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Quality based critical review (QBCR) of the epidemiological literature on silica, silicosis, tobacco smoking and lung cancer

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Quality based critical review (QBCR) of the epidemiological literature on silica, silicosis, tobacco smoking and lung cancer

Abstract

The potential relationship between silica, silicosis and lung cancer was examined in many epidemiological studies. Interpretation of study results is often difficult due to insufficient assessment of exposure and potential confounders (especially tobacco smoking) as well as other deficiencies in methods.

The present publication summarizes the relevant epidemiological studies selected based on specific quality criteria. The analysis of these studies considers the quality of exposure data, possible confounders and the influence of the status of silicosis and smoking.

Overall, these studies of relatively high quality demonstrate an increased risk for lung cancer among occupational groups with high crystalline silica exposure, accounting for the potential influence on the risk estimates of silicosis and tobacco smoking. However, due to the lack of reliable data on crystalline silica exposure in any of the available studies, recommendations for a health-based exposure limit value are not possible at this time.

Qualitätsbasierter kritischer Review (QBCR) der epidemiologischen Literatur zu Quarz, Silikose, Rauchen und Lungenkrebs

Kurzfassung

Der mögliche Zusammenhang zwischen Quarz, Silikose und Lungenkrebs wurde bisher in zahlreichen epidemiologischen Studien untersucht. Eine Interpretation der Studienergebnisse ist häufig – bedingt durch unzureichende Expositionserfasssung, mangelnde Berücksichtigung von Confounder (insbesondere Rauchen) und durch methodische Mängel – schwierig.

Die vorliegende Publikation fasst eine qualitätsbasierte Auswahl relevanter epidemiologischer Studien zusammen. Die Analyse dieser Studien bezieht die Qualität der Expositionsdaten, mögliche Confounder und den Einfluss des Silikose- und Raucherstatus mit ein.

Zusammenfassend können die folgenden Schlussfolgerungen für die ausgewählten qualitativ hochwertigen Studien gezogen werden: Für Hochexpositionsgruppen ist ein erhöhtes Lungenkrebsrisiko erkennbar, das nicht ausschließlich durch Rauchen oder andere Confounder erklärbar ist. Da in den epidemiologischen Studien zuverlässige Expositionsdaten für Quarz fehlen, ist eine Empfehlung für einen gesundheitsbasierten Grenzwert für Quarz derzeit nicht ableitbar.

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1 Introduction

Although the epidemiological literature on the carcinogenicity of occupational crystalline silica in humans is relatively vast, several uncertainties remain. Currently unknown, for example, are the level of exposure at which lung cancer risk is elevated, and the role, if any, of silicosis on the carcinogenic process. Much of the published literature, however, is challenged by the difficulties of historical exposure reconstruction; potential biases due to competing risks from often highly prevalent non-malignant respiratory diseases including silicosis and tuberculosis; and the presence of strong confounding factors, especially cigarette smoking. The goal of this study is to conduct a quality based critical review (QBCR) of the existing epidemiological literature on silica, silicosis, smoking and lung cancer, focusing on and reviewing in depth a subset of the available literature that meets several quality criteria. A better understanding of the risk of lung cancer, if any, associated with exposure levels found in various industries today will provide scientific support for appropriate policies and interventions for protecting employee health.

Other recent reviews have attempted to clarify the relationship between occupational silica exposure and lung cancer risk; however, some of these reviews – including a pooled analysis by investigators of the International Ageny for Research on Cancer (IARC) – either failed to justify the selection of studies upon which their conclusions are based, or to adequately take into consideration the potential impact of confounding due to smoking. This QBCR examines the relationship between silica exposure and lung cancer, taking into consideration smoking, silicosis and other possible risks factors. The specific objectives of this QBCR are as follows:

- to comprehensively search the published epidemiological literature to identify papers of adequate quality that address the risk of lung cancer in

the context of reasonably measured or estimated silica exposures, other relevant occupational exposures, and tobacco smoking;

- to examine the exposure-lung cancer relationship within the subset of literature of greatest methodological quality;
- to explore the possible role of silicosis on lung cancer risk, specifically to elucidate whether silicosis is a necessary precursor to lung cancer; and
- to synthesize and communicate results of relevant studies so that scientific information may be accessible to and used by policy and decision makers.

Studies in which competing risks are likely are excluded from review. Ultimately we are interested in evaluating studies of populations that are exposed to silica at levels relevant to modern European and North American workplaces, and not those where silica exposure and other obvious hazards lead to high mortality and possible selective survival bias.

2 Material and Methods

2.1 Literature Search

We applied a two-stage strategy for identifying papers for review. First, we identified all papers addressed in several of the recent reviews: IARC (1997), McDonald (1999), Checkoway (2000), Hessel (2000) and Soutar (2000). Second, we searched the published literature since 1995 using Medline to identify papers published subsequent to those cited in the reviews above. Using this approach we identified 174 publications for preliminary screening. Based on the abstract or keywords, papers were excluded if there was no mention of smoking or silica exposure; the reports were not of epidemiological studies; the study design was population based case-control or proportional mortality; the outcome did not include lung cancer; or exposure to silica could not be separated from other exposures. Exceptions were made for methodological papers, such as exposure reconstructions, which were directly related to relevant epidemiological studies.

After these exclusions, the remaining 113 papers were reviewed in full. Multiple publications on unique study populations were evaluated together. In the case of related publications, we identified where possible the main paper or the one with the most complete results for inclusion in the QBCR. Papers that contained relevant information on the study population (e. g. exposure assessment) were retained for background purposes. An additional 35 papers were excluded or set aside in this process. Figure 1 summarizes the selection process.

2.2 Quality Assessment

Several general quality criteria were applied to determine whether individual publications, or groups of papers on the same cohort, might provide valid and useful information on the research questions of interest. These criteria were based on good epidemiological practice of the (CMA 1991) and included

- the assessment of the objectives of a study,
- the appropriateness of the methods used in the study (including the study design, data sources, data analyses, etc.),
- the validity of outcome definition and diagnosis,
- the quality of exposure assessment,
- the potential and control for confounding or other bias (in particular additional exposures and smoking),
- the overall quality assessment (inadequate, limited),
- systematic and actual overview of studies.

Of special interest in this QBCR is the quality of the exposure assessment. Direct measurement of exposure on each individual in occupational epidemiological studies is ideal, but unusual, and many studies have no direct exposure measurement whatsoever. Possible indicators of silica exposure used in the reviewed studies included occupation/industry; silicosis status; duration of employment in a job with possible or likely silica exposure; measured total dust levels and area air and personal air samples of respirable silica.

Because tobacco smoking is a strong risk factor for lung cancer, and smoking habit might be related to level of exposure to silica, it may be difficult to identify the separate contribution of each risk factor to disease risk. For exposure to tobacco smoke, subjects should be at minimum classified by smoking behavior or status; however, much greater detail is essential if the risks due to smoking are to be adequately evaluated.

Additional risk factors that might confound the association between silica and lung cancer include radon, polycyclic aromatic hydrocarbons (PAH), diesel exhaust, asbestos, chromium, arsenic, other hazardous dusts and tuberculosis. Therefore, the validity of risk estimates for the association between silica and lung cancer depends

upon the degree to which confounding due to smoking and other risk factors for lung cancer are controlled.

The overall quality of a study, for the purposes of this review, was assessed in terms of its ability to address the relationship between reliably estimated silica exposure and lung cancer, adequately recognizing and taking into account (or preventing) possible confounding from both smoking and other occupational risk factors. The evidence provided by studies deemed of adequate quality will be synthesized to address each of the specific review objectives. The quality assessment process is summarized in Figure 2.

2.3 Description of Study Populations by Industry Group

The 78 most relevant publications are listed by industry and study population in Table 1. We grouped the studies into eight major industry classifications: pottery/ceramics, refractory brick, foundry/steel, silicon carbide, mining, stone, industrial sand and diatomaceous earth. Additionally we evaluated three studies not falling under any of these industry groups (see "miscellaneous" below). In some instances study populations included workers who fell into multiple, separate industry groups. However, study populations were only listed as separate industry groups if the cohorts were clearly enumerated and could be differentiated. A total of 35 discrete industry-specific populations were defined (Table 2).

Each of the study populations is described briefly, by industry group, as an overview to the body of relevant literature available for in-depth quality review. The summaries below suggest a broad range of industrial settings in which silica exposures of different types have been studied using various epidemiological methods.

2.3.1 Pottery/Ceramics

We reviewed the literature on five cohorts of pottery/ceramic workers. Some of these cohorts included small numbers of refractory, sandstone or quarry workers. Silica sand is the principal ingredient in the making of ceramics, pottery and glass. Actual exposure to crystalline silica varies greatly, according to the quartz content of the raw materials. Workers who repair or maintain the kilns may be exposed to cristobalite released in the repair of refractory materials.

The British pottery workers are represented by two possibly overlapping populations: a 1990 cohort study of workers from 40 potteries throughout Great Britain (Winter, 1990) and the later studies of Staffordshire pottery workers (Burgess, 1997; Cherry, 1995; Cherry, 1997; Cherry, 1998; McDonald, 1995; McDonald, 1997). Among the papers on the Staffordshire cohort there are reports on subsets of the full cohort, often with different follow-up periods.

Winter (1990) published preliminary findings from a cohort of current workers, as of 1970/1971, assembled from a sample of 40 plants in the British pottery industry. The cohort was followed until 1985. Because of difficulties in tracing older cohort members the analysis was restricted to 3,669 men under age 60 years at the time of the survey. A total of 60 lung cancer deaths was observed, leading to significantly elevated SMRs (Standardized Mortality Ratio) using both national (SMR = 1.40) and locally adjusted rates (SMR = 1.32). Smoking information was obtained from the survey and exposure assessment was based on exposure measurements made at the time of the survey. Radiographic findings were not reported in this publication.

Subjects for the second study of British pottery workers were selected from a registry of dust-exposed employees. Employers in Great Britain were required to register dust-exposed employees between the years 1931 to 1984. Inclusion for the cohort was restricted to the Staffordshire region, the center of the British pottery and ceramics industry. Cherry (1998) published a summary report on a cohort of 5,115 pottery

workers (including about 10 % refractory and sandstone workers) born between 1916 and 1945, with no previous employment with asbestos, in foundries, or more than one year in coal mining or other dusty jobs. Because earlier death records may have been destroyed, follow-up was restricted to 4,822 persons alive in 1985, and they were followed through 1992. Excess deaths due to all causes, lung cancer (68 cases) and non-malignant respiratory disease (NMRD) were reported. Lung cancer (SMR = 1.91, 95% CI 1.48-2.42) (CI = confidence interval) was significantly elevated compared with national rates (England and Wales) and marginally with regional reference rates (SMR = 1.28, 95% CI 0.99-1.62).

A job-exposure matrix (JEM) was developed (Burgess, 1997) by 10 year calendar periods beginning in 1930 and twelve job groups. Exposures estimates were based on 1,400 area and personal monitoring samples for respirable silica recorded since the 1950's and on professional judgement for earlier periods. This JEM was validated in a sub-cohort for prevalence of radiographic change and showed a clear dose-response relationship for cumulative and average silica exposure. The JEM was used in a nested case-control study based on 52 of the 88 lung cancer cases – those pottery workers with available work history data. Smoking information was extracted from medical records from the employment period. There was no case observed among never smokers. Average concentration of respirable silica (100 $\mu g/m^3$), but not cumulative exposure or duration of exposure, was significantly associated with lung cancer after adjustment for smoking (OR = 1.67; 95% CI 1.13-2.47) (OR = Odds Ratio).

We reviewed two papers of a German case-control study among ceramic and stone workers (Ulm, 1998; Ulm, 1999). However, only the earlier report, published in German, presented detailed results for the separate industry groups and adjusted for smoking. Additionally, the earlier report presented results with and without silicotic persons, whereas the later report, published in English, was restricted to non-silicotics.

Using various data sources, 122 lung cancer cases occurring between 1980 and 1994 were identified and 571 controls were drawn from a register of participants in a preventive check-up and silicosis screening program covering roughly 95 % of all workers. Experts assessed individual exposure based on available information. Smoking data were collected using both existing medical records and interviews, and an index of smoking intensity and duration was developed.

Results are presented for peak, average and cumulative exposure and adjusted for different confounders (age at start, latency, duration of exposure, other occupational exposures) but surprisingly not smoking. The publication in German reported elevated but non-significant ORs for all exposure indices (around 1.4) and a significant increase in risk for silicotics, while the paper published in English reported ORs around unity for cumulative and average exposure, after adjusting for year first exposed, but not for smoking.

Meijers (1996) identified a cohort of 1,794 male Dutch ceramic workers based on a cross-sectional survey of those employed for at least two years between 1972 and 1984. Follow-up was through 1991. SMR analysis showed a strong healthy worker effect in this cohort (all cause mortality SMR = 0.7); 30 cases of lung cancer were detected (SMR = 0.88), 3 among non-smokers.

No quantitative exposure measurements were available, but the authors stated that exposure was highly correlated with production stage, and each worker was classified as having none, low, moderate or high exposure. Further details were not reported and could not be derived from earlier publications (Meijers, 1990a; Meijers, 1990b): it remains unclear whether exposure was or could have been assessed over time. Smoking information was collected during the survey. Lung cancer risk was elevated for the 124 individuals identified through the survey as having silicosis (SMR = 2.2, 95% CI not reported). The authors noted as limitations of the study the relatively

young group of workers (mean age at start of follow-up around 40) and short follow-up period (14 years on average).

Lagorio (1990) conducted a case-control study in a small town in northern Italy, where a high proportion of the male inhabitants were employed in the pottery industry. Cases and controls were identified from deaths occurring between 1968 and 1984. Cases were 71 lung cancer decedents, and controls consisted of 319 decedents with causes of death other than lung cancer, cancer of unspecified site, silicosis or chronic bronchitis. Work history and smoking data were obtained through interviews with next-of-kin. No quantitative exposure measurements were presented, but the authors reported heavy silica exposures in the past with relatively high exposure levels persisting through the study period. They also noted a high number of compensated silicosis cases in the town over the previous 40 years. After adjustment for smoking, no excess in risk was found for a smaller group of quarrymen, but overall excess was seen for ceramic workers (OR = 2.0, 95% CI 1.1-3.5), with a higher risk among silicotics than non-silicotics (OR = 3.9 and 1.4, respectively).

We reviewed six papers on highly exposed Chinese pottery workers that were part of a large study of mine and pottery workers combined. Chen (1992) reported SMR analyses for 13,719 pottery workers that were followed between 1972 and 1989, and found a significant decrease in lung cancer risk (SMR = 0.58) but significant elevated risks for pulmonary tuberculosis, non-malignant respiratory diseases (especially pneumoconiosis) and pulmonary heart diseases. A further analysis of 9,017 members of this cohort with an extended follow-up period through 1994 was presented in the IARC multi-center study (Steenland, 2001a). It is unclear why nearly 5,000 members of the cohort were excluded from this follow-up. According to the later report, approximately 50 % of the Chinese pottery workers were unexposed and the reported SMR for lung cancer for the exposed group was 1.1 (95% CI 0.84-1.4) compared with national rates; the SRR (Standardized Relative Risk) comparing the exposed with the non-exposed group was 2.8 (95% CI 1.6-4.8).

A JEM was developed (Dosemeci, 1993; Dosemeci, 1995; Wu, 1992; Zhuang, 2001) based on approximately 1,100 total dust measurements, and a small number of historical respirable silica content measurements, both collected using a standard Chinese sampling system and comparison measurements, taken at the end of the 1980's. The results showed a relatively constant and high respirable silica concentration over time (mean concentration 0.72 mg/m^3). The JEM was used for a nested case-control study conducted by McLaughlin (1992). Smoking information was collected by interview with subjects or next-of-kin.

After adjustment for smoking (7 % of the lung cancer cases were among non-smokers) the authors reported a relationship of lung cancer to cumulative silica exposure (non-exposed as referents), but without a significant dose-response trend. There was a correlation of silica and PAH (polycyclic aromatic hydrocarbons) exposure (r = 0.56) but adjustment for PAH slightly raised the OR for silica exposure. The fact that no study subject had PAH exposure in the absence of silica exposure (Cocco, 2001) prevented an investigation of possible interaction effects. Silicosis was negatively related to lung cancer (OR = 0.5).

2.3.2 Refractory Brick

Refractory bricks or firebricks are produced for use in other industrial processes. Like ceramics, the composition of the brick depends on the end use. Raw materials (including crystalline silica) are fashioned into bricks and fired at extremely high temperatures (1,000 °C) to form bricks or blocks used in the construction of furnaces (e. g. coke ovens, kilns, foundry molds) (IARC, 1997).

Two overlapping studies were conducted among male refractory brick workers at a plant in Genoa, Italy, which opened in 1931, closed in 1952, and reopened in 1957. The first study (Puntoni, 1988) included 231 workers actively employed on January 1, 1960 and followed through 1979 for mortality. Compared with regional rates, an

excess of lung cancer was seen, based on 11 observed deaths (SMR = 1.83, 95% CI 0.91-5.2). A significant excess of non-malignant respiratory diseases (including tuberculosis) was also observed (SMR = 3.04, 95% CI 1.77-4.86).

Because exposure measurements first were available in 1973 and there was a high mobility between the different departments, exposure assessment in this study was restricted to silicosis status, based on a high proportion (59 %) of compensated silicotics in this cohort. Smoking data were only available for a portion of the lung cancer cases, and at least 3 lung cancer cases occurred among non-smokers.

Among the group of compensated silicotics, significant excesses of overall mortality, laryngeal cancer and non-malignant respiratory disease were observed. Lung cancer mortality rates were similar among silicotics (SMR = 1.67) and non-silicotics (SMR = 2.08), but both estimates were imprecise, as they were based on small numbers.

A later study of this plant (Merlo, 1991) included all male workers (n = 1,022) employed for at least six months between 1954 and 1977, with follow-up through 1986. Excesses of lung cancer (SMR = 1.51, 95% CI 1.0-2.18) and non-malignant respiratory disease were found, with greater excess noted among those employed before 1957. Exposure assessment remained qualitative in this study and smoking data were only available for a quarter of the cohort surveyed in 1984. Indirect adjustment for smoking was conducted based on the method presented by Axelson (1978) and the authors reported that less than 2 % of the excess in lung cancer could be attributed solely to smoking. Silicosis status was not known and therefore could not be evaluated.

Dong (1995) studied 6,266 male refractory brick workers, employed before 1962 and subjected to medical health examinations for silicosis beginning in 1963. Follow-up of this cohort was conducted until 1985. The mortality of this cohort was

compared with a cohort of steel workers not exposed to silica or to other occupational lung carcinogens. Significant excess risks were found for overall mortality (SRR = 1.44), lung cancer (SRR = 1.49, based on 65 cases), pulmonary heart diseases, diseases of the circulatory system, as well as for respiratory diseases and pulmonary tuberculosis (SRR = 13.33, based on 237 cases).

Exposure was reported to be mainly to relatively pure quartz, but no exposure measurements were reported. Exposure assessment was restricted to silicosis status (1,827 cases of silicosis/silico-tuberculosis). Smoking data presumably were available from medical examination records.

Analysis by silicosis status showed, that nearly all of the causes of death of interest were restricted to the silicotic sub-cohort. The SMR for lung cancer was 2.1 for silicotics compared with 1.1 for non-silicotics. Analysis by smoking showed a higher SRR for smoking silicotics compared to smoking non-silicotics (SRR = 2.34 vs. 1.20) and for non-smoking silicotics compared to non-smoking non-silicotics (SRR = 2.13 vs. 0.85, based on 12 and 7 cases, respectively). Lung cancer SRR increased with increasing severity of silicosis.

The authors discussed the high and early mortality of silicotics in China and in the cohort: approximately 70 % of the silicotics in the cohort died of pulmonary heart disease or tuberculosis and 46 % of the tuberculosis cases died within a 20 year latency compared with only 12 % of the lung cancer cases.

2.3.3 Foundry/Steel

We included four cohorts in the foundry, steel or iron industry with some overlap in the industry classifications. Processes in the foundry industry often include refractory operations. Casts and molds created in the foundry process are made from sand with a wide range of quartz content (5-100 %) (IARC, 1997). Foundry workers may have

long-term exposure to silica sand. Previous research has demonstrated increased risks of lung cancer among foundry workers, who are also recognized to be at increased risk of silicosis and other respiratory complaints (Andjelkovich, 1990).

Rodriguez et al. (2000) conducted a nested case-control study within a large cohort of Spanish foundry workers. Production at the foundry included all processes from raw materials to finish products. Cases and controls were selected from a cohort of 24,490 workers, employed for at least 12 months. Case identification was through record linkage of job history and cancer registries. Controls were matched to cases by year of birth. Occupational exposure assessment consisted of job title and production processes. Analyses were performed comparing employees ever having worked in seven major production processes and by longest job held. In addition to silica, the steel foundry workers were likely exposed to other lung carcinogens including welding fumes, PAHs, arsenic, and chromium.

The authors reported a high prevalence of smoking (99 % cases/80 % controls) and concluded that smoking was a confounder within the study. The age adjusted OR for smokers was 32.5 ($p < 0.05$) though the confidence limits were wide due to only one never-smoker among the cases.

Age adjusted odds of lung cancer by longest job held suggested slight excess risks of lung cancer, which was reduced further for some processes after adjustment for smoking. In the analyses by longest job held, no estimate excluded the null. Subjects whose longest job held was blast furnace operator had an OR of 1.73 (95% CI 0.70-4.30); after adjustment for smoking the OR was 2.11 (95% CI 0.78-5.73). For those who ever worked in the blast furnaces the smoking adjusted OR was 2.55 (95% CI 1.25-5.21). Other results for "ever worked" are not discussed here, as the job categories were not mutually exclusive. Given the potential for other exposures and confounding by smoking, the results for this population are limited in furthering an understanding of a relationship between silica and lung cancer.

Workers in a gray iron foundry[1] employed for a minimum of six months during 1950-1979 were the subjects of a series of papers. The early reports (Andjelkovich, 1990; Andjelkovich, 1992) contained qualitative exposure estimates and smoking was controlled through indirect adjustment.

In a later nested case-control study (Andjelkovich, 1994) cumulative exposure to crystalline silica was estimated based on industrial hygiene data. Basic smoking data were available for about 70 % of the cohort. Regression analyses showed significantly elevated risk for smokers (OR = 5.23, 95% CI 2.81-9.77; compared to non-smokers). Results from analyses with 10-, 15- and 20-year lags were similar. Estimates based on work area or quartile of silica exposure showed no pattern of increased risk. Birth cohort (1915+ vs. < 1915) was significantly related to risk of lung cancer (OR = 1.75, 95% CI 1.16-2.64) controlling for smoking and silica exposure.

The final paper in the series was conducted primarily to assess lung cancer risk following exposure to formaldehyde. The authors also assessed risks associated with exposure to crystalline silica and lung cancer (Andjelkovich, 1995). Poisson regression analyses indicated a clear association between silica exposure and both lung cancer and non-malignant respiratory disease, though there were few observed cases of the later. Compared to the lowest quartile of exposure, lung cancer risk was elevated for the second (RR 2.34, 95% CI 0.68-10.7), third (RR 3.41, 95% CI 1.16-14.5) and fourth quartile (RR 3.98, 95% CI 1.41-16.6) (RR = Relative Risk). The RR for smoking was 2.11 (95% CI 1.10-4.58) (Andjelkovich, 1995). The authors suggest that the discrepancy between the current findings and those of the nested case-control study (1994) are the due to similarity in silica exposure between cases and controls in the earlier study.

[1] Gray iron is a term specific to the amount and nature of carbon added to the metal.

Increased risk of lung cancer has been reported among stainless steel workers. Moulin et al. reported on a cohort of French workers (n = 4,227) with potential exposure to silica (as well as PAHs and chromium, among other substances). Silica exposure can occur in foundry and ferroalloy processes in the stainless steel industry. The initial cohort study was suggestive of an association between foundry work and lung cancer (SMR = 2.29, 95% CI 1.14-4.09). Based on indirect adjustment the authors conclude that the excess is not the result of confounding due to smoking (Moulin, 1993).

