Kidney Disease and Arthritis in a Cohort Study of Workers Exposed to Silica

Kyle Steenland, Wayne Sanderson, Geoffrey M. Calvert

Silica exposure has been associated with kidney disease and rheumatoid arthritis; an autoimmune mechanism has been proposed. Approximately 2 million people are occupationally exposed to silica in the United States, 100,000 at more than twice the National Institute for Occupational Safety and Health recommended exposure limit of 0.05 mg/m^3. We examined renal disease morbidity and mortality, as well as arthritis mortality, in a cohort of 4,626 silica-exposed workers in the industrial sand industry (an industry previously unstudied). We compared the cohort with the U.S. population and also conducted internal exposure-response analyses using a job-exposure matrix based on more than 4,000 industrial hygiene samples. We found excess mortality from acute renal disease [standardized mortality ratio (SMR) = 2.61, 95% confidence intervals (95% CIs) = 1.49–4.24; 16 deaths], chronic renal disease (SMR = 1.61, 95% CI = 1.13–2.22; 36 deaths), and arthritis (SMR = 4.36, 95% CI = 2.76–6.54; 23 deaths) on the basis of multiple-cause mortality data, which considered any mention of disease on a death certificate. Linking the cohort with the U.S. registry of end-stage renal disease for the years 1977–1996, we found an excess of end-stage renal disease incidence (standardized incidence ratio = 1.97, 95% CI = 1.25–2.96; 23 cases), which was highest for glomerulonephritis (standardized incidence ratio = 3.85, 95% CI = 1.55–7.93; 7 cases). We found increasing end-stage renal disease incidence with increasing cumulative exposure; standardized rate ratios by quartile of cumulative exposure were 1.00, 3.09, 5.22, and 7.79. A positive exposure-response trend was also observed for rheumatoid arthritis on the basis of death certificate data. These data represent the largest number of kidney disease cases analyzed to date in a cohort with well-defined silica exposure and suggest a causal link between silica and kidney disease. Excess risk of end-stage renal disease due to a lifetime of occupational exposure at currently recommended limits is estimated to be 14%, above a background end-stage renal disease risk of 2%. (EPIDEMIOLOGY 2001;12:405–412)

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In the 1980s, there were an estimated 1.7 million U.S. workers exposed to crystalline silica outside of the mining industry.[1] Industries in which exposure occurs include foundries, stonework, sandblasting, and potteries. Miners are also commonly exposed. Data from the Occupational Safety and Health Administration (OSHA) have been used to estimate that about 100,000 workers outside the mining industry are exposed to levels two or more times higher than 0.05 mg/m^3, which is the exposure limit recommended by the National Institute for Occupational Safety and Health.[2]

Crystalline silica exposure in recent years has been associated in epidemiologic studies with nonmalignant renal disease, rheumatoid arthritis, and other autoimmune diseases.[3,4] These associations, however, are not widely accepted, and the literature to date remains sparse.

From the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH.

Address correspondence to: Kyle Steenland, National Institute for Occupational Safety and Health R13, 4676 Columbia Parkway, Cincinnati, OH 45226.

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The initial evidence for renal disease was at first based on case reports of renal failure among workers with high silica exposure, for example, sandblasters who developed silicosis and then renal failure.[5,6] Most of these workers were affected by glomerular disease, and in some cases immune complexes were observed deposited on the basement membrane. Immunologic injury to the glomerulus could be a pathogenic mechanism for renal disease.[7] 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 and anti-nuclear antibodies, and the release of other immune complexes.

The initial case reports were followed by epidemiologic cohort studies of workers exposed to silica. These cohort studies consistently showed excesses for renal disease. Cohort mortality studies of granite workers and gold miners with high silica exposure found two- to threefold excess renal disease risk based on death certificates (34 renal deaths in each study)[8,9]; the finding in gold miners was later confirmed using data on end-stage renal disease incidence (11 cases), with the excess concentrated in glomerulonephritis.[7] A cohort study of Italian ceramic workers found a threefold excess of end-stage renal disease, based on six cases.[10] Case-control

studies have also shown an exposure effect. A 1990 population-based case-control study of 325 end-stage renal patients in Michigan found a twofold excess for workers exposed to silica.[11] An Italian hospital-based case-control study of 32 patients with rapidly progressing glomerulonephritis and anti-neutrophil cytoplasmic antibodies found a 14-fold excess risk of the disease for those with a history of silica exposure.[12] Finally, Rosenman *et al*[13] have recently found a twofold excess of elevated serum creatinine (above 1.5 mg/dl) among 583 silicotic patients in Michigan compared with controls.

