Review of the Epidemiology of Occupational Exposure to Cristobalite

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1 Introduction

Crystalline silica is composed of silicon and oxygen atoms arranged in a three-dimensional repeating pattern (OSHA 2013). Polymorphs or different forms of silica exist because silica tetrahedrons—pyramidal structures of four triangular sides with a silicon atom located in the center and an oxygen atom at each of the four corners—can combine in different crystalline structures (OSHA 2013). The most common form of crystalline silica is quartz (accounting for almost 12% of the earth's crust by volume), followed by cristobalite and tridymite (OSHA 2013). In the amorphous state, silicon and oxygen atoms are present in the same proportions as in quartz, cristobalite, and tridymite but are not organized in a repeating pattern (OSHA 2013).

Occupational exposure to respirable crystalline silica has been recognized to cause silicosis for centuries. These exposures also have been associated with the development of other diseases, including lung cancer, pulmonary tuberculosis, airways diseases, certain autoimmune disorders and chronic renal disease (OSHA 2013).

The current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for crystalline silica was established in 1971 and differs by crystalline silica polymorph. For quartz measured as respirable dust, the PEL in general industry is approximately equal to 100 µg/m^3 (0.1 mg/m^3) as an 8 hour time-weighted average (TWA). For cristobalite and tridymite measured as respirable dust, the PEL in general industry is approximately equal[1] to 50 µg/m^3 (0.05 mg/m^3) measured as an 8 hour TWA, i.e., half that of quartz.

OSHA recently proposed revising the permissible exposure limit (PEL) to 50 µg/m^3 (0.050 mg/m^3) as an 8-hour time-weighted average (TWA), irrespective of polymorph (Proposed Rule for Occupational Exposure to Respirable Crystalline Silica, issued September 12, 2013, 78 FR 56274).

OSHA has requested feedback and a rationale for whether a single PEL is appropriate or whether OSHA should maintain separate PELs for the different forms of respirable crystalline silica. The objective of this report is to critically review and synthesize the quality and consistency of the epidemiological evidence for health effects of occupational exposure to cristobalite, with focus on the outcomes lung cancer and silicosis.

Additionally, this report examines the epidemiological studies that evaluate the relationship between quantified estimates of exposure to cristobalite and risks of silica-related diseases to determine whether increased risks are documented below the existing PEL of 0.1 mg/m^3 (8-hr TWA) for quartz measured as respirable dust over an occupational lifetime (i.e., 45 years, or cumulative exposures less than 4.5 mg/m^3-years) and if so 2) below the current PEL of 0.05 mg/m^3 (8-hr TWA) for cristobalite measured as respirable dust over an occupational lifetime (2.25 mg/m^3-years).

[1] The current OSHA PEL (8-hr TWA) for crystalline silica as respirable quartz is expressed as a formula: (10 mg/m^3)/(% SiO_2 + 2). For cristobalite or tridymite, the PEL is one-half the value calculated from the quartz formula.

1.1 Crystalline Silica Polymorphs: Quartz, Cristobalite, and Tridymite

Alpha quartz (stable below 573 °C), commonly found in nature in minerals, rocks, and soils, is the most prevalent form of crystalline silica in the workplace (OSHA 2013). It is used in many products throughout various industries and is a common component of building materials (Madsen, Rose, et al. 1995; OSHA 2013). Cristobalite, while relatively rare in nature compared with quartz, is formed at higher temperatures (>1470 °C) (OSHA 2013). Diatomaceous earth (DE)—a mineral derived from the skeletal remains of diatoms (microscopic marine algae) deposited on marine and lake floors—is often processed by heating with flux (e.g. sodium carbonate or sodium chloride), which generates a finished product that can contain between 40–60% cristobalite (Checkoway, Heyer, et al. 1993; OSHA 2013). Cristobalite is formed during the DE calcining process by heating in a kiln (Checkoway, Heyer, et al. 1993). DE workers are also exposed to amorphous (non-crystalline) silica and quartz from open pit mining of DE (Checkoway, Heyer, et al. 1993).

DE has numerous uses, including as a filtration aid for water, foods, and beverages; as a functional additive in construction materials, paints, and insulation; and as a carrier or anticaking agent for agricultural chemicals (Checkoway, Heyer, et al. 1993). In the past, DE was cut from quarries and used as refractory bricks and as a constituent of formed insulation bricks (Seixas, Heyer, et al. 1997) that were heated in kilns above 1000 °C (Puntoni, Goldsmith, et al. 1988). In addition, pottery workers are potentially exposed to cristobalite formed during heat treatment (“firing”) in ovens (sometimes in excess of 1500 °C) (McDonald, Cherry, et al. 1995). Pottery workers are exposed to quartz dusts in most job locations up to firing.

In summary, cohort studies of workers in the diatomaceous earth, refractory ceramics, and pottery industries provide the best information on exposure to cristobalite because these populations are exposed to cristobalite formed when silica is processed under conditions of high heat. These same populations, however, are also potentially exposed to quartz from open pit mining (DE workers) and in raw materials used by refractory workers (Dong, Xu, et al. 1995) and pottery workers (McDonald, Cherry, et al. 1995). In contrast, workers in the granite, sand, or coal industries are exposed to crystalline silica primarily in the form of quartz.

2 Methods

Occupational studies addressing the health risks of cristobalite exposure were identified by reviewing the OSHA Proposed Rule for Occupational Exposure to Respirable Crystalline Silica (issued September 12, 2013) as well as conducting searches of PubMed (US National Library of Medicine).

The following keywords were used in the PubMed searches: “cristobalite”, “silicon dioxide”, “diatomaceous earth”, “epidemiology”, “silicosis”, “radiographic silicosis”, and “lung cancer”. Titles and abstracts were reviewed to identify studies that focused on potential cristobalite exposures.

In considering the health risks associated with occupational cristobalite exposures, the OSHA Proposed Rule reviewed primarily occupational cohorts exposed to DE or cristobalite formed during heating processes. These included studies of 1) DE workers in California (Checkoway,

Heyer, et al. 1993; Checkoway, Heyer, et al. 1996; Checkoway, Heyer, et al. 1997; Checkoway, Hughes, et al. 1999; Hughes, Weill, et al. 1998); 2) refractory workers in China (Dong, Xu, et al. 1995), Italy (Merlo, Costantini, et al. 1991), and the UK (Cherry, Burgess, et al. 1998); and 3) pottery workers in the UK (Cherry, Burgess, et al. 1998; McDonald, Cherry, et al. 1995).

Six additional studies not discussed in the OSHA rule were identified in PubMed searches: three occupational cohort studies addressing cristobalite exposure (Bugge, Kjaerheim, et al. 2012; Cherry, Harris, et al. 2013; Rafnsson and Gunnarsdottir 1997), one ecological study of volcanic cristobalite exposure (Higuchi, Koriyama, et al. 2012), and two reviews (Gamble 2011; Soutar, Robertson, et al. 2000). We also obtained from the IDPA an additional review on occupational cristobalite silica exposure and silicosis published online but not indexed in PubMed as of the initial drafting of this review (Mossman and Glenn 2013). Furthermore, an additional cohort study (Bugge, Foreland, et al. 2011) was identified from the references of an included study (Bugge, Kjaerheim, et al. 2012).

Information on the key features of each study were abstracted into Excel spreadsheets, including the following: study type/design, population, and location; comparison group; disease/outcome; exposure assessment (method); exposure metrics or categories; measure of effect and result (with 95% confidence interval (CI)); covariates adjusted for in analysis; likelihood of selection bias; likelihood of confounding; and overall quality. Criteria used to evaluate the quality of the studies included: 1) quantitative exposure measurement used in analyses, preferably at the individual level; 2) exposure dominated by cristobalite, versus mixed cristobalite and quartz exposure or predominant quartz exposure; 3) control for potential confounding by smoking, especially for studies of lung cancer; and 4) radiographic assessment of outcome for studies of silicosis. Studies were classified into three quality tiers (tier one being the highest and tier three being the lowest) based on whether they met the outlined quality criteria. We subsequently summarized the studies, including strengths and weaknesses, then summarized their results by disease and synthesized the evidence in this report with emphasis placed on studies of better quality (tier one).

After preliminary review, Higuchi 2012 (Higuchi, Koriyama, et al. 2012) was excluded from further consideration. This study compared lung cancer, chronic obstructive pulmonary disease (COPD), and acute respiratory disease incidence rates in a high volcanic ashfall town to a low ashfall town in Japan. Although cristobalite constituted a portion of this volcanic ash, that portion was very small (approximately 7% by weight with approximately 10% assumed to be respirable material), and the ecological study design did not provide individual estimates of exposure to cristobalite or individual-level surrogates of exposure.

The three reviews (Gamble 2011; Mossman and Glenn 2013; Soutar, Robertson, et al. 2000) and two quantitative risk assessments (Park, Stayner, et al. 2012; Rice, Park, et al. 2001) were also excluded from further consideration, as these papers do not present primary epidemiological evidence. The QRAs used the epidemiological data from the California DE cohort to calculate excess lifetime risk of lung cancer associated with exposure to crystalline silica (Rice, Park, et al. 2001) and excess lifetime risk of lung diseases other than cancer, including silicosis (Park, Rice, et al. 2002). While the studies on which the QRAs were based

were of higher quality (tier one) relative to the other studies reviewed for this report, they still lacked detailed information on smoking habits (i.e. amount or duration) such that residual confounding by smoking is possible for lung cancer.

3 Summary of Study Populations and Exposure Information

3.1 Diatomaceous earth (DE) industry

3.1.1 Initial cohort study (Checkoway et al. 1993)

Workers in the diatomaceous earth (DE) industry in Lompoc, CA were first enumerated for cohort study in an occupational cohort mortality study published in 1993. Subsequent studies updated mortality or morbidity in this initial cohort and addressed identified weaknesses related to exposure assessment and the evaluation of potential confounding factors.

Checkoway et al. (1993) followed 2,570 white men employed for at least 12 months (cumulatively) in the DE industry and at least one day during the period 1942–1987 at two specific facilities. Mortality from all causes, lung cancer, and non-malignant respiratory diseases (NMRD) was evaluated through 1987 in relation to two surrogates of cumulative exposure: duration of employment in jobs with potential for dust exposure (categories <5, 5–9, 10–19, ≥20 years) and a semi-quantitative estimate of cumulative exposure (categories <50, 50–99, 100–199, ≥200 units of exposure intensity score x years) (Checkoway, Heyer, et al. 1993).

This cumulative exposure index was derived by assigning weights (0=none, 1=low, 3=moderate, 6=high) to each job to reflect different intensities of exposure between jobs and over time. Weights were applied to intensity of exposure after review of historical documents of process and engineering changes in the plants and consultation with knowledgeable industry personnel. Work history dates were divided into five periods, selected to reflect temporal changes in dust exposure: before 1944, 1944-53, 1954-63, 1964-73, and 1974-87. Each period was assigned corresponding relative exposure weightings of 12, 6, 2, 1.5, and 1. The cumulative exposure index also accounted for the absence of respiratory protection and the percentage of crystalline silica in the materials handled over time. Cumulative exposure reflected the sum of weighted exposures over the entire working history for each employee (Checkoway, Heyer, et al. 1993).

