Respirable crystalline silica - Phase 2

Carcinogenicity

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This document looks at the relationship between silicosis and lung cancer when exposed to respirable crystalline silica through a series of epidemiological studies, cohort studies, notably in granite and stone workers in various parts of the world, combined with evidence gained through animal studies.

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Foreword

This Hazard Assessment Document has been published by the UK Health and Safety Executive (HSE). It is aimed at a technical audience and reports on the scientific information which underpins the hazard assessment of a specific substance.

In Great Britain, substances which cause harm to health are subject to the Control of Substances Hazardous to Health Regulations (COSHH) 1999. The Regulations require employers to prevent or, if that is not reasonably practicable, adequately control employees' exposure to hazardous substances.

Hazard Assessment Documents are produced to facilitate the development of HSE's regulatory position on a specific health-related issue, which may relate to an individual hazardous substance, or may involve consideration of more general issues related to chemicals and ill health. The documents in this series cover issues relating only to toxicological hazards; other document series address issues which involve consideration of occupational exposure and risk:
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Summary

Weight of evidence for lung cancer

The weight of evidence from epidemiological studies, combined with evidence from animal studies and current understanding of the likely toxicological mechanisms underpinning the development of lung cancer in rats exposed to respirable crystalline silica (RCS), supports the view that RCS has the potential to cause lung cancer in humans.

There are a number of cohort studies, notably in granite and stone workers, that reveal increased risks of lung cancer based on comparison with external population groups. Internal cohort analyses show exposure-response trends for an increased risk of lung cancer with increasing cumulative exposure and/or duration of exposure. The relative risks for those in the highest exposure categories compared with those in the lowest exposure categories tend to be of the order of twofold. It seems unlikely that there could be some systematic bias or confounding that could account for these findings. The fact that the exposure-response trends are apparent in internal stratified cohort analyses suggests that socio-economic differences and differences in smoking history are also unlikely to account for the observed exposure-response relationships.

It is also noted that the studies that provide the most convincing evidence of carcinogenicity indicate that increased risks of lung cancer are restricted to those groups with the highest cumulative exposures, suggesting the existence of a threshold. The groups with the highest cumulative exposures tend to be the early hire workers who commenced employment before the introduction of adequate dust controls.

Overall therefore, the balance of evidence suggests that heavy and prolonged occupational exposures to RCS can cause an increased risk of lung cancer. However, it is notable that, of the very many studies available, most of which clearly demonstrate excess mortality and morbidity from silicosis, there are few studies that, taken in isolation, provide reasonably convincing evidence for an increase in lung cancer that can be attributed to RCS. This appears to support the view that RCS is a relatively weak carcinogen, otherwise the evidence for lung cancer would be far clearer and convincing than is the case.

Relationship between silicosis and lung cancer

Where evidence is available concerning the relationship between lung cancer and silicosis, it tends to show that excess lung cancer mortality in RCS-exposed workers is restricted to those with silicosis, and the more severe the category of silicosis, the higher the risk of lung cancer. The weight of evidence also suggests that exposures to RCS insufficient to cause silicosis would be unlikely to lead to an increased risk of lung cancer, although the evidence for this is not definitive.

Evidence for variability in carcinogenic potential

The evidence for variability in the carcinogenic potency of RCS is far less clear than for fibrogenic potency. There does seem to be a slight pattern in the evidence in that the studies with the clearest evidence for lung cancer (granite/stone workers) represent exposure conditions in which there would be exposure to freshly fractured quartz surfaces. Studies in industrial sand workers also showed positive evidence for carcinogenicity, and it is likely that there would have been some exposure to freshly fractured surfaces for some of the tasks involved in this industry, particularly in the plants in which ball milling was in operation. Silica flour produced by the ball milling of industrial sand is of very small particle size.

The Phase 1 review concluded that fibrogenic potency would be enhanced with freshly fractured surfaces and extremely small particle size, and to this extent there is some consistency with the evidence for variability in carcinogenic potency.

The Phase 1 review concluded that cristobalite and quartz would be of equal fibrogenic potency under equivalent conditions of occupational exposure. The evidence relating to carcinogenic potency is limited, particularly as there is no direct information from animal studies to inform on this issue. From the limited information available, there is nothing to indicate that cristobalite would be any different in its carcinogenic potency to quartz.

Conclusions relating to the effects of other minerals on the carcinogenic potency of RCS are difficult to draw, particularly as exposure conditions have been so poorly characterised in most studies. It does appear that coating with clay minerals such as might occur in coal mining might reduce the carcinogenic potency of RCS, but on the other hand the lack of evidence for RCS-induced lung cancer in coal miners might simply reflect the relatively small percentages of quartz in coal mine dust compared to quartz-containing dusts in many other industries.

It is believed that the fibrogenic and carcinogenic potencies of RCS both derive from similar biological processes involving macrophage activation. The extent of macrophage activation will depend on the surface properties of RCS, so it seems reasonable to predict that the same potency factors that apply to fibrogenicity would also apply to carcinogenicity. Although the pattern of evidence from empirical observations in epidemiological studies shows some support and consistency with this contention, there is not enough firm evidence on this subject to allow any stronger conclusions to be drawn at this time.

Background

This document aims to address a number of questions raised by HSE's Field Operations Directorate (FOD) relating to the carcinogenic potential of respirable crystalline silica. A previous document (HSE, 2002) focused on questions and issues relating to variability in the fibrogenic potency of RCS, and on characterising the exposure-response relationships for the development of silicosis.

The UK regulatory position relating to RCS was described in the Phase 1 document. In brief, there is currently a maximum exposure limit (MEL) of 0.3 $mg.m^{-3}$ (eight-hour time weighted average (TWA)) for RCS. The main health concern underlying the MEL, which was originally established in 1992, was that of silicosis.

In recent years, views have been published in the scientific literature suggesting that the fibrogenic potential of RCS is variable, depending on the surrounding features of occupational exposure such as the extent of processing and the presence or absence of other minerals. In addition, there have been many recently published evaluations and commentaries on the ability of RCS to cause lung cancer. Most prominently, in 1997 IARC concluded that 'crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans'. However, the IARC Working Group also concluded that 'carcinogenicity was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs.'

These developments prompted FOD to ask HSE's Industrial Chemicals Unit to undertake a project to address the following issues:

(i) Does the fibrogenic capability of RCS vary depending on its source?
(ii) Are there good dose-response data for silicosis which might be of use in making judgements on sector-related industries and to provide guidance on what is reasonably practicable in different industries or processes?
(iii) Is there any evidence to indicate that the potential carcinogenic activity of RCS may vary depending on its source?
(iv) Is silicosis a necessary precursor for the development of lung cancer such that controlling for silicosis would minimise any risk of cancer?

The first two of these issues were dealt with in the Phase 1 document. However, given that FOD has raised questions about variability in the carcinogenic potency of RCS, it seems pertinent to summarise the key conclusions from Phase 1 concerning variability in fibrogenic potency.

The Phase 1 document concluded:

- All forms of RCS of industrial relevance are capable of causing silicosis, but the potential to cause silicosis may be influenced by the type of industrial process and by the presence of surrounding minerals associated with RCS. Such factors are capable of modifying the surface chemistry of RCS as well as changing the particle size characteristics. Thus, in different occupational settings, exposures to the same airborne mass concentrations of RCS might pose greater or lesser risks to health depending on the influence of such factors, referred to as 'potency factors'.
- The fibrogenic potency of RCS appears to be enhanced by the production of newly formed surfaces with increased cytotoxicity due to the formation of reactive surface radicals. Freshly formed surfaces are produced in many industrial processes, eg grinding and drilling. The fibrogenic potency of RCS is likely to be enhanced by the production of dusts of extremely small particle size such as silica flours, due to a relative increase in the specific surface area of such dusts.
- Fibrogenic potency is likely to be reduced for 'age' RCS dusts, ie dusts which have not been freshly fractured or ground or subject to high energy abrasive processing. Fibrogenic potency is likely to be reduced when the surfaces of RCS are coated by aluminium-containing clay minerals such as may be encountered in the heavy clay industry or in mines producing low-rank coal.
- The fibrogenic potency of cristobalite appears to be the same as for quartz under equivalent similar exposure circumstances.

These conclusions were drawn from a synthesis of evidence from human experience and from experimental research. Although there are likely to be a number of differences in the precise nature of the toxicological events leading to the development of silicosis and lung cancer, nonetheless it is reasonable to consider that the fibrogenic and carcinogenic potency of RCS would show similarities given that they both ultimately relate to the biological reactivity of the surfaces of inhaled RCS particles. Pathological observations in animals also suggest that fibrosis and lung cancer both stem from a background of chronic lung inflammation. Hence, it might be considered that the same potency factors identified for fibrogenicity might also apply to carcinogenicity, and that such factors may explain the observation made by the IARC Working Group that the carcinogenic activity of RCS was not seen in all industrial circumstances.

However, the evidence relating to silicosis is in many ways far clearer than that relating to lung cancer. Causal associations between exposure to RCS and the development of silicosis are easier to identify than for lung cancer, for which the role of confounding factors such as smoking and exposure to known occupational carcinogens such as polycyclic aromatic hydrocarbons (PAHs) may complicate the interpretation of a number of studies. In general, it is easier to compare the quantitative risks of silicosis in different industrial settings and circumstances of exposure than it is for lung cancer. Furthermore, although an enormous literature has built up concerning the issue of lung cancer in RCS-exposed workers, most of the evidence and debate has focused on whether or not RCS poses a carcinogenic hazard. There has been far less attention paid to issues concerned with potential variability in carcinogenic potency. Animal evidence is of very limited value in terms of informing on this issue; only quartz from two sources (Min-U-Sil and DQ12) has been investigated in carcinogenicity studies in animals. The design of these studies, mainly involving the use of only one dose level per study, does not allow any reliable comparisons of the carcinogenic potency of these forms of quartz.

This review has been structured into three different sections. Section 1 provides a summary analysis of three key issues: (i) the weight of evidence relating to the carcinogenic potential of RCS; (ii) the relationship between silicosis and lung cancer; (iii) evidence for variability in the carcinogenic potential of RCS.

Section 2 provides a detailed critical appraisal of the most informative epidemiological studies. These studies were identified from a number of recent good quality reviews (Weill and McDonald, 1996; IARC, 1997; Soutar et al, 2000; Hessel et al, 2000). More recently, NIOSH has published a comprehensive review of RCS, but this did not highlight any additional useful studies (NIOSH, 2002). In addition, six recently published studies not covered by these reviews have also been included, leading to a total of 28 studies included in Section 2. In addition, a brief summary of three published meta-analyses and one unpublished pooled analysis has been included in Section 2.

Section 3 consists of summary assessments of the published animal evidence relating to carcinogenicity and a summary of the current state of scientific knowledge and thinking regarding the toxicological mechanisms of RCS-induced carcinogenicity.

Section 1 - Conclusions on key issues

The questions underpinning this review relate to, firstly, the ability of RCS to cause lung cancer; the nature of the relationship between silicosis and lung cancer; and then, for any carcinogenic potential that is apparent, the possible variability in carcinogenic potency. At the time of starting this review, the evidence for the carcinogenicity of RCS was still the subject of debate and contention. Given this situation, this section begins with an analysis of the weight of evidence for the ability of RCS to cause lung cancer, before moving on to a consideration of the remaining two questions.

1.1 Weight of evidence concerning the ability of RCS to cause lung cancer

There are many epidemiological studies that have investigated the ability of RCS to cause lung cancer. Virtually all of these studies are limited in some respect, but particularly with respect to inadequate exposure data and lack of information on smoking history. These limitations have helped to fuel the debate in the scientific community on the interpretation of the evidence relating to the carcinogenic potential of RCS in humans. Indeed, opposing conclusions have been drawn by different review authors. In 1997 the IARC Working Group concluded that there was sufficient evidence for the carcinogenicity of quartz and cristobalite in humans. In contrast, Hessel et al (2000) argued against the view that RCS was carcinogenic in humans. This might seem strange given that there is good agreement among different reviewers on which studies are the best available. What seems to differ is the degree of proof each author judges to be necessary.

The approach taken in this review has been to identify the best-quality studies available and to assess them using a weight of evidence approach. No undue emphasis has been placed on the evidence from any individual study. Rather, each study only provides a contribution to the overall weight of evidence, the strength of which is dependent on the specific details of the study. Of the apparently 'positive' studies, some appear to provide more convincing evidence for the ability of RCS to cause lung cancer than others, in that the lung cancer findings cannot be readily dismissed as being due to confounding factors or bias. Such studies show good evidence for dose-response relationships apparent in cohort and nested case-control analyses. The latter type of analysis provides some reassurance that confounding due to socio-economic or lifestyle factors is unlikely to be an issue. By contrast, some such studies are consistent with the possibility that RCS has caused lung cancer, but co-exposures to other carcinogens or misclassification of exposure cannot be ruled out as explanations for the lung cancer increases, and so such studies are regarded as providing less convincing evidence.

In relation to the 'negative' studies, ie those indicating no clear evidence for an excess of lung cancer associated with RCS exposure, these also need careful interpretation. For some studies, it is possible that the cumulative exposures to RCS they contain were relatively low such that no clear increase in the risk of lung cancer prevailed, or was detectable under such circumstances (in contrast to the position with higher exposures).

Section 2 of this document presents detailed accounts and a critical appraisal of all the key studies included in this review. The remainder of this section (1.1) aims to illustrate the diversity of findings from these studies. The studies selected are representative examples, rather than a comprehensive coverage of all of the studies outlined in detail in Section 2. The end of the section also considers what contribution to the weight of evidence can be gained from animal and other experimental evidence.

1.1.1 Most convincing studies indicating carcinogenic potential in humans

Most of the best-quality studies available are retrospective cohort mortality studies. A strength of these studies is that they provide an indication of lung cancer mortality in relatively large cohorts of workers. The studies presented below have been highlighted because they provide reasonably strong evidence for RCS carcinogenicity which is unlikely to be significantly compromised by confounding by smoking or other sources of bias.

The most convincing evidence for the carcinogenicity of RCS derives from cohort studies in granite and stone workers and, to a lesser extent, from studies in industrial sand workers and diatomaceous earth workers. It is notable that the studies in granite/stone/sand workers represent industries in which dust exposures contain relatively high percentages of quartz (almost pure quartz in the case of industrial sand workers), and these industries are the least confounded by exposures to other known or suspected occupational carcinogens.

The results from a cohort study in Vermont granite workers showed an excess of lung cancer cases that was confined to the granite shed workers (standardised mortality ratio (SMR) of 1.27 based on general population rates), with no excess in lung cancer mortality in the quarry workers (Costello and Graham, 1988). The shed workers had more intensive exposures to RCS due to the processing work they undertook, which was conducted indoors with less ventilation than applied to the outdoor quarry workers. Stratified analyses based on tenure and latency showed that excesses in lung cancer mortality (SMRs >1.67) were all confined to the early hire workers with long duration of exposure, who began their employment before the implementation of dust controls. Although all of the lung cancer cases in this study were smokers, there was no evidence that they had smoked more heavily than the quarry workers, and it did not seem likely that the lung cancer excesses in the shed workers could be explained by smoking or exposure to other confounding factors. The most likely explanation for the higher rate of lung cancer in the shed workers compared to the quarry workers was their higher exposures to freshly fractured respirable quartz.

A study in Finnish granite workers showed higher rates of lung cancer in workers from two regions of Finland where the granite contained around 30% quartz, compared with similar workers from a region where the local stone did not contain quartz (Koskela et al, 1994). As with the study in Vermont granite workers, confounding by smoking or other exposures did not appear to be likely explanations for the difference in lung cancer rates for these worker groups. A cancer incidence study in Danish stone workers revealed a standardised incidence ratio (SIR) of 2 for the entire cohort when compared to regional cancer incidence rates. The use of regional data was thought to provide an indirect adjustment for smoking patterns, suggesting that the excesses of lung cancer could not be clearly attributed to smoking. Furthermore, within the cohort, higher rates of lung cancer were found in sandstone workers compared with granite workers, which could conceivably be due to the higher quartz content of sandstone (Guénel et al, 1989a,b).

Recent studies in separate cohorts of US industrial sand workers showed increased SMRs for lung cancer for the overall cohort. SMRs of 1.5 and 1.39 were obtained in one study based on national and local mortality rates respectively (McDonald et al, 2001), and in the other cohort an SMR of 1.49 for workers with >6 months' employment (Steenland and Sanderson, 2001). The latter study included an indirect adjustment for smoking. However, the studies in US industrial sand workers are not entirely conclusive. For example, in the cohort study of McDonald et al, the excess risks of lung cancer were seen in only four of the nine plants studied, and the plants with the highest rates of silicosis appeared to show the lowest lung cancer rates, which seems counter to what might be expected if RCS was the reason for the lung cancer excess. The adequacy of the indirect adjustments for smoking is also uncertain. Nonetheless, there is a consistency in the pattern of evidence for an increased risk of lung cancer in these studies in granite/stone and sand workers. It seems unlikely that there could be some systematic bias or confounding throughout these studies which could be responsible for the consistent finding of excess lung cancer based on comparisons with external reference groups, and also on internal cohort analyses in which relative risks increased in subsets of workers with the highest cumulative exposures to RCS.

The results of a series of studies in a cohort of diatomaceous (DE) workers revealed an excess of lung cancer and also non-malignant respiratory disease (NMRD) that was restricted to early hire workers who commenced work before the implementation of dust controls in this industry (pre-1930s), and who had the longest durations of employment (Checkoway et al, 1993, 1996, 1997).
The excess of lung cancer has been attributed to the exposures to cristobalite produced from calcining the DE. Uncertainties in the interpretation of this study relate to the historical use of asbestos to line the kilns used for calcining, and the fact that there was only very limited information on smoking habits in this cohort. Calcining was first introduced in the 1920s, and would not have become widespread for some time. Therefore, in the early hire workers who showed the highest risks of lung cancer, the proportionate exposure to cristobalite may have been lowest in these early times, although this may be counter-balanced by high absolute dust exposures. Uncertainty will always apply to this issue due to the absence of dust exposure records for these early times. As with many other studies, these results are fully consistent with the possibility that high cumulative exposures to RCS (in this case in the form of cristobalite) were responsible for the lung cancer cases observed in the early hire workers. However, there are some grounds for uncertainty such that this study in isolation could not be regarded as entirely conclusive.

Demonstration of an exposure-response relationship is often the strongest indicator of a true association between an exposure and effect. An IARC Working Group recently conducted a pooled analysis of 10 cohorts of RCS-exposed workers for which quantitative data on exposure were available (Steenland et al, 2001). Detailed summaries of all of these 10 studies are presented in Section 2, although mortality follow-up was extended for five of these studies beyond published data and additional exposure data were collected and converted to a common exposure metric by Mannetje et al (2002) for the analysis. The results showed that the log of cumulative exposure lagged 15-years was a significant predictor of lung cancer, and there was a consistency of results for underground mines and other facilities. Categorical analyses by quintiles of cumulative exposure showed clear trends of increasing odds ratios. The excess lifetime risk of lung cancer from a working lifetime (45 years) exposure to 0.1 $mg.m^{-3}$ RCS was calculated to be up to 2.8% above background risks of 3-6%, depending on the model used. The background risks of lung cancer of 3-6% reflect the variation in lung cancer rates found in different countries. The authors noted that misclassification of exposure or inaccuracy in exposure measurement was probably present throughout the analysis, but would be unlikely to account for the positive exposure-response trend observed. This pooled analysis provides strong supporting evidence that RCS is a carcinogen.

The studies in the industrial sand industry (Hughes et al, 2001 and Steenland and Sanderson, 2001) and the diatomaceous earth industry (Checkoway et al, 1997) included internal analyses to calculate the risk of lung cancer in increasing categories of cumulative exposure relative to the risk in the lowest exposure category. As described in Section 2, the underlying exposure assessments are fraught with uncertainty and may only be rough estimates of the true exposures. Random errors in exposure data are only likely to reduce the slopes of the exposure-response curves. It seems unlikely that there could have been some systematic bias throughout the exposure assessments of these studies that could explain the consistency of the exposure-response patterns observed. The use of an internal reference group in these study analyses also reduces confounding by other factors such as socio-economic status.

Each of these internal analyses showed a clear trend for increasing risks of lung cancer with increasing cumulative exposure of RCS. The relative risks were generally only statistically significantly increased in the highest exposure categories, which is consistent with other studies showing that relative heavy and prolonged exposure is required for RCS to cause lung cancer.

1.1.2 Less conclusive studies

A study in Chinese tin miners showed a clear trend of increasing risk of lung cancer with increasing cumulative exposure to RCS (McLaughlin et al, 1992). However, due to the strong correlation between exposures to RCS and arsenic in these miners, there are grounds for uncertainty concerning the role of RCS exposure. A cohort study in Italian refractory brick workers showed an SMR for lung cancer of 1.5 for the overall cohort, and a higher SMR of 1.7 for those employed pre-1957, who presumably had the highest cumulative exposures (Merlo et al, 1991). This study was limited by the absence of any useful exposure data. A study in Chinese refractory brick workers also showed a clear excess of lung cancer in the overall cohort compared to an external referent group of workers from steel rolling mills, with a standardised rate ratio of 1.49 (Dong et al, 1995). Internal analyses showed that the excess of lung cancer was restricted to those with silicosis, and lung cancer risk showed a clearly increasing trend with increasing latency/duration of exposure. The pattern of results, as with many other studies, indicated that long duration of exposure to RCS is needed to cause an increased risk of lung cancer. Although there was no clear evidence for confounding factors in this study, there were nonetheless some uncertainties derived from the reporting (see Section 2.5.3.1), so again this study is regarded as inconclusive.

A thorough study in UK pottery workers showed that lung cancer rates decreased with increasing length of tenure and increasing cumulative exposure to RCS, although they did show a positive trend with increasing 'average' levels of exposure (Cherry et al, 1998). It is difficult to interpret this pattern of findings, but they do not clearly point to a role of crystalline silica in lung cancer development. Furthermore, those studies which provide more convincing evidence in this regard all indicate that lung cancer excesses are only found in the early hire workers with long durations of exposure. It is noted that the cumulative exposures to RCS estimated for this study are relatively low compared to other studies, consistent with the low observed rates of silicosis. Hence, the lack of clear evidence for carcinogenicity may be due to the low cumulative exposures.