In addition to kidney disease, silica exposure has been linked to rheumatoid arthritis. A cohort study of Finnish granite workers[14] found a fivefold excess of rheumatoid arthritis, based on ten cases receiving medical disability. A nested case-control study of 157 South African gold miners with arthritis found little association between level of silica exposure and rheumatoid arthritis, but silicotics had a fourfold increased risk of arthritis.[15] Multiple-cause mortality analyses have shown twofold excess risks of arthritis in cohort studies of granite workers and gold miners (17 deaths in each study).[8,9] Rosenman *et al*[16] found a threefold risk of prevalent rheumatoid arthritis among 160 silicotics in Michigan, whereas Brown *et al*[17] found an eightfold excess prevalence of rheumatoid arthritis (44 cases) in a cohort of Swedish and Danish men hospitalized for silicosis. In a significant exception to the associations between exposure and arthritis found in the aforementioned studies, Turner and Cherry[18] found no relation between level of silica exposure and subsequent rheumatoid arthritis (58 cases) among 8,325 English ceramic workers. Cases in that study were restricted to those diagnosed while employed; it is possible that a latency period is required before an effect can be observed and that this period had not passed for many workers in that study.

We have investigated kidney disease and arthritis in a cohort study of workers in the industrial sand industry. Many industrial sand plants process sand into silica flour, which is composed of fine particles of crystalline silica and which has been associated with high levels of silicosis in the past.[19,20] There are no prior published cohort studies of this industry. Lung cancer, another disease linked to silica, is the subject of a separate report.[21]

Subjects and Methods

Background on the Industry

In 1987, the industrial sand industry employed approximately 2,600 workers in 60 plants.[22] Industrial silica sand is obtained from a variety of sources—from loose, unconsolidated grains to hard, highly compacted rocks; the ore form of quartz determines how it will be mined. Hard rock mining is usually done in an open pit quarry where holes are drilled into the rock layers and filled with explosives that are detonated to break the rock into movable pieces. Uncompacted sand is collected using dredges, hydraulic pumps, scrapers, or clamshells. Trucks are often used to transport the sand to the plant for processing, but pipelines and belt conveyors are also used. At the plant, rocks are crushed to obtain progressively smaller sizes; if the sand is already granular, crushing is usually not necessary. The crushed and granular sand is screened and sized. The screening and sizing operation may be either a wet process or a dry one; dry screening typically has higher dust exposures. Often the sand is milled in rotating ball mills to reduce the sand to a fine powder. The final sand products, varying in particle size and quartz content, are bagged or bulk-loaded for shipment. Silica sand has a variety of industrial uses. It is used in sandblasting, fine polishing, glass making, and rubber manufacture (where silica powder is used as a dry lubricant); it is also used as a filler in plastics and paints and as a carrier in cosmetics.[23]

Cohort Definition

The present study covers 18 plants in 11 different states, chosen because they were part of a trade association (the National Industrial Sand Association), had adequate records, and participated in a silicosis surveillance program sponsored by the trade association. The cohort included approximately 40% of the current workers in the industry as of 1987.

The cohort consisted of all workers in the personnel records at each company who had worked at least 1 week and who had not died or been lost to follow-up before 1960 when comparison rates (U.S. multiple-cause mortality rates) were first available.

There were 5,086 personnel records of former and current workers collected in 1987–1988 at these plants. In all of these plants, the records of workers who terminated before a specific year had been discarded. For eight plants, this "first year of records" was later than 1960 (ranging from 1962 to 1977). For these eight plants, a worker's person-time at risk began at first year of records for current employees, or later for subsequent hires (workers could not be at risk of dying before the first year of records).

Two-hundred forty-nine workers had worked less than 1 week (5%). An additional 156 workers (3%) had inadequate data for birth date or work history dates (first and last employment dates) to be included, leaving 4,681 subjects who had worked for a week or more available for analysis. Another 55 people (13 deaths) who had not been followed through 1960 were eliminated, leaving a final cohort of 4,626. Additional exposure-response analyses of subgroups of employees were also conducted using a job-exposure matrix in which estimated exposure levels were assigned to workers on the basis of the jobs they held, the plants they worked in, and the calendar period in which they worked (see below). Thirteen per cent of employees were lacking any information regarding where they worked, that is, personnel records did not provide information on which jobs these workers held. These were eliminated for exposure-response analyses, leaving 4,027 workers available for such analyses. Workers who worked at some time in an unknown job were included in exposure-response analyses; the unknown jobs were assigned the plant-specific and calendar time-specific exposure level

for a worker in the "other" category (see Table 2), which is the most common of our ten collapsed job categories (see below) and includes common job titles such as "general laborer." This job category had an exposure level that was in the middle of the different exposure levels across all ten job categories (Table 2). Only 215 of the 4,027 workers (5%) in the exposure-response analyses had an unknown job at some point during their work history, and these unknown jobs represented only 2% of all jobs held by all workers (workers had a mean of three jobs during their employment).