Mortality of the cohort was updated and a nested case-control study conducted. Overall mortality was below expected based on 649 deaths. The SMR for lung cancer was 1.19 (95% CI 0.88-1.55). The 54 lung cancer cases were matched to controls selected from the full cohort. The crude OR for silica exposure was 2.47 (95% CI 1.28-4.77), which adjusted for smoking was reduced to 1.82 (95% CI 0.74-4.46). Smoking data were known for 71 % of subjects. Moulin et al. reported a significant risk of lung cancer based on quantitative exposure estimates for silica (OR = 1.33 for increasing exposure levels). However, silica exposure was strongly correlated with PAH exposure (r = 0.84) and independence of effect can not be determined (Moulin, 2000).

Xu reported on iron and steel workers employed at the Anshan steel complex in China, in two related papers. The first described proportional mortality ratio (PMR) analyses and the second, of interest for this review, described incident lung cancer cases (Xu, 1996a; Xu, 1996b). It is possible that the population studied by Xu overlapped with that described by Dong (1995), as subjects worked at the same complex. 610 lung cancer cases were identified from hospitals associated with the steel complex. Odds ratios for lung cancer were calculated controlling for smoking, family history of lung cancer and NMRD. For those who worked more than 15 years in smelting/rolling, refractory, coke ovens or general loading areas, ORs exceeded

1.0. Refractory workers with 15+ years of employment had an adjusted OR of 2.9 (95% CI 1.4-5.9). Far more cases than controls were smokers (86 % vs. 61 %), and the authors report a "strong dose-response gradient". There was no exposure assessment for asbestos at either the plant level or the individual level, and the authors stated that they were not able to distinguish an effect of silica separate from that of other dusts (Xu, 1996a).

2.3.4 Silicon carbide

Only recently has the silicon carbide industry come under scrutiny for possible lung cancer risks. Quartz sand is a principal component in the production of silicon carbide (SiC) and is combined at high temperatures with coke to create silicon carbide (IARC, 1997). The process is dusty and produces silica, SiC fibers and particles, as well as CO, SO_2 and PAHs (Infante-Rivard, 1994; Peters, 1984; Romundstad, 2001; Smith, 1984). The potential for increased risk of respiratory impairments and pneumoconioses has been recognized for some time (Peters, 1984; Smith, 1984). Peters et al. (1984) reported an association between radiographic opacities and respirable dust, possibly enhanced by smoking, though frequencies were similar regardless of smoking when cumulative dose measures were high. However, a recurrent theme in the literature is the difficulty separating the effects of the different exposures.

Dufresne (1998) measured particles retained in lungs of workers with silica-induced diseases and among other findings, reported higher concentrations of ferruginous bodies among those with both fibrosis and lung cancer. This suggests that exposure to silicon carbide "whiskers", ceramic fibers or asbestos may be a factor in the development of both malignant and non-malignant lung disease.

We reviewed two studies of silicon carbide (SiC) workers. Infante-Rivard published the first cohort study of silicon carbide workers in 1994. A total of 585 workers from three

plants in Quebec were followed through 1989. 167 deaths were observed. Excess deaths due to lung cancer (SMR = 1.69, 95% CI 1.09-2.52) as well as non-malignant respiratory disease deaths were observed (SMR = 2.03, 95% CI 1.21-3.22) (Infante-Rivard, 1994). Cox regression analysis was used to assess the relationship between cumulative exposure to total dust and death due to lung cancer. Cumulative exposure was categorized as < 105, 105-272 and > 275 mg/m^3. The smoking adjusted rate ratios were 1.48 and 1.67 for the highest and middle categories compared to baseline (< 105 mg/m^3), respectively. Rate ratios were lower allowing for 15-year latency. However, exposure was to total dusts as opposed to respirable silica. Concentrations of quartz and cristobalite in respirable air at the Quebec plants were in the range of 0-113 μg/m^3 for quartz and 0-36 μg/m^3 for cristobalite, below levels considered to pose health risks.

Cancer incidence was examined among 2,620 Norwegian silicon carbide workers with 6 or more months continuous employment after 1953 and followed to the end of 1996 (Romundstad, 2001). The incidence of cancer was higher overall than expected, due largely to lung cancer (SIR 1.9; 95% CI 1.5-2.3; based on 74 cases). Exposures were estimated for total dust, crystalline silica, SiC fibers and SiC particles. Poisson regression analysis was used to evaluate exposure dose-response as well as the effect of smoking. Exposure categories were ranked, or the mean cumulative exposure was used in the regression model. The regression model including total dust and smoking, lagged by 20 years, demonstrated increased risk with increasing exposure. The model is compromised by the fact that there was only one subject in the non-smoking referent category. SiC fibers appeared to be a stronger predictor of lung cancer than crystalline silica when both variables were included in the regression model. However, Romundstad noted the high correlation between the two (r = 0.8). The authors were cautious in their interpretation of the findings, noting correlation of exposures and regional variations of lung cancer incidence (Romundstad, 2001).

2.3.5 Mining

We reviewed a total of 30 papers on mining populations representing twelve reasonably discrete cohorts, presented below by type of mine or ore produced. Exposure to silica is quite different depending on the type of mine (surface or underground), the ore (metal, non-metal) and the mineralogical properties of the surrounding rock. Potential confounding due to other substances is dependent on rock composition and work practices (e. g. ventilation). The studies of Chinese miners pose some additional issues that are not germane to studies conducted in Europe and North America.

Two populations of metal miners, one in the United States and one in Italy, provide only basic exposure information. A Finnish study of sulfide ore miners provides semi quantitative silica exposure data and indirect adjustment for smoking.

2.3.6 Gold Miners

We reviewed five cohorts of gold miners from North America (2), Australia (1) and South Africa (2). There is probable overlap between the South African cohorts.

Kusiak (1991) reported on a cohort of miners employed throughout Ontario, Canada, and followed for mortality from 1955 through 1986. The mines were not exclusively gold mines; other ores included nickel, silver, uranium, iron lead and zinc. In addition to silica dust, potential exposures included arsenic, radon, and mineral fibers including tremolite and amphibole asbestos. Smoking data were available for a random sample of miners (born before 1938) that represented only 2 % of the entire cohort (n = 54,128). Provincial mortality rates were used to calculate expected deaths. Excess lung cancers were observed in gold miners first exposed before 1946 (SMR = 1.40, 95% CI 1.22-1.59) and nickel miners first exposed before 1936 (SMR = 1.41, 95% CI 1.05-1.84). Kusiak et al. concluded that the observed excess is

most likely due to exposure to radon and arsenic, and that smoking is unlikely to explain the excess.

The cohort of Australian gold miners was initially assembled from participants in a respiratory health survey in the early 1960's. We reviewed three papers based on this cohort (Armstrong, 1979; de Klerk, 1995; de Klerk, 1998). Authors of the earlier reports concluded that excess lung cancer was likely related to cigarette smoking. However, the preliminary follow-up focused on lung cancer only, excluding from the referent pool all other outcomes possibly related to silica exposure (de Klerk, 1995). The most recent report included subjects from the earlier follow-up as well as participants in a respiratory health survey conducted in 1974-1975 (de Klerk, 1998). Smoking history was collected as part of the initial survey and was not updated. Employment history was based on survey results and employment history maintained in records of the chest clinic. De Klerk reported a consistent association between smoking and silicosis, based on a model that also included latency and employment duration. Silicosis was also associated with estimated intensity and duration of dust exposure. Incidence of silicosis peaked at about 45 years since first employment; 631 of 1,040 applicants were compensated for silicosis. The SMR for pneumoconioses was 11.2 (95% CI 8.4-14.8).

Lung cancer was the primary cause of death for 138 miners. Only one case of lung cancer occurred among never smokers. Risk of lung cancer was related to smoking and with recent compensation for silicosis. The overall SMR for lung cancer was 1.49 (95% CI 1.26-1.76), and adjusted for smoking and bronchitis was 1.31 for cumulative exposure (log of exposure score year). The SMR for lung cancer by cigarettes/day ranged from 10.7 for ex-smokers to 32.5 for smokers of 25 or more cigarettes/day.

The Homestake Mine in Lead, South Dakota, began operations in 1876. The ore at this mine contains a crystalline form of cummingtonite-grunerite as well as quartz. In

the early 1970's respirable dust measurements contained on average 13 % free silica and were below the OSHA limit (OSHA, Occupational Safety and Health Administration). The first report included miners identified through a US Public Health Survey of silicosis in miners (Gillam, 1976). Those selected (n = 440) had to have worked at least 60 months underground at the Homestake mine and have no other history of underground mining. Excess mortality was observed for malignant and non-malignant respiratory diseases. Subsequent analyses of mineral content of dusts at the Homestake mine indicated that fibrous amosite was present in the mine. Gillam et al. concluded that the excess lung cancer was likely due to the presence of asbestiform cummingtonite-grunerite. The role of cigarette smoking was not directly analyzed.

Concurrently McDonald et al. (McDonald, 1978) conducted a separate study of the Homestake miners, selecting as subjects miners who had worked for at least 21 years at the mine (n = 1,358). Mortality ratios were calculated based on appropriate state rates and on an internal comparison using the total cohort for the period 1937-1973. In the external comparison excess mortality was observed, primarily due to pneumoconioses (37 observed), respiratory tuberculosis (39 observed/3.6 expected) and heart disease. For all but two deaths from pneumoconiosis, silicosis was listed as the cause of death on the certificate. Silicosis was also listed on the death certificates of 28 subjects whose primary cause of death was coded heart disease. Excess mortality due to lung cancer was not observed.

Steenland and Brown reported on another cohort of Homestake miners (Gillam, 1976; Steenland, 1995). This later cohort was comprised of miners with at least one year underground between 1945 and 1960. Mortality was ascertained through 1990. Smoking data were available for a subset of the cohort based on the 1960 silicosis survey described by Gillam (1976). Indirect estimation of smoking prevalence was made based on lung cancer rates. A job exposure matrix for cumulative exposure to dust was estimated based on average dust measurements for job categories and estimates of time spent underground.

Mortality ratios based on US rates indicated small excess all cause mortality (SMR = 1.13, 95% CI 1.07-1.19). The SMR for tuberculosis was 3.52 based on 36 deaths (95% CI 2.47-4.87) though in analyses by year of hire excess was restricted to those hired before 1930. A similar pattern was observed for non-malignant respiratory disease. The overall SMR was 1.86 (95% CI 1.58-2.16) and 2.61 (95% CI 2.11-3.20) for pneumoconioses (including other respiratory disease). When stratified by date of hire, there were excesses in all categories, but confidence intervals excluded 1.0 only for the before 1930 and 1930-1950 sub-cohorts. Slight excess mortality due to lung cancer was observed, but chance was not ruled out.

A number of studies of white South African gold-miners have been published. The major mining region in South Africa spans what is known as the Witwatersrand Reef. Within South Africa all miners are required to undergo periodic exams at the Medical Bureau of Occupational Diseases (MBOD) for certification to work in the mines. Upon death, a substantial proportion of miners are autopsied by the National Center for Occupational Health.

The average working level (WL) of radon in South African gold mines is reported to be 0.4 (range 0.1-3.0). It is possible that long-term miners had accumulated 100 WL months or more. Free silica content of dust is estimated to be about 30 % with concentrations between 0.05 and 0.84 mg/m^3 in underground mine operations.

Two early case-control studies were reviewed (Hessel, 1986, 1990), based on non-overlapping populations. In the first study of white South African gold miners, 133 lung cancer cases and 266 matched controls were selected (Hessel, 1986) from death records of the pension fund (available only to white miners). Subjects were matched on year of birth (± 2 yrs) and smoking status 10 years prior to death (± 2 yrs and ± 5 cigarettes/day). Not all deaths are reported to the pension fund; however, deaths among active employees, those with 15 or more years of service, or those discharged

within the last 2 years are automatically recorded. It is not evident how many inactive employees were missed. Elevated, though not statistically significant, odds ratios for lung cancer were observed for all but the highest quartile of exposure (in unmatched analyses). Potential confounding by smoking and radon exposure were not evaluated.

The second case-control study was conducted with a more complete selection of cases. Examination of cardio-respiratory organs at autopsy is completed for an estimated 86 % of white gold miners. Hessel et al. (1990) identified 571 miners with potential lung tumors, and after application of exclusion criteria, 231 lung cancer cases and 318 matched controls remained. Cumulative dust exposure was estimated according to number of shifts worked on each job and a weighted estimate of dust for each job.

Smoking status was categorized according to status as near the time of death as possible. Hessel at al. (1990) reported no association between silicosis or silica exposure and lung cancer. They did note, however, that miners compensated for silicosis while living are likely underrepresented in the study population.

Two additional groups of South African gold miners have been studied. One cohort was selected from all white miners from the East Rand-Central Rand-West Rand region who attended the Medical Bureau for Occupational Diseases in 1969, were alive as of the beginning of 1970 and were at that time 39-54 years old. Wyndham (1986) described the initial follow-up. More recently Reid and Sluis-Cremer reported on a 20-year follow-up of these miners (Reid, 1996). They reported the mortality experience of 4,925 miners, 2,032 of whom had died. Most of the cohort (87 %) had worked at least 85 % of their shifts in the gold mines. It is possible that members of this cohort also worked in amphibole mining operations. SMRs were calculated based on the white male population of South Africa. The SMR analyses do not incorporate any of the available smoking data, nor were work histories extracted for the miners.

Overall mortality was elevated (SMR = 1.30, 95% CI 1.24-1.35), as were deaths due to lung cancer (SMR = 1.40, 95% CI 1.18-1.65), tuberculosis (SMR = 3.06, 95% CI 1.92-4.64), chronic obstructive pulmonary diseases (COPD), including 16 deaths from pneumoconioses, cirrhosis of the liver, and ischemic heart disease (IHD). Results of a nested case-control study of lung cancer, COPD and IHD are also reported. Smoking, years of underground mining, and cumulative dust (mg/m^3-y) were evaluated as risk factors. The authors reported that concentrations of radon in the South African mines were low. The average subject had 27 years underground service and 3.7 mg/m^3-y of dust exposure, but estimates of cumulative dust were not related to lung cancer. Four lung cancers were reported among non-smokers, though one apparently had documented exposure to asbestos. The RR for amount smoked (packs of 20/day) was 2.41 (95% CI 1.2-4.2).

Hnizdo published two reports on a group of South African miners who began mining between 1936 and 1943 and were selected for a study of respiratory disease in 1968-1971 (Hnizdo, 1991; Hnizdo, 1997). It is possible that there is overlap between this cohort and the cohort initially enumerated by Wyndham, however, it is not likely that the overlap is complete. A total of 2,209 white gold miners were selected, with an average of 23.5 years employment in the mines. All subjects had to have worked at least 10 years as underground gold miners to be included. Smoking data, collected between 1968 and 1971, included current status as well as duration of smoking. Information was checked against records at the MBOD.

Cumulative exposure to respirable silica dust was estimated based on actual dust measures for occupations within the mines and the number of shifts per job for each miner. Total years worked and cumulative exposure was calculated for each decade (dust particle-years) as well as totals at the beginning and end of the follow-up period. A total of 77 lung cancer cases were observed; 92 % of which were confirmed at autopsy or through biopsy. Autopsy records were used to identify miners known to have silicosis.

Hnizdo and Sluis-Cremer (1991) reported an increasing trend for lung cancer risk with both smoking and dust exposure. Their data also demonstrated an effect of dust and smoking that together was greater than additive, with the highest risk among subjects with 35+ pack/years and who had accumulated 30,000 particle-years of dust exposure. The adjusted risk of lung cancer was 3.18 (95% CI 1.34-7.45) for men in the highest exposure category. Adjusted odds ratios demonstrated an increased risk of lung cancer associated with silicosis of the hilar gland (OR = 3.9, 95% CI 1.2-12.7) but not for silicosis of the lung or pleura. Smoking was negatively associated with silicosis of the pleura.

A subsequent nested case-control study evaluated 78 lung cancer cases, each matched to five controls selected from the cohort of 2,260 miners (Hnizdo, 1997). Dust exposure was defined as cumulative dust years (mg/m^3-y) and net years of underground dusty work. Similar estimates were calculated for exposure to uranium (radon). Uranium exposure variables were not significantly related to lung cancer and were not included in final models. All models included cigarette exposure as pack-years. Smoking was not related to silicosis risk (OR = 1.00, p = 0.40) or age at onset (result not reported). Exposure indices lagged 20 years were not related to risk of lung cancer when silicosis was included in the models, though were strongly associated with risk of lung cancer without silicosis in the model. The smoking adjusted RR for the highest category of cumulative dust exposure (CDE20 > 6.3 mg/m^3) was 3.19 (95% CI 1.3-7.6); with the addition of silicosis to the model the RR was 1.93 (95% CI 0.8-5.0). Analyses by silicosis status and pack years of smoking showed the highest RR for subjects who were both heavy smokers and silicotics, though some strata had few observed cases. Among those with silicosis, the RR for smokers by pack-years was 7.9 (1.4-46.4) and 48.9 (8.5-281.4) for 10-29 and 30+ pack-years respectively. Among miners without silicosis the RRs for pack-year categories were 5.1 (1.2-22.4) and 11.7 (2.7-49.8) for 10-29 and 30+ pack-years. Of note is the

observation that cases with silicosis had significantly higher cumulative exposure than controls with silicosis ($p < 0.05$).

2.3.7 Metal Mining

A large cohort of metal miners was assembled as part of a US Public Health Service survey conducted during 1959-1961 (Amandus, 1991), with miners followed through 1975. The cohort represents workers from a number of different types of mines, excluding miners exposed to underground diesel exhaust. This cohort likely overlaps with the South Dakota gold miner's cohort. SMR analyses were completed for silicotics and non-silicotics for smoking status at start of follow-up, ore type, years underground, estimated radon exposure and year of hire. There were 118 lung cancer deaths among non-silicotics and 14 among silicotics. Lung cancer mortality was increased for heavy smokers (25+ years), among silicotics (SMR = 2.69, 95% CI 1.16-5.30) and non-silicotics (SMR = 1.76, 95% CI 1.36-5.30), but the estimates are based on a combined smoking and non-smoking reference population. Age and smoking adjusted relative risks indicated small excess lung cancer for silicotics compared to non-silicotics 1.57 (95% CI 0.94-2.64).

Ahlman (1991) reported mortality among 597 Finnish copper and zinc sulfide ore miners. No silica exposure assessment was made, and exposure to other potential lung carcinogens was possible. Excess lung cancer was observed, however, IHD was the cause of death with the greatest excess noted.

Two papers reported on mortality of metal miners in Italy. The first reported on mortality for men and the second for women (Carta, 1994; Cocco, 1994). Miners were selected from two lead and zinc mines located in a region of Sardinia. The mines differed with respect to rock composition, resulting in different exposure potentials. Respirable dust in mine A ranged from 0.2-2.0 % whereas the range in mine B was 6.5-29 %. Radon levels also differed with higher WL measured in mine A

than mine B. Carta (1994) followed 1,741 miners from 1973-1988. Deaths from non-malignant respiratory disease were significantly greater than expected based on 39 observed deaths (SMR = 2.39, 95% CI 1.70-3.27). Twenty-four miners were reported to have died from lung cancer resulting in slight excess (SMR = 1.12, 95% CI 0.71-1.66). Seventeen of the lung cancer deaths were in workers from mine A, whereas more of the deaths from other respiratory deaths were in workers from mine B (23 deaths).

The study of women miners (Cocco, 1994) was based on 526 subjects followed from 1951-1988. Fewer than expected deaths were observed overall, suggesting a strong healthy worker effect (SMR = 0.78, $p < 0.05$). Excess deaths due to lung cancer and non-malignant respiratory diseases were observed but chance could not be ruled out. Smoking behavior among these miners was unknown.

2.3.8 Chinese Mining Studies

Publications examining Chinese miners presented a unique challenge, as the workers from 21 mines may partially overlap with other studied cohorts, including tin miners studied by Fu 1994. Beyond potential problems with overlapping cohorts, these mineworkers appear to have experienced greater mortality due to other respiratory diseases as well as unintentional injuries at the work site indicative of more hazardous working conditions than typically found in Western countries.

The study of Chinese mine and pottery workers included 21 mines: tungsten (10), tin (4), iron/copper (6) and clay (1). We reviewed ten papers that were clearly the same cohort first described in Chen 1992. Study details relating to the potteries were previously described. The clay mine is not mentioned beyond the initial description.

The average total dust exposure in the tungsten mines was estimated to be 6.1 mg/m^3 (2.0-26.3). The study population included 28,442 tungsten miners, 65 % of whom

were classified in the highest exposure category. 2,870 deaths were observed during follow-up from 1972-1989. There was a serious deficit of lung cancer deaths among these workers (SMR = 0.53, $p < 0.05$). Cancer deaths combined were significantly below expected though overall mortality was higher than expected. The only cancer reported to be in excess was nasopharyngeal cancer. The largest excesses noted were due to heart diseases, with SMRs for hypertension and pulmonary heart disease of 4.3 and 8.19, respectively (both statistically significant). Respiratory deaths were also seen in significant excess (SMR = 1.85), though pulmonary tuberculosis deaths were observed at half the expected number. SMR analyses of deaths from 1985-1989, based on 1987 national mortality rates, were also reported. Based on 1,097 total deaths significant excesses were observed for deaths due to pulmonary heart disease and respiratory disease (primarily due to pneumonia and pneumoconiosis). A deficit of lung cancer was again observed.

McLaughlin (1992) reported further analyses of 93 male lung cancer cases and 400 controls selected from the cohort of tungsten miners. For miners smoking 20 or more cigarettes per day, the OR for lung cancer was 3.9. Analyses based on cumulative exposure indices, and adjusting for smoking and age, showed a trend towards reduced risk with exposure including cumulative dust, respirable silica and possibly arsenic, radon and PAHs. In a recent report, Cocco (2000) presented analyses that included non-malignant respiratory disease. Silicosis was related to higher respirable dust and silica in the tungsten mines. Other papers on this cohort do not present risk estimates by specific facility types.

There were 1,108 deaths among the 18,231 iron/copper miners from the Chen 1992 cohort. Lung cancer deaths were close to expected for the 1972-1989 follow-up, but excess deaths were observed for heart disease (ischemic and pulmonary), accidents, and liver cancer. A deficit was observed for pulmonary tuberculosis (SMR = 0.40, $p < 0.05$). There was no apparent relationship between lung cancer and cumulative exposure indices reported in the nested case-control study (McLaughlin, 1992). Lung

cancer risk among miners with silicosis was elevated compared to those without (SMR = 2.22, 95% CI 1.2-4.0).

Results for tin miners were considerably different. There were 705 deaths among the 7,849 tin miners included in the study. Excess deaths were reported for lung cancer (SMR = 1.98, $p < 0.05$), nasopharyngeal cancer, as well as pulmonary and hypertensive heart disease. Pulmonary tuberculosis was lower than expected (SMR = 0.4). SMRs for the later follow-up showed a similar pattern as well as a significant excess of pneumoconiosis deaths (SMR = 29.6). The RR for lung cancer for silicotics compared with non-silicotics was modestly elevated (SMR = 1.38, 95% CI 0.9-2.1).

Adjusted odds ratios reported in the nested case-control study showed a dose response trend for cumulative dust and cumulative respirable silica (McLaughlin, 1992). For the latter, those with the highest exposure ≥ 26.3 mg/m^3 had a relative risk of 3.1 ($p < 0.05$). Analyses of cumulative arsenic exposure also suggested a dose response relationship, though arsenic and silica were highly correlated ($r = 0.80$). Lastly, tin miners with silicosis had double the risk of lung cancer compared to those without silicosis. Silicosis was more prevalent in the tin mines, which, compared to other mines, had higher silica exposures (Cocco, 2000).