1.1.3 Studies showing no exposure-response relationship for RCS and lung cancer

There is a body of studies in gold miners that, taken together, provide some evidence against the carcinogenic potential of RCS. A cohort study in US goldminers (Steenland and Brown, 1995) showed that although there was a slightly raised SMR for lung cancer in the overall cohort based on local population rates, internal analysis of the cohort showed no relationship between estimates of cumulative exposure to RCS and risk of lung cancer. Another study by these authors (see the HSE Phase 1 review) showed that silicosis had been a substantial problem in the South Dakota US goldminers, indicating that significant exposures to RCS had occurred in this workforce.

A study in Australian gold miners (De Klerk and Musk, 1998) found that there was a slightly raised SMR for lung cancer in the overall cohort based on general population rates, but that the excess of lung cancer was restricted to those compensated for silicosis. No excess of lung cancer was seen in those without silicosis.

A series of five studies in South African gold miners with some overlap in the populations studied have been reported. The results from two of these studies, a cohort study by Hnizdo and Sluis-Cremer (1991) and a nested case-control study by Hnizdo et al (1997) each pointed to an increased risk of lung cancer in those with the longest durations of exposure and highest estimates of cumulative exposure. However, these factors were also surrogates for long duration of smoking and longest cumulative exposure to radon daughters. The case-control studies by Hessel et al (1986 and 1990) in South African goldminers showed no differences in the estimates of cumulative exposure to RCS between cases and controls; neither did the larger-scale cohort study of Reid and Sluis-Cremer (1996) show any relationship between exposure to RCS and risk of lung cancer. However, there was a marked all-cause premature mortality in the South African goldminers, including a high number of deaths from NMRD (including silicosis). It seems possible that the early deaths from NMRD may have obscured the full potential for lung cancer development in this cohort. For this reason, the absence of a clear relationship between lung cancer and exposure to RCS in this cohort cannot be taken as good evidence for an absence of carcinogenic potential.

1.1.4 Animal evidence on carcinogenicity

Animal evidence reveals that RCS has the potential to cause lung cancer in rats, although not in mice and hamsters (see Section 3.1). Other dusts, some of which are believed not to possess carcinogenic potential in humans such as carbon black, talc and titanium dioxide have also been shown to cause lung cancer in rats but not in mice. The pattern of evidence implies that the rat is generally more susceptible to dust-induced lung cancer than other rodents. There is therefore a question as to the relevance to human health of the RCS-induced tumours in rats. Hence, the available animal evidence is not definitive concerning the potential for RCS to cause lung cancer in humans.

1.1.5 Mechanisms of RCS-induced lung cancer in rats

Current knowledge of the mechanisms of RCS lung carcinogenicity in rats invokes a role of oxidative damage to DNA caused by reactive oxygen species produced by alveolar macrophages and neutrophils. Direct RCS-induced genotoxicity is less likely to occur. Oxidative DNA damage would be seen in association with markers of pulmonary inflammation (neutrophil influx, macrophage aggregation, alveolar epithelial cell hyperplasia etc). Species differences in response might relate to differences in anti-oxidant defence mechanisms and differences in macrophage activation responses. Chronic inflammatory lung damage would lead to repeated cycles of alveolar epithelial cell hyperplasia and cell proliferation which, together with the potential for oxidative DNA damage leading to unrepaired DNA damage in these actively dividing cells, constitute the proposed underlying toxicological mechanisms for RCS-induced carcinogenicity in the rat. The mechanism outlined clearly requires the initial development of a chronic lung inflammatory condition. This in itself would not only lead on to silicosis development, but might render the lung more susceptible to other carcinogenic influences such as cigarette smoking. Overall, although the cellular mechanisms leading on to silicosis and lung cancer are distinct, it is postulated that both conditions stem from the same background of lung inflammation.

Whether or not the human lung would respond in quantitatively the same way as the rat lung is uncertain, given that the rat lung responds with a more prominent inflammatory response to dusts in general compared with other experimental species. However, from what is proposed for the mechanisms of RCS-induced lung cancer in rats, it is possible that these mechanisms could also occur in the human lung.

1.1.6 Summary of weight of evidence

The weight of evidence from epidemiological studies, combined with evidence from animal studies and current understanding of the likely toxicological mechanisms of RCS-induced lung cancer in rats, supports the view that RCS has the potential to cause lung cancer in humans.

There are a number of cohort studies, notably in granite and stone workers, that reveal increased risks of lung cancer based on comparison with external population groups; internal cohort analyses show exposure-response trends for an increased risk of lung cancer with increasing cumulative exposure and/or duration of exposure. The relative risks for those in the highest exposure categories compared with those in the lowest exposure categories tend to be of the order of twofold. It seems unlikely that there could be some systematic bias or confounding that could account for these findings. The fact that the exposure-response trends are apparent in internal stratified cohort analyses suggests that socio-economic differences and differences in smoking history are also unlikely to account for the observed exposure-response relationships.

When considering what exposures to RCS would be required to cause an increased risk of lung cancer, it is noted that the studies that provide the most convincing evidence of carcinogenicity indicate that increased risks of lung cancer are restricted to those groups with the highest cumulative exposures, typically early hire (pre-1940) workers employed before the introduction of effective dust control measures. This suggests the existence of a threshold.

However, when trying to quantify the relation between cumulative exposure and increased risk, it has to be borne in mind that all of the available epidemiological studies suffer from various uncertainties and weaknesses in their exposure assessments. In particular, the early hire workers who have the highest risk of lung cancer were employed in times when dust levels were highest, but for which no reliable exposure data were available. Studies in the industrial sand and diatomaceous earth industries showed that statistically significantly increased risks of lung cancer were observed only in subgroups exposed to >1.23 and ≥5 mg m^{-3}.years respectively. These cumulative exposure estimates would equate to 40 years' average exposure to 0.03 - 0.125 mg.m^{-3} of RCS. Little confidence can be placed on these values in view of the uncertainties in the underlying exposure assessments. A recent pooled-analysis of 10 cohort studies suggested that the excess risk of lung cancer (over and above background risks) would be up to 3% with cumulative exposure to 4.5 mg.m^{-3}.years. Again, given the inherent weaknesses in the underlying exposure assessments of the individual studies, the accuracy of this risk assessment is uncertain.

Overall therefore, the balance of evidence suggests that heavy and prolonged occupational exposures to RCS can cause an increased risk of lung cancer. However, it is notable that of the very many studies available, most of which clearly demonstrate excess mortality and morbidity from silicosis, there are few studies that, taken in isolation, provide reasonably convincing evidence for an increase in lung cancer that can be attributed to RCS. This appears to support the view that RCS is a relatively weak carcinogen, otherwise the evidence for lung cancer would be far clearer and more convincing than is the case.

1.2 Relationship between silicosis and lung cancer

As discussed in Section 1.1.5, it is considered that silicosis and lung cancer are both likely to stem from a common background of chronic inflammatory lung damage. However, they are distinct disease conditions involving different cell types and develop via different toxicological mechanisms.

Most of the available information from epidemiological studies concerning the relationship between silicosis and lung cancer is of limited usefulness. Classification of study subjects as 'silicotic' and 'non-silicotic' is likely to be fraught with error; diagnosis based on chest radiography is not necessarily specific for silicosis, at least for the lower ILO grades of 0/1 and 1/0. Chest radiographs may have been negative when taken for some subjects, leading to classification as 'non-silicotic'. However, some workers may have proceeded to develop silicosis after the last chest radiograph was taken, and if they subsequently died from lung cancer, their silicosis may well have gone undetected. In two case-control studies of lung cancer and silicosis in South African goldminers, silicosis was diagnosed at autopsy, which may seem to provide a 'gold-standard' for unambiguous diagnosis. However, at these autopsies, silicosis was positively identified on the basis of only one silicotic nodule. This may or may not be appropriate, but points to the difficulty in determining exactly what should constitute a diagnosis of silicosis. This point is supported by the fact that silicosis was separately diagnosed for the parenchyma, pleura and hilar glands in these autopsy studies, with no clear consistency or relationships between these separate diagnoses.

A number of studies have shown no increases in the expected number of lung cancer cases in groups without silicosis. A study in Australian goldminers showed no excess lung cancer mortality in those without silicosis (De Klerk and Musk, 1998). The same finding was observed in a study in German stone, quarry and ceramics workers (Ulm et al, 1999). A study in Chinese refractory brick manufacturing workers also showed that the excess of lung cancer in this cohort was entirely restricted to those with silicosis, and that the risk of lung cancer increased with increasing grades of silicosis (Dong et al, 1995). In contrast, a study in diatomaceous earth workers showed a trend of increasing lung cancer risk with increasing cumulative exposure to RCS in the absence of silicosis (Checkoway et al, 1999). However, small group sizes and lack of statistical precision mean that little weight of evidence can be placed on this observation.

Studies of workers with compensation for silicosis consistently reveal increased risks of lung cancer in such groups, but such studies suffer from selection bias and confounding by smoking, and do not help to address the question of whether RCS can cause lung cancer in the absence of silicosis.

1.2.1 Summary of conclusions on silicosis and lung cancer

Overall, where evidence is available concerning the relationship between lung cancer and silicosis, it tends to show that excess lung cancer mortality in RCS-exposed workers is restricted to those with silicosis, and the more severe the category of silicosis, the higher the risk of lung cancer. The implication of this is that exposures to RCS insufficient to cause silicosis would be unlikely to lead to a significant increase in the risk of lung cancer over and above background levels. The weight of evidence is generally consistent with this contention although, due to the limited power of the available epidemiological studies to detect small excesses of lung cancer risk at lower exposure levels, the evidence for this is not definitive.

1.3 Variability in carcinogenic potency

As noted in the Background section above, HSE's Phase 1 review of RCS concluded that the fibrogenicity of RCS (ie ability to cause silicosis) may be influenced by factors, referred to as 'potency factors'. These factors all affect the surface properties and particle size characteristics of RCS dusts. It would seem reasonable to predict that such potency factors might exert a similar influence on carcinogenic potency, given that it is the surface properties of RCS that determine its biological reactivity. Furthermore, the proposed mechanisms of silicosis and lung cancer development are both indirect mechanisms mediated by alveolar macrophages; the initial stages of macrophage activation are likely to be similar for silicosis and lung cancer development.

The Phase 1 review noted that the fibrogenic potency of RCS is likely to be enhanced by the production of freshly fractured crystalline surfaces, due to the formation of highly reactive surface radicals. Freshly fractured surfaces are formed in industrial processes involving grinding, blasting, drilling and high-energy abrasive processes. The studies with the least confounded and clearest evidence for lung cancer in RCS-exposed workers derive from the granite and stone working industries. In these industries, stone with relatively high quartz content is quarried and processed in ways which are very likely to produce freshly fractured surfaces of quartz. This observation might be viewed as being consistent with the variability contention.

Studies in industrial sand workers also showed increases in lung cancer mortality again unconfounded by exposures to other known or suspected carcinogens. Compared to other studies, dust exposures in this industry would have the highest (almost 100%) quartz content. However, the pattern of exposures in this industry is varied. Obtaining the raw material from loose unconsolidated sand does not require any high-energy processes, and there is unlikely to be any production of freshly fractured surfaces. In contrast, in some cases the sand is obtained from hard compacted rock, and some drilling and blasting is required. The processing of the sand may require crushing and screening, but it is uncertain whether these processes are energetic enough to produce freshly fractured surfaces. However, often the plants concerned operated ball-milling processes to produce silica flour, and workers exposed to these processes are likely to have had exposures to freshly fractured reactive surfaces, as well as to very small size particles of very high specific surface areas. Unfortunately, the available epidemiological studies do not allow job-specific risks to be identified, and so the possible contributions made by the two potency factors (freshly fractured surfaces and small particle size) to the observed carcinogenicity findings cannot be discerned.

In relation to cristobalite, the Phase 1 review concluded that it is likely to be of equal fibrogenicity to quartz under equivalent conditions of occupational exposure. The main epidemiological evidence that informs on the risks of lung cancer in workers exposed to cristobalite derives from studies in diatomaceous earth workers. In this situation, the cristobalite is produced from the calcining of diatomaceous earth. The cristobalite so produced would not have freshly fractured surfaces. The calcined dust is then subject to further processing, grading and bagging, but it is uncertain whether or not these processes would produce freshly fractured surfaces. The recent pooled analysis by an IARC working group (Steenland et al, 2001) concluded that, in relation to the diatomaceous earth workers' data, 'the exposure-response trend within this cohort did not differ notably from trends in the remaining cohorts. Nonetheless, we suspect that physical differences in silica between cohorts (eg freshness of particle cleavage, degree of coating with dust) may be a partial explanation of observed differences between studies.'

In a study of UK pottery workers, there did not appear to be any higher risk of lung cancer in those exposed to heated quartz compared to the rest of the cohort, although the authors implied that an effect of cristobalite would have been hard to discern due to the close correlation between heat-related jobs and high exposure.

Overall, there is no evidence to indicate that the carcinogenic potency of cristobalite would be any different from that of quartz under equivalent conditions of occupational exposure.

In relation to other 'potency factors', the Phase 1 review concluded that the fibrogenic potency of RCS may be reduced when the surface of quartz has been coated with aluminium-containing clay minerals, a situation which results from the close physical association between quartz and other minerals in some geological conditions. Such conditions may occur in relation to the presence of quartz in coalmines. Over the millions of years of the geological formation of coal, the surface of quartz grains in dirt bands associated with the coal strata can become coated or intergrown with clay minerals. This reduces the amount of 'free' quartz surface available. An IARC working group concluded in 1997 that there was no excess mortality from lung cancer associated with coalmining, although there was increased mortality due to non-specific respiratory diseases, and in some studies there were excesses of gastric cancer. The absence of evidence for lung cancer may appear to be consistent with the variability contention as portrayed in HSE's Phase 1 review. However, the percentage of quartz in coal mine dust varies from mine to mine, and also within mines depending on the seams being worked. Typically, percentages of 2-5% quartz in coalmine dust have been quoted, although in some mines higher percentages have been found. By comparison, the percentage of quartz in granite may be up to 30%, and is virtually 100% in industrial sand. Thus, while surface coating of quartz in coal mines may protect against the carcinogenicity of quartz, it is difficult to draw firm conclusions in the absence of precise comparisons of cumulative exposure to quartz in coalmining compared with other industrial groups.

1.3.1 Summary of evidence for variability in carcinogenic potential

The evidence for variability in the carcinogenic potential of RCS is far less clear than for fibrogenic potency. There does seem to be a slight pattern in the evidence in that the studies with the clearest evidence for lung cancer (granite/stone workers) all represent exposure conditions in which there would be exposure to freshly fractured reactive quartz surfaces. Studies in industrial sand workers also showed positive evidence for carcinogenicity, and it is likely that there would have been some exposure to freshly fractured surfaces for some of the tasks and processes involved in this industry, particularly in the plants in which ball-milling was in operation.

The Phase 1 review concluded that fibrogenic potency would be enhanced with freshly fractured surfaces and extremely small particle size, and to this extent there is some consistency with the evidence for variability in carcinogenic potency.

The Phase 1 review concluded that cristobalite and quartz would be of equal fibrogenic potency under equivalent conditions of occupational exposure. The evidence relating to carcinogenic potency is limited, particularly as there is no direct information from animal studies to inform on this issue. From the limited information available, there is nothing to indicate that cristobalite would be any different in its carcinogenic potency to quartz.

Conclusions relating to the effects of other minerals on the carcinogenic potency of RCS are difficult to draw, particularly as exposure conditions have been so poorly characterised in most studies. It does appear that coating with clay minerals such as might occur in coal mining might reduce the carcinogenic potency of RCS, but on the other hand the lack of evidence for RCS-induced lung cancer in coal miners might simply reflect the relatively small percentages of quartz in coal mine dust compared to quartz-containing dusts in many other industries.

It is believed that the fibrogenic and carcinogenic potencies of RCS both derive from similar biological processes involving macrophage activation. The extent of macrophage activation will depend on the surface properties of RCS, so it seems reasonable to predict that the same potency factors that apply to fibrogenicity would also apply to carcinogenicity. Although the pattern of evidence from empirical observations in epidemiological studies shows some support and consistency with this contention, there is not enough firm evidence on this subject to allow any stronger conclusions to be drawn at this time.

Section 2 - Individual appraisal of key epidemiological studies

The epidemiological database concerning crystalline silica and lung cancer is very large. Numerous recent reviews (Goldsmith, 1982; Pairon et al, 1991; McDonald, 1995; Weil and McDonald, 1996; IARC, 1997; McDonald and Cherry, 1999; Hessel et al, 2000; Soutar et al, 2000; Checkoway and Franzblau, 2000; CICAD, 2000) have focused on those studies which provide the least confounded and most reliable information. These studies are presented in detail in this section, together with several more recently published studies.

2.1 Studies in stone workers

2.1.1 Finnish stone workers

Koskela and co-workers have published several studies of the mortality experience of Finnish granite workers (Koskela et al, 1987a,b, 1990, 1994). The latter publication included the longest follow-up period and is presented in detail below.

2.1.1.1 Koskela et al (1994). The results of this study revealed an excess of lung cancer in Finnish granite workers with long latency and duration of exposure to quartz-containing granite dusts. The influence of smoking could not be assessed. The study provided no information on the relationship between lung cancer and silicosis.

The aim of this study was to investigate the relationship between lung cancer and occupational exposure to quartz in Finnish granite workers. The study was of an unusual design consisting of a number of different analyses, some of which were not clearly presented.

The cohort consisted of 1026 male workers employed in quarries and processing yards in three main granite-working areas of Finland (Vehmaa, Kuru and Viitasaari). The workers in the cohort had started work in the industry between 1940 and 1971 and had worked for at least three months. No further details on selection were presented, and so it is not known if this was a representative or comprehensive sample of the workers in this industry. Hence, the possibility of bias stemming from the selection criteria cannot be assessed.

The cohort was initially followed up to 1985, and mortality findings were published in detail in a previous report (Koskela et al, 1990). The period of follow-up was subsequently extended by an additional four years to 1989. The mortality data for both periods of follow-up were analysed separately.

The mortality data up to 1985 were analysed separately for each region, comparing the observed cases of lung cancer with expected numbers in the national male population. However, SMRs were not calculated in the conventional manner by applying five-year age-specific and calendar time-specific rates from the national population, but instead were based on national statistics for the median year of deaths in the cohort (1975). The IARC Working Group was uncertain what effect this may have had on the findings. The lung cancer cases observed to 1985 were included in a nested case-control analysis, the aim of which was to compare the cumulative exposures of the cases and matched controls for each region. Controls were matched on age, time of entry into granite work and quality of information on lifetime quartz dust exposure.

As above, mortality findings up to 1989 were analysed for each region, comparing the observed cases of lung cancer with expected numbers from national figures for men in the median years of deaths in the cohort (1977). A nested case-control study was not conducted for the longer follow up period.

In addition to the lung cancer mortality investigations, lung cancer incidence in the cohort was also determined between 1953 and 1987. The Finnish cancer registry was used to determine cancer incidence in the cohort and in the national population during the same period. The observed age-and cause-specific incidence was compared against the national figures (grouped by five-year calendar periods) using the Poisson distribution model.

An additional poorly reported analysis compared the lung cancer incidence and mortality of granite workers to workers in other occupations for each region. The age- and cause-specific mortality for the period 1962-1985 was obtained from national mortality statistics. The lung cancer incidence was investigated by linking the regional census data for the target population groups (for 1970, 1975, 1980 and 1985) to the Finnish cancer registry for the same time period. The authors indicated that the comparisons were between granite workers and workers from other occupations. However, no information on the other occupations was discussed, and the comparisons presented seemed to be between granite workers and the remaining male population.

Occupational histories and information on smoking were obtained from company records and a questionnaire issued in 1986. No details on smoking were provided other than a statement that the smoking habits of granite workers were similar to other Finnish male workers, and there was no difference in smoking habits between each region. However, it is not known how their smoking habits compared to the general population against whom the excess of lung cancer was compared, and so there is some uncertainty regarding the potential for confounding by smoking.

The cause of death for these analyses was determined from death certificates. There was no explanation of how silicosis as a contributory cause of death was diagnosed, either from previous chest radiographic evidence or assumed on the basis of medical examination and known exposure to quartz.

Dust measurements were made at 28 quarries and processing yards and in four rock crushing plants in surveys in the early 1970s. Presumably these were the same quarries and plants in which the cohort had worked, but this was not specified. The paper presenting the details of these surveys could not be traced. The surveys showed geometric means of total airborne dust ranging from around 1-40 $mg.m^{-3}$ and around 1-1.5 $mg.m^{-3}$ for quartz. Whether these values are task-specific or eight-hour TWAs is not known. No information on respirable dust levels was presented.

Each area covered by the study mined different types of granite, each containing different levels of quartz: red granite (36% quartz) mined at Vehmaa, grey (31%) mined at Kuru, and black (0% quartz) mined at Viitasaari. In the latter case, the rock was not true granite; the term 'granite' was used by the authors to indicate its building stone quality rather than mineral structure (Pilkington et al, 1996). These differences would be predicted to give different levels of quartz exposure for similar jobs in different regions, and quartz exposures in Viitasaari would be expected to be negligible. There was limited information on confounding exposures, but at least three of the lung cancer cases had previous experience in foundries or welding.

At the end of 1985, 296 subjects had died. It was not stated how many subjects had been lost to follow-up. The results showed a non-statistically significant excess of death in the whole cohort from all causes (SMR 107), and statistically significant excesses of death from non-malignant respiratory diseases (SMR 225) (40 deaths, including 13 due to silicosis) and lung cancer (SMR 156) (106-221; 31 deaths). Mortality from lung cancer was reported to be particularly high (SMR 220) (147-319; 28 deaths) for those 'followed' for at least 15 years. It was unclear if this referred to 15 years of latency or duration of exposure.

There were clear regional differences in lung cancer mortality (SMR 126 (71-208; 15 deaths) in Vehmaa and SMR 211 (120-342; 16 deaths) in Kuru), with no excess in Viitasaari. Stratifying the number of lung cancers observed in each region by latency (years since hire) showed a marginal difference between each region, with a higher proportion of cases in Vehmaa having latencies of $\geq$ 25 years (10/15) compared to Kuru (6/16). However, the number of cases in each category of latency for each region were small, and so no reliable conclusions can be drawn from this analysis.

By the end of 1989, another 67 deaths had occurred, of which five were due to lung cancer, leading to an all-cause SMR of 1.09, and for lung cancer the SMR was 1.4; $p<0.05$ 95% CIs were not presented. The SMR for lung cancer for the earlier time period (up to 1985) was higher at 1.56.

