Using Epidemiologic Data for a Risk Assessment of Silica Exposure

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Introduction

Silica has been recognized as a cause of respiratory disease since ancient times. Hippocrates described lung diseases in miners in approximately 400 B.C. Despite the early recognition of this relationship, silicosis is still a major problem in modern societies around the world. Approximately 200 deaths from silicosis were reported in the U.S. in 1996 (NIOSH 1999). The number of non-fatal cases of silicosis in the U.S. is more difficult to estimate. However, 256 cases of silicosis were identified in 1993 in Illinois, Michigan, New Jersey, North Carolina, Ohio, Texas, and Wisconsin combined (CDC , 1997).

More recently, exposure to silica has been associated with an increased risk of lung cancer. Crystalline silica has been recognized by the National Institute for Occupational Safety and Health (NIOSH) as a potential occupational carcinogen since 1988, and the International Agency for Research on Cancer (IARC) classified crystalline silica as being carcinogenic to humans (Group I) in 1996 (IARC, 1997). The purpose of our research was to quantitatively estimate the relationship between exposure to silica and the risk of mortality from respiratory diseases (cancer and non-cancer) and of morbidity from silicosis using the results from a study of diatomaceous earth workers (Checkoway et al. 1997, and Hughes et al. 1998).

Methods

The study population, which was described extensively in the original mortality study [Checkoway 1997], included 2,342 white men employed at a diatomaceous earth mining and processing facility in Lompoc, California for at least 12 months of cumulative service and at least one day between 1 January 1942 and 31 December 1987. The cohort was followed from 1 January 1942 through 31 December 1994. Seventy-seven deaths from cancer of the trachea, bronchus, or lung and occurred in that period. Sixty-seven deaths from lung diseases other than cancer, pneumonia or infectious diseases (henceforth referred to as LDOC) were also identified for the analysis. Finally, 70 cases with onset of positive radiographic evidence of silicosis (ILO: >=1/0 or greater) were identified from a company x-ray surveillance system for analysis.

Retrospective Exposure Assessment

A strength of this study is the availability of relatively high quality exposure information for estimating historical occupational crystalline silica exposures, and the absence of exposures to radon progeny, arsenic, and diesel exhaust. In addition, asbestos exposures were accounted for in the analysis. Quantitative dust exposure was estimated with complex methods described elsewhere (Seixas et al. 1997). Mean cumulative concentrations of respirable dust and respirable crystalline silica dust were 7.31 milligram/m^3-years (maximum: 168.84 milligram/m^3-years) and 2.16 milligram/m^3-years (maximum: 62.52 milligram/m^3-years), respectively. The mean concentration of respirable crystalline silica averaged over the cohort's years of employment was 0.29 milligram/m^3.

Poisson Regression

Epicure DATAB, (Preston et al., 1993) was used to generate files for Poisson regression analysis. Person-years were counted from when a worker met the study requirements until he was lost to follow-up, died, or reached the end of follow-up. The person-years and deaths were stratified by cumulative silica exposure, time since first observation, calendar time, age, and Hispanic ethnicity. Fifty levels of cumulative silica exposure were formed, in addition to a non-exposed level, by using stratum widths that gradually increased beginning with 0.33 milligram/m^3-years at low cumulative exposures where the population is dense, and ending with 2.2 milligram/m^3-years at maximum cumulative exposure where there was very little observation time.

Poisson regression models were fit using the AMFIT program of Epicure (Preston et al., 1993). Alternative model forms were evaluated to detect a wide range of possible exposure-response patterns including linear, sublinear, and supralinear (Breslow and Day, 1987). Models were fitted in which the background incidence rates for lung cancer were derived from the cohort, or from the U.S. population. Cubic smoothing spline models were also fitted for comparisons with the fit of the parametric models. Cox proportional hazards models were also fitted and the results y were very similar to those from the Poisson regression analyses.

Prediction of working lifetime risks

Estimates of excess lifetime risk of death from lung cancer, LDOC, and silicosis morbidity for varying concentrations of crystalline silica dust exposure were developed using an actuarial method previously developed for a risk analysis of radon exposures (BEIR, 1988). Excess risks associated with given silica concentrations were estimated for workers exposed during a 45-year occupational lifetime between the ages of 20 and 65. The annual risks were accumulated up to age 85. For lung cancer and LDOC, age-specific background mortality rates for lung cancer and for competing causes of death were derived from U.S. vital statistics. For silicosis morbidity, the background rates were derived from the Poisson regression model.