The most recent publication of tin miners followed the cohort identified by Chen (1992) to the end of 1994. From the original cohort, 130 lung cancer cases and 627 controls were included in a nested case-control study (Chen, 2002). Overall, cancer was the leading cause of death within the cohort, and the SMR for lung cancer was 2.39. Prevalence of smoking was high in the cohort: 88 % of cases and 82 % of controls. Total average dust before the 1950's was 25 mg/m^3 but declined over the next three decades to 1-4 mg/m^3 (in the 1980's). Adjusted analyses of lung cancer risk, controlling for smoking, demonstrated a dose response trend for both cumulative indices and duration of exposure. Cumulative exposure to *total* dust (mg/m^3-y) was

categorized as low (< 50), medium (50-119.9) and high (120+). The ORs (95% CI) for lung cancer by cumulative dust categories (low, medium and high) were 2.1 (1.1-3.8), 1.7 (0.9-3.1) and 2.8 (1.5-5.0), respectively. Estimates by ten-year duration categories (0-9.99, 10-19.9, 20+ years) adjusted for smoking were significant as well. Exposure to silica in the tin mines is highly correlated with exposure to arsenic ($r = 0.82$, $p = 0.0001$).

Increased lung cancer risk according to silicosis was reported for subjects from three of the mines in Dachung (OR = 2.4, 95% CI 1.6-3.8) but not in the fourth located in Limu (OR = 0.8, 95% CI 0.3-1.9). The authors note that few subjects were classified as stage 3 silicotics because they likely died from other causes.

2.3.9 Stone

We reviewed three studies of stone workers, one of which was discussed above under the ceramic industry (Ulm, 1998). Although a few additional studies included some stone or quarry workers, either their results were not specifically reported (e. g. British pottery workers) or numbers were too small (e. g. Italian refractory brick workers). Exposure to respirable silica in the stone industries is directly related to the quartz content of the stone as well as the industrial process (i. e. crushing, milling, or quarrying). Dust levels are discussed within the context of the individual studies.

The case-control study conducted within the German ceramic and stone industries was reported by Ulm (1998). Among stone workers, 133 lung cancer cases were identified between 1980 and 1994 using different sources of information. A total of 231 controls were drawn from a register of all workplace accidents occurring during the same time period. Experts generated individual exposure estimates based on available records and knowledge of the work tasks. Smoking information was collected using existing records and by interview, and an index for smoking intensity and duration was developed.

Results are presented for peak, average and cumulative silica exposure and adjusted for different confounders (age at start, latency, duration of exposure, other occupational exposures). Slightly elevated but non-significant ORs were reported for all indices. The OR for stone and quarry workers was elevated for peak exposure (1.25, 95% CI 0.58-2.69), but not for time weighted or cumulative exposures (Ulm, 1999).

Costello (1988) conducted a cohort study of 5,414 male Vermont granite workers (stone sheds and quarries), employed and followed between 1950 and 1982. Subjects had to have at least one radiograph available, taken through a voluntary surveillance program within the same period. Mortality of this cohort was compared with US national rates. All-cause mortality was significantly decreased in this cohort (SMR = 0.91, 95% CI 0.87-0.95), lung cancer mortality slightly elevated (SMR = 1.16, 95% CI 0.96-1.39, based on 118 cases), NMRD mortality significantly increased (SMR = 1.21, 95% CI 1.01-1.44) including 41 cases of silicosis, and a strong excess for tuberculosis was found (SMR = 5.86, 95% CI 4.88-6.99; based on 124 cases).

Exposures before 1940 were reported to be high, especially for shed workers, with a clear reduction after 1940. Exposure assessment was qualitative. A JEM was later developed for the IARC pooled analysis. Smoking information was available for lung cancer cases only (70 %); there were no non-smokers among those with smoking information. Other potential occupational exposures were not reported.

Excess tuberculosis and silicosis mortality was restricted to workers who started work before 1940. Excess lung cancer mortality was found for shed workers, especially for those who started before 1930 (SMR = 1.45; 95% CI 1.05-1.91). No excess risk was seen for quarry workers.

Information on silicosis prevalence was only partially available for the lung cancer cases. The authors concluded that deaths from silicosis and tuberculosis, for those who started work after 1940, were prevented by the implementation of dust control measures and the availability of effective antibiotic therapy.

Finnish granite workers were studied since the 1970's, with the latest follow-up reported by Koskela (1990; 1994). A total of 1,026 male workers first employed between 1940 and 1971, and having worked for at least three months in three regions of Finland were followed through 1989. All cause mortality (SMR = 1.09, 95% CI 0.98-1.21), NMRD mortality (SMR = 2.11, 95% CI 1.55- 2.80) and lung cancer mortality (SMR = 1.40, 95% CI 0.98-1.93; 31 cases) were elevated compared with Finnish national mortality rates.

Dust exposure measurements were available for the period 1970-1972 with geometric means for quartz dust reported of 1.0-1.5 mg/m^3. Cohort members from the smallest region worked with black granite without any silica content. An industrial hygienist generated individual exposure estimates for cases and controls in the nested case-control study (the exposure assessment was later expanded to the full cohort for the IARC pooled analysis). In contrast, the exposure assessment for the cohort analysis was qualitative. Work history and smoking data were available from plant records and questionnaires. Smoking prevalence was assessed, and considered by the authors unable to explain the lung cancer excess.

Analysis of the two regions in which employees worked with granite that contained silica showed differences in lung cancer mortality: in the red granite area the SMR was 1.17 (95% CI 0.69-1.85), and in the gray granite area the SMR was 1.75 (95% CI 1.02-2.81). An analysis of the lung cancer morbidity 1953-1987 showed no difference between regions (SIR = 1.61 vs. 1.81, both statistically significant). Results of the nested case-control analysis were only briefly reported and added little to the overall study.

For 37 silicosis cases identified through death certificates or a disability register, the lung cancer SIR was similar to that of employees without a diagnosis of silicosis (both around 2).

2.3.10 Industrial Sand

Quartz is extracted from sandstone and processed to create silica sand and flour for end use in other industries such as glass and foundries. Potential for exposure varies by job/work areas as well as changes in industrial processes and practices.

We identified two industrial sand worker studies from the United States and Canada. McDonald (2001) conducted a cohort study of 2,670 male workers employed in one of nine plants between 1940 and 1980 with a minimum total duration of employment of 3 years. The cohort was followed through 1994. Steenland (2001b) followed a cohort of 4,626 workers, employed for at least one week in one of 18 plants. Because the earliest years for which records were available varied by plant, follow-up began in 1960 or at the point when records were adequately complete, and ended at the end of 1996. While it appeared that these two studies represented different cohorts, Steenland reported that there could be considerable overlap (Steenland, 2001b).

McDonald reported significant excesses of all cause mortality (SMR = 1.18), lung cancer mortality (SMR = 1.50, based on 83 cases), tuberculosis and non-malignant respiratory disease (SMR = 3.93 and 1.78) in the total cohort with at least 20 years latency, using national rates. Steenland reported similar results, without consideration of latency: all cause mortality (SMR = 1.23, 95% CI 1.16-1.31), lung cancer (SMR = 1.60, 95% CI 1.31-1.93; based on 109 cases), NMRD not reported, but significant excesses were noted for silicosis/pneumoconiosis and tuberculosis.

In both studies JEMs were constructed (Rando, 2001; Sanderson, 2000) based mostly on personal sampling data obtained since 1974, and some historical data from unpublished reports of industry wide surveys conducted in 1946 or later. These were used in the nested case-control study by Hughes (2001) and in the cohort and nested case-control analyses by Steenland (2001b). Smoking data were collected from medical records and interviews with next-of-kin for the nested case-control study (Hughes, 2001). Smoking data in the Steenland study were obtained from company records for the period 1978-1989 for less than 10 % of the cohort; based on the sample, influence of smoking was assessed by indirect adjustment.

Hughes reported that smoking adjusted ORs for lung cancer were significantly related to cumulative (OR = 2.07, for highest category > 4.5 mg/m^3-y) as well as to average silica exposure (OR = 2.48, for highest category > 0.26 mg/m^3). Seven cases were non-smokers. There was no indication of any interaction between smoking and silica exposure.

Positive, but non-significant exposure-response trends were found in the Steenland cohort and in the nested case-control study. Trends were more pronounced when short term workers (less than 6 months) were excluded (OR = 1.70 for highest cumulative exposure category > 1.285 mg/m^3-y; OR 2.25 for highest average exposure category > 0.065 mg/m^3). Indirect adjustment for smoking suggested little influence on risk estimates.

Data on silicosis status were not available for either cohort. It was reported that other occupational lung carcinogens played no or only a minimal role in the health effects of these cohorts.

2.3.11 Diatomaceous Earth

Exposure in the diatomaceous earth industry is to amorphous silica, a form considered less toxic than crystalline silica. Conversion of amorphous silica to cristobalite occurs during processing of diatomaceous earth that involves temperatures of 1,000 °C or higher. Levels of quartz in diatomaceous earth are believed to fall below 4 %. We reviewed studies for two cohorts of diatomaceous earth industry workers.

The first, a study of workers from the United States was conducted by Checkoway (1993; 1996; 1997; 1999). The cohort consisted of diatomaceous earth workers employed on or after 1942. The first follow-up (Checkoway, 1993) included white male workers from two plants, employed for at least for one year between 1942 and 1987, with no known exposure to asbestos from previous employment. Women, black males and a group of potentially asbestos-exposed workers were investigated separately. Exposure assessment was semi-quantitative and smoking data were available for about half of the cohort. Significant excesses of lung cancer and NMRD were found, based on both national and local referent rates, with increasing RR for increasing cumulative exposure. The possible effect of asbestos exposure was subsequently reanalyzed, based on exposure assessment, and was found not to be an important confounder (Checkoway, 1996).

The follow-up through 1994 (Checkoway, 1997) was restricted to 2,342 workers from the larger plant, including the asbestos-exposed workers, and utilized a quantitative exposure assessment. Compared with the national population, no excess in all cause mortality (SMR = 1.02, 95% CI 0.94-1.09), an excess of lung cancer (SMR = 1.29, 95% CI 1.01-1.61; based on 77 cases) and an excess of NMRD (SMR = 1.79, 95% CI 1.44-2.20) were found. The SMR for lung cancer based on local rates was somewhat higher (SMR = 1.44, 95% CI 1.14-1.80).

A JEM was developed (Seixas, 1997) based on more than 5,700 air monitoring samples (total dust, respirable dust) taken since 1962, and approximately 700 particle count measurements available from reports for the period 1948-1962. Crude smoking data were available for around 50 % of the cohort from company medical surveillance program in place since the 1960's.

A strong exposure response trend was found for NMRD, and a weaker, monotonically increasing one for lung cancer. The RR for the highest cumulative exposure category ($\geq$ 5.0 mg/m^3-y) lagged by 15 years was 2.15 (95% CI 1.08-4.28). Asbestos was not a confounder and did not appear to have a synergistic effect. The influence of smoking on these results was assessed to be low.

For 77 % of the cohort, chest radiographs were available beginning in the 1930's from the companies' medical surveillance programs. A total of 81 cases with radiographs at or above ILO 1/0 were detected (Checkoway, 1999). An excess of lung cancer was found in the highest exposure group ($\geq$ 5 mg/m^3-y) for both the non-silicotic (SMR = 2.40, 95% CI 1.24-4.20) and the silicotic group (SMR = 2.94, 95% CI 0.80-7.53, based on 4 cases). Indirect adjustment for smoking partially reduced the observed excesses. Because the surveillance program ended with termination of employment, the authors tried to evaluate the possible influence of undetected silicosis among the non-silicotic group by truncating follow-up 15 years after the final negative radiograph. No real differences were observed and the SMR trend remained significant.

The Icelandic study investigated cancer incidence among a cohort of 1,346 men and women employed in a diatomaceous earth plant that operated until 1967 and followed the cohort through 1991 (Rafnsson, 1997). Relatively high exposures were reported for different jobs, based on measurements made in 1978. No excess of lung cancer was observed (SIR 1.14; 95% CI 0.37-2.65, based on five cases). Exposure assessment was conducted qualitatively and smoking data were available from a

survey for 65 % of the cohort. No cases of silicosis were detected in the cohort. The authors mentioned the short exposure time and follow-up period of the cohort as a weakness of the study.

2.3.12 Miscellaneous Studies

A hospital-based case-control study was conducted to investigate the relationship of lung cancer to silica exposure through work in "dusty trades" (Mastrangelo, 1988). Subjects were quarry, tunnel or mine workers. Occupation was unknown for nine subjects and an additional 58 were classified as "other". Cases were 309 incident lung cancer patients admitted to hospital in Belluno. Controls were patients admitted to the same hospital for other conditions, excluding chronic bronchitis. Estimates of lung cancer relative risk were largely close to null. There was slight increase in risk with increased duration though the trend was not significant. Estimates from conditional logistic regression analyses for those in the longer duration categories 10-14 or 15+ years were 1.4 and 1.6, respectively.

Nakagawa (2000) conducted a mortality study of Japanese tunnel workers, based on a survey conducted in 1977-1978 among all male inhabitants over age 30 from five areas with a high incidence of silicosis, with a response rate of 94 %. Among respondents, 603 persons had a history of tunnel work and 1,125 had no history of any occupational dust exposure. Both groups were followed through 1994. Compared with national rates all cause mortality (SMR = 1.20, 95% CI 1.04-1.38) and lung cancer mortality (SMR = 1.88, 95% CI 1.13-2.94) were elevated among the tunnel workers but not in the non-exposed population.

Exposure was reported to be high but neither quantitative nor more precise qualitative exposure assessments were conducted. Smoking information for both cohorts was available from the baseline survey. After adjustment for age and smoking, tunnel workers showed a higher lung cancer risk compared to the non-exposed cohort

(RR = 2.15; 95% CI 1.05-4.38). Other occupational exposures were not controlled in the analysis but assumed to be negligible. No information about silicosis was presented.

Neuberger (1990) identified and followed two cohorts that included silica-exposed workers. Between 1950 and 1960 around 250,000 workers in Vienna participated in a voluntary screening (an estimated 75 % of the active workforce). Of these, 1,630 male workers, age 40 and over, were determined to have been exposed to high levels of silica (at least 5 years to more than 6 mg/m^3). Included in the cohort were an equal number of male workers from the same source, matched by age, year of examination and smoking history. Compared with local mortality rates, all-cause mortality among the silica-exposed cohort showed a small but significant excess (SMR = 1.14, 95% CI 1.08-1.20). Also elevated were mortality from lung cancer (SMR = 1.69, 95% CI 1.45-1.96, based on 179 cases) as well as from NMRD and tuberculosis (numerical results not reported). The non-dust-exposed cohort had a reduced all-cause mortality, but had a slightly elevated lung cancer mortality (SMR = 1.18, 95% CI 1.00-1.40).

Risk estimates for lung cancer by industry were presented for foundries (SMR = 1.64, 95% CI 1.31-2.03), other metal industries (SMR = 1.33, 95% CI 0.96-1.79), the ceramics and glass industry (SMR = 2.37, 95% CI 1.57-3.43) and the stone and construction industry (SMR = 2.94, 95% CI 1.64-4.85). Compared with the non-dust-exposed cohort, the lung cancer RR was 1.4. The possible influence of other occupational exposures was discussed in the paper. Information concerning silicosis was not reported.

3 Quality Review/Assessment

In the previous section we described the methodological criteria necessary for a quality assessment of epidemiological studies on occupational silica exposure and lung cancer. An overview of the selected literature was provided, structured according to industry and study population. For each study population, an overview was provided on the various publications available and their relevant results were summarized. This section provides more detailed review of studies by examining the quality of their treatment of the essential elements pertaining to silica exposure, exposure to other occupational lung carcinogens, and tobacco smoking. Any study population for which these aspects have not been convincingly addressed was excluded from the synthesis of the evidence in the next chapter.

In addition to specific design characteristics, studies were examined for the following areas of particular relevance:

- ability of the studies to separate effects associated with silica exposure from possible effects of other *relevant* occupational exposures;
- ability of the studies to assess and control the influence of tobacco smoking characteristics of the populations on the risk estimates for silica and lung cancer; and
- ability of the studies to provide estimates for different silica exposure levels or a dose-response analysis.

Studies were also assessed to determine the ability of the studies to inform the relationship between silica exposure, silicosis and lung cancer.

One possible problem relevant to a number of reviewed studies was the potential for selective survival bias, as a result of competing causes of death. In other words, some of the study populations experienced high mortality due to causes

other than lung cancer. The resulting ("surviving") population is not representative of the population as a whole or the silica-exposed group at risk. In populations subjected to extremely hazardous conditions, including very high concentrations of silica dust, death may occur in a substantial proportion of individuals that otherwise would have developed cancers had they survived. Thus, the relationships observed between exposure and lung cancer among selectively surviving populations may be biased due to selective survival. For this reason, we believe that the results of studies in which competing causes of mortality are substantial are unlikely to validly reflect the relationship between silica exposure at levels relevant to modern workplaces in Europe and North America today and lung cancer. Such studies were also excluded from the final assessment of evidence.

3.1 Other Occupational Exposures

Many of the workplaces in which silica is present may have other lung carcinogens present. The following factors have been identified as potential occupational risk factors for lung cancer, and therefore must be considered as potential confounders in the reviewed studies: radon and radon daughters; polycyclic aromatic hydrocarbons (PAHs) including diesel exhaust, coke fumes and other products of the combustion of organic materials; asbestos; chromium; and arsenic. The extent to which any of these correlate with silica exposure will determine the extent to which confounding is likely, and the stronger the correlation the more difficult it is to separate the effects of each exposure using epidemiological methods. These potential lung carcinogens are also of concern, but to a lesser extent, in workplaces where silica-exposed individuals might have been employed prior to the silica-exposed job.

In the industry overviews we reported on the potential for confounding by other occupational exposures for each industry and population. Table 3 summarizes these results by industry and study population. Each cohort has been assigned a summary assessment, if possible, of whether important potential confounders have been identified and controlled.

Within the *pottery/ceramics industry* only the Chinese cohort reported significant exposure to other lung carcinogens (PAH), and it was not possible to separate effects from those of silica exposure (Cocco, 2001; McLaughlin, 1992). For all other study populations it was stated that there was no relevant influence of other exposures, or they were reasonably controlled by other means (e. g. persons with other occupational exposures were excluded).

In both cohorts of *refractory brick* workers, no or only weak influence of other occupational exposures on the risk estimates was reported. It is possible, however,

that the Chinese cohort had substantial asbestos exposure, as Xu (1996a) reported asbestos exposure among a cohort that probably overlapped with this refractory brick cohort.

In the cohorts of *silicon carbide* workers, the potential for PAH exposure was assessed to be low, and exposure to asbestos was controlled in one study (Infante-Rivard, 1994; Romundstad, 2001). This study (Norwegian) also showed a high correlation between silica and SiC fiber exposure, precluding separation of any effects of each.

In the studies of *foundry workers* simultaneous exposures to other occupational lung carcinogens were reported, mainly PAH, which could not be separated or controlled in the analysis. Therefore, the influence on the silica risk estimates is difficult to assess, with the possible exception of the US study, were coal tar pitch was not used and therefore relevant PAH exposure was assessed to be unlikely.

The group of *miner* studies represents a diverse range of mining products and other possible occupational exposures including radon, asbestos, diesel exhaust (PAHs), and arsenic. Some of these potential confounders would vary by mine location (geographically as well as underground vs. surface), and the methods of ore extraction used.

In the Chinese study of mine and pottery workers, assessment of other occupational risk factors for lung cancer was based on measurements made in 1988-1989, with little or no information available before that time. These measurements showed only low exposures for copper/iron miners to arsenic and other metal and compounds (Wu, 1992). PAH exposure levels were higher, and in some mines, substantial radon levels were measured, however, no assessment of the possible correlation between silica exposure and radon and PAH exposure was reported. No asbestos exposure was detected.

For *tungsten* miners from this cohort, the only information available is based on the distribution of cases and controls across categories of cumulative exposure. Arsenic exposure was classified as low to medium, and PAH and radon exposure were assessed as relatively high.

Exposure data for the *tin miners* was also only available for recent years, beginning 1988-1989. In both studies, radon exposure was estimated to be low, but in the larger study by Chen (2002), exposure to arsenic was estimated to be relatively high. More importantly, a high correlation between dust, silica, arsenic and PAH exposure was reported, and therefore any individual effects of these could not be separated in the statistical analysis.

Most studies of *gold miners* acknowledged the presence of other exposures and at least partially assessed them, with the exception of the Canadian miners, who were potentially exposed to a variety of unmeasured substances including arsenic, radon and asbestos. For the Australian and two of the three South African study populations, radon levels were measured and the potential for confounding discussed. However, it is not possible to completely rule out some confounding by radon, as it is likely correlated with silica exposure which could result in an overestimate of risk associated with either exposure.

In neither the study of the *Finnish copper and zinc sulfide ore miners* nor the *Sardinian metal miners* were other occupational exposures adequately addressed, although some efforts were made to identify and in some cases estimate exposure levels. However, most of these factors were not considered in the statistical analyses.

The studies of *stone workers* reported no relevant influence from other exposures and controlled for exposures in previous employment periods outside the industry.

Both cohorts of *sand workers* reported a possible influence of asbestos exposure or exposure to diesel exhaust fumes, but these were assessed by the researchers to have little or no influence on the silica risk estimates.

Asbestos as a potential confounder was discussed in the *diatomaceous earth* cohorts, but seemed to be irrelevant in the Iceland cohort. In the US cohort, asbestos exposure was controlled by use of an asbestos exposure assessment in the analysis.

Other possible occupational risk factors are not mentioned in the hospital-based case-control study in Italy (Mastrangelo, 1988) and in the study of Japanese tunnel workers. They are also not controlled in the Austrian dusty trade study.

3.2 Smoking

Cigarette smoking is a recognized risk factor for lung cancer and a clear dose response relationship exists between the number of cigarettes smoked per day and risk of lung cancer. Risk is also strongly related to duration of smoking as well as time since smoking cessation for former smokers, as risk drops substantially shortly after quitting (Blot, 1996; Finkelstein, 1998; Peto, 1986). Therefore, dose and duration are important exposure measures for assessing the risk of lung cancer among smokers. It is necessary to fully control for confounding bias that might otherwise hamper a valid assessment of lung cancer risks associated with other exposures or risk factors.

Quality of individual smoking data depends on the source and completeness of the information. The overall reliability and validity of information concerning smoking habits should be reasonable if they are based on periodic standard interviews (e. g. during medical examinations) rather than on single interviews

recorded at one point in time for other purposes (e. g. start of surveillance, one time survey, or compensation claims).

One limitation of several reviewed studies was that large proportions of study subjects had no smoking data available. In such cases it was often assumed that the available data were representative for the whole group; however, this assumption rarely is or can be tested. In numerous populations the prevalence of smoking is high, often reaching or exceeding 80 %, making it difficult to control for smoking by comparing rates of lung cancers among smokers exposed to silica with those of non-smokers exposed to silica. Often there are very few lung cancer cases among non-smokers, resulting in highly unstable risk estimates.

Cohort studies most often incorporate general population reference rates. Typically, the main concern regarding the use of external referent populations is that the cohort and the reference population differ in their distribution of smoking habits. A specific problem arises when the SMR analysis for smoking specific strata is conducted and expected values for the specific strata are based on the combined smoking and non-smoking reference population rates. This leads to an unavoidable overestimation of the risk for the exposure among smokers, and to an underestimation among non-smokers. Although this should be a well-known problem, it can still be found in publications (e. g. in the Dutch ceramic worker and in the Sardinian miner studies included in this review).

A simple assessment of the possible effect was presented by Axelson (1978) and is often used, mostly in the absence of complete smoking data, to assess the influence of the confounder "smoking" on the calculated summary risk estimate for lung cancer. Though this approach seems intuitive, it may not always succeed in eliminating confounding, and, under certain circumstances, can be shown to increase confounding in the study data. Additionally, indirect adjustment should consider differences in the age structure of the cohort and the reference

population with regard to prevalence rates, but this is rarely the case in practice. Further, choice of standard RRs for indirect adjustment may influence the results, and may be population-specific.

Because of the strong association between smoking and lung cancer, even moderate correlation between smoking and the risk factor of interest can lead to a spurious association between the risk factor and lung cancer. In many of the studies reviewed, smoking and silica exposure were correlated. Studies that fail to adequately control for the effects of confounding due to smoking cannot be considered valid for purposes of this review and are excluded from the final synthesis of evidence.

