung cancer by a factor of 10 compared with non-smokers.⁵¹ Smoking prevalence in the reference category varied from 30% to 70%. Table 9 shows that under these hypothetical conditions, a very strong relation between smoking and exposure would be

needed to account for the observed gradient. Moreover, with these assumptions, it would be virtually impossible for the RR estimate for the highest exposure category (2.74) to be explained completely by confounding from smoking.

Table 9 Distributions of smoking required to eliminate observed exposure response trend for crystalline silica exposure and lung cancer assuming a 15 year latency and a relative risk of 10 for smoking

Cumulative exposure level*	Obs RR	Proportion of smokers in reference group		
		0.30	0.50	0.70
<50 (reference)	1.00	0.30†	0.50	0.70
50–99	1.19	0.38	0.62	0.85
100–199	1.37	0.45	0.73	1.00
≥ 200	2.74	(1.02)‡	(1.56)‡	(2.11)‡

* Exposure intensity score x years.

† Proportion of smokers required in exposure category to reduce observed RR to 1.00.

‡ () number larger than 1.00 impossible.

Table 10 Prevalence of cigarette smoking by estimated exposure to crystalline silica, lagged 15 years: 2570 white men

Cumulative silica exposure level*	Entire cohort (n = 2570)		Born 1890–1939 (n = 1765)	
	No workers with smoking data	Smokers (%)	No workers with smoking data	Smokers (%)
<50 (reference)	796	65.3	276	79.3
50–99	160	78.8	114	78.1
100–199	77	77.9	74	78.4
≥ 200	80	77.5	80	77.5

* Exposure intensity score x years.

Table 11 Mortality among other groups of workers: 1942-87

Group	Cause of death					
	All causes		Lung cancer		Non-malignant respiratory disease	
	Obs	SMR†	Obs	SMR†	Obs	SMR†
Asbestos exposed* (n = 104)	14	0.94	4	3.54	1	1.97
Black men (n = 37)	1	0.36	1	5.23	0	0
White women (n = 242)	31	1.44	3	2.76	5	7.77

* All white men.

† Based on rates for sex /race group in United States, 1942-87.

Based on the available smoking data, there seemed to be a lower prevalence in the lowest crystalline silica exposure group, lagged by 15 years (table 10). Incompleteness in the smoking data undoubtedly biased the association found between smoking and the crystalline silica exposure index. There was no smoking information for workers employed for short durations before the early 1960s when smoking data were first taken. Such workers could have been in the lowest exposure group, and would have been working during periods before smoking prevalence declined in the United States.⁵² To evaluate the possible biasing influence of the timing of collection of the smoking data, we examined smoking prevalence, again in relation to crystalline silica lagged by 15 years, among the segment of the cohort (1765) that was born between 1890 and 1939. This birth year interval was chosen because there were at least some smoking data for workers in each exposure category. Smoking prevalence was unrelated to the crystalline silica index among workers born between 1890 and 1939 (table 10). Moreover, the gradient of risk of lung cancer in relation to the crystalline silica index, assuming a 15 year latency, among this subset of 1765 workers was in reasonably close agreement with the trend for all 2570 white men (table 6); estimated RR values were 1.00, 1.21, 1.37, and 2.67.

OTHER GROUPS OF WORKERS

Table 11 shows SMRs for all causes, lung cancer, and NMRD for the other smaller groups. Although based on small numbers, there are indications of excess lung cancer and risks for NMRD among these workers. A possible confounding influence of exposure to asbestos on risk of lung cancer cannot be discounted for the 104 exposed white men.

Discussion

The findings for the main study cohort of 2570 white men deserve most emphasis because this group represents the largest segment of the work-

force. The overall excess of lung cancer and the apparent exposure response relation with duration of employment in dust exposed jobs, and with the crystalline silica exposure index were the most noteworthy findings. The cohort's SMR for lung cancer (1.43 compared with the national population) is not large, but is similar in magnitude to overall estimates of relative risk reported from previous studies of granite and quarry²⁰⁻²³ and refractory brick workers.^{24,25} Similar to our study of diatomaceous earth industry workers, some earlier studies also provide evidence of dose response relations.²³⁻²⁵ We also observed excesses of lung cancer mortality among black men, white women, and white men with potential for asbestos exposure. Small numbers limit the interpretations of specific results in these groups, but the data provide some indication of consistency.

An excess of NMRD was anticipated in view of the earlier studies showing risk of silicosis in the DE industry, including the plants under study.³¹⁻³³ The relatively strong gradient for NMRD with the cumulative crystalline silica exposure index is consistent with a plausible, and anticipated, dose response relation for silicosis. Reliance on death certificate data for identification of NMRD is an important limitation. Undoubtedly, the true association between silicosis and crystalline silica dust exposures is stronger than that found for NMRD because of dilution introduced by combining a heterogeneous grouping of diseases in this category. A more conclusive assessment of the magnitude of risk of silicosis and dose-response relation would require analysis of radiographic and other clinical information. This was beyond the scope of the present investigation.

Interpretations of the findings, especially those pertaining to lung cancer, require an assessment of the relative strengths and limitations of the study. The main strengths were the ability to track the long term mortality experience of the cohort (the mean duration of follow up was nearly 24 years), and our ability to link mortality data with complete information on work history. This involved estimation of cumulative exposure to crystalline silica. Most previous studies of cohorts exposed to silica have relied on crude indicators of exposure, typically total employment duration, in exposure response analyses.