Exposure Data and Job-Exposure Matrix

Quantitative estimates of exposure to respirable silica were estimated for each worker over time. A thorough description of this procedure is available elsewhere.[24] Briefly, data for 4,269 personal samples for respirable silica were available for the years 1974–1996 either from the Mine Safety Health Administration (available at all 18 plants) or from company data (available at 7 of 18 plants). These samples covered a wide variety of jobs. These data were restricted to the period 1974–1988 (1988 was the end of data collection for our study, so work histories ended in 1988) and then modeled using general linear models. A job-exposure matrix was created for the period 1974–1988 in which we estimated exposure levels for four categories of plants (low, medium, medium-high, and high silica exposure), three time periods (1974–1979, 1980–1984, and 1985–1988), and ten job categories. The time periods were chosen by observing when changes in levels appeared to have taken place, and the job categories were based on the main areas where subjects worked and have been used in other surveys.[25]

Although no personal respirable dust measurements were available from the silica sand industry before 1974, an exposure assessment study using midget impingers was conducted in 19 silica sand plants in 1946. In this study, dust particles smaller than 5 μm in diameter were counted optically and reported in concentrations of millions of particles per cubic foot. A summary report of this study presented the results of the sampling as mean dust concentrations by job and plant.[25] These mean impinger-dust concentrations were converted to respirable-mass quartz concentrations in $\mu g/m^3$ by multiplying them by the percentage of quartz found by job in the respirable dust samples from 1974 through 1988 and a conversion factor of 0.1.[26–28] The converted, job-specific medians of the same ten job categories considered in the 1974–1988 data were used to estimate job-specific exposures in 1946. The respirable dust concentrations were then extrapolated linearly between 1946 and 1974 for each job category. We considered exposures before 1947 to be constant.

Follow-Up and Analytic Methods

Mortality follow-up was conducted via the National Death Index (NDI) for the years 1979–1996, via the Social Security death tapes, and via the Internal Revenue Service. Cause of death was obtained from NDI or from death certificates obtained from the states for deaths occurring before 1979 (not covered by NDI). Although we did some mortality analyses restricted to underlying cause, much of our focus in the mortality analyses was on "multiple-cause" mortality. In multiple-cause mortality, the data for underlying cause, contributory causes, and other significant conditions are combined (all causes listed on the death certificate). Such multiple-cause mortality analyses are particularly important for the diseases of interest here, which may be prevalent at death but which are often not the underlying cause.[8] Although throughout the text we will use the term multiple-cause mortality to describe these analyses, it should be remembered that kidney disease and arthritis are usually not the underlying cause of death but instead appear more often as a contributory cause or other significant condition. On U.S. death certificates, kidney disease appears five times more often, and arthritis appears ten times more often, as a contributory cause or other significant condition than as underlying cause.[8]

Data on end-stage renal disease morbidity were also available by matching our cohort by Social Security number to the national registry of treated end-stage renal patients and then determining by inspection that name and date of birth matched as well. The national registry is called the End-Stage Renal Disease Program Management and Medical Information System (PMMIS), from which data are available from 1977 through 1996.[29] Cases first receiving treatment before 1977 are not included. The End-Stage Renal Disease PMMIS data are maintained by the Health Care Financing Administration and include all individuals who received Medicare-covered treatment for end-stage renal disease (dialysis and transplant). The data include a date of first treatment, which we used as a surrogate date of diagnosis, and a diagnostic category for the type of end-stage renal disease. Approximately 92% of end-stage renal disease patients have Medicare coverage and are therefore included in the database. Noncovered end-stage renal disease cases may include those treated by the Veterans Administration hospitals before 1990, those treated in military hospitals, and those under 65 years of age not covered by Medicare who die before Medicare coverage could begin (60–90 days after beginning dialysis).

