FINAL REPORT

SILICA, SILICOSIS, AND LUNG CANCER IN DIATOMITE WORKERS

(R01 OH03126)

Submitted to: The National Institute for Occupational Safety and Health

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November, 1996

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LIST OF ABBREVIATIONS

CI, confidence interval

DE, diatomaceous earth

f/mL, fibers per milliliter

ILO, International Labour Office

mg/m^3, milligrams per cubic meter

mppcf, million particles per cubic foot

NDI, National Death Index

NMRD, non-malignant respiratory disease

RR, rate ratio

SMR, standardized mortality ratio

USPHS, United States Public Health Service

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SIGNIFICANT FINDINGS

This project was an update of a cohort mortality study of workers exposed to crystalline silica, mainly in the form of cristobalite, in the mining and processing of diatomaceous earth (DE) in two California facilities. Previously, we had found excessive mortality rates from non-malignant respiratory diseases (NMRD) and lung cancer that were related to intense prolonged dust exposures. This update extended follow-up by 7 years, and included an evaluation of radiographically-determined silicosis among the cohort. We were also able to re-construct historical exposures to crystalline silica in gravimetric units (milligrams per cubic meters) that are used for standard-setting. The majority of analysis was performed for the larger of the two plants because exposure data were more complete in this facility. The most noteworthy findings were:

- As expected, radiographically-determined silicosis was strongly related to cumulative exposure to crystalline silica

- Compared to national rates, mortality rates from both NMRD and lung cancer were elevated among DE workers.

- A strong dose-response association was found for cumulative exposure to crystalline silica and NMRD mortality

- Lung cancer mortality was also associated with cumulative exposure to crystalline silica, but the association was not as strong as for NMRD

- Confounding by either smoking or occupational asbestos exposure was unlikely to account for the observed exposure-response relations with NMRD and lung cancer mortality

USEFULNESS OF FINDINGS

The results of this study clearly indicate that prolonged, intense exposures to crystalline silica are causally related to silicosis and mortality from non-malignant respiratory diseases. This study adds further support to a suspected etiologic association between crystalline silica and risk of lung cancer. On balance, the study indicates the necessity for minimizing crystalline silica exposures in the workplace. The study results have certain limitations,

largely related to the absence of complete information on dust exposures. Insofar as risks potentially associated with exposures to crystalline silica continue to be important occupational health concerns, industries where silica exposures are likely to occur should be advised to collect and archive exposure monitoring data in as complete and systematic manner as possible. These efforts will permit more thorough, valid assessments of relations between exposure and disease risks in future epidemiological studies, and will be necessary for devising strategies for protecting worker health.

ABSTRACT

Background: This project was an update of an historical cohort mortality study among workers exposed to crystalline silica in the diatomaceous earth (DE) industry. A previous study of this cohort, demonstrated increased mortality risks for non-malignant respiratory diseases (NMRD) and lung cancer, as well as increasing risks gradients with cumulative exposure to crystalline silica.

Objectives: The objectives of this project were: 1) to extend mortality follow-up by 7 years, through 1994, and to estimate cause-specific mortality excesses and deficits in the cohort; 2) to derive quantitative historical exposure estimates for respirable dust and respirable crystalline silica in gravimetric units (milligrams per cubic meter [mg/m^3]); 3) to estimate dose-response relations of cumulative exposures with NMRD and lung cancer; 4) to determine the past prevalence of radiographically defined silicosis in the cohort, and to estimate dose-response relations for silicosis.

Methods: The cohort was comprised of 2,961 workers employed for at least 12 months cumulative service at either of two DE plants in Lompoc, California. Mortality follow-up was conducted for the years 1942-94, which extended the original follow-up by 7 years. Quantitative exposures to crystalline silica were reconstructed for workers from historical data from the larger of two plants, spanning the years 1948-88. Data at the smaller plant were not considered adequate for quantitative reconstruction. Cause-specific mortality comparisons against national and local county rates were performed to identify disease excesses and deficits. Dose-response analyses for NMRD and lung cancer were conducted with respect to cumulative exposure to respirable crystalline silica. In addition, we obtained readable chest radiographs for 2,520 (85%) of the cohort. Median International Labour Office (ILO, 1980) profusion scores of final available films were determined from readings performed by three independent readers. Dates of first positive film ("onset") were estimated from readings of earlier films for workers whose final films were ILO category 1/0 and higher. These data were combined with historical exposure estimates to estimate dose-response relations for radiographically-determined silicosis.

Results: The majority of the mortality analysis was performed on the subset of 2,342 white males from the larger plant (the former Manville Corporation), for whom exposure data were most complete. During the years 1942-1994, mortality excesses were detected for non-malignant respiratory diseases (NMRD) (standardized mortality ratio (SMR) = 2.01, 95% confidence interval (CI) 1.56-2.55) and lung cancer (SMR = 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 (RR) for the highest exposure stratum

($\geq$5.0 mg/m^3-years) was 5.35 (95% CI 2.23-12.8). The RR for lung cancer reached 2.15 (95% CI 1.08-4.28) in the highest exposure category. Lung cancer and NMRD mortality excesses were also found among white males from the smaller plant (Grefco, Inc.), and among white females and black males from both plants. No deaths were found among a small group of black female workers. The observed exposure-response associations for lung cancer and NMRD were unlikely to have been confounded by smoking or asbestos exposure. As expected, the risk of silicosis (ILO category 1/0 and greater for small opacities, or large opacities) increased sharply with cumulative exposure to respirable crystalline silica. The prevalence of positive radiographs was approximately 24 percent among workers with cumulative respirable crystalline silica exposures of $\geq$6.0 mg/m^3-yrs; the cumulative probability of silicosis reached 55 percent among workers who attained cumulative exposures of 18 mg/m^3-yrs.

Conclusions: The findings indicate a strong dose-response relation for crystalline silica and NMRD mortality. Parallel findings for radiographically-determined silicosis are consistent with an NMRD hazard at the highest exposure levels. The lung cancer results, although less pronounced, add further support to an etiologic role for crystalline silica.

BACKGROUND

Pulmonary fibrosis and associated restrictive lung disease are well established consequences of prolonged intense occupational exposures to crystalline silica [Silicosis and Silicate Disease Committee, 1988]. In spite of the long history of recognition of silicosis as an occupational hazard, there is surprisingly scant literature on the quantitative dose-response relation. Recent studies of Canadian hard rock miners [Muir et al., 1989], South African Gold miners [Hnizdo and Sluis-Cremer, 1993], and Chinese tungsten miners [Pang and Yang, 1992] provide dose-response estimates, although considerable variability in risk per unit exposure estimates among these studies has hindered establishment of scientifically-based occupational exposure standards.

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 [Smith et al., 1995], although questions have been raised regarding confounding from cigarette smoking and selection biases in some of these cohorts [McDonald, 1989]. Potential confounding by co-occurring exposures to other known and suspected lung carcinogens (e.g., radon in underground mines) has clouded the interpretation of the epidemiologic literature [Weill and McDonald, 1996]. Nonetheless, excessive lung cancer risks 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 [Koskela et al., 1994; Costello et al., 1995], refractory brick [Merlo et al., 1991; Dong et al., 1995], and diatomaceous earth [Checkoway et al., 1993; Rafnsson and Gunnarsdottir, 1996] industries. Overall cohort relative risks in these studies have not been large (most less than 2.0), although some provide indications of dose-response relations, evidenced by greatest excesses among silicotics [Dong et al., 1995] or among workers with the largest cumulative exposures [Merlo et al., 1991; Checkoway et al., 1993; Koskela et al., 1994]. Dose-response estimation for cancers and other diseases, notably pneumoconiosis and other non-malignant respiratory 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 silicosis and mortality risks among a cohort of workers in the diatomaceous earth (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 (non-crystalline) silica, from open-pit mines, DE is crushed and calcined in kilns to produce the final product consisting of 40-80 percent crystalline silica, principally in the form of cristobalite. The respirable fraction of the final product contains 10-25 percent crystalline silica. The primary commercial uses of DE are as a filtration medium for water, foods and beverages, and as a filler in paints and construction materials, and as a carrier of agricultural chemicals.