Where individual smoking data are available, the role of smoking may be assessed or at least controlled using multivariable analyses such as logistic regression. In table 4 we describe the sources of information on smoking for each study population, the completeness of information, and the estimated prevalence of smoking in the specific study populations. While many studies have at least one measure of smoking on most cohort members, completeness of smoking information varied considerably between the studies. The observed prevalence of "current" smoking (not always representing the same time period) also varied.

Table 5 lists the approach used to assess the influence of smoking on the risk estimates from each population, as well as an assessment of both the quality of the available data and the use of the data in the analyses. Considering the importance of potential confounding due to smoking on the validity of study results, a surprising proportion of reviewed studies were found to have no useful smoking data or to have inadequately used the available data to evaluate the role of smoking as a confounder.

Table 6 shows the distribution of lung cancer cases from each study population by smoking status. It can be seen from this table that most of the lung cancers were observed among smokers – not surprising in the light of the high prevalence in the cohorts and the fact that smoking is a strong risk factor. However, lung cancer cases were not restricted to smokers. Lung cancers among non-smokers were consistently highest among the Chinese study populations, groups previously noted as having a high probability of exposure to multiple occupational lung carcinogens.

3.3 Silica Exposure Assessment

While it is relatively clear that all study populations have been exposed to silica, the levels at which individuals or even the study group as a whole were exposed is often even unknown. Even if total dust measurements are available, the silica content of the dust can vary considerably. Ideally, the exposure of interest is the level (intensity and duration of exposure) of crystalline silica in the respirable fraction of airborne dust. Also unclear is the type of crystalline silica to which each study population was exposed. There may be different risks associated with the different types (such as cristobalite, or freshly fractionated quartz, etc.).

Apart from the different types of silica exposure possible, levels of exposure vary tremendously by industry, geographical location, and especially historical time periods. Other potentially important – but rarely addressed – factors include availability and use of personal protective equipment, workplace ventilation and individual work practices.

Most of the studies reviewed were not able to provide detailed exposure information beyond a qualitative exposure assessment based on crude surrogate measures or indicators for levels of exposure (e. g. duration of employment or calendar year of employment in an exposed industry). Some studies estimated

individual exposure using job titles or specific job groups or sections of the industry. Even in settings where personal monitoring is performed, rarely are data adequate to directly estimate individual exposures. Inevitably, estimates of exposure are ecological, increasing the potential for misclassification of exposure and subsequently limiting the validity of risk estimates. Table 7 presents an overview of the reported exposure assessment techniques used for each study population as well as an assessment of the relative quality of these measures. Because the quality of the exposure assessment directly influences and may determine the validity of the study results, the exposure aspects of each study are considered in greater detail, by industry.

Exposure in the *British Pottery workers* study was to quartz, but with conversion of a proportion during heating processes into tridemyte and cristobalite. The study exposure was based on 390 area air samples (1950's-1960's) with particle counts, and 1,000 personal samples with gravimetric silica mass (late 1960's on) collected for government or industry surveys under "representative" conditions. Particle counts were converted according to Rice (1984): 1mppcf silica = 0.09 mg/m^3. For the earlier (and heaviest) exposure periods from 1930 to the 1960's, when no or only few measurements were available, judgements based on engineering changes or dust control measures were made. A JEM by 10 year calendar period and 12 job/work areas was constructed with mean estimated exposure levels in the range of 0-0.80 mg/m^3, usually between 0.05 and 0.20 mg/m^3.

There was an overall trend of reduction over the 60 years, approaching a 10-fold decrease for most jobs, but with considerable variation by process and decade. Prevalence of radiographic change in a sub-cohort (minimum employment 10 years, started work before 1960) was used to validate the matrix. The JEM was applied in the nested case-control study for cumulative, average and peak

exposure, either as dichotomous or continuous variable, with and without lagging of exposure.

A JEM (Dosemeci, 1993; Dosemeci, 1995) was constructed for the study of 29 Chinese mines and potteries based on more than two million historical total dust records and, for more recent years, a much smaller number of samples of free and respirable silica content. For estimates of respirable crystalline silica, median current and historical measurements over all jobs and time periods on a facility level were used and linked to individual work histories.

Because Chinese and US/European sampling and analysis techniques differ, 143 side-by-side samples were collected during a 1988-1989 survey, using both techniques (Zhuang, 2001). Substantial differences in results were noted, indicating that exposure levels obtained for the Chinese studies were not comparable to those derived from Western studies. A conversion factor was derived based on the ratio of the respirable silica concentration as measured by the US/European method to the Chinese total dust concentration for every sample. The combination of industry-wide and facility-specific conversion factors was then used to estimate the historical respirable silica exposure for each job/facility/time period for the JEM, with the assumption, that the historical relationship was unchanged.

Estimates were used in the nested case-control study published by McLaughlin (1992) grouped by mine/facility type. In a paper by Zhuang (2001), a modified JEM was described, later used in the Chen (2002) tin miner study. More than 17,000 total dust estimates from the earlier JEM and 347 samples of crystalline silica in settled dust were available. Most (20 of 23) samples collected from the copper/iron mines and around 40 % of the samples in the other mines/facilities were below the limit of detection for silica.

Exposure assessment for the *pottery* facilities was based on 1,113 total dust measurements (area samples) since 1956 in the nine plants. Assignments to seven exposure levels were made by the local hygienists/physicians for facility/job/calendar year based on available monitoring data (time dependent) and consensus estimates. The JEM described above was used. For respirable dust and free silica content, median historical (14 % of total measures) and current measurements were calculated over all jobs and time periods for each facility and used in the analysis (because of lack of historical information on job level). Estimated average respirable silica exposure between 1950 (0.75 mg/m^3) and 1987 (0.65 mg/m^3) was consistently high with only weak reductions over time. Categorized by job title, the highest exposures were estimated for ore crusher and ore mixer (1.47 vs. 4.70 mg/m^3; average over all periods) and the lowest for maintenance workers (0.32 mg/m^3). Risk estimates were reported by categories of cumulative exposure.

No "usable" quantitative exposure measurements were reported to be available in the *Dutch ceramic workers* study. Exposure was highly correlated to stage of production and therefore classification according to job description included "high", "medium", "low" or "no" silica exposure, but the basis for this assignment was unclear, even after reviewing two earlier published papers on the same group.

In the *German ceramic workers* study individual exposure assessment – assignment to 6 classification levels around the MAK value of 0.15 mg/m^3 – was made by expert judgement based on available information for the individual job (measurements, technical work place information) and the individual work history. Median exposures for both cases and controls were reported by year of hire, falling from 0.07 mg/m^3 in the years before 1960 to 0.04 mg/m^3 after 1980. The reported median cumulative exposures were 2.91 mg/m^3 (0.15-22.32) for cases and 2.91 mg/m^3 (0.18-11.52) for controls. Risk estimates were presented for

cumulative, average and peak exposure as dichotomous variables. Results were also adjusted for duration of employment and year of hire, which might have lead to over-adjustment (essentially controlling for the risk factor of interest, exposure, which artificially reduces risk estimates in the presence of an effect).

The *Italian ceramic workers* study reported no quantitative exposure assessment nor any information concerning exposure levels – except that exposure was "heavy" in the past and there were still fairly high dust concentrations in most plants. Further, the exposures in the 1980's were reported to have a high percentage of free silica (data not presented). Analysis was conducted by job title and duration of employment as exposure surrogates or indicators.

In the *refractory brick industry* exposure was reported to be to relatively pure quartz. No exposure assessment was provided in the *Chinese study,* and the *Italian* study relied on a qualitative assessment, e. g. by calendar period. Respirable dust measurements were available for 1975 to 1977, with geometric means in the range of 0.2-0.56 mg/m^3 and the maximum percentage crystalline silica in three areas was reported to be between 29.5 % and 64.6 %.

Both studies in the *silicon carbide industry*, where exposures are to quartz, cristobalite and silicon carbide fibers, conducted a quantitative exposure assessment. The assessment in the *Canadian* study was restricted to "total dust" because information was not available for all jobs. The assessment was based on 121 measurements from two of the three plants, and a JEM was constructed for 29 job titles. Analysis was conducted using cumulative exposure.

Exposure assessment in the *Norwegian* study was based on more than 6,000 dust measurements, two thirds of them conducted between 1950 and 1974 as short-term dust measurements (particle count) and about 2,000 as personal measurements of total dust. Between 1982 and 1988 around 200 short-term SiC

fiber measurements and 200 crystalline silica measurements were conducted. These were used to characterize the dust exposures for the entire study period. The crystalline silica content consisted of quartz and cristobalite combined, with different proportions of each in different areas. Measurements based on particle count were not converted but used to assess the relative changes in exposure. Exposure before 1950 was estimated. A JEM was constructed by job and time period. The authors expressed uncertainties about their exposure assessment, particularly in the categorization of total dust into different types of particulates. They also noted substantial differences between their estimates and those of the Canadian study, which could not be due to differences in technology or production processes. Results were reported by cumulative exposure, with and without lagging of exposure.

Exposure assessment in the *Spanish foundry* study was qualitative, by job category, year of hire and duration of exposure.

The nested case-control study within the *US foundry* cohort provided a semi-quantitative exposure assessment, where an industrial hygienist assigned levels of exposure (high, medium, low) to 107 job titles based on measurements, technical information, job descriptions, workplace knowledge, etc. To conduct an analysis for cumulative exposure, quantitative values which were derived from actual sampling data were assigned to the different levels and summarized over the respective work history.

The exposure assessment in the *French foundry study* was similar. For analysis of cumulative exposure, an intensity score was constructed, but not for the specific plant areas (e. g. foundry). In an earlier follow-up of the cohort, a qualitative exposure assessment was conducted within the foundry area.

The exposure assessment for the *Chinese iron and steel* complex was based on more than 80,000 dust and benzo-a-pyrene (BaP) measurements between 1956 and 1992. A JEM was constructed for total dust and for BaP. Exposure levels before 1955 were assumed to have been the same as the 1955 level. Details of the available measurements, the sampling methods, conversion factors used, and determination of the respirable silica content were not reported. Risk estimates were presented for cumulative exposure (high levels of silica exposure), but not specific plant areas (e. g. foundry).

A panel of experts ranked potential exposure for each job for all *Australian gold miners.* Actual measures from the Kalgoorlie mines had been destroyed. Semi-quantitative and cumulative exposure estimates were made for all miners based on job history. Separate estimates were made for surface and underground miners. Radon levels were believed to be negligible (de Klerk, 1998). Armstrong (1979) reports maximum levels measured in the early 1970's at 0.045 WL, with most measures considerably lower.

Ontario gold miners were likely exposed to arsenic, radon and mineral fibers as well as to silica. Miners had histories of work in other types of mines, including nickel, silver, iron lead/zinc and uranium. Measurements of dust before the 1950's indicated concentrations as high as 1,000 particles/ml for some jobs. Average concentrations by the 1960's were along the order of 200-400 p/ml. Radon was not measured prior to 1961. Average estimates from measures in the 1980's were 0.02-0.3 WL depending on the mine and location. Estimates of WLM (working level months) were calculated based on the average WL. An index of arsenic exposure was calculated for all miners based on duration of employment and arsenic measures in each mine. Percentage of free silica was based on a 1978 survey of respirable silica and dust. The reported range was 4.3-11.8 % free silica. Analyses incorporated exposure indices for arsenic and radon, though no analyses were presented that directly addressed silica exposure. Analyses were

presented by year of first employment in the mines, years since first employment and type of ore (nickel or gold).

South African gold miners were likely exposed to radon as well as silica. The rock composition in the Witwatersrand Reef is mostly quartz (70-90 %). All of the studies we reviewed of South African miners calculate exposure estimates using results for the number of respirable particles per cubic meter as well as surface area of respirable dust from a 1971 paper by Beadle (1971) detailing shift-long dust exposures for 20 South African gold mines. Estimates of exposure in the two case-control studies (Hessel, 1986, 1990) were based on the number of shifts in a dusty occupation weighted by a proportional estimate of the dust level for each job. Estimates in the cohort and nested case-control study of Hnizdo are calculated for cumulative exposure and duration underground in dusty jobs. Reid and Sluis-Cremer created six categories of dust exposure based on shift and occupation. None of the South African mining studies had direct measures of radon, though all describe the average WL as low.

The exposure assessment in the *US gold mines* was based on job titles and average dust exposures. Dust measurements were available for the years 1937-1975. No measurements were available for the early years of mine operations (1900-1937). Wet drilling was not introduced until approximately 1920 (McDonald, 1978). Median exposure levels in 1937 were in the range of 4.3-28.9 mppcf. Given the estimates of silica in settled dust (39 %) the American Conference of Governmental Hygienists (ACGIH) exposure limit would be approximately 6.1 mppcf. Steenland (1995) reports that levels prior to 1950, when 58 % of the cohort began work would have ranged from 10-30 mppcf. Cumulative exposure was based on estimated daily dust for each job category multiplied by an estimate of time spent underground. Risk estimates were calculated for cumulative dust days (one day of 1 mppcf exposure) and by year of

hire. Exposure assessment was based on total dust only. Exposure estimates for silica or other factors (non-asbestiform amphiboles) were not available.

Reported total dust exposures in a *Chinese tin mine* (Fu, 1994) were around 25 mg/m^3 in 1952, much higher between 1955 and 1957 (up to 128 mg/m^3), but much lower after implementation of wet drilling, ventilation and personal protective measures in 1957 (between 2 and 5 mg/m^3). Silica content of total dust was estimated to be around 24 %. Despite the availability of some actual exposure monitoring results, exposure assessment in the study was qualitative.

Exposure assessment for *Chinese tin miners* was based on the JEM constructed for the whole study cohort of Chinese miners and pottery workers. Measurements were available beginning before the 1950's, and total dust concentrations were determined to have fallen from 25 mg/m^3 total dust before 1950 to 1-4 mg/m^3 in the 1980's. Respirable silica concentration of the total dust was estimated to be 3.6 % (± 0.8 %). The more recent analysis of the tin miners used only cumulative exposure to total dust in the statistical analysis, while the first analysis conducted in 1992 also reported estimates for cumulative respirable silica exposure, showing high levels of exposure (average 1950-1987: 1.31 mg/m^3) but also high correlations among different exposures.

Similar results were found for *tungsten* miners from the same study. Average respirable silica exposure was assessed to be 1.75 mg/m^3 between 1950 and 1987. Estimates for cumulative exposure are reported. The average silica exposure for *iron and copper* miners from the same study and time period was estimated to be 0.32 mg/m^3.

Dust exposure was estimated to be extremely high (several hundred mg/m^3 total dust) before implementation of ventilation and wet drilling between 1955 and 1963 in two *Chinese iron ore mines* (Chen, 1990). Few more recent

measurements were available and no levels of respirable silica are reported. Exposure assessment was conducted by grouping job titles into levels of estimated dust exposure (none, low, medium, high); 64 % of the exposed were classified in the highest category.

Exposure assessment was qualitative (years worked as an underground miner and year of hire) in the *US metal miners* study; information concerning exposure levels in the mines is not reported.

Exposures in the *Finnish sulfide ore miners study* are described only and not considered in the analysis. Mean estimated concentrations of respirable silica in one of the two new mines under study were noted to range from 0.16 mg/m^3 before 1965 to 0.08 mg/m^3 in the 1980's, but were much higher for specific jobs.

The *Sardinian miner studies* were conducted in two mines with very different quartz content of the ore. One mine had a low quartz content (between 0.2 and 2 %), but higher radon levels (average 0.13 WL), and the other mine had higher quartz contents (between 6.5 and 29 %) but low radon levels (average 0.12 WLM/year). The reported respirable dust concentrations were similar in the underground mines and estimated to be between 3 and 5 mg/m^3 until the 1960's and, based on measurements, approximately 1.7 mg/m^3 in the 1980's. For the surface workers the reported silica levels averaged 0.007 mg/m^3 in one mine and 0.09 mg/m^3 in the other. Exposure to silica therefore could be assumed to be low over the whole period in one mine, but not in the other. However, no quantitative exposure assessment was conducted and analysis was restricted to duration of employment, specific mine, and underground or surface work.

Methods for exposure assessment among *German stone workers* were described previously in the pottery/ceramics section. Median exposures for cases and controls were reported by year of hire, falling from 0.24 mg/m^3 before 1940 to

0.05 mg/m^3 after 1980. Estimated median cumulative exposures were 3.24 mg/m^3 (0.12-25.9) for cases and 2.61 mg/m^3 (0.12-27.9) for controls.

Exposure assessment for the *Vermont granite workers* was qualitative in the primary reports, though a JEM was later developed for the IARC pooled analysis (median cumulative exposure 0.71 mg/m^3; median average exposure 0.05 mg/m^3). No details about the methods of exposure assessment have been published to date; it can be assumed that they may be based on measurements reported by Theriault (1974). Exposures were reported to be high before 1940, on average 40 mppcf total dust for cutters. After implementation of a program for dust control at the end of the 1930's, average values were estimated to be less than 10 mppcf total dust (approximately 0.1 mg/m^3 respirable quartz).

Dust exposure measurements were available in the *Finnish granite worker study* for the period 1970-1972, with geometric means for quartz dust reported at 1.0-1.5 mg/m^3. Subjects from the smallest region within the cohort worked with black granite without any silica content. An estimation of individual exposure in the nested case-control study was made by an industrial hygienist (the exposure assessment was later expanded to the full cohort for the IARC pooled analysis). The exposure assessment of the full cohort, however, was on a qualitative level.

Both *industrial sand worker studies* used quantitative exposure assessment in their analyses. In the sand worker study conducted by McDonald (2001), roughly 14,250 exposure measurements taken between 1974 and 1998 (mostly personal samples), plus about 500 samples from 1947-1955 (particle counts from a portion of plants under study) were available for assessment. A conversion factor was computed based on 14 samples (1 mppcf = 0,276 mg x % silica) and a JEM constructed for exposures on or after 1970 using the arithmetic mean of each of 244 job groupings for a time segment where no process changes occurred. For the time period before the 1970's the data were extrapolated back until some

process change was known to have occurred. For the periods preceding the changes, available historical data from three plants were used, and in the others industry-wide geometric mean values were used. Historical data were assumed to be representative for the period before 1947. The geometric mean after 1973, based on a nine plants, was estimated to be 0.042 mg/m^3 (range by plant 0.02-0.107), with wide variation between job groups. The JEM was used for the nested case-control study. Estimates for cases and controls were constructed for the years 1910-1996. For the 1930's and 1940's the exposure was estimated to be approximately 0.4-0.5 mg/m^3 and less than 0.05 mg/m^3 in the 1980's. Results were reported for categories of cumulative and average silica exposure, with and without lagging of exposure.

The second *sand workers study*, conducted by Steenland (2001b), was based on similar exposure data. About 4,270 exposure measurements were collected between 1974 and 1988 (personal samples) and roughly 150 samples were available from 1946 (again particle counts were from only some of the plants under study) for the exposure assessment. The conversion factor used in this study was based on conversion factors estimated for other studies (e. g. North Carolina dusty trades, Vermont granite) and was much lower (1 mppcf = 0.1 x % silica) than in the McDonald study. A JEM was constructed by predicted values from a general linear model with four categories of plants, three time periods and ten job categories for the period 1974-1988. Linear extrapolation from 1946-1974 for each job category was conducted and exposures before 1946 were assumed to be constant. The median exposure for 1946/1947 was 0.078 mg/m^3; the geometric means for 1974-1979 and for 1985-1988 were 0.051 mg/m^3 and 0.012 mg/m^3, respectively. The validity of the matrix was supported by positive dose-response trends for diseases related to silica. Results were reported by categories of cumulative and average exposure, though the correlation between cumulative and average exposure estimates was reported to be 0.45.

A JEM was developed (Seixas, 1997) for the *US diatomaceous earth* industry workers based on more than 5,700 air monitoring samples for total and respirable dust (particle count and mass) and around 700 particle counts taken from reports from the period 1948-1962. Conversion factors for respirable dust were derived from periods where two comparable measurement methods were used. Pre-1948 exposures were estimated by extrapolation, based on temporal changes and knowledge of exposure reduction interventions. The silica content estimates were based on measured concentrations of bulk product samples, not on airborne dust measurements. The estimates for silica content and respirable dust were combined by using estimated job-specific fractions of exposure times to these products. The mean cumulative exposure to respirable crystalline silica (mostly in the form of cristobalite) was estimated to be 2.16 mg/m^3-years (median: 1.06). Risk estimates were reported for categories of cumulative exposure, with and without exposure lagging, and later using different regression models (Rice, 2001).

Analyses in the *Icelandic diatomaceous earth* cohort were based on a simple qualitative exposure assessment. Exposure assessment in the Italian hospital-based case-control study of workers in *dusty trades* was qualitative, as it was in the Austrian *dusty trade study*. Both studies reported results by categories of industry.

3.4 Silicosis

The diagnosis of silicosis, like many of the pneumoconioses, is complex and subject to misdiagnosis. For each publication we evaluated the diagnostic criteria used, including radiograph, ILO standards, pulmonary function tests, time of diagnosis, and elimination of other possible pneumoconioses.

Pneumoconioses, physiological responses of lung tissues to the presence of various dusts, can be defined clinically by radiologic or pathologic appearances

related to accumulation of and tissue response to dust deposits in the lungs. For legal or compensation purposes, this definition often includes work history and dust-related impairments independent of the radiograph (e. g. pulmonary function deficits). Some pneumoconioses are considered benign (such as siderosis) while others can cause serious disease among exposed populations (e. g. asbestosis, silicosis, coal-worker's pneumoconiosis (CWP)).

Silicosis is diagnosed where there is a presumed history of exposure to silica and the appearance of parenchymal abnormalities consistent with silicosis. Ideally, the possibility that radiographic abnormalities are a result of other exposures is eliminated. Radiographic changes characteristic of silicosis are discrete rounded nodules (< 10 mm) generally in the upper lobes of the lungs. Large opacities are observed where silicosis is complicated by progressive massive fibrosis (PMF).

Table 8 provides an overview of the number of silicotics, the diagnostic criteria used and remarks especially with regard to the completeness of the detected cases, where available, for each of the study populations reviewed.

3.5 Final Quality Assessment

Table 9 summarizes, for each study population reviewed, the assessments made based on study methods. Specific attention is paid to the quality of the exposure assessment and the ability of the study to prevent or control possible confounding due to exposure to occupational lung carcinogens and especially smoking. Based mainly on these criteria and in some cases on other study attributes (strengths or weaknesses), an overall quality assessment rating is presented. Studies providing lung cancer risk estimates based on some reasonable exposure assessment and taking into account other potential carcinogenic exposures, including smoking, are considered further in the next chapter, in a synthesis of evidence.

While reviewing some of the selected papers, it became evident that the conditions under which study subjects were observed may have been substantially different from those generally encountered in Europe and North America. Specifically, several of the Chinese studies provided clues suggesting that competing risks of mortality, including silicosis and other pneumoconioses, generated a study context that might have distorted the results such that they would not be representative of or even relevant to modern western occupational settings. Additionally, many of these studies (as well as others) suffered from one or more deficits that alone might not have disqualified the studies from further consideration. However, in combination with the competing mortality problem, these studies were not considered further in addressing the review objectives.

In the next chapter, evidence is summarized from studies considered to be of at least adequate quality to address, at a minimum, part of the review objectives. The final conclusions are based on a synthesis of this quality based evidence.

4 Synthesis of the Scientific Evidence

The underlying purpose of this QBCR was to improve the current understanding of lung cancer risk following occupational exposure to silica, at levels found in present day workplaces. An adequate understanding of the science, including strengths and limitations, is essential to inform policies and practices necessary to the ongoing protection of employee health. The impact of other occupational exposures and lifestyle choices (e. g. smoking) on the risk of lung cancer in silica-exposed persons is central to an understanding of the relationship between silica exposure and lung cancer risk.