Once end-stage renal disease cases had been identified by matching to the registry, standard life-table analyses[30] for person-time data were used to compare the cohort with the national population. We calculated standardized incidence ratios (SIRs) for all end-stage disease and for specific types of end-stage disease (for example, glomerulonephritis). SIRs are indirectly standardized rate ratios using stratified data; in our case the data were stratified by age (5-year intervals), race (white/nonwhite), sex, and calendar time (5-year intervals). The comparison rates were the U.S. incidence rates for end-stage renal disease developed by the National Institute for Occupational Safety and Health, based on numerators from the end-stage renal disease registry data and denominators of the general population from U.S. census data, also stratified by age, race, sex, and calendar time. The methodology has been described in more detail elsewhere.[7] For end-stage renal disease incidence,

follow-up began on January 1, 1977, or the date of first exposure, whichever was later. Follow-up for cases was stopped at the date of first treatment, and follow-up for all other subjects continued until the date of death if deceased or until December 31, 1996, if not deceased.

We also used life-table analyses for mortality analyses in which we examined the rates of kidney disease (multiple-cause mortality and incidence) and arthritis (multiple-cause mortality), to compare the exposed population with the U.S. population,[30] via standardized mortality ratios (SMRs). Again the data were stratified by age, race, sex, and calendar time. Follow-up for mortality began either on January 1, 1960, or the date of first exposure, or on the date when records first became available, whichever was later. For the mortality data, follow-up continued until the date of death for deceased subjects, until December 31, 1996 (the end of the NDI search), or until a subject was last known to be alive if that date was earlier than January 1, 1979. Subjects known to be alive after January 1, 1979, and not found to be deceased in NDI were assumed to be alive as of December 31, 1996.

Use of national reference rates was preferred over use of state rates for the SMR and SIR analyses. Workers had worked in 11 states and died in 33 states, which suggests the use of national rates. As a practical matter, we did not have age-specific sex-specific calendar time-specific state rates available for either multiple-cause mortality analyses or end-stage renal disease incidence analyses. Mortality rates for renal disease in the 11 states where plants were located were generally evenly divided above and below national rates. For example, for male chronic renal disease mortality (underlying cause), age-adjusted state rates for the period 1970–1994 ranged from 4.3 to 9.9 per 100,000 across 11 states, whereas the national rate was 8.0 per 100,000. Similarly, end-stage renal disease incidence rates in 1997 for men and women combined ranged from 283 to 348 per million across the 11 states, whereas the national rate was 296 per million.

The data were divided into quartiles of cumulative exposure for the purposes of internal exposure-response analyses, via calculation of directly standardized rate ratios (SRRs). In these analyses, the weights for direct standardization were the age-specific, sex-specific, race-specific, and calendar time-specific person-years of the entire cohort.[30] Quartile cutpoints were chosen before analysis by using the distribution of cumulative exposure for all decedents; this decision was motivated by the desire to obtain approximately equally precise estimates of effect in each quartile (for example, equal variance in effect estimates). Evaluation of linear trends in SRRs with increasing exposure were calculated via methods outlined by Rothman.[31] The midpoints of the exposure categories were used as scores; for the last category we used the upper category boundary plus 50% of the upper category boundary.

More detailed internal exposure-response analyses for end-stage renal disease incidence (N = 18) and rheumatoid arthritis (N = 18) were conducted via nested case-control analyses using conditional logistic regression. These analyses permitted more detailed examination of the shape of the exposure-response curve than was possible via life table methods; we considered models using cumulative exposure, cumulative exposure lagged, the log of cumulative exposure, peak exposure, and average exposure. We also fit a cubic spline model (with knots at the 5th, 25th, 50th, 75th, and 95th percentiles of cumulative exposure of controls), which provided a relatively unconstrained model of exposure response. In these analyses, 100 controls were chosen randomly per case from among all those who had survived to the same age as the case or later than the case. An SAS procedure (PHREG) was used to do the analysis.[32] Controls were matched to cases on race, sex, and date of birth within 5 years. For arthritis we analyzed all arthritis, including rheumatoid arthritis [International Classification of Diseases, 9th revision (ICD-9) code 714] and nonrheumatoid arthritis (ICD-9 codes 711–713, 715–716, and 720–721), separately. Cutpoints for quartile analyses in these analyses were the same as those use in the life table analyses.

Lifetime excess risk of end-stage renal disease was calculated taking into account competing risk of death from other causes.[33] For this calculation, we used age-specific male end-stage renal disease rates from the period 1995–1997[29] and the U.S. death rates for all males from the period 1995–1997.[34] The relative risk for end-stage renal disease by log cumulative exposure was taken from the case-control analysis of end-stage renal disease cases.

Results

Table 1 gives descriptive data on the cohort. The average length of follow-up was 24 years, and the average year of first employment (or first exposure) was 1967 (median year was 1969). The average length of employment was 9 years, with a wide range; 25% were employed for less than 1 year, whereas 21% were employed for more than 10 years. Twenty-four per cent of the cohort had died, and cause of death was available for 95% of the deceased. If missing causes of death were distributed equally among different causes, then one would expect that cause-specific mortality rates in our cohort would be underestimated by approximately 5%.