Concern about silicosis in the DE industry in California heightened in the early 1950s following the appearance of articles in the lay press concerning silicosis in the industry and a strike in 1952 in which adverse health effects was a major issue [Abrams, 1954; 1990]. In 1957, the U.S. Public Health Service conducted a radiographic survey of 869 workers at five DE plants located in California, Nevada, and Oregon [Cooper and Cralley, 1958]. The survey revealed a 9 percent prevalence of "probable" silicosis and 9 percent "doubtful" silicosis among all workers. However, there was a 25 percent prevalence of silicosis among the 251 workers who had been employed for 5 or more years in the DE industry and who had no prior occupational dust exposure. A nearly 50 percent prevalence of silicosis was detected radiographically among 101 workers employed in processes where the dust contained a high percent of cristobalite [Cooper and Cralley, 1958]. Subsequent radiographic surveys conducted at these plants indicated marked reductions in silicosis prevalence (e.g., 2.3 percentage by 1984), that appear to have paralleled reductions in dust exposure levels [Cooper and Jacobson, 1977; Cooper and Sargent, 1984].

In 1988, following the IARC classification of crystalline silica as a probable human carcinogen [IARC 1987], we initiated a cohort mortality study of workers from two DE mining and milling plants in Lompoc, California [Checkoway et al., 1993]. The original study was sponsored by the International Diatomite Producers Association located in San Francisco. Mortality excesses and exposure-response gradients were detected for lung cancer and non-malignant respiratory diseases (NMRD) from the original follow-up of white males employed at either of the two DE plants. Among 2,570 white males, standardized mortality ratios (SMR) of 1.43 and 2.59 were observed for lung cancer and NMRD, respectively, when mortality comparisons were made against rates for U.S. white males during 1942-87. 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 percentage of crystalline silica in the various DE product types. Exposure intensity weights based on occupational hygienists' ratings were used to derive the cumulative exposure index primarily 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 (mg/m^3).

Following publication of the earlier results, concerns were raised that the extent of asbestos exposure, not evident from recorded job assignments in two DE and asbestos mixing areas, may have been underestimated. Subsequently, Gibbs and Christensen [1994] performed an independent exposure assessment to determine the extent of asbestos exposure in the industry. Re-analysis of the lung cancer data indicated no confounding by asbestos [Checkoway et al., 1996].

SPECIFIC AIMS

The specific aims of this project were:

1) To determine further the cohort's long-term temporal patterns of risk for NMRD, lung cancer, and other diseases by adding 7 years of mortality and exposure information to the previously conducted study;

2) To estimate quantitative historical exposures to crystalline silica in gravimetric units (milligrams per cubic meter [mg/m^3]) for use in dose-response analyses;

3) To determine the past frequency of radiographically-detectable pulmonary fibrosis ("silicosis") by reading the most recent and available previous chest radiographs;

4) To quantify the dose-response relations between occupational exposure to crystalline silica and mortality from lung cancer, for other diseases of a *priori* interest (e.g., non-malignant respiratory diseases, including pneumoconiosis);

5) To quantify the dose-response association between occupational exposure to crystalline silica and radiographically-detected silicosis;

6) To examine separately dose-response relations between silica exposure and lung cancer risks among workers with and without radiographic evidence of silicosis; this analysis will permit a test of the hypothesis that pulmonary fibrosis is a necessary condition for lung carcinogenesis by permitting estimation of the unique (independent) and potentially synergistic effects of cumulative exposure and fibrosis on lung cancer risk.

MATERIALS AND METHODS

Cohort enumeration and follow-up

The two DE plants are located in Lompoc, California, approximately 50 miles north of Santa Barbara. The larger plant was operated by the Manville Corporation until 1992 when it was bought by the Celite Corporation of Lompoc, CA. The smaller plant has been operated by the Grefco, Co. since 1952. DE mining and milling operations at the larger plant, on which the analyses reported here are based, began in 1902 and continue currently. The study cohort and procedures have been described previously [Checkoway et al., 1993]. 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. We identified 2,961 workers who met these inclusion criteria, including 2,674 white males, 37 black males, 242 white females, and 8 black females. The main study cohort from the earlier analysis was composed of 2,037 non-Hispanic and 533 Hispanic white males.

The cohort for whom the majority of analysis was conducted, and hence most data are presented, differs in two respects from the previously defined main study cohort: 1) in this analysis, workers employed at the smaller plant were excluded because their exposure data were judged to be inadequate for quantitative estimation; and 2) 89 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. Eight workers known to have had asbestos exposure in other industries prior to employment at the DE plant were excluded from this analysis. Most of the analysis is therefore based on mortality and radiographic findings for 2,342 white males. Separate mortality findings are shown for Grefco white males, female workers, and black male workers.

Vital status was determined previously for the years 1942-87 using several data sources, including the National Death Index (NDI), state drivers' license bureaus, and a commercial credit bureau [Checkoway et al., 1993]. Vital status information for the years 1988-94, inclusive, was determined from an updated NDI search. Workers known to be alive in 1979 and 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 [Rich-Edwards et al., 1994]. Copies of death certificates for identified deaths were obtained from state vital statistics offices, and were coded by a trained nosologist according to the International Classification of Disease codes in effect at the times of death (5th-9th Revisions).

Exposure Assessment

The facility where this study was conducted is located in Lompoc, California and is a major producer of diatomaceous earth (DE) products in the US. Operations began at the plant in 1902. The company was bought by the Johns Manville Corporation in 1928 and it remained with the company until 1992 when it was purchased by the Celite Co. which is the current operator. Crude diatomite was quarried in both bulk and solid brick form, transported to the mill areas, dried as crude DE products or crushed in mills and sent through large rotary calcining kilns with or without a carbonate flux. Powdered DE could be further processed by mixing with other materials before being bagged and shipped. A large quantity of airborne dust was generated in each production step during early years and efforts to reduce the amount of dust released to the atmosphere have been made since the 1930s. Significant dust suppression efforts at the plant included the change to paper bags from burlap for shipping product around 1940, and the introduction of cyclone dust collectors during the 1940s, and baghouses for air cleaning beginning around 1945. Of particular importance was the extensive study of pneumoconiosis and dust exposure in the DE industry, including this plant, by the California State Department of Public Health and the US Public Health Service (USPHS) from 1952 to 1954 [Cooper and Cooper, 1958]. The study resulted in a recommended exposure limit for crude DE (with <5% crystalline silica) of 20 million particles per cubic foot (mppcf), and for calcined DE containing cristobalite of 5 mppcf. In addition, this study resulted in major new efforts to reduce exposures at the source, and in an on-going program of quantitative exposure monitoring.

Quantitative air monitoring data available in computer files were provided by the Manville Corporation for the original study [Checkoway, et al. 1993]. These data included 5714 records of samples taken over the period 1962-1988 and formed the basis for the initial exposure characterization. These data were coded according to the year in which the sample was obtained and the units in which it was measured: mppcf (millions of particles per cubic meter determined by light microscopy from an impinger sample), mg/m^3 Total (milligrams per cubic meter determined gravimetrically from open face filter cassette sample), or mg/m^3 Respirable (milligrams per cubic meter determined gravimetrically from a filter cassette sample using a cyclone pre-selector to obtain the respirable fraction). The location and type of sample was determined by sampling station codes which specified the Department in which the station was located and whether the sample was an area or personal sample. Two of the major Departments in which much of the exposure data were derived (Baghouse and Powder Mill) were further classified according to Area within the Department, reflecting the major process or type of material being handled. Maps provided by the company were used to identify the location of the sampling station and assign the Area codes. The Department and Area codes are described in Table 1.

Early in this study, it was reported to us that routine air monitoring had begun during the late 1940s to early 1950s. The substantial monitoring effort conducted during the USPHS study in the 1950s added support to this contention [Cooper and Cralley, 1958]. Because these data could not be located through direct contacts, a search was conducted at the Manville Archives which maintains all records concerning health and the workplace environment from the Manville Corporation. We searched all of the boxes available at the archives that were specifically related to the Lompoc facility, and about 150 boxes relating to health and the environment for the Corporation. Although the original log books with complete records of sampling were not located, numerous reports were found detailing a wide variety of quantitative air sampling activities for the years 1948 through 1962 (no later records were obtained, because data since 1962 had been computerized). The records found in the archives varied widely in their level of detail and the purpose for which the report was generated. Despite their limitations, these data allowed our quantitation of exposure to be extended back to important earlier periods.