Smoking information was available for 1113 (43%) study subjects. In order to assess confounding due to smoking, the authors used an indirect adjustment method (Axelson and Steenland 1988). The authors concluded that smoking was unlikely to explain the increased relative risks of lung cancer, especially for the highest exposure category.

3.1.2 Re-Analysis to Address Asbestos Exposure (Checkoway et al. 1996)

Checkoway 1996 (Checkoway, Heyer, et al. 1996) re-analyzed lung cancer mortality through 1987 among 2,266 white men who worked at the larger of the two facilities included in the initial analysis to account for asbestos exposure as a confounder, which was not evaluated in Checkoway 1993. Checkoway et al. (1996) reported products containing chrysotile asbestos were manufactured at the plant from the 1920s to 1977 (Checkoway, Heyer, et al. 1996). Previously, Checkoway et al. identified and conducted a separate analysis of 104 men known to have worked in asbestos mixing jobs who had been excluded from the main cohort

(Checkoway, Heyer, et al. 1993). The SMR for lung cancer for the 104 men was 3.54 based on 4 deaths.

Details of the reconstruction of asbestos exposure were provided in a separate report (Checkoway, Heyer, et al. 1996; Gibbs and Christensen 1994). Based on review of historical production records to identify jobs where asbestos was handled (including maintenance jobs) and quantities of asbestos included in mixed products, as well as measurements of fiber concentration reported from occupational hygiene measurement surveys, a quantitative index of asbestos exposure in fibers/ml (f/ml) was generated for each job (Checkoway, Heyer, et al. 1996; Gibbs and Christensen 1994). Workers first employed before 1930 were not included in the reanalysis because information on asbestos use was reliable only after 1930 (Checkoway, Heyer, et al. 1996). 89 of the 104 men known to have worked in asbestos mixing jobs whose mortality was previously reported separately from the main cohort were included. The authors chose asbestos exposure categories (0, >0-<2.7, 2.7-<6.8, ≥6.8 f/ml-years) that matched those of a study of asbestos textile workers in the US (Checkoway, Heyer, et al. 1996; Dement, Brown, et al. 1994). Exposure assessment consisted of a cross-classification according to cumulative exposure categories from the Checkoway 1993 crystalline silica index and asbestos exposure categories.

The authors concluded that asbestos exposure was not an important confounder of the association between crystalline silica and mortality from lung cancer in this cohort. Despite this conclusion, subsequent analyses (Checkoway, Heyer, et al. 1997) also attempted to assess potential confounding due to chrysotile asbestos exposure.

3.1.3 Exposure Assessment and Reconstruction (Seixas et al. 1997)

Seixas et al. (1997) (Seixas, Heyer, et al. 1997) developed quantitative exposure measures for respirable dust based on 6,395 air sampling records for the period 1948-1988 to improve on the semi-quantitative exposure estimates used by Checkoway et al. (1993; 1996) (Checkoway, Heyer, et al. 1993; Checkoway, Heyer, et al. 1996). Seixas et al. converted results obtained by particle counting (expressed as million particles per cubic foot (mppcf)) or gravimetrically from a filter cassette (expressed as mg/m^3 total) to mg/m^3 respirable dust using a conversion factor derived from data obtained by the different methods during overlapping periods at the plant (Seixas, Heyer, et al. 1997). After converting the available data to mg/m^3 respirable dust, the geometric mean (geometric standard deviation) concentrations were 0.37 (2.43) mg/m^3 during the 1950s and 0.17 (2.35) mg/m^3 during later periods (Seixas, Heyer, et al. 1997). The average estimated respirable dust concentrations for 135 jobs were 3.55 (±1.25) for the years before 1949, 1.37 (±0.48) for 1949–1953, 0.47 (±0.16) for 1954–1973, and 0.29 (±0.10) mg/m^3 for 1974–1988. Figure 1 from Seixas 1997 (below) illustrates the decrease in concentration of respirable dust over time.

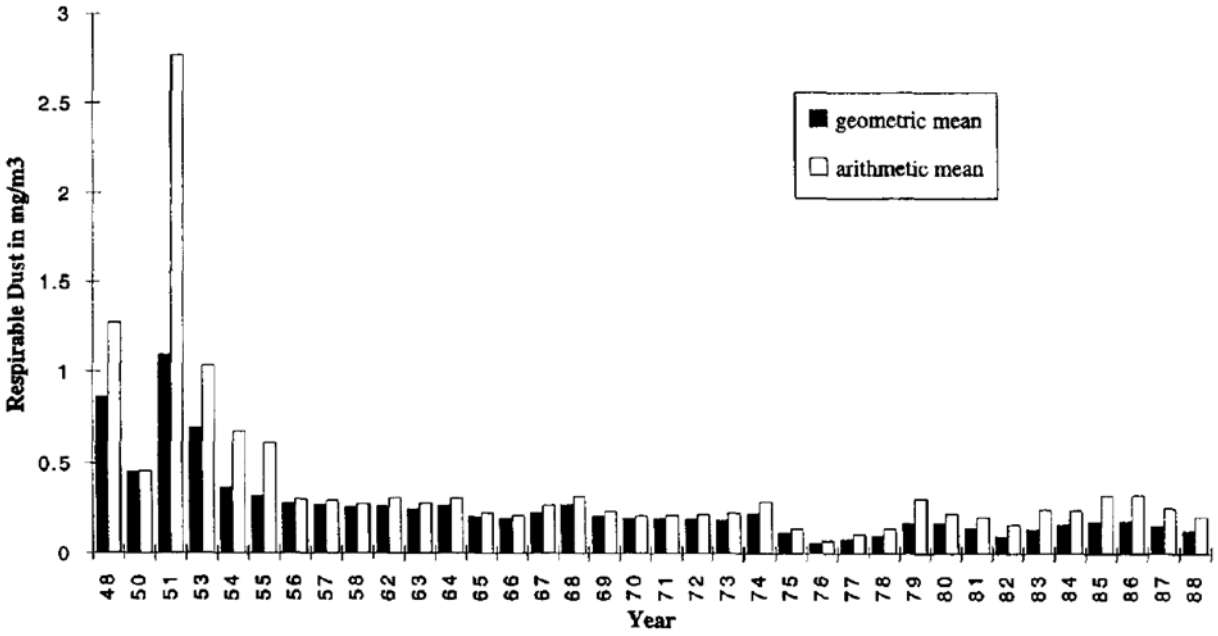

Fig. 1. Crude arithmetic and geometric mean respirable dust concentrations by year.
(Source: Seixas 1997)

Seixas et al. (1997) compared semi-quantitative exposure categories (low, medium, and high) used in Checkoway 1993 and 1996 to the quantitative estimates of job-specific means for the period 1974-1988 and found a high degree of overlap between exposure categories, revealing the potential for substantial misclassification of exposure based on expert judgment in the earlier studies by Checkoway et al. (1993, 1996) (see Figure 2 from Seixas 1997 below).

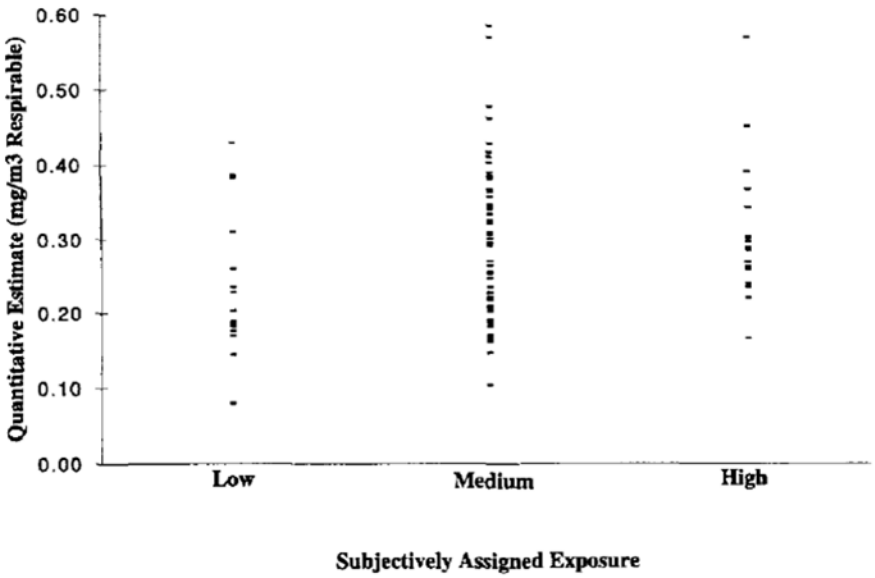

Fig. 2. Estimated job-specific means for the post-1973 period in comparison with the previously used subjective exposure assignments.

Source: Seixas 1997

Comparison of the semi-quantitative exposure categories used in Checkoway 1993 and 1996 versus the quantitative estimates developed by Seixas 1997 suggested potential exposure misclassification occurred in the early studies of the California diatomaceous earth workers (Checkoway, Heyer, et al. 1993; Checkoway, Heyer, et al. 1996). Seixas et al. concluded that it is plausible that either the subjective estimates included a high degree of measurement error, as demonstrated by the overlap of the distributions, or that the quantitative estimates are highly uncertain (and therefore inaccurate), as suggested by the wide variability within an exposure category and the lack of a difference in means between the two higher categories. In the case of misclassification (whether in the earlier studies or in Seixas 1997 (Seixas, Heyer, et al. 1997)), the exposure-response relationship would likely be biased toward the null.

3.1.4 Checkoway et al. 1997

Checkoway et al. (1997) (Checkoway, Heyer, et al. 1997) extended follow-up of 2,266 white men by seven years through 1994 and applied the exposure assessment for respirable dust developed by Seixas et al. (1997) (Seixas, Heyer, et al. 1997). Checkoway et al. used historical records, professional judgment of industry personnel, and percentages of crystalline silica in product mixes (uncalcined DE, calcined DE, and flux-calcined DE) to modify the respirable dust concentrations to estimate respirable crystalline silica concentrations. They computed cumulative respirable crystalline silica exposures as the summed products of job-specific exposure intensities and time in job (categories <0.5, 0.5–<1.1, 1.1–<2.1, 2.1–<5.0, and ≥5.0 mg/m^3-years) (Checkoway, Heyer, et al. 1997). Cumulative exposures to asbestos (used in two small operations from the 1920s-1977) in f/ml-years were estimated previously for the years since 1930 (Gibbs 1994) (Gibbs and Christensen 1994). The 1930 job-specific intensity estimates were extrapolated to earlier years of plant operation to characterize asbestos over all

relevant periods of employment (Checkoway, Heyer, et al. 1997). Three categories of cumulative asbestos exposure were used for statistical analysis: non-exposed, >0-1.20, and >1.20 f/ml-years. Checkoway et al. (1997) ran Poisson regression models for cumulative exposures to respirable crystalline silica and lung cancer mortality or radiological silicosis adjusted for cumulative exposure to asbestos (fibers/ml-years) and, consistent with their previous study (Checkoway, Heyer, et al. 1996), reported no evidence of confounding by asbestos...

