

# Pooled Analyses of Renal Disease Mortality and Crystalline Silica Exposure in Three Cohorts

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Respirable crystalline silica exposure has been associated with renal disease in recent literature. Approximately 2000000 people are occupationally exposed to silica in the USA, 100000 at more than twice the NIOSH recommended exposure limit of 0.05 mg/m<sup>3</sup>. We have examined renal disease mortality in three silica-exposed cohorts totaling 13382 workers; 51 died with renal disease (ICD codes 580–587, 9th revision) as the underlying cause and 153 others had renal disease as a contributory cause on their death certificates. All three of these cohorts had job-exposure matrices that enabled estimation of exposure over time; all three also had data on multiple cause mortality, particularly desirable for kidney disease, which may not be the underlying cause of death. Results from two cohorts have been published previously; follow-up for one has been extended by 6 yr. Using both underlying cause and contributory analyses (multiple cause), we compared renal disease in these cohorts with the US population and also conducted exposure-response analyses. We found excess mortality from renal disease [standard mortality ratio (SMR) 1.41, 95% CI 1.05–1.85] as the underlying cause and also using multiple cause analysis (SMR 1.28, 95% CI 1.10–1.47). Exposure-response analyses showed a monotonic increase in renal disease mortality with increasing exposure. Odds ratios by quartile of cumulative exposure were 1.00, 1.24, 1.77 and 2.86 ( $P = 0.0002$ ) for multiple cause analyses and 1.00, 1.88, 1.96 and 3.93 ( $P = 0.03$ ) for underlying cause analysis. Pooled analyses provide large sample sizes; these data represent the largest number of renal disease deaths analyzed to date in workers with well defined silica exposure and suggest a causal link between occupational exposure to silica and renal disease. Excess risk of death from renal disease (underlying cause) by age 75 due to a lifetime of occupational exposure at 0.1 mg/m<sup>3</sup> (the OSHA standard when respirable dust is 100% silica) is estimated to be 1.8% (95% CI 0.8–9.7%), above a background risk of 0.3%.

**Keywords:** renal disease; silica

## INTRODUCTION

In the 1980s there were an estimated 1700000 US workers potentially exposed to crystalline silica outside the mining and agricultural industries (NIOSH, 1991). Industries in which exposure occurs include foundries, stonework, sand blasting and potteries. Miners are also commonly exposed. Data from the Occupational Safety and Health Administration (OSHA) has been used to estimate that ~100000 workers outside the mining industry are exposed to levels two or more times higher than 0.05 mg/m<sup>3</sup>, which is the exposure limit recommended by the

National Institute for Occupational Safety and Health (NIOSH) (Linch *et al.*, 1998).

Crystalline silica exposure in recent years has been associated in epidemiological studies with non-malignant renal disease; an autoimmune mechanism has been postulated, although direct toxicity to the kidney is also possible (Steenland and Goldsmith, 1996; Parks *et al.*, 1999). However, the silica-renal disease association is still not widely accepted and the literature to date remains somewhat sparse.

The initial evidence for renal disease was at first based on case reports of renal failure among workers with high silica exposure, e.g. sand blasters who developed silicosis and then renal failure (Osorio *et al.*, 1987; Sherson and Jorgensen, 1989). Most of

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these workers were affected by glomerular disease and in some cases immune complexes were observed deposited on the basement membrane. Immunological injury to the glomerulus could be a pathogenic mechanism for renal disease (Calvert *et al.*, 1997). Crystalline silica is known to cause a strong immune response in the lung, which can lead to granuloma formation and silicosis. Immune activation may be linked to a variety of responses: hypergammaglobulinemia, production of rheumatoid factor, anti-nuclear antibodies (ANA) and release of other immune complexes.

