# Development of Quantitative Exposure Data For a Pooled Exposure-Response Analysis of 10 Silica Cohorts

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**Background** *Comprehensive quantitative silica exposure estimates over time, measured in the same units across a number of cohorts, would make possible a pooled exposure-response analysis for lung cancer. Such an analysis would help clarify the continuing controversy regarding whether silica causes lung cancer.*
**Methods** *Existing quantitative exposure data for 10 silica-exposed cohorts were retrieved from the original investigators. Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligram per cubic meter (mg/m$^3$) respirable crystalline silica.*
**Results** *Quantitative exposure assignments were typically based on a large number (thousands) of raw measurements, or otherwise consisted of exposure estimates by experts (for two cohorts). Median exposure level of the cohorts ranged between 0.04 and 0.59 mg/m$^3$ respirable crystalline silica. Exposure estimates were partially validated via their successful prediction of silicosis in these cohorts.*
**Conclusions** *Existing data were successfully adopted or modified to create comparable quantitative exposure estimates over time for 10 silica-exposed cohorts, permitting a pooled exposure-response analysis. The difficulties encountered in deriving common exposure estimates across cohorts are discussed.* Am. J. Ind. Med. 42:73–86, 2002.


***KEY WORDS: crystalline silica; quantitative exposure estimates; cohorts; diatomaceous earth; granite; industrial sand; pottery; metal mines***

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Contract grant sponsor: NIOSH; Contract grant sponsor: NCI; Contract grant sponsor: OSHA.
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Accepted 2 May 2002
DOI 10.1002/ajim.10097. Published online in Wiley InterScience (www.interscience.wiley.com)

## INTRODUCTION

Occupational exposure to crystalline silica has been recognized as a carcinogen to humans [IARC, 1997]. However, relatively few studies included a quantitative exposure-response analysis, which provides the strongest evidence for causality and can be a basis for standard setting. Furthermore, the studies that did include quantitative exposure-response analyses have used different exposure metrics, making conventional meta-analysis impossible.

A pooled analysis of 10 occupational cohorts with quantitative exposure data was conducted in order to provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer [Steenland et al., 2001]. To make possible that effort, it was necessary to pool exposure data across the 10 cohorts.

We present the methods that were applied to pool exposure data from the 10 occupational cohorts. For most cohorts, some job-specific quantitative exposure data were available, but had not been previously linked to each subject's work history. For three cohorts, complete quantitative estimates over time for all cohort members were already available and could be adopted.

## METHODS

All cohort studies considered in the most recent IARC monograph on silica [IARC, 1997] were reviewed and a Medline search was run to identify all occupational cohorts exposed to crystalline silica, for which a quantitative exposure assessment was available or could be developed. Foundry cohorts were excluded because of the likely presence of concomitant exposures to other possible lung carcinogens in the work environment, and coalmines were excluded due to low and perhaps qualitatively different silica exposure (e.g., silica particles coated with clay). Mines with low exposure to radon decay products were included but were also considered separately in the eventual lung cancer analysis. Exposure estimates had to be at least potentially specific for all different jobs within each cohort, and cover all time periods when exposure occurred. If existing exposure estimates were available in gravimetric total dust, respirable dust or particle count, they had to be convertible to milligram per cubic meter (mg/m$^3$) respirable crystalline silica (the common measure used in the lung cancer analysis), in order to permit a direct comparison between cohorts and with regulatory standards for respirable crystalline silica. We identified 13 cohorts, 10 of which we included in the pooled analysis. Three cohorts were excluded due to confidentiality issues (Dutch ceramic workers, [Meijers et al., 1996]), unavailability of data (one cohort of South African gold miners [Reid and Sluis-Cremer, 1996]), or incompatibility of data (English case-control study of pottery workers [Cherry et al., 1998]).

The following paragraphs describe the way quantitative exposure estimates were developed for use in the pooled analysis. Additional information is included in Table I.

## US Diatomaceous Earth Workers

Members of this cohort worked in two plants in California where diatomaceous earth is mined and processed [Checkoway et al., 1993, 1996, 1997; Seixas et al., 1997]. Job-specific quantitative exposure estimates had previously been made and assigned to each cohort member, [Seixas et al., 1997], and were adopted without change. Estimates were originally derived as follows.

Raw exposure data included records of company routine air monitoring samples taken over the period 1962–1988 (5,714 records) and other industrial hygiene reports for the years 1948–1962. Different sampling methods were used over time: light microscopy from impinger samples until the late 1970s [in millions of particles per cubic foot (mppcf)], and thereafter, the respirable dust fraction (in mg/m$^3$) was obtained from filter cassette samples using a cyclone preselector. All data were converted to mg/m$^3$ respirable dust, using a conversion factor (see Table I) derived from linear regression using data of years in which both measurement techniques were used. Job- and time-specific exposure estimates were extracted from the available data using unweighted means. Each job was assigned with specific fractions of working time exposed to the different products in the industry (natural, calcined, and flux-calcined diatomaceous earth). Respirable dust concentrations were converted to respirable crystalline silica based on percentages of crystalline silica measured in the three different products [Checkoway et al., 1993]. Job-specific exposures for years before measurements (pre-1949) were estimated by regression modeling extrapolation based on temporal changes and knowledge on dates when dust exposure reduction interventions occurred. These exposure estimates were linked to the cohort by worker ID for analyses.