Checkoway et al. (1997) and subsequent studies (Checkoway, Hughes, et al. 1999) assumed that smoking alone increased the risk of lung cancer by a factor of 20 compared with nonsmokers and applied an indirect adjustment method (Axelson and Steenland 1988) to evaluate potential confounding by smoking. The authors concluded that smoking was unlikely to account fully for the apparent dose-response relation seen between cristobalite exposure and lung cancer and highlighted the absence of consistent excesses for smoking-related diseases other than lung cancer as further evidence that substantial confounding did not occur. Furthermore, the trend of increasing lung cancer risk with exposure to crystalline silica among the subset of workers with an apparently homogeneous smoking prevalence was similar to the trend found for the entire cohort. Nevertheless, confounding or residual confounding by smoking remains possible, as detailed individual smoking data were unavailable.

3.1.5 Hughes et al. 1998

Hughes 1998, (Hughes, Weill, et al. 1998) also used the Seixas 1997 exposure assessment methods but focused solely on radiographic silicosis. The cohort included 1,809 white men for whom readable chest radiographs were available that were taken more than one month after hire (Hughes, Weill, et al. 1998). Estimates of respirable dust and crystalline silica exposure were summed to obtain cumulative exposures (mg/m^3-years) for each worker up to the time of the chest radiograph used for analyses. Cumulative exposures were divided by total years employed at time of radiography to obtain average concentrations of exposure (mg/m^3), which exhibited the same patterns over time as respirable dust levels reported previously (Hughes, Weill, et al. 1998; Seixas, Heyer, et al. 1997). Mean crystalline silica concentrations for workers with a chest radiograph for 1932-1943, 1944-1953, 1954-1973, and 1974-1994 were approximately 0.90, 0.40, 0.15, and 0.10 mg/m^3 respectively. Percentage of each worker's exposure to respirable dust comprised of crystalline silica was calculated for each year as cumulative crystalline silica exposure divided by cumulative respirable dust exposure, multiplied by 100. Mean percent crystalline silica steadily increased from approximately 25% in the early 1930s to approximately 35% in the early 1960s (indicating increased use of calcined products), then remained relatively constant. For all cohort members, quantitative estimates of exposure to asbestos (used at various times in two operations) were also derived (Checkoway, Heyer, et al. 1996; Hughes, Weill, et al. 1998). Three experienced "B" readers independently read radiographic films according to the International Labour Organisation (ILO) 1980 Classification System (Hughes, Weill, et al. 1998; ILO 1980). Films were considered positive for opacities if at least two readers judged the film to be positive for either large opacities or small opacities of profusion ≥1/0 (Hughes, Weill, et al. 1998).

With respect to potential confounding factors, the relative risk of opacities was adjusted by age. Information on smoking status (ever smoker or not) was available for 71% of workers with an

average crystalline silica exposure ≤0.50 mg/m^3. For workers with an average crystalline silica exposure >0.50 mg/m^3, who generally worked in earlier time periods, smoking status information was not generally available (no percentage reported). Among the 71% of workers with an average crystalline silica exposure ≤0.50 mg/m^3 and smoking status information available, smoking was significantly related to opacities; 0.4% (1/269) of nonsmokers had opacities, whereas 2.6% (20/756) of smokers had opacities (one-tailed p=0.01). Despite this, Hughes et al. (1998) cited previous reports on the same cohort (Checkoway, Heyer, et al. 1993; Checkoway, Heyer, et al. 1997) concluding that after adjusting for calendar year, only a minimal correlation between smoking and exposure was observed and that "an unrealistically high correlation would be needed for smoking to account for the observed relations between opacities and cumulative exposure".

3.1.6 Checkoway et al. 1999

In another re-analysis including follow-up through 1994, Checkoway et al. used Seixas 1997 (Seixas, Heyer, et al. 1997) respirable crystalline silica exposure assessment with four categories of exposure (<0.5, 0.5–<1.9, 2.0–4.9, ≥5.0 mg/m^3-years) and focused on lung cancer mortality and radiological silicosis (radiographic category ≥1/0 or large opacity) (Checkoway, Hughes, et al. 1999). The cohort again included 1,809 white men.

Smoking data to classify cohort members as ever versus never smokers were available for 58% of the 1,809 DE workers with readable chest radiographs. Percentages of ever smokers among non-silicotic workers (N=1,728) with available smoking data for the four exposure categories of crystalline silica were, respectively, 63.5%, 80.5%, 85.1%, and 78.9%. Percentages of ever smokers by exposure category among the 81 cases of silicosis were 66.7%, 100%, 100%, and 94.7%.

By applying Axelson's method of indirect adjustment for confounding, and assuming a 20-fold increased risk of lung cancer for smokers compared with nonsmokers, the authors concluded that the smoking adjusted relative risk was 1.88 among the study subjects without silicosis. Adjustment of relative risks for differences in smoking prevalence was complicated for those with silicosis because all four lung cancer deaths occurred among workers in the highest exposure stratum and none occurred among those in the lowest exposure stratum. Assuming the risk in the lowest exposure category was the same as seen for non-silicotic subjects, the smoking-adjusted relative risk for lung cancer between the highest and lowest exposure categories in subjects with silicosis would be 2.04 (no 95% CI provided because of the indirect method used). Nevertheless, there was limited statistical precision due to the relatively small number of workers with silicosis (N=81) and lung cancer deaths among silicotics (N=4).

3.1.7 DE Workers in Iceland (Rafnsson et al. 1997)

Rafnsson et al. 1997 (Rafnsson and Gunnarsdottir 1997) examined lung cancer incidence among 919 men and 423 women exposed to cristobalite while employed in the DE industry in Iceland (not cited in the OSHA proposed silica rule). Cohort members were divided into those exposed during production of diatomite and those exposed while handling the finished product during loading of ships (Rafnsson and Gunnarsdottir 1997). Personal respirable cristobalite sample records showed variation by a person's type of work and location within the factory (Rafnsson and Gunnarsdottir 1997; Reimarsson 1986). Personal sample dust measurements

from 1978 showed comparatively high levels of respirable cristobalite for packers, oven operators, shiploaders, maintenance men, and cleaners, averaging 0.6, 0.3, 0.3, 0.2, and 0.1 mg/m^3 respectively (Rafnsson and Gunnarsdottir 1997). Since then, work conditions improved. However, respirable cristobalite in personal samples from 1978-1981 ranged from 0.03-0.7 mg/m^3 in loading and from 0.02-0.5 mg/m^3 in production (Rafnsson and Gunnarsdottir 1997; Reimarsson 1986). Separate analyses were performed according to cumulative years and hours of employment. Cut points for comparison were arbitrarily chosen as 5 years and 300 hours (Rafnsson and Gunnarsdottir 1997). Because part-time work was common, hours of employment were judged a more precise indicator of exposure (Rafnsson and Gunnarsdottir 1997). The investigators allowed 5 and 9 years to elapse before follow-up began to avoid selecting subjects into different exposure groups between the analysis by cumulative years and hours of employment; (McDonald, Liddell, et al. 1980; Rafnsson and Gunnarsdottir 1997). There was very little difference in number of employees in each 5-year or 300-hour category between the 5 and 9-year lapses before start of follow-up (difference ≤2 employees).

No asbestos exposure occurred at the facility. To assess potential confounding of exposure by other possible carcinogens (not specified by the authors) at the processing plant, Rafnsson et al. (1997) conducted analyses restricting the cohort exclusively to men involved with transport and loading of ships. The Standardized Incidence Ratios for these men were slightly elevated compared with those for the total cohort (lung cancer SIR 1.62 (95% CI 0.53-3.79) vs. 1.14 (95% CI 0.37-2.65), suggesting that confounding by other possible carcinogens was not present in the total cohort. However, the number of observed lung cancers cases in the total cohort was small (5 cases) and all occurred in shiploaders).

A survey on smoking habits was administered to cohort members in 1993 via postal questionnaire. 65.0% of men and 72.1% of women responded. Results from this survey were compared to those from a national survey on smoking habits in 1990. The prevalence of smoking was lower in the DE cohort than in the general population of Iceland (26.8% vs. 33.4% for men, respectively; 23.2% vs. 31.7% for women, respectively) but similar patterns across categories of never smoked, quit smoking > 1 year ago, quit smoking < 1 year ago, smoke but not daily, and smoke daily. Thus, Rafnsson et al. (Rafnsson and Gunnarsdottir 1997) concluded that it was unlikely that smoking explained the excess of lung cancer. However, again, the number of observed cases (5) was small.

3.2 Refractory Brick Workers

3.2.1 Merlo et al. 1991

Workers in the refractory brick industry were first enumerated for cohort study of silica exposure in relation to mortality with a focus on lung cancer and respiratory diseases in 1991 with follow-up of a cohort of 1,022 white men in Genoa, Italy, employed during 1954–1977 (Merlo 1991) (Merlo, Costantini, et al. 1991). The first environmental analyses of respirable dust were performed in 1973 and 1975 (Merlo, Costantini, et al. 1991). The geometric mean concentrations of respirable dust ranged from 0.20 to 0.56 mg/m^3 (Merlo, Costantini, et al. 1991; Puntoni, Goldsmith, et al. 1988). While crystalline silica was detected in all work areas, those with the highest percentages of crystalline silica in respirable dust were grounding [*sic*], mixing, and pressing areas (64.6, 54.2, and 29.5% respectively) (Merlo, Costantini, et al. 1991). While data prior to 1973 on silica levels in the working environment are not available, exposures

are likely to have been higher before improvements in the mid-1950s (Merlo, Costantini, et al. 1991).

3.2.2 Dong et al. 1995

Dong et al. (1995) (Dong, Xu, et al. 1995) followed a cohort of 6,266 male workers (silica and clay brick workers at 11 refractory brick plants in China) employed before 1962 for mortality from 1963 through 1985. No quantitative crystalline silica or cristobalite exposure measurements or industrial hygiene data were reported. Exposure to crystalline silica was assessed by interview and examination of personnel records to determine year of first exposure (<1950, 1950–1954, 1955–1959, 1960–1962), as well as duration of exposure or years since first employment (0-9, 10-19, 20-29, ≥30 years).