The study had some notable limitations, including incomplete vital status and cause of death ascertainment, the absence of quantitative and representative industrial hygiene data spanning all years of the cohort's employment, and incomplete data on confounding variables, especially cigarette smoking. The vital status tracing rate of 91% is less than desired, and may have caused slight inflations of the overall SMRs. Control for duration of follow

up, however, minimised potential bias from incomplete ascertainment of vital status in the internal exposure-response trend analyses. A further examination of the effect of incomplete vital status on the associations of dust exposure and crystalline silica index on lung cancer was conducted in which SMRs were computed by exposure category, assuming all unknowns had lived until the end of the follow up. The trends did not differ materially from those obtained when follow up for unknowns was curtailed at dates of last contact. Incomplete cause of death ascertainment (94%) may have had a slight counterbalancing effect of underestimating the overall SMRs, but probably had minimal effect on the exposure-response analyses.

Insufficient dust monitoring data precluded a direct quantification of the exposure-response trends. The dose surrogate used for crystalline silica was based on industrial hygiene judgments of differences in exposure intensity between jobs and over time, and estimates of the percentages of crystalline silica in the respirable fractions of the various DE materials. Other sources of uncertainty in this dose index are imprecision in the estimates of amounts of materials produced and handled in different jobs, and the effectiveness of respiratory protection. Errors in the crystalline silica index would lead to an attenuation of the estimated dose response relation because of misclassification, which one would expect to be non-differential with respect to health outcome, if indeed there is a true underlying dose response relation.⁵³ The trends for lung cancer with duration of exposure to dust and with the crystalline silica index differed only slightly. One interpretation is that the content of crystalline silica was not the sole or most important aetiological component of the dust. Alternatively, some of the assumptions underlying the crystalline silica index may have been erroneous. The use of alternative weighting schemes for differences in intensity of exposure between jobs did not alter the trends for crystalline silica to any appreciable extent. By contrast, the exposure-response relation for NMIRD became sharper when the crystalline silica index was used as the dose surrogate. More complete exposure monitoring data than were available for this study would be needed to construct a more valid dose index.

The most important potential confounding factor was cigarette smoking. There are three lines of evidence indicating that the excess of lung cancer was not due entirely to smoking. Firstly, examination of the associations between smoking status, as determined from the limited available data, and exposure to crystalline silica showed that smoking was unlikely to account fully for the apparent dose-response relation. Secondly, the absence of consis-

tent excesses for smoking related diseases other than lung cancer also argues against significant confounding. Thirdly, the lung cancer trend with exposure to crystalline silica among the subset of workers with an apparently homogeneous smoking prevalence was similar to the trend found for the entire cohort.

Confounding by Hispanic ethnicity was minimised in the internal analyses by including this variable as a covariate. Classification of Hispanic ethnicity was based on last name, and is thus subject to error, but the extent of confounding was probably minimal. An indirect control for confounding was achieved by computing an SMR for lung cancer relative to local county death rates; the local counties have a more similar ethnic distribution to the cohort than does the national population. The SMR based on local county rates ($SMR = 1.59$) was larger than the SMR based on United States rate comparisons ($SMR = 1.43$), suggesting that the second underestimated the overall excess. To the extent that data on work history accurately identified exposure to asbestos, we were able to control for this factor by performing separate analyses for the main study cohort and the workers exposed to asbestos. Use of asbestos was limited to a few small operations during short periods, and thus was not a widespread hazard in the DE industry. Unlike foundries and underground mines where exposures to other carcinogens occur, exposures to potentially confounding lung carcinogens (for example, radon, arsenic) do not exceed ambient background in DE mining and milling. The absence of data before and after employment in other occupations and industries precludes control of potential confounding from non-DE occupational exposures. There is no obvious reason however, to suspect that exposures to carcinogens in other occupational settings were related to exposure levels in the DE industry.

Our summary interpretation of the findings for lung cancer is that the overall excess and the increasing risk gradients with duration of exposure to dust and cumulative exposure to crystalline silica indicate a causal relation. The main contributors to the lung cancer excess were probably intense exposures that occurred before the 1950s when major programmes for control of exposure were initiated. This study was not able to distinguish between the unique effects of the crystalline silica content and other components of the dust (for example, amorphous silica), although prior evidence indicates that crystalline silica is the most plausible candidate carcinogen.⁴ The interpretation of the results for NMIRD is more complicated because of potential diagnostic misclassification; however, the trends are consistent with prior expectations and are similar in magnitude to the lung cancer trends.

Reductions in exposure to dust due to improvements in engineering and technological controls and the use of respiratory protective equipment, have taken place in the industry over time, particularly since the early 1950s. The absence of an excess of lung cancer among workers hired since 1960 indicates that lung cancer risks may have diminished in the industry. Further follow up of the cohort will be needed to assess long term trends, especially among workers hired since dust exposures have been reduced. Also, it is noteworthy that no deaths attributed to silicosis as underlying cause have been noted among workers hired since 1950. This finding should only be regarded as suggestive of a diminished risk because of the limitations of death certificates for identifying incident cases of silicosis. Extended follow up of the cohort accompanied by a review of radiographic information will be needed for a proper accounting of the temporal patterns of and dose response relations for silicosis.

To our knowledge, our study is the first epidemiological investigation of mortality risks among workers in the DE industry. There are other DE mining and milling operations elsewhere in the United States and in Europe. Epidemiological studies of workers in other DE plant populations would add greatly to knowledge gained from this study. Some unresolved questions that could not be evaluated in the present study but warrant investigation are the relative effects of amorphous and crystalline silica on risk of disease, and the influence of the source of the DE, marine or fresh water, on toxic potential.

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