## Finnish Granite Workers

This cohort consisted of workers hired between 1940 and 1971, in granite quarries and processing barns in three main granite areas of Finland [Koskela et al., 1987a,b, 1994; Koskela, 1995]. Only quantitative exposure estimates over time had previously been available for a nested case-control study.

Dust exposure was measured in the Finnish granite industry in 1970–1972 and 1980–1989 by the Institute of Occupational Health. The measurements were carried out in the workplaces where the cohort members worked. Each worker's work history was collected from the employers' personnel records. Complete occupational histories were available for all the cohort members. In a previous nested

**TABLE I.** Characteristics of Available Exposure Data and Constructed Exposure Estimates For Each Silica Cohort

| Cohort | Number of raw exposure measurements used | Raw measurements correspond to period | Main purpose of measurements | Other data available (from summaries and reports) | No data available prior to | Measurement strategy (unit) | Conversion to gravimetric respirable silica | Job/ID dimension of assignments | Time dimension of assignments | Job history in cohort |
|---|---|---|---|---|---|---|---|---|---|---|
| US | | | | | | | | | | |
| Diatomaceous earth workers | 5,714 computerized measurements (area and personal) | 1962–1988 | Routine measurements by Manville Corporation | For 1948–1962, 41 documents were extracted, coded, and entered by year and department. Not known if they are personal or area samples | Before 1948: exposure estimated by regression modeling | Impinger sampling (mppcf); open face filter cassette sampling ($mg/m^3$ total dust); cyclone + filter cassette sampling ($mg/m^3$ respirable dust) | Respirable dust ($mg/m^3$) = 0.069 × mppcf; respirable dust ($mg/m^3$) = 0.228 × total dust [Seixas et al., 1997]. Using data of years in which both measurement techniques were used. Respirable dust was converted to respirable silica based on percentage of crystalline silica in product mixes [Checkoway et al., 1993] | 135 original company job titles | Each year from 1920–1994 | Complete job history in the plant was available |
| Finland | | | | | | | | | | |
| Granite workers | 329 measurements in industry, and experts personal experience | 1970–1972: 231 samples (for the cohort study); 1980–1989: 98 samples (stone industry) | 1970–1972: epidemiological follow-up of granite workers; 1980–1989: work environmental surveys and inspections | Reports from the mines (1945–); the Finnish foundry study (1970–1974); environmental survey and inspection measurements (1980–) | 1970 for stone industry; 1945 for mine industry | Filter sampling, personal, and stationary. Most measurements on which the expert assessment was made were total dust samples ($mg/m^3$ total dust) | Region specific conversion factors for total dust to respirable silica were used. $mg/m^3$ respirable silica = 0.04–0.06 × total dust | ID specific expert assessment was done | < 1940<br>1940–1949<br>1950–1959<br>1960–1969<br>1970–1979<br>1980–1989 | Lifelong job history until 1986 was available for each cohort member from the questionnaire in 1986 and medical records |

(*Continued*)

**TABLE I.** (*Continued*)

| Cohort | Number of raw exposure measurements used | Raw measurements correspond to period | Main purpose of measurements | Other data available (from summaries and reports) | No data available prior to | Measurement strategy (unit) | Conversion to gravimetric respirable silica | Job/ID dimension of assignments | Time dimension of assignments | Job history in cohort |
|---|---|---|---|---|---|---|---|---|---|---|
| US | | | | | | | | | | |
| Granite workers | 1,963. Only summary results were available extracted from six reports | 1924–1926: 220 samples; 1964: 80 samples; 1972: 879 samples; 1973: 784 samples | Environmental surveys | | 1924 | Impinger sampling (mppcf); mass respirable samples (mg/m$^3$ respirable dust) | The conversion factor of mg/m$^3$ respirable silica $= 0.0075 \times$ mppcf [Davis et al., 1983] was used, based on simultaneous measurements of mass respirable and impinger samples | 22 jobs | Two time periods (pre- and post-dust control) plus period in between | Complete job history in the plant was available |
| US | | | | | | | | | | |
| Industrial sand workers | 4,272 personal measurements from MSHA | 1974–1996 | Routine and compliance inspections, MSHA | Midget impinger dust measurements (mppcf) in 1947 for a cross-sectional dust exposure assessment study of 19 silica sand plants | Before 1946: exposure in 1946 was used | Personal cyclone + filter cassette sampling (mg/m$^3$ respirable dust) with median cut-point 3.5 μm | For the measurements before 1974: mg/m$^3$ respirable silica $= 0.157 \times$ mppcf $\times$ % quartz in dust samples; based on side by side samples [Sanderson et al., 2000]; after 1973: no conversion: X-ray diffraction was used to determine silica content | 4 plants, 10 job categories each | $< 1974$<br>1974–1977<br>1978–1981<br>1982–1988 | Complete job history in the plant was available |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| China | | | | | | | | | | |
| Pottery workers, tin miners, and tungsten miners | 2,100,000 extracted from plant files (area samples) | 1950–1987 | Routine measurements | | Before 1950: exposure in 1950 was used | Total dust measurement using a gravimetric method ($mg/m^3$ total dust); sampling duration 15–30 min, flow rate 20–25 L/min | Used 1 conversion factor for each type of plant/mine from total dust to $mg/m^3$ respirable silica; potteries [Zhuang et al., 2001]: $mg/m^3$ respirable silica $= 0.042 \times$ total dust; tungsten mines: 0.083; tin mines: 0.036 | 22 plants and for each plant about 20 jobs | Every 1–2 years between 1950 and 1994 | Only one job title was available for each cohort member |
| South Africa | | | | | | | | | | |
| Gold miners | 22,000 from an occupational dust survey | 1956–1960 | Occupational hygiene survey | Reports to the chamber of mines | Before 1956: exposure in 1956 was used | Konimeter measurements (particles per ml) | Described in Page-Shipp and Harris [1972] | 11 occupational categories | 1940–1950<br>1950–1960<br>1960–1970 | Complete job history in the plant was available |
| US | | | | | | | | | | |
| Gold miners | Not published | 1937–1977 | Routine samples by mines | NIOSH industrial hygiene report 1977 | Before 1937: all 25 mppf | Total dust measurements (in mppcf); by impinger sampling | The conversion factor of $mg/m^3$ respirable silica $= 0.01 \times$ mppcf [Steenland and Brown, 1995a] | Six occupational groups | Each year between 1937 and 1975 | Complete job history in the plant was available |
| Australia | | | | | | | | | | |
| Gold miners | Expert assessment based on available measurement summaries | | Occupational hygiene surveys | | 1925 | Konimeter measurements (in particles per ml); total dust and respirable dust measurements (in $mg/m^3$) | 1 conversion factor was used: $mg/m^3$ respirable silica $= 0.002 \times$ ppcc ($= 0.07063 \times$ mppcf) | 10 occupational groups (rank scores) | $< 1925$<br>1925–1935<br>1935–1940<br>1940–1950<br>1950–1960<br>1960–1970<br>1970–1975<br>$> 1975$ | Complete job history in the plant was available |