The initial case reports have been followed by three cohort studies of workers exposed to silica (Calvert *et al.*, 1997; Rapiti *et al.*, 1999; Steenland *et al.*, 2001a). These cohort studies were all positive; for two of these studies incidence data confirmed the mortality findings. Another case-control study was also positive (Steenland *et al.*, 1990b). These studies tended to show an approximately 2- to 3-fold risk of renal disease mortality or morbidity for all exposed workers or for subsets of the most highly exposed workers. Two other case-control studies of 18 patients with rapidly progressive glomerulonephritis positive for anti-neutrophil cytoplasmic autoantibodies (ANCA) (Gregorini *et al.*, 1993) and 16 patients with Wegener's granulomatosis, 80% of whom were ANCA-positive (Van Nuyts *et al.*, 1995), showed relative risks of 14 and 5, respectively, for silica exposure, suggesting an autoimmune mechanism. There have also been a number of cross-sectional studies linking exposure to silica with decreased renal function (for a recent review see Rosenman *et al.*, 2000).

We have investigated renal disease mortality in three cohorts of workers exposed to silica for which both underlying cause and multiple cause mortality were available. Multiple cause (any mention on the death certificate) was of particular interest because renal disease is often listed on death certificates without being the underlying cause (Steenland *et al.*, 1992). In these cohorts there were 51 renal disease deaths using underlying cause, versus 204 using multiple cause mortality. The cohorts were gold miners ( $n = 3348$ ), industrial sand workers ( $n = 4626$ ) and granite workers ( $n = 5408$ ). Results for renal disease mortality in two of these cohorts have been published previously (gold miners and industrial sand workers) (Steenland and Brown, 1995; Steenland *et al.*, 2001a), while the third (granite workers) (Costello and Graham, 1998) has not. For this analysis we have extended the follow-up of the gold miner cohort 6 yr beyond the published data. Job-exposure matrices were available for all three studies, enabling us to estimate exposure to respirable silica ( $\text{mg}/\text{m}^3$ ) for all three of these cohorts over time and, therefore, allowing a pooled analysis of exposure-response trends.

## MATERIALS AND METHODS

### *Cohort definition and job-exposure matrices*

The three cohorts have been described previously. Briefly, 4626 industrial sand workers were employed in 18 plants from the 1940s to the 1980s, extracting ore from open pit quarries and subsequently extracting sand from the ore (Steenland *et al.*, 2001). Most of these plants produced silica flour, a nearly 100% pure and finely ground crystalline silica (quartz), which carries a high risk of silicosis. Extensive silicosis has been documented in this industry (Banks *et al.*, 1981a,b). Over 4000 historical industrial hygiene measurements of silica in this industry were used to create a job-exposure matrix which enables estimation of exposure level for each study subject over time (Sanderson *et al.*, 2000). Early personnel records in this industry were often discarded; personnel records were generally available only for workers terminating after a specific date, which varied plant to plant, but was typically in the 1960s. Hence person-time at risk began at each plant at this date and continued until death or 31 December 1996. Thirteen percent of the cohort lacked a sufficiently detailed work history to enable quantitative estimates of cumulative exposure to silica and these were excluded from the exposure-response analyses, which was restricted to 4027 workers.

The 3348 gold miners studied here had been employed for at least 1 yr between 1940 and 1965; 58% of the cohort had been first employed before 1950, when exposures were particularly high (Steenland and Brown, 1995a). Appreciable silicosis has been documented at this mine (Steenland and Brown, 1995). Quantitative job-specific estimates of exposure were available over time for this cohort, based on existing dust measurements taken in the mine from 1937 to 1975. Impinger dust measurements in units of million particles per cubic foot (m.p.p.c.f.) were converted to respirable silica ( $\text{mg}/\text{m}^3$ ) (quartz) by assuming that 1 m.p.p.c.f. dust equaled  $0.01 \text{ mg}/\text{m}^3$  silica, based on the estimated silica content of the dust (13%) and historical conversion factors from the Vermont granite industry. Follow-up of this cohort began 1 yr after first employment or 1950, whichever was later, and continued until death or 31 December 1996.

The 5408 granite workers studied here extracted granite from open pit quarries and then cut, polished and finished the granite to make monuments (Costello and Graham, 1998). Dust generated by work in this industry was estimated to contain ~9–10% respirable silica (quartz). High levels of dust were documented in the quarries and sheds until dust controls were implemented in the 1940s. The granite worker cohort was composed of workers employed

during 1950–82 who were X-rayed at least once in a silicosis surveillance program.