Table 2 gives exposure data for the ten job categories used in the analysis for the period 1974–1996. It is apparent from Table 2 that high exposures (that is, above the National Institute for Occupational Safety and Health recommended exposure limit) were not un-

TABLE 1. Description of Cohort (N = 4,626)

Percentage white	96.2%
Percentage male	98.9%
Percentage dead	23.5%
Average year of birth	1941(SD 17)
Average year last observed	1991(SD 9)
Average year first employed	1967(SD 12)
Average year last employed	1976(SD 10)
Average length of employment (years)	8.8(SD 10.7)
Average year of death	1984(SD 8)
Percentage dead with known cause of death	95%

common in these plants. Exposures have dropped considerably over time. The geometric mean exposure in 1974–1979 (based on 1,278 samples) was 51 $\mu g/m^3$, dropping to 11.6 $\mu g/m^3$ for the period 1985–1988 (based on 680 samples). The median exposure in the period 1946–1947 was 78 $\mu g/m^3$ (based on 125 sample means).

Table 3 presents mortality results for the outcomes of interest and pneumoconiosis for the exposed cohort *vs* the U.S. population, for both underlying and multiple causes. There is a general increase of 23% in mortality for this cohort from all causes combined, which is reflected in both heart disease and cancer. It is likely that life-style characteristics such as smoking account for some of this increase. Limited smoking data available collected at four plants in the 1980s indicates that the cohort smoked more than the general population. For data collected in 1987 for 147 men in the cohort 25–64 years of age, 26% were never-smokers, 39% were current smokers, and 35% were former smokers. For U.S. males in 1987, the respective age-adjusted figures were 34%, 35%, and 33%.[35] Smoking is not known to be related to renal disease or arthritis.

Exposure to silica is also likely to play a role in the excesses seen for cancer and heart disease. Silica is associated with lung cancer in this cohort (described in a separate report).[21] Respiratory disease induced by silica may also contribute to mortality from heart disease. Nonmalignant respiratory disease is elevated, because this category includes silicosis, as well as nonspecific chronic obstructive pulmonary disease, which in a number of cases is actually likely to be silicosis.

Several other categories of death known to be related to silica were elevated. Silicosis and nonspecified pneumoconioses were elevated for underlying cause (rates for these diseases were not available for multiple-cause analyses). Tuberculosis, often related to silica exposure, was also elevated.

Excesses of acute renal disease, chronic renal disease, and arthritis were found in multiple-cause analyses, as well as an excess of other musculoskeletal disease. Twelve of the 23 deaths mentioning arthritis on the death certificate were classified as rheumatoid arthritis. SMRs specific for rheumatoid arthritis could not be calculated owing to the lack of specific mortality rates. Among the musculoskeletal disease deaths, four of the eight deaths resulted from systemic sclerosis (three deaths) and lupus (one death), both autoimmune disorders.

Table 4 presents exposure-response analyses for selected causes of interest. Silicosis and other unspecified pneumoconioses as underlying causes show an increasing trend in SRRs with cumulative exposure, suggesting that

TABLE 2. Exposure Levels 1974–1996 by Job Category

Job Category*	No. of Samples, 1974–1996	Geometric Mean, $\mu g/m^3$ Silica	GSD	% Samples More than NIOSH REL (>50 $\mu g/m^3$)
Quarry (11%)	680	9.6	9.3	27
Crushing (2%)	282	17.1	11.1	42
Wet process (4%)	280	17.7	11.0	43
Drying (5%)	427	30.6	8.7	54
Screening (2%)	163	44.6	9.6	66
Milling (6%)	392	30.2	10.6	58
Bagging (7%)	1,142	60.2	9.9	69
Loading (7%)	252	28.5	9.8	54
Administration (15%)	97	3.5	6.6	1
Other (41%)	554	21.3	10.2	46
Overall	4,269	25.9	10.9	51

GSD = geometric standard deviation; NIOSH REL = National Institute for Occupational Safety and Health recommended exposure limit.
* Based on cohort of 4,027 workers used for exposure-response analyses; percentages of workers in the cohort in this category, based on last job held, are shown in parentheses.