Data obtained from 41 documents covering the period 1948 through 1962 were extracted, coded and entered into a database and summarized as arithmetic mean values by year and Department. Because these data were poorly described in many of the reports, it was not

consistently possible to determine if they were personal or stationary samples; thus, they were defined as unknown sample type. All of these results were reported in units of mppcf. Some reports noted dust conditions such as 'heavy' or 'extremely heavy' were not be used in the analysis. Reports concerning measurements of ambient releases to the environment, or reporting tests of specific pieces of equipment such as tractor cab enclosures were also not included. Thus, the reports utilized in this analysis include only those specifically measuring dust concentrations in defined work areas. The sampling station codes were inconsistently reported in these data and were coded by the Department in which they occurred, without additional location or job specificity. Unweighted mean concentrations were used in order to give equal weight to each report because the number of samples used to generate the value was frequently missing from the reports. Duplicate records including 25 records that were redundant with the company's dataset (in 1962) were excluded.

Exposure data were assigned to a set of 135 job codes which had been defined previously from the original company job titles. Matching of exposure data to individual jobs was done in the previous study by interviewing knowledgeable plant personnel and by walk-through of the facility [Checkoway et al, 1993]. Individual sampling stations were assigned to jobs which were conducted in the same area. Any particular job code could have several sampling stations assigned to it, and some sampling stations were not assigned to any specific job.

The first step in the quantitative analysis was conversion of all data to a uniform measure. Respirable dust in mg/m^3 was selected as the measure to be used in the analyses because the recent data were all measured in these units, respirable dust is the most biologically relevant exposure fraction for silicosis or lung cancer, and any likely recommendations derived from the study would most appropriately be expressed in these units. Therefore, data collected as mppcf or mg/m^3 Total were converted to mg/m^3 Respirable. Data for years in which samples were obtained using both mg/m^3 Respirable and either mg/m^3 Total or mppcf were selected for calculation of conversion factors. Means (and mean of the logs) were calculated by sampling station. If means were available in two units for the same sampling station, the difference in the mean of the logs, and the ratio of the means were calculated. These factors were then averaged across appropriate categories of year, Area or Department. The relationship between the two units was thus expressed as:

$$\Delta_s = \overline{\ln(x)}_{s(resp)} - \overline{\ln(x)}_{s(mppcf)}$$

or

Equation 1a and 1b

$$P_s = \frac{\bar{x}_{s(resp)}}{\bar{x}_{s(mppcf)}}$$

where Δ_s is the conversion factor for sampling station s based on the log scale, P_s is the ratio factor based on the natural scale. $\bar{x}_{s(resp)}$ is the station-specific mean of the dust concentration, expressed in the units specified within parentheses. The sampling station-specific factors were then averaged across appropriate categories. Δ was selected as the appropriate conversion factor because the data were generally lognormal and it helped control the large influence of a few high samples in the calculation of sampling station-specific means. Additionally, P_s was calculated in order to provide a comparison to previously cited conversion factors [Jacobsen and Tomb, 1967; Tomb and Haney, 1988 Montgomery, et al, 1991]. After selecting a final conversion factor, the data originally measured in mppcf or mg/m^3 Total were converted to mg/m^3 Respirable by the use of the factor on each sample. For instance,

$$\hat{x}_{i(Resp)} = \exp(\ln(x)_{i(mppcf)} + \Delta)$$ Equation 2

where $\hat{x}_{i(Resp)}$ is the estimated concentration expressed in mg/m3 Respirable dust and $\ln(x)_{i(mppcf)}$ is the actual sample result in mppcf.

The company data from 1962-1988 and the Manville Archives data from 1948 to 1962 were combined into a single dataset, and analyzed using a linear regression model to describe the location-specific exposures and changes over time (Model 1):

$$\hat{x}_{i(Resp)} = \alpha + \sum \beta_L L + \sum \beta_T T + \sum \beta_p S + \varepsilon$$ Equation 3

in which L represents indicator variables for location using Department or Department and Area codes (See Table 1), T represents time periods and S represent indicators for sample type (area, personal or unknown). The definition of the time periods was made examining average dust concentration changes by year. Model selection was conducted by considering its parsimony and fit using the model R-square. The change in concentration over time from this model, β_T , was used to estimate concentrations for each earlier period as described below.

There was no simple method by which the jobs could be linked directly to the model-derived exposure estimates because each specific job may have been associated with only a portion of the process described by its Department, some jobs spanned multiple area assignments and samples from any particular station could be assigned to multiple jobs working in a given area. In addition, the Archives data could not be matched completely to specific jobs because the location frequently was inadequately described. An alternative approach was therefore used to derive job-specific exposures.

Sampling stations were assigned to each job. All samples derived from those stations were used to calculate the job-specific means (on the log scale). Because these data included both area and personal data, and spanned the years 1962-1988, the means were calculated stratified by sample type and time period. These means were then used in a linear model (Model 2), to estimate exposure on the basis of personal samples for the most recent time period.

$$[\overline{\ln(x)}]_{STJ} = \alpha + \beta_S P + \beta_T T + \sum \beta_J J + \varepsilon \qquad \text{Equation 4}$$

where $[\overline{\ln(x)}]_{STJ}$ is the mean of the log concentrations for a specific sample type, S, time period, T and job, J. Because the data used in this analysis were not independent (the same sample result was assigned to multiple jobs and the dependent variable represented the means of multiple samples), this model violates the assumption of independent observations. Regression with correlated (non-independent) observations can usually result in inflated variances, but valid point estimates; thus, Model 2 was used to provide estimates of job-specific mean personal exposures in the later time period using all of the relevant data.

Final job and time specific dust exposure estimates were calculated by adjusting for historical period and converting to the arithmetic mean:

$$\hat{\bar{x}}_{STJ} = \exp[(\overline{\ln(x)_{STJ}} + \beta_P) + \frac{1}{2}\hat{\sigma}^2], \qquad \text{Equation 5}$$

where $\overline{\ln(x)_{STJ}}$ is the mean of the logs for personal samples in the most recent time period for job j in the most recent time period estimated from Model 2, and β_P is the factor

associated with historical time periods, and $\hat{\sigma}^2$ is the variance of the logs of the exposure data estimated from Model 1.

The final job- and time- specific dust estimates were compared to the qualitative ratings of high, medium and low given each job and the factors associated with time used in the previous analysis [Checkoway, et al. 1993], in visual plots and by analysis of variance. These dust concentration estimates were further modified using an additional factor for the percent crystalline silica to estimate personal exposure to crystalline silica. The percent silica was estimated by the amounts of natural, calcined and flux calcined product produced at the plant in each year and the average level of crystalline silica in each of those products. These estimates of dust and crystalline silica exposure levels were then assigned to the cohort's work histories to derive estimates of personal cumulative exposure to respirable dust or respirable crystalline silica.

Employment history data, including assignment dates in various jobs, extracted from personnel work history records [Checkoway et al., 1993], were updated through 1994 for workers still employed as of the end of 1987. The respirable dust estimates were derived from the procedures just described. The respirable crystalline silica estimates incorporated data on the measured percentages of crystalline silica in the various product mixes and estimated job-specific fractions of exposure times to these products [Checkoway et al., 1993]. Cumulative exposures (mg/m^3-yrs) 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 [1994] derived quantitative estimates of asbestos exposures (fibers/mL) for all cohort members. These estimates were based on historical exposure monitoring data for jobs where 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 re-lining. The assessment provided asbestos exposure estimates for the years since 1930 [Gibbs and Christensen, 1994]. In order 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 (f/mL-yrs) were derived in similar manner as for the silica exposure indices.