Attfield and Costello (2001) developed job-specific quantitative exposures estimates over time for this cohort, using published data on the exposure to silica of the Vermont granite workers previously summarized by Davis *et al.* (1983) from six industrial hygiene surveys undertaken between 1924 and 1977 (Russell *et al.*, 1929; Bloomfield and Waldemar, 1934; Urban, 1939; Hosey *et al.*, 1957; Theriault *et al.*, 1974; Eisen *et al.*, 1984). Impinger dust levels were converted to respirable silica by assuming 1 m.p.c.f. = 0.0075 mg/m<sup>3</sup> respirable silica, based on historical side-by-side sampling (Davis *et al.*, 1983).

Follow-up for this cohort began at time of first employment or 1950, whichever was later, and continued until death or 31 December 1994. This caused a slight underestimate of mortality given that workers were not at risk of death until date of first X-ray. However, as the X-ray program was continual, it should have captured most workers in the industry in the early 1950s for those who began employment before 1950 or shortly after employment for new workers in the industry. Hence, only a small number of person-years at risk should have been incorrectly added and many of these would have been at younger ages when little mortality would be expected.

All of the three job-exposure matrices used in these cohorts to estimate cumulative silica exposure have been previously used in exposure-response analyses for silicosis morbidity or mortality (Steenland and Brown, 1995b; Attfield and Costello, 2001; Steenland *et al.*, 2001b). These analyses resulted in monotonically increasing exposure-response trends, which tends to validate the exposure estimates, since cumulative silica levels are known to predict silicosis.

All three of these cohorts were part of a larger pooled analysis of 10 cohorts focusing on lung cancer (Steenland *et al.*, 2001b). However, only these three cohorts had multiple cause mortality data, important for kidney disease; this motivated their inclusion in the present analysis.

#### Analytical methods

Conventional life table analyses were conducted for the combined cohort ( $n = 13382$ ), comparing the renal disease mortality with that of the US population, after stratification for age, race, sex and calendar time (Steenland *et al.*, 1990a). Renal disease (ICD 9th revision codes 580–587) included acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, renal sclerosis and nephritis/nephropathy not specified as acute or chronic. The analyses were based on both underlying cause and any mention of renal disease on the death certificate (multiple cause mortality). Cause-specific

referent rates for the US population for multiple cause mortality have been developed by NIOSH for the years 1960–99 (Steenland *et al.*, 1992), while underlying cause rates are available for the years 1940–99. The renal disease mortality of the entire exposed group was at first compared with that of the US population, the non-exposed referent group. Subsequent analyses were done by dividing the exposed workers by categories of cumulative exposure (mg/m<sup>3</sup> yr respirable crystalline silica) and comparing the renal disease mortality of each category with the US population. Analyses by level of cumulative exposure were based on 12783 workers (95% of the cohort), a smaller number than the overall exposed/non-exposed analysis because 13% of the industrial sand workers had inadequate work histories and therefore did not have estimates of cumulative exposure.

More detailed exposure-response analyses were conducted within the cohort with adequate exposure information (95% of the total cohort) via nested case-control analyses of either 50 cases (underlying cause) or 194 cases (decedents with renal disease, either underlying or contributory). Each case was matched to a risk set of 100 controls from the cohort who had survived past the age of the case when the case died (incidence density matching). The risk set for each case was also matched on race, sex and date of birth within 5 yr. Prior analyses have shown that the use of 100 controls per case yields results which are essentially equivalent to using the entire cohort in developing the risk sets for each case (Steenland and Deddens, 1997). Nested case-control analyses were done using conditional regression via the SAS PHREG procedure (SAS, 1991). Heterogeneity of exposure-response trends across studies were tested by inclusion of interaction terms between the study and the exposure-response coefficient. Various exposure metrics were tried, including average exposure, cumulative exposure, cumulative exposure lagged 15 yr, log of cumulative exposure and log of cumulative exposure lagged 15 yr. The referent group for these internal analyses was the lowest quartile of cumulative exposure.