The SMRs for lung cancer in each region were 1.17 in Vehmaa and 1.75 in Kuru, similar to the SMRs calculated at the end of 1985. There was one new case of lung cancer in Viitasaari since 1985. Mortality from lung cancer was also assessed when stratified in terms of latency (more or less than 20 years) and duration of exposure (more or less than 10 years) for the Vehmaa and Kuru regions separately or combined. There was clearly higher mortality from lung cancer in the category of long latency and duration of exposure compared to other combinations of lower tenure or duration of exposure – SMR 1.48 (22 deaths), 1.33 (13 deaths) and 1.76 (9 deaths; $p<0.05$) in both regions combined, Vehmaa and Kuru, respectively, for long latency and duration of exposure.

The co-occurrence of lung cancer and silicosis was considered by the authors not to be common in this cohort. However, the uncertainties surrounding the reliability of the diagnosis of silicosis means that the reliability of this conclusion is uncertain.

Lung cancer incidence in the cohort was followed from 1953 to 1987. The observed number of lung cancers was compared to the expected numbers calculated from figures from the national cancer registry for five-year calendar periods. The results were presented as SMRs, which seems inappropriate. However, this may have been an error in terminology, using SMR instead of SIR, and the results will be presented as SIRs in this document. In the whole cohort there were 43 lung cancers against 25.3 expected (SIR 170 (123-229)). When broken down for each region, there were 25 lung cancers in Vehmaa (SIR 162 (105-240; 15.4 expected)), 17 lung cancers in Kuru (SIR 181 (105-290; 9.4 expected)) and only one lung cancer in Viitasaari (0.5 expected). There was no statistically significant difference in incidence rates between Vehmaa and Kuru. There was a slight difference between the incidence and mortality from lung cancer (an incidence of 43 cases from 1953-1987, and 36 deaths from 1940-1989). The reasons for this are unknown and were not discussed by the authors.

A nested case-control analysis was conducted to inform on the relative cumulative dust exposure (calculated as the sum of the length of exposure in each job title multiplied by the job-specific quartz dust concentration during the corresponding calendar period) of cases and matched controls in each region (14 cases in both Vehmaa and Kuru and none in Viitasaari). The findings were expressed in terms of the number of cases who had higher or lower cumulative exposures than their matched control. No quantitative information on cumulative exposure levels was presented. More cases had more exposure than their matched controls in Vehmaa than in Kuru (nine against three, respectively). A case-case analysis, with 10 age-matched case pairs from Kuru and Vehmaa, indicated that cases in Vehmaa were statistically significantly more exposed than those in Kuru (no more details presented). This is a very limited analysis of exposure patterns between cases and controls and regions and, given the unreliable exposure data, this analysis is not considered to provide any useful information.

Overall, the results of this study demonstrated an increased risk of lung cancer in granite workers. There was no reliable information on quantitative exposures to respirable quartz for these workers, and no reliable information on the prevalence or severity of silicosis. The influence of smoking on the excess lung cancer mortality is uncertain, with the only information on this aspect being that smoking habits in the cohort were thought to be similar to other male workers in other occupations. No evidence for this was provided. Some aspects of the study were not clearly presented and did not always follow conventional statistical methods. The selection criteria for cohort members were not stated, and it is not known whether the cohort was completely enumerated. However, it does appear that lung cancer mortality was clearly greater in granite workers from the two regions where quartz was present in the stone, compared with a region where quartz was not present. There are no grounds to consider that smoking differences could account for this striking pattern of lung cancer distribution. For this reason, the results of this study are consistent with the possibility that RCS may cause an increased risk of lung cancer.

2.1.2 Danish stone workers

2.1.2.1 Guénel et al (1989a,b) conducted a study of lung cancer incidence in Danish stone workers. The findings provided some evidence of an excess of lung cancer due to RCS exposure, particularly in workers employed pre-1940. Smoking was unlikely to wholly account for the observed excess.

Guénel et al (1989a,b) investigated lung cancer incidence in a cohort of 2071 Danish stone workers. The stone industry in Denmark is divided into two main branches – the stone cutting industry and the road and building material industry. Granite is the main type of stone used in these industries, but sandstone and flint are also used. Granite is a mixture of quartz, feldspar and mica, and sandstones consist of grains of quartz cemented together with clay.

Subjects were drawn from small stone cutting workshops throughout Denmark (from the Bornholm, Copenhagen and 'other' regions), and from one road and building material factory. Only limited information on each subject, such as age and job title, was available from national sources, such as census, union lists and company records. There was no information on date of hire or length of employment, or on smoking history. Workers were born before 1942, and were less than 65 years old at the start of the study. The cohort was followed for 42 years, and the average length of followup was around 24-30 years. Lung cancer cases were identified by linkage with the national cancer registry, which recorded all cancer cases diagnosed throughout the period of the study.

Workers were classed as either skilled (1081) or unskilled (990) based upon their work tasks. The skilled or unskilled status reflected likely differences in work patterns and RCS exposure. Skilled workers in the stone cutting industry tended to work in the industry for their whole working life, whereas unskilled workers tended to work in the industry for short periods. The lack of information on the work histories of these workers did not allow an assessment of whether they were exposed to asbestos or other potential confounders in previous employment. In addition, there was some evidence that RCS exposures of skilled workers were generally lower than those for unskilled workers. However, from the information available, no firm conclusions can be drawn regarding the relative cumulative exposures of these groups. All unskilled workers were from Bornholm.

There was limited exposure information on dust and RCS exposure in the road material and building industry (11 companies) and stone cutting industry (nine companies) between 1948 and 1980. Before 1970, most dust measurements were area samples, taken using an impinger or electrostatic precipitator, in terms of respirable particles per cubic meter. After 1970, measurements were taken using personal samplers in the breathing zone, in terms of gravimetric units. The silica content of the dust was determined by X-ray diffraction. There were only a small number of measurements available (163 and 34 measurements in the road material and building industry and stone cutting industry, respectively). Measurements in the stone cutting industry from the 1970s showed a median respirable quartz exposure of 0.03 and 0.06 $mg.m^{-3}$ in the 'other' and Copenhagen regions (no measurements for Bornholm), and in the road and building material industry, the highest median respirable quartz exposures was 0.16 (probably for all Denmark) to 0.29 (in Bornholm) $mg.m^{-3}$ (Guénel et al, 1989b). Exposures were primarily to quartz, but it was reported that cristobalite, constituting 2-11% of the respirable dust, was detected in eight measurements from two road material industries. It is not known if these exposure levels are representative of the sites covered by the study. Radiographic surveys among stone cutters in the 1930s and 1950s revealed high prevalences of silicosis, indicative of high levels of exposure, although the introduction of mechanical ventilation into the industry in the 1950s probably resulted in significantly lower levels subsequently.

Standardised incidence ratios were calculated for each region using national cancer incidence rates. No information on smoking was available, so the authors used two indirect methods to assess the possible influence of smoking. The relative risk of lung cancer varied regionally, between 0.4 and 1.66 times that of the national rates, allowing SIRs for each region to be adjusted according to the relative cancer rate in that region. In addition, the incidence of bladder cancer, a disease linked to smoking but not RCS exposure, was used as a surrogate indicator of smoking.

In skilled workers, there was an overall excess of lung cancer cases compared to national rates (SIR 1.38; 95%CI 1.00-1.89; 44 cases), and after regional adjustment (SIR 2.00; 95%CI 1.49-2.69). When analysed for regions, there were also excesses in Copenhagen (4.65 and 3.06; 18 cases) and 'other' (1.61 and 1.92; 18 cases) regions, but not in Bornholm (0.48 and 1.19; 8 cases) compared to national rates and adjusted for region, respectively.

For the Copenhagen region, additional information was available on the main stone material, sandstone or granite, worked by each subject. There were excess risks of lung cancer for sandstone workers (SIR 8.08; 7 cases in 47 subjects) and granite (4.04; 11 cases). These findings suggest a significant excess of lung cancer, although the relatively small number of cases introduces the possibility that these excesses are a chance finding. In this group, most cancers occurred before 1940 (SIR 3.57; 95%CI 1.95-5.99; 14 cases pre-1940, and 2.21; 95%CI 0.60-5.66; 4 cases, post-1940, respectively).

Unskilled workers were exposed mainly to granite. There was a significant excess of lung cancer when adjusted for local rates (SIR 0.72; 95%CI 0.46-1.08 and 1.81; 95%CI 1.16-2.70; 24 cases, for unadjusted and adjusted, respectively). An excess risk of lung cancer was only found in workers in the road and building material industry when adjusted for local rates (SIR 2.46; 95%CI 1.43-3.94; 17 cases).

There was no statistically significant increase in SIR for bladder cancer in skilled or unskilled workers in any region. Some SIRs were raised, but the confidence interval included 1 in all cases. No information was presented to inform on the possible relationship between the presence of silicosis and lung cancer.

This study provided evidence of an excess incidence of lung cancer in stone workers. The average length of follow-up was over 20 years. The limited information presented on time of diagnosis indicated that there was a stronger excess risk of lung cancer pre-1940, when dust levels were probably relatively high. The evidence for an excess risk of cancer was strongest in the skilled workers. However, the lack of reliable information on RCS exposure and different work patterns between the skilled and unskilled workers precludes any meaningful comparison of lung cancer rates between these two groups. Sandstone workers appeared to be at higher risk than granite workers, possibly due to the higher silica content of sandstone.

The study had some notable weaknesses. One of the main weaknesses was the lack of information on smoking. The use of regional lung cancer incidence data generally increased the risk estimates. This indirect adjustment may be a reasonable correction if the smoking habits of workers were typical of the regional population in which they worked, and suggests that the excess lung cancer risk was not explained by smoking. The absence of any clear excess of bladder cancer provides further support that the lung cancer excess was not entirely due to smoking. Also, there was only limited information on occupational histories of individuals and differences between the skilled and unskilled work. While the limited evidence suggests that skilled workers were exposed to lower average RCS concentrations, there is no information on the relative cumulative RCS exposures of the two groups. There is probably little exposure to confounders in this industry, but there is no information to inform on possible exposure to confounders in the unskilled workers who may have worked in other industries with such exposures. Silicosis was probably quite prevalent in this cohort, but its association with lung cancer was not addressed. Overall, this study provides some evidence for an association between RCS exposure and lung cancer.

2.1.3 Vermont granite workers

Several studies have been conducted in Vermont granite workers. Davis et al (1983) and Costello and Graham (1988) conducted a proportional mortality study and cohort mortality study, respectively, in the same population of Vermont granite workers. A later mortality study of US stone workers by Costello et al (1995) was not considered by HSE to provide any useful information over the earlier study by Costello and Graham and so was not included.

2.1.3.1 Davis et al (1983) conducted a proportionate mortality study investigating lung cancer in Vermont granite workers. The results showed no evidence for an excess of lung cancer mortality based on cause-specific proportional mortality in the US population. Internal analyses showed no association between lung cancer risk and cumulative exposure to RCS. However, the relative risk of death from silicosis and tuberculosis showed strong trends with estimates of cumulative dust exposure.

The Vermont granite industry consists of several quarries and a number of small manufacturing plants (called sheds) where stone is cut, polished and finished into monuments. It is likely that shed workers would have been exposed to relatively high dust levels compared to quarry workers. Effective dust controls were installed in the granite sheds by 1940 and were in place in the quarries by 1950.

The cohort consisted of 969 deceased granite workers who had worked in the industry between 1952 and 1978 for at least one year and had died before July 1978. There was a voluntary medical surveillance programme in this industry from 1937 which included chest radiography. By 1963 most (98%) employees had at least one chest radiograph. The average year of hire was 1934, with an average duration of employment of 31 years and death at 62 years. A majority of the men (73%) had worked in the granite sheds only, with the remainder working in the quarries or with experience in both areas. A small number of cases (26) had worked in saw plants or grit mills.

A job-exposure matrix was constructed from dust measurements taken in several surveys over a 50-year period from 1924 to 1977, which covers the range of this study. The earlier measurements were in terms of particle counts and the later ones as gravimetric units. As most measurements were in particle counts, the gravimetric values were converted into particle counts to allow all data to be used. This conversion may have introduced errors in the exposure estimates which may have reduced the power of the study to detect modest lung cancer risks (Soutar et al, 2000). Average dust exposures ranged from around 1-140 mppcf pre-1950 and 1-10 mppcf post-1950. The quartz content of the granite was high at around 30%. No confounding exposures other than to 'abrasives', possibly in blasting type operations, were reported.

Work histories were obtained from formal records and appeared to be complete. No information on smoking was presented. The cause of death was obtained from death certificates. Proportional mortality (number of deaths from a specific cause per an arbitrary number of total deaths) was calculated relative to the general US male population. The mortality rates for Vermont were similar to US rates during the study period, suggesting that the national population was an appropriate reference population to use.

The results were presented as observed to expected ratios (OER), calculated as the ratio of deaths from a specific cause divided by the expected number of deaths. Due to the high number of deaths from silicosis and tuberculosis, the expected numbers of deaths were derived in two ways: either based on all causes of death in the study population, or after silicosis and tuberculosis deaths were excluded. The OER values were based on the latter number of expected deaths.

There were 65 deaths from tuberculosis and 89 deaths from respiratory diseases, of which 28 were due to silicosis and 22 from emphysema (OER 1.5 95% CI 1.0-2.2), the latter being possibly suggestive of heavy smoking within the study population. Virtually all of the deaths from tuberculosis and silicosis occurred before the introduction of dust controls in 1950. However, chest radiographic evidence suggested that the prevalence of silicosis was higher in this cohort than may have been indicated from the silicosis death rates.

There were 62 deaths from lung cancer versus either 57.9 or 52.6 expected (according to whether or not silico-tuberculosis deaths were excluded). This led to an OER of 1.2 (95% CI 0.9-1.5). Analyses of the mortality findings were conducted based on year of entry into the cohort (either before or after 1950 when dust controls had been introduced), based on quartiles of cumulative exposure, and based on job classification.

Cumulative exposure was categorised as low (<200), medium (199-400), high (399-800) or very high (>800 mppcf-year). The results were unexpected. Workers in the highest two cumulative exposure groups had all worked in the industry prior to the introduction of dust controls and had worked on average longer than those in the lower exposure groups. However, the average age of death and time from hire to death was lower in the lowest exposure group despite later hires and considerably lower duration of exposure. The reason for this apparently anomalous pattern is not clear, but may be related to socio-economic factors, eg the high mortality often observed in transient workers, or other exposures in previous employment.

There was a clear trend of increasing relative risk (RR) for silicosis and tuberculosis with increasing cumulative exposure. However, there were no associations with cumulative exposure for other causes of death, including lung cancer. Similarly, there were no clear trends for lung cancer when stratified on year of hire, age at hire, duration of employment, time between hire and death, age at death or year of death.

When mortality was stratified on job description, there was an excess of lung cancer among sawyers (OER 2.08 (5 deaths)) and emphysema in shed workers (OER 2.78 (5 deaths)). It would be anticipated that dry sawing of granite with no dust suppression would lead to high dust exposures. However, the small number of cases limited the reliability of drawing conclusions on whether the lung cancer risk was higher in sawyers and others workers doing similar work.

Overall, the analyses showed no association between lung cancer risk and cumulative exposures to quartz, even in subjects with the highest cumulative dust exposures. There are a number of factors which may have weakened the ability of the study to detect small excess risks of lung cancer. The cases were drawn from a number of jobs with a large range of exposures. There was some limited evidence that sawyers, who would be predicted to be exposed to higher levels of respirable dust than workers in an open quarry, had an excess of lung cancer. The pooling of cases from these diverse jobs would tend to reduce the overall excess, particularly if the number of cases in each job was small. In addition, there was high mortality from silicosis and silico-tuberculosis, and so it is possible that deaths from other causes could potentially have obscured a real association between granite exposure and lung cancer. Also, there is the possibility that uncertainties in the exposure estimates may have weakened the ability of the study to identify a weak relationship of lung cancer with cumulative dose. However, the clear trend of increased risk of silicosis and silico-tuberculosis with cumulative exposure provides some indication that the exposure estimates were reasonably reliable.

There was no information on smoking, but the authors recognised that workers in these sorts of industries often tend to smoke more than the general population. Some limited evidence to suggest that this population smoked more than the general population comes from the observed excess of deaths from emphysema and respiratory diseases which are often associated with smoking. On the other hand, heavier smoking in this group would have been predicted to produce some increase in lung cancer mortality, which was not observed. Overall, the results do not support a causal association between exposure to RCS and lung cancer.

2.1.3.2 Costello and Graham (1988) conducted a cohort mortality study in Vermont granite workers. The results showed an increased mortality from lung cancer in shed workers but not in granite workers based on comparisons with US male population rates. The lung cancer excess was restricted to those who commenced employment prior to the 1940s, when dust controls began to be introduced.

This study followed on from an earlier proportionate mortality study by Davis et al (1983), but included a larger number of death certificates by enlarging the period of observation from 1950-1982, and by a more rigorous searching of files from the State health department. The authors thus identified an additional 558 death certificates that had not been included in the earlier study. Furthermore, unlike the previous study, smoking history was traced for those men who developed lung cancer from clinical records. This showed that all lung cancer cases were either current or ex-smokers. Previous chest radiographs for lung cancer cases were reviewed to determine the presence of silicosis (defined as ILO Category 1/1+). In most cases, the lag between the last available film and death was several years (so it is conceivable that some ‘negative’ X-ray films would have progressed to a positive status in the intervening period, thus leading to an underestimate of the true extent of silicosis).

The cohort contained a total of 5414 subjects; there were 1643 deaths by 1982, and death certificates were available for 1527 deaths (93%). A substantial proportion of the cohort had relatively long service in the industry, with 57% serving for more than 15 years and 31% serving more than 30 years; around 22% had less than five years' service.

In the cohort as a whole, there was a deficit of all-cause mortality with an SMR of 0.91. There were 124 deaths from tuberculosis (SMR 5.86) and 41 deaths from silicosis (SMR 6.36). Deaths from these causes were restricted to those hired before 1950 and were particularly excessive pre-1930, when dust levels were highest. There was no significant excess of deaths from any other specific causes, including lung cancer and emphysema. The SMR for lung cancer was 1.16 (95% CI 0.96-1.39) and for emphysema was 1.12 (95% CI 0.84-1.75).

When mortality was analysed according to work in either the sheds or quarries, some important differences emerged. The SMRs for silicosis and tuberculosis were >two-fold higher in shed workers compared to quarry workers. Also, there was a statistically significant excess of mortality from lung cancer and respiratory diseases in shed workers, with SMRs of 1.27 (98 deaths) and 1.28 (106 deaths) respectively. However, no such excesses were seen in quarry workers.

There were no stratified analyses of mortality rates according to estimates of cumulative exposure, but there were various separate analyses of the data from the shed and granite workers, taking into account year of hire, length of tenure and latency. The analyses revealed that statistically significant excesses of lung cancer were found in shed workers with a combination of long tenure (10-29 years) and long latency (25-39 years) (SMR 1.64 (21 deaths)), and also in those with a tenure of more than 30 years combined with a latency of over 40 years (SMR 1.81 (47 deaths)), but not in other combinations. It is possible that the marked excess of deaths from silicosis and tuberculosis may have reduced the potential for subsequent lung cancer development in some of the earlier hire workers.

In terms of the relationship between lung cancer and silicosis, the only information of relevance is that there was radiographic evidence of silicosis in 68% of the lung cancer cases hired pre-1930 and in 26% of cases hired between 1930-39. The prevalence of silicosis in those without lung cancer was not stated.

The most striking feature of this study is that the lung cancer excess was restricted to granite shed workers, with no observable excess in the quarry workers. The shed workers were likely to have been more heavily exposed to respirable quartz dust from the processing work, pointing to a causal role for quartz. Among shed workers, the excess of lung cancer was restricted to those with long tenure and long latency (the early hire workers), factors which may also be surrogates for long duration or smoking. All of the lung cancer cases were smokers, and it is possible that some of the excess lung cancer was due to smoking. However, no evidence was presented to suggest that shed workers were heavier smokers than quarry workers, and so smoking seems unlikely to be able to account for all the observed excess of lung cancer. Therefore, this study does provide some evidence to support the view that exposure to dusts containing high proportions of silica (30%), much of which may have contained freshly fractured surfaces, can lead to lung cancer development. This conclusion is strengthened by the absence of any obvious confounding factors (other than smoking). The design of the study was not adequate to allow for any worthwhile analysis of the relationship between silicosis and lung cancer.

2.1.4 German stone workers

2.1.4.1 Ulm et al (1999) conducted a case-control study in German stone/ quarrying and ceramics workers. The selection process specifically excluded workers with compensated silicosis. There was no evidence of an excess of lung cancer in these workers due to RCS exposure.

Ulm et al (1999) conducted a case-control study of workers in the German stone/quarrying or ceramics industry diagnosed with lung cancer between 1980 and 1994. A total of 247 (133 and 114 from the quarry and ceramics industry, respectively) lung cancer cases were identified from insurance and hospital records, and all diagnoses were confirmed by histopathological examination (no further details presented). A total of 795 controls were drawn from the quarrying and ceramics industry (231 and 564, respectively), all of whom had occupational exposure to RCS. There was a difference in the way the controls from each industry were selected. In the ceramics industry, controls were selected from a silicosis surveillance programme, in which virtually all workers have medical examinations, involving a chest radiograph, every three years. The equivalent programme in the stone/quarry industry only includes those workers with higher exposures, and consequently higher risk of silicosis, who are not representative of the whole industry. For this reason, controls were selected from an alternative source, namely records of accidents occurring at or travelling to or from work. The selection of controls from this source was not regarded by the authors as introducing any significant bias into selection. Subjects (cases and controls) compensated for silicosis (requiring at least ILO category 1/1 opacities, and reduced lung function) were excluded. Smoking was assessed from medical files and from personal interview. For each industry, cases were 'frequency matched' (undefined) to controls on sex, age, industry and smoking habit.

The details of the exposure assessment were only briefly presented. Exposures were estimated by expert judgement, using complete occupational histories, details of changes in hygiene practice and either measured dust levels or levels estimated by hygienists familiar with the industry. No information was presented on the methods used to determine dust or RCS dust levels. The possibility that workers in the ceramics industry could have been exposed to cristobalite was not addressed.