Radiographic Readings

Readable quality chest radiographs were obtained from the company medical files for 2520 (85.1%) of 2961 DE cohort members. The most recent film was read independently by three experienced readers according to the 1980 International Labour Office (ILO) system [ILO, 1980]. Median profusion scores, indicative of pulmonary fibrosis, were obtained by median readings. It has been recognized that the radiographically detectable lung parenchymal effects associated with dust exposure in the diatomite industry differ somewhat from the silicotic appearance due to quartz exposure. In contrast to the predominant discrete nodular pattern of small rounded opacities, the pneumoconiosis of diatomite exposure is more likely to have poorly-defined opacities and small irregular or linear densities. It has therefore been decided that a distinction between rounded and irregular opacities is not appropriate for this cohort. Radiographically-determined silicosis cases were defined as workers with median ILO profusion scores $\geq$1/0 and/or the presence of large opacities. The dates of first positive radiographs were determined from serial readings of earlier films for workers whose final acceptable quality radiograph was classified by median reading as 1/0 or higher. Presence of pleural plaques or thickening, generally related to asbestos exposure, was also recorded from the final acceptable quality chest film.

Data Analysis

Cause-specific mortality rate comparisons were made against rates for U.S. white males for the years 1942-94. Standardized mortality ratios (SMR) and 95% confidence intervals (CI) were calculated using the National Institute for Occupational Safety and Health life-table program [Steenland et al., 1990] which provides 5-year age- and calendar year-specific mortality rates. Lung cancer mortality rates for white male residents of local counties in southern California (Kern, Santa Barbara, San Luis Obispo, Ventura), obtained from the University of Pittsburgh, were used to compute a regionally-based SMR. Person-time accumulation for each worker began at the later of January 1, 1942 or the date when one year of cumulative service was attained.

Dose-response estimation for lung cancer and non-malignant respiratory diseases was conducted using Poisson regression modeling [Breslow and Day, 1987]. 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 (RR) were estimated treating the lowest cumulative exposure category as the referent. Covariates included: age (<40, 45-49, 50-54,...,≥80), calendar year (<1955, 1955-59, ..., 1985-89, 1990-94), duration of follow-up (<10, 10-19, ≥20 years), and Hispanic ethnicity treated as a binary variable. Hispanic ethnicity was included as a covariate because of well-documented lower lung cancer risks among Hispanic compared to non-Hispanic white males [Wiggins et al., 1993]. Cumulative exposure to asbestos (f/mL-yrs) was included as a covariate to assess potential confounding. Asbestos categories were defined as non-exposed (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. Exposure variables and covariates were treated in a time-dependent manner. Poisson regression modeling was performed using the AMFIT Version 2.0 program of the Epicure™ statistical package [Preston et al., 1995].

The radiographic data were analyzed with a loglogistic model which expresses cumulative risk of silicosis in relation to cumulative exposure to dust. Separate analyses were performed for cumulative exposures to respirable dust and respirable crystalline silica. Several other models, including those based on Weibull, gamma, lognormal, and normal distributions were fitted, but the loglogistic provided the best fit to the data. The SAS procedures, LIFEREG and LIFETEST [SAS, 1990] were used in these analyses.

Evaluation of confounding by cigarette smoking

Data on smoking habits were collected since the early 1960s as part of the company's radiographic screening program [Checkoway et al., 1993]. These data permitted distinctions of ever vs. never smoked for 1,171 (50%) cohort members. Smoking prevalence was examined in relation to cumulative exposures, and the method described by Axelson [1978] was applied to estimate confounding bias in observed rate ratios.

RESULTS

Estimation of quantitative exposures

Quantitation of exposures was possible for the Manville plant, but could not be accomplished for the Grefco plant because the available industrial hygiene sampling data

for the latter were not adequate for this purpose. The department and work areas at the Manville plant are described in Table 1. There were 140 station-specific matched means obtained during 1979 and from 1983 through 1988 with which measurements in mppcf could be compared to measurements in mg/m^3 Respirable units (Table 2). Likewise, there were 160 matched means from 1980-1983 with which measurements in mg/m^3 Total could be compared to measurements in mg/m^3 Respirable units. The average difference in mean of logs (Δ) was -2.67 for mppcf and -1.48 for mg/m^3 Total. When calculated within major Departments, there were no clear or substantial differences. The Δ's were not substantially different between the Baghouse (-2.69) and all other Departments (-2.67), although the ratio of arithmetic means (P) did appear to be different, especially comparing mppcf to mg/m^3 Respirable (0.18 vs. 0.09). This difference was due to a limited number of samples within a single year and was not generally representative of the data. As a result of this analysis, a single conversion factor for Total mg/m^3 (Δ= -1.48) and one for mppcf (Δ=-2.67) was used to convert the data into consistent units of mg/m^3 Respirable.

Of the 5714 samples in the company dataset, five samples were very high (maximum, 52 mg/m^3) and appeared as outliers compared to the remaining data. These five samples were removed from all subsequent analyses, leaving 5709 samples. These data were combined with those derived from the Manville Archives (n=686) resulting in a master dataset used for analysis containing 6395 air concentrations over the years 1948 to 1988 (Table 3). After conversion to mg/m^3 Respirable units, these data were well described by the lognormal model as determined by visual inspection of probability plots. The measured concentrations were generally low, with mean values well under 1 mg/m^3 and an overall geometric mean of 0.18 mg/m^3. About half the dataset (n=3268) were personal samples and about 1000 samples, including 686 from the Archives data, were of unknown sample type.

Time and location variables were grouped in order to provide stable estimates and a parsimonious model. The crude average concentration by year was somewhat variable from year to year, but three reasonably distinct periods could be identified. Prior to 1954, the average concentration was clearly higher. Through the 1950s and 1960s, there were no clear changes in concentrations, but after about 1974, average concentrations were somewhat lower, but more variable. Thus, time was grouped into three categories ($<$1954, 1954-1973, $\geq$1974). These particular period boundaries were also chosen to be consistent with the earlier analysis of these data [Checkoway et al., 1993]. A four-level grouping was also considered, by dividing the middle period into 1954-1962 and 1963-1973,

representing the change in the source of the exposure data. Grouping the data by sampling station was rejected because of the very large number of stations (419), and because sampling station was not consistently available for the pre-1962 years. Thus, location was considered on the basis of Department (9 levels) or Department/Area (22 levels), as defined in Table 1.

Linear models (Model 1, Equation 3) were developed to compare alternative levels of grouping for time and location, while also considering the difference between area and personal samples. The dependent variable was the log of the converted dust concentration ($\ln(mg/m^3)$ Respirable). The difference between area and personal samples was significantly different and explained about 10% of the total variability. Year explained 20% of the variability; however, grouping year into the three distinct periods explained 13%. There was no substantial improvement in the model (R^2=0.14) when the years were divided into four periods representing the change in source of data in 1962, suggesting that the data were consistent across this time period. Department, surprisingly, explained only 4% of the variability, and this was somewhat improved by sub-dividing the major dusty Departments, Baghouse and Powder Mill, into distinct Areas. With the combination of sample type, time in three groups and Department/Area, the model explained almost 22% of the variability and this model was selected to provide estimates of time-related changes in dust concentration.

The available exposure data from the company (1962-1988), in which the sampling station information was complete, were matched by station to 135 distinct jobs and means (of log concentrations) were calculated for each job by sample type and time period. Estimates of the mean personal exposure in the post 1973 time period were calculated using Model 2 (Equation 4) with the means (of logs) as the dependent variable. The model-derived job-specific exposures (on the log scale for personal samples in the post-1973 period) were then extrapolated to the earlier time periods using Equation 5. The estimates of the change in dust concentrations over time, (β_T) derived from Model 1, were 0.48 for the 1954-1973 and 1.54 for prior to 1954 periods. No data were available prior to 1948; however, evidence from the company's history suggested that substantially higher concentrations were present in the 1930s and early 1940s. In about 1944 the conversion from paper to burlap bags was completed and other substantial dust control efforts were reported during this period. To be consistent with the previous analysis, we chose 1944 for the boundary and assigned a factor of 2.5 (log scale) to extrapolate the dust concentrations to jobs prior to this time.