case-referent study of lung cancer [Koskela et al., 1994], an industrial hygienist estimated the cumulative exposure to total dust and quartz dust, using the dust measurements done by the Finnish Institute of Occupational Health as well as his expertise in mine and quarry exposure in Finland and lifelong exposure histories.

For this pooled analysis, Finnish investigators extended these estimates to the entire cohort. Sixty-five occupational labels within granite works were classified into five job categories. To estimate historical exposure, a period factor reflecting the time trend of exposure was used with which the exposure data of 1971–1985 were multiplied. The period factor was specific for each occupation and each period (before 1940, 1940–1949, 1950–1959, 1960–1969, 1970–1979, 1980–1989). Plant-specific conversion factors were used to convert from total dust exposure to respirable silica exposure ($< 5$ μm).

## US Granite Workers

This cohort consisted of workers from the Vermont granite industry including several quarries and a number of small manufacturing plants (sheds) where the stone is cut, polished, and finished [Theriault et al., 1974; Davis et al., 1983; Eisen et al., 1984; Costello and Graham, 1988]. Job-specific quantitative exposure assignments were not directly available for this cohort, but were developed by one of the previous investigators (Michael Attfield, personal communication), based on published exposure data which is summarized below.

Summary results of six different environmental surveys provided exposure estimates of granite dust exposure for the period 1924–1977 (1924–1926: 220 samples; 1964: 80 samples; 1972: 879 samples; 1973: 784 samples). In the early environmental surveys, impinger samples were taken (in mppcf) and in the later surveys mass respirable samples were taken (mg/m$^3$ respirable dust). The conversion factor of 1 mppcf = 0.0075 mg/m$^3$ respirable silica was used [Davis et al., 1983]. Average pre- and post-dust control exposures had previously been calculated for 22 job groups [Davis et al., 1983]. The work history data of the cohort included 150 different job titles. For this pooled analysis, a correspondence was made between the cohort job titles and the job titles for which exposure estimates were available. To account for a transition period for the implementation of dust control measures, three time periods were included: before 1940, 1940–1949, 1950 and after, resulting in quantitative exposure assignments for 66 job-year categories.

## US Industrial Sand Workers

This cohort consists of workers from 18 industrial sand plants [Steenland et al., 2001]. Job-specific quantitative exposure assignments in terms of respirable silica were developed for this study by US investigators [Sanderson et al., 2000] and were used by us unmodified in the pooled analysis. Below we summarize how they were developed.

For this cohort, NIOSH obtained 4,272 personal respirable dust measurements from Mine Safety and Health Administration (MSHA) compliance inspections and from the archives of seven of the plants, which had collected samples (from 1974 to 1996). Samples were typically collected using portable pumps with cyclone pre-separator collecting respirable dust on a filter. Quartz content of all samples was determined using X-ray diffraction. Historical exposure data were available from a dust exposure assessment study of 19 silica sand plants conducted in 1946 with measurements available in mppcf. These data were converted to mg/m$^3$ respirable dust by multiplying them by 0.157 and to mg/m$^3$ respirable silica by multiplying with a job category specific percentage of quartz found in the historical dust mass samples. All available data were introduced in a model to predict the quartz exposure for 120 plant-job-period categories (4 plants, 10 jobs, 3 time periods): (job categories: quarry, crushing, wet process, drying, screening, milling, bagging, loading, administration, other. Time categories: 1974–1977, 1978–1981, 1982–1988). The job codes in the occupational histories of the cohort were recoded to the 10 job-categories used for the exposure data.