Around 30% of cases and controls were considered to have been exposed to potentially confounding agents (asbestos, PAHs, radon, diesel exhaust, welding fumes and heavy metals), but there were no clear differences between each group. The largest difference was in the stone/quarry industry, where more cases were exposed to diesel exhaust than controls (13 against 9.2%). The percentage of smokers and ex-smokers was similar in cases and controls, although more cases were heavier smokers (82.4 against 66.1% smoking >10 cigarettes/day), and had less time since cessation of smoking (4 and 14 years, respectively).

A comparison of exposure levels in each industry revealed that exposures had historically been significantly higher in the stone/quarry industry than in the ceramic industry. However, in each industry there had been a considerable reduction in dust and RCS exposure over the last few decades, and current exposures were similar (median 8-hr TWA exposures of 0.24, 0.12 and 0.05 $mg.m^{-3}$ in the stone/quarry industry and 0.07, 0.07 and 0.04 $mg.m^{-3}$ in the ceramics industry, pre-1940, 1940-1950 and post-1980, respectively).

For both cases and controls, the median year since first exposure was around 40 years, duration of exposure around 30 years, and year of first exposure around 1953. The average and cumulative RCS exposures were similar in cases and controls (median values of around 0.08 $mg.m^{-3}$ and 2.9 $mg.m^{-3}$.years, respectively), although some cases received higher exposures than controls (0.32 against 0.19 $mg.m^{-3}$, for time-weighted average, and 11.81 against 7.33 $mg.m^{-3}$years, for cumulative exposure, at the 90th percentile in cases and controls, respectively). Peak exposure, considered as either above or below 0.15 $mg.m^{-3}$ (the German MAK limit for RCS dust), showed that a slightly higher proportion of cases had peak exposures above 0.15 $mg.m^{-3}$ (53.4 and 45.7 cases and controls, respectively). The odd ratios (ORs) for lung cancer were calculated in relation to these different indices of exposure (TWA, cumulative and peak) and stratified according to high and low exposure (0.15 $mg.m^{-3}$ and 2.88 $mg.m^{-3}$.years, respectively) for each industry separately and combined and adjusted for age at first exposure year of first exposure, duration of exposure and additional exposures in the workplace. All ORs were around 1.0. Hence, in these cases of lung cancer, exposure to RCS did not differ significantly compared to controls.

To assess the possible exposure-response relationship, ORs (for both industries combined) for lung cancer, adjusted for age and year of first exposure, duration and latency, were calculated for four categories of average or cumulative exposure, chosen to include approximately equal numbers of subjects. There was no trend with either average exposure or cumulative exposure.

Overall, this study provided reasonably reliable evidence to demonstrate that exposure to RCS did not account for the observed cases of lung cancer in non-silicotic workers from the stone/quarry and ceramics industry. However, this finding may only inform on the lung cancer risk in populations with relatively low RCS exposure. The exclusion of subjects with radiographic opacities would tend to select those workers with the lowest RCS exposures. Also, the limited exposure information suggests that exposure in these industries is relatively low, particularly in the last few decades, and only a minority of workers appeared to have been employed in the earliest, most dusty decades.

2.2 Studies in diatomaceous earth workers

Checkoway and co-workers have published a number of analyses of the mortality experience in a cohort of US diatomaceous earth (DE) workers (Checkoway et al, 1993, 1996, 1997 and 1999). These studies presented information on the dose-response relationship for lung cancer with semi-quantitative (Checkoway et al, 1993) and quantitative (Checkoway et al, 1997) measure of RCS exposure, assessed the potential confounding by asbestos (Checkoway et al, 1996) and the relationship between lung cancer and silicosis (Checkoway et al, 1999).

2.2.1 Checkoway et al (1993). The results from this study demonstrated an excess of NMRD and lung cancer in a cohort of DE workers. The excess mortality from lung cancer was most prominent in those who had joined the industry earlier, particularly before 1930, and had the longest periods of exposure. There was also a strong trend of increasing risk of lung cancer with a semi-quantitative measure of cumulative RCS exposure. There was only limited information on smoking, but it did not appear that the observed excess of lung cancer could be wholly explained by smoking.

The original cohort contained 2570 white men employed at two DE plants for at least one year of cumulative service who had worked at least one day during the follow-up period 1942-1987 (Checkoway et al, 1993). At the time of this initial investigation, no adequate exposure measurements were available from which to estimate quantitative exposures, and so two indirect measures were used to estimate cumulative exposure to RCS. The first measure used duration in jobs with potential for dust exposure as a surrogate for cumulative exposure. In addition, a semi-quantitative job-exposure matrix was constructed using expert judgement and plant records. The matrix contained various weighting factors for each job and time period, chosen to give a proportional measure of the relative intensity of exposure, percentage of crystalline silica in the material handled, and assumed effectiveness of respiratory protection. A semi-quantitative index of cumulative exposures was then calculated as the summed product of time spent in different jobs and the corresponding weighting factors. In a later analysis, additional historical exposure data were obtained which allowed quantitative exposures to be estimated (Checkoway et al, 1997). The authors noted that exposure to potential confounders such as radon, arsenic or other occupational carcinogens is likely to be minimal in this industry. However, it is uncertain whether the calcining process might involve the release of PAHs.

Information on smoking was available from the industry's medical surveillance programme which had been conducted since the 1960s. The data were only sufficient to permit a distinction between ever- and never-smokers for around half of the cohort, and did not provide any information on the amount smoked or duration of smoking. These data were insufficient to directly adjust RRs for smoking. However, they could be used to estimate the extent to which the observed risk gradients might have been biased by differences in smoking pattern between the cohort and general population using the method of Axelson (1978). SMRs were calculated using US males as the referent population.

At the end of follow-up, vital status was available for around 91% of workers and death certificates were available for around 94% of the deaths. The mean duration of follow-up was 24 years. There was a slight excess of mortality from all causes (SMR 1.12; 95%CI 1.03-1.21). The most prominent cause of death was non-malignant respiratory diseases (NMRD; SMR 2.59; 95%CI 1.96-3.36 – excluding pneumonia and infectious diseases), accounting for 56 deaths. In 17 cases, the underlying cause of death was listed as various types of pneumoconiosis. There were no cases of asbestosis. These data are consistent with what might be expected for workers in a 'dusty trade' with excessive dust exposure. However, how much of the pneumoconiosis was silicosis as opposed to non-specific mineral dust pneumoconiosis is unknown.

There was a significant excess of lung cancer compared to national or local mortality rates (SMR 1.43 (95%CI 1.09-1.84; 59 cases) and 1.59; 95%CI not presented, respectively). Further analysis of the importance of year of hire, years since first employment and tenure (years of employment) on lung cancer mortality suggested greater risk of lung cancer in those who had joined the industry earlier and had the longest periods of exposure. The mortality was significantly increased in those hired before 1930 (SMR 2.63 (95% CI 1.12-5.15, number of cases = 8)), but then tended to decrease with successive hire periods, with no deaths occurring in the most recent hire period, 1970-1986. Mortality generally increased with years since first employment, but was statistically significantly increased only in those with at least 30 years since first employment (SMR 1.5 (95% CI 1.02-2.09; 33 deaths)). Similarly, there was an internal trend of increasing risk of lung cancer with tenure, which was most prominent with an exposure lag period of 15 years (RR (95% CI) of 1, 1.29 (0.6-2.76), 2 (1.01-3.95) and 2.88 (1.13-7.33) for <5, 5-9, 10-19 and ≥20 years' tenure, respectively). It would be expected that there would have been a strong correlation between duration of exposure and cumulative RCS exposure. Consistent with this, there was a strong trend of risk of lung cancer with estimates of cumulative RCS exposure (RR (95% CI) of 1, 1.19 (0.52-2.73), 1.37 (0.61-3.06) and 2.74 (1.38-5.46) at <50, 50-99, 100-199 and ≥200 exposure units, respectively, with 15 years' exposure lag).

The pattern of mortality from NMRD was broadly similar to that of lung cancer, with significant excesses limited to those employed in early decades and a trend of increasing mortality with increasing cumulative exposure.

The pattern of other diseases related to smoking was used as a crude indicator of smoking within the cohort. There was no overall excess of oral, pancreas, larynx, kidney or bladder cancers which are often associated with smoking. There was a deficit in ischaemic heart disease which the authors regarded as more likely an indicator of a healthy worker effect than an absence of excessive smoking in the cohort. Using the method of Axelson, the authors calculated that it would be highly unlikely that confounding by smoking could account for the observed increase in risk of lung cancer. From the limited smoking information available, it did not appear that there was any difference in the prevalence of smoking in relation to cumulative exposure category.

This study demonstrated an excess risk of lung cancer in the cohort and a trend of increasing risk of lung cancer with a semi-quantitative measure of cumulative RCS exposure. The excess of lung cancer was limited or most prominent in those who had joined the industry earlier, particularly before 1930, when dust levels were probably at their highest. The semi-quantitative exposure measure was relatively crude, but the trend of risk for lung cancer and NMRD with increasing measure of cumulative exposure and greatest risk in earlier times when dust levels were highest suggests that the estimates were sufficiently robust to identify these trends and were not systematically biased. The main weakness of this study was the limited information on smoking. However, indirect assessment of the potential confounding by smoking and the clear trend of increasing risk with increasing cumulative exposure suggests that smoking did not account for the whole excess of lung cancer observed.

2.2.2 Checkoway et al (1996). The data from the above study were re-analysed to assess the potential confounding by chrysotile exposure. There was no evidence that exposure to chrysotile had a significant influence on the lung cancer mortality in this cohort.

Chrysotile asbestos had been used in limited quantities in some operations in these plants. The authors re-analysed the data to assess the potential confounding by asbestos (Checkoway et al, 1996). The re-analysis was limited to 2266 workers from the larger of the two plants who had been employed after 1930 and for whom quantitative estimates of asbestos exposure could be determined. Workers first employed before 1930 were excluded due to the lack of information available relating to their asbestos exposure. A job-exposure matrix for asbestos exposure was constructed from historical production records, hygiene measurement surveys and expert judgement, for each job type. The authors indicated that the assessment of asbestos exposure was reported to have been conducted independently of previous assessments of RCS exposure and without knowledge of mortality outcome for individual workers, implying that the expert judgement used in determining exposures was not biased by such knowledge.

There were 52 deaths from lung cancer in the whole sub-cohort (SMR 1.41 (95% CI 1.05-1.85)), and 31 deaths in those with no asbestos exposure (SMR 1.34 (95% CI 0.91-1.91)). The cohort was stratified according to cumulative RCS exposure and cumulative asbestos exposure, and SMRs were calculated for each combination of RCS and asbestos exposure, relative to the general male population.

In those with no asbestos exposure, there was a trend of increasing SMR with increasing cumulative RCS exposure (SMR (95% CI) of 1.13 (0.63-1.86); 0.87 (0.18-2.53); 2.14 (0.86-4.41) and 2.0 (0.73-4.35) at <50, 50-99, 100-199 and ≥200 units, respectively, and an SMR of 1.34 (0.91-1.91) overall). Within each category of cumulative RCS exposure, the trends of risk with increasing asbestos exposure were not particularly consistent. There were high SMRs in the two highest cumulative RCS exposure categories, but these were based on small numbers of deaths and therefore may have been spuriously high (SMR 6.03 based on 1 death and 8.31 based on 3 deaths, respectively).

The RR for lung cancer increased with increasing cumulative RCS exposure (up to 1.83 in the highest exposure category). The trend was somewhat weaker than that determined in the previous study, possibly because of the exclusion of workers hired before 1930 who had the largest excess of lung cancer in the original cohort. The RRs were only marginally changed when adjusted for asbestos exposure, suggesting that asbestos exposure had no significant confounding effect on the risk of lung cancer by exposure to asbestos. Overall, this analysis suggested that exposure to chrysotile did not have a significant influence on lung cancer mortality in this cohort.

2.2.3 Checkoway et al (1997) followed-up the cohort above for an additional seven years and also made quantitative estimates of cumulative RCS and asbestos exposure. The findings were broadly similar to Checkoway et al (1993).

A subsequent paper reported on mortality during a seven-year extended follow-up period (Checkoway et al, 1997). This study was also able to use additional quantitative air monitoring data which allowed a more detailed analysis of the relationship between lung cancer risk and cumulative RCS exposure. The cohort consisted of 2342 males, comprising all the workers from the previous study who worked at the larger of the two DE plants, and also workers with suspected asbestos exposure hired before 1930 (66 workers) whose asbestos exposure could now be quantified.

Quantitative air monitoring data were available for the period pre-1962 to 1988 (Seixas, 1997). All pre-1962 and around half of post-1962 measurements were in particle counts, which were converted to gravimetric units using side-by-side sampling data for both measurement methods. Dust exposures for years before 1944 were estimated by extrapolating from measurements taken in 1948-1988, taking into account knowledge of the working practices and documented changes in engineering interventions. Some of the exposure measurements were for personal sampling, and some were for area sampling; it was not always possible to know which was which. Some of the sampling was thought to be 'worst-case' sampling, leading to possible overestimation of average exposures. There was no compositional analysis of the dust to determine the percentage presence of crystalline silica (and what percentage was in the form of cristobalite). Mirliss (1998) indicated that calcining was first introduced in 1923, and even in 1929 calcined products only comprised less than half of the total production. This raises some concerns over the reliability of RCS exposure estimates for pre-1940 and suggests that exposure to RCS may have been over-estimated prior to 1930 when calcining was not commonly used. Checkoway responded by acknowledging the weaknesses in the exposure assessment, but indicated that it was not possible to say whether the exposures were under- or over-estimated and that they have produced the best estimates of exposure based on the available data, personal job histories and plant and production records and reasonable hygiene judgement (Checkoway et al, 1998). The average cumulative exposure to respirable dust and RCS was estimated to be 7.31 and 2.16 $mg.m^{-3}$.years, respectively.

Quantitative estimates of asbestos exposure since 1930 were based on historical exposure monitoring data for jobs in which asbestos was handled directly, production records and recorded quantities of asbestos included in various mixes. Asbestos exposures for pre-1930 were extrapolated from job-specific exposures in 1930. Gibbs (1998) suggested that no asbestos was used in the facility in 1930, and therefore workers may have been mis-classified as exposed to asbestos. However, radiographic evidence revealed a similar prevalence of pleural abnormalities consistent with asbestos exposure (plaques and diffuse thickening) among workers hired before or during the 1930s (4.2% and 4.9%, respectively), suggesting that this extrapolation is reasonable. The mean cumulative exposure to asbestos was estimated to be 1.44 fibres/ml.years.

There was no excess of mortality within the cohort (SMR 1.02 for all causes), and lower than expected mortality from ischaemic heart disease, and other diseases suggesting a possible healthy worker effect. There was a slight statistically significant excess of cancer of the lung/trachea/bronchus, relative to national (SMR 1.29; 95%CI 1.01-1.61) or local (SMR 1.44; 95% CI 1.14-1.8) rates. There was a very high SMR for lung cancer in those hired pre-1920 based on a small number of deaths (SMR 20.8 based on three deaths), and a slight but clear trend of decreasing excess mortality with more recent decades. There was a general trend of increasing RR for lung cancer with increasing cumulative exposure to respirable dust and RCS. For cumulative RCS exposure, the trend was similar for lag periods of 0 or 15 years. The relative risks (95% CI) were 1, 0.96 (0.47-1.98), 0.77 (0.35-1.72), 1.26 (0.62-2.57) and 2.15 (1.08-4.28) at <0.5, 0.5-<1.1, 1.1-<2.1, 2.1-<5 and ≥5 $mg.m^{-3}$.years, respectively, and increases were only statistically significant in the highest exposure category. The trend was of borderline statistical significance for each lag period, with relative risks (95% CI) of 1.06 (1.01-1.11) and 1.05 (0.99-1.11) for 0 and 15 years' lag, respectively. These trends were not changed when adjusted for asbestos exposure.

The limited data on smoking suggested that the prevalence of smoking was lowest in the lowest cumulative dust and RCS exposure categories, compared to the higher exposure categories where smoking prevalence was similar (63, 82, 80, 86 and 83%). Using the method of Axelson (1978), and assuming that smokers had 20 times greater risk of lung cancer than non-smokers, the authors estimated that smoking would reduce the observed RRs for lung cancer, although they would still stay elevated (RR 1.59 and 1.67 for cumulative dust and RCS exposure, respectively).

The cohort was stratified according to cumulative RCS and asbestos exposure and RR calculated for each combination. There was no evidence of confounding by asbestos. The highest RR was in workers with ≥5 mg.m-3.years cumulative RCS exposure and no exposure to asbestos (SMR 2.03; 95%CI 0.93-4.45). This excess was based on 13 deaths, of which five were in men hired before 1930. This led Gibbs (1998) to question how much of this risk was due to these early hires. Checkoway re-analysed the data to address this point, excluding the pre-1930 hires. They determined RRs of 1.74 and 2.05 (CI not presented) using national and local rates (Checkoway et al, 1998). Gibbs (1998) also suggested that the arbitrary selection of asbestos exposure categories may have weakened the effects at higher asbestos concentrations and influenced the conclusion regarding confounding by asbestos. In response, the authors re-analysed the relation with asbestos using the same asbestos exposure categories as in Checkoway et al (1996) and confirmed the absence of confounding by asbestos.

There was an excess of deaths from NMRD (SMR 2.01; 95%CI 1.56-2.55; 67 deaths). These included 27 deaths with underlying causes listed as pneumoconiosis. There was a general decrease in mortality from NMRD with more recent decades of hire, with statistically significant excesses limited to those hired before 1950. There was also a strong trend of increasing RR for NMRD with increasing cumulative RCS exposure (1, 1.52, 1.98, 2.34 and 4.79 lagged 0 years and 1, 2.04, 1.96, 3.17 and 5.35 lagged 15 years at <0.5, 0.5-<1.1, 1.1-<2.1, 2.1-<5 and ≥5, $mg.m^{-3}$.years, respectively). There was a similar but slightly less pronounced increasing trend with total cumulative respirable dust.

2.2.4 Rice et al (2001) used data from Checkoway et al (1997) to perform a quantitative risk assessment for lung cancer mortality.

Of various models applied to the data, the linear relative rate Poisson regression model (with external adjustment for US lung cancer mortality in 1992) was reported to provide the best fit for the data and was used to calculate lifetime excess risks of lung cancer (assuming 45 years of exposure between ages 20 and 65 years and accumulating annual risks up to age 85 years) with a 10-year exposure lag period. For white males (who constituted the cohort), the risks were 0.04, 0.19, 0.38, 1.9 and 3.7% at 0.001, 0.005, 0.01, 0.05 and 0.1 $mg.m^{-3}$ RCS, respectively. Calculated for the whole population (white and black men and women) using sex- and race-specific background rates, the corresponding risks were 0.03, 0.15, 0.29, 1.5 and 2.9%. The estimates were reported to be the same or increased with other exposure-response models.

2.2.5 Checkoway et al (1999). This study investigated the relationship between silicosis and lung cancer. The findings tended to suggest that there was an excess of lung cancer related to RCS exposure in those without radiographically apparent silicosis, although no definitive conclusions could be drawn.

Further analysis was conducted in this cohort of DE workers to investigate the relationship between radiographic evidence of pneumoconiosis (silicosis) and lung cancer (Checkoway et al, 1999). Chest radiographs were available for 1809 men from the cohort for whom chest radiographs of adequate quality were available from the company's radiographic surveillance programme, which had been operative since the 1930s. The prevalence of opacities at ILO category ≥1/0 was taken as indicating the presence of pneumoconiosis (referred to as silicosis below). There was a relatively low prevalence of opacities, of around 4.5% (81 cases). Of these, 77 had small opacities (62 with category 1/0-1/2; 8 with 2/1 and 7 with category 2/2+) and 4 had large opacities.

The overall mortality from lung cancer was higher in silicotics, compared to non-silicotics (SMR 1.57; 0.43-4.03 based on 4 deaths and 1.19; 95% CI 0.87-1.57 based on 48 deaths, using national rates), although neither increase was statistically significant. There was a clear difference in the pattern of lung cancer mortality between silicotics and non-silicotics. In silicotics, there were approximately the same number of lung cancer deaths in each category of cumulative RCS exposure, whereas for silicotics, deaths only occurred in the highest exposure category. There was a statistically significant trend of increasing mortality from lung cancer with increasing cumulative exposure in non-silicotics with SMRs (based on national rates) of 1.05, 0.86, 1.25 and 2.4 (95% CI 1.24-4.2) at <0.5, 0.5-1.9, 2-4.9 and ≥5 $mg.m^{-3}$.years, respectively ($p<0.02$). The SMR in silicotics was 2.94 (95% CI 0.8-7.53) at ≥5 $mg.m^{-3}$.years.

Indirect adjustment of these SMRs for smoking was performed using the method of Axelson. The method was used to estimate the SMR in the highest cumulative RCS exposure group relative to the lowest group, adjusted for smoking. Following adjustment for smoking, it was estimated that the SMR in non-silicotics would be reduced from 2.29 to 1.88, and in silicotics reduced from 2.94 to 2.04 (CIs not presented).

There are grounds to consider that silicosis may have been under-ascertained in this study. Most significantly, surveillance did not extend beyond the termination of employment, raising the possibility that silicosis could have developed after the last available negative radiograph, thereby under-estimating the true prevalence of silicosis. In support of this, the mean duration of time from first hire to final radiograph was substantially longer in silicotics than in non-silicotics (21.3 and 11.5 years, respectively). No temporal information on the progression from negative to positive radiographs was presented, but 10 years is a significant length of time during which silicosis could have developed. To address this possibility, the SMRs were calculated for non-silicotics with follow-up truncated at 15 years, a time-point which was chosen to minimise the potential progression of silicosis, but sufficiently long to detect lung cancer mortality. However, it still seems possible that silicosis could have become manifest during this time and be undetected. The SMRs and the trend with cumulative RCS exposure were not significantly altered from those obtained with the full follow-up. These findings tend to suggest an excess of lung cancer related to RCS exposure in those without radiographically apparent silicosis.