In order to convert to arithmetic means, an estimate of the variance was required. Because the variance was highly unstable, and is even more sensitive to biases in the data than the mean, we chose to use the average variance observed in the later time period derived from the Model 1. The estimated variability represented by σ was 0.909 which represents as geometric standard deviation of 2.48. This variance estimate was applied using Equation 5 to estimate arithmetic mean concentrations for all jobs and time periods. The final estimated mean dust concentrations are presented in Table 4.

In the earlier analyses [Checkoway, et al. 1993], each job was assigned a concentration represented on a qualitative scale of High, Medium or Low dustiness. Analysis of variance of the estimates between the three levels indicated a statistically significant difference ($p=0.02$), although the average estimate in the "High" category (0.29 mg/m^3) was slightly lower than that for the "Medium" category (0.31 mg/m^3).

Mortality findings for 2,342 white males from the former Manville plant

Descriptive characteristics and vital status follow-up data for the cohort are summarized in Table 5. Vital status was determined for 91 percent of the cohort, and death certificates were obtained for 716 (96%) 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 6.

Mortality comparisons with rates for U.S. white males for causes of death with expected numbers greater than 2.0 are presented in Table 7. 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 [Choi, 1992].

As in the earlier analysis [Checkoway et al., 1993], we excluded pneumonia and infectious diseases from the non-malignant respiratory disease (NMRD) category in order to focus on the chronic conditions most plausibly associated with occupational dust exposure. The NMRD category included 27 deaths from silicosis, pulmonary fibrosis, or pneumoconiosis not otherwise specified, including one due to "silicosis and asbestosis." There was a

prominent mortality excess of NMRD (SMR=2.01), whereas a smaller excess was found for lung cancer (SMR=1.29). The lung cancer SMR increased to 1.44 (95% CI 1.14-1.80) on 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, 4 Observed) and brain and central nervous system (SMR=1.38, 7 Observed).

The largest NMRD mortality excesses occurred among workers hired between 1920-1939 (Table 8). The NMRD elevations among workers hired since 1960 suggest a persistent risk, although the corresponding SMRs 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 9, there were consistently strong mortality gradients for NMRD with respect to the dust exposure indices. The association of NMRD mortality with cumulative exposure to respirable crystalline silica was stronger than with the less specific respirable dust index, irrespective of latency interval. The most pronounced trend was seen for respirable crystalline silica, allowing for a 15-year latency; RR for the highest exposure stratum ($\geq$5.0 mg/m^3-yr), compared to the lowest exposure category (<0.5 mg/m^3-yr), reached 5.35 (95% CI 2.23-12.8). It is noteworthy that the trend slopes were unchanged when adjustments were made for cumulative exposure to asbestos.

Dose-response trends for lung cancer (Table 10) 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 RR for the $\geq$5.0 mg/m^3-yr stratum was 2.15 (95% 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 to 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 [Checkoway et al., 1996]. Rate ratios for joint strata of crystalline silica and asbestos cumulative exposures, each lagged 15 years, are presented in Table 11. 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 (rightmost column), 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. A similar distribution was detected with respect to cumulative exposure to crystalline silica lagged 15 years: 0.63, 0.82, 0.80, 0.86, 0.83. We applied the Axelson [1978] method 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 to non-smokers, 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.

Mortality findings for other groups of workers

SMR results for all causes, all cancer, lung cancer, and NMRD for 359 Grefco white males (including 26 workers also employed at Manville), 242 white females from both companies, and 37 black males from both companies are given in Tables 12-14, respectively. There were only 8 black females in the study, and no deaths among them. Among Grefco white males, the lung cancer (SMR=1.23, 5 observed) and NMRD (SMR=1.49, 3 observed) mortality findings were similar to findings for the Manville workers (Table 7). Excessive mortality from both disease categories were also found for white females (Table 13) and black males (Table 14). Although based on small numbers, the mortality experience among these smaller worker groups indicates consistent mortality excesses for lung cancer and NMRD throughout the workforce of the two plants.

Radiographic evidence of silicosis

As mentioned earlier, a case of silicosis was defined as the presence of ILO profusion category 1/0 or higher for small opacities or the presence of large opacities. Acceptable quality final films were available for 2520 (85%) of the total cohort of 2961 workers.

Findings are presented for Manville and Grefco white males, with most emphasis on the former for whom exposure-response analyses were possible.

Prevalences of radiographically-defined silicosis among white males are summarized by year of hire and company in Tables 15 and 16. Also shown are prevalences of pleural thickening and/or calcification. The overall prevalence of radiographically-defined silicosis was 3.9% at Manville and 4.0% at Grefco. There were 99 cases, 86 from Manville, 12 from Grefco, and 1 who worked at both companies (this last case does not appear in either Table 15 or 16). Of the combined total of 99 silicosis cases, 65 (65.7%) had small opacities only, 4 (4.0%) had large opacities only, and 30 (30.3%) had both small and large opacities. Silicosis prevalence was clearly greatest among workers hired before 1940 at Manville (Table 15). A similar trend of silicosis reduction by year of hire is also evident among Grefco workers, although based on small numbers (Table 16). These findings are consistent with earlier radiographic surveys demonstrating diminishing secular trends of silicosis prevalence among DE workers [Cooper and Jacobson, 1977; Cooper and Sargent, 1984].

The crude prevalence of silicosis according to cumulative exposure categories of respirable dust and respirable crystalline silica suggest positive gradients (Table 17), with the highest prevalences found among workers with $\geq$20 mg/m3-yrs of cumulative respirable dust (23.5%) or $\geq$6.0 mg/m3-yrs respirable crystalline silica (24.3%).

Under the loglogistic model, the cumulative risk [R(x)] of having a positive radiograph, following cumulative respirable crystalline silica exposure level x, was observed to be:

$$R(x) = 1 - [1 + 0.067x^{1.804}]^{-1},$$

The results of the modeling of cumulative risk in relation to cumulative respirable crystalline silica modeling are presented in Table 18. The data fit well with a log-logistic model, as indicated by the close correspondence of the observed and fitted (predicted) models. There was a strong, monotonically increasing trend of increasing silicosis prevalence with cumulative exposure to respirable crystalline silica. The cumulative probability of silicosis reached nearly 57% at 18.0 mg/m^3-yrs. The cumulative probability of 40 working years at 0.1mg/m^3 is estimated at 5.8% from the observed data and 7.6% from the fitted data.

Analyses examining mortality risks, especially for lung cancer and NMRD, in relation to ILO profusion category and the presence of pleural disease are currently underway and will be reported in subsequent publications. The most important goal of these analyses will be to determine whether radiographic evidence of pulmonary fibrosis is a risk factor for lung cancer, apart from the contribution to risk conferred by cumulative exposure to crystalline silica.

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. There are, however, certain limitations of our study that deserve comment. Vital status could not be ascertained for 9 percent of the cohort. This may have caused inflated SMRs for the cohort as a whole because person-year accumulation was truncated for unknowns at dates last known 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%) than for workers hired in earlier years (87%) when exposures and disease risks were highest.

The validity of our dose-response estimates is largely dependent on the quality and completeness of exposure data. Available dust monitoring data spanned the years 1948-88, with the majority of measurements made since the early 1960s. Consequently, extrapolation models were necessitated to estimate exposure concentrations for earlier years. 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. The percentages of crystalline silica in respirable dust were estimated from measurements made on product samples rather than from assays of airborne respirable dust, because data on the latter were not available. Nonetheless, exposure assessment was performed in a blinded manner with regard to health outcome, thus virtually ensuring that there was non-differential misclassification, which ordinarily, although not always, will result in attenuated dose-response relations [Brenner and Loomis, 1994]. Exposures to asbestos could be documented from personnel records for workers assigned to two small dust mixing operations during 1952-77; 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 re-lining [Gibbs and Christensen, 1994].

Therefore, misclassification of asbestos exposure may have hindered our ability to control for asbestos as a potential confounder [Ahlbom and Steineck, 1992].