3.3 Pottery Workers

3.3.1 McDonald et al. 1995

McDonald et al. (1995) (McDonald, Cherry, et al. 1995) studied a cohort of 7,020 male pottery workers born in 1916–1945 to investigate proportional mortality from lung cancer in relation to silica exposure. Since the late 1960s, airborne dust concentration measurements were made in various parts of the industry, for which extensive records exist (McDonald, Cherry, et al. 1995). Respirable dust measurements were made gravimetrically with a personal sampler and ranged from 0-800 µg/m^3 (0-0.8 mg/m^3, mostly between 100-200 µg/m^3 (0.1-0.2 mg/m^3)) (McDonald, Cherry, et al. 1995). Dust concentrations were sparse for earlier years, although some dated to the 1930s and earlier (McDonald, Cherry, et al. 1995). These earlier measurements mainly consisted of dust particle counts from impinger methods and static samplers (McDonald, Cherry, et al. 1995). For analyses, exposures were categories of duration of occupational dust exposure (<3, 3-4, 5-9, 10-19, ≥20 years).

3.3.2 UK Pottery, Refractory Brick, and Sandstone Industries (Cherry et al. 1998)

Cherry et al. (1998) (Cherry, Burgess, et al. 1998) followed a cohort of 5,115 men for mortality through 1992. Study subjects born during 1916–1945 and employed in the pottery, refractory brick, and sandstone industries in the UK were included. Since the late 1960s, airborne dust concentration measurements were made in various parts of these industries, for which extensive records exist (Burgess 1998; Cherry, Burgess, et al. 1998). Up to the 1960s, static (breathing area) sample methods were widely used in the UK for particle counting. In the 1960s, cyclone technology was introduced to collect personal samples of respirable dust for analysis of gravimetric silica mass (Cherry, Burgess, et al. 1998). Over 1,000 personal samples were identified, ranging from 0-800 µg/m^3 (0-0.8 mg/m^3) (mostly between 50-200 µg/m^3 (0.05-0.2 mg/m^3)) (Cherry, Burgess, et al. 1998). The authors identified 350 existing measurements of static sampler dust particle counts from the 1950s and 1960s (Cherry, Burgess, et al. 1998). The investigators reported that the existing personal and static measurements were from random surveys within the industry that did not appear to favor reporting exceptionally high exposures (Cherry, Burgess, et al. 1998).

To convert results from one method to another, an approach was chosen that equated 1 mppcf to 0.09 mg/m^3 respirable dust (Cherry, Burgess, et al. 1998; Rice, Harris, Jr., et al. 1984). Respiratory protective device use did not seem to have been a practice in this industry, which might otherwise have complicated exposure estimates (Burgess 1998; Cherry, Burgess, et al.

1998). The 569 individual job titles were combined into 11 major process groups with similar levels of exposure (Cherry, Burgess, et al. 1998). To tabulate a preliminary job exposure matrix, air sample results were averaged, and particle counts were converted to gravimetric mass, categorized by job and decade. The matrix was then refined using published literature and unpublished reports of dust control measures or changes to the process or work rate, especially for periods when sample results were not available. In general, an overall trend toward reduction in exposure was observed over the 60 year span with considerable variations by process and decade (Cherry, Burgess, et al. 1998). Exposures for cohort members in a pneumoconiosis subcohort and in a nested case-referent study of 52 lung cancer mortality cases and 197 matched referents were additionally tabulated as cumulative exposure categories (<2000, 2000-3999, 4000-5999, and ≥6000 $\mu g/m^3$-years (divided by 1000 in the case-referent study)), mean concentration in $\mu g/m^3$ (divided by 100 in the nested case-referent study), and duration in years (divided by 10 in the nested case-referent study).

3.3.3 Cherry et al. 2013

Cherry et al. (2013) (Cherry, Harris, et al. 2013) updated mortality through 2008 for the cohort of 5,115 men previously followed through 1992 (Cherry, Burgess, et al. 1998).

Among the studies of pottery, refractory brick, and sandstone workers described in sections 3.2 and 3.3 above, it is important to note that exposures were mostly mid-20th century, when exposure was higher, fewer protective measures were in place, and smoking prevalence was higher. In general, non-differential misclassification of exposure is possible because many past exposure assessments were based on expert judgment and incomplete measurements based on particles counts and later converted to gravimetric mass. Additionally, although assessment or adjustment was made for confounding by smoking in each of the above summarized studies, detailed information on smoking frequency, duration, or type of use is lacking, and the possibility of residual confounding by smoking remains.

3.4 Silicon Carbide (SiC) workers

3.4.1 Bugge et al. 2011

Bugge et al. (2011) (Bugge, Foreland, et al. 2011) studied mortality from non-malignant respiratory diseases among 1,687 workers employed during 1913–2003 in the silicon carbide (SiC) industry in Norway. These workers were exposed to cristobalite and other forms of silica. To assess exposure, Bugge et al. 2011 used dust measurements from surveillance and studies by the Norwegian National Institute of Occupational Health to develop a historical job exposure matrix for all job groups in each of three plants for all years since start of production (Bugge, Foreland, et al. 2011). Historical exposure levels were modelled based on total dust measurements collected from 1967 to 2005. Exposure to specific agents (i.e., cristobalite, quartz, non-fibrous SiC) was predicted using mixed effect models that were based on results from a large comparative study performed in 2002-2003. Approximately 700 parallel personal measurements of total dust, fibers, and respirable dust were collected and the respirable dust was analyzed for quartz, cristobalite and non-fibrous SiC content (Bugge, Foreland, et al. 2011; Foreland, Bye, et al. 2008). Standardized mortality ratios and incidence rate ratios from Poisson regression analyses were reported for all employees and all ever-smokers separately for the outcome obstructive lung disease as underlying (OLD-u) or contributing (OLD-uc) cause of death during 1951–2007 for workers employed during 1913–1920 by three strata of

cumulative exposure to each silica polymorph, adjusted for age and period of diagnosis. Incidence rate ratios were additionally presented for ever-smokers for OLD as underlying or contributing cause of death during 1951–2007 by log-transformed cumulative exposure to dust fractions by polymorph and employment duration, adjusted for exposure to other polymorphs, age, and period of diagnosis.

3.4.2 Bugge et al. 2012

Bugge et al. (2012) (Bugge, Kjaerheim, et al. 2012) studied lung cancer incidence among the previously defined cohort of 1,687 workers employed during 1913–2003 in the silicon carbide (SiC) industry in Norway. These workers were exposed to cristobalite and other forms of silica. Lung cancer incidence was reported by three levels of exposure to each silica polymorph using the exposure assessment previously reported (Bugge, Foreland, et al. 2011; Foreland, Bye, et al. 2008). For periods without dust measurements, exposure estimates were extrapolated backward by applying multipliers for estimated relative changes in exposure based on information about process-related and work hour changes. Estimates were produced for total dust exposure for all job groups in the three plants for all years of production from 1913 to 2005. The estimates were converted from geometric to arithmetic means and summarized in a job exposure matrix covering job groups in the three plants in the years 1913-2005 (Bugge, Kjaerheim, et al. 2012). Asbestos exposure categorized as never-exposed/ever-exposed was linked to job groups with probable asbestos exposure in relevant time periods (Bugge, Kjaerheim, et al. 2012).

4 Results of Quality Assessment of Studies

As described previously, the following criteria were used to evaluate the quality of the studies: 1) quantitative exposure measurement used in analyses, preferably at the individual level; 2) exposure dominated by cristobalite, versus mixed cristobalite and quartz exposure or predominant quartz exposure; 3) control for potential confounding by smoking, especially for studies of lung cancer; and 4) radiographic assessment of outcome for studies of silicosis. Three studies were judged of the highest quality because they included a quantitative exposure assessment in which the predominant exposure was cristobalite (Checkoway, Heyer, et al. 1997; Checkoway, Hughes, et al. 1999; Hughes, Weill, et al. 1998). Checkoway 1999 and 1997 also considered potential confounding by smoking for lung cancer (Checkoway, Heyer, et al. 1997; Checkoway, Hughes, et al. 1999) and Hughes 1998 (Hughes, Weill, et al. 1998) used radiographic criteria for silicosis diagnosis.

The second tier included six studies. Rafnsson 1997 and McDonald 1995 studied occupational cohorts predominantly exposed to cristobalite but did not evaluate risk using quantitative exposure estimates. Bugge 2011, Bugge 2012, Cherry 1998, and Cherry 2013 each used quantitative exposure estimates in analyses but studied cohorts with mixed exposures to cristobalite and other polymorphs, or predominant exposure to quartz.

The third and lowest quality tier included the remaining four studies. Checkoway 1993 and 1996 studied workers who were exposed predominantly to cristobalite, but used semi-quantitative exposure estimates based on professional judgment in analyses. These semi-quantitative exposure estimates likely misclassified actual exposure concentrations as evidenced by the

exposure assessment analysis by Seixas 1997. Merlo 1991 and Dong 1995 did not use quantitative exposures in analyses and studied workers who had h predominant exposure to quartz and fewer workers exposed to cristobalite.

Findings are summarized below by disease categories with emphasis on the studies of better quality (i.e. tier one). Nevertheless, the studies of higher quality lacked detailed information on smoking habits (i.e. amount or duration) such that residual confounding by smoking is possible. Additionally, these studies had small numbers of cases and low statistical power.

5 Findings by Disease Categories

5.1 Lung cancer mortality or incidence

Lung cancer was the primary disease outcome reported in relation to occupational cristobalite exposure. The main results (i.e., estimates of relative risk) for lung cancer mortality for the studies of better relative quality (i.e. tier one) are summarized in Table 1.

Checkoway et al. (1997) (Checkoway, Heyer, et al. 1997) updated mortality through 1994 and reported a SMR of 1.29 (95% CI 1.01–1.61) for lung cancer. Poisson regression models were fit for lung cancer and NMRD mortality by cumulative exposure to respirable crystalline silica lagged 0 and 15 years and adjusted for age, calendar year, duration of follow-up, ethnicity, and cumulative exposure to asbestos (fibers/ml-years). The rate ratio for lung cancer mortality was statistically significant only at the highest exposure category of respirable crystalline silica (≥5.0 mg/m^3-years) lagged 15 years to allow for disease latency (RR= 2.15, 95% CI 1.08–4.28).

Checkoway et al. (1999) (Checkoway, Hughes, et al. 1999) conducted additional analyses to evaluate whether the excess risk of lung cancer is limited to those with silicosis. Checkoway et al. 1999 reported lung cancer SMRs separately for workers with and without radiological silicosis according to cumulative exposure categories of respirable crystalline silica. Overall, a higher SMR for lung cancer mortality was found among subjects with silicosis (SMR 1.57, 95% CI 0.43–4.03, based on 4 lung cancer deaths) than in workers without silicosis (SMR 1.19, 95% CI 0.87–1.57, based on 48 lung cancer deaths) when compared to US mortality rates. A statistically significant (p=0.02) increasing trend for lung cancer mortality risk was seen with increasing category of cumulative exposure among those without silicosis. Among silicotics, all 4 lung cancer deaths were in the highest exposure category (>5.0 mg/m^3-years) (SMR=2.94, 95% CI 0.80 to 7.53). Among those without silicosis, the SMR was statistically significant at the highest exposure category (>5.0 mg/m^3-years) only (SMR=2.40, 95% CI 1.24–4.20) (Checkoway, Hughes, et al. 1999).