TABLE 3. Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals for Selected Causes of Death, Underlying and Multiple-Cause Analyses (Full Cohort, N = 4,626)

Cause (ICD-9 Code)	Observed Deaths, Underlying Cause	SMR	95% CL	Observed Deaths, Multiple Cause*	SMR	95% CI
Respiratory tuberculosis (001–008)	5	3.39	1.09–7.92	16	4.41	2.52–7.12
Silicosis (502)	11	66.3	33.1–118.7	NA†		
Pneumoconioses, not specified (550, 503, 505)	6	7.77	2.83–16.90	NA†		
Acute renal disease (580, 581, 584)	3	3.37	0.70–9.86	16	2.61	1.49–4.24
Chronic Renal Disease (582, 583, 585–587)	10	2.22	1.06–4.08	36	1.61	1.13–2.22
Arthritis (711–716, 720 –721)	1	1.63	0.04–9.03	23	4.36	2.76–6.54
Other musculoskeletal causes (710, 717–719, 722–729, 731–739)	2	2.35	0.06–8.46	8	2.18	0.93–4.28
Ischemic heart disease (410–414)	330	1.22	1.09–1.36	474	1.22	1.11–1.33
All cancers (140–208)	254	1.28	1.12–1.44	416	1.33	1.20–1.46
All nonmalignant respiratory disease (460–519)	104	1.80	1.47–2.18	330	1.69	1.52–1.89
All causes	1,073	1.23	1.16–1.31	2,819	1.33	1.28–1.38

* Uses any mention of disease on death certificate; multiple cause comparison rates were not available for silicosis and pneumoconiosis.
† Multiple-cause mortality rates for the U.S. population were not available for these categories.

TABLE 4. Exposure-Response Analyses: Standardized Rate Ratios* (SRR) and Observed Deaths by Quartile of Cumulative Exposure for Selected Causes, Based on Subcohort with Adequate Work Histories (N = 4,027)

	SRRs (Internal Referent)									
	>0–0.10 mg/m³-Years		0.10–0.51 mg/m³-Years		0.51–1.28 mg/m³-Years		1.28+ mg/m³-Years			
Cause of Death	SRR	Observed Deaths	SRR	Observed Deaths	SRR	Observed Deaths	SRR	Observed Deaths	Slope†	95% CL
Silicosis and unspecified pneumoconiosis	1.00	1	1.22	2	2.91	4	7.39	7	0.00016	0.00010, 0.00022
Acute renal disease, multiple cause‡	1.00	2	1.65	2	1.56	2	4.13	5	0.00007	0.00003, 0.00012
Chronic renal disease, multiple cause‡	1.00	5	1.57	7	2.62	12	2.02	6	0.00014	−0.00005, 0.00032
Arthritis, multiple cause‡	1.00	1	1.73	3	3.73	7	6.91	7	0.00018	0.00017, 0.00019

95% CL = 95% confidence limits.
* Directly standardized rate ratios using the low-exposure group as the referent and using weights from person-years for entire cohort.
† Based on multiple-cause analysis, which uses any mention of the disease on death certificate.
‡ The slope represents the increase in the multiple-cause mortality rate for each mg/m³-year. The slope is based on a weighted linear regression for directly standardized rates.[31]

our job-exposure matrix may be reasonably accurate, that is, able to classify workers so that increasing cumulative exposure led to more silicosis, as would be expected. Multiple-cause mortality analyses for kidney disease showed increasing SRRs with increasing cumulative exposure for both acute and chronic renal disease.

Multiple-cause mortality analyses of arthritis also showed a positive trend with increased cumulative exposure. This analysis, however, included osteoarthritis (ICD-9 code 715) as well as rheumatoid arthritis (ICD-9 code 714), which was the outcome of specific interest (see below for separate case-control analysis of rheumatoid arthritis). Other musculoskeletal diseases were too few and results for trend are not presented.

Incidence rate ratios for end-stage renal disease from the period 1977–1996 are shown in Table 5. There is an overall twofold excess of end-stage renal disease, based on 23 cases [SIR = 1.97, 95% confidence interval (95% CI) = 1.25–2.96]. The excess is most marked for glomerulonephritis, which has a rate ratio of 3.85 (95% CI = 1.55–7.93). It should be noted, however, that the type of kidney disease causing end-stage disease is often not well known; biopsies are often not conducted for patients presenting with kidney failure.

Of the 23 end-stage renal disease cases, nine had died, and of these, seven had renal disease listed somewhere on their death certificates. Eighteen of these 23 cases had adequate detailed work history and were included in exposure-response analyses. Of these the average time since first exposure was 29 years (range = 10–48), the average duration of exposure was 19 years (range = 0.2–42), and the average age at failure (date first treated) was 58 year (range = 32–72). By way of comparison, for the entire cohort the average time since first exposure was 15 years, and the average duration of exposure was 9 years (Table 1).