Silicosis has been documented as a hazard in this DE facility since the 1930s [Legge and Rosencrantz, 1932], with declining prevalence noted subsequent to dust exposure reductions [Cooper and Sargent, 1984]. Our analysis also demonstrates decreasing temporal trends with year of hire, which agrees generally with earlier cross-sectional evaluations [Cooper and Cralley, 1958; Cooper and Jacobsen, 1977; Cooper and Sargent, 1984]. Predictably, we observed unambiguous evidence for a dose-response association of cumulative crystalline silica and radiographically-determined silicosis. Our findings fall between those from studies of Ontario, Canada hard rock miners [Muir et al., 1989] and South Africa gold miners [Hnizdo and Sluis-Cremer, 1993]. For example, Muir et al. [1989] estimated a cumulative risk of 1.2% following 40 years of exposure at 0.1 mg/m^3, whereas Hnizdo and Sluis Cremer [1993] report an approximately 60% risk at that level. Our corresponding observed and fitted estimates were 5.8% and 7.6%, respectively. Direct comparisons between findings may not be fully appropriate because of differences in exposure units, percentages of crystalline silica, and even in the radiographic definition of silicosis.

Mortality from NMRD bore a strong relation with cumulative dust exposure. The dose-response trends observed for NMRD mortality undoubtedly reflect the association with silicosis and its sequelae. The parallel exposure-response trend for radiographically-detected silicosis prevalence with cumulative exposure to crystalline silica supports this assertion. Further analyses will address specific mortality risks, from NMRD and lung cancer, among workers with radiographic evidence of pulmonary fibrosis. Obstructive diseases included in the NMRD grouping, notably emphysema, have been associated with silica exposures among metal miners [Hnizdo, 1990; Carta et al., 1994], particularly among smokers [Becklake et al., 1987; Reid and Sluis-Cremer, 1996], and among pottery workers [Neukirch et al., 1994]. Thus, our findings for NMRD indicate strong associations with crystalline silica from DE operations, and are consistent with other studies of silica-exposed cohorts.

The lung cancer findings suggest a dose-response association with dust exposure, but are less convincing than the NMRD results. For the main cohort of Manville white males, the overall lung cancer excess relative to national (SMR=1.29) or local mortality rates (SMR=1.44) is similar to those reported for other silica-exposed cohorts [McDonald,

1995], but slightly reduced from the SMRs (1.43 and 1.59 compared to national and local rates, respectively) that we observed previously for 1942-87 [Checkoway et al., 1993]. Consistent excesses of lung cancer mortality were also found among the other worker groups: Grefco white males, white females, and black males. The decreased SMRs found compared to the first analysis [Checkoway et al., 1993] may be partly due to more complete vital status tracing for the extended follow-up interval. Alternatively, a diminishing temporal pattern of risk subsequent to exposure reduction might be inferred from the observation that lung cancer was not excessive among workers hired since 1960 (SMR=0.72).

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-yr of crystalline silica (1.05-1.06) was slightly greater than the corresponding trend for respirable dust ignoring the crystalline component (1.01). In contrast, the association with NMRD risk was considerably stronger with the crystalline silica metric than with respirable dust. One possible interpretation is that components of dust other than crystalline silica (e.g., amorphous silica, trace metals) may contribute to lung cancer risk. It was not possible to determine the unique effects of amorphous silica or trace metals, even among workers not exposed to calcined dust, because there are small quantities (1-2 percent) of quartz in the mined ore and we have no information on metal concentrations.

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, there was no evidence for an independent association of asbestos on lung cancer risk; among workers with the lowest crystalline silica exposures, there was a downward mortality gradient with asbestos (Table 11). 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 prevalence of pleural plaques or thickening, often regarded as a marker of asbestos exposure, was low (roughly 2%) and in the range found in populations without occupational asbestos exposure [Anderson et al.,

1979]. The amount of asbestos used in filtration products was quantitatively very small compared to 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 highest two exposure strata of respirable crystalline silica lagged 15 years (0.86 vs. 0.83), as contrasted with a marked difference in lung cancer rate ratios (1.26 vs. 2.15) (Table 6).

The lung cancer results for our cohort are generally consistent with those from a considerably smaller cohort of Icelandic workers [Rafnsson and Gunnarsdottir, 1996]. Compared to 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 [1991] detected a positive dose-response association of respirable dust (particle 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 [Steenland and Brown, 1995], despite a past history of very intense silica exposures revealed by pronounced NMRD risks [McDonald et al., 1978].

CONCLUSIONS

Our findings for NMRD are clearly supportive of an etiologic role of crystalline silica. The exposure-response analyses for radiographic silicosis indicate a strong gradient, that is consistent with previous literature of silica-exposed populations. Our dose-response analyses also add support to 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. There may be differences in carcinogenic potential among the various silica polymorphs that 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.

REFERENCES

Abrams HK (1954). Diatomaceous earth pneumoconiosis. *Am J Public Health* 44: 592-599.

Abrams HK (1990). Historical perspective in Occupational Medicine: diatomaceous earth silicosis. *Am J Ind Med* 18: 591-597.

Ahlbom A, Steineck G (1992). Aspects of misclassification of confounding factors. *Am J Ind Med* 21:107-112.

Anderson HA, Lilis R, Daum SM, Selikoff IJ (1979). Asbestosis among household contacts of asbestos factory workers. *Ann NY Acad Sci* 300:386-399.

Axelson O (1978). Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health* 4:98-102.

Becklake MR, Irwig L, Kielkowski D, Webster I, De Beer M, Landau S (1987). The predictors of emphysema in South African gold miners. *Am Rev Respir Dis* 135:1234-1241.

Brenner H, Loomis D (1994). Varied forms of bias due to nondifferential error in measuring exposure. *Epidemiology* 5:510-517.

Breslow NE, Day NE (1987). *Statistical Methods in Cancer Research. Vol. II. The analysis of cohort studies*. Lyon, France: International Agency for Research on Cancer, (IARC scientific publication no.82).

Checkoway H, Heyer NJ, Demers PA, Breslow NE (1993). Mortality among workers in the diatomaceous earth industry. *Brit J Ind Med* 50:586-597.

Checkoway H, Heyer NJ, Demers PA, Gibbs GW (1996). Re-analysis of lung cancer mortality among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure. *Occup Environ Med* 53:645-647.

Choi BCK (1992). Definition, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. *J Occup Med* 34:979-988.

Cooper WC, Cralley LJ (1958). *Pneumoconiosis in Diatomite Mining and Processing*. Wahington, DC: U.S. Government Printing Office, Public Health Service Publication no. 601.

Cooper WC, Jacobson G (1977). A 21-year radiographic follow-up of workers in the diatomite industry. *J Occup Med* 19: 563-566.

Cooper WC, Sargent EN (1984). A 26-year radiographic follow-up of workers in a diatomite mine and mill. *J Occup Med* 26: 456-460.

Costello J, Castellan RM, Swecker GS, Kullman GJ (1995). Mortality of a cohort of U.S. workers employed in the crushed stone industry, 1940-1980. *Am J Ind Med* 27:625-640.

Dong D, Xu G, Sun Y, Hu P (1995). Lung cancer among workers exposed to silica dust in Chinese refractorry plants. *Scand J Work Environ Health* 21(Suppl 2):69-72.

Gibbs GW, Christensen DR (1994). *The asbestos exposure of workers in the Manville diatomaceous earth plant, Lompoc, California.* Final report to the International Diatomite Producers Association, San Francisco, CA.

Hnizdo E (1990). Combined effect of silica dust and tobacco smoking on mortality from chronic obstructive lung disease in gold miners. *Brit J Ind Med* 47:656-664.

Hnizdo E, Sluis-Cremer GK (1991). Silica exposure, silicosis, and lung cancer: a mortality study of South African gold miners. *Brit J Ind Med* 48:53-60.

Hnizdo E, Sluis-Cremer GK(1993). Risk of silicosis in a cohort of white South African gold miners. *Am J Ind Med* 24:447-457.

International Agency for Research on Cancer [IARC] (1987) *Evaluation of Carcinogenic Risks to Humans: an Updating of IARC Monograph 1 to 42 (Supplement 7).* Lyon France: IARC, pp 341-343.

International Labour Office [ILO] (1980). *International Classification of Radiographs for Pneumoconiosis*. Revised ed., No. 22, Geneva: Interantional Labour Office.

Jacobsen M, Tomb TF (1967). Relationship between gravimetric respirable dust concentration and midget impinger number concentration. *Am Ind Hyg Assoc J* 28: 554-556.