Table 1. Lung cancer mortality in higher quality studies of occupational cristobalite silica exposure

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
Checkoway 1997	Overall	77	SMR 1.29 (1.01–1.61)	Compared to US white male mortality rates
	Cumulative exposure			Cumulative exposure lagged 15 years. Internal analysis conducted using Poisson regression. Rate ratio adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic)
	<0.5 mg/m^3-years	22	RR 1.00 (referent)	
	0.5–<1.1 mg/m^3-years	12	RR 0.96 (0.47–1.98)	
	1.1–<2.1 mg/m^3-years	9	RR 0.77 (0.35–1.72)	
	2.1–<5.0 mg/m^3-years	14	RR 1.26 (0.62–2.57)	
	≥5.0 mg/m^3-years	20	RR 2.15 (1.08–4.28)	
Checkoway 1999	Workers with silicosis (Radiographic category ≥1/0)	4	SMR 1.57 (0.43–4.03)	Cumulative exposure lagged 15 years. SMR adjusted for age, calendar year
	Cumulative exposure			Cumulative exposure lagged 15 years. SMR adjusted for age, calendar year
	<0.5 mg/m^3-years	0	SMR 0 (0–12.2)	
	0.5–1.9 mg/m^3-years	0	SMR 0 (0–19.3)	
	2.0–4.9 mg/m^3-years	0	SMR 0 (0–5.32)	
	≥5.0 mg/m^3-years	4	SMR 2.94 (0.80–7.53)	
	Workers without silicosis (Radiographic category <1/0)	48	SMR 1.19 (0.87–1.57)	Cumulative exposure lagged 15 years. SMR adjusted for age, calendar year
	Cumulative exposure			

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
	<0.5 mg/m^3-years	13	SMR 1.05 (0.56–1.79)	Cumulative exposure lagged 15 years. SMR adjusted for age, calendar year
	0.5–1.9 mg/m^3-years	13	SMR 0.86 (0.46–1.48)	
	2.0–4.9 mg/m^3-years	10	SMR 1.25 (0.60–2.29)	
	≥5.0 mg/m^3-years	12	SMR 2.40 (1.24–4.20)	

SMR=Standardized Mortality Ratio; RR=Rate Ratio

Lung cancer results of studies of lower relative quality (tier two and three) among those reviewed for this report are presented in Appendix Table 1.

Rafnsson et al. (1997) (Rafnsson and Gunnarsdottir 1997) studied workers who were exposed predominantly to cristobalite but did not analyze cancer incidence using quantitative exposure estimates. When compared to national cancer incidence rates, the investigators reported a lung cancer SIR of 1.14 (95% CI 0.37–2.65) for men and women combined, based on five observed lung cancer cases. Despite small numbers and low statistical power, the authors performed additional analyses stratified by number of years worked and number of hours worked as surrogates for duration of exposure, which generated unstable SIR estimates as indicated by wide confidence intervals.

McDonald et al. (1995) (McDonald, Cherry, et al. 1995)reported a PMR of 1.22 (90% CI 1.04–1.43) for lung cancer among workers predominantly exposed to cristobalite and without recorded asbestos exposure when compared to national rates from England and Wales. No quantitative estimates of exposure were available for the analysis. When local rates (Stoke-on-Trent) were used, the PMR dropped to 1.04 (no 90% CI reported). The authors also performed a logistic regression analysis based on 75 nested case-referent pairs with chest radiographs. The lung cancer mortality odds were higher for workers with past asbestos exposure (OR=3.3, 90% CI 1.1-10.2) and with ≥10 years silica exposure (OR=1.4, 90% CI 0.7-2.7). There was no association between the odds ratio for lung cancer and the presence of small opacities on radiographs (OR=0.9, 90% CI 0.2-3.7). When the analysis was restricted to 47 pairs in which both the case and referent had a history of smoking, there was evidence that the odds of lung cancer were increased for those with previous asbestos exposure (OR=3.8, 90% CI 1.1 – 12.8) and ≥10 years of silica dust exposure in pottery work (OR= 2.8, 90% CI 1.1–7.5) but not for those with small opacities (OR=0.8, 90% CI 0.2–3.6) (McDonald, Cherry, et al. 1995).

Cherry (1998) (Cherry, Burgess, et al. 1998) reported results in relation to quantitative exposures of cumulative exposure and average exposures in analyses. Cohort members were predominantly exposed to quartz although workers assigned to firing or post-firing jobs were exposed to cristobalite and possibly tridymite. Cherry 1998 reported an SMR for lung cancer of 1.28 (95% CI 0.99–1.62) when compared to male mortality rates for Stoke-on-Trent. Results from the nested case-referent study included a significantly increased odds ratio for lung cancer of 1.66 (95% CI 1.14–2.41) per $\mu g/m^3$/100 average silica concentration lagged 10 years and adjusted for smoking. Odds ratios were not significantly increased for duration or cumulative exposure as continuous variables. The presence of small opacities was unrelated in the logistic regression analysis to lung cancer either alone (p=0.78) or after adjustment for mean concentration and smoking (p=0.08) (Cherry, Burgess, et al. 1998).

The update to Cherry et al. 1998 (Cherry, Harris, et al. 2013) used quantitative exposure estimates in analyses and followed cohort members for mortality from 1985 to 2008. When compared to Stoke-on-Trent mortality rates for the period 1993–2008, the lung cancer SMR was 1.07 (95% CI 0.92–1.25), down from SMR=1.36 (95% CI 1.07 to 1.70) for the years 1985-1992 (Cherry, Harris, et al. 2013).

Bugge et al. (2012) (Bugge, Kjaerheim, et al. 2012) also evaluated lung cancer risk in relation to quantitative exposures estimates in a cohort that had mixed exposures to cristobalite and other silica polymorphs. Bugge et al. compared lung cancer incidence to Norwegian national cancer incidence rates for men in 5-year age and period groups. The investigators also lagged exposures by 20 years to allow for lung cancer latency. Relative risk estimates increased with increasing tertile of cumulative cristobalite exposure: SIR 1.2 (95% CI 0.8–1.8) in low cristobalite tertile (0-0.028 mg/m³-years); SIR 2.0 (95% CI 1.2–3.2) in medium cristobalite tertile (0.028-0.093 mg/m³-years); and SIR 2.4 (95% CI 1.5–3.7) in high cristobalite tertile (0.093-2.7 mg/m³-years). Incidence rate ratios among ever smokers with exposure lagged 20 years also increased with increasing tertile of cumulative cristobalite exposure: IRR 1.0 (referent) in low cristobalite tertile (0-0.028 mg/m³-years); IRR 2.0 (95% CI 1.0–3.9) in medium cristobalite tertile (0.028-0.093 mg/m³-years); IRR 2.2 (95% CI 1.1–4.1) in high cristobalite tertile (0.093-2.7 mg/m³-years). After adjusting for SiC fibers and SiC particles, the IRR for cristobalite in ever smokers was reduced to 1.6 (95% CI 0.8–3.3) (Bugge, Kjaerheim, et al. 2012) from an unadjusted IRR of 1.9 (95% CI 1.2 – 2.9) for cristobalite alone. Quartz was not included in these models that adjusted for other exposure factors due to its collinearity with cristobalite. The authors reported that quartz was highly correlated with cristobalite making it difficult to disentangle of effect of quartz from the effect of cristobalite.

Checkoway et al. 1993 (Checkoway, Heyer, et al. 1993) developed semi-quantitative exposure estimates for cohort members who were predominantly exposed to cristobalite. Misclassification of exposure, which had been assessed using expert judgments, was evident by the exposure assessment analyses by Seixas 1997. Through 1987, the SMR for lung cancer was 1.43 (95% CI 1.09–1.84) when compared to mortality rates for US white males. SMRs were additionally presented by categories of year of hire, year of death, years since first employment, and age at death. Poisson regression was used for internal comparisons of cumulative exposure indices in the cohort and rate ratios were adjusted for age, calendar year, duration of follow up and ethnicity (Hispanic v. non-Hispanic). Duration of employment was lagged by 5, 10, and 15 years to account for latency. The relative risk (RR) of lung cancer mortality among workers employed for ≥20 years and employment lagged 15 years was 2.88 (95% CI 1.13–7.33) when compared to the referent group (workers with <5 years of employment). Increasing trends in relative risk of lung cancer mortality with respect to duration of employment were observed for all assumed latency intervals. On the other hand, trends in lung cancer mortality RRs for cumulative exposure to crystalline silica were strong but did not increase with latency interval.

Checkoway et al. (1996) (Checkoway, Heyer, et al. 1996) evaluated asbestos exposure as a potential confounder for lung cancer mortality. The SMR for lung cancer mortality was 1.41 (95% CI 1.05–1.85) with exposures lagged 15 years to account for disease latency and compared to US mortality rates. SMRs for the four semi-quantitative exposure index categories of increasing crystalline silica (<50, 50–99, 100–199, ≥200 units of exposure intensity score x years) among the workers not exposed to asbestos were 1.13 (95% CI 0.63–1.86), 0.87 (095% CI 0.18–2.53), 2.14 (95% CI 0.86–4.41), and 2.00 (95% CI 0.73–4.35), respectively. For workers with the highest cumulative exposure to both crystalline silica and asbestos dusts (asbestos cumulative exposure categories: 0, >0–<2.7, 2.7–<6.8, ≥6.8 f/ml-years), the lung cancer mortality SMR was 8.31 (95% CI 1.71–24.3, based on 3 observed deaths). Exposure-response relations were examined by means of internal rate comparisons with Poisson

regression modelling. After adjustment for asbestos exposure, age, calendar year, duration of follow-up, and ethnicity (Hispanic v. non-Hispanic), lung cancer mortality rate ratios for the same categories of exposure to crystalline silica lagged 15 years were: 1.00 (reference), 1.37 (95% CI 0.61–3.08), 1.80 (95% CI 0.82–3.92), and 1.79 (95% CI 0.77–4.18). The authors concluded that asbestos exposure was not an important confounder of the association between crystalline silica and mortality from lung cancer in this cohort (replicated in later cohort update studies) (Checkoway, Heyer, et al. 1996).

Merlo et al. (1991) (Merlo, Costantini, et al. 1991) reported excess mortality for lung cancer (SMR=1.51, 95% CI 1.00-2.18) among refractory brick workers with mixed exposure to cristabolite and quartz. Individual estimates of crystalline silica exposure were not available. Analysis by year of first employment generated a slightly higher SMR of 1.77 (95% CI 1.03-2.84) in the subcohort of workers first employed before 1957. For workers who were greater than 19 years since first exposure and who had worked more than 19 years of cumulative employment in the plant, increased risks were observed for lung cancer (SMR=2.01, 95% CI 1.07-3.44). The largest excess of mortality from lung cancer was observed among the subgroup of workers hired ≤1957 and who had had least 19 years since first exposure (SMR=2.24, 95% CI 1.20-3.83). Analysis by age at hire showed the lung cancer SMR decreased with increasing age at first employment (Merlo, Costantini, et al. 1991).