Cut-off points for the cumulative exposure analyses for both standard mortality ratios (SMRs) and the nested case-control analyses were based on quartiles of the controls used in the nested case-control analysis based on multiple cause data. Tests for trend in SMRs were based on a test described in Breslow and Day (1987), while tests for trend in the nested case-control analyses were based on the parameter for the (continuous) exposure coefficient.

Excess risk of dying by age 75 of renal disease (underlying cause) was calculated for males (99% of the workers in the three cohorts were male) by converting rates to risks and taking into account competing risks of death (Gail, 1975). US male age-

Table 1. Exposure–response analyses: SMRs<sup>a</sup> (observed deaths) by quintile cumulative silica exposure for renal disease (ICD codes 580–587, 9th revision) in three cohorts

Outcome	SMR (mg/m <sup>3</sup> yr)				<i>P</i> value for trend
	>0–0.15	0.15–0.55	0.55–1.67	1.67+	
Any mention on death certificate (multiple cause)	0.93 (32)	0.93 (36)	1.51 (52)	1.60 (62)	<0.000001
Underlying cause	0.55 (4)	0.94 (8)	1.17 (10)	2.23 (28)	0.0007

<sup>a</sup>SMRs are indirectly standardized rate ratios using the US population as the referent.

Table 2. Exposure–response analyses: odds ratios (95% CIs) by quartile of cumulative silica exposure for renal disease (ICD codes 580–587, 9th revision) in nested case–control analysis of three cohorts<sup>a</sup>

Outcome	Odds ratio (mg/m <sup>3</sup> yr)				<i>P</i> value for linear trend <sup>b</sup>	<i>P</i> value for log trend
	>0–0.15 (referent)	0.15–0.55	0.55–1.67	1.67+		
Any mention on death certificate (multiple cause)	1.00	1.24 (0.77–2.01)	1.77 (1.10–2.85)	2.86 (1.73–4.72)	0.004	0.0002
Underlying cause	1.00	1.88 (0.62–5.70)	1.96 (0.66–5.84)	3.93 (1.31–11.76)	0.21	0.03

<sup>a</sup>Multiple cause analyses here include 194 deaths, more than in Table 1 because multiple cause analyses for SMRs are restricted to deaths in 1960 or later, because rates exist only as of 1960. Underlying cause includes the same 50 deaths as in Table 1.

<sup>b</sup>Trend statistics are the *P* value for the parameter for the continuous exposure variable, either untransformed cumulative exposure (linear trend) or the log of cumulative exposure (log trend).

specific background rates for all causes of mortality for 1990 were used in this calculation.

## RESULTS

The combined cohort numbered 13 382 workers, of whom only 1.3% were female and 0.5% were non-white. There were 5504 deaths in the cohort (41%). Among these deaths, 204 had renal disease listed on the death certificate as an underlying or contributory cause (51 underlying cause). The average age at death of the 51 men who died of renal disease as the underlying cause was 64. For the 204 men who died with renal disease mentioned on the death certificate, the average age at death was 68; 25% of these men died before age 60. Analyses based on exposure were restricted to 12783 workers (193 renal disease deaths, 50 as underlying cause) with adequate exposure information.

The mean duration of exposure, cumulative exposure and crystalline silica exposure levels of these three cohorts were 13.6 yr, 1.2 mg/m<sup>3</sup> yr and 0.07 mg/m<sup>3</sup>, respectively. The current OSHA standard for respirable dust which is 100% crystalline silica is 0.10 mg/m<sup>3</sup>, so that on average these workers were exposed to below the current standard level. However, exposures were higher in the early years, especially before 1950.

Multiple cause mortality analysis resulted in a SMR for renal disease (ICD 9th revision codes 580–587) of 1.28 (95% CI 1.10–1.47, 193 observed deaths). Underlying cause analysis resulted in a SMR of 1.41 (95% CI 1.05–1.85, 51 observed deaths).