Koskela R-S, Klockars M, Laurent H, Holopainen M (1994). Silica dust exposure and lung cancer. *Scand J Work Environ Health* 20:407-16.

Legge RT, Rosencrantz E (1933). Observations and studies on silicosis by diatomaeous silica. *Am J Publ Health* 32: 1055-1060.

McDonald JC, Gibbs GW, Liddell FDK, McDonald AD (1978). Mortality after long exposure to cummington-grunerite. *Am Rev Respir Dis* 118:271-277.

McDonald JC (1989). Silica, silicosis, and lung cancer [Editorial]. *Brit J Ind Med* 46: 289-91.

McDonald C (1995). Silica, silicosis, and lung cancer: an epidemiological update. *Appl Occup Environ Hyg* 10:1056-63.

Merlo F, Costantini M, Reggiardo G, Ceppi M, Puntoni R (1991). Lung cancer risk among refractory brick workers exposed to crystalline silica: a retrospective cohort study. *Epidemiology* 2:299-305.

Montgomery JS, Horstman S, Breslow NE, Heyer NJ, Stebbins A, Checkoway H (1991) A comparison of air sampling methods for airborne silica in the diatomaceous earth industry. *Appl Occup Environ Hyg* 6:696-702.

Muir DCF, Julian JA, Shannon HS, Verma DK, Sebestyen A, Bernholz CD (1989). Silica exposure and silicosis among Ontario hardrock miners. III. Analysis and risk estimates. *Am J Ind Med* 16:29-43.

Neukirch F, Cooreman J, Korobaeff M, Pariente R (1994). Silica exposure and chronic airflow limitation in pottery workers. *Arch Environ Health* 49:459-464.

Pang D, Fu SC, Yang GC (1992). Relation between exposure to respirable silica dust and silicosis in a tungsten mine in China. *Brit J Ind Med* 49:38-40.

Preston DL, Lubin JH, Pierce DA, McConney ME (1995). Epicure™ Version 1.8 User's Guide. Seattle, WA: HiroSoft International Corp.

Rafnsson V, Gunnarsdottir H (1996). Lung cancer incidence among an Icelandic cohort exposed to diatomaceous earth and cristobalite. *Scand J Work Environ Health* (in press).

Reid PJ, Sluis-Cremer GK (1996). Mortality of white South African gold miners. *Occup Environ Med* 53:11-16.

Rich-Edwards JW, Corsana KA, Stampfer MJ (1994). Test of the National Death Index and Equifax National Death Search. *Am J Epidemiol* 140:1016-1019.

Statistical Analysis System [SAS] (1990). *SAS User's Guide*, Cary, NC: SAS Institute.

Silicosis and Silicate Disease Committee (1988). Diseases associated with exposure to silica and other nonfibrous silicate minerals. *Arch Pathol Lab Med* 112:673-720.

Smith AH, Lopipero PA, Barroga VR (1995). Meta-analysis of studies of lung cancer among silicotics. *Epidemiology* 6:617-24.

Steenland K. Beaumont JJ, Spaeth S, et al.(1990). New developments in the life table analysis system of the National Institute for Occupational Safety and Health. *J Occup Med* 32:1091-1098.

Steenland K, Brown D (1995). Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of follow-up. *Am J Ind Med* 27:217-29.

Tomb T, Haney R (1988) Comparison of number and respirable mass concentration determinations. In: *Advances in Air Sampling*, American Conference of Governmental Industrial Hygienists. Chelsea, MI: Lewis Publishers, Inc.

Weill H, McDonald JC (1996). Exposure to crystalline silica and risk of lung cancer: the epidemiological evidence. *Thorax* 51:97-102.

Wiggins CL, Becker TM, Key CR, Samet JM (1993). Cancer mortality among New Mexico's Hispanics, American Indians, and non-Hispanic whites, 1958-87. *J Natl Cancer Inst* 85:1670-8.

PUBLICATIONS FROM THIS GRANT

Already published:

Checkoway H (1995). Methodological considerations relevant to epidemiology studies of silica and lung cancer. *Appl Occup Environ Hyg* 10:1049-1055.

Checkoway H, Heyer NJ, Demers PA, Gibbs GW (1996). Re-analysis of lung cancer mortality among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure. *Occup Environ Med* 53:645-647.

Submitted manuscripts

Seixas NS, Heyer NJ, Welp E, Checkoway H. Quantitation of historical exposures in the diatomaceous earth industry. *Ann Occup Hyg.*

Checkoway H, Heyer NJ, Seixas NS, et al. Dose-response associations of silica with non-malignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. *Am J Epidemiol.*.

Planned mansucripts

Hughes JM, Checkoway H, Heyer NJ, Seixas NS, Weill H. Silicosis risks among diatomaceous earth industry workers.

Hughes JM, Checkoway H, Heyer NJ, Seixas NS, Weill H. Radiographic pulmonary fibrosis and mortality from non-malignant respiratory disease and lung cancer among diatomite industry workers.

TABLE 1. Definitions of locations within the DE mine and mill

Department	Area	Description
Powder Mill		Main powder processing areas including crude crushers, drying and calcining kilns and bag packing stations.
	Packing Station	Bag packing stations.
	Dry End	Processing after drying on mills 3,4,5,6.
	Wet End	Crushing and feeding crude materials prior to drying, mills 3,4,5,6..
	Natural #11	Mill 11 in which no calcined material was processed.
	Mill #11 Unspecified	Processing or Baghouse for Mill 11
	Dry End #7	Mill 7, prior to drying.
	Wet End #7	Mill 7 after drying.
	Other	Any other areas in Powder Mill.
	Unspecified	Unknown.
Bag House		Dust control and maintenance operations
	Dry End	Baghouse operations located at the dry end of the powder mills 3,4,5,6.
	Natural #11	Dedicated to natural product in mill 11.
	Dry End #7	Baghouse for mill 7, near dry end of mills.
	Natural #7	Baghouse used only for natural DE.
	Other	All other bag house areas.
	Unspecified	Unknown.
Specialty Products		Mixing and packing various mineral and chemical powdered products with lesser amounts of DE.
Quarry		Quarrying and transport of natural product to mill.
Brick Plant		Production and drying of DE bricks.
Maintenance		Building and maintenance operations and shops.
Quality Control		Quality control jobs throughout plant.
Shipping/Warehouse		Shipping and warehouse operations.
Other		All other departments.

TABLE 2. Factors calculated to convert measurements of total dust in mg/m^3 or mppcf into respirable dust in mg/m^3

	mppcf to mg/m^3 Respirable			mg/m^3 Total to mg/m^3 Respirable		
Classification	n_m*	Δ**	P***	n_m	Δ	P
All	140	-2.67	0.11	160	-1.48	0.29
By Department						
Powder Mill	47	-2.62	0.10	47	-1.73	0.20
Bag House	20	-2.69	0.18	18	-1.29	0.38
Specialty Prod's.	12	-2.77	0.09	12	-1.24	0.39
Quarry	16	-2.90	0.07	21	-1.54	0.25
Shipping/Warehouse	12	-2.54	0.08	14	-1.76	0.20
Maintenance	10	-2.57	0.14	20	-1.15	0.40
Other	23	-2.67	0.09	30	-1.35	0.32
Non-Baghouse	120	-2.67	0.09	142	-1.51	0.28

* Number of means matched by sampling station containing data in paired sets of units (e.g., mppcf and respirable mg/m^3).
** Difference in the mean of the log values by sampling station defined in Equation 1A.
*** Ratio of arithmetic means by sampling station defined in Equation 1B.