A simplified conceptual model of the epidemiological relationships relevant to this review is presented in Figure 3. The model does not attempt to describe the physiological relationships linking silica exposure with lung cancer, but rather offers an epidemiological (observational) construct for evaluating the relationships of interest. Known risk factors for lung cancer – especially smoking and occupational lung carcinogens – add to the total risk of lung cancer in exposed populations (depicted in the right half of the figure). For purposes of this review, selected studies included only those that employed methods that allowed separation of the possible effects of silica (on the left) from those of these other risk factors on lung cancer. On the other hand, workplace hazards that preferentially increased risk of death among silica-exposed employees may prevent latent silica-related lung tumors from being detected, reducing the apparent lung cancer burden (depicted in the lower portion of the figure).

Table 10 identifies each of the studies that remain after evaluating the quality of the overall methodology, exposure assessment, control of confounding due to other occupational lung carcinogens and especially smoking, and eliminating those studies with serious methodological problems. Although the remaining studies represent those we believe to be both relevant to the assessment of lung

cancer risk associated with exposure to silica within Europe and North America, and of better overall quality for the purposes of this review, each has limitations. Most of the main issues stem from a general lack of valid quantitative exposure data.

4.1 Smoking

By definition, studies were considered of acceptable quality only if they evaluated and controlled the potential influence of smoking on estimates of lung cancer risk associated with silica exposure. Incomplete or inadequate smoking data was the limiting factor for some studies (Merlo, 1991; Puntoni, 1988); in other studies the available data were not used in the analyses (Andjelkovich, 1994). Few or no lung cancer cases among non-smokers were reported for some populations, limiting interpretation of risk estimates. The actual level of control of confounding achieved varied by study, ranging from indirect adjustment based on data from less than 10 % of cohort members (Steenland, 2001b) to adjustment for individual pack-years smoked using multivariable regression models (Hnizdo, 1997). In all studies where such evaluation was possible, smoking was found to be a strong risk factor for lung cancer, but could not entirely explain the associations observed between silica and lung cancer.

4.2 Other Occupational Confounders

As illustrated in the conceptual model presented in Figure 3, occupational exposure to silica may be hypothesized to independently increase risk of lung. Where these risk factors are correlated with silica exposure, the potential for confounding exists, and the effects of these factors must be separated from those of silica, so that the independent contribution of silica exposure to lung cancer risk may be assessed. While full control of potential confounding is rarely achieved, the need to control for occupational lung cancer risk factors, and the ability to achieve reasonable control, vary by study and study setting. Consideration of other

occupational risk factors must be considered in addition to the role of smoking, as discussed above.

In the pottery industry, occupational exposure to potential lung carcinogens might include products of combustion from the firing of pottery (PAHs were only noted in the Chinese pottery studies, which were excluded), pigments/colorants, and asbestos. The British pottery workers study – the only study of pottery workers considered of adequate quality – eliminated the potential for confounding by these factors by excluding cohort members known to have been exposed to known lung carcinogens. Lung carcinogens in the sand industry might include asbestos and diesel exhaust. In the two studies of industrial sand workers remaining in the final quality assessment, these factors were identified as potential confounders but not considered serious threats to validity, as relatively few subjects were likely exposed to them. Radon exposure was identified in the study of gold miners (Hnizdo, 1997) as a potential confounder, however, indirect estimates of radon exposure were not found to be related to lung cancer risk, and therefore were considered not to be confounders. In the diatomaceous earth study considered to be of adequate quality, asbestos exposure was possible, and was controlled in the statistical analysis.

For each of the studies selected for the final synthesis, all considered and reasonably addressed the possible impact of confounding by other occupational lung carcinogens. Though most studies mentioned at least some possible confounders, it seems unlikely that the main study results are strongly biased due to such confounding. If any bias exists, however, it would derive from a failure to separate the risk due to other occupational lung carcinogens from that of silica, and silica-specific risks may therefore be overestimated. Despite efforts to control for some of these correlated risk factors, they may be so strongly correlated (e. g. silica and radon among miners) that the risks cannot be differentiated, in which case confounding is likely to persist despite attempted control measures. It is

unlikely that the presence of other lung carcinogens in the workplace would lead to confounding that artificially reduces risk estimates for silica and lung cancer (i. e. the potential bias is conservative).

4.3 Exposure

Expert assignments of exposure levels were made in some studies; however, such an approach to exposure assessment is problematic, as judgements must be made without specific knowledge of workplace conditions, practices, or variability of exposure over time. Seixas (1997) demonstrated in the US diatomaceous earth study that expert judgements from the first follow-up, and exposure estimates from the JEM developed for the second follow-up based on available industrial hygiene measurements, did not consistently agree. This highlights the probability of misclassification of exposure, and the resulting unreliability of specific study results. Because misclassification is not certain to be random (or non-differential), it is not possible to predict the impact on risk estimates.

Quantitative exposure assessments were constructed for other studies, an approach that potentially improves the validity of exposure assessment over more qualitative strategies. Essentially, air monitoring samples are analyzed to determine quantitatively the concentration of silica present in the workplace air, regardless of any personal protection in use. Because adequate individual measurements, i. e., several measurements per year for each individual employee, are rarely available, results from several employees over many years – and often from various work locations – are combined to form aggregate or average estimates. This "quantitative" estimate is then applied to all individuals working in these areas over the time period represented by the data. Again because of limited availability of data, estimates for years lacking monitoring results are frequently derived by extrapolating from time periods with data available to those without data. Ultimately, individual exposure estimates are derived from these

average and extrapolated data, with no direct means of differentiating individuals with actual high and low level exposures.

In most studies for which actual silica exposures were available, real data represented only the most recent years of operation, and estimates for the earlier, more relevant exposure years had to be extrapolated. These extrapolations also are based on expert judgements and anecdotal information about historical exposure; the ecological estimates may be poor surrogates for individual dose estimates. For cumulative exposure estimates, many years of extrapolated data may be summed, with the potential for multiplying estimation errors. While the actual quantitative values derived using these methods might have little relationship to the actual exposures sustained, they may, on average, reasonably represent qualitative levels of exposure. In other words, for those with high quantified values of exposure, actual exposure may be relatively high, and for those with lower values the actual exposure might be lower.

Often measured historically (but not consistently) were total dust, respirable fraction and silica content of dust, using various methods over time. Conversions and standardization of exposure measures over time were therefore necessary, and many important assumptions were required. This issue is underscored by the fact that two different conversion factors were derived and used in the two industrial sand studies. This may partly explain the substantially lower estimates of exposure derived by Steenland (2001b) compared with other studies (but with similar pattern of increased risk at the highest exposure category). Another example of discrepancies across studies within an industry is the two different silica fraction estimates in the two diatomaceous earth industry studies.

Ultimately the studies selected for synthesis do include some indicators of exposure, though none can accurately assess individual levels over time. Therefore, the available literature cannot reliably assess the adequacy of the

current exposure standard of 0.15 mg/m^3 at this time. Rather, we believe that the studies actually qualitatively estimate broad categories or ranks of exposure, often using numerical indicators of cumulative or average exposures to label categories. These might more accurately be represented as "low", "moderate", or "high" relative exposure categories. How the actual exposure levels relate across studies or industries cannot easily be determined.

Despite the limitations of these crude exposure measures, most studies – not necessarily limited to those remaining in the final synthesis – do demonstrate some increased risk of lung cancer in the higher categories of exposure to silica. Interpretation of this pattern is not easy, however.

4.4 Dose-response

Given reasonable consideration of potential confounding by occupational exposures and smoking, and in light of their overall weakness with regard to exposure assessment, studies were examined for evidence of a dose-response relationship between silica exposure and lung cancer. Note that the term "dose-response" is used to indicate a relationship of greater risk with increasing level of exposure, and that actual dose is never determined.

In the British pottery workers cohort, ORs around 1.7 (95% CI 1.1-2.4) were found for average silica concentration, whether or not lagged, and controlling for smoking. Interestingly, no association was seen between duration of exposure or cumulative exposure, suggesting that exposure intensity is the more important determinant of risk than duration (cumulative exposure reflects a combination of intensity and duration). Categories of average exposure were not reported, so no relationship with increasing average exposure could be assessed. Steenland (2001b) did observe a dose-dependent increase in risk with level of cumulative exposure lagged 15 years, but not with duration of exposure. The OR was

statistically significantly elevated only for the highest exposure category (above 1.23 mg/m^3, but the mean cumulative exposure for this open-ended category cannot be determined from the publication).

All other studies reported elevated risk of lung cancer among workers with higher cumulative exposure, although Hughes (2001) was the only other study that considered both cumulative and average exposure. Hughes reported elevated risk only at cumulative exposure levels above 1.8 mg/m^3 or average exposure levels above 0.26 mg/ m^3 (and no increase in risk at the lowest two levels of exposure for either type of measure). Hnizdo (1997) reported elevated risk estimates for lung cancer at all levels greater than 2.7 mg/m^3, although the risk was not statistically significantly elevated except for the highest cumulative exposure group (over 6.3 mg/m^3, OR = 3.19). Similarly, Checkoway (1997) reported elevated risk only for the highest cumulative exposure category (5.0 mg/m^3 or higher, RR = 2.11) for respirable silica and lung cancer.

As noted above, however, we consider the quantitative labels for these categories only rough estimates that indicate relative rank exposure (such as "low", "moderate" or "high" relative exposure categories). For the highest categories of exposure, most were open-ended, with the actual upper bounds of these ranges undefined.

4.5 Silicosis

Not all study populations reviewed were able to inform the question of whether a diagnosis of silicosis is independent of lung cancer risk, a risk indicator or susceptibility factor, or a necessary precursor to lung cancer. Where data on silicosis status of the study population were available, they were mostly incomplete because information was usually available only during the period study subjects were employed. Also, the criteria constituting a quality study for purposes of

evaluating the silica-lung cancer relationship are not necessarily the same as those for studies evaluating the silicosis-lung cancer question (e. g. other occupational exposures may not play an important role in silicosis risk), though there are some parallels. Further, because of the potential for multiple, complex relationships among silica, silicosis and lung cancer, isolating and understanding the role silicosis might play in lung carcinogenesis became an ancillary goal of this review, limited by the available data. Whether silicosis acts as a marker of substantial silica exposure, a propensity for pulmonary fibrogenesis, or a condition which predisposes the lungs to the carcinogenic potential of other substances such as silica, remains unknown.

5 Summary and Conclusions

In conclusion, an extensive search of the published literature on silica exposure and lung cancer identified a substantial pool of relevant papers. Upon more comprehensive quality review and assessment of each study (often comprised of multiple published papers) with a focus on the treatment of other risk factors such as smoking, known occupational lung carcinogens, and silicosis, the selection was considerably reduced. Among these better papers exposure assessment was still generally weak.

Due to a general lack of individual dose measures, methods of silica exposure assessment used in the studies were limited to assessment of the potential for exposure. Furthermore, because of largely absent historical exposure measurements, especially for times where exposures were assumed to be high, judgements and extrapolations of the more recent data have to be combined to derive exposure estimates. Methods to convert data from historically different measurement and analytic methods have to be developed and applied. While it seems reasonable to assume that the final derived exposure estimates may reflect relative differences in exposure levels between groups of exposed employees in a specific study population, the concrete estimated values contain many uncertainties and may in fact be far from the unknown "true" exposure. Therefore, estimates of relative risk based on quantitative exposure estimates must be interpreted cautiously.

Because the exposure assessments in the separate studies are based on different (in quality and quantity) exposure data and often applied dissimilar methods, including assumptions for unknown exposure situations, comparisons between estimated exposure values from separate studies are likely invalid. Nevertheless, most studies indicated excess lung cancer risk among the most heavily exposed using both cumulative and average exposure, with some conflicting results for

cumulative exposure. The level at which risk is increased, however, cannot easily be quantified from these studies. The observed excesses of lung cancer at high exposure indicator levels could not be entirely explained in any study by cigarette smoking, other occupational risks, or silicosis.

Scientific understanding of the observed epidemiological data is still somewhat limited, but the conclusions of the present review are consistent with a physiological model recently proposed by the Berufsgenossenschaftliches Institut für Arbeitsschutz – BIA (Figure 4). While it is clear that silica exposure can lead to silicosis, the relationship between silica exposure and lung cancer is more complicated, and depends on the type of silica exposure, the ability of the silica to induce DNA damage, failure of the affected cells to repair the damage, and an adequate latency for the tumor to progress (which may depend on numerous factors not depicted in the figure). Smoking may directly influence lung cancer risk and must be taken into consideration. Smoking also may indirectly impact lung cancer risk by impairing the mechanisms for clearing inhaled particulates, leading to a greater effective silica dose. Because only parts of the proposed model may be evaluated epidemiologically, it may be necessary to combine toxicological and epidemiological perspectives in the interpretation of available evidence.

Overall, these studies of relatively high quality demonstrate an increased risk for lung cancer among occupational groups with high crystalline silica exposure, accounting for the potential influence on the risk estimates of silicosis and tobacco smoking. However, due to the lack of reliable data on crystalline silica exposure in any of the available studies , recommendations for a health-based exposure limit value are not possible at this time.

6 Recommendations

The practical implications of the conclusions of this review are limited, as the level of silica exposure (in dimensions of average concentration and duration of exposure) at which lung cancer risk is elevated cannot be derived from the available studies of reasonable methodological quality. Therefore, whether the current exposure standard is protective also remains unanswered. The synthesized literature does, however, suggest that the elevated lung cancer risks observed occurred at the highest estimated levels of estimated exposure, generally well above the current exposure limit.

Greater clarification of these issues might be achieved by extended follow-up to the present of established occupational cohorts with reasonable silica (and other relevant occupational exposure) measurements and with valid smoking histories. Older cohorts exposed to substantially higher levels of silica than are generally prevalent today, and cohorts subject to other extreme conditions resulting in high competing mortality, are less likely to be of value. Ideally, more recent cohorts with documented or estimatable individual exposure to silica and known smoking histories will be followed for both malignant and non-malignant lung diseases. Such cohorts are more likely to be useful in evaluating the efficacy of current employee protective policy and practices.

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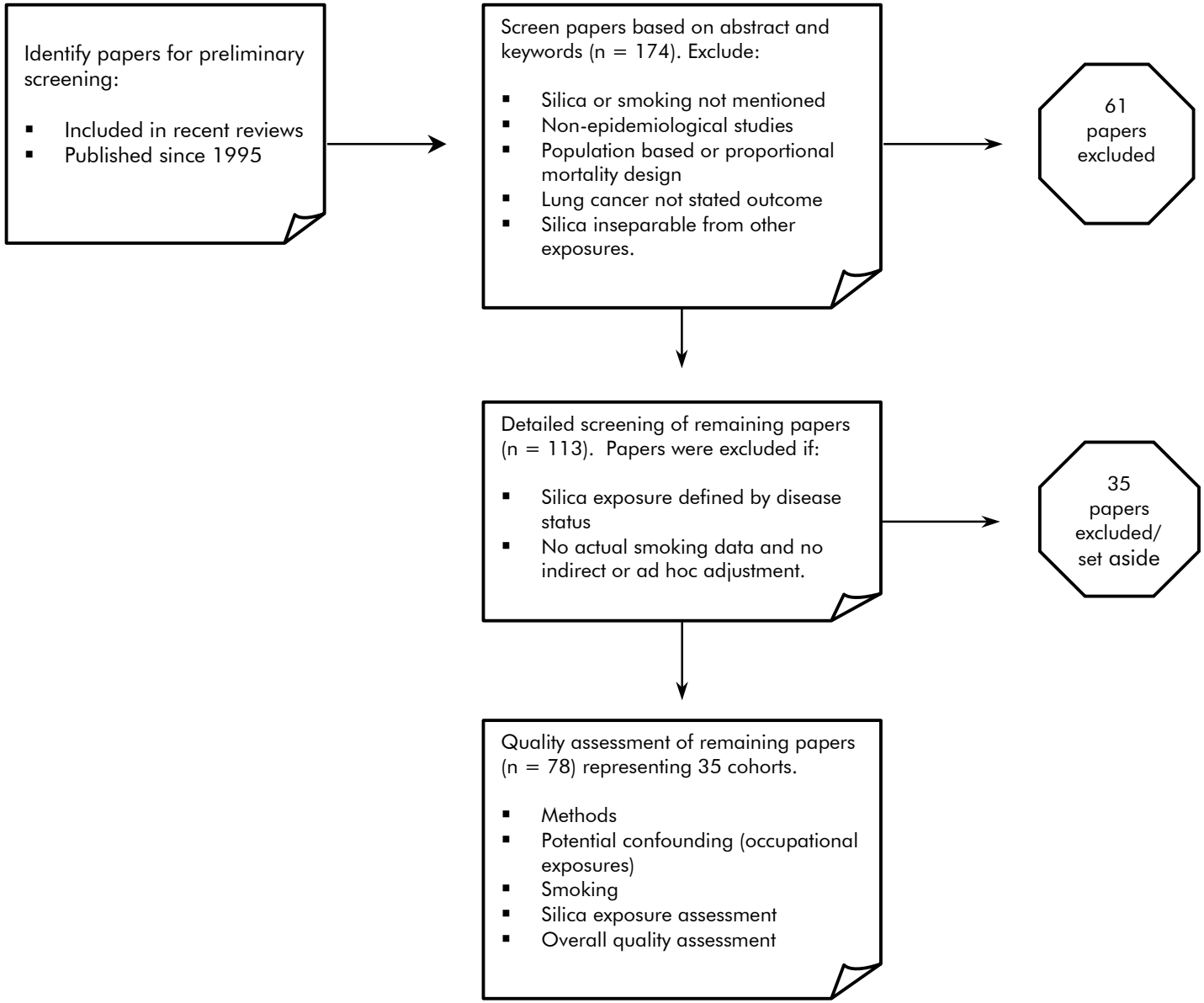

Figure 1 Selection process utilized for the QBCR

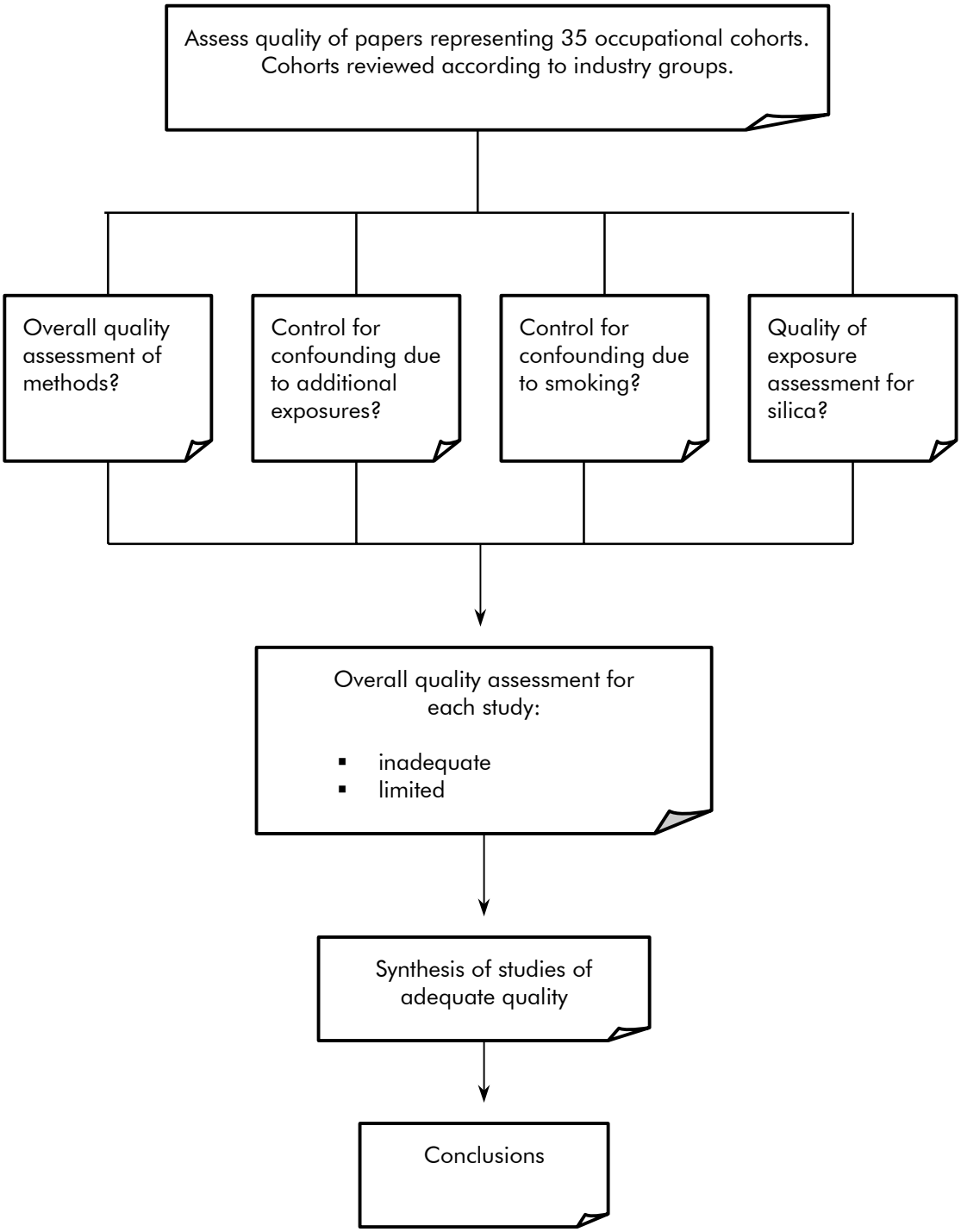

Figure 2 Schematic for quality assessment of publications reviewed

Table 1 Key characteristics and description of the populations and related publications reviewed

Industry		Reference	Population	Outcome [a]	Comment(s)
Pottery/Ceramics					
	1.a	Winter 1990	Sample of 40 British potteries.	Mortality	Preliminary study based on cross sectional survey.
		Cherry 1995	Pottery workers from companies where workers were entered into a health surveillance program. Men born 1916-1945 were selected from surveillance register.	Mortality	Workers were selected from potteries in the area of Stoke-on-Trent (Staffordshire). Probable overlap with Winter 1990.
		McDonald 1995	Identical to Cherry 1995.	Lung cancer mortality	Nested case-referent in addition to PMR analysis. Smoking, record of asbestos work, radiograph and employment duration available for the nested analyses.
		Burgess 1997	Exposure assessment; validation based on radiographs.	--	--
		Cherry 1997	Decedents with lung cancer listed on death certificate.	Lung cancer	Records for 32 of 88 pottery workers had been destroyed.
		McDonald 1997	Subset of original cohort; subjects included in exposure matrix validation.	Lung cancer	Smoking status and radiograph data included.
		Cherry 1998	Full report of lung cancer risk among Staffordshire potters.	Lung cancer	Analyses include full cohort, nested case-referent and pneumoconiotic sub-cohort.

Industry		Reference	Population	Outcome [a]	Comment(s)
	1.b	Chen 1992	Workers from 21 mines [b] and 8 potteries in Southern China.	Mortality	Tungsten miners (n = 28,442); Iron/copper miners (n = 18,231); tin miners (n = 7,849); pottery workers (n = 13,719). Some results are reported by facility type.
		McLaughlin 1992	Male lung cancer cases identified in Chen 1992 cohort.	Lung cancer mortality	
		Dosemeci 1995	Exposure assessment for 20 mines and 8 potteries.	--	--
		Cocco 2001	Same sub-cohort as McLaughlin 1992.	Lung cancer	Pooled analysis based on data in Cocco 2000.
	1.c	Ulm 1998	Subjects were from stone, quarry or pottery industries.	Lung cancer	German language report; silicotics and non-silicotics.
		Ulm 1999	Subjects were from stone, quarry or pottery industries.	Lung cancer	Matched on smoking. Some results are presented by industry type; only non-silicotics.
	1.d	Meijers 1990a	Ceramic workers; lung cancer cases from one region.	Silicosis; lung cancer	Ceramic workers and coal miners in the hospital-based case-control study.
		Meijers 1990b	Lung cancer cases from one region.	Lung cancer	More detailed description of the case-control study.
		Meijers 1996	Ceramic workers, 2+ yrs employment.	Mortality	

Industry		Reference	Population	Outcome [a]	Comment(s)
	1.e	Forastiere 1986	Subjects selected from all male residents of a town dominated by pottery industry 1968-1984.	Lung cancer mortality	Deaths due to lung cancer, silicosis, bronchitis or cancer unspecified were excluded from referent pool.
		Lagorio 1990	Subjects selected from all male residents of a town dominated by pottery industry 1968-1984.	Lung cancer mortality	Extended analysis.
Refractory Brick					
	2.a	Dong 1995	Silica and clay brick workers employed in 11 refractories; Anshan Iron and Steel Co., China.	Lung cancer mortality	Referents were steel mill workers. Silicotic and smoking status included.
	2.b	Puntoni 1988	Refractory brick workers, 1 plant.	Mortality	Fixed cross-sectional cohort of workforce in 1960.
		Merlo 1991	Refractory brick workers, 1 plant.	Mortality	Dynamic cross-sectional cohort of workforce beginning in 1954.
Silicon Carbide					
	3.a	Infante-Rivard 1989	Workers from 3 plants, identified via union records.	Mortality	Smoking data available on 98 % of study group.
	3.b	Romundstad 2001	Silicon carbide workers.	Cancer incidence	Smoking data available on 80 % of study group.