The studies by Checkoway have provided a thorough investigation of lung cancer among workers in the DE industry. These studies are relatively strong in terms of the length of follow-up, radiographic surveillance of the cohort, good information on work history and, in the later studies, reasonably reliable estimates of exposure (although no compositional analyses of workplace dusts were undertaken to determine actual percentages of crystalline silica present). The studies demonstrated a clear excess of lung cancer among these workers. In the cohort as a whole, the excess of lung cancer was only significantly increased in those hired before 1930 with long latency. A weakness was limited information on smoking, although the information presented suggests that confounding by smoking could not completely explain the excess of lung cancer. There was an slight exposure-response relationship observed for lung cancer with a semi-quantitative measure of cumulative exposure, lagged 0 or 15 years. The trend was of borderline statistical significance and the RR was only statistically significant at the highest cumulative exposure (>5 mg.m-3.years). There appeared to be an excess of lung cancer in workers in the absence of evidence for radiographic silicosis. This provides some limited evidence that the increased risk of lung cancer in RCS-exposed workers is not limited to those with radiological silicosis, although the lack of statistical precision renders the findings non-conclusive.

2.3 Studies in industrial sand workers

Two important studies in the industrial sand industry have recently been published. Industrial silica sand is obtained from a variety of sources, from a loose, unconsolidated granular state, to hard, highly compacted rocks. The ore form of quartz determines how it will be mined. Hard-rock mining involves explosives to break the rocks into manageable sizes, and uncompacted sand is collected by dredging or with hydraulic pumps. The processing can involve crushing and grinding operations to reduce the particle size. This can be a wet or dry process. The industrial sand industry is regarded as having little potential for confounding exposures (Steenland and Sanderson, 2001).

2.3.1 McDonald et al (2001) and Hughes et al (2001) conducted a cohort mortality and nested case-control study in US industrial sand workers. Studies in this industry are particularly useful because there is little potential for exposure to known lung carcinogens such as radon. There was an excess of mortality from lung cancer and silicosis in this cohort, and the risk of each cause of death increased with increasing cumulative and average RCS exposure. There was a high prevalence of smoking among lung cancer cases, but this was judged unlikely to completely account for the observed excess of lung cancer. Overall, the study provided reasonably strong evidence of a causal link between quartz exposure and lung cancer.

McDonald and co-workers investigated mortality from lung cancer, silicosis and other causes in the North American industrial sand industry. There are three publications relating to these investigations: a cohort mortality study (McDonald et al, 2001) in which all causes of mortality were investigated in relation to national or local rates; a nested case-control analysis (Hughes et al, 2001) focusing on mortality from lung cancer and silicosis; and an occupational hygiene assessment (Rando et al, 2001).

A notable feature of this industry is that workers are exposed to relatively pure quartz, said to be usually above 98% purity, with no real problems of confounding by exposure to known carcinogenic chemicals. Raw sand was said to be extracted either by drilling and blasting hard sandstone, hydraulic mining of friable sandstone using a water cannon, or dredging from ponds. The first steps in processing involve wet processes to remove clays and other contaminants, followed by drying stages. Dried sand is size-separated and bagged. Some companies ball-mill the sand into a silica flour.

The study population for the cohort mortality study consisted of men who were employed at eight sand-producing plants, (seven in the US and one in Canada) or in an associated office complex where most of the employees had worked previously in the production plants. The final cohort consisted of 2670 men; eligibility required at least three years' service in the industry between 1909 and 1990, of which at least one month was served in or later than 1940. Most of these workers were unskilled and transient (although they must have worked for at least three years). Subjects contributed person-years, either three years after hire or from 1940, whichever was later. One particular weakness was that company records from these plants were reported to be often incomplete and lacking adequate information on occupational history and smoking habits. The lack of this type of information is particularly important for unskilled and transient workers who may smoke more than average and may have been exposed to confounding factors in previous or subsequent employment. On average, men were hired in 1957 at the age of 30 years, and worked for around 19 years. The average length of follow-up in 1994 was 30 years. The mortality experience in the cohort was compared to that of the general US and local male populations.

At the end of follow-up (December 1994), vital status was ascertained for 99% of the cohort. Results showed that around 40% (1039) of the cohort had died, and death certificates were available for 1025 of these deaths. Of these, there were 96 coded as lung cancer, 30 as silicosis and 7 as silico-tuberculosis. There were also 3 certificates listing mesothelioma as the cause of death, suggesting exposure to asbestos. SMRs were calculated for the cohort stratified on latency (years since first employment) of more or less than 20 years.

There was a statistically significant excess of mortality from all causes (SMR 1.18; 811 deaths), tuberculosis (SMR 3.93; 8 deaths) and NMRD (SMR 1.78; 97 deaths) in those with over 20 years' latency. In those with less than 20 years' latency, the only significant cause of death was tuberculosis (SMR 2.82; 9 deaths). Around 26% of deaths listed as NMRD were due to silicosis, although in the absence of autopsy verification, there is some uncertainty surrounding these numbers. The authors drew attention to the raised mortality from renal disease in this cohort, with 16 deaths from nephritis/nephrosis versus 7.56 expected (SMR 2.12). The excess was present only in workers employed for 10 years or more. However, there was no increase in the expected number of renal cancer deaths. There was a statistically significant excess of all cancers (SMR 1.19; 192 deaths) and cancer of the trachea/bronchus/lung (SMR 1.50; 83 deaths) in those with over 20 years' latency, and no excess in those with less than 20 years' latency. No positive associations were found between lung cancer risk and duration of employment. The SMRs were reduced, but were still statistically significantly raised when calculated using local mortality rates (SMR 1.09 and 1.39 for all causes and lung cancer, respectively).

When lung cancer, silicosis and nephritis/nephrosis deaths were analysed in terms of plant location, one of the difficulties was the small numbers of cases in each plant. The largest region (West Virginia/Pennsylvania) showed only a slight excess of lung cancer (SMR 1.14), but had a relatively high risk rate of 0.46 (number of cases per thousand person-years) for silicosis. Most of the lung cancer excess came from four plants in New Jersey and Illinois (SMRs of 1.83 and 2.23, respectively), but these regions had the lowest risk rates for silicosis (0.21 and 0.27, respectively). The authors could not explain this apparent discrepancy. The difference in lung cancer rate cannot be explained in terms of relative levels of dust exposure in each plant as the risk of silicosis and NMRD was substantially higher in those plants with lowest lung cancer mortality. In the plants with the excess lung cancer rates, no positive associations were found between lung cancer risk and durations of employment.

There was a moderate excess of lung cancer in this cohort. However, there are a number of limitations which prevent this excess being attributed to quartz exposure. Most importantly there was no information on smoking habit. The workers in the cohort were mostly unskilled and transient workers whose social and smoking habits may not be typical of the reference population potentially producing a spurious excess in calculated SMRs. The study did not include any information on cumulative dust exposure, but there was no relationship between lung cancer risk and duration of exposure as would be expected if quartz were the cause of the lung cancer. Also, the excess risk of lung cancer was limited to a small number of plants with relatively low levels of silicosis and NMRD, whereas there was no excess of lung cancer in plants with much higher levels of these diseases.

The nested case-control study was conducted to address some of the problems in the cohort study, by obtaining more detailed information on each subject on smoking habit and quantitative cumulative exposure to quartz. The primary aim of the study was to investigate whether lung cancer risk was related to quantitative measures of exposure to quartz. A secondary aim was to do the same for silicosis, primarily as a means of validating the estimated levels of exposure.

The final analyses were based on 91 cases of lung cancer and 32 cases of silicosis. A small number of cases for whom at least one appropriately matched control could not be found was excluded. One death caused by mesothelioma but coded as lung cancer was excluded from the cases and, as described above, this may indicate that some workers in this industry may have had occupational exposure to asbestos. Cases were matched to one or two controls on plant, age and time of hire and a later death. Six of the controls thus selected subsequently died from either lung cancer or silicosis, and were retained as controls, but were also classed as cases and subsequently allocated their own matched controls. There may be some uncertainty as to the appropriateness of using a few subjects as both cases and controls in this manner, particularly when as controls they may well have already been developing the disease for which they became a case, given the long latency of these diseases. However, it is HSE's opinion that using cases for controls in this way would, if anything, tend to underestimate risk.

Job histories were obtained from company records for most (97%) of the subjects. The quality and thoroughness of the company records was not described, but they did apparently contain enough information to determine subjects who may have had jobs with potential exposure to asbestos. Limited information on smoking was obtained from medical records and from inquiry from family and friends, in terms of never- or ever-smoker, for 91% of the subjects. The proportion of ever-smokers was statistically significantly higher in cases of silicosis (85 against 70% in controls) and lung cancer (91 against 69% in controls).

A job-exposure matrix was constructed using quantitative exposure monitoring data (Rando et al, 2001). There were essentially two sets of measurement data, from post-1970 and the period 1947-1954. The more recent data consisted of around 14 000 mostly personal samples obtained using a cyclone and measured in gravimetric units. Quartz content was determined using X-ray diffraction; the percentage content was not presented in this report, but from McDonald (2001) would seem to be high at around 98%. The earlier samples (around 500) were made using impingers and were measured in terms of particle counts. Rando et al converted these to gravimetric units using a conversion factor (1 million particles per cubic foot = 276 $mg.m^{-3}$ calculated using data from the sand industry). The authors indicate that the proportion of quartz in the dust may have been over-estimated for the earlier period. This error would affect comparison of exposures from early and later periods, but it should affect cases and controls equally and so should not introduce any systematic bias into the findings.

Dust measurements were available for all plants since 1970, and for at least three of the plants in the earlier period. The details of how each sample was collected were not specified, and so it was unclear if the dust levels represented average exposures over a typical whole shift. The exposure matrix reflected estimated exposure levels for relevant jobs by time period and included adjustment for the use of respiratory protection. The exposure matrix and job history allowed cumulative exposure and average exposure (cumulative exposure divided by duration of exposure up to the death of the case) to be calculated for each subject in the nested case-control analysis.

The dust data demonstrated a significant decline in exposure to respirable quartz over the period of the study, falling from 400-500 $\mu g.m^{-3}$ in 1930-40, to less than 50 $\mu g.m^{-3}$ in the late 1980s.

Matched analyses were conducted by conditional multiple logistic regression, including exposure as a continuous or stratified variable and smoking status (ever- or never smoker or unknown smoking history). The mean year of hire was around 10 years earlier for cases of silicosis than of lung cancer (1940 and 1950, respectively) and silicosis deaths occurred at a slightly younger age (62 and 66 years, respectively). The mean age at hire was the same to within a year for cases and controls, and the years employed was similar at around 22 years.

For both lung cancer and silicosis cases, the median value of cumulative exposure for cases was higher than for controls. For average exposure, the median value was higher for lung cancer cases than their controls, but there was no difference for the silicosis cases and controls. The median concentration of exposure was approximately 200 $\mu g.m^{-3}$ for silicosis cases and controls. This was higher than for lung cancer cases and controls combined (113 $\mu g.m^{-3}$), possibly reflecting their overall earlier hire dates when exposures were likely to have been higher than in more recent times. Silicosis cases had higher cumulative exposures than their matched controls (5198 against 3227 $\mu g.m^{-3}$.years, respectively). For lung cancer, cases had slightly higher cumulative quartz exposures than controls (2732 and 2487 $\mu g.m^{-3}$.years, respectively).

For the analysis of mortality from silicosis and lung cancer, cumulative exposure to quartz was stratified into quartiles, with categories chosen to include approximately equal number of deaths. The exposures were lagged by 0 or 15 years to assess latency. ORs were calculated for each exposure category relative to the lowest category and were adjusted for the effects of smoking.

For silicosis, the ORs generally increased with cumulative exposure, and the increase was particularly prominent and statistically significant when exposure was lagged 15 years (OR 1, 2.54, 4.55 and 5.16 at 700, 700-1800, 1800-5100 and >5100 $\mu g.m^{-3}$.years, respectively; CIs not presented). When two categories of average exposure concentration ($\leq$100 $\mu g.m^{-3}$ and $\geq$100 $\mu g.m^{-3}$) were compared, the OR for silicosis was marginally statistically significantly higher in those exposed to more than 100 $\mu g.m^{-3}$ average quartz level compared to those exposed to less than 100 $\mu g.m^{-3}$ (either lagged 15 years or unlagged). There was no clear relationship between silicosis and years of employment when years of employment was considered as a discontinuous variable (ie categorised). However, ORs did increase with years employed lagged 15 years when years of employment was considered as a continuous variable. These findings suggest that the risk of silicosis was related to cumulative exposure to quartz with a less strong relationship to years of exposure, providing some support for the view that the exposure estimates were reasonably reliable.

Similarly, for lung cancer there was a statistically significant trend (p=0.04) of increased OR with cumulative exposure (1, 0.84, 2.02 and 2.08 at <300, 300-1100, 1100-3300 and >3300 $\mu g.m^{-3}$.years, respectively, lagged 15 years). A slightly more pronounced trend was observed with no lag with an OR of 2.58 in the highest exposure quartile. There were similar trends in ORs with increasing average exposure, but there was no trend with years of employment. The study did not include any information on radiographic screening for silicosis, and so it could not provide any information to inform on the relationship between silicosis and lung cancer.

There were nineteen workers identified who had been employed in jobs with potential asbestos exposure. However, there was no significant difference in the proportion of cases or controls employed in such jobs (around 6% of cases and controls) or time in these jobs (6 and 10 years for cases and controls), and so the authors considered it was unlikely that asbestos exposure was a confounding factor in the findings for lung cancer.

The nested case-control study did not present any analyses in relation to plant location, hence the reasons why the excess of lung cancer was confined to only four of the nine plants, as noted in the cohort mortality study, were not investigated.

The studies by McDonald et al (2001) and Hughes et al (2001) provide important new epidemiological information in an industry where confounding exposures to known carcinogens is unlikely. The cohort study revealed an excess of lung cancer but because of a lack of detailed information on smoking and quartz exposures, as well as some inconsistencies in the findings in different plants, the excess could not be clearly attributed to exposure to quartz. The nested case-control study investigated dose-response relationships for mortality from lung cancer and silicosis in relation to cumulative and average exposures to quartz adjusted for cigarette smoking. The investigations into silicosis mortality were primarily to validate the exposure estimates. The results showed a trend of increasing risk of silicosis mortality with increasing cumulative exposures to quartz, but there was a lack of a clear trend with either average exposure or duration of exposure. Thus the silicosis mortality analysis provided some broad support for the validity of the exposure assessment, but a number of caveats surround this conclusion. Silicosis as a cause of death on the death certificate is likely to grossly underestimate the true burden of silicosis in this cohort, and it is clear from the analysis that most of the silicosis deaths derived from the earlier years of hire, a period for which the exposure assessment was least reliable. The observation that SMRs for silicosis were highest in those plants with the lowest SMRs for lung cancer is also difficult to interpret. The results for lung cancer showed a clear trend of increasing risk with cumulative and average RCS exposure, but showed no trend with duration of employment. Whether or not there may have been unknown confounding due to exposures in other jobs outside the industrial sand industry is uncertain. Overall, these results are consistent with the possibility of a causal association between exposure to quartz and lung cancer, but no conclusions on the relationship between silicosis and lung cancer can be drawn.

2.3.2 Steenland and Sanderson (2001) conducted a cohort and nested case-control study of lung cancer in US industrial sand workers. There was a significant excess of lung cancer in the cohort and a trend of increasing risk with increasing cumulative exposure. The prevalence of smoking was higher among the cases, but this was judged unlikely to completely account for the observed excess risk of lung cancer.

Steenland and Sanderson (2001) conducted a cohort mortality and nested case-control study of lung cancer among 4626 workers in the US industrial sand industry. The study covered 18 plants (in 11 different states), which were part of a trade association and had adequate personnel records.

The mortality of these workers was calculated as SMRs, using the general US population as reference, or as standardised rate ratios (SRRs), using the lowest quartile group of the cohort as the referents. The SRR is probably a more reliable measure of lung cancer risk, as the risks are relative to an internal referent group, thereby minimising the potential influence of socioeconomic factors etc. Further analysis was conducted using a nested case-control design analysed by conditional logistic analysis to assess the response in terms of average (cumulative exposure/duration of exposure) and peak exposures. In this analysis, each cancer case was matched with 100 controls on age, sex, race, and at least as long survival. The average year of first employment was 1967, with an average length of employment of 8.8 years (20 and 31% employed for less than 6 months and more than 10 years, respectively). There was also an analysis of possible exposure-response trends in a sub-cohort of 4027 workers with the most detailed work histories.

Quantitative estimates of exposure to RCS were determined for each worker using a job-exposure matrix. The matrix was constructed using 4269 personal samples of respirable silica exposure from cyclones, taken from a wide range of jobs in all of the 18 plants, during the period 1974 to 1996 (Sanderson et al, 2000). In addition to these measurements, midget impinger measurements of particles <5 µm were available from a study in 1946. These measurements were converted into gravimetric units, using the percentage of silica found in the more recent samples and a conversion factor, 0.1, that has been used in other studies. RCS between 1946 and 1974 were estimated using linear extrapolation of these measurement data. There was a significant reduction in RCS exposure over the period of the study, from the 1940s to the 1980s (78 to 11.6 $\mu g.m^{-3}$, respectively), and a wide range of mean respirable RCS exposures in different job categories (3.5-60.2 $\mu g.m^{-3}$).

There was increased mortality from all causes combined (SMR 1.23; 1.16-1.31; 24% of cohort), all cancers (SMR 1.28; 1.12-1.44) and other diseases. In particular, there was a large excess of deaths from silicosis (SMR 66.3) or unspecified pneumoconiosis (SMR 7.77), and cancers of the lung/trachea/bronchus (SMR 1.6; 95% CI 1.31-1.93).

There was a clear trend of increased deaths from silicosis with increasing cumulative exposure (SMR 8.3, 10.1, 19.6 and 36.7 and SRR of 1, 1.22, 2.91 and 7.39 at >0-0.1, >0.1-0.51, >0.51-1.28 and >1.28 $mg.m^{-3}$.years, respectively). There was no clear trend in the SMR for lung cancer deaths (unlagged or lagged by 15 years), although there did appear to be increased mortality in the highest quartile (SMR 1.63, 1.28, 1.61 and 2.38 and SRR 1, 0.78, 1.51 and 1.57 at >0-0.1, >0.1-0.51, >0.51-1.28 and >1.28 $mg.m^{-3}$. years, respectively, lagged 15 years; CI not presented). The trend in SRR was of borderline statistical significance (p=0.07).

Lung cancer mortality did not show any consistent trend with duration of employment. However, there was an elevated risk in those with less than six months' exposure, and therefore those with low cumulative exposure (SMR 2.38; 95%CI 1.17-4.22; 11 deaths). The authors indicate that short-term workers can have relatively high mortality, often for reasons unrelated to exposure. When the data were re-analysed to exclude those with less than six months' exposure (leaving 3361 subjects), the SMRs for the whole cohort and those in the lowest quartile of exposure were reduced but still statistically significant (SMR 1.49 reduced from 1.6 for the whole cohort, and SMR 1.4 reduced from 1.63 for the lowest quartile, lagged 15 years). This suggests that the observed excess risk was not due to the influence of short-term workers.

The nested case-control analysis revealed statistically significant trends of increasing ORs for lung cancer with both cumulative (lagged 15 years) and average (cumulative exposure/exposure duration) exposure, in those with more than six months' employment. The ORs (95% CI) in relation to cumulative exposure were 1, 1.35, 1.63 and 2 at 0-0.18, >0.18-0.59, >0.59-1.23 and >1.23 $mg.m^{-3}$.years, respectively, based on 16 lung cancer deaths. The ORs (95% CI) for average exposure were 1, 0.92, 1.44 and 2.26 (based on 28 deaths) at 0-0.18, >0.18-0.59, >0.59-1.23 and >1.23 $mg.m^{-3}$.years, respectively. Duration of exposure was not associated with lung cancer risk. There was no evidence of an association between silicosis and lung cancer, as only 2/109 death certificates of lung cancer cases mentioned silicosis as being present.

There was very little information on smoking available, limited to 404 men from four of the largest plants, collected during 1978-1989. However, the limited information available suggested that the cohort smoked more than the general population, particularly in those aged 25-44, ie 24-27% of the cohort in this age group were non-smokers compared to 42% in the general population, and 45-50% were current smokers compared to 36% in the general population.

If this smoking pattern was typical of the whole cohort, then lung cancer rate ratios of up to 1.18, relative to the national rate, would be expected. This suggests that the magnitude of the observed lung cancer risk in the cohort cannot be solely due to smoking. Also, there was no significant difference in smoking pattern between each cumulative exposure category, and so smoking is unlikely to have influenced the internal exposure response trends.

Overall, this was a well reported study which provides valuable information on lung cancer mortality among workers exposed to silica sand. The population is unlikely to have been exposed to other confounding agents. The results showed a significant excess of lung cancer in RCS-exposed workers with an SMR of 1.60 relative to the national population, and a trend of increasing mortality with increasing cumulative exposure. The cohort smoked more than average, but smoking was estimated to only account for up to around 20% of the observed excess. It is therefore unlikely that smoking can entirely explain the overall excess of lung cancer in this cohort.

2.4 Studies in metal-ore miners

2.4.1 Studies in gold miners

A relatively large number of epidemiological studies investigating the health effects of RCS have been conducted among cohorts of gold miners, particularly those in South African, US and Australian gold mines. In general, gold miners are exposed to RCS liberated from rock as a result of the mining process. In addition to typical confounders, such as smoking, which affect most occupational groups, miners may also be exposed to other agents which can cause lung cancer – mainly radon, asbestos and diesel fumes. The concentration of radon daughters is generally considered to be low, although in some instances it has been suggested that miners with more than 20 years of gold mining may theoretically accumulate a level of exposure associated with an increased risk of lung cancer (Hnizdo and Sluis-Cremer, 1991). Most reviews have considered the studies of gold miners as providing valuable information on issues surrounding RCS carcinogenicity.

2.4.1.1 Studies in US gold miners

2.4.1.1.1 Steenland and Brown (1995) conducted a cohort and nested-case control mortality study in US gold miners. There was excess mortality from NMRD and pneumoconiosis which was related to cumulative dust exposure and was particularly prevalent pre-1950, when dust levels were highest. There was an increased SMR for lung cancer, but this was only statistically significant when based on local mortality rates. Overall, there was no convincing evidence of a causal role of RCS exposure.

Steenland and Brown (1995) conducted a cohort and nested case-control mortality study in South Dakota gold miners. The cohort consisted of 3328 miners who had worked underground for at least one year between 1940 and 1965 and were followed-up to 1990. The study extended several earlier studies of mortality in this workforce.