TABLE 3. Air sampling data available by data source, sample method, sample type and time period

	n Total (mppcf)	n Total (mg/m^3)	n Respirable (mg/m^3)	Converted to Respirable (mg/m^3) n	AM	GM	GSD
Archived Data (1948-1962)	686	0	0	686	0.68	0.37	2.43
Company Data (1962-1988)	2931	973	1805	5709	0.25	0.17	2.35
Sample Type							
Area	1066	337	689	2092	0.19	0.13	2.38
Personal	1574	625	1069	3268	0.27	0.20	2.23
Unknown	291	11	47	349	0.30	0.20	2.25
Complete Data	3617	973	1805	6395	0.30	0.18	2.44

TABLE 4. Estimated arithmetic mean exposures (mg/m^3) by time period for 135 jobs

Period	Mean	SD	Minimum	Maximum
<1948	3.55	1.25	0.97	7.14
1949-1953	1.37	0.48	0.38	2.75
1954-1973	0.47	0.16	0.13	0.95
1974-1988	0.29	0.10	0.08	0.59

TABLE 5. Descriptive characteristics and vital status ascertainment, 1942-1994, for the cohort of 2,342 white males

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 (yrs)	5.54	1.00-49.3
Duration of follow-up (yrs)	29.9	<1-53.0
Vital Status as of December 31, 1994	**Number**	**Percent**
Alive	1379	58.9
Dead	749	32.0
-with certificate	716	95.6*
-without certificate	33	4.4*
Unknown	214	9.1

*Percent of deaths

TABLE 6. Distributions of cumulative exposures to respirable dust, respirable crystalline silica, and asbestos

	Mean (SD)		Percentile						
			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

*milligrams per cubic meter x years (mg/m^3 - yrs)

†fibers per milliliter x years (f/mL - years)

TABLE 7. Standardized mortality ratios (SMR) 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
Non-malignant 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 U.S. white males, 1942-94
†Malignant neoplasms

TABLE 8. Non-malignant respiratory disease (NMRD) and lung cancer mortality comparisons with U.S. white males, 1942-94, by year of hire, year of death, and age at death

	NMRD			Lung Cancer		
	No. deaths	SMR*	95% CI	No. 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
1990-1993	6	0.69	0.25-1.50	12	0.87	0.45-1.53
Age at death						
<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

*Standardized mortality ratio, based on rates for U.S. white males, 1942-94

TABLE 9. Non-malignant respiratory disease (NMRD) mortality trends by cumulative exposure to respirable dust and cumulative exposure to respirable crystalline silica

Respirable dust							Respirable crystalline silica						
	Latency interval (yrs)							Latency interval (yrs)					
Cumulative exposure (mg/m^3 x yrs)	0			15			Cumulative exposure (mg/m^3 x yrs)	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† (95% CI)		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 x yrs) (95% CI)		1.02 (1.00-1.03)			1.02 (1.00-1.03)				1.08 (1.02-1.14)			1.08 (1.03-1.14)	

*Rate ratio, adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)
†Rate ratio per mg/m^3 x yr exposure, adjusted for aforementioned covariates

TABLE 10. Lung cancer mortality trends by cumulative exposure to respirable dust and cumulative exposure to respirable crystalline silica

Respirable dust							Respirable crystalline silica						
	Latency interval (yrs)							Latency interval (yrs)					
Cumulative	0			15			Cumulative	0			15		
exposure (mg/m^3 x yrs)	Deaths	RR*	95% CI	Deaths	RR*	95% CI	exposure (mg/m^3 x yrs)	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† (95% CI)		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 x yrs) (95% CI)		1.01 (1.00-1.03)			1.01 (1.00-1.03)				1.06 (1.01-1.11)			1.05 (0.99-1.11)	

*Rate ratio, adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)

†Rate ratio per mg/m^3 x yr exposure, adjusted for aforementioned covariates

TABLE 11. Lung cancer mortality by cumulative exposures to respirable crystalline silica and asbestos, each lagged 15 years

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

*Rate ratio, adjusted for age, calendar year, duration of follow-up, ethnicity (Hispanic vs. non-Hispanic)
†Reference category

TABLE 12. Standardized mortality ratios (SMR) for selected causes of death, 1942-1994: 359 Grefco white males‡

Cause of death	Observed	Expected*	SMR	95% CI
All causes	56	52.4	1.07	0.81-1.39
All cancers	12	12.0	1.00	0.52-1.74
Lung cancer	5	4.05	1.23	0.40-2.88
Non-malignant respiratory diseases†	3	2.02	1.49	0.31-4.34

*Based on rates for U.S. white males, 1942-94

†Excludes pneumonia, infectious diseases

‡Includes 26 workers also employed at Manville

TABLE 13. Standardized mortality ratios (SMR) for selected causes of death, 1942-1994: 242 white females (both companies)

Cause of death	Observed	Expected*	SMR	95% CI
All causes	43	33.8	1.27	0.92-1.71
All cancers	18	11.1	1.62	0.96-2.56
Lung cancer	8	2.05	3.90	1.67-7.68
Non-malignant respiratory diseases†	5	1.39	3.61	1.17-8.43

*Based on rates for U.S. white females, 1942-94

†Excludes pneumonia, infectious diseases

TABLE 14. Standardized mortality ratios (SMR) for selected causes of death, 1942-1994: 27 Black males

Cause of death	Observed	Expected*	SMR	95% CI
All causes	2	5.01	0.40	0.05-1.44
All cancers	1	1.03	0.97	0.02-5.42
Lung cancer	1	0.38	2.63	0.07-14.6
Non-malignant respiratory diseases†	1	0.13	7.75	0.19-43.2

*Based on rates for U.S. non-white males, 1942-94

†Excludes pneumonia, infectious diseases

TABLE 15. Results of radiographic readings by year of hire: Manville white male workers

Year of hire	No. workers with film(s)	No. (%) positive for opacities*	No. (%) positive for pleural charges
1908-19	4	2 (50.0)	0 (0)
1920-29	44	9 (21.0)	2 (4.5)
1930-39	113	24 (21.2)	5 (4.4)
1940-49	645	37 (5.7)	18 (2.8)
1950-59	545	4 (0.7)	8 (1.5)
1960-69	388	8 (2.1)	3 (0.8)
1970-87	453	2 (0.4)	3 (0.7)
All years	2192	86 (3.9)	39 (1.8)

*Small opacities ≥ 1/0 ILO category or large opacities

TABLE 16. Results of radiographic readings by year of hire: Grefco white male workers

Year of hire	No. workers with film(s)	No. (%) positive for opacities*	No. (%) positive for pleural charges
1940-49	5	1 (20.0)	0 (0)
1950-59	52	3 (5.8)	0 (0)
1960-69	138	7 (5.1)	6 (4.4)
1970-87	107	1 (0.9)	0 (0)
All years	302	12 (4.0)	6 (2.0)

*Small opacities ≥ 1/0 ILO category or large opacities

TABLE 17. Presence of radiographic opacities* by cumulative exposure to respirable dust and cumulative exposure to respirable crystalline silica: Manville white males

Respirable dust			Respirable crystalline silica		
Cumulative exposure (mg/m^3-yrs)	No. positive/total	(%)	Cumulative exposure (mg/m^3-yrs)	No. positive/total	(%)
0	1/249	(0.4)	0	1/249	(0.4)
>0-<1.5	0/436	(0)	>0-0.4	2/412	(0.5)
1.5-<3.5	7/405	(1.7)	0.4-<1.0	3/395	(0.8)
3.5-<8.0	14/428	(3.3)	1.0-<2.0	11/349	(3.2)
8.0-<11.5	13/182	(7.1)	2.0-<4.0	17/312	(5.5)
11.5-<20	19/160	(11.9)	4.0-<6.0	19/143	(13.3)
≥20	27/115	(23.5)	≥6.0	28/115	(24.3)

*ILO ≥ 1/0 or large opacities

TABLE 18. Life-table analysis of observed and fitted cumulative risk of radiographic opacities* by cumulative exposure to crystalline silica: Manville white males

Cumulative exposure (mg/m^3-yrs)	Number entering exposure level	Number becoming positive	Observed cumulative risk of opacity at end of interval	Fitted† cumulative risk of opacity at end of interval
0-<1.0	1975	6	0.004	0.007
1.0-<2.0	919	11	0.019	0.023
2.0-<4.0	570	17	0.058	0.076
4.0-<6.0	258	19	0.150	0.146
6.0-<8.0	115	10	0.237	0.222
8.0-<12.0	69	10	0.372	0.373
12.0-18.0	34	8	0.569	0.553

*small opacities ≥1/0 or large opacities

†Fitted value from log-logistic model