RESULTS

Lung Cancer

The results from fitting the alternative model forms to the exposure-response relationship for lung cancer are illustrated in Figure 1. Exposure to respirable crystalline silica dust was a significant predictor ($p<0.05$) in nearly all of the models evaluated. The linear relative rate model with a 10-year exposure lag appeared to give the best fit in the Poisson regression analysis. The linear relative rate model predicted mortality rate ratios of about 1.6 for the mean cumulative respirable silica exposure of the lung cancer decedents compared with no exposure. The excess lifetime lung cancer mortality risk to age 85 for white males exposed for 45 years and with a 10-year lag period at the current Occupational Safety and Health Administration (OSHA) standard of about 0.05 milligram/m³ for respirable cristobalite dust is 19 per 1000 (95% CI: 5 , 46 per 1000).

LDOC

The results from fitting the alternative model forms to the exposure response relationship for LDOC are illustrated in Figure 2. Exposure to respirable crystalline silica dust was a significant predictor ($p<0.05$) in all of the models evaluated. There was a downturn in the dose-response relationship at higher exposure levels as reflected by the cubic spline model. This downturn, which was also evident in the silicosis analysis, is believed to be most likely due to a healthy worker survivor effect bias and the subsequent analyses were restricted to exposures less than 10 mg/m³-yrs. In the restricted data, a linear relative rate model with external rates gave the best fit. Based on this model, the estimated rate ratio at the mean cumulative silica exposure of LDOC cases was 3.8 ($p<0.0001$). The excess lifetime risk for white men exposed (up to 45 years) to respirable cristobalite dust at the current Occupational Safety and Health Administration PEL (about 0.05 milligram/m³) was 48 per 1000 (95% CI: 15,130 per 1000).

Silicosis

The results from fitting the alternative model forms to the exposure response relationship for radiographic silicosis are illustrated in Figure 3. Exposure to respirable crystalline silica dust was a significant predictor ($p<0.05$) in all of the models evaluated. The best fitting model was again a linear relative (rate) model. The model predicted a rate ratio of 25.6 for silicosis at mean cumulative exposure of the cases. The predicted excess lifetime risk for silicosis at the current OSHA PEL was 75 per 1000 (95% CI: 19,580 per 1000).

CONCLUSIONS

The results from the extensive exposure-response analyses presented in this paper clearly demonstrate strong evidence of a significant relationship between exposure to crystalline silica and mortality from lung cancer and LDOC, and silicosis morbidity. These findings are consistent with those from the previous investigations of this cohort (Checkoway et al. 1997, Hughes et al. 1998).

These findings also clearly that the current OSHA standard for crystalline silica is associated with a risk of malignant and non-malignant respiratory disease that is unacceptably high by current standards in the U.S. While there are no formal guidelines in the U.S. for what is an acceptable risk for occupational exposures, in practice OSHA has consistently sought to set standards that are associated with a lifetime risk of less than 1 per 1000 workers (Infante 1995). The risk estimates produced by these analyses are well over an order of magnitude greater than 1 per 1000 for either lung cancer (19 per 1000), LDOC (48 per 1000) or silicosis morbidity (75 per 1000).

Clearly there are uncertainties and limitations in this epidemiologic data set that must be borne in mind when interpreting the results from our analysis. Concerns about potential confounding from exposures to asbestos and smoking in this cohort have been raised. Although the data are not complete for examining these potential confounders, there was no evidence from analyses relating these factors with silica exposure to suggest that they are confounders.

Perhaps the greatest limitation of this analysis is that it is based on a cohort that was predominantly exposed to cristobalite, and it is unclear as to the extent to which these risk estimates may be generalized to workers with exposures to other forms of silica (e.g., quartz). Early toxicologic studies indicated that cristobalite may be more fibrogenic than quartz, but this has not been confirmed by epidemiologic studies. We are currently working on a pooled analysis of all the major studies of occupational silica exposure and malignant or non-malignant respiratory diseases with exposure-response information. These analyses should provide us with more insight as to whether the exposure-response relationships observed in this investigation differ significantly from those observed in other investigations with exposures to other forms of silica.

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Figure 1: Lung cancer mortality rate ratio by cumulative silica exposure from Poisson regression models using external adjustment for US lung cancer death rates, 10 year lag.