A job-exposure matrix was constructed using dust measurements from konimeters (dust particle counts) made each year from 1937 to 1975. Pre-1937 exposures were said to be estimated, presumably using expert judgement. The proportion of silica in respirable and settled dust (13 and 39%, respectively) was determined in a hygiene survey in the mid-1970s. A conversion factor derived in the Vermont granite industry was used to convert the dust counts into gravimetric silica concentrations, and the median average exposure was estimated to be approximately 0.05 $mg.m^{-3}$, although there was a considerable decrease over time (0.15 to 0.02 $mg.m^{-3}$ from 1930 to after 1950).

Cumulative exposures were estimated in terms of 'dust-days' (equivalent to 1 mppcf-day of dust exposure). These were estimated from job-specific daily dust exposure weighted by a factor to represent the time spent underground and adjusted for calendar period to take into account changes in exposure level over time. No job data were collected after 1975 because the mining operation scaled down considerably after this time, retaining only 15% of the cohort in employment in jobs with low exposure. Therefore, there would have been little underestimation of cumulative exposure by ignoring exposures after this date. There was no information on the subsequent employment of the workers leaving the mining operation to inform on possible confounding exposures in subsequent work.

The miners were exposed to non-asbestiform amphibole minerals or cleavage fragments of amosite and tremolite-actinolite. These particulates are generally shorter than asbestos fibres. The level of exposure to fibres in the mid-1970s was below 0.44 fibres/ml (for fibres >5 µm in length), but may have been higher in the earlier years. There was also possible exposure to arsenic and radon daughters, although levels in the mid-1970s were below the occupational exposure limits in place at the time. The authors considered that cumulative exposure to radon daughters was below any levels required to cause lung cancer.

Smoking data (mostly never/occasional-, current- or former-smokers, with some information on amount smoked) were available for 602 men from the cohort who took part in a voluntary silicosis survey in 1960. The voluntary nature of this survey casts some doubt on whether it investigated a representative sample of the workers. The influence of smoking was assessed using the method of Axelson (1978). The cause of death was determined from death certificates.

Vital status was ascertained for 98% of the cohort. The average length of follow-up and employment underground was 37 and 9 years, respectively. The average year of first exposure was 1945, and around half of the cohort were first employed before 1950, suggesting that most of the cohort were exposed to the higher dust and RCS levels present in these earlier years.

There was a small and significant excess of deaths from all causes (SMR 1.13 (95%CI 1.07-1.19)). The most pronounced cause of mortality was NMRD (SMR 1.86 (1.58-2.16; 170 deaths)), pneumoconiosis and other respiratory diseases (PORD) (SMR 2.61 (95% CI 2.11-3.2; 92 deaths)) and tuberculosis (3.52 (95% CI 2.47-4.87; 36 deaths)). Silicosis was very prevalent in this population. Around 9% of the other death certificates made some mention of silicosis either as an underlying or contributory cause of death, and the authors speculated that the excess of asthma (SMR 2.61 (95% CI 1.09-5.61; 7 deaths)) may also have been the result of misdiagnosed silicosis. There were no cases of mesothelioma, providing limited reassurance that there was no exposure to asbestos. There was an excess of alcoholism in those hired after 1950 (SMR 2.56 (1.28-4.58; 11 deaths)), which might indicate that this workforce generally had lifestyle factors which may have contributed to the overall excess mortality.

There was evidence of a slight excess of lung cancer, although this was influenced by the choice of referent population. When using national rates, the excess was not statistically significant (SMR 1.13 (95% CI 0.94-1.36; 115 deaths)). However, when compared to local county or South Dakota rates, the SMRs achieved statistical significance (SMR 1.25 (95% CI 1.03-1.51) and 1.59 (95% CI 1.31-1.92), respectively). Which of these reference populations is most appropriate is not clear. The authors note that South Dakota has a notably lower rate of lung cancer than the rest of the US, but consists of varied demographic groups (larger cities and less well populated areas). The county rates may be more appropriate, as they are local to the area of the mine, but they suffered from small numbers and instability.

The SMRs for various diseases were calculated for quartiles of dust-days (<8000, 8000-32 000, 32 000-48 000 and >48 000 dust-days). There were marked trends of increasing SMR with increasing dust-days for tuberculosis, and pneumoconiosis. There was a weak trend for lung cancer, but this was not statistically significant (SMR 1.17 (44), 1.01 (35), 0.97 (8) and 1.31 (28 deaths) in each successive quartile).

The SMRs were also calculated for three periods of year of hire (<1930, 1930-1950 and >1950). There was a pronounced excess of pneumoconiosis and tuberculosis pre-1930 which declined considerably in the later periods (SMR 5.37 (36), 2.12 (48) and 1.36 (8 deaths) in each period for pneumoconiosis). A similar but far less pronounced trend was observed for lung cancer (SMR 1.3 (21), 1.14 (71) and 1.01 (23 deaths) for each period).

Overall, this part of the study demonstrated a small excess of lung cancer. The excess was only statistically significant when compared to local rates, and not when compared to national rates. There was a weak but not statistically significant trend of lung cancer with increasing quartile of cumulative exposure, and some evidence that the risk of lung cancer was highest in those hired pre-1930.

A nested case-control analysis was conducted to allow cumulative exposure to be treated as a continuous variable in a logistic regression model. Each case was matched to five controls. Controls were selected randomly from all those who had achieved the age of the case when the case died. There was no mention of matching on other parameters such as smoking or time of hire etc, although there was no difference in year of first exposure or year of birth between cases and controls. The controls had slightly higher cumulative exposure than cases (28 389 and 31 060 dust-days for cases and controls, respectively). There was a negative and non-significant trend with cumulative or log-cumulative dust exposure (data not presented). Also, duration of exposure was not related to risk of lung cancer.

Based on the limited smoking information, there was some difference in smoking habits between these miners and the general population. The miners generally smoked more than the general population (around 23, 65 and 12% were never/ occasional, current and former smokers, respectively compared to 33, 57 and 11%, respectively, in the general population), but fewer of the smokers were heavy smokers (77 and 18% for miners against 58 and 29% in general population smoking 10-19 or 20 or more cigarettes/day, respectively).

The authors used these data to estimate that smoking alone could account for an excess risk of lung cancer of 1.07 in the cohort relative to the general population. A more informative comparison would have been with the local population against which the excess of lung cancer was statistically significant, but this was not performed. The validity of this estimate is uncertain because smoking habits for the cohort were based on a cross-section of the miners, and the representativeness of these findings for the whole cohort is unknown.

There was no detailed analysis of the association between lung cancer and silicosis. However, information on death certificates indicated that only 3/115 (3%) of lung cancer cases also had silicosis, silico-tuberculosis or pneumoconiosis compared to 140/1551 (9%) for all deaths, suggesting that silicosis was not more prevalent among those with lung cancer.

In conclusion, there was excess mortality from all causes in this cohort, with particularly high mortality from lung diseases (NMRD, pneumoconiosis and tuberculosis), indicative of high dust exposure in earlier years. There was a slight increase in the SMR for lung cancer in the cohort, but the increase was only statistically significant when using local mortality rates and was not significantly increased over the general population. The mortality from lung cancer was not related to cumulative exposure nor duration of employment, which suggests that the lung cancer excess cannot be attributed to dust or RCS exposure. However, it should be borne in mind that the increased mortality from other causes, notably NMRD and PORD, may have reduced the power of the study to detect small excesses of lung cancer. There was evidence to suggest that lung cancer was not more prevalent in silicotics, although the relationships between quartz exposure, silicosis and lung cancer was not specifically investigated.

2.4.1.2 Studies in South African gold miners

There are five studies, with some overlap of the study populations, that have investigated lung cancer in South African gold miners. These studies clearly and consistently reveal an excess of lung cancer mortality, and that cigarette smoking is the main risk factor. The underground gold miners were said to have worked in stressful conditions of heat and humidity, with exposures to diesel exhaust, nitrous fumes from blasting operations, radon and its daughters, dust containing moderate amounts of crystalline silica (thought to be about 30% of respirable dust), and there is also possible exposure to heavy metals including a small percentage of uranium. A key strength of these studies is that reasonably detailed occupational, smoking and medical histories were available for study subjects. However, all of the studies suffer from very limited exposure data, basically deriving from a survey conducted in the late 1960s in which dust exposures were measured as particle counts in different job categories in a number of mines. Specific exposures to respirable RCS were not measured. Two of the five studies pointed to an increasing risk of lung cancer with increasing cumulative dust exposures, but there was a lack of consistency overall in the apparent importance of silicosis as a risk factor. One of the studies revealed a 30% excess of all cause mortality in this mining population, largely from lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, and other causes including fibrotic lung diseases, tuberculosis and cirrhosis of the liver. The deaths from lung cancer appeared to show no association with cumulative exposures to dust. There is the possibility that competing causes of death led to a reduction in the potential for lung cancer development in this mining population. Overall, therefore, taken together these studies do not consistently point to a causal role of either cumulative dust exposure or silicosis in lung cancer development, but neither do they provide reassuring evidence to the contrary.

Two case-control studies by Hessel et al (1986 and 1990) investigated the association between lung cancer and RCS exposure and silicosis in South African gold miners. The method of case selection was similar for each study. The latter study specifically excluded those cases in the earlier study providing an investigation in essentially two separate populations within the same industry.

2.4.1.2.1 Hessel et al (1986) investigated the relationship between silicosis and lung cancer for quartiles of dust exposure. There was no evidence of an association between lung cancer and RCS exposure. There was some limited evidence of an association between silicosis and lung cancer.

In Hessel et al (1986), the study population (cases and controls) was selected from all deaths reported to the Gold Miners' Provident pension fund. Deaths among miners with at least 15 years' service are reported to this fund, regardless of when the miner died. Cause of death was obtained from death certificates and lung cancer verified from autopsy records, which were available for around 86% of subjects. The site and histological type of lung cancer was recorded when available. The presence of silicosis was based on blind readings of the most recent radiographs taken at least three years prior to death (using a four-point scale for profusion), and from autopsy reports (the presence of a single nodule taken as representing slight silicosis).

From these subjects, 133 cases (those dying from primary lung cancer) were each matched to two controls on age and tobacco consumption 10 years prior to death (or 5 or 15 years if unavailable), excluding those with less than 1000 dusty shifts (equivalent to around four years of work) and those with more then one year of service in asbestos mines or as boiler makers (potentially exposed to asbestos). Deaths among controls were from any cause, other than primary lung cancer.

Cumulative RCS exposures were estimated qualitatively from the number of shifts worked in a dusty atmosphere multiplied by various arbitrary weighting factors to reflect relative differences in dust levels and intensity of exposure for each job type. There were no significant differences between cases and controls in terms of cumulative dust exposure (around 36 300 arbitrary units), number of dusty shifts (around 7000) or average intensity, or number of shifts in high dust conditions (around 500) or in smoking history (12, 15.6 and 16.5 in cases against 10.8, 14.5 and 15.9 in controls for average cigarettes/day at 5, 10 and 15 years prior to death, respectively).

From autopsy findings, ORs for lung cancer of 1.49, 0.72 and 0.85 were calculated for silicosis of the parenchyma, pleura and hilar glands, respectively (p values >0.05). Of the lung cancer cases with radiographically diagnosed silicosis, 18 matched controls did not have silicosis and in 6 cases one of the two matched controls did have silicosis. For cases with no silicosis, 72 controls had no silicosis, in 35 cases 1 control had silicosis and in 2 cases both controls had silicosis. The OR for lung cancer and radiological silicosis was not statistically significant at 1.08 (as calculated by Hessel et al, 2000).

Odds ratios were calculated for lung cancer and silicosis by quartiles of dust exposure. For both radiological silicosis and parenchymal silicosis found at autopsy, ORs for lung cancer and silicosis decreased with increasing category of dust exposure (1.56, 1.26 and 0.67 at second, third and fourth quartiles, respectively, for radiological silicosis and 2.43, 1.72, 1.35 and 0.62 at first, second, third and fourth quartiles, respectively, for silicosis at autopsy), but no ORs were statistically significant. Logistic regression did not reveal a statistically significant interaction between parenchymal silicosis at autopsy and dust exposure. A comparison of cases and controls by severity of parenchymal silicosis at autopsy revealed a non-statistically significant but 'suggestive' trend toward increasing severity of silicosis among cases (40, 25, 21 and 14% of cases and 50, 23, 17 and 11% of controls with none, slight, moderate or marked silicosis, respectively; ORs approximately 1, 1.5, 1.7 and 1.8, as calculated by Hessel et al (2000); p for trend = 0.08). No trends were detected in the ORs calculated for various levels of smoking.

This study did not directly investigate the association between exposure to RCS and lung cancer. However, cumulative and average exposure to RCS was roughly the same for cases and controls, which would tend to suggest no direct association between RCS exposure and lung cancer. The exposure assessment was only approximate. It has been suggested that the fund from which this study population was selected is more likely to contain those with over 15 years' service than those with shorter service, possibly leading to over-matching for dust exposure (Hnizdo et al, 1997). Whether over-matching is a real problem or not in this study is difficult to assess from the available information. If the fund was biased towards subjects with longer service, then this would potentially over-match on cumulative exposure. However, the fact that cases and controls had similar average exposures would tend to suggest that such over-matching did not occur. There was no significant association between radiological silicosis or silicosis in the parenchyma, pleura or hilar glands and lung cancer, although it has to be acknowledged that the relatively small number of cases in various sub-groups limits the statistical power of the study to detect small excess risks. There was a weak trend of increasing severity of parenchymal silicosis among cases. This observation provides some limited evidence of an association between silicosis and lung cancer.

2.4.1.2.2 Hessel et al (1990) investigated the relationship between silicosis (diagnosed by autopsy) and lung cancer. There was no evidence of a relationship between lung cancer and silicosis, although the selection criteria may have weakened the ability of the study to detect small risks.

In this study, the lung cancer cases were selected from records of autopsies, which were routinely conducted on the majority of South African miners between 1974 and 1986. It is possible that those with the most severe ill health were under-represented in this study population. The authors indicate that the next of kin of miners who are fully compensated for silicosis in life cannot benefit financially as a result of autopsy findings. Therefore, a lower proportion of miners with the highest degree of compensation in life are subject to autopsy. This may apply particularly to those who are heavy smokers, since miners with pneumoconiosis and COPD tend to receive the highest compensation awards (Hnizdo et al, 1997).

Subjects with no information on smoking, less than 1000 shifts (about four years' service; 48 and 63 cases and controls, respectively), or more than one year's exposure to asbestos mine or as boiler makers were excluded. There were 231 cases who had lung carcinoma found at autopsy. Each was matched with one or two controls on age of death. Matching on age of death, rather than the era in which the subject joined or worked in the industry, is potentially problematic because of the substantial improvements in occupational hygiene and reductions in dust exposure observed in the industry (Hnizdo et al, 1997). Cumulative and average exposures were estimated as previously described (Hessel et al, 1986).

There were no significant differences between cases and controls in terms of age, or measures of RCS exposure, although cases smoked statistically significantly more cigarettes than controls (average of 12.4, 14.7, 17.7, 18.7 cigarettes/day for cases compared to 8.2, 11.3, 13.4 and 13.7 cigarettes/day for controls at 5, 10, 15 and 20 years prior to death, respectively). The figure for average intensity exposure corresponds to a dust level of about 0.2 $mg.m^{-3}$ dust.

There was no excess of silicosis among the lung cancer cases compared to the controls or evidence of an association between lung cancer and the presence of silicosis. The unmatched ORs for lung cancer and silicosis in the parenchyma, pleura and hilar glands were 1.1, 0.8 and 1.29, respectively; none of these values were statistically significant. There was no significant trend of OR for lung cancer with severity of silicosis (ORs approximately 1, 1, 1.4, 1.1 and 0.6 for none, minimal, slight, moderate and pronounced parenchymal silicosis, as calculated by Hessel et al, 2000). The proportion of cases and controls having silicosis in each site was similar (around 54, 22 and 83% for parenchyma, pleura and hilar glands, respectively).

The prevalence of silicosis was compared in cases and matched controls for each anatomical site by quartile of cumulative dust exposure. There was no clear trend in OR for lung cancer with silicosis in the parenchyma (1.84, 0.8, 0.94 and 1.21, respectively) or pleura (0.47, 0.65, 1.5 and 0.58, respectively), although there was an apparent decrease with increasing exposure for hilar glands (1.64, 1.53, 1.02 and 0.67, respectively for successive quartiles). There was no trend between lung cancer, silicosis and number of cigarettes smoked per day 10 years before death.

Overall, this study did not demonstrate any clear association between lung cancer and silicosis. However, there are a number of factors which reduce the power of the study to detect any relationship. In particular, the selection criteria may have resulted in under-representation of those with the most pronounced manifestations of RCS exposure, leading to an underestimate of the true association between lung cancer and silicosis. A reasonably high proportion of lung cancer cases were excluded on the basis of relatively short exposure, and this may also have reduced the power to detect any association (IARC, 1997).

The studies by Hessel et al aimed to investigate the association between RCS exposure, silicosis and lung cancer. One limitation of these studies is that each had a relatively small number of cases. The semi-quantitative estimates of dust exposure were only approximate, and of uncertain reliability. Both studies failed to detect an association between lung cancer and cumulative dust exposure. In terms of the risk of lung cancer in the presence of silicosis, there was some inconsistency in findings. Hessel et al (1986) found a slight, but not statistically significant, trend of increasing risk of lung cancer with increasing severity of parenchymal silicosis, but this finding was not reproduced in the subsequent study. The reasons for this inconsistency are not clear.

2.4.1.2.3 Hnizdo and Sluis-Cremer (1991). The results of this study revealed an increased risk of lung cancer with increasing cumulative exposures to dust in a cohort of South African gold miners. However, no adjustment could be made for exposure to radon daughters, and dust exposure assessment was relatively crude. The results relating to the association between silicosis and lung cancer were inconclusive.

Hnizdo and Sluis-Cremer (1991) conducted a cohort mortality study in 2209 white South African gold miners who started their exposures in 1936-1943 and were followed up to 1986. Subjects had been selected in 1968-1971 for a separate study on respiratory impairment in which one of the selection criteria was at least 10 years of underground exposure in gold mines and minimal (not defined) exposure in other mines. By the start of follow-up, miners had an average of 24 years of employment, with at least 10 years' underground exposure. The vital status of the cohort was established from the records of the Provident gold miners' pension fund, Medical Bureau for Occupational Diseases and from the Department of the Interior. Medical files and death certificates were available for all the miners.

No exposure measurements were made as part of this study. Dust measurements taken during a previous study (Beadle, 1967) were used to construct job-exposure matrices. Briefly, dust exposures were measured in terms of particle counts (particles per cm^3) using either a thermal precipitator method or using a konimeter. Detailed exposure assessments had been made in five mines, and less detailed assessments in a further 15 mines. There were no substantive differences in the results across these mines. The proportion of crystalline silica in the airborne dust was not measured, but was reported to be high, at approximately 30%. Cumulative dust counts and actual years of exposure were calculated for each decade. Overall, the exposure estimates for this study are probably a fairly crude surrogate for exposures to RCS.

Information on smoking habits was obtained by questionnaire as part of the earlier respiratory study and from medical records. Cause of death was established from the available information by an experienced specialist physician reported to be blinded to the purpose of the study and without considering dust or smoking habits. Occupational records indicated that none of these cases had worked in jobs where exposure to asbestos would be expected.

During the follow-up period, 945 (43%) of the cohort died, and post-mortem examinations were conducted on most (84%) of these subjects. Post-mortem examinations allowed the presence and location (lung, pleura and hilar glands) of silicosis to be identified reliably. Of these deaths, a more detailed assessment of the available information and autopsy findings revealed 66 confirmed cases of lung cancer. From occupational records it did not appear that any of the lung cancer cases had had occupational exposure to asbestos.

A statistical method (Cox's proportional hazards model) was used to select the smoking and dust exposure variables most strongly related to the presence of lung cancer, taking into account the individual period of follow-up. Relative risks were calculated using Poisson regression. Smoking was considerably higher among cases, 87 and 9% of which were smokers and ex-smokers respectively, and the corresponding values in non-cases were 69 and 20%. Smoking was strongly related to death from lung cancer. Of the various smoking parameters examined, pack-years was most strongly related; after adjustment for age and year at risk there was an increasing trend of RR (95% CI) of 3.3 (1.3-8.9), 4.6 (1.7-12.4) and 8.91 (3.5-22.7) for ≤10, 11-25, 26-35 and ≥36 pack-years, respectively.

Lung cancer cases had higher cumulative dust exposures than non-cases for various time intervals examined. Thus, cases had a mean cumulative exposure of approximately 38 000 particle.years compared to 33 400 particle.years in non-cases for the most recent period 1940-86. The smoking-adjusted relative risk (RR) for lung cancer associated with a unit of 1000 particle.years of cumulative exposure, cumulated to the start of the follow-up period, was calculated to be 1.023 (95%CI 1.005-1.042). Using this figure, the expected RR in the highest exposure category (with an average exposure of 50 000 particle.years), relative to the lower category (with less than 15 000 particle.years but with more than 10 years of gold mining was 3.18 (95%CI 1.34-7.45). The actual duration of the mining exposure was not a significant risk factor.

The RR for lung cancer showed an increasing trend with increasing cumulative dust exposure. Hence, the RRs (95% CI) were as follows: 1, 1.54 (0.6-4.3), 2.07 (0.7-6.0) and 2.92 (1.02-8.4) for ≤15, 16-30, 31-40 and ≥41 particle.years/1000, respectively. Further analysis investigated the trend of RR with cumulative exposure within various categories of smoking. There was an apparent increase in the RR of lung cancer related to cumulative dust exposure in the low and high smoking groups (0, 0, 0.94 and 1.76 deaths/1000 for ≤10 pack-years and 3.26, 2.91, 7.64 and 9.33 deaths/1000 for >36 pack-years for ≤15, 16-30, 31-40 and ≥41 particle. years/1000, respectively. The steep rise in deaths in the highest smoking category compared to the lowest category led the authors to suggest that dust and smoking may act synergistically to cause lung cancer.

Further analysis was conducted to investigate the relationship between silicosis and lung cancer. ORs (adjusted for smoking, cumulative exposure and age) were calculated for lung cancer and the presence of silicosis. No association was observed between lung cancer and silicosis of the lung parenchyma (OR 0.9; 95% CI 0.5-1.6) or pleura (1.2; 95% CI 0.7-2). However, there was an apparently significant association with silicosis of the hilar glands (OR 3.9; 95% CI 1.2-12.7), although the trend with severity was less clear, with ORs (95% CI) of 1, 2.9 (0.8-10.7), 4.2 (1.3-14) and 3.1 (0.9-11.2) for none, slight, moderate and marked silicosis, respectively.