## China Pottery Workers, Tin Miners, and Tungsten Miners

This study consists of three cohorts: tin miners in four mines, tungsten miners in 10 mines, and pottery workers in eight pottery factories [Chen et al., 1992; McLaughlin et al., 1992; Dosemeci et al., 1993]. Job-specific quantitative exposure assignments in terms of total dust had been previously constructed for subjects in a nested case-control study done within this cohort [Dosemeci et al., 1993]. We adapted these data for use in the entire cohort.

Raw exposure data were available from routine company air measurement surveys between 1950 and 1987. All exposure data were area total-dust measurements using a gravimetric method with a sampling duration of 15–30 min. A total of 2,100,000 dust monitoring records were abstracted from company records by trained local industrial hygienists following a standard protocol. Data were grouped by facility, job, and calendar year. Based on these data, for every facility, job and calendar year combination, an assignment to one of seven quantitative categories of exposure for total dust was made by local hygienists and occupational physicians. These exposure data, as received from investigators, could not be applied to the work history data of the cohort as such, because for cohort members only one 2-digit job-title was available (the usual job over the whole work period), while the exposure data were specific for 3-digit job-titles (more specific jobs within each 2-digit group). The exposure data were, therefore, collapsed to 2-digit job titles using the average exposure of the 3-digit jobs within the 2-digit categories, weighted by the number of subjects in each 3-digit code in the previously published case-control data-set, [McLaughlin et al., 1992]. A list of non-exposed jobs was also constructed by local hygienists and added to the job-specific exposure assignments, and all non-exposed jobs were assigned a minimal exposure of 0.01 mg/m$^3$ total dust in any time period.

For the purpose of the pooled analysis, total dust data were converted to respirable silica using a one-step conversion (specific for pottery, tungsten mines, and tin mines), based on side by side sampling of the traditional Chinese total-dust method and airborne dust sampling (NIOSH supplied) using nylon cyclones followed by X-ray diffraction [Zhuang et al., 2001]. The correlation between NIOSH sampling and Chinese measurements were highly correlated ($r^2 = 0.84$) [Chen et al., 2001]. Job- and time-dependent exposure data were linked to the work history of the cohort using 2-digit job title and facility as common identifier.

## South African Gold Miners

Members of this cohort worked in South African gold mines [Page-Shipp and Harris, 1972; Hnizdo and Sluis-Cremer, 1991, 1993; Reid and Sluis-Cremer, 1996; Hnizdo et al., 1997; Hnizdo and Murray, 1998]. Job-specific quantitative exposure assignments had previously been developed and used by investigators to estimate cumulative exposure for each miner in the cohort, although analyses to date had focused on a nested case-control study of lung cancer [Hnizdo et al., 1997]. We adapted the exposure assignments for use with the entire cohort.

Exposure data were available from an occupational dust survey between 1956 and 1960 [Page-Shipp and Harris, 1972]. About 22,000 konimeter samples were available, which were taken at 10-min intervals throughout the shift carried by an observer who accompanied the miner whose exposure was being measured. The men chosen for sampling were divided into 11 occupational groups. Average respirable dust counts for each of these groups were calculated by Beadle [1971]. Mean respirable mass concentrations were derived by du Toit [1991]. It was assumed that dust conditions had not varied greatly in the period 1936–1960, which was supported by routine measurements from the Chamber of Mines over this period [Page-Shipp and Harris, 1972].

The cumulative respirable dust was calculated as a sum of number of shifts working in each occupational category multiplied by the mean respirable mass for each specific job, and weighted by the average hours that each job category spent underground. This was converted to mg/m$^3$-years by dividing it by 270, i.e., the average number of shifts per year. In the database, the actual years (shifts/270) spent in different occupational categories were coded for each decade (1940–1950, 1950–1960, and 1960–1970). For purpose of the pooled analysis, respirable dust was converted to respirable silica (based on a 30% silica content of respirable dust), and exposure assignments were linked to the work histories of the cohort by using ID as the common identifier.

## US Gold Miners

Members of this cohort worked in a gold mine in South Dakota, mainly underground [Zumwalde et al., 1981; Brown et al., 1986; Steenland and Brown, 1995a,b]. Job-specific quantitative exposure assignments in terms of respirable dust counts had previously been developed [Brown et al., 1986] and were used by us after conversion of total dust counts to gravimetric respirable silica.

For the Homestake gold mine, regular routine impinger measurements were taken starting 1937 through 1977. These company data were supplemented by personal dust measurements from an industrial hygiene survey conducted in 1977, using NIOSH impinger sampling [Brown et al., 1986]. NIOSH impinger sampling was compared with company sampling and a good agreement was found [Zumwalde et al., 1981]. Quantitative exposure estimates were developed for each major occupational group (laborers, miners, motormen, supervisors, and skip loaders, nonexposed) using yearly averages (1937–1975). Exposures prior to 1937 were estimated at 25 mppcf of respirable dust. No job history data were collected after 1975. Each exposure estimate was weighted by a factor estimating how much time was spent underground. Measurements were in millions of particles per cubic foot (mppcf) and a conversion factor of 0.01 (the traditional conversion factor for Vermont granite) was used to convert these to mg/m$^3$ respirable silica [Steenland and Brown, 1995a]. Occupational group ($n = 6$) was used to link exposure data to the cohort.