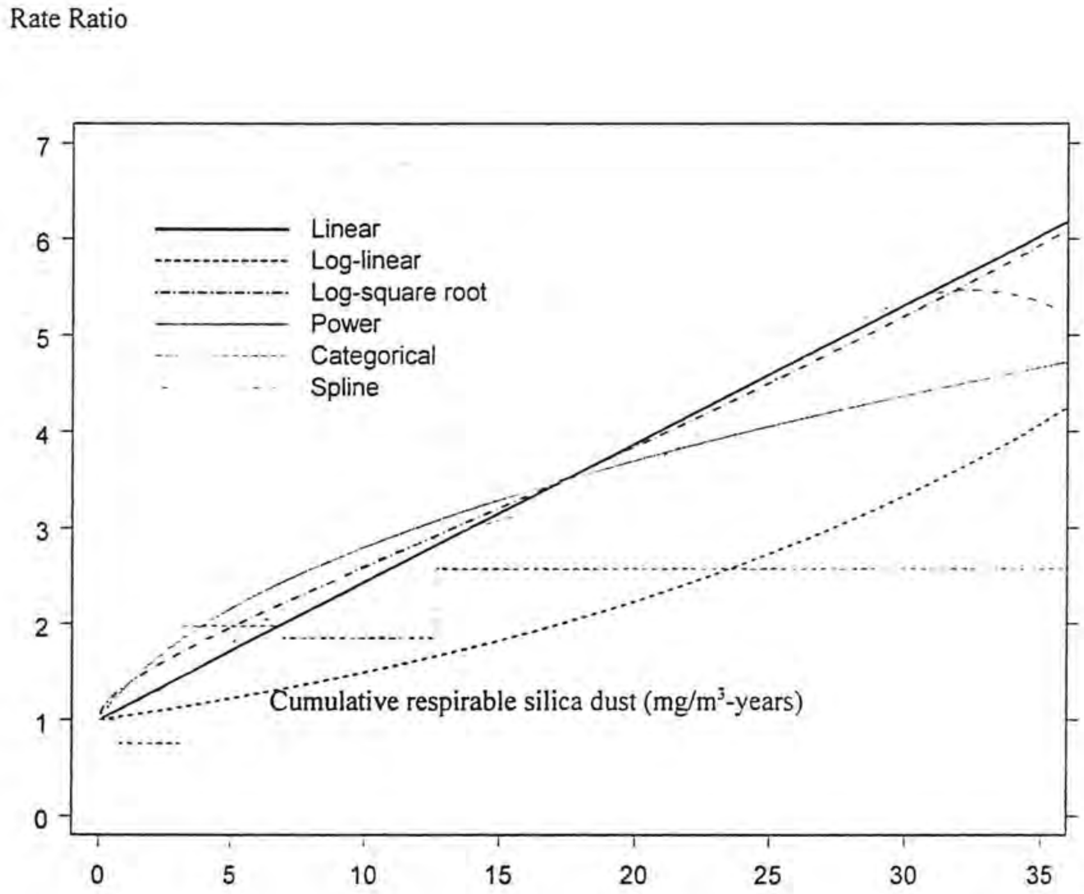


Figure 2: Lung disease other than cancer rate ratio by cumulative silica exposure

Poisson regression models using external adjustment for US LDOC death rates, no lag