The results of this study suggest an apparent trend of increasing risk of lung cancer with increasing cumulative dust exposure, although the risk was only statistically significant in the highest cumulative exposure category. Duration of exposure was not a risk factor, suggesting that intensity of dust exposure, which is independent of time, may have been more important than cumulative exposure. When considering how best to interpret these results, it needs to be borne in mind that the exposure estimates were based on relatively limited data and are relatively crude, although are likely to be more well-founded than in some studies. Furthermore, the authors did not make any adjustment for exposure to radon daughters in these mines. Other potential confounders noted in a review by Pilkington et al (1996) were the exposures to heavy metals and diesel exhaust.

The results did not point to a clear relationship between silicosis and risk of lung cancer. Miners with silicosis in the lung parenchyma and pleura did not show an increased risk of lung cancer than those without silicosis at these sites. However, the results did suggest a higher risk of lung cancer in miners with silicosis of the hilar glands. The reason for this was not discussed. An autopsy study in South African gold miners provided evidence that hilar gland fibrosis precedes the development of silicosis in the lung (Murray et al, 1991). Thus, the findings may reflect differences in the relative timescales for development of lung cancer and silicosis in different regions of the lungs. Smoking in itself was a significant risk factor for lung cancer, but there was also some evidence to suggest that it may act synergistically with RCS exposure to increase the risk of lung cancer.

2.4.1.2.4 Hnizdo et al (1997). The results of the following case-control study are consistent with the possibility that high cumulative exposures to silica-containing dust lead to an increased risk of lung cancer. However, other interpretations are possible and a definitive conclusion cannot be drawn from this study in isolation.

Hnizdo et al (1997) conducted a nested case-control study in a cohort of 2260 South African gold miners. The study population was essentially the same as in the previous study. There were 78 cases of lung cancer, each of which was matched on year of birth and survival of the case to five controls from the cohort. An autopsy had been carried out on 67 of the lung cancer cases, at which the histological type of lung cancer was determined.

The presence of silicosis in cohort members was assessed by means of radiological examinations taken regularly during employment, with 'less regular' radiographs taken after retirement. The presence of silicosis was indicated by year of onset of at least ILO grade 1/1 opacities. Radiographs taken within three years of death were rejected to prevent bias due to radiographic changes caused by the lung cancer. In addition, subjects whose last radiograph was taken more than five years before this three-year period (with the exception of those not diagnosed with silicosis at autopsy) were considered lost to follow-up on the basis that silicosis may have developed during this period. Smoking habit was assessed by questionnaire (1968-1972) and recorded during annual medical examinations.

The exposure assessment for this study was only briefly described, but as with the previous study, it appears that the exposure measurements derived from a survey conducted in the South African gold mines in the late 1960s were used. For this study, the previously recorded particle count data had been converted into units of $mg.m^{-3}$, although it is not clear how the conversion was carried out. Occupational histories were available from the Chamber of Mines' records, which revealed the number of shifts worked in a particular mine and the occupation over the entire career for each miner. Occupations were grouped into nine categories, and each group was assigned average dust levels and average time spent underground. Two measures of exposure were determined: cumulative dust exposure (CDE) in $mg.m^{-3}$.years (referring to respirable dust), and the net number of years worked underground. CDE and YEARs were lagged by 0, 5, 10 and 20 years from the death of the case and related to the risk of lung cancer. No measurements of radon daughters were available, so weighting factors relating to the total uranium production of the mine or the uranium grade of the ore were determined.

Cases and controls were matched on age at first diagnosis of silicosis and last exposure, and death or reaching the end of follow-up. Around 10% of cases and controls were lost to radiographic follow-up, but this was not considered to have biased the findings. The cases generally had higher cumulative exposure and years worked underground than controls, which was reflected in the higher prevalence of silicosis among cases; 15 (19%) of cases had silicosis compared to 34 (9%) of the controls.

Cases with silicosis had statistically significantly higher cumulative exposures than their matched controls. Mean CDE values were 12, 10.7 and 7.4 $mg.m^{-3}$.years for cases, and 9.8, 8.7 and 6.2 $mg.m^{-3}$.years for controls, lagged 0, 10 and 20 years, respectively. In contrast, there were no differences in the mean CDEs between cases and controls without silicosis. Cases were heavier smokers than controls, but there was no difference in smoking between silicotic and non-silicotic cases (36.1 and 37.7 pack-years for silicotic and non-silicotic cases, respectively, and 21.8 and 23 pack-years for silicotic and non-silicotic controls, respectively). The finding of no difference in CDE between cases and control non-silicotics, and the fact that silicotic controls had higher cumulative exposures than non-silicotic cases, argues against a causal link between RCS and lung cancer, or at least suggests that cumulative RCS exposure is not a risk factor for lung cancer.

A table was presented showing the relative risks for lung cancer estimated from five different logistic regression models using different sets of risk factors. Smoking was the most significant predictor of lung cancer (RR of around 3, 5 and 12 for 6.5-20, 21-30 and >30 pack-years, respectively). The relative risk of lung cancer increased markedly in silicotics – 4.1, 7.9 and 48.9 for silicotics and 1, 5.1 and 11.7 for non-silicotics with <10, 10-29 and >29 pack-years, respectively. The 95% CI exceeded 1.0 for both groups in the two highest smoking groups.

Variables relating to uranium production did not significantly relate to the risk of lung cancer and were not included in the table. The table showed that of the exposure variables, CDE lagged by 20 years, and years worked underground lagged by 20 years were most strongly associated with risk of lung cancer. The RR (95% CI) for lung cancer related to CDE was 1.83 (0.8-4.1), 1.85 (0.8-4.3) and 3.19 (1.3-7.6) for 2.7-4.3, 4.4-6.3 and >6.3 mg.m-3.years, respectively. The corresponding values for years worked underground were 1.63 (0.6-4.6), 2.07 (0.7-6.3) and 3.36(1.02-10.7) for 10-15, 16-20 and >20 years, respectively. When silicosis diagnosed up to three years before death of a matched case was included in the models together with CDE or years worked underground, neither of these two parameters showed a trend with lung cancer, and only silicosis and smoking remained statistically significant. This suggested that silicosis may be more of a risk factor than exposure to dust. The best predictive model included silicosis (RR 2.45; 95% CI 1.2-5.2).

The most common lung tumour types observed at autopsy were small cell- and squamous cell-carcinoma (around 40% each) and a smaller proportion of adenocarcinoma (16%) and large cell carcinoma (5%).

This study showed that by far the most significant risk factor for lung cancer in these subjects was smoking. The data suggested a strong multiplicative combined effect of smoking and the presence of silicosis on the risk of lung cancer. The authors of the study felt that interpretation of the findings was difficult because CDE, years underground and presence of silicosis were highly correlated. They suggested three possible causal relations: (1) high RCS dust exposure together with silicosis is required to increase the risk of lung cancer, and subjects who are susceptible to silicosis are also at increased risk of developing lung cancer; (2) high RCS dust exposure, mainly in heavy smokers, increases the risk of lung cancer and silicosis is incidental in the process; and (3) the risk is increased in miners who spend the longest hours underground in high levels of dust and the increased risk results from exposure to radon.

This study is limited by the lack of measured data on exposure to radon daughters. Variables relating to uranium production were felt to be too crude as an indicator of radiation exposure. The proportion of small cell lung carcinoma in the lung cancer cases was about 40%, and a review by Pilkington et al (1996) suggests that this is consistent with a causal link to radon exposure. Although the results showed a trend of increasing risk of lung cancer with increasing CDE, the dust exposure estimates for this cohort are also relatively crude. Overall, the results are consistent with the possibility that high cumulative exposures to crystalline RCS lead to an increased risk of lung cancer. However, other interpretations are possible and a firm conclusion cannot be drawn.

2.4.1.2.5 Reid and Sluis-Cremer (1996) conducted a cohort and nested case-control study in South African gold miners. The results showed that although there was an excess mortality from lung cancer in white South African gold miners, this did not show any significant association with estimates of cumulative dust exposure, nor with duration of service in underground mining. However, the study did not provide any specific information on exposure to RCS or on the prevalence of silicosis. The high excess mortality from all causes may have obscured to some extent the true potential for lung cancer development in this population. Overall, no reliable conclusions concerning the carcinogenic potential of RCS can be drawn from this study.

Reid and Sluis-Cremer (1996) conducted a cohort mortality and nested case-control study in 4925 white South African gold miners, at work in 1970, and followed up to 1990. The white male population of South Africa was used as the reference population for the determination of SMRs. The case-control study was designed to investigate whether underground dust exposure contributed to the development of lung cancer, chronic obstructive pulmonary disease (COPD) or ischaemic heart disease (IHD). The authors noted that the miners worked in stressful conditions of heat and humidity, with exposures to low levels of dust containing a moderate amount of silica, and to low concentrations of radon daughters (not quantified). They are also exposed to unknown concentrations of other airborne substances including nitrous fumes from blasting operations and diesel exhaust. The object of the case-control study was to see whether service in the gold mines contributed to these diseases due to the years of underground service or due to cumulative dust exposure.

No information was presented on the prevalence of silicosis within the cohort. Information on smoking was available for all subjects, and the results showed that 86% of the miners smoked, and most admitted to smoking on average a pack a day. There was no information of the prevalence of smoking in the general population. At the end of follow-up, vital status was established for all but 50 members of the cohort. In the absence of a death certificate or other evidence, they were assumed to be still alive. For the nested case-control analysis, cases with lung cancer with 85% of their service in gold mines and at least 15% of shifts underground, were matched on age to one or two controls.

For the case-control analysis only two measures of exposure were determined: total duration of underground service, and cumulative respirable dust exposures. For the latter, job-exposure matrices were constructed using exposure data from an earlier study described above. The matrix contained seven occupational categories, identified on the basis of relative dustiness (ranging from no dust to high dust). Employment records gave details for each subject of the number of shifts worked by calendar period and occupation. Cumulative respirable dust exposures were calculated for up to five years before the death of the case in each case-control set. No attempt was made to determine exposures to RCS specifically. The duration of underground service was said to be a surrogate for a miner's lifetime exposure to radon and its daughters.

At the end of follow-up, 2892/4925 subjects in the cohort were still alive. There was a significant excess of deaths from all causes (SMR 129.6; 95% CI 124-135.4), lung cancer (SMR 139.8; 95% CI 117.8-164.6; 143 deaths), fibrotic lung diseases (pneumoconiosis, silicosis and asbestosis combined; SMR 2133; 95% CI 1219-3465; 16 deaths), COPD (SMR 189; 95% CI 162.1-219; 176 deaths) and other diseases (including tuberculosis, ischaemic heart disease (IHD) and liver cirrhosis), compared to the general white male population. The average cumulative exposure to RCS was reported to be 3.7 $mg.m^{-3}$.years, with 27 years of underground service. The uncertainties surrounding the exposure estimates for this mining population have already been discussed in the Phase 1 HSE review of RCS.

The nested case-control analysis indicated that smoking was the most important risk factor for lung cancer (RR 2.41; 95% CI 1.4-4.2), as well as for COPD (RR 4.3; 95% CI 2.2-8.3) and for IHD. No deaths from COPD occurred in non-smokers, and only four non-smokers developed lung cancer, one of which had known exposure to asbestos. Miners with a history of exposure to asbestos had not been excluded from the study, as such details of work history had been made available too late in the study. Cumulative dust exposure was associated with an excess risk of COPD (smoking-adjusted RR 1.2; 95% CI 1.0-1.4), and weakly, but not statistically significantly, associated with lung cancer (smoking-adjusted RR 1.12; 95% CI 0.97-1.3). There was no association between years of underground mining and lung cancer or COPD.

This study demonstrated a pronounced excess of deaths within the cohort. The authors suggest that much of the excess mortality can be attributed to the relatively heavy drinking and alcohol consumption of the miners, a fact supported by the high mortality from diseases (lung cancer, COPD, cirrhosis, heart disease) associated with these activities. The excess lung cancer mortality in this cohort did not appear to be associated with cumulative dust exposure. However, given the high all-cause mortality, it is possible that an association between cumulative dust exposure and lung cancer may have been obscured by the excess deaths from other causes, particularly COPD. Some of the miners in the cohort were known to have been exposed to asbestos, and mesothelioma was stated on four death certificates as the cause of death (although there is a suggestion that this may be an underestimate of the true number of mesothelioma cases). This suggests the possibility that including subjects in the study with asbestos exposure may have diluted out the possibility of detecting specific effects due to RCS exposure. Furthermore, the dust exposure estimates for the case-control analysis are of uncertain reliability, and may not have been able to adequately identify a possible specific contribution to lung cancer mortality made by cumulative exposures to RCS. However, taken overall, this study provided no reliable evidence of an increased risk of lung cancer from exposure to silica-containing dust.

2.4.1.3 Australian gold miners

2.4.1.3.1 De Klerk and Musk (1998) conducted a cohort and nested case-control study in Australian gold miners. The results indicated an excess of lung cancer mortality in this cohort compared to the Western Australian population (SMR between 1.26 and 1.49), but the excess was restricted to subjects with silicosis. There was no evidence that RCS caused lung cancer in the absence of silicosis. The study provided no measured data relating to RCS exposure.

De Klerk and Musk (1998) conducted a cohort and nested case-control study in a cohort of 2297 Australian gold miners. Subjects were identified from cross-sectional survey investigations into respiratory symptoms, lung function and smoking in 1961, 1974 and 1975 (around 95% response rate), and were followed up to 1993. Detailed employment histories and medical histories, including compulsory annual chest radiographs and information on smoking, were available. The majority of the cohort were current- or ex-smokers (69 and 16%, respectively). Compensation for silicosis, based on a consensus diagnosis by a board of occupational and respiratory physicians, taking into account level of disability, radiographs and other medical information, was used as indicating the presence of silicosis. The authors acknowledged that symptoms due to smoking may have increased the likelihood of a worker making a successful claim for compensation for silicosis.

No quantitative measurements of dust exposures were available, and nor was there any indication regarding the composition of the dust and its percentage of crystalline silica. However, the fact that about 29% of the study subjects were compensated for silicosis suggests substantive exposures to quartz. A semi-quantitative job-exposure matrix was constructed using a subjective ranking scale of 0-10 to indicate the relative level of dust exposure for each job type. Potential exposure to radon was considered to be negligible. Cases of lung cancer were matched to all subjects in the cohort who did not have lung cancer of the same age and were alive at the time of diagnosis of the case. Consequently, subjects could be controls for more than one case, and cases could be controls in years before the diagnosis of their cancer. The median length of underground work was around 16 years; 29% (631 miners were compensated for silicosis from 1040 applications) were compensated for silicosis; most were first employed before 1960.

The risk of silicosis showed a clear positive trend with tobacco consumption, with duration of underground employment, and intensity of exposure. At the end of follow-up, more than half of the cohort had died, including 138 and 48 deaths from lung cancer and pneumoconiosis, respectively.

Two SMRs were calculated for each cause of death, SMR1, calculated with the assumption that all subjects lost to follow-up (11%) were still alive in 1993, and SMR2, calculated after censoring all subjects at the date they were last known to be alive. These two values were regarded as providing the lower and upper estimates of the true SMR, respectively. There was evidence of excess of deaths from all causes (SMR1 (95% CI) was 1.0; (0.95-1.05) and SMR2 (95% CI) was 1.23 (1.17-1.3)); the corresponding values for lung cancer were 1.26 (1.07-1.59) and 1.49 (1.26-1.76); and for pneumoconiosis were 9.5 (7.2-12.7) and 11.2 (8.4-14.8) compared to the sex- and age-specific death rates for the Western Australian population. There was a very strong effect of smoking on the risk of lung cancer, with a relative rate of 32.5 (95% CI 4.4 -241.2) for ≥25 cigarettes/day compared to never smokers. The presence of silicosis was also associated with an increased risk of lung cancer, with a relative rate of 1.59 (95% CI 1.1-2.28), with the strongest effect evident 0-1 years after compensation (data not presented).

The only measure of dust exposure that was significantly associated with an increased risk of lung cancer was log-cumulative exposure. This association was of borderline statistical significance when adjusted for smoking, and became insignificant (though still positive) when adjusted for silicosis.

There was a significant excess of deaths in this cohort, from all causes, lung cancer and pneumoconiosis. The excess of lung cancer appeared to be limited to those compensated for silicosis. This finding may have been confounded by smoking for two main reasons. Firstly, smoking was by far the main risk factor for lung cancer, and this would tend to obscure any excess risk due to RCS. Also, the adverse health effects due to smoking are regarded as increasing the likelihood of a successful claim for compensation, leading to an over-estimate of the prevalence of silicosis within the cohort. This, coupled with the fact that compensated silicotics may generally smoke more, could potentially lead to an over-estimate of the true association between silicosis and lung cancer. There is limited evidence available to address this issue, but the trend of increasing compensation with increasing years in employment, and decrease with decade of first employment, would tend to suggest that the diagnosis of silicosis may be reasonably accurate and not systematically biased. Overall, this study provided evidence of an excess of lung cancer associated with cumulative RCS exposure that was limited to silicotics.

2.4.2 Studies in other metal ore miners

2.4.2.1 Chinese miners

2.4.2.1.1 McLaughlin et al (1992) conducted a nested case-control study in Chinese clay, tungsten, copper-iron and tin mines. There was a trend of increased lung cancer risk with increasing cumulative RCS exposure in tin mines, but the potential confounding by arsenic and PAHs could not be adequately accounted for.

McLaughlin et al (1992) conducted a nested case-control study in 68 000 male Chinese workers employed in the pottery industry (described in section 2.5.2.1) or metal-ore (clay, tungsten, copperiron and tin) mines in 1972-1974 and followed up to 1989 (a cohort study of the same population was conducted by Chen et al, 1992). All the mines and factories in the study had a silicosis registry requiring each worker to have chest radiographs taken every 2-3 years. These radiographs were graded according to the Chinese scoring system, which corresponds closely with the ILO system. Information on smoking, medical history and demographic background was obtained by questionnaire, completed by the subject or next of kin (presumably if the subject had deceased). Cause of death was determined from hospital and employment records; diagnosis of lung cancer was by chest radiograph or needle biopsy in most cases. Each case of lung cancer was matched with up to four controls, randomly selected and matched on age (decade of birth) and factory, and must have survived to at least the same age as the case when diagnosed.

A semi-quantitative job-exposure matrix was constructed using information from dust monitoring data collected between 1950 and 1988 (Dosemeci et al, 1993; Wu et al, 1992). Briefly, around 2.1 million gravimetric measurements of total dust (mostly for mining operations, with around 1000 measurements in the potteries) from area sampling using cascade impactors were available from three sampling stations at each of 29 facilities (10 tungsten, 6 iron/copper and 4 tin mines and 9 pottery factories), starting from the 1950s. Determination of percent silica in the dust was performed irregularly and less frequently, starting in the 1960s. For each facility, job title and calendar year combination from 1950 to 1987, assignment to seven levels of exposure for total dust was made using the available historical exposure data. On average, around half of the total dust estimates for these combinations were based on actual measurement data, with a higher proportion in more recent times (3.1% and 73.9% for 1950-1952 and 1984-1986 periods, respectively). Current exposure information (in 1988), including of total dust levels, particle size and percent silica and exposure to possible confounders, including asbestos, PAH and arsenic, were obtained from three sampling stations at each of the 29 facilities (Wu et al, 1992).

These hygiene data were analysed further to produce a retrospective assessment of exposure to total dust and RCS in each industry (Dosemeci et al, 1995). Information on the silica percentage of respirable dust was limited to recent years and a few job types (around 14% of the total measurements). Mean silica content in total dust was 32.7%, ranging from 10.6% in iron-copper mines to 47.6% in the tungsten mines. There were also industry-specific differences in the respirable portion of total dust with a mean of 48%, ranging from 25.7% for potteries to 65.1% for iron-copper mines. The findings demonstrated reductions over time in concentrations of total dust and RCS in the working environments, with mean total dust concentrations of 17.68 and 3.85 $mg.m^{-3}$, and mean RCS dust concentrations of 3.89 and 0.43 $mg.m^{-3}$, in the 1950s and 1980s, respectively.

In a separate analysis, the authors demonstrated a strong dose-response relationship between RCS exposure and silicosis, providing some reassurance that the measures of exposure to RCS and the diagnoses of silicosis were valid. Cumulative exposures to total dust and RCS were grouped into quartiles defined as none, low, medium and high (0, 0.1-73.3, 73.4-220.5 and $\geq$ 220.6 mg.m^{-3}.years for dust and 0, 0.1-8.69, 8.7-26.2 and $\geq$26.3 mg.m^{-3}.years for RCS, respectively). Exposures to potential confounders, asbestos, nickel, talc and cadmium, were reported to be minimal. Details on smoking were only briefly presented. It was reported that smoking was heavy among cases and controls (93 and 80%, respectively). Findings for pottery workers are presented in section 2.5.2.1.

There were 265 lung cancer cases in miners (96, 89 and 80 in tungsten, tin and iron-copper mines, respectively). Tungsten miners were the most heavily exposed to dust; 40, 29 and 8% of the miners had cumulative exposures $\geq$26.3 mg.m^{-3}. years, respectively. There was an increased risk of lung cancer in smokers (OR 3.9, 1.7 and 7.3 for tungsten, tin and iron-copper miners, respectively, for more than 20 cigarettes/day).

For each group of miners, age and smoking-adjusted ORs for lung cancer were calculated for quartiles of cumulative exposure. All ORs were calculated relative to the lowest quartile. The only significant trend was observed in tin miners (OR 1, 1.4, 3.19 and 2.69 for dust and 1, 1.5, 1.9 and 3.1 for RCS at none, low, medium and high levels, respectively). Confidence intervals were not presented, but it was reported that only in the case of 'high' cumulative RCS exposure did the confidence interval exclude 1. However, in tin mines there was significant confounding by arsenic and PAHs. There was a statistically significant excess risk with arsenic (OR 2.8 at $\geq$28.6 mg.m^{-3} .years) and a non-statistically significantly elevated excess with PAHs (highest OR of 2.7 at 108-250 mg.m^{-3} .years). Exposure to both of these agents was highly correlated to RCS exposure preventing any adjustment for their effect. There were no consistent trends or significant excess risks in the other miners.