## Australian Gold Miners

This cohort consisted of Kalgoorlie gold miners, Western Australia [Hewson, 1993; DeKlerk et al., 1995; DeKlerk and Musk, 1998]. Job-specific quantitative exposure assignments in terms of respirable silica had been previously developed by investigators (Nicholas DeKlerk, personal communication) but were not published and had not been used in cohort analysis. We adopted these previous estimates. Below, we summarize how they were developed.

Measurements of dust have been undertaken in Western Australian gold mines from 1925 to 1977 using konimeters and after 1977 gravimetric dust sampling techniques (total and respirable dust). Summaries of konimeter surveys appeared in Annual Reports of the Department of Mines (now Minerals and Energy) in 1925, 1929, and for the period 1939–1977. From the 1950s, typically 1,000 or more konimeter measurements (average of three spot samples) were taken in underground workplaces and in various locations of surface operations [Hewson, 1993]. These konimeter surveys could, however, not be applied directly to the work history data of the cohort. The principal investigator of the study (DeKlerk) developed estimates of dust exposure for six time windows between 1925 and 1975, for 10 "rank scores," interpretable as uniformly exposed groups within the gold mine. All occupations in the cohort were assigned a rank score. All estimates were in mppcc of dust, and were converted to mg/m$^3$ respirable silica by using a conversion factor of 0.002. This conversion factor was based on a conversion from mppcc to respirable dust of 0.01, and a conversion of respirable dust to respirable silica of 0.2 (based on a silica content of 20% in respirable dust) [Hewson, 1993]. Exposure estimates were applied to the cohort by using the rank scores as common identifier.

## Quality of the Pooled Quantitative Exposure Estimates

The developed exposure estimates could not be verified directly against a 'gold standard.' In an attempt to indirectly validate the quantitative exposure estimates, we determined whether increasing exposure led to increasing silicosis, given the known relationship between cumulative exposure and that disease.

Nested case-control analysis for silicosis or unspecified pneumoconiosis (underlying cause ICD9 code 502, 505) in the pooled data set was performed using conditional logistic regression. A risk set for each case was assembled composed of those who had survived to an age at least as great as the case, and which was matched for race, sex, date of birth (within 5 years) and study to the index case, and 100 controls were chosen randomly from each risk set. Internal analyses were performed based on quintile cut-points of cumulative exposure of the cases, with the lowest quintile as the baseline.

Standardized Rate Ratios (SRRs) for silicosis were calculated for each cohort, through life table analysis. The purpose of this analysis was to determine if a positive exposure-response trend for silicosis existed within each cohort, keeping in mind that exposure levels differed greatly between cohorts. Each cohort was stratified by cumulative exposure, using as cut-points cohort-specific quartiles of cumulative exposure for the deceased in each separate cohort. The SRR was calculated for each cumulative exposure group compared to the lowest exposure group.

## RESULTS

Table II shows the numbers of workers in each cohort, and the quartiles of cumulative and average exposure level for cohort members within each cohort. The median of the

**TABLE II.** Cohort-Specific Quartiles of Average* and Cumulative Respirable Silica Exposure For Each Cohort

| | Number of workers | Average* respirable silica exposure (mg/m$^3$) | | | | Cumulative exposure (mg/m$^3$ years) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Median | Q3 | Maximum | Q1 | Median | Q3 | Maximum |
| US | | | | | | | | | |
| Diatomaceous earth workers | 2,342 | 0.11 | 0.18 | 0.46 | 2.43 | 0.38 | 1.05 | 2.48 | 62.71 |
| Finland | | | | | | | | | |
| Granite workers | 1,026 | 0.39 | 0.59 | 1.29 | 3.60 | 0.84 | 4.63 | 15.42 | 100.98 |
| US | | | | | | | | | |
| Granite workers | 5,408 | 0.02 | 0.05 | 0.08 | 1.01 | 0.14 | 0.71 | 2.19 | 50.00 |
| US | | | | | | | | | |
| Industrial sand workers | 4,027 | 0.02 | 0.04 | 0.06 | 0.40 | 0.03 | 0.13 | 0.52 | 8.265 |
| China | | | | | | | | | |
| Pottery workers | 9,017 | 0.18 | 0.22 | 0.34 | 2.10 | 3.89 | 6.07 | 9.44 | 63.15 |
| China | | | | | | | | | |
| Tin miners | 7,858 | 0.12 | 0.19 | 0.49 | 1.95 | 2.79 | 5.27 | 5.29 | 83.09 |
| China | | | | | | | | | |
| Tungsten miners | 28,481 | 0.15 | 0.32 | 1.28 | 4.98 | 3.47 | 8.56 | 29.79 | 232.26 |
| South Africa | | | | | | | | | |
| Gold miners | 2,260 | 0.15 | 0.19 | 0.22 | 0.31 | 3.22 | 4.23 | 5.35 | 9.28 |
| US | | | | | | | | | |
| Gold miners | 3,348 | 0.02 | 0.05 | 0.10 | 0.24 | 0.10 | 0.23 | 0.74 | 6.20 |
| Australia | | | | | | | | | |
| Gold miners | 2,213 | 0.25 | 0.43 | 0.65 | 1.55 | 6.52 | 11.37 | 17.31 | 50.22 |