A statistically significantly increased mortality from lung cancer was observed by Dong et al. (1995) (Dong, Xu, et al. 1995) among refractory brick workers in China (standardized rate ratio (SRR)=1.49, $p<0.01$, no 95% CI provided). The increased lung cancer risk was attributed to the presence of silicosis (SRR=2.10, $p<0.01$ (95% CI not provided)). Among non-silicotics, there was no excess risk of lung cancer (SRR=1.11, $p>0.05$). Higher lung cancer risk was found with increasing latency (0-9, 10-19, 20-29, ≥30 years since first employment) and severity (radiological category 0, 0-1, 1, 2, and 3) of silicosis (data were not shown). Among the silicotics, there was a twofold excess of lung cancer risk among both nonsmokers and smokers (Dong, Xu, et al. 1995).

5.2 NMRD mortality

Fewer studies examined NMRD mortality than lung cancer mortality, but SMRs for NMRD were of greater magnitude than those for lung cancer. The main results (i.e., estimates of relative risk) for NMRD mortality for the studies of better relative quality (i.e. tier one) among those reviewed for this report are summarized in Table 2.

In Checkoway 1997 (Checkoway, Heyer, et al. 1997) , which had both a quantitative exposure assessment and predominant exposure to cristobalite, the SMR compared to US white male rates for NMRD mortality was 2.01 (95% CI 1.56–2.55). Poisson regression models were fit for NMRD mortality by cumulative exposure to respirable crystalline silica lagged 0 and 15 years and adjusted for age, calendar year, duration of follow-up, ethnicity, and cumulative exposure to asbestos (fibers/ml-years). The rate ratio for NMRD mortality in the highest cumulative respirable crystalline silica exposure stratum (≥5.0 mg/m3-years) was 5.35 (95% CI 2.23–12.8) with 15-year lag. NMRD mortality rose with cumulative exposure to respirable crystalline silica: the trend slope adjusted for asbestos exposure was 1.08 (95% CI 1.03–1.14).

Table 2. NMRD mortality in studies of occupational cristobalite silica exposure of higher quality

Study	Exposure category/strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Checkoway 1997	Overall	67	SMR 2.01 (1.56–2.55)	Compared to US white male mortality rates. Respiratory diseases except pneumonia, infections
	Cumulative exposure <0.5 mg/m^3-years	7	RR 1.00 (referent)	Cumulative exposure not lagged. Rate ratio adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic)
	0.5–<1.1 mg/m^3-years	8	RR 1.52 (0.55–4.20)	
	1.1–<2.1 mg/m^3-years	10	RR 1.98 (0.75–5.22)	
	2.1–<5.0 mg/m^3-years	12	RR 2.34 (0.91–6.00)	
	≥5.0 mg/m^3-years	30	RR 4.79 (2.01–11.9)	
	Cumulative exposure <0.5 mg/m^3-years	10	RR 1.00 (referent)	Cumulative exposure lagged 15 years. Rate ratio adjusted for age, calendar year, duration of follow-up, and ethnicity (Hispanic vs. non-Hispanic)
	0.5–<1.1 mg/m^3-years	9	RR 0.96 (0.47–1.98)	
	1.1–<2.1 mg/m^3-years	8	RR 0.77 (0.35–1.72)	
	2.1–<5.0 mg/m^3-years	13	RR 1.26 (0.62–2.57)	
	≥5.0 mg/m^3-years	27	RR 5.35 (2.23–12.8)	

SMR=Standardized Mortality Ratio; RR=Rate Ratio

NMRD mortality results of studies of lower relative quality (tier two and three) among those reviewed for this report are presented in Appendix Table 2.

Bugge et al. (2011), which used quantitative exposure estimates in analyses but studied cohorts with mixed exposures to cristobalite and other polymorphs, observed an increased risk of mortality from respiratory diseases, SMR 1.6 (95% CI 1.3-2.0, 91 cases) (Bugge, Foreland, et al. 2011). Relative risk estimates increased with increasing tertile of cumulative cristobalite exposure, adjusting for age (</≥75 years) and period of diagnosis (</≥1 January 1990): SMR 1.7 (95% CI 0.9–3.0) in low cristobalite tertile 0–10.3 μg/m^3-yrs (0–0.0103 mg/m^3-yrs); SMR 1.8 (1.0–3.0) in medium cristobalite tertile 10.4–47.6 μg/m^3-yrs (0.0104–0.0476 mg/m^3-yrs); SMR 2.4 (1.6–3.7) in high cristobalite tertile ≥47.7 μg/m^3-yrs (≥0.0477 mg/m^3-yrs).

Cherry et al. (1998) (Cherry, Burgess, et al. 1998), which used quantitative exposures in analyses but had cohort members with mixed exposures to cristobalite and other silica polymorphs, reported an SMR for NMRD for the period 1985-1992 compared with regional Stoke-on-Trent rates of 2.04 (95% CI 1.55–2.65).

Subsequently, Cherry et al. (2013), which similarly used quantitative exposure estimates in analyses but studied cohorts with mixed exposures to cristobalite and other polymorphs, reported a lower SMR for NMRD for the later period 1993-2008 compared with regional Stoke-on-Trent rates of 1.27 (1.11-1.45) (Cherry 2013) (Cherry, Harris, et al. 2013) .

Merlo et al. (1991) (Merlo, Costantini, et al. 1991), which did not use quantitative exposures in analyses and did not have cohort members with predominant exposure to cristobalite, observed excess mortality for respiratory tract diseases (SMR=2.41, 95% CI 1.72-3.28). Analysis by year of first employment revealed a slightly higher SMR in the subcohort of workers first employed before 1957 (SMR of 3.15 (95% CI 2.19-4.38)). After a latency period of 19 years in the subgroup of workers with more than 19 years of cumulative employment in the plant, the nonmalignant respiratory diseases SMR was 3.89 (95% CI 2.59-5.63) and was similar (SMR=4.03, 95% CI 2.68-5.83) among the subgroup of workers hired ≤1957. Analysis by age at hire showed decreasing respiratory tract diseases SMR with increasing age at first employment.

In Checkoway 1993 (Checkoway, Heyer, et al. 1993), the SMR for NMRD (excluding infectious diseases and pneumonia) was 2.59 (95% CI 1.96–3.36) (additionally presented in Checkoway 1993 by categories of year of hire, year of death, years since first employment, and age at death).

5.3 Silicosis

While silicosis was examined as a secondary endpoint and stratification variable in some of the lung cancer mortality studies, very few silicosis-specific studies were located. The main results (i.e., estimates of relative risk) for silicosis for the studies of better relative quality (i.e. tier one) among those reviewed for this report are summarized in Table 3.

In Hughes 1998 – the only study with quantitative exposure assessment of silicosis risk – 81 workers out of 1,809 (4.5%) were judged to have opacities on chest radiographs (Hughes 1998) (Hughes, Weill, et al. 1998). Relative risk of opacities, adjusted for age, increased significantly with cumulative exposure to crystalline silica (Hughes, Weill, et al. 1998) (see Table 3 below).

Concentration of respirable crystalline silica was highly correlated with period of hire (>0.50 mg/m^3 with hired <1950 and ≤0.50 mg/m^3 with hired ≥1950). After accounting for cumulative exposure, concentration of respirable crystalline silica to which workers were exposed was an important determinant of risk. Workers with an average exposure to crystalline silica of ≤0.50 mg/m^3 (or hired ≥ 1950) (cumulative exposure to crystalline silica of 2.0 mg/m^3-years) had a cumulative risk of opacities of approximately 1.1%. Workers with an average exposure >0.50 mg/m^3 (or hired <1950) had a corresponding cumulative risk of 3.7%. The authors concluded that these findings indicate an exposure-response relationship between cumulative exposure to crystalline silica and radiographic opacities (Hughes, Weill, et al. 1998).

Checkoway et al. (1999) (Checkoway, Hughes, et al. 1999)assessed radiological silicosis, but used it only as a stratification variable for analyses of lung cancer mortality (see Table 1).

Table 3. Silicosis risk in studies of occupational cristobalite silica exposure of higher relative quality

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
Hughes 1998	Cumulative crystalline silica			
	≤1 mg/m^3-years	6	RR 1.00 (referent)	Poisson regression, risk estimates adjusted for age
	>1-≤3 mg/m^3-years	17	RR 4.35 (1.7–11.1)	
	>3-≤6 mg/m^3-years	30	RR 20.13 (8.2–49.7)	
	>6 mg/m3-years	28	RR 40.37 (16.1–101.3)	

RR=Relative Risk
*NR=Not Reported

Silicosis results of studies of lower relative quality (tier two and three) among those reviewed for this report are presented in Appendix Table 3.

Cherry et al. (1998)— which used quantitative exposures in analyses but had cohort members with mixed exposures to cristobalite and other polymorphs—reported 64 cases of pneumoconiosis out of the 1,080 men employed at least 10 years who had started working in the industry before 1960 in the subcohort (5.9% prevalence). Of those with abnormal radiographs, the year born and year started work were earlier than of those whose radiographs were normal (ILO score ≤1/0) (Cherry, Burgess, et al. 1998). Of those with first radiograph ≥2/1, year started work was earlier than of those with first radiograph ILO score of 1 (1/0, 1/1, or 1/2), and the opacities were detected after a shorter period of employment (Cherry, Burgess, et al. 1998). Prevalence of small opacities increased with cumulative exposure category: none were observed among 109 workers in the <2000 μg/m^3-years category; of the 449 with exposures 2000-3999 μg/m^3-years, 2.0% had small opacities; of the 257 with exposures 4000-5999 μg/m^3-years, 6.4% had small opacities; and for the 225 with exposure ≥6000 μg/m^3-years, there was a 16.0% prevalence of small opacities (Cherry, Burgess, et al. 1998).

The prevalence of small opacities among non-smokers was about half that among those who had ever smoked (Cherry, Burgess, et al. 1998). Separate odds ratios were calculated for cumulative exposure, duration, and average concentration (cumulative exposure divided by duration) before and after adjustment for smoking (Cherry, Burgess, et al. 1998) (see Appendix Table 3). Entered as continuous variables, duration of exposure was not significantly related to radiographic score, but cumulative exposure and average concentration were both strongly related to the presence of small opacities (Cherry, Burgess, et al. 1998). Inclusion of smoking (itself associated with presence of small opacities, OR 2.28 (95% CI 1.02-5.10)) marginally reduced the size of the exposure effect in all analyses (Cherry, Burgess, et al. 1998). Working in firing and post-firing jobs at the potteries did not increase prevalence of radiographic changes (OR 0.83, 95% CI 0.41-1.67) (Cherry, Burgess, et al. 1998).