Exposure-response analyses for end-stage renal disease for the subset of the cohort with adequate work history (87%) are shown in Table 6. We found a pronounced trend of increasing end-stage renal disease risk by increasing cumulative exposure.

More detailed exposure-response analyses for end-stage renal disease (N = 18) were conducted in case-control analyses analyzed via conditional logistic regression for the subcohort with adequate work histories (N = 4,027). We found rate ratios by quartile of cumulative exposure of 1.00, 2.68, 4.00, and 4.38. The log of cumulative exposure showed a better fit to the data (coefficient = 0.31, 95% confidence limits = −0.04, 0.66) than other exposure metrics such as cumulative exposure itself, average exposure, or peak exposure. A cubic spline curve did not improve the fit over the model with the log of cumulative exposure. Figure 1 shows these two curves, which are similar.

For arthritis, conditional logistic regression for nine cases of rheumatoid arthritis in the subcohort with adequate work histories (N = 4,027) showed trends of increased risk with increasing cumulative exposure, the best fit again being for the log of cumulative exposure (coefficient = 0.84, 95% CI = 0.15–1.22). Analyses of arthritis deaths other than rheumatoid arthritis (including arthritis) showed no evidence of increased risk with increasing exposure.

The excess lifetime risk of end-stage renal disease through 75 years of age for males exposed at 0.05 mg/m³ respirable silica (the National Institute for Occupational Safety and Health recommended exposure limit) from 20 to 65 years of age was 14% (95% confidence limits = −1%, 70%), based on the coefficient for log cumulative

TABLE 5. Standardized Incidence Rate Ratios (SIRs) for End-Stage Renal Disease, 1977–1996

Diagnostic Category*	Cases Observed/ Expected	Rate Ratio	95% CI
Glomerular	7/1.82	3.85	1.55–7.93
Diabetic	5/3.84	1.30	0.42–3.03
Hypertensive	6/2.34	2.56	0.94–5.57
Other	5/3.70	1.35	0.44–3.15
All diagnoses combined	23/11.70	1.97	1.25–2.96

* SIRs for other diagnostic categories were not calculated owing to small numbers; two cases were due to collagen vascular disease, one was due to congenital nephropathy, and two could not be classified.

TABLE 6. SRRs* (No. of cases) by Exposure Categories for End-Stage Renal Disease

	SRRs (Internal Referent)									
	>0–0.10 mg/m³-Years		0.10–0.51 mg/m³-Years		0.51–1.28 mg/m³-Years		1.28+ mg/m³-Years			
	SRR	No. of Cases	SRR	No. of Cases	SRR	No. of Cases	SRR	No. of Cases	Slope†	95% CI
All end-stage renal disease	1.00	2	3.09	5	5.22	6	7.79	5	0.00043	0.00027 –0.00062

* Directly standardized incidence ratios in which the end-stage renal disease rates of the upper quartiles of cumulative exposure of the exposed cohort are each compared with the end-stage renal disease rate of the lowest quartile; weights for standardization are taken from the person-time of the entire cohort. SRRs could not be calculated for glomerulonephritis separately because there were no cases in the lowest quartile of exposure. There were 5 cases of glomerular disease, 5 of hypertensive neuropathy, 4 of diabetic neuropat

exposure from the nested case-control analysis restricted to end-stage renal disease cases. This greatly exceeds the usual OSHA permissible lifetime excess risk of 0.1%, although the CI is broad. The background lifetime risk for a nonexposed male for end-stage renal disease is 2%.

Discussion

We have studied a cohort of 4,626 people exposed to silica, among whom we observed 67 cases of renal disease; of these, 23 were found on a registry of end-stage renal disease patients, and an additional 44 were found via death certificates only. These data represent the largest number of renal cases observed to date in a cohort study of subjects with well-documented exposure to silica.

The workers in this study had appreciable silica exposure (particularly in the past), as indicated by the excess of silicosis in the cohort. On the other hand, the average level of silica exposure for workers in this cohort was 0.05 mg/m³ (standard deviation = 0.5), which is the National Institute for Occupational Safety and Health recommended exposure limit. Ten per cent of the cohort averaged levels above