Industry		Reference	Population	Outcome [a]	Comment(s)
Foundry/Iron					
	4.a	Rodriguez 2000	Iron and steel foundry workers, Spain.	Lung cancer	Nested case-control study of iron and steel workers. Smoking history available for 96 % of subjects. Exposure estimates based on job processes.
	4.b	Andjelkovich 1990	Gray iron foundry workers; subjects worked 6+ months between 1935-1979.	Mortality	Smoking indirectly adjusted.
		Andjelkovich 1992	Same population.	Mortality	Analyses included exposure based on work/production areas.
		Andjelkovich 1994	Subjects drawn from the cohort study.	Lung cancer	Exposure assessment based on work history; cumulative exposure was estimated. Smoking history available for 71 % of subjects.
		Andjelkovich 1995	Sub-cohort of foundry workers with exposure to formaldehyde.	Mortality	Analyses presented included lung cancer and NMRD risks for silica exposure.
	4.c	Moulin 1993	Stainless steel workers.	Lung cancer, cardiovascu-lar mortality	Smoking known for 24 % of cohort.
		Moulin 2000	Follow-up report of Moulin 1993.	Lung cancer mortality	JEM; exposures included silica, asbestos, chromium and iron. Partial smoking data available for nested analyses (67 % for cases and 73 % for controls).

Industry		Reference	Population	Outcome [a]	Comment(s)
	4.d	Xu 1996a	Iron and steel workers, Anshan complex.	Mortality	Possible overlap with Dong 1995.
		Xu 1996b	Subset of full cohort.	Lung and stomach cancer	Incident cases analyzed.
Miners					
	5.a	Armstrong 1979	Gold miners, Kalgoorlie; Coal miners, Collie, W. Australia. Identified in surveys 1961-1962.	Mortality	Survey focus was respiratory health, smoking and occupational history.
		de Klerk 1995	Gold miners, Kalgoorlie W. Australia. Follow-up of Armstrong 1979 cohort.	Lung cancer mortality	Considered possible association with duration of underground mining, smoking, and pre-existing bronchitis.
		de Klerk 1998	Gold miners from de Klerk 1995 and new subjects surveyed in 1974-1975.	Silicosis; lung cancer	Follow-up of 1995 report. Considered association between degree of silica exposure, smoking, pre-existing bronchitis in the absence of silicosis.
	5.b	Kusiak 1991	Gold miners from mines throughout Ontario.	Lung cancer	Miners were not exclusively gold miners, though uranium miners were excluded.
	5.c	Hessel 1986	Subjects selected from national occupational necropsy records. Deaths 1979-1983.	Lung cancer, silicosis mortality	Matched case-control (based on age and smoking status 10 years prior to death of case).
		Hessel 1990	Same selection method as Hessel 1986. Population is not identical as deaths occurring during 1979-1983 were excluded.	Lung cancer; silicosis	Approximately 52 % of the subjects were diagnosed with silicosis.

Industry		Reference	Population	Outcome [a]	Comment(s)
	5.d	Wyndham 1986	White, South African gold miners, born 1916-1930, examined in 1969 through Medical Board of Occupational Diseases (MBOD) and alive at the start of 1970.	Mortality	Also included case-referent analyses for lung cancer, IHD and chronic respiratory disease. No case or referent had known asbestos exposure.
		Reid 1996	White, miners examined in 1969 through Medical Board of Occupational Diseases (MBOD) aged 39-54 at start of 1970. Follow-up to Wyndham 1986.	Mortality: Lung cancer, COPD and IHD.	Miners on the "Witwatersrand". Exposure was based on total duration of underground mining and cumulative dust exposure (y-mg/m^3). This cohort may overlap with Hnizdo 1991.
	5.e	Hnizdo 1991	Gold miners originally selected for respiratory disease study, who began mining 1936-1943.	Mortality	This cohort may overlap with Hessel 1986 and 1990 and with Reid 1996.
		Hnizdo 1997	Subjects drawn from Hnizdo 1991 cohort.	Lung cancer	Smoking, cumulative dust, uranium, silicosis and years underground were assessed. 7 cases and 41 controls were lost to radiological follow-up.
	5.f	Gillam 1976	Participants of silicosis survey, employed at hard rock gold mine; 5+ yrs underground employment. Homestake Mine, Lead, South Dakota.	Mortality	Asbestos likely confounder.
		McDonald 1978	Gold miners.	Mortality	Ore contains cummingtonite-grunerite, (non-asbestiform amphibole).
		Steenland 1995	Follow-up of McDonald 1978.	Mortality	Underground miners.

Industry		Reference	Population	Outcome [a]	Comment(s)
	5.g	Amandus 1991	Miners examined by US public health service 1959-1961 from 38 separate underground mines.	Lung cancer mortality	369 subjects were silicotics. Mines were all non-uranium. Ores represented include: copper, lead-zinc, iron, mercury, tungsten and gold. Overlap with Gillam 1976 possible.
	5.h	Ahlman 1991	Sulfide ore miners from old copper mines and miners from 'new' copper and zinc mines.	Lung cancer mortality; COPD, IHD	Three comparison groups used; National rates, regional rates and a sample of surface workers at one of the mines. Radon and PAHs among potential confounders.
Chinese miners					
	5.i	Fu 1994	Tin miners, Dachang Tin Mine, Guangxi province.	Lung cancer	37 cases and 56 controls diagnosed with silicosis.
	5.j	Chen 1992	Workers from 21 mines [b] and 8 potteries in Southern China.	Mortality	Tungsten miners (n = 28,442); Iron/copper miners (n = 18,231); tin miners (n = 7,849); pottery workers (n = 13,719). Some results are reported by facility type.
		McLaughlin 1992	Male lung cancer cases identified in Chen 1992 cohort.	Lung cancer mortality	
		Wu 1992	Exposure assessment in iron and copper mines (Wuhan Iron and Steel Co., Hubei Province).	--	--
		Dosemeci 1993	Exposure assessment.	--	--
		Dosemeci 1994	Indirect exposure assessment validation.	--	--

Industry		Reference	Population	Outcome [a]	Comment(s)
		Dosemeci 1995	Exposure assessment for 20 mines and 8 potteries.	--	--
		Cocco 2000	Same sub-cohort as McLaughlin 1992.	NMRD; lung cancer.	Presents some results by facility type.
		Chen 2001	Tin miners, Guangxi province.	Silicosis	Analyses of cumulative dust measures and silicosis.
		Cocco 2001	Same sub-cohort as McLaughlin 1992.	Lung cancer	Pooled analysis based on data in Cocco 2000.
		Zhuang 2001	Exposure estimation for pottery/miner cohort.	--	Modified JEM.
		Chen 2002	Follow-up of tin miners, from 3 mines in Dachang and 1 in Limu, Guangxi province. See Chen 1992.	Lung cancer	Smoking, arsenic exposure, and silicotics status were considered in analyses. Overall prevalence of silicosis was 32 % (cases/controls: 45 %/30 % respectively).
	5.k	Chen 1990	Miners from Longyan and Taochong iron ore mines (Hebei and Anhui provinces).	Mortality	25 % of miners diagnosed with silicosis. Observed deaths was 550; 41 % were due to NMRD.
	5.l	Carta 1994	Male workers from two metal mines in Sardinia.	Mortality	Radon considered a potential confounder.
		Cocco 1994	Female workers from two lead/zinc mines.	Mortality	Exposure differed between mines. No smoking data. Assumed non-smokers.

Industry	Reference	Population	Outcome [a]	Comment(s)
Stone/Quarry				
6.a	Ulm 1998	See Pottery/ceramics industry section.		
	Ulm 1999			
6.b	Theriault 1974	Exposure estimates for Vermont granite sheds.	--	--
	Costello 1988	Granite workers employed 1950-1982.	Mortality	No smoking data except for lung cancer cases: 84 of 118 lung cancers categorized as ever smokers.
6.c	Koskela 1990	Granite workers from three regions of Finland.	Mortality; lung cancer	
	Koskela 1994	Identical population as Koskela 1990.	Mortality; lung cancer	Follow-up report includes additional analyses by region (extended follow-up) and mineral content of granite.
Industrial Sand				
7.a	McDonald 2001	Sand workers with 3+ years of employment < 1980 from 9 facilities (8 production plants and 1 office complex).	Mortality	Lung cancer and silicosis were stated outcomes of interest. Results were also presented for a selection of other causes.
	Hughes 2001	Lung cancer and silicosis deaths only.		Also included silico-tuberculosis deaths. Smoking status available for 91 % of subjects. Asbestos considered a potential confounder.

Industry		Reference	Population	Outcome [a]	Comment(s)
		Rando 2001	Exposure estimation (average and cumulative).	--	--
	7.b	Sanderson 2000	Exposure estimation.	--	--
		Steenland 2001 a+b	Sand workers from 18 plants in 11 US states.	Lung cancer mortality	Smoking data for small sub-sample; indirect adjustment.
Diatomaceous Earth (DE)					
	8.a	Checkoway 1993	DE workers with 1+ years of employment from 2 plants.	Mortality	Smoking adjustment indirect; workers with possible previous asbestos exposure excluded from the main cohort.
		Checkoway 1996	DE workers with 1+ years of employment from 1 plant.	Lung cancer mortality	Assessment of confounding by asbestos exposure; nearly identical to cohort reported later on.
		Seixas 1997	Exposure assessment.	--	--
		Checkoway 1997	DE workers with 1+ years of employment from 1 plant.	Mortality	Extended follow-up.
		Checkoway 1999	DE workers with available chest radiographs.	Lung cancer mortality	Around 77 % of the total cohort. Dose-response analysis of cumulative exposure by silicosis status.
		Rice 2001	DE workers with 1+ years of employment from 1 plant.	Lung cancer mortality	Exposure response and risk assessment.

Industry		Reference	Population	Outcome [a]	Comment(s)
	8.b	Rafnsson 1997	Workers from Diatomite plant.	Lung cancer incidence	Exposures were to diatomaceous earth and cristobalite. Smoking status available for sample of cohort.
Miscellaneous					
	9.a	Mastrangelo 1988	Hospital-based study.	Lung cancer incidence	Smoking dichotomized. Subjects with unknown smoking or exposure history were excluded. Primary industries were quarry, tunnel or mining.
	9.b	Neuberger 1988	Cohort selected from records of preventive medical exams in 1,089 plants.	Mortality	Exposure to non-fibrous dusts.
		Neuberger 1990	Same population.	Cancer mortality	
	9.c	Nakagawa 2000	Tunnel workers selected from areas with high incidence of silicosis.	Lung cancer mortality	Smoking data categorized according to pack years.

[a] Where mortality is listed as the outcome, the study included multiple causes of death. Listing of a specific outcome(s) indicates the analyses were restricted.

[b] Clay mine listed in materials/methods, but not mentioned elsewhere.

Table 2 Characteristics of study populations

	Study population	Gender/Race	Design	Size	Follow-up period
1.a	British pottery workers	males	cohort	4,822	1985-1992
		males	nested case-control	52/195	
1.b	Chinese pottery workers	males and females	cohort	13,719	1972-1989
		males	nested case-control	62/238	
1.c	German ceramic workers	males and females	case-control	114/564[a]	1980-1994
1.d	Dutch ceramic workers	males	cohort	1,794	1972-1991
1.e	Italian ceramic workers	males	case-control	72/319	1968-1984
2.a	Chinese refractory brick workers	males	cohort	6,266	1963-1985
2.b	Italian refractory brick workers	males	cohort	1,022	1954-1986
3.a	Canadian silicon carbide workers	males	cohort	585	1950-1989
3.b	Norwegian silicon carbide workers	males	cohort	2,620	1953-1996
4.a	Spanish foundry workers	males	nested case-control	144/558	1952-1995
4.b	Michigan foundry workers (US)	males	cohort	8,147	1950-1984
		males	nested case-control	220/2,200	1950-1989
4.c	French stainless steel workers	males and females	cohort	4,897	1968-1991
		males	nested case-control	54/162	1968-1991
4.d	Chinese iron/steel workers	males	nested case-control	610/959	1987-1993
5.a	Australian gold miners	males	cohort	2,297	1961-1993
5.b	Canadian gold miners	males	cohort	54,128	1955-1986

	Study population	Gender/Race	Design	Size	Follow-up period
5.c	South African gold miners (Hessel 1986)	males, white	case-control (1)	133/266	1979-1983
	(Hessel 1990)	males, white	case-control (2)	231/318	nr
5.d	South African gold miners (Reid 1996)	males	cohort (1)	4,925	1970-1989
		males	nested case-control (1)	159/318	1970-1989
5.e	South African gold miners (Hnizdo 1991, 1997)	males	cohort (2)	2,260	1968-1986
		males	nested case-control (2)	78/386	1968-1986
5.f	US gold miners	males	cohort	3,328	1977-1990
5.g	US metal miners	males, white	cohort	9,912	1959-1975
5.h	Finnish sulfide ore miners	males	cohort	597	1954-1986
5.i	Chinese tin miners (Fu 1994)	males	nested case-control	79/188	1973-1989
5.j	Chinese miners (21 mines)	males and females	cohort	54,522	1972-1989
		males	nested case-control	254/1,114	1972-1989
5.k	Chinese iron ore miners	males	cohort	6,444	1970-1982
5.l	Sardinian metal miners	males	cohort	1,741	1974-1988
			nested case-control	17/68	
		females	cohort	526	1951-1988
6.a	German stone workers	males	case-control	133/231[a]	1980-1994
6.b	Vermont granite workers (US)	males	cohort	5,414	1950-1982
6.c	Finnish granite workers	males	cohort	1,026	1940-1985
		males	nested case-referent	31/62	1940-1985
7.a	US sand workers (1)	males	cohort	2,670	1940-1994
			nested case-control	91/162	

	Study population	Gender/Race	Design	Size	Follow-up period
7.b	US sand workers (2)	males and females [b]	cohort	4,626	1960-1996
			nested case-control	75/7,500	
8.a	US DE workers	white males	cohort	2,342	1942-1994
8.b	Icelandic DE workers	males and females	cohort	1,346	1967-1992
9.a	Italian dusty trades	males	case-control	309/309	1973-1980
9.b	Austrian dusty trades	males	cohort	1,221	-1985
9.c	Japanese tunnel workers	males	cohort	603	1978-1994

DE = diatomaceous earth.

[a] Subjects with silicosis were excluded.
[b] About 95 % of subjects were white males.

Table 3 Control for confounding by other occupational risk factors

Study population		Influence of other occupational exposures on risk estimates controlled?			Comment
		yes	no	unclear	
1.a	British pottery workers	x			Subjects with known asbestos exposure, work in foundries (ever) or > 1 year in coal mines or other dusty jobs (masonry, talc in rubber industry) were excluded.
1.b	Chinese pottery workers		x		PAH, highly correlated.
1.c	German ceramic workers			x	Primarily from previous employment, yes-no classification, adjustment in analysis.
1.d	Dutch ceramic workers	x			Talc, but assessed to be not relevant.
1.e	Italian ceramic workers	x			Separate analysis of jobs/departments with potential exposure to talc, chromate pigments, diesel exhaust fumes.
2.a	Chinese refractory brick workers			x	Relatively pure silica exposure mentioned, but Xu (1996) reported asbestos exposure in an overlapping cohort.
2.b	Italian refractory brick workers	x			No asbestos exposure, low PAH.
3.a	Canadian silicon carbide workers		x		Asbestos exposure could not be measured; PAH measured only at one location; no assessment for SiC fibers.
3.b	Norwegian silicon carbide workers			x	PAH exposure present in low concentrations; asbestos exposure indirectly controlled by job; high correlation of SiC fibers with silica.
4.a	Spanish foundry workers		x		PAH, chromium, nickel, welding fumes mentioned, but not controlled.
4.b	Michigan foundry workers (US)			x	No control or information concerning other exposures (except formaldehyde); coal tar pitch not used.
4.c	French stainless steel workers		x		In the foundry area, simultaneous exposure to chromium, nickel, iron, PAH and asbestos; high correlation between silica and PAH.

Study population		Influence of other occupational exposures on risk estimates controlled?			Comment
		yes	no	unclear	
4.d	Chinese iron/steel workers		x		Simultaneous exposures to silica, PAH and other dust in the foundry area; asbestos widely used but no information about exposure.
5.a	Australian gold miners	x			Radon reported to be 0.045 WL (7.65 WLM) or lower; arsenic average exposure 49 ppm; about 10 % of workforce had work history with asbestos, coal or other mine. Miners with known asbestos or nickel exposure excluded from analyses.
5.b	Canadian gold miners		x		Exposure to arsenic, radon and mineral fibers (tremolite and amphiboles) possible. Potential exposures also included nickel, silver, uranium, iron and lead/zinc.
5.c	South African gold miners (Hessel 1986, 1990)			x	Asbestos exposed miners excluded. Exposure measure used was total dust. No data available on levels of radon.
5.d	South African gold miners (Reid 1996)	x			Subjects worked at least 85 % of service in gold mines. Average radon exposure estimated to be 35.8 ± 0.4 WLM.
5.e	South African gold miners (Hnizdo 1991, 1997)	x			Subjects worked at least 85 % of service in gold mines. Average WL for radon 0.4 (range 0.1-3.0). Exposure estimates based on previous measures in South African gold mines.
5.f	US gold miners			x	Potential exposures included radon (0-0.17 WL in the 1970's), low levels of arsenic and high percentage of amphibole fibers in airborne dusts.
5.g	US metal miners			x	Radon roughly controlled; only non-uranium mines; no diesel engines before 1961.
5.h	Finnish sulfide ore miners		x		Exposure to radon daughters and diesel exhaust fumes, no exposure assessment in analysis; possible exposures in other employment described.
5.i	Chinese tin miners (Fu 1994)			x	Low radon levels (0.3 WLM/year) but possible influence of arsenic and cadmium reported.

Study population		Influence of other occupational exposures on risk estimates controlled?			Comment
		yes	no	unclear	
5.j	Chinese miners (21 mines)				Little information on potential confounders. Based on cumulative exposure estimates: arsenic low to medium, PAH and radon relatively high.
	tungsten		x		
	copper/iron		x		Measurements mostly post 1988; potential for confounding in some mines by radon, PAH, low exposure levels of arsenic and other metal compounds, but not asbestos.
	tin		x		High correlations (r = 0.8) between silica/dust, arsenic and PAH exposure (but all estimates based on post 1988 measurements), radon levels low.
5.k	Chinese iron ore miners			x	Radon and radon daughters (actual exposures around 0.2 WL), but could have been much higher before ventilation was introduced; BaP low levels, other substances like arsenic only in traces detected; radon exposure levels paralleled dust exposure levels.
5.l	Sardinian metal miners			x	Low radon exposure in one mine, low to moderate in the other, PAH exposure not measured but assessed to be low, possible arsenic exposure not measured.
6.a	German stone workers			x	Primarily from previous employment, yes-no classification, adjusted in analysis.
6.b	Vermont granite workers (US)	x			No other exposures reported.
6.c	Finnish granite workers	x			Authors reported no relevant influence from other exposures or from previous employment.
7.a	US sand workers (1)	x			Asbestos, controlled.
7.b	US sand workers (2)	x			Diesel exhaust, assessed to be minimal.
8.a	US DE workers	x			Asbestos controlled, but mean length of employment only 5.5 years and mean age at hire 24.5 years.

Study population		Influence of other occupational exposures on risk estimates controlled?			Comment
		yes	no	unclear	
8.b	Icelandic DE workers	**x**			No asbestos exposure.
9.a	Italian dusty trades		**x**		Neither controlled nor discussed.
9.b	Austrian dusty trades		**x**		Estimates by industry, but not specifically controlled.
9.c	Japanese tunnel workers			**x**	Pure silica exposure reported, no other exposures mentioned.

DE = diatomaceous earth.