Checkoway et al. (1993)—which used semi-quantitative exposures in analyses and had cohort members with predominant exposure to cristobalite but had likely misclassification of exposure measurements (based on subjective judgments), as evidenced by the exposure assessment analyses by Seixas 1997—reported that within the subcategory of NMRD mortality (not including pneumonia and infectious diseases, N=56, SMR 2.59 (95% CI 1.96-3.36)), there were 17 deaths from pneumoconiosis, as listed on death certificates (including 5 with silicosis, 5 with DE pneumoconiosis, and 7 with pneumoconiosis). A separate SMR for silicosis was not reported. Checkoway et al. (1997) reported that within the subcategory of NMRD mortality (respiratory diseases except pneumonia infections, N=67, SMR 2.01 (95% CI 1.56–2.55)), there were 27 deaths with underlying causes indicative of pneumoconiosis or silicosis, as listed on death certificates (including 7 with silicosis, 5 with diatomaceous earth pneumoconiosis, 1 with silicosis and asbestosis, 9 with pneumoconiosis (not otherwise specified), 4 with pulmonary fibrosis, and 1 with idiopathic pulmonary fibrosis).

5.4 Other diseases

For reference, summary tables are presented below for other outcomes highlighted in the OSHA proposed rule for which information was available from the studies included in this review. The

main results (i.e., estimates of relative risk) for all-cause mortality for the studies of better relative quality (i.e. tier one) among those reviewed for this report are summarized in Table 4. All-cause mortality results of studies of lower relative quality (tier two and three) among those reviewed for this report are presented in Appendix Table 4. Similarly, the main results (i.e. estimates of relative risk) for kidney diseases for the studies of better relative quality (i.e. tier one) among those reviewed for this report are summarized in Table 5. Kidney diseases results of studies of lower relative quality (tier two and three) among those reviewed for this report are presented in Appendix Table 5.

Table 4. All-cause mortality risk in studies of occupational cristobalite silica exposure of higher relative quality

Study	Exposure category/ strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Checkoway 1997	Overall	749	SMR 1.02 (0.94–1.09)	Compared to US white male mortality rates

SMR=Standardized Mortality Ratio

Table 5. Kidney disease risk in studies of occupational cristobalite silica exposure of higher relative quality

Study	Exposure category/ strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Checkoway 1997	Genitourinary diseases	10	SMR 1.06 (0.51–1.94)	Compared to US white male mortality rates.
	Kidney cancer	3	SMR 0.70 (0.14–2.04)	Compared to US white male mortality rates.

SMR=Standardized Mortality Ratio

6 Discussion, Synthesis, and Conclusions

Few occupational studies have addressed disease risks in relation to respirable cristobalite exposure and those that have are limited by small cohort sizes. The highest quality studies examine disease risk according to categories of quantitative estimates of crystalline silica exposure where the predominant exposure is known to be cristobalite, such as diatomaceous earth workers (e.g., Checkoway 1997, Hughes 1998, Checkoway 1999). For lung cancer and NMRD, indirect methods of adjusting for smoking were applied by study investigators. In addition, the California DE worker study evaluated asbestos exposure as a potential confounder in the lung cancer analysis. Despite these considerations of potential confounding factors, these studies report results for essentially a single cohort of workers for which mortality or disease incidence was updated over time. Therefore, too few studies of high quality exist on which to assess risks associated with cristobalite exposure (as compared to quartz exposure). Even among the studies of higher relative quality among those reviewed for this report, concomitant exposure to quartz was possible among those exposed predominantly to cristobalite. Many other studies of lower relative quality (i.e. tier two and three) among those reviewed for this report included cohort members with mixed exposures to cristobalite and quartz or predominantly quartz.

Thus, regardless of outcome studied, there is insufficient epidemiological evidence to support a lower PEL for cristobalite versus quartz. For lung cancer, the relative risk estimates among workers exposed predominantly to cristobalite (SMR=1.3, 95% CI 1.0 – 1.6 for DE workers) do not differ consistently or substantively from study cohorts in which the workers were exposed to crystalline silica from quartz (SMR=1.4, 95% CI 1.0 – 2.0 for Finnish granite workers; SMR=1.2, 95% CI 1.0 – 1.3 for US granite workers; SMR=1.6, 95% CI 1.2 – 1.9 for US industrial sand workers; SMR=1.1, 95% CI 0.84 – 1.4 for China pottery workers; SMR=2.1, 95% CI 1.7 – 2.6 for China tin workers; SMR=1.2, 95% CI 1.0 – 1.4 for US gold miners; and SMR=1.8, 95% CI 1.5 – 2.1 for Australian gold miners) (as summarized by Steenland et al. 2001 (Steenland, Mannetje, et al. 2001)).

Additionally, the small number, modest size, and overall absence of a quantitative exposure assessment in most of the studies reviewed limit the ability to determine the specific level of exposure to cristobalite that is associated with an increased risk of each of the diseases related to crystalline silica exposure.

For the evaluation of lung cancer – for which there is the greatest number of published studies – questions of confounding by smoking and occupational asbestos exposure remain. Nevertheless, most studies demonstrate increased risks of lung cancer with higher categories of crystalline silica exposure, with no remarkable differences seen among cohorts more likely exposed to cristobalite than to quartz (see Steenland et al. 2001 (Steenland, Mannetje, et al. 2001) for a summary of lung cancer risk estimates in cohorts exposed to quartz).

Although the majority of the studies used a cohort study design, many were limited to SMR analyses, which rely on an external referent group and generally are best suited for evaluating the presence of an excess of observed lung cancer deaths. When excess lung cancers are detected, additional analyses with internal comparison groups are preferred for evaluating the

exposure-disease relationships, especially where confounding (such as by smoking and asbestos exposure in lung cancer) is possible. There are few relevant studies with quantitative crystalline silica exposure assessments where cristobalite is prevalent, likely because exposure to cristobalite is far less common than exposure to quartz. Additionally, while there are multiple studies of workers in the DE industry, they used the same base cohort, thus there are few independent observations and consequently, limited opportunity for comparison of findings across studies within and across industries.

Among studies of higher relative quality among those reviewed for this report with quantitative exposure assessment for individual cohort members, clear excesses of lung cancer mortality occurred at concentrations of ≥5.0 mg/m^3-years respirable silica (Checkoway, Heyer, et al. 1997) and ≥5.0 mg/m^3-years respirable silica among non-silicotics (Checkoway, Hughes, et al. 1999). Among a study of medium relative quality compared with the others reviewed for this report with quantitative exposure assessment for individual cohort members, excesses of lung cancer mortality occurred in the second and third cumulative cristobalite exposure tertiles (0.028-0.093 mg/m^3-years and 0.93 – 2.7 mg/m^3-years, respectively) (Bugge, Kjaerheim, et al. 2012). The pattern and magnitude of standardized incidence ratios across cristabolite exposure tertiles could not be distinguished from the pattern and magnitude of standardized incidence ratios seen across quartz exposure tertiles within the Bugge et al. cohort. The effect of cristabolite exposure could not be distinguished from the effect of quartz exposure because of the high correlation between quartz and cristabolite exposures. In addition, although excess lung cancer risk was observed at lower reconstructed estimates of cumulative cristabolite exposure in this study than the DE worker study, the magnitude of the risk estimates was similar between the studies. Whether this reflects actual differences in exposure levels between the cohorts or reflects methodological limitations of the exposure assessment in Bugge et al. cannot be determined.

Among studies of higher relative quality among those reviewed for this report, excesses of non-malignant respiratory disease occurred at concentrations of ≥ 2.1-<5 mg/m^3-years (Checkoway, Heyer, et al. 1997). Observable excesses of opacities (silicosis) occurred at concentrations greater than the category >1-≤3 mg/m^3-years in the only study with quantitative exposure assessment of silicosis risk in the cohort of workers (Hughes, Weill, et al. 1998).

In general, although there was low statistical power in most studies, there were observable trends (especially with longer latency intervals or lags of exposure) for increasing duration of exposure, earlier decade or period of exposure, and increasing cumulative exposure.

While the OSHA proposed rule emphasized increased risk of lung cancer mortality with occupational exposure to respirable cristobalite, several studies suggest that the increase in lung cancer risk is driven by a positive diagnosis of radiographic silicosis resulting from exposures at historically higher levels than the current PEL. A recent review not discussed in the OSHA proposed rule summarizes the literature on silicosis risk in relation to occupational cristobalite exposure (Mossman and Glenn 2013). From the quantitative exposure data that does exist from studies examining other diseases, it is probable that until the middle of the last century, crystalline silica exposures were poorly controlled, and even after the advent of OSHA

exposure limits, compliance and enforcement of the PEL in earlier years of its existence was likely poor in some industries.

Overall, the evidence for an association between occupational exposure to respirable crystalline silica (mainly cristobalite) and lung cancer among non-silicotics is weak, or lacking. While there is stronger evidence of an association between occupational exposure to silica and lung cancer among silicotics, it remains unclear whether this increased risk for both diseases resulted from much higher exposures to crystalline silica decades prior to the epidemiological studies reporting increased risks. Direct relevance to whether such risks persist at levels below 100 $\mu g/m^3$ or even below 50 $\mu g/m^3$ may not be answerable from such studies where exposures were often orders of magnitude greater and only crudely measured, if at all. Exposure assessment and inadequate measurement of potential confounding variables such as smoking prevents a conclusion that silica itself causes lung cancer. There is consistent evidence of an association between occupational exposure to respirable cristobalite and non-malignant respiratory diseases, and some evidence of increased risk of lung cancer at very high exposure levels.