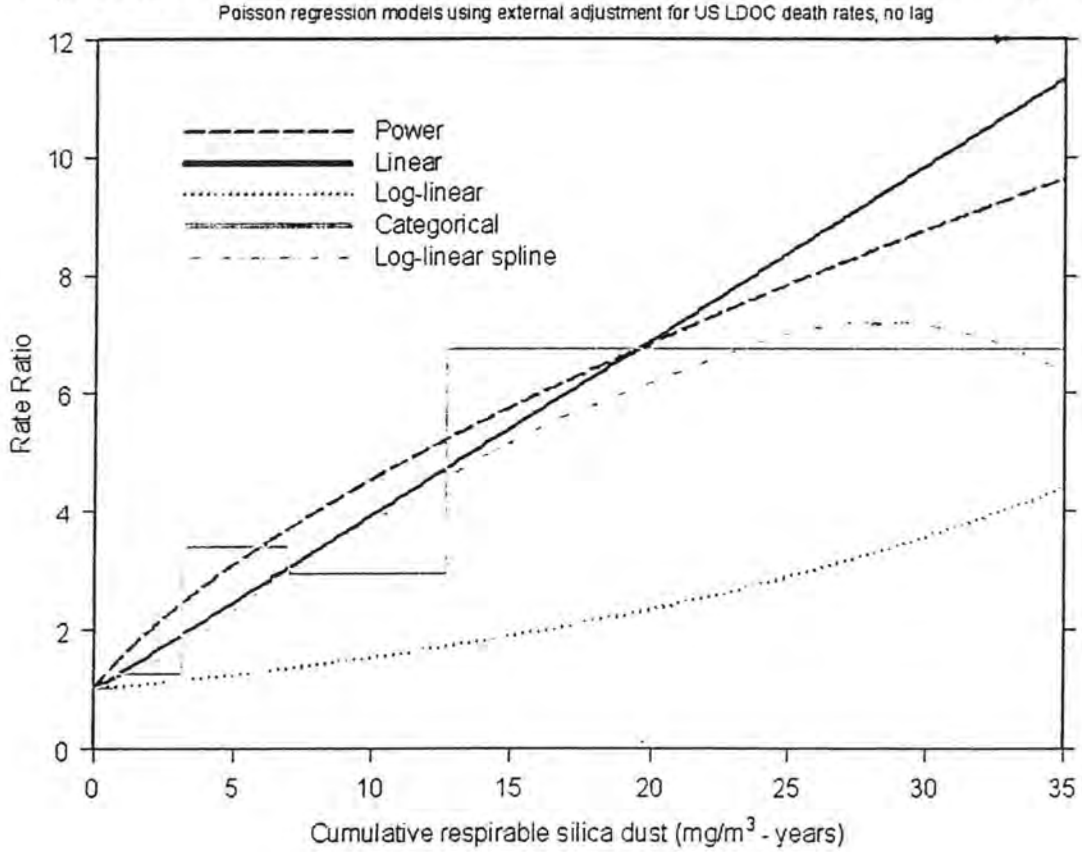
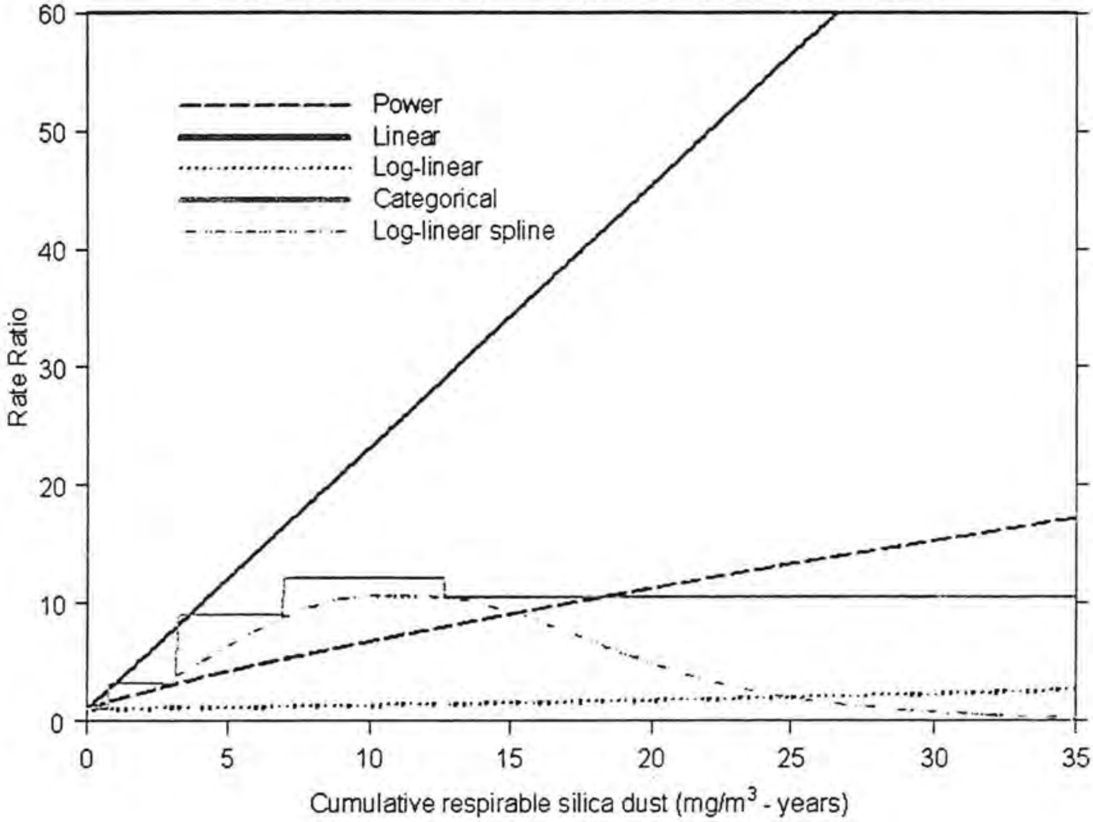


Figure 3: Radiographic silicosis rate ratio by cumulative silica exposure

Poisson regression models using internal adjustment for age and calender time, no lag



ABSTRACTS

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