*Average exposure is cumulative exposure averaged of the whole exposure period.

average exposure to respirable crystalline silica ranged between 0.04 (US industrial sand) and 0.59 mg/m$^3$ (Finland granite), indicating that the cohorts include many workers who were exposed above current standards. The cohort-specific median of cumulative exposure ranged between 0.13 (US industrial sand) and 11.37 mg/m$^3$-years (Australia gold miners). This wide range provided the opportunity to evaluate risk of disease in the lung cancer analysis across a wide range of cumulative exposure.

The conditional logistic regression analysis for the relation between cumulative exposure and silica mortality in the pooled data set resulted in odd ratios, of 1.0, 3.1 (2.5–4.0), 4.6 (3.6–5.9), 4.5 (3.5–5.8), and 4.8 (3.7–6.2), using cut-points for based on quintiles of cumulative exposure of the silicosis deaths (4.45, 9.08, 16.26, 42.33 mg/m$^3$-years). These results indicate that the exposure estimates were reasonably successful in estimating exposure, in so much as a positive and reasonably monotonic exposure-response trend was observed. The trend for duration alone by quintile was not as consistently monotonic (1.0, 1.3, 1.8, 1.4, 1.2) indicating that our estimates of intensity of exposure were an improvement over simple duration of exposure.

The study-specific exposure-response trends were also reasonably monotonic, even though exposure levels differed by study. Table III presents the SRRs for silicosis mortality by cohort-specific quartiles of cumulative exposure. A significant trend was present for most cohorts even with small numbers of silicosis deaths within each exposure stratum. For the South African cohort, silicosis SRRs could not be calculated because no deaths were coded to silicosis as underlying cause, for reasons, which appear specific to coding practices in South Africa.

## DISCUSSION

This study discusses the use of existing exposure data for 10 silica-exposed cohorts to create mutually comparable (in the same units) quantitative estimates of exposure for all cohort members across all jobs and across time. These estimates in turn permitted an exposure-response analysis for lung cancer for the pooled cohort data.

Similar pooled cohort analyses that make use of existing exposure data have previously been done for other occupational exposures, including man-made mineral fibers [Dodgson et al., 1987] dioxin [Kauppinen et al., 1994; Piacitelli et al., 2000] and bitumen [Burstyn et al., 2000]. As mentioned by Stewart et al. [1996], 'historical exposure assessment

**TABLE III.** SRRs For Silicosis Mortality and Number of Silicosis Deaths (Underlying Cause), by Cohort-Specific Quartile of Cumulative Exposure to Respirable Silica*

| | Non-exposed | | 1st Quartile | | 2nd quartile | | 3rd quartile | | 4th quartile | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SRR | (n) | SRR | (n) | SRR | (n) | SRR | (n) | SRR | (n) | for trend** |
| US | | | | | | | | | | | |
| Diatomaceous earth workers | | | 0.00 | (0) | n.a.[a] | (0) | n.a.[a] | (0) | n.a.[a] | (7) | < 0.001 |
| Finland | | | | | | | | | | | |
| Granite workers | | | 0.00 | (0) | n.a.[a] | (0) | n.a.[a] | (4) | n.a.[a] | (10) | < 0.001 |
| US | | | | | | | | | | | |
| Granite workers | | | 1.00 | (3) | 2.02 | (4) | 1.23 | (5) | 4.14 | (15) | 0.10 |
| US | | | | | | | | | | | |
| Industrial sand workers[b] | | | 0.00 | (1) | 1.22 | (2) | 2.91 | (4) | 7.39 | (7) | < 0.00001 |
| China | | | | | | | | | | | |
| Pottery workers[b] | 1.00 | (1) | 34.8 | (17) | 41.3 | (16) | 44.3 | (19) | 77.3 | (31) | < 0.001 |
| China | | | | | | | | | | | |
| Tin miners[b] | 1.00 | (4) | 1.62 | (3) | 7.81 | (20) | 11.2 | (33) | 6.21 | (16) | 0.05 |
| China | | | | | | | | | | | |
| Tungsten miners[b] | 1.00 | (2) | 31.6 | (72) | 53.2 | (122) | 73.0 | (143) | 69.1 | (132) | 0.02 |
| US | | | | | | | | | | | |
| Gold miners | | | 0.00 | (0) | n.a.[a] | (2) | n.a.[a] | (3) | n.a.[a] | (20) | 0.10 |
| Australia | | | | | | | | | | | |
| Gold miners | | | 1.00 | (4) | 1.97 | (7) | 4.06 | (13) | 4.23 | (16) | < 0.001 |

*Follow-up in this table from 1960 onwards; life table program had silicosis as a specific category of death available only after 1960. Silicosis defined as ICD 502 (9th revision code). There were no deaths with silicosis as the underlying cause in the South African cohort, although significant positive trends were seen for other silica-related causes of death (TB, COPD).
**Linear trend in SRRs.
[a]SRRs cannot be calculated when there are no deaths in the lowest quartile, but a trend test can be.
[b]Combines unspecified or unknown pneumoconiosis (ICD9 500, 503, 505) with silicosis (ICD9 502).

requires an opportunistic approach, taking advantage of what information is available and developing creative and innovative approaches to exploit that information.' When available measurement data are not sufficient to estimate exposure for all cohort members and all relevant time periods, one has to rely on either statistical modeling to estimate missing data, or on use of measurement data from surrogate exposure agents, or on professional judgment.