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Appendix

Additional Tables of Results for Studies in Lower Quality Tier

Appendix Table 1. Lung cancer mortality or incidence in studies of occupational crystalline silica exposure of lower relative quality

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
Rafnsson 1997	Overall	5	SIR 1.14 (0.37–2.65)	Compared to Icelandic male and female rates
	Number of years worked			9 year interval before start of follow-up
	<5 years	2	SIR 1.19 (0.14–4.30)	
	≥5 years	3	SIR 2.70 (0.56–7.90)	
	Number of hours worked			9 year interval before start of follow-up
	<300 hours	2	SIR 1.29 (0.16–4.65)	
	≥300 hours	3	SIR 2.42 (0.50–7.07)	
McDonald 1995	Overall	122	PMR 1.24 (1.06–1.44)	Compared to England and Wales mortality rates. 90% CI
	With pneumoconiosis	7	PMR 1.75 (0.70–3.60)	90% CI
	Without pneumoconiosis	115	PMR 1.23 (1.05–1.44)	
	Workers without recorded asbestos exposure	112	PMR 1.22 (1.04–1.43)	90% CI
	Overall	122	PMR 1.04 (no 90% CI)	Compared to regional Stoke-on-Trent mortality rates
Bugge 2012	Cumulative exposure to cristobalite			Compared to Norwegian male rates. Cumulative exposure lagged 20 years
	0–0.028 mg/m³-years	25	SIR 1.2 (0.8–1.8)	
	0.028–0.093 mg/m^3-years	17	SIR 2.0 (1.2–3.2)	
	0.093–2.7 mg/m³-years	20	SIR 2.4 (1.5–3.7)	
	Cumulative exposure to cristobalite 0–0.028 mg/m³-years	21	IRR 1.0 (referent)	Cumulative exposure lagged 20 years. Adjusted for age (0–54/55–74/≥75)

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
	0.028–0.093 mg/m^3-years	18	IRR 2.0 (1.0–3.9)	
	0.093–2.7 mg/m^3-years	19	IRR 2.2 (1.1–4.1)	
	Ever smokers exposed to cristobalite	58	IRR 1.6 (0.8–3.3)	Cumulative exposure log-transformed. Adjusted for age, SiC fibers, SiC
Cherry 1998	Overall	68	SMR 1.28 (0.99–1.62)	Compared to England and Wales mortality rates; 1985–1992
Cherry 2013	Overall	76	SMR 1.36 (1.07–1.70)	Compared to regional Stoke-on-Trent mortality rates; 1985–1992
	Overall	167	SMR 1.07 (0.92–1.25)	Compared to regional Stoke-on-Trent mortality rates; 1993–2008
	Mean exposure to respirable silica** < 0.1 mg/m^3	117 NR	HR 1.0 (referent)	Internal analysis using Cox regression with age at last contact as time scale; hazard ratios adjusted for smoking, non-smokers excluded; 1985-2008
	0.1 – < 0.15 mg/m^3	NR	HR 1.07 (0.65 – 1.74)	
	0.15 – < 0.2 mg/m^3	NR	HR 0.76 (0.43 – 1.32)	
	≥ 0.2 mg/m^3	NR	HR 0.96 (0.58 – 1.60)	
Checkoway 1993	Overall	59	SMR 1.43 (1.09–1.84)	Compared to US white male mortality rates
	Duration of employment <5 years	31	RR 1.00 (referent)	Duration of employment lagged 15 years. Relative risk adjusted for age, calendar year duration of follow-up, ethnicity (Hispanic v non-Hispanic)
	5-9 years	9	RR 1.29 (0.60–2.76)	
	10-19 years	13	RR 2.00 (1.01–3.95)	
	≥20 years	6	RR 2.88 (1.13–7.33)	

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
	Semi-quantitative cumulative exposure (intensity score *x* years) <50 units	23	RR 1.00 (referent)	Cumulative exposure lagged 15 years. Relative risk adjusted for age, calendar year duration of follow-up, ethnicity (Hispanic v non-Hispanic)
	50–99 units	8	RR 1.19 (0.52–2.73)	
	100–199 units	9	RR 1.37 (0.61–3.06)	
	≥200 units	19	RR 2.74 (1.38–5.46)	
Checkoway 1996	Overall	52	SMR 1.41 (1.05–1.85)	Compared to US white male mortality rates
	Semi-quantitative cumulative exposure (intensity score *x* years) <50 units	NR	RR 1.00 (referent)	Cumulative exposure lagged 15 years. Rate ratio adjusted for age, calendar year duration of follow-up, ethnicity (Hispanic v non-Hispanic), asbestos lagged 15 years
	50–99 units	NR	RR 1.37 (0.61–3.08)	
	100–199 units	NR	RR 1.80 (0.82–3.92)	
	≥200 units	NR	RR 1.79 (0.77–4.18)	
Merlo 1991	Overall	28	SMR 1.51 (1.00–2.18)	Compared to Italian male mortality rates
	Year first employed ≤1957	17	SMR 1.77 (1.03–2.84)	
	>1957	11	SMR 1.23 (0.61–2.20)	
	Years since first exposure, years length employment ≤19 years, ≤19 years	7	SMR 1.05 (0.42–2.16)	
	>19 years , ≤19 years	8	SMR 1.75 (0.75–3.46)	

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
	>19 years, >19 years	13	SMR 2.01 (1.07–3.44)	
	Age at hire ≤29 years	10	SMR 1.89 (0.91–3.48)	
	30–39 years	8	SMR 1.54 (0.67–3.04)	
	≥40 years	10	SMR 1.24 (0.56–2.28)	
Dong 1995	Overall	65	SRR 1.49 (p<0.01)	Compared to population of Chinese male steel workers' rates
	Workers with silicosis	35	SRR 2.10 (p<0.01)	
	Workers without silicosis	30	SRR 1.11 (no p-val)	
	Duration of exposure 0–9 years	2	SRR 0.88 (no p-val)	
	10–19 years	11	SRR 0.76 (no p-val)	
	20–29 years	35	SRR 1.77 (p<0.01)	
	≥30 years	17	SRR 2.39 (p<0.01)	

SIR=Standardized Incidence Ratio; SMR=Standardized Mortality Ratio; IRR=Incidence Rate Ratio; PMR=Proportional Mortality Ratio; RR=Relative Risk; SRR=Standardized Rate Ratio

*NR=Not Reported

**Authors reported cumulative exposure was not related to lung cancer or any other outcome studied (hazard ratios not reported).

Appendix Table 2. NMRD mortality in studies of occupational crystalline silica exposure of lower relative quality

Study	Exposure category/strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Bugge 2011	Obstructive lung diseases as underlying cause of death (OLD-u) Cumulative exposure to cristobalite 0–10.3 µg/m^3-yrs (0–0.0103 mg/m^3-yrs)	45 NR	SMR 1.7 (0.9–3.0)	Compared to male incidence rates for Norway. 1951-2007
	10.4–47.6 µg/m^3-yrs (0.0104–0.0476 mg/m^3-yrs)	NR	SMR 1.8 (1.0–3.0)	
	≥47.7 µg/m^3-yrs (≥0.0477 mg/m^3-yrs)	NR	SMR 2.4 (1.6–3.7)	
Cherry 1998	Overall	57	SMR 2.04 (1.55–2.65)	Compared to Stoke-on-Trent rates; 1985-1992
Cherry 2013	Overall	217	SMR 1.27 (1.11-1.45)	Compared to regional Stoke-on-Trent mortality rates; 1993–2008
	Chronic Obstructive Pulmonary Disease Mean exposure to respirable silica** < 0.1 mg/m^3	108 NR	HR 1.0 (referent)	Internal analysis using Cox regression with age at last contact as time scale; hazard ratios adjusted for smoking, non-smokers excluded;
	0.1 – < 0.15 mg/m^3	NR	HR 1.58 (0.88–2.87)	
	0.15 – < 0.2 mg/m^3	NR	HR 0.98 (0.57–1.68)	

Study	Exposure category/strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
	≥ 0.2 mg/m^3	NR	HR 0.92 (0.55–1.56)	1985-2008
Merlo 1991	Overall	40	SMR 2.41 (1.72–3.28)	Compared to Italian male mortality rates
	Year first employed			
	≤1957	35	SMR 3.15 (2.19–4.38)	
	>1957	5	SMR 0.91 (0.30–2.12)	
Checkoway 1993	Overall	56	SMR 2.59 (1.96–3.36)	Compared to US white male mortality rates. NMRD excluding infectious diseases and pneumonia
	Duration of employment			
	<5 years	26	RR 1.00 (referent)	Duration of employment lagged 15 years.
	5-9 years	11	RR 1.80 (0.87-3.74)	Relative risk adjusted for age, calendar year duration of follow-up, ethnicity (Hispanic v non-Hispanic)
	10-19 years	13	RR 1.89 (0.94-3.80)	
	≥20 years	6	RR 1.82 (0.71-4.66)	
	Semi-quantitative cumulative exposure (intensity score *x* years)			
	<50 units	19	RR 1.00 (referent)	Cumulative exposure lagged 15 years.
	50–99 units	6	RR 1.13 (0.44-2.93)	Relative risk adjusted for age, calendar year duration of follow-up, ethnicity (Hispanic v non-Hispanic)
	100–199 units	9	RR 1.58 (0.69-3.63)	
	≥200 units	22	RR 2.71 (1.35-5.46)	

SMR=Standardized Mortality Ratio; RR=Relative Risk; HR=Hazard Ratio

*NR=Not Reported

**Authors reported cumulative exposure was not related to lung cancer or any other outcome studied (hazard ratios not reported).

Appendix Table 3. Odds of silicosis in studies of occupational cristobalite silica exposure of lower relative quality

Study	Exposure category/strata (if applicable)	Number of Observations*	Measure of Effect (95% CI or p-value)	Notes
Cherry 1998	Cumulative exposure/1000 (µg/m^3-y)	64	OR 1.37 (1.24–1.53)	Small parenchymal opacities (≥1/0). Adjusted for ever or never smoked
	Mean concentration/100 (µg/m^3)	64	OR 2.66 (1.94–3.66)	Small parenchymal opacities (≥1/0). Adjusted for ever or never smoked
	Duration/10 (years)	64	OR 1.08 (0.83–1.405)	Small parenchymal opacities (≥1/0). Adjusted for ever or never smoked

OR=Odds Ratio

Appendix Table 4. All-cause mortality in studies of occupational crystalline silica exposure of lower relative quality

Study	Exposure category/ strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Bugge 2011	Overall	788	SMR 1.1, CI 1.0 to 1.2	Compared with Norway mortality rates
Cherry 1998	Overall	470	SMR 1.15 (1.05–1.26)	Compared with Stoke-on-Trent rates; 1985-1992
Cherry 2013	Overall	1405	SMR 1.01 (0.96-1.06)	Compared with Stoke-on Trent rates; 1993-2008
Merlo 1991	Overall	243	SMR 1.10 (0.97–1.25)	Compared to Italian male mortality rates
Dong 1995	Overall	871	SRR 1.44 (p<0.01)	Compared to population of Chinese male steel workers' rates
Checkoway 1993	Overall	628	SMR 1.12 (1.03–1.21)	Compared to US white male mortality rates

SMR=Standardized Mortality Ratio; SRR=Standardized Rate Ratio

Appendix Table 5. Kidney diseases in studies of occupational crystalline silica exposure of lower relative quality

Study	Exposure category/ strata (if applicable)	Number of Observations	Measure of Effect (95% CI or p-value)	Notes
Rafnsson 1997	Kidney cancer	1	SIR 0.60 (0.02-3.34)	Compared to Icelandic male and female rates
Cherry 2013	Renal cancer	7	SMR 1.36 (1.07-1.70)	Compared to rates for Stoke-on-Trent; 1985-1992
	Renal cancer	12	SMR 1.10 (0.57-1.92)	Compared to rates for Stoke-on-Trent; 1993-2008
Checkoway 1993	Genitourinary diseases overall	10	SMR 1.42 (0.68–2.61)	Compared to US white male mortality rates.
	Glomerulonephritis: Renal failure	2	SMR 3.17 (0.38–11.5)	
	Chronic nephritis	4	SMR 1.21 (0.33–3.10)	
	Kidney cancer	2	SMR 0.65 (0.08–2.35)	Compared to US white male mortality rates. Kidney cancer

SIR=Standardized Incidence Ratio; SMR=Standardized Mortality Ratio