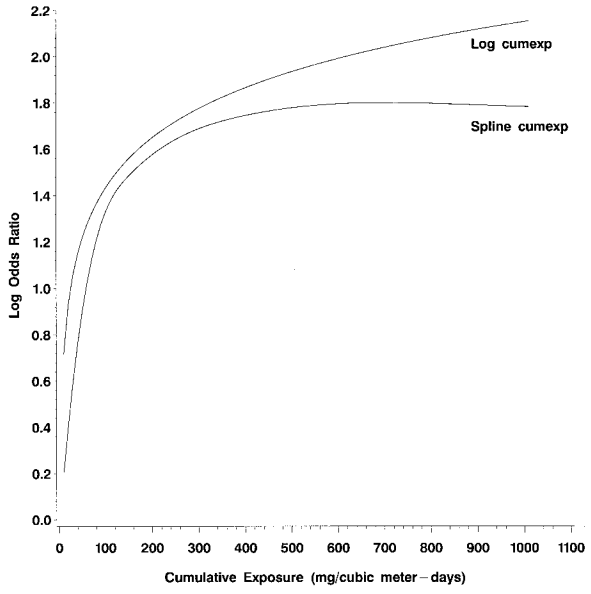

FIGURE 1. Exposure response analysis for end-stage renal disease incidence. cumexp = cumulative exposure.

0.10 mg/m³, which is the OSHA limit for respirable dust when the dust is 100% crystalline silica.

Strengths of our study include the inclusion of both renal disease morbidity (end-stage renal disease) and mortality data and the ability to analyze for exposure-response trends on the basis of quantitative estimates of silica exposure over time. A limitation in our data is the lack of certainty about exposure estimates before the 1970s, for which existing data on exposure are sparse (available only for 1946). On the other hand, the database for estimating historical exposures in this cohort is relatively extensive compared with many other occupational cohorts. Other limitations are inherent to the use of multiple-cause mortality data, in which the date of disease incidence is not known. It is possible that in some of our multiple-cause cases the renal disease occurred before exposure. Renal disease, however, is generally a disease of older age and is likely to have occurred after most workers quit working (in some cases it is disabling, forcing workers to leave work). Multiple-cause SMRs may also be biased upward when all-cause mortality based on underlying cause is high, as was true in this cohort (all-cause SMR = 1.23), because there are more deaths (and death certificates) than expected and therefore more opportunities for multiple causes to be listed. Nevertheless, this bias is likely to be small and will not account for twofold excesses of multiple-cause SMRs.

Our findings confirm other recent findings in the literature that silica exposure is related to subsequent kidney disease. We found an overall twofold excess of end-stage renal disease. This excess was greatest for glomerular disease, which also conforms to prior literature. The glomerular excess is consistent with a possible immune (deposition of immune complexes) or autoimmune mechanism[4] (for example, via anti-nuclear antibodies or anti-neutrophil cytoplasmic antibodies; see review of the latter by Gregorini *et al*[36]). We cannot, however, exclude a mechanism of direct toxicity to the kidney; there is evidence of tubular damage among silica-exposed workers, which might lead to later glomerular disease.[37]

Our mortality data (based on multiple causes) were consistent with the morbidity data, also showing an approximate twofold excess of renal disease *vs* the U.S. population. We found positive exposure-response trends, with more cumulative silica exposure leading to more renal disease risk, based on either morbidity or mortality

data. These exposure-response trends tend to confirm a causal relation between silica exposure and subsequent renal disease.

Renal disease is an important public health burden in the United States. In 1997, the incidence rate of end-stage renal disease was 29 per 100,000 persons (34 per 100,000 for males), there were 79,000 new cases (42,000 males), and there were 300,000 prevalent cases (165,000 males).[29] Medicare costs were more than $10 billion per year for dialysis and transplants.[29] Let us assume that the great majority of all U.S. exposed workers (approximately 2 million) are male, that about 200,000[2] or 10% have exposures above 0.05 mg/m^3 (the National Institute for Occupational Safety and Health recommended exposure limit), and that these would be expected to experience a fourfold end-stage renal disease risk such as we found in our study for those in the upper half of cumulative exposure (in our cohort the median exposure level was 0.04 mg/m^3). If about 0.4% of the male workforce (200,000 of 50 million) has a relative risk of 4.0, then using standard formulas for etiologic fraction,

$$(RR - 1) \times p/[RR - 1) \times p + 1]$$

where p = proportion exposed, about 1.1% of new male end-stage renal disease cases (460 of 42,000) and approximately 1.1% of male prevalent cases (1,815 of 165,000) may be due to silica exposure, with an approximate treatment cost of $60 million per year.

In addition to the findings for kidney disease, we also found an excess of arthritis as determined by any mention on the death certificate. Although numbers were small, exposure-response analyses indicated that a positive exposure-response trend existed for rheumatoid arthritis but not for nonrheumatoid arthritis. These findings are consistent with the literature indicating that silica may cause rheumatoid arthritis. Coupled with the renal disease findings, these data suggest that silica may cause multiple diseases via immunotoxicity.

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