SMR results by category of cumulative exposure are shown in Table 1 for multiple cause analyses. Total renal disease deaths for these analyses are slightly less than the exposed/non-exposed analyses due to the elimination of 13% of the industrial sand cohort who lacked an adequate work history to estimate cumulative exposure. Both multiple and underlying cause analyses show highly significant positive trends of increasing renal disease mortality with increasing cumulative exposure.

Table 2 shows exposure–response analyses conducted via the nested case–control study. These analyses differ from Table 1 in that they are internal analyses, in which the referent group is the lowest exposure group. Both underlying and multiple cause analyses showed monotonic trends of increasing risk with increasing exposure. The log of cumulative exposure fits better than cumulative exposure. Cumulative exposure, lagged cumulative exposure and average exposure do not fit as well. The exposure–response trend was homogeneous across the three cohorts; addition of interaction terms did not increase the log likelihood of the model (change in likelihood, *P* = 0.67 for the model with underlying cause, *P* = 0.42 for the model with multiple cause). For example, the rate ratios by quartile of cumulative exposure using the multiple cause data were 1.00, 1.20, 1.36 and 3.31 for granite workers, 1.00, 1.15, 2.01 and 2.69 for gold miners and 1.00, 1.56, 1.87 and 1.88 for industrial sand workers.

We used the exposure–response coefficient for the model with the log of cumulative exposure to calculate risk of death (underlying cause) from renal disease by age 75 for an exposure of 0.10 mg/m<sup>3</sup>



crystalline silica over a working lifetime from age 20 to 65. This leads to an estimated excess lifetime risk of 1.8% (95% CI 0.8–9.7%), above a background risk of 0.3%. This is an order of magnitude above the excess lifetime risk of 1 in 1000 that is typically sought in setting occupational standards.

## DISCUSSION

The value of our data is that it unites three different cohorts, all of which have good quantitative estimates of exposure in a common unit [ $\text{mg}/\text{m}^3$  respirable crystalline silica (quartz)]. Hence, analyses are based on a reasonable sample size, which is difficult in cohort studies of rare diseases, and exposure is well documented, which is sometimes difficult in case-control studies. Furthermore, all of these studies have reasonably well constructed job-exposure matrices, enabling us to analyze in some detail exposure-response trends. The existence of such trends is often a key point in inferring causality for an exposure-disease association. We found a positive and monotonic increase in disease risk with increasing exposure whether we used underlying cause or multiple cause data in our analysis.

This study adds to the growing body of evidence that non-malignant renal disease is associated with exposure to crystalline silica, in addition to its well known relationship with silicosis and recently established relationship with lung cancer. Physicians diagnosing renal disease should be aware of a possible occupational etiology. There is some evidence that an autoimmune mechanism may be important. Future research in this area should probably consider analysis of immune system markers in relation to silica exposure.

In our data markedly elevated odds ratios and SMRs were seen primarily for cumulative exposures  $>0.5 \text{ mg}/\text{m}^3 \text{ yr}$ . This exposure level is equivalent to working for only 5 yr at an exposure level of  $0.1 \text{ mg}/\text{m}^3$  (the OSHA standard when respirable dust is 100% crystalline silica) or 10 yr at an exposure level of  $0.05 \text{ mg}/\text{m}^3$  (the NIOSH recommended exposure level). A working lifetime of 45 yr exposed at  $0.1 \text{ mg}/\text{m}^3$  confers a 1.8% excess risk of dying of renal disease (underlying cause), versus a relatively small background risk of 0.3%.

Mortality data are usually not as valuable as morbidity or incidence data for studies of etiology of renal disease. The use of multiple cause mortality data, however, is an improvement over simply studying underlying cause mortality and more closely approximates incidence. For example, for white males aged 60–65 in 1995–99, the underlying cause of mortality rate was 10/100000, the multiple cause of mortality rate was 76/100000 and the end-stage renal disease incidence rate was 93/100000. Some analyses of the incidence of end-stage renal disease

for two of the three cohorts analyzed here have been published elsewhere (Calvert *et al.*, 1997; Steenland *et al.*, 2001a) and tend to support our mortality findings.

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