In this pooled cohort, exposure assessment was based on all these methods depending on the possibilities within each study. A number of difficulties were encountered in this process, which we found to be typical for other pooled analyses.

The measurement methods for dust differed between studies but also within studies over time. In only one study [US industrial sand cohort, Sanderson et al., 2000] was gravimetric silica measured directly using X-ray diffraction; even in this study, investigators had to rely on some impinger samples and a statistical model to estimate exposures prior to the 1970s. For the other studies, measurements in mppcf, mppcc, mg/m$^3$ total dust, and mg/m$^3$ respirable dust had to be converted to mg/m$^3$ respirable crystalline silica. Cohort-specific conversion factors were applied to convert particle counts to gravimetric measures, taking into account the silica fraction of the dust to which the cohort was exposed. Different conversion factors were applied within a cohort, when workers were thought to be exposed to different types of dust (e.g., Finnish granite workers worked in three granite areas with different silica content; US diatomaceous earth workers who were exposed to product mixes with different crystalline silica content).

Cohort-specific conversion factors were sometimes based on separate steps converting particle count to gravimetric dust, total gravimetric dust to respirable dust, and respirable dust to respirable crystalline silica. In other cases, step conversion factors were used based on side-by-side measurements. This made it difficult to compare conversion factors between cohorts. Those studies for which a conversion of particle count to gravimetric respirable crystalline silica is used (US diatomaceous earth, Finland granite, US granite, Australian goldmine), conversion factors (mppcf to mg/m$^3$ respirable silica) ranged between 0.008 and 0.07 (Table I). Not taking into account cohort specific differences in conversion factors could, therefore, result in an over- or underestimation of the exposure estimates by a factor of 10. When just looking at the percentage silica in respirable dust, the range between cohorts is 10–33% (Table I). Disregarding these differences in silica content could have resulted in an under- or overestimation of a factor of three. One weakness of our data is our reliance on these conversion factors, for which generally we have no way to assess the validity. Some amount of uncertainty is likely to be related to these estimates illustrated by the problem of the lack of international consensus on the definition of respirable fraction. ACGIH, ISO/CEN, and NIOSH currently use a median cut-point of 4 μm for respirable dust sampling. For federal regulations, OSHA inspectors must, however, use cyclones that meet the old ACGIH curve with a 3.5-μm cut-point. The British Medical Research Council (BMRC) uses a more conservative collection efficiency curve, with a median cut-point of 5 μm, which is also adopted by Australia. In our pooled data set, this might have resulted in an overestimation of respirable silica in the Australian cohort, as compared to respirable dust measurements done in the US. We considered the effect of this possible overestimation by using a lower conversion factor for the Australian cohort in some of the epidemiologic analyses. Results of the pooled epidemiologic analyses were virtually unchanged when this lower conversion factor was used for the Australian data.

The pooled data include silica exposure from different sources and production processes. In the overall evaluation, qualifying crystalline silica as a Group 1 carcinogen [IARC, 1997], the working group noted that carcinogenicity might depend on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs. For example, the biological activity of cristobalite particles is higher than of quartz particles and freshly crushed silica particles have a higher surface activity than aged dust particles. The presence of trace amounts of metals may enhance the surface activity or neutralize it. Also a higher relative percentage of silica in respirable dust has been postulated to be associated with a higher lung cancer risk [Muir, 1994]. Differences in dust composition are shown in Table IV.

Seven cohorts had complete occupational history information of the subjects within the plant, and changes in exposure resulting from changes in job could be taken into account. For the three Chinese cohorts, however, each subject's job history consisted of only one job title, which was defined as the 'usual job' of the subject over the whole employment period (2-digit code). Complete occupational history information was only available for a sub-set of the Chinese cohorts (in a nested case-control study) in which tungsten and tin miners had on average four jobs and pottery workers three jobs (3-digit code). Most of these jobs were similar and would have the same 2-digit code (denoting the same work area). However, for the Chinese cohort non-differential misclassification of exposure has likely occurred due to a lack of detail in the occupational history information.