Table 4 Available smoking data and smoking prevalence

Study population	Design	Source	Completeness of information (%)	Classification	Percentage in smoking categories [a]		
					current ever	former	non
1.a British pottery workers	cohort	medical examinations	99	ever, never	76		24
	ncc	medical examinations	76.9/83.7 [b]	cigarettes/day (1-9, 10-19, ≥ 20, unknown)	87.5/69	12.5/31	0
1.b Chinese pottery workers	cohort	nr	nr	nr	nr	nr	nr
	ncc [c]	questionnaire by study subject or next-of-kin	nr	cigarettes/day	93/80		7/20
1.c German ceramic workers	cc	records, interviews, etc.	100/100	current, ex-, never-smoker (ever smoker categories: >, ≤ 10/day)	59/43	37/53	4/4
1.d Dutch ceramic workers	cohort	cross-sectional survey, one time medical examination 1972-1984	nr	smoker, non-smoker	nr	nr	20
1.e Italian ceramic workers	cc	interview with next-of-kin	100 [d]	daily consumption (0, 1-20, > 20)	90/79		10/21
2.a Chinese refractory brick workers	cohort	nr	nr	smoker, non-smoker	nr	nr	nr
2.b Italian refractory brick workers	cohort	survey 1984	27.1	current, ex-, never-smoker (current smoker categories: >, ≤ 20/day)	56.6	11.9	31.5

Study population	Design	Source	Completeness of information (%)	Classification	Percentage in smoking categories [a]		
					current ever	former	non
3.a Canadian silicon carbide workers	cohort	interview	97.8	nr	65.4	20.6	14.0
3.b Norwegian silicon carbide workers	cohort	medical records	80	current, former, never, unknown	63	11	26
4.a Spanish foundry workers	ncc	medical records	91.7/97.5	non-smoker, >, < 20 day, unknown	99.2/80.1		0.7/19.9
4.b Michigan foundry workers (US)	cohort	nr	nr	nr	nr	nr	nr
	ncc	questionnaire, medical records (plant, hospitals)	75.5/68.6	smoker, non-smoker, unknown	92.2/66.9		7.8/33.1
4.c French stainless steel workers	cohort [e]	medical examination, 1986	24	current smoker (amount), non-smoker	42.7		57.3
	ncc [f]	medical records	66.7/72.8	never, current (amount), former, unknown	88.9/59.3	5.6/5.1	5.6/35.6
4.d Chinese iron/steel workers	ncc	interview	95.8/94.4	pack years	85.9/60.7		14.1/39.3
5.a Australian gold miners	cohort	survey	99.8	never, former, current (amount), pipe/cigar	67	16	15
5.b Canadian gold miners	cohort	random sample (< 2 % surveyed)	nr	nr	nr	nr	nr

	Study population	Design	Source	Completeness of information (%)	Classification	Percentage in smoking categories [a]		
						current ever	former	non
5.c	South African gold miners (Hessel 1986)	cc (1)	unclear (presumably medical records)	nr	nr	nr	nr	nr
	South African gold miners (Hessel 1990)	cc (2)	medical records	100	non-smoker, ex-smoker (light, heavy), current smoker (light, heavy)	nr	nr	nr
5.d	South African gold miners (Reid 1996)	cohort (1)	medical records	nr	smoker/non-smoker	86		14
		ncc (1)	medical records	nr	nr	nr	nr	nr
5.e	South African gold miners (Hnizdo 1991, 1997)	cohort (2)	medical examination 1968-1971	100	never-, current, ex-smoker (also daily amount, duration, pack years)	69.2	19.3	11.5
		ncc (2)	medical records	nr	nr	nr	nr	nr
5.f	US gold miners	cohort	1960 survey (US population, 1955)	18	never-, current, former smoker	64.6 (56.6)	12.0 (10.6)	23.4 (32.8)
5.g	US metal miners	cohort	medical examination 1959-1961	> 99	current, ex-, non-smoker, duration (<, ≥ 25 years)	71	11	18
5.h	Finnish sulfide ore miners	cohort	questionnaire 1986	76 [g]	nr	80		20
5.i	Chinese tin miners (Fu 1994)	ncc	interview	100	pack-years	87/68		13/32
5.j	Chinese miners (21 mines)	cohort	nr	nr	nr	nr	nr	nr

Study population	Design	Source	Completeness of information (%)	Classification	Percentage in smoking categories [a]		
					current	former ever	non
	ncc [b]	questionnaire	nr	nr	93/80		7/20
tin [h]	ncc	questionnaire	100/100	pack-years	88.5/82.5		11.5/17.5
5.k Chinese iron ore miners	cohort	questionnaire	nr	current, former, never	75	3	22
5.l Sardinian metal miners, males	cohort	survey 1973	98.5 [g]	pack-years	65.8	7.6	26.6
	ncc	survey 1973, 1 plant		never, former, ever	82.3		17.7
6.a German stone workers	cc	records, interviews, etc.	97/100	current, ex-, never-smoker (ever smoker categories: >, ≤ 10/day)	53/43	46/57	1/0
6.b Vermont granite workers (US)	cohort	hospital records		ever, never	nr	nr	nr
6.c Finnish granite workers	cohort, ncc	questionnaire 1972, 1986	75	non-smoker, ever smoker, amount	79.8		20.2
7.a US sand workers (1)	cohort	nr	nr	nr	nr	nr	nr
	ncc	medical records, next-of-kin, friends	91	ever, never regularly	91.4/69		9.6/31

Study population	Design	Source	Completeness of information (%)	Classification	Percentage in smoking categories [a]		
					current ever	former	non
7.b US sand workers(2)	cohort, ncc	company records 1978-1989, 4 plants	< 10	current, ex-, never-smoker (current smoker categories: >, ≤ 1 pack/day)	41.3	36.1	22.5
8.a US DE workers	cohort	medical surveillance program since 1960's	50	ever, never	63-86 [i]		
8.b Icelandic DE workers	cohort	survey 1993	65 m 72 f	current, former, never	31.5 m 28.7 f	32 m 25.5 f	37.5 m 44.8 f
9.a Italian dusty trades	cc	clinical records	100 [d]	ever, never	98.1/85.8		1.9/14.2
9.b Austrian dusty trades	cohort	screening examination at start of follow-up, 1950-1960	nr	smoker, non-smoker	nr	nr	nr
9.c Japanese tunnel workers	cohort	questionnaire	94 [g]	non smoker, >, < 40 pack-years	nr	nr	nr

ncc = nested case-control; nr = not reported; cc = case-control; DE = diatomaceous earth; m = males; f = females.
[a] Of those with known smoking habits. Current and former columns are combined where the classification is "ever".
[b] Cases/controls
[c] Reported smoking data are for miners and pottery workers combined.
[d] Persons with missing smoking data were excluded from the study.
[e] Reported in earlier follow-up, Moulin 1993.
[f] For foundry workshop, information available for 50 % of cases and 64 % of controls.
[g] Response rate.
[h] Reported in extended follow-up, Chen 2002.
[i] Range of reported smoking prevalence across cumulative exposure categories for crystalline silica, lagged 15 years.

Table 5 Quality of smoking assessment method

Study population		Design	Smoking assessment method			Quality	Comment
			none	indirect	direct		
1.a	British pottery workers	cohort	**x**			**inadequate**	No assessment in the cohort study.
		ncc			**x**	**adequate**	Unadjusted and adjusted for number/day; no non-smokers among cases with available smoking information; all referents had to be smokers.
1.b	Chinese pottery workers	cohort	**x**			**inadequate**	No assessment in the cohort study.
		ncc			**x**	**adequate**	Adjusted risk estimates.
1.c	German ceramic workers	cc			**x**	**adequate/ limited**	Frequency matched by smoking; adjusted using smoking index (not done in English paper).
1.d	Dutch ceramic workers	cohort			**x**	**inadequate**	SMR analysis, biased.
1.e	Italian ceramic workers	cc			**x**	**adequate**	Adjusted and stratified results reported.
2.a	Chinese refractory brick workers	cohort			**x**	**limited**	SRR analysis; no details reported on the referent cohort or indication if this cohort had smoking categories.
2.b	Italian refractory brick workers	cohort		**x**		**limited**	High proportion unknown, 2 scenarios presented.

Study population		Design	Smoking assessment method			Quality	Comment
			none	indirect	direct		
3.a	Canadian silicon carbide workers	cohort		x	x	**adequate**	Adjusted in internal analysis, also indirect adjustment.
3.b	Norwegian silicon carbide workers	cohort			x	**adequate**	Adjusted.
4.a	Spanish foundry workers	ncc			x	**adequate**	Some adjusted and unadjusted estimates presented.
4.b	Michigan foundry workers (US)	cohort		x		**inadequate**	Compared other smoking related diseases. For indirect adjustment (Axelson), external survey data for automotive workers were used as surrogate for smoking prevalence for the cohort.
		ncc			x	**adequate/ limited**	Missing data problems; crude categorization for adjustments (ever, never).
4.c	French stainless steel workers	cohort [a]		x		**limited/ inadequate**	Prevalence data available; "non-smoking" category includes never and former smokers for both study and reference.
		ncc			x	**limited**	Adjusted and unadjusted estimates; incomplete information for foundry area.
4.d	Chinese iron/steel workers	ncc			x	**limited**	Not specific to foundry area.
5.a	Australian gold miners	cohort			x	**adequate/ limited**	Smoking status at initial survey not updated. SMR analyses biased, but regression analysis appropriate.

Study population		Design	Smoking assessment method			Quality	Comment
			none	indirect	direct		
5.b	Canadian gold miners	cohort		x		**inadequate**	Little smoking data reported. Smoking habits obtained for 1,189 miners. Reported smoking prevalence estimated based on proportions in the sample.
5.c	South African gold miners (Hessel 1986)	cc			x	**limited**	Subjects matched on smoking status.
	South African gold miners (Hessel 1990)				x	**limited**	OR for lung cancer and silicosis by smoking level 10 years prior to death of case.
5.d	South African gold miners (Reid 1996)	cohort (1)	x			**inadequate**	No assessment in the cohort study.
		ncc (1)			x	**adequate**	Adjusted and unadjusted estimates reported.
5.e	South African gold miners (Hnizdo 1991, 1997)	cohort (2)			x	**adequate**	Cox proportional hazard model; adjusted and unadjusted estimates from regression analyses.
		ncc (2)			x	**adequate**	Cox proportional hazard model; adjusted and unadjusted estimates from regression analyses.
5.f	US gold miners	cohort		x		**limited**	SMR analysis. Indirect adjustment based on 1955 population survey.
5.g	US metal miners	cohort			x	**limited**	SMR analysis biased; adjusted estimates compare subjects by silicotic status.
5.h	Finnish sulfide ore miners	cohort, ncc	x			**inadequate**	Smoking data used for descriptive purposes only.

Study population		Design	Smoking assessment method			Quality	Comment
			none	indirect	direct		
5.i	Chinese tin miners (Fu 1994)	ncc			x	**adequate**	Regression analysis.
5.j	Chinese miners (21 mines)	cohort	x			**inadequate**	No assessment in the cohort study.
	tungsten, copper/iron; tin	ncc			x	**adequate**	Adjusted risk estimates.
5.k	Chinese iron ore miners	cohort			x	**limited/ inadequate**	SMR analysis biased; also by current smokers for dust levels.
5.l	Sardinian metal miners	cohort		x	x	**limited/ inadequate**	SMR analysis biased; indirect adjustment reported for some analyses, no significant differences.
	males						
		ncc			x	**adequate**	Matched, adjusted estimates.
	female	cohort	x			**inadequate**	Assumed subjects were non-smokers. No assessment.
6.a	German stone workers	cc			x	**adequate**	Frequency matched by smoking; adjustment using smoking index in the German report, not controlled in English paper.
6.b	Vermont granite workers (US)	cohort	x			**inadequate**	Data only for part of lung cancer cases.
6.c	Finnish granite workers	cohort	x			**inadequate**	Only descriptive use of smoking data.
		ncc			x	**limited**	Adjusted estimates, poor reporting.

Study population		Design	Smoking assessment method			Quality	Comment
			none	indirect	direct		
7.a	US sand workers (1)	cohort	**x**			**inadequate**	No smoking data reported for the cohort study.
		ncc			**x**	**adequate**	Basic smoking data used in the assessment.
7.b	US sand workers (2)	cohort		**x**		**limited**	Smoking data unavailable for most of cohort. Considered age specific prevalence in indirect adjustment.
		ncc	**x**			**inadequate**	Smoking data not utilized in analysis.
8.a	US DE workers	cohort		**x**		**limited/ adequate**	Smoking estimates based on data from only 50 % of the cohort.
8.b	Icelandic DE workers	cohort		**x**		**limited/ adequate**	Smoking prevalence lower than in a population sample.
9.a	Italian dusty trades	case-control			**x**	**adequate**	Non-smokers defined as having never smoked; stratified and matched analysis presented.
9.b	Austrian dusty trades	cohort			**x**	**limited**	Reference cohort matched by smoking status.
9.c	Japanese tunnel workers	cohort			**x**	**adequate**	Adjusted ORs presented.

ncc = nested case-control; nr = not reported; cc = case-control; DE = diatomaceous earth.

[a] Only reported in earlier follow-up, Moulin 1993.

Table 6 Smoking status and lung cancers

Study population		Design	Lung cancers	Smokers (%)	Former (%)	Non-smoker (%)	Unknown (%)
1.a	British pottery workers	cohort	68 (88)	--	--	--	--
		ncc	52	35 (67.3)	5 (9.6)	0 (0.0)	12 (23.1)
1.b	Chinese pottery workers [a]	cohort/ ncc	316	294 (93.0) [b]		22 (7.0)	0 (0.0)
1.c	German ceramic workers	cc	122	72 (59.0)	45 (36.9)	5 (4.1)	0 (0.0)
1.d	Dutch ceramic workers	cohort	30	27 (90.0)		3 (10.0)	0 (0.0)
1.e	Italian ceramic workers	cc	33	30 (90.9)		3 (9.1)	--
2.a	Chinese refractory brick workers	cohort	65	42 (64.6)		19 (29.2)	4 (6.2)
2.b	Italian refractory brick workers [c]	cohort	11	6 (54.5)		3 (27.3)	2 (18.2)
3.a	Canadian silicon carbide workers	cohort	24	21 (87.5)	3 (22.5)	0 (0.0)	0 (0.0)
3.b	Norwegian silicon carbide workers	cohort	74	53 (71.6)	2 (2.7)	1 (1.4)	18 (24.3)
4.a	Spanish foundry workers	ncc	144	131 (91.0)	1 (0.7)	0 (0.0)	12 (8.3)
4.b	Michigan foundry workers (US)	cohort/ ncc	220	153 (69.5)		13 (5.9)	54 (24.5)
4.c	French stainless steel workers [d]	cohort/ ncc	54	32 (59.3)	2 (3.7)	2 (3.7)	18 (33.3)
4.d	Chinese iron/steel workers [e]	ncc	610	501 (82.1)		82 (13.4)	27 (4.4)
5.a	Australian gold miners	cohort	138	137 (99.3)		1 (0.7)	--
5.b	Canadian gold miners	cohort	378	--	--	--	--
5.c	South African gold miners (Hessel 1986)	cc (1)	133	--	--	--	--
	South African gold miners (Hessel 1990)	cc (2)	231	--	--	--	--
5.d	South African gold miners (Reid 1996)	cohort/ncc (1)	143 (159) [f]			4	

Study population		Design	Lung cancers	Smokers (%)	Former (%)	Non-smoker (%)	Unknown (%)
5.e	South African gold miners (Hnizdo 1991, 1997)	cohort/ncc (2)	77	67	7	3	--
5.f	US gold miners	cohort	115 (121)	--	--	--	--
5.g	US metal miners	cohort	132	115 (87.1)	11 (8.3)	6 (4.5)	0 (0.0)
5.h	Finnish sulfide ore miners	cohort	10	--	--	--	--
5.i	Chinese tin miners (Fu 1994)	ncc	79	70 (88.6)		9 (11.4)	0 (0.0)
5.j	Chinese miners (21 mines)	cohort/ ncc		see Chinese pottery workers			
	tin [g]	ncc	130	115 (87.5)		15 (11.5)	0 (0.0)
5.k	Chinese iron ore miners	cohort	29	27	--	1	--
5.l	Sardinian metal miners						
	males	cohort/ ncc	24	19 (79.2)		5 (20.8)	0 (0.0)
	females	cohort	5	--	--	--	--
6.a	German stone workers	cc	159	79 (49.7)	73 (45.9)	3 (1.9)	4 (2.5)
6.b	Vermont granite workers (US)	cohort	118	84 (71.2)		0 (0.0)	34 (28.8)
6.c	Finnish granite workers	cohort/ ncc [h]	31	29 (93.5)		0 (0.0)	2 (6.5)
7.a	US sand workers (1)	cohort	96	--	--	--	--
		ncc [i]	83	74 (91.4)		7 (8.6)	0 (0.0)
7.b	US sand workers (2)	cohort	109	--	--	--	--
		ncc	75	--	--	--	--
8.a	US DE workers	cohort	77	--	--	--	--
8.b	Icelandic DE workers	cohort	5	--	--	--	--
9.a	Italian dusty trades	cc	309	303 (98.1)		6 (1.9)	--
9.b	Austrian dusty trades	cohort	179	--	--	--	--
9.c	Japanese tunnel workers	cohort	19	--	--	--	--

-- = not reported or not available; ncc = nested case-control; cc = case-control; DE = diatomaceous earth.

[a] Smoking status combined for potteries and miners.
[b] Current and former columns are combined where the classification is “ever”.
[c] Data only available for the first cohort, Puntoni 1988.
[d] Reported for entire steel factory; 12 cases observed among foundry workers.
[e] Reported for entire iron/steel complex; 48 cases observed among foundry workers.
[f] Based on best available estimate.
[g] From extended follow-up, Chen 2002.
[h] Information for follow-up through 1985, Koskela 1990.
[i] For those with at least 20 years latency.

Table 7 Quality of silica exposure assessment

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
1.a	British pottery workers	cohort		**x**			**limited**	IH data were used to construct and validate (in a sub-cohort) the JEM but not applied in cohort analyses.
		ncc				**x**	**adequate**	Utilized JEM; average, cumulative and maximum lifetime exposures estimated.
1.b	Chinese pottery workers	cohort				**x**	**limited/ inadequate**	Only measurements were to total dust.
		ncc				**x**	**limited**	Uncertainties about validity of respirable silica estimates.
1.c	German ceramic workers	cc			**x**		**limited/ adequate**	Individual assignment by experts.
1.d	Dutch ceramic workers	cohort			**x**		**limited**	No quantitative measures; exposure levels (high, moderate, low, none) based on processes.
1.e	Italian ceramic workers	cc		**x**			**limited**	Categories of exposure were based on job title and department.
2.a	Chinese refractory brick workers	cohort	**x**				**inadequate**	Analysis by silicosis status only.

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
2.b	Italian refractory brick workers	cohort		**x**			**limited**	Exposure was based on period of employment, not actual measures.
3.a	Canadian silicon carbide workers	cohort				**x**	**limited/ inadequate**	Only total dust assessed based on a small number of samples.
3.b	Norwegian silicon carbide workers	cohort				**x**	**limited**	Uncertainties about validity of JEM.
4.a	Spanish foundry workers	ncc		**x**			**inadequate**	Only available by department (e. g. foundry).
4.b	Michigan foundry workers (US)	cohort		**x**			**limited**	Work areas grouped according to production processes; length of employment also considered.
		ncc			**x**		**limited**	Exposures were ranked according to work area based on IH sampling data, production processes, etc.
4.c	French stainless steel workers	cohort		**x**			**limited**	Only available for early study.
		ncc			**x**		**limited/ inadequate**	Not "foundry" specific.

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
4.d	Chinese iron/steel workers	ncc				**x**	**limited/ inadequate**	Exposure assessment limited; exposures not plant specific; based on process/ occupation; quantitative estimates not mutually exclusive.
5.a	Australian gold miners	cohort			**x**		**limited/ adequate**	Detailed measurements were not available. Exposure was based on expert ranking and job history.
5.b	Canadian gold miners	cohort				**x**	**limited/ adequate**	Estimates of respirable silica (%) were based on 1978 survey data from some, but not all, mines.
5.c	South African gold miners (Hessel 1986, 1990)	cc (1, 2)			**x**		**limited**	Total dust.
5.d	South African gold miners (Reid 1996)	cohort (1)		**x**			**limited**	SMR analysis did not incorporate exposure estimates.
		ncc (1)				**x**	**adequate**	Cumulative estimates as well as years underground.

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
5.e	South African gold miners (Hnizdo 1991, 1997)	cohort (2)				**x**	**adequate**	Report 60-80 % of rock contains silica; 30 % respirable free silica dust. Estimates of 0.05-0.84 mg/m^3 concentrations underground.
		ncc (2)				**x**	**adequate**	See comment above.
5.f	US gold miners	cohort				**x**	**limited**	13 % free silica. Potential exposure to asbestiform fibers uncontrolled; importance unclear.
5.g	US metal miners	cohort		**x**			**limited**	Broad categories of exposure based on ore type, year of hire and years underground.
5.h	Finnish sulfide ore miners	cohort	**x**				**inadequate**	Exposure descriptive only.
5.i	Chinese tin miners (Fu 1994)	ncc		**x**			**limited**	Exposure defined as: total years underground and years of underground exposure to dust.
5.j	Chinese miners (21 mines)	cohort				**x**	**limited/ inadequate**	Total dust measures used in analysis; levels reported as none, low, medium, high.
		ncc				**x**	**limited**	Uncertainties about validity of respirable silica estimates.

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
5.k	Chinese iron ore miners	cohort			**x**		**limited**	Job titles assigned to no, low, medium or high "dust" exposure categories.
5.l	Sardinian metal miners males	cohort		**x**			**limited**	Potential exposures differed between mines. Exposure strata defined by mine (A or B), job locale (surface v. underground) and number of years underground.
		ncc		**x**			**limited**	Subjects from mine A; exposure defined by work underground.
	females	cohort		**x**			**limited**	Exposure categories defined by specific mine or by job title. Duration also considered.
6.a	German stone workers	cc			**x**		**limited/ adequate**	Estimates of peak, cumulative and average exposure dichotomized (high, low).
6.b	Vermont granite workers (US)	cohort		**x**			**limited**	By job title, locale and duration of employment.
6.c	Finnish granite workers	cohort		**x**			**limited**	Exposure based on occupational history questionnaire.
		ncc			**x**		**limited**	Poor description of exposure; total and quartz dust estimated.

	Study population	Design	Exposure assessment [a]				Quality	Comment
			none	qualitative	semi-quantitative	quantitative		
7.a	US sand workers (1)	cohort		x			**limited**	Latency was considered.
		ncc				x	**adequate**	JEM constructed based on historical and personal samples.
7.b	US sand workers (2)	cohort				x	**adequate**	JEM constructed using predictive values derived from a model based on actual measures. Respirable silica was also extrapolated.
		ncc				x	**adequate**	In addition, average, peak and cumulative exposure indices were calculated.
8.a	US DE workers	cohort				x	**adequate**	Linked historical IH data to detailed work history.
8.b	Icelandic DE workers	cohort		x			**limited**	By duration of exposure and work locale only.
9.a	Italian dusty trades	cc		x			**limited**	By industry and duration of exposure only.
9.b	Austrian dusty trades	cohort		x			**limited/ inadequate**	Analysis by industry; according to cohort definition all high exposed.
9.c	Japanese tunnel workers	cohort	x				**inadequate**	No exposure assessment.

ncc = nested case-control; cc = case-control; IH = industrial hygiene; DE = diatomaceous earth.

[a] Based on highest level of exposure assessment.

Table 8 Assessment and prevalence of silicosis

Study population		Design	Number (%) with silicosis	Diagnostic criteria for silicosis or source	Comments
1.a	British pottery workers	cohort	64/(5.9 % of sub-cohort [a])	radiograph ≥ 1/0	Radiographs only during employment period.
		ncc	3 cases/10 controls (8/2 without radiograph)	radiograph ≥ 1/0	Radiographs only during employment period.
1.b	Chinese pottery workers	cohort	~6,500 [b] (~ 10 % total cohort)	Chinese classification system	Registry; also recorded after employment period.
		ncc	8 (12.9 %) cases/32 (13.4 %) controls	Chinese classification system	Registry; also recorded after employment period.
1.c	German ceramic workers	cc	8 (6.6 %) cases/7 (1.2 %) controls	accepted/compensated disease (ILO or Johannesburg convention); various records	Unclear whether all silicotics registered.
1.d	Dutch ceramic workers	cohort	124 (6.9 %)	ILO radiograph ≥ 1/0	Radiographs during a one time nation wide cross-sectional survey of silicosis, 1972-1984.
1.e	Italian ceramic workers	cc	15 (45.5 %) cases/25 (24 %) controls	compensated silicotics	Referents with silicosis, chronic bronchitis etc. excluded.
2.a	Chinese refractory brick workers	cohort	1,827/(30.4 %)	Chinese classification system	Simple silicosis and silico-tuberculosis.
2.b	Italian refractory brick workers	cohort	136/(58.9 %)	compensated silicotics	Information for the first cohort/follow-up reported in Puntoni 1988; no information in Merlo 1991.

Study population		Design	Number (%) with silicosis	Diagnostic criteria for silicosis or source	Comments
3.a	Canadian silicon carbide workers	cohort	nr	nr	Silicosis not mentioned.
3.b	Norwegian silicon carbide workers	cohort	nr	nr	Silicosis not mentioned.
4.a	Spanish foundry workers	ncc	nr	nr	Silicosis not mentioned.
4.b	Michigan foundry workers (US)	cohort	nr	nr	Silicosis not mentioned.
		ncc	nr	nr	Silicosis not mentioned.
4.c	French stainless steel workers	cohort	nr	nr	Silicosis not mentioned.
		ncc	nr	nr	Silicosis not mentioned.
4.d	Chinese iron/steel workers	ncc	nr	nr	Prevalence of silicosis before 1960 in silica-exposed workers around 28 %.
5.a	Australian gold miners	cohort	662 (29 %)	compensation (based on radiograph and other symptoms)	Changes over time in award criteria were considered. Subjects with bronchitis at time of initial survey: 1,110 (48 %).
5.b	Canadian gold miners	cohort	nr	nr	nr

Study population		Design	Number (%) with silicosis	Diagnostic criteria for silicosis or source	Comments
5.c	South African gold miners (Hessel 1986)	cc (1)	nr	radiograph 3 years prior to death	Silicosis reported as parenchymal, pleural or hilar gland.
	South African gold miners (Hessel 1990)	cc (2)	nr	necropsy	Silicosis reported as parenchymal, pleural or hilar gland.
5.d	South African gold miners (Reid 1996)	cohort (1)	nr	nr	nr
		ncc (1)	nr	nr	nr
5.e	South African gold miners (Hnizdo 1991, 1997)	cohort (2)	nr	nr	nr
		ncc (2)	49	radiograph	Status lagged by three years before lung cancer diagnosis.
5.f	US gold miners	cohort	nr	nr	
5.g	US metal miners	cohort	369 (3.7 %)	1959 ILO	During initial survey in 1959-1961, one point in time.
5.h	Finnish sulfide ore miners	cohort	nr	nr	Silicosis not mentioned.
5.i	Chinese tin miners (Fu 1994)	ncc	37 (46.8 %) cases/ 56 (28.8 %) controls	Chinese classification system	From medical records/surveillance.
5.j	Chinese miners (21 mines)	cohort	~6,500 [b] (~ 10 % total cohort)	Chinese classification system	Registry; also recorded after employment period.
	tungsten	ncc	20 (21.5 %) cases/106 (26.4 %) controls	Chinese classification system	Registry; also recorded after employment period.