The availability of historical data was considered an important inclusion criterion, since for most silica exposed industries exposure was reduced over time. Exposure assessment based on only recent measurements would therefore underestimate exposures, especially in time windows important to long latency diseases such as lung cancer. The time period for which extensive measurements were available ranged between 4 and 38 years for the included studies, but was often complemented with summary data from older sources. Most of the studies, however, did not have any

**TABLE IV.** Characteristics of Dust For Each Cohort

| | Origin of dust | Type of silica | % Silica in respirable dust | Age of the dust | Trace constituents of the dust |
|---|---|---|---|---|---|
| US | | | | | |
| Diatomaceous earth workers | Natural form of DE mined from open pits is mostly amorphous silica (1% crystalline silica). Processing to crystalline silica: calcined diatomaceous earth (10–20% crystalline silica), flux calcined DE (20–25%) [Checkoway et al., 1993] | Cristobalite in processed diatomaceous earth | Raw material: $< 0.1-4\%$; end product: 10–25% [Checkoway et al., 1993] | Processed DE is fresh dust | Processed DE is supposed to be free from contaminants. Depending on use, the product will be mixed with other materials [Seixas et al., 1997] |
| Finland | | | | | |
| Granite workers | Red granite: 41% feldspar, 36% quartz, grey granite: 38% feldspar, 31% quartz, black granite: 60% plagioclase, 20% augite [Koskela et al., 1994] | Quartz. No quartz is present in black granite, but can be present in surrounding rock | 10–30% depending on the type of granite [Koskela, 1995] | Fresh dust from quarrying and processing | |
| US | | | | | |
| Granite workers | Granite containing around 30% quartz [Davis et al., 1983] | Quartz | 9% [Theriault et al., 1974] | Fresh dust from quarrying and processing | Silicon carbide, aluminium oxide, tin oxide abrasives (used for polishing operations), tungsten carbide (present in pneumatic cutting tools) [Eisen et al., 1984] |
| US | | | | | |
| Industrial sand workers | Source: from a loose, unconsolidated granular state to hard, highly compacted rocks. Followed by crushing and milling | Quartz | 25% [Sanderson et al., 2000] | Fresh dust from crushing and milling | |
| China | | | | | |
| Pottery workers | | | 4.2% in total dust, 16.8% in respirable dust assuming 25% respirable dust in total dust | Aged dust, but heated | Nickel, cadmium [Dosemeci et al., 1993] |
| China | | | | | |
| Tin miners | | | 3.6% in total dust, 14.4% in respirable dust assuming 25% respirable dust in total dust | Fresh dust originating from mining process | Arsenic, nickel, cadmium [Dosemeci et al., 1993]; radon |
| China | | | | | |
| Tungsten miners | | | 8.3% in total dust; 33% in respirable dust assuming 25% respirable dust in total dust | Fresh dust originating from mining process | Arsenic, nickel, cadmium [Dosemeci et al., 1993]; radon |

(*Continued*)

**TABLE IV.** *(Continued)*

| | Origin of dust | Type of silica | % Silica in respirable dust | Age of the dust | Trace constituents of the dust |
|---|---|---|---|---|---|
| South Africa | | | | | |
| Gold miners | Rock containing 70–90% quartz [Hnizdo et al., 1997] | Quartz | 30% [Hnizdo and Sluis-Cremer, 1991] | Fresh dust originating from mining process | Gold and uranium-bearing minerals; radon daughters: 0.1–3.0 WL |
| US | | | | | |
| Gold miners | | Quartz | 39% in settled dust and 13% in respirable dust [Brown et al., 1986] | Fresh dust originating from mining process | Gold; radon daughters: 0–0.17 WL; arsenic: under 5 μg/m$^3$; nonasbestiform CG (cummingtonite-gruerite) (69% of all fibers), tremolite-actinolite (15%), nonasbestiform varieties (15%) [Steenland and Brown, 1995b] |
| Australia | | | | | |
| Gold miners | | Quartz | 15–25% averaging 20% relatively constant [Hewson, 1993] | Fresh dust originating from mining process | |

measurements or reports available from before the 1950s. Exposure before this time was either estimated by using the exposure of the oldest periods for which exposure measurements were available, or by modeling which took changes in dust-prevention measures into account. For some studies, a gradual decrease in exposure over time was incorporated (e.g., industrial sand workers), for others only a few cut-points for exposure decreases were introduced, (e.g., for the Vermont granite workers).

Our exposure estimates for the entire cohort over time were generally based on existing measurements, which were taken routinely or during exposure surveys. The reason for doing such measurements may have biased the overall level of exposure within a cohort, since compliance inspections focus on tasks with the highest dust exposure, while workplace surveys often include all tasks. Fortunately, in our case, exposure estimates were primarily based on routine measurements or on industrial hygiene surveys and for none of the cohorts the exposure estimates were solely based on compliance inspections.

An obvious shortcoming in this and similar studies, is the difficulty in validating the exposure estimates in the absence of a gold standard. As an indirect validation, we determined whether our exposure estimates predicted silicosis mortality. A steady increase in silicosis mortality risk by increasing cumulative exposure was apparent in the pooled analysis and in most individual cohorts, although the range in cumulative exposure differs greatly between cohorts. This shows that misclassification of exposure has clearly not obscured any exposure-response relation, but a certain level of misclassification will have occurred because estimates are job- or department-based and personal exposure factors can not be taken into account. An advantage of the retrospective cohort design is, however, that misclassification can be assumed to be nondifferential and will not generate spurious associations. While some measurement error certainly occurred in our estimates, a categorical analysis based on broad exposure groups should not be much affected by the resulting level of misclassification.

## ACKNOWLEDGMENTS

This work was supported in part by the U.S. National Institute for Occupational Safety and Health (NIOSH), the National Cancer Institute (NCI), and the US Occupational Safety and Health Agency (OSHA).

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