Study population		Design	Number (%) with silicosis	Diagnostic criteria for silicosis or source	Comments
	copper/iron	ncc	15 (20.3 %) cases/37 (10.6 %) controls	Chinese classification system	Registry; also recorded after employment period.
	tin [c]	ncc	58 (44.6 %) cases/185 (29.5 %) controls	Chinese classification system	Registry; also recorded after employment period.
5.k	Chinese iron ore miners	cohort	1,335 (24.7 %) cases	Chinese classification system	42 % of silicotics were diagnosed with silico-tuberculosis.
5.l	Sardinian metal miners, males	cohort, ncc	43 (0.6 % mine A, 4.6 % mine B)	ILO, ≥ 1/1	One time survey from 1973.
	females	cohort	nr	nr	nr
6.a	German stone workers	cc	26 (16.4 %) cases/8.1 % controls [d]	accepted/compensated disease (ILO or Johannesburg convention); various records	Unclear if all silicotics registered.
6.b	Vermont granite workers (US)	cohort	nr	nr	Data available for some of the lung cancer cases only.
6.c	Finnish granite workers	cohort, ncc	nr	nr	"Manifest pulmonary silicosis was not common."
7.a	US sand workers (1)	cohort, ncc	nr	nr	No radiographs available.
7.b	US sand workers (2)	cohort, ncc	nr	nr	No radiographs available.

Study population		Design	Number (%) with silicosis	Diagnostic criteria for silicosis or source	Comments
8.a	US DE workers	cohort	81/(4.5 % of 1,809 with radiographs)	ILO, radiograph ≥ 1/0	During employment period only; mean duration of employment 5.54 years.
8.b	Icelandic DE workers	cohort	0	nr	During employment period only.
9.a	Italian dusty trades	cc	50 (16.2 %) of cases; 30 (9.7 %) of controls	ILO/compensated	Cases identified from registry.
9.b	Austrian dusty trades	cohort	nr	nr	Silicosis not mentioned.
9.c	Japanese tunnel workers	cohort	nr	nr	Silicosis not mentioned.

ncc = nested case-control; cc = case-control; nr = not reported; DE = diatomaceous earth.

[a] Sub-cohort subjects entered before 1960, employed at least 10 years and no history of other occupational exposure.
[b] Pottery and mining workers combined.
[c] Extended follow-up from Chen 2002.
[d] Combined control group from German publication; not comparable with English paper.

Table 9 Final quality assessment

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
1.a	British pottery workers	+o	+	+	+	**adequate**	Very restrictive cohort definition, possible healthy worker survivor effect, only 60 % of lung cancer cases in nested case-control.
1.b	Chinese pottery workers	o	o	-	+	**inadequate**	Possible occupational confounding, mainly PAH, high competing risks.
1.c	German ceramic workers	-	o+	o+	o+	**limited**	Methodological problems; unclear differences between the German report and English paper.
1.d	Dutch ceramic workers	-	o	+	-	**inadequate**	Strong healthy worker effect combined with young age at start follow-up and short follow-up period, limited exposure assessment and biased analysis of smoking data.
1.e	Italian ceramic workers	o	o	+	+	**limited**	Small number of cases.
2.a	Chinese refractory brick workers	-	-	o	o	**inadequate**	Little information about the cohort and the reference population provided. No exposure assessment; validity of smoking analysis cannot be verified; exposure to asbestos possible.

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
2.b	Italian refractory brick workers	+	o	+	o	**limited**	Qualitative exposure assessment.
3.a	Canadian silicon carbide workers	o	-o	-	+	**inadequate**	Small study; only total dust based on few samples, possible occupational confounding.
3.b	Norwegian silicon carbide workers	+	+o	o	+	**limited**	Possible occupational confounding.
4.a	Spanish foundry workers	o	-	-	+	**inadequate**	No silica specific exposure assessment; no information about exposure levels or other occupational confounders.
4.b	Michigan foundry workers (US)	o+	o	o	o	**limited**	Limited smoking information and limited exposure assessment; uncertainties about occupational confounding.
4.c	French stainless steel workers	o	o-	-	o	**inadequate**	Few cases among foundry workers, limited smoking and exposure information, simultaneous exposure to other agents.
4.d	Chinese iron/steel workers	+	o-	-	o	**inadequate**	Exposure assessment not specific for foundries but for whole complex, simultaneous exposures to other agents, uncontrolled asbestos exposure.

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
5.a	Australian gold miners	**o**	**o**	**+**	**+o**	**adequate/ limited**	Consideration of other exposures reasonable.
5.b	Canadian gold miners	**o**	**o**	**-**	**-**	**inadequate**	Confounding by other exposures possible; smoking assessment poor.
5.c	South African gold miners (Hessel 1986, 1990)	**-**	**o**	**-o**	**o**	**limited/ inadequate**	Selection bias likely. Exposure measures are total dust.
5.d	South African gold miners (Reid 1996)	**+**	**+**	**o**	**+**	**adequate[a]**	Nested analyses adjusted. Confounding by radon unlikely.
5.e	South African gold miners (Hnizdo 1991, 1997)	**+**	**+**	**o+**	**+**	**adequate[a]**	Cox proportional hazard models used to derive adjusted estimates.
5.f	US gold miners	**o-**	**o-**	**o-**	**o**	**inadequate**	Potential for other confounders too difficult to assess. Unable to adequately control smoking in the analyses.
5.g	US metal miners	**o**	**o**	**o**	**o**	**limited**	Short follow-up period.
5.h	Finnish sulfide ore miners	**-o**	**-**	**-**	**-**	**inadequate**	Small cohort, high potential for occupational confounding; no exposure assessment, no real use of the smoking data.
5.i	Chinese tin miners (Fu 1994)	**+**	**o**	**-o**	**+**	**limited/ inadequate**	Possible influence of arsenic and other exposures not clear.

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
5.j	Chinese miners (21 mines)	**o**	**o**	**-o**	**+**	**inadequate**	High competing risks, adequateness of external reference data questionable, high exposure levels combined with uncertainties of the quantitative exposure assessment, other occupational risk factors.
5.k	Chinese iron ore miners	**-o**	**o**	**-o**	**-o**	**inadequate**	High competing risks, adequateness of external reference rates questionable; probably high but unknown exposure levels; short follow-up for relatively young cohort (> 60 % younger than 40 years at start of 12 year follow-up); biased SMR analysis; relevance of radon exposure unclear.
5.l	Sardinian metal miners, males	**-o**	**o**	**o**	**+**	**inadequate**	Relatively small sample size (especially among the part with relevant silica exposure), young age and short follow-up.
	Sardinian metal miners, females	**-**	**o**	**o**	**-**	**inadequate**	Small sample size, short duration of employment, no smoking data.

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
6.a	German stone workers	o-	o+	o-	+	**limited**	Possible confounding by other exposures unclear; inconsistencies between reports (German, English).
6.b	Vermont granite workers (US)	+	o	+	-	**inadequate**	Smoking information for a part of the lung cancer cases, only qualitative exposure assessment published, high competing risks reported.
6.c	Finnish granite workers	+	o	+	o	**limited**	Semi-quantitative exposure assessment in the ncc; poorly described.
7.a	US sand workers (1)	+	+	+	+	**adequate**	Other exposures controlled; data on silica exposure and smoking were utilized in nested case-control.
7.b	US sand workers (2)	+	+	+	o	**adequate**	Smoking data for only 9 % of the cohort, short median employment duration.
8.a	US DE workers	+	+	+o	+o	**adequate**	Smoking data available for only 50 % of the cohort, short median employment duration.
8.b	Icelandic DE workers	-	o	+	+o	**inadequate**	Short potential exposure period, young age at hire.

Study population		Methods	Exposure assessment	Control for confounding by		Quality assessment	Comments
				occupational exposures	smoking		
9.a	Italian dusty trades	**o**	**o**	**-**	**+**	**inadequate**	No control for confounding by other occupational risk factors, possible bias by selecting referents from a chest clinic.
9.b	Austrian dusty trades	**o**	**o**	**-**	**o**	**inadequate**	High silica-exposed cohort, but only historical information and no control for confounding.
9.c	Japanese tunnel workers	**+**	**-**	**-**	**+**	**inadequate**	No exposure assessment; role of other exposures unknown.

+ = adequate; **o** = limited; **-** = inadequate; ncc = nested case-control; DE = diatomaceous earth.

[a] Based on the more detailed analyses, we included the Hnizdo 1997 study in the final synthesis and not Reid 1996.

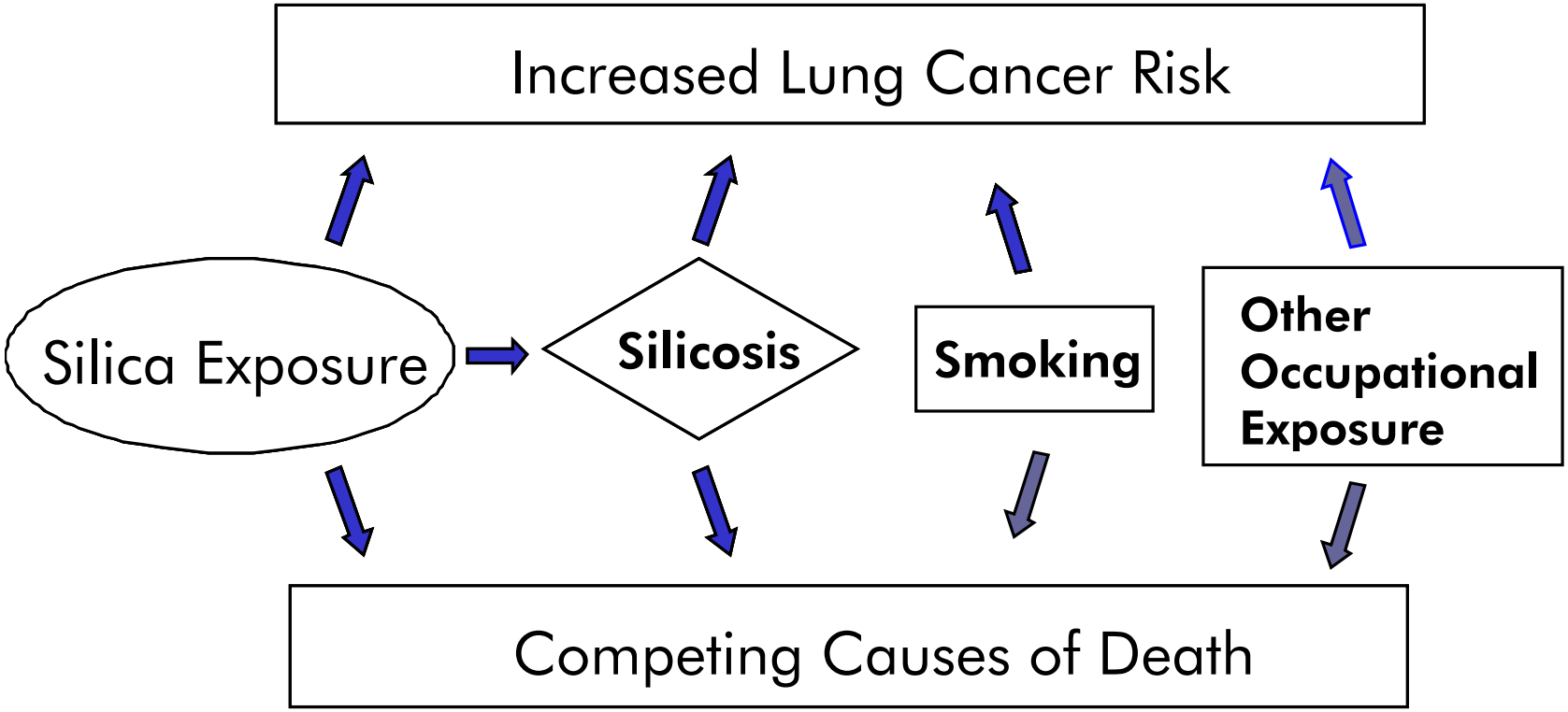

Figure 3 Epidemiological conceptual model

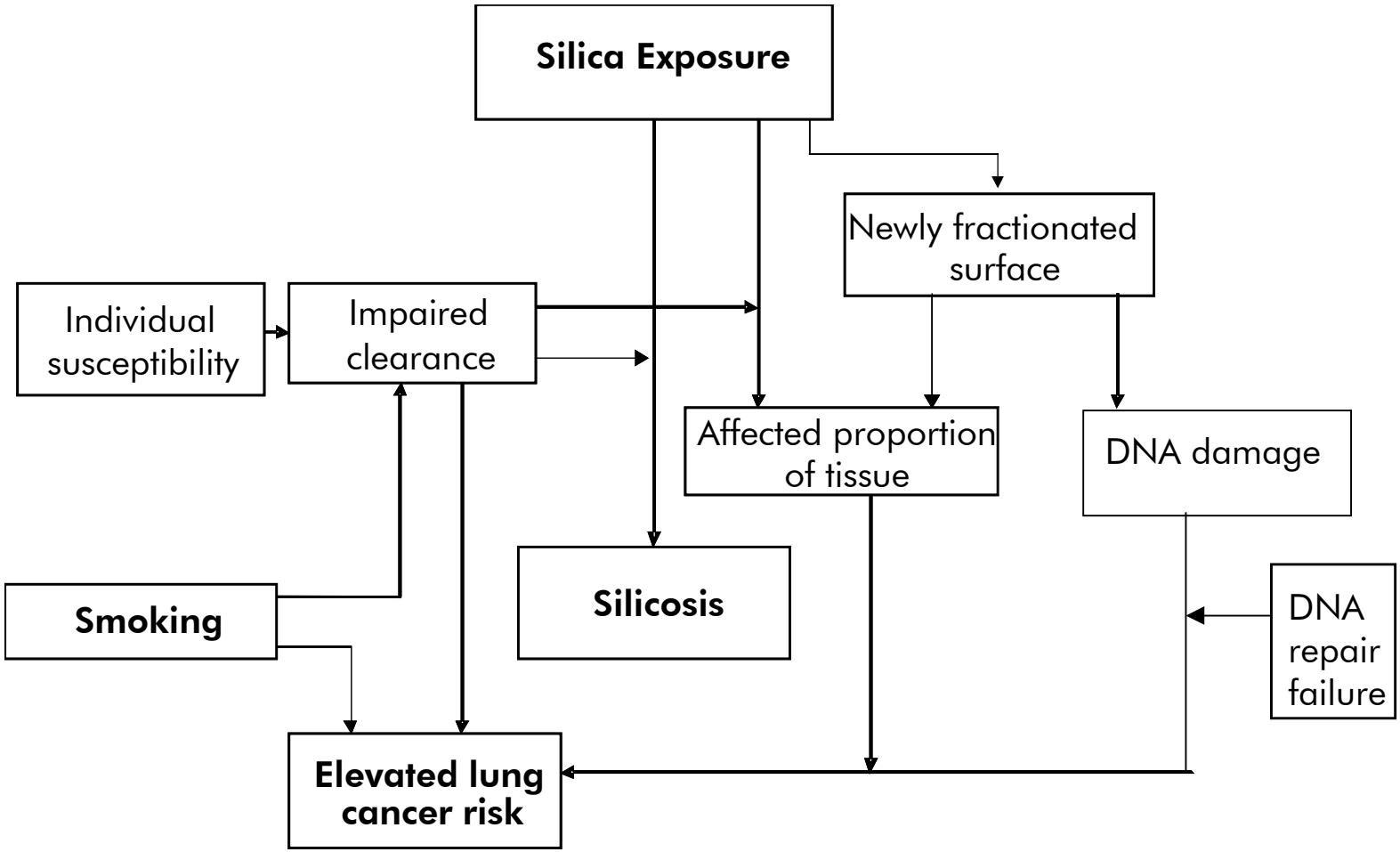

Figure 4 **Conceptual toxicological model for silica and lung cancer**

Table 10 Studies that are most relevant to the assessment of lung cancer risk associated with exposure to silica

Population/ Reference	Effects of other *occupational exposures* on lung cancer risk estimates	Influence of *smoking* on lung cancer risk estimates	Estimates by *exposure level* or *dose response*
1.a British pottery workers			
Cherry 1998	Not relevant. Subjects known to have exposure to potential confounders were excluded.	All cases were ever smokers and by design, all referents as well. Authors report significant difference in smoking status (ex-smokers) between cases (9.6 %) and referents (26.2 %). Smoking was unknown for 12 of 58 cases. Crude and smoking adjusted OR (95% CI) for average concentration (years lagged): Crude: / Adjusted: 1.70 (1.18-2.44) 1.67 (1.13-2.47) (no lag) 1.67 (1.18-2.35) 1.66 (1.14-2.41) (10 y lag) 1.57 (1.12-2.20) 1.60 (1.11-2.30) (20 y lag)	Authors report no association between duration of exposure and lung cancer risk (OR = 0.75; 95% CI 0.48-1.18, w/10yr lag) and also, none with cumulative exposure (OR = 1.02; 95% CI 0.86-1.21, w/10yr lag). Cases had shorter duration of exposure than referents. Risk of lung cancer risk appears related to average concentration, but not impacted by duration of exposure.
7.a Industrial sand (1)			
Hughes 2001	Asbestos was identified as a potential confounder.	Reported estimates from nested case-referent analyses were adjusted for smoking (see exposure, right). A significant difference in prevalence was reported between cases and referents. Reported no association between employment duration and lung cancer, adjusted for smoking. Lung cancer risk was more strongly related to non-lagged exposures whereas silicosis risk was more strongly related to lagged exposures.	Exposure categories Cumulative (mg/m^3-yrs) / OR (no lag) ≤ 0.70 1.00 $> 0.70 \leq 1.80$ 0.82 $> 1.80 \leq 4.50$ 2.15 > 4.50 2.58 Average (mg/m^3) / OR ≤ 0.07 1.00 $> 0.07 \leq 0.16$ 1.17 $> 0.16 \leq 0.26$ 1.83 > 0.26 2.48

Population/ Reference	Effects of other *occupational exposures* on lung cancer risk estimates	Influence of *smoking* on lung cancer risk estimates	Estimates by *exposure level* or *dose response*
7.b Industrial sand (2)			
Steenland 2001	Potential exposure to diesel exhaust for ~11 % of workers, though not in confined space. No other relevant occupational exposures.	Limited data on smoking status of cohort. Indirect adjustment of risk estimates applied. Little association between cumulative exposure categories, controlling for age (p = 0.25). Using two categories of cumulative exposure (< 0.59, 0.59+), for those aged 45+ yrs higher exposed expected rate ratio of 1.04 compared to lower exposed. For those under 45 the expected rate ratio was 1.10. Authors conclude that confounding due to smoking unlikely to explain the increased risk of lung cancer in the cohort.	OR (95% CI) for lung cancer, quartiles of cumulative exposure (mg/m^3-yrs) to respirable silica, 15 yr lag: Cumulative (mg/m^3-yrs) — OR (15 yr lag) 0-0.18 — 1.00 > 0.18-0.59 — 1.35 (0.72-2.54) > 0.59-1.23 — 1.63 (0.83-3.18) > 1.23 — 2.00 (1.00-4.01) SMR for lung cancer (workers with 6+ months employment) was 1.49 (1.17-1.87). Authors report positive exposure response trends for cumulative exposure lagged 15 years and for average exposures. Found no significant positive trend for duration of exposure.

Population/ Reference	Effects of other *occupational exposures* on lung cancer risk estimates	Influence of *smoking* on lung cancer risk estimates	Estimates by *exposure level* or *dose response*
5.e South African gold miners			
Hnizdo 1997	Analyses included variables for uranium mining (cumulative and duration estimates). Authors report that no significant association was observed for uranium and lung cancer risk (results not reported). Radon assessed to be low level. Average concentration estimated to be 0.4 WL (range 0.1-3.0 WL).	Cigarette pack years were included in the regression models as well as variables for exposure and silicosis status. *Model 1: Smoking and cumulative exposure.* Cigarette pack years: 6.5-20: 2.9 (0.8-11.0); 21-30: 4.9 (1.4-17.0); > 30: 10.1 (3.1-33.6) CDE20 (mg/m^3-years): 2.7-4.3: 1.83 (0.8-4.1); 4.4-6.3: 1.85 (0.8-4.3); > 6.3: 3.19 (1.3-7.6) *Model 2: Smoking, cumulative exposure and silicosis.* Cigarette pack years: 6.5-20: 3.2 (0.7-15.6); 21-30: 5.6 (1.2-25.0); > 30: 13.3 (3.1-56.6) CDE20 (mg/m^3-years): 2.7-4.3: 1.78 (0.8-4.1); 4.4-6.3: 1.29 (0.5-3.2); > 6.3: 1.93 (0.8-5.0) SILICOSIS: 2.10 (1.0-4.6)	Exposure was entered into the regression models as cumulative exposure (CDE) and duration (YEARS), both lagged by 20 years. SILICOSIS was defined for the models as diagnosed up to three years prior to case death. Where SILICOSIS was included in the regression model, neither CDE nor YEARS showed a significant trend.

Population/ Reference	Effects of other *occupational exposures* on lung cancer risk estimates	Influence of *smoking* on lung cancer risk estimates	Estimates by *exposure level* or *dose response*

Model 3: Smoking and duration.

Cigarette pack years		YEARS20	
6.5-20	3.1 (0.8-11.7)	10-15	1.63 (0.6-4.6)
21-30	4.9 (1.4-17.0)	16-20	2.07 (0.7-6.3)
> 30	10.1 (3.0-33.5)	> 20	3.36 (1.02-10.7)

Model 4: Smoking, exposure duration and silicosis.

Cigarette pack years		YEARS20		SILICOSIS
6.5-20	3.3 (0.7-16.2)	10-15	1.61 (0.6-4.5)	2.35 (1.1-5.1)
21-30	5.4 (1.2-24.2)	16-20	1.53 (0.5-4.8)	
> 30	12.7 (3.0-54.1)	> 20	1.59 (0.5-5.5)	

Model 5: Smoking and silicosis.

Cigarette pack years		SILICOSIS
6.5-20	3.5 (0.7-16.8)	2.45 (1.2-5.2)
21-30	5.7 (1.3-25.8)	
> 30	13.2 (3.1-56.2)	

Population/ Reference	Effects of other *occupational exposures* on lung cancer risk estimates	Influence of *smoking* on lung cancer risk estimates	Estimates by *exposure level* or *dose response*
8.a US diatomaceous earth industry			
Checkoway 1999, 1997	Asbestos exposure controlled.	Smoking status categorized as ever/never. Data available for 58 % of cohort. Based on the observed prevalence, indirect adjustment for smoking among those without silicosis resulted in a RR equal to 1.22, due to confounding, for highest v. lowest exposure strata. Controlling for assumed confounding, the ratio of SMRs for the highest v. lowest exposure strata would be reduced to 1.88. Estimated that the smoking adjusted RR among silicotics (comparing highest to lowest exposure) would be 2.04.	Lung cancer risk increased with cumulative exposure for workers without silicosis ($p = 0.02$ for trend). Lung cancer among silicotics was observed for those with the highest exposures. Lung cancer mortality according to cumulative exposure of respirable silica: mg/m^3-years — RR (95% CI) < 0.5 — 1.00 0.5-< 1.1 — 1.07 (0.53-2.18) 1.1-< 2.1 — 0.55 (0.23-1.32) 2.1-< 5.0 — 1.19 (0.59-2.41) 5.0 + — 2.11 (1.07-4.11) Trend slope was 1.06 (1.01-1.11). Additional adjustment for asbestos did not change the trend slope. RR adjusted for age, calendar year, duration of follow-up and ethnicity.