In iron-copper mines, there was a non-statistically significant trend of increasing risk with cumulative dust exposure (OR 1, 1.3, 1 and 2.1), but no trend was apparent for RCS exposure (OR 1, 1.3, 1.3 and 0.7 at none, low, medium and high cumulative exposure, respectively). There was a statistically significant trend towards decreasing risks in tungsten miners (OR 1, 1.4, 0.5 and 0.6 for dust and 1, 1.4, 1.1 and 0.5 for RCS at none, low, medium and high cumulative exposure, respectively) which the authors could not explain. There was no clear relationship between lung cancer risk and first year of work or duration of tenure, apart from in tin miners where the increased risk of lung cancer was mostly in those employed before 1956 (no further information presented).

Silicosis (grade not specified) was prevalent in all groups of miners (28, 23-27 and 10% for tin, tungsten and iron-copper miners, respectively). There was a statistically significant excess of silicosis among iron-copper and tin miners with lung cancer (age- and smoking-adjusted OR of 3.1 and 2, respectively), but not in tungsten miners (age- and smoking-adjusted OR 0.8).

This study provides little evidence of an excess risk of lung cancer due to RCS exposure. The strongest association between cumulative RCS exposure and risk of lung cancer was observed in tin miners. However, the potential confounding from co-exposure to the known carcinogens arsenic and PAHs could not be adequately controlled for. There was conflicting evidence for a relation between silicosis and lung cancer. An excess risk of lung cancer was found among silicotic iron-copper and tin miners, but not among tungsten miners who had the heaviest exposures to RCS.

2.4.2.1.2 Cocco et al (2001) further analysed the data from the study by McLaughlin et al (1992) to inform on the association between silicosis and lung cancer and the potential confounding by other agents. The findings were consistent with the possibility of an association between lung cancer and cumulative exposure to RCS, but no reliable conclusions could be drawn.

Cocco et al (2001) used the data generated in the previous nested case-control study in Chinese workers (McLaughlin et al, 1992) to investigate the potential role of other workplace carcinogens (cadmium, arsenic, PAHs, nickel and radon daughters), as well as the presence of silicosis, in the association between RCS exposure and lung cancer.

The study was based on 316 lung cancer cases and 1356 controls drawn from 29 different facilities in China (10 tungsten mines, 6 copper and iron mines, 4 tin mines, 1 clay mine and 8 pottery factories). The lung cancer cases were identified mainly from death certificates and also hospital and work records. Cases and controls were appropriately matched for decade of birth, facility and smoking status.

Odds ratios (ORs) for lung cancer did not show a clear positive trend with increasing quartiles of estimated cumulative exposure to RCS. The highest OR of 1.6 (95% CI 1.1-2.4) occurred in the 3rd highest exposure quartile, but this declined to an OR of 1.2 (95% CI 0.8-1.9) in the 4th and highest quartile of exposure. This did not change substantially when those with silicosis were excluded from the analysis. The lack of a clear exposure-response trend calls into question the accuracy of the exposure estimates, which were based on a number of assumptions and likely to be subject to error. However, a previous analysis (Dosemici et al, 1994) had shown a strong exposure-response relationship between the prevalence of silicosis and estimates of cumulative exposure to RCS, suggesting that even if the exposure estimates were inaccurate, there is unlikely to have been any systematic error in the estimates. Hence, the lack of a clear dose-response trend for lung cancer in relation to cumulative exposure to RCS does not seem entirely attributable to errors in the exposure estimates.

When the OR for lung cancer was determined in relation to the severity of silicosis for different quartiles of cumulative exposure to RCS, the results showed an increase in the OR with increasing severity of silicosis, but the OR was lowest in the highest category of cumulative exposure. When stratification for category of cumulative exposure to RCS was removed, there was no longer any increase in the OR for lung cancer with increasing severity of silicosis. However, the results did suggest that there was a higher risk of lung cancer in those with silicosis. In a combined analysis, the OR for having lung cancer in those with silicosis (regardless of degree of severity) was 1.4 (95% CI 1.1-2).

In relation to the role of other workplace carcinogens, the results of this study were rather inconclusive. This was because of the strong correlation between exposures to RCS and the other workplace carcinogens, which made it difficult to discriminate their effects. The authors concluded that lung cancer risk was only increased in silicotics that also had exposure to cadmium and PAHs.

When considering possible limitations in the interpretation of this study, the authors noted that the average age at death for lung cancer cases was 57.2 $\pm$ 9 years, and they did not consider that the possibility of competing causes of death related to silicosis (ie workers who would otherwise have developed lung cancer died earlier from other silica-related causes) would have affected the results.

Overall, the results of this study suggest the possibility of an association between lung cancer and cumulative exposure to RCS, and that the risks of lung cancer were higher in those with silicosis. However, the exposure-response pattern for lung cancer and cumulative exposure did not show a convincing positive trend. Finally, the data from this study proved to be unsuitable for a definitive assessment of the potential role of other lung carcinogens in contributing to the burden of lung cancer in these silica-exposed workforces. In view of these factors, this study does not allow a reliable conclusion to be drawn regarding the role of RCS as a potential causal factor in lung cancer development.

2.4.2.1.3 Chen and Chen (2002) conducted a nested case-control study in workers from four tin mines that were included in the cohort described in McLaughlin et al (1992) to investigate potential confounding by arsenic. No definitive conclusions could be reached, but it did not appear that the whole cancer excess was due to arsenic exposure.

Chen and Chen (2002) conducted a nested case-control study of lung cancer mortality in miners from the four Chinese tin mines that had formed part of the earlier study by McLaughlin et al (1992). The principal aim was to investigate the potential confounding by arsenic. The mortality experience of the tin miners was followed up to 1994, providing an additional five years of follow-up compared to the earlier study.

These miners (6544 males and 1311 females; 91 subjects lost to follow-up) were drawn from four underground tin mines in China (three in Dachang and one in Limu) with known exposure to arsenic and radon. Each lung cancer case was matched to around five controls on decade of birth and mine. Medical history and smoking information was obtained from mine records and from a questionnaire completed by each subject or a member of their family. The diagnosis of primary lung cancer was confirmed through hospital records, and all chest radiographs of cases were reviewed by a panel of radiologists. Silicosis was diagnosed by chest radiography, using the Chinese pneumoconiosis scale, stage I, II and III, which agrees closely with the ILO categories 1, 2 and 3, respectively. Exposure assessment was as described in McLaughlin et al (1992; see above). The respirable fraction of the total dust was around 20-30%, and RCS was around 3-4.5% of the total dust. Exposure to arsenic was also assessed (Wu et al, 1992). Airborne levels of arsenic were measured from 1988. Before 1988, arsenic exposures were estimated as the product of the arsenic content of dust and total dust concentration at each work site. Cumulative arsenic exposures were estimated by combining this information with work histories.

In the study population, cancer was the leading cause of death (38.2%). Lung cancer was the most common cancer (33.4% of cancers), giving an SMR of 2.39, relative to the general Chinese population. The nested case-control analysis included 130 cases and 627 controls. Most of the subjects were smokers (88.5 and 82.5% of cases and controls, respectively) and there was no significant difference in smoking habit between cases and controls (39 and 35.4 pack-years and 33.9 and 32.8 pack-years for cases and controls, respectively). Smoking more than 20 cigarettes/day was associated with 1.6 (95% CI 1.1-2.4) fold increased risk of lung cancer.

The mean total dust concentration was similar in each mine and had decreased progressively since 1950 due to improved work practices (25, 4-8, 3-6 and 1-4 $mg.m^{-3}$ pre-1950, 1960s, 1970s and after 1980, respectively). The percentage of silica in the dust ranged from 20-40%. There was a significant difference in levels of arsenic in dust measured in each mine in 1988 (6.03 and 0.46% in Dachang and Limu, respectively). High concentrations of respirable arsenic were found in Dachang (up to 38.3 and 1.2 $mg.m^{-3}$ in Dachang and Limu, respectively). There were also higher levels of PAHs in Dachang (372.9 and 7.6 $\mu g.m^{-3}$ in Dachang and Limu, respectively), although it was reported that 'carcinogenic' PAHs were not detected in all mines. Radon exposure was low in all mines and asbestos was not detected. Most of the 112 cases in jobs involving exposure to dust were first exposed before 1960 when dust levels were highest (26, 74 and 11 with first exposure before 1950, 1950-60 and after 1960, respectively).

Cumulative dust exposure was stratified into low (<50), medium (50-119.9) or high ($\geq$120 $mg.m^{-3}$ .years). There was a statistically significant trend of increasing risk of lung cancer with increasing cumulative exposure (smoking-adjusted OR 1, 2.1 (1.1-3.8), 1.7 (0.9-3.1) and 2.8 (95% CI 1.6-5) for none, low, medium and high cumulative exposure, respectively). A similar trend was also found for exposure duration (smoking-adjusted OR (95% CI) 1, 1.9 (1-3.5), 2.3 (1.3-4.1) and 2.3 (1.2-4.2) for 0, 0-9.9, 10-19.9 and $\geq$20 years' exposure).

When analysed separately for each region, these trends were only statistically significant in Dachang (smoking-adjusted OR (95% CI) 1, 2 (1-4), 1.7 (0.8-3.5) and 3 (1.6-5.8) for no, low, medium and high cumulative exposure, respectively) and duration of exposure (smoking-adjusted OR 1, 1.8 (1-3.5), 2.5 (1.3-4.1) and 2.3 (95% CI 1.2-4.2) for 0, 0-9.9, 10-19.9 and $\geq$20 years' exposure, respectively). In Limu, the ORs were similar to those in Dachang, but were not statistically significant (smoking-adjusted OR 2.4 (95% CI 0.6-10.2) with high cumulative exposure and 2.0 (95% CI 0.4-9.4) for $\geq$20 years' exposure). It is not clear if this was a consequence of the lower number of subjects from Limu which might have reduced the power to detect an exposure-related effect.

The prevalence of silicosis was similar in the mines in each region (31 and 35% in Dachang and Limu, respectively), but a statistically significant excess risk of lung cancer in workers with silicosis was only found at Dachang (OR (95% CI) 2.4 (1.6-3.8) and 0.8 (0.3-1.9) at Dachang and Limu, respectively). The ORs for lung cancer were calculated by category of silicosis, after correction for smoking. There was a statistically significant trend with silicosis stage in Dachang (smoking-adjusted OR (95% CI) 2.3 (1.3-3.9), 2.2 (1.1-4.3) and 1.4 (0.4-5) for stage I, II and III, respectively). There were few subjects with severe silicosis, particularly grade III (3 and 1 cases with stage III in Dachang and Limu, respectively), said to be due to workers dying from complications before reaching this stage (no further information presented). Such premature deaths may have weakened the ability of the study to identify a possible relationship between lung cancer and silicosis. There was no significant excess of lung cancer in Limu with any grade of silicosis (OR (95% CI) 0.4 (0.1-1.6), 1.4 (0.5-3.9) and 0.7 (0.1-5.7) with stage I, II and III, respectively).

The ORs for lung cancer were calculated for various combined categories of cumulative exposure to arsenic and dust. There was a trend of increasing lung cancer risk with increasing cumulative arsenic exposure for both regions combined (smoking-adjusted OR (95% CI) 1, 2.0 (1.1-3.7), 2.0 (1-3.7), 1.9 (1-3.7) and 3.5 (1.8-7) at 0, <100, 100-499.9, 500-999.9 and ≥1000 $\mu g.m^{-3}$.years, respectively). Within each category of cumulative dust exposure, there was no clear trend of lung cancer risk with cumulative arsenic exposure; in the medium cumulative dust exposure category, the smoking-adjusted ORs (95% CI) for lung cancer were 1.7 (0.7-4.1), 1.9 (0.9-4), 1.5 (0.6-3.5) at <100, 100-499.9 and 500-999.9 mg $arsenic.m^{-3}$.years respectively, and in the high cumulative dust exposure category the smoking-adjusted ORs (95% CI) were 2.2 (0.9-5), 3.4 (0.9-12.6), 2.3 (1-4.9) and 3.5 (1.8-7) at 0, <100, 100-499.9, 500-999.9 and ≥1000 mg $arsenic.m^{-3}$. years, respectively. The mean concentration and cumulative arsenic exposure in the lowest exposure category was 3.7 $mg.m^{-3}$ and 46.6 $mg.m^{-3}$.years, respectively, which were considered by the authors to be too low to cause cancer. There was a high statistically significant correlation between exposure to RCS and to arsenic (r=0.82), which prevented an adjustment for arsenic in the estimate of risk related to RCS.

These data were also analysed using a number of unconditional logistic regression models to assess the importance of various factors, including smoking and presence of silicosis. These models confirmed that smoking combined with exposure to dust, exposure to arsenic and duration of exposure were associated with the risk of cancer. Silicosis did not contribute to the risk of lung cancer.

Overall, the results for lung cancer mortality in tin miners from mines in two separate regions showed that total dust exposures and silica content of the dust were similar in each region, although miners in Dachang were exposed to substantially higher levels of arsenic than in Limu. There was an increasing risk of lung cancer with increasing dust exposure and duration of exposure, after adjustment for smoking. The ORs were of similar magnitude in each region, although they were not statistically significant in the Limu region, perhaps because of the small number of cases. The high correlation between dust and arsenic exposure precluded any attempt to separate the contribution to the lung cancer risk from these two agents.

The importance of silicosis as a risk factor for lung cancer is unclear. There was a statistically significant excess risk of lung cancer risk in silicotics in Dachang. In contrast, there was no evidence of an excess of lung cancer among silicotics in Limu, despite a similar prevalence of silicosis to Dachang, and regression models did not support a role for silicosis. These findings raise the possibility that the greater arsenic exposure in Dachang was responsible for the lung cancer excess in silicotics, rather than silica in the dust. However, the statistically significant excess of lung cancer even in the lowest arsenic exposure category does tend to suggest that the whole excess of lung cancer cannot be totally explained by arsenic exposure. Overall, no definitive conclusions on the carcinogenicity of RCS can be reached from this study.

2.5 Studies in pottery and refractory workers

A number of studies in the pottery and refractory brick industries are available. Exposures in these industries are mainly to quartz, but where high temperatures are used, such as in ovens or furnaces, there is the potential for exposure to cristobalite. There has been a general belief that cristobalite is more toxic than quartz, and this has extended into a presumption that the carcinogenic potential of these two polymorphs may also differ. An HSE assessment of the evidence surrounding the relative toxicity of these two polymorphs concluded that there was no reliable evidence of a different level of toxicity between the two polymorphs, and there was no clear basis on which to regard them as separate entities. There is no reason to consider them as distinct entities for carcinogenicity. Therefore, studies from these industries which may involve exposure to cristobalite are considered to be relevant to the overall discussion of RCS carcinogenicity.

2.5.1 UK pottery workers

2.5.1.1 Cherry et al (1998) conducted a cohort and nested case-control study in UK pottery workers. The results of this well-reported study revealed an increased risk of lung cancer in UK pottery workers. The risk was clearly related to average exposure concentration, but not to duration of exposure or to cumulative exposure.

The cohort comprised men who had worked in the pottery, refractory and sandstone industries of Stoke-on-Trent, born 1916-1945, who mostly started work before 1970 and were followed up to 1992. The cohort was identified from health surveillance records detailing date of birth, employment history, smoking habit, and the results of periodic chest radiography. Such records had been held since 1931. A cohort of 7064 workers was initially identified, but after exclusions (eg those known to have worked in coal mining, foundries, exposure to asbestos), the final cohort comprised 5115 men.

Vital status up to June 1992 was ascertained for 99% of the cohort, and death certificates were obtained for 96.6% of the deaths. Only workers who died after 1985 (n=470) were included in the study; this was to avoid bias because it was known that some employment records may have been destroyed for some workers who died prior to 1985. Of the 470 deaths thus identified, there were 68 from lung cancer. Standardised mortality ratios (SMRs) were computed based on both national rates for England and Wales, and on local rates for Stoke-on-Trent.

There was an excess of deaths in the cohort from all causes (SMR 1.46 (1.33-1.6), NMRD; SMR 2.87 (2.17-3.72)) and lung cancer (SMR 1.91 (1.48-2.42)) based on national mortality rates. These SMRs were reduced when based on Stoke-on-Trent rates (SMRs (95% CI) of 1.15 (1.05-1.26), 2.04 (1.55-2.65) and 1.28 (0.99-1.62), for all causes, NMRD and lung cancer, respectively). Although the latter SMR for lung cancer was only of borderline significance in terms of confidence intervals, another statistical (chi-squared) test indicated that there were statistically significantly more lung cancer cases than would be expected.

For the nested case-control analysis, lung cancer cases were eliminated if their employment records had been destroyed (n=32), or if their records identified past employment in the sandstone or refractory industry where exposure data were not available, and one case was eliminated because the death occurred within only five years of commencing employment. This led to a selection of 52 lung cancer cases for the case-control analysis, each of which was matched with three or four controls based on date of birth and date of first employment (247 controls). All lung cancer cases had a history of smoking, so controls were considered ineligible if they were known never to have smoked, or if they had predeceased the case.

For each case and control, estimates of cumulative exposure to RCS and average lifetime exposures were computed based on employment records and a detailed job-exposure matrix. The latter had been constructed from extensive dust measurements, taking into account knowledge of the tasks/processes/controls going back from 1992 to 1930. Dust measurements included 1000 personal samples of respirable dust collected using a cyclone. In addition, there were also several hundred dust particle measurements based on area sampling (said to be in the breathing zone). Particle numbers were converted to gravimetric units using a conversion factor (1 mppcf=0.09 $mg.m^{-3}$ respirable dust) derived from dusty trades in the US. There were substantial reductions in exposures to RCS between 1930-1992.

As a means of validating the exposure estimates, the study included a sub-cohort for an exposure-response analysis for pneumoconiosis as described in the HSE Phase 1 Review. The results indicated that the risk of opacities (ILO ≥1/0) was strongly related to estimates of cumulative and average RCS exposure and was roughly twice as high in smokers compared to non-smokers. Overall, the pneumoconiosis sub-cohort study appeared to confirm the likely validity of the exposure estimates.

The nested case-control analysis for lung cancer revealed that cases tended to smoke more than controls, with fewer ex-smokers (around 9 and 26%, respectively) and more heavy smokers (around 27 and 13% smoking >20 cigarettes/day). ORs were calculated using conditional logistic regression analysis for the risk of lung cancer in relation to cumulative and average exposure and duration of exposure. There was no association between cumulative exposure or duration of exposure and lung cancer. However, average exposure was statistically significantly associated with lung cancer; the smoking-adjusted OR (95% CI) was 1.67 (1.13-2.47) with no lag, and similar ORs with lags of 10 and 20 years. Mean exposures were 21% higher in cases than in controls. However, on average, cases had shorter durations of employment than controls; 37% of cases had been employed for <5 years compared with only 27% of controls. The observation that lagging had little effect on the ORs was thought to be due to the long period between last employment in exposed jobs and death. The logistic regression model also entered exposure to heated crystalline silica as a variable, to reflect possible exposure to cristobalite. This did not change the results significantly. This may possibly reflect the close correlation between high exposures and heat-related jobs, but nonetheless provides no evidence to suggest that cristobalite might be more carcinogenic than quartz.

The results also revealed no evidence of a relationship between pulmonary opacities and lung cancer. The prevalences of opacities were similar in cases and controls, at about 6% and 5% respectively.

Overall, this was a clearly reported and well conducted study with particular strengths including reasonably reliable exposure estimates, information on smoking history, and information from chest radiographs. One possible weakness may be that only 13.9% of the cohort had died at the end of follow-up, raising uncertainties about the representativeness of the findings for the future pattern of mortality in this cohort. The results revealed an excess mortality from all causes, in particular from NMRD and lung cancer relative to national and local rates. The nested case-control analysis revealed that lung cancer risk was not associated with cumulative exposure to RCS, or with duration of employment, but was related to average lifetime exposure concentration. The reliability of the exposure estimates seems reasonable based on the evident trends between cumulative exposure and pneumoconiosis. The lack of an evident association between the observed excess of lung cancer with cumulative exposure to RCS is difficult to interpret, and furthermore there was no evidence of a greater risk of lung cancer in those with pulmonary opacities compared to those without. The observation that 37% of lung cancer cases had been exposed for less than five years also raises questions about the possibility of exposure to carcinogenic substances in other jobs, undermining the observed association with exposure to RCS. In conclusion, the results point towards an increased risk of lung cancer caused by high average exposures to RCS, but the lack of an exposure-response for cumulative exposure means that no firm conclusions can be drawn.

2.5.2 Chinese pottery workers

2.5.2.1 McLaughlin et al (1992) conducted a nested case-control study in Chinese pottery workers. There was a trend of increasing risk of lung cancer with increasing cumulative RCS exposure, which was unlikely to be explained by confounding by PAHs. There was no evidence of an increased risk of lung cancer among silicotics compared to non-silicotics.

A case-control study by McLaughlin et al (1992), described above, investigated lung cancer in Chinese pottery workers. There were around 57 lung cancer cases. The risk of lung cancer was significantly increased in smokers (OR 7.4 for >20 cigarettes/day). The age- and smoking-adjusted ORs were presented for quartiles of cumulative dust or RCS exposure. There was no clear trend with cumulative dust exposure (OR 1, 2, 1.7 and 1.5 for none, low, medium or high exposure, respectively), but there was a suggestive trend with RCS (1, 1.8, 1.5 and 2.1 at none, low, medium and high, respectively; CI not presented). The main confounder in pottery workers was exposure to PAHs, although adjustment for this exposure was reported to slightly increase, rather than reduce, ORs for exposure to RCS. There was no significant excess of silicosis in those with lung cancer (age- and smoking-adjusted OR for lung cancer by silicosis of 0.5 and 1.0 for silicotics and non-silicotics, respectively). Silicosis was present in around 13% and 12% of cases and controls.

This study demonstrated a suggestive but not significant trend for lung cancer with increasing cumulative RCS exposure. Workers were co-exposed to PAHs, but adjustment for exposure to this confounder did not change the findings significantly. Despite the high prevalence of silicosis, there was no evidence of an increased risk of lung cancer among silicotics compared to non-silicotics.

2.5.3 Chinese refractory brick workers

2.5.3.1 Dong et al (1995) conducted a retrospective cohort mortality study in Chinese refractory brick workers. The results of this study revealed an excess of lung cancer which was confined to those with silicosis. The risk of lung cancer increased with grade of silicosis.

The cohort consisted of 6266 male workers who had been hired before 1962 in manufacturing 'silica' or clay bricks and were followed up to 1985. All of these workers had received periodic health examinations for silicosis between 1963 and 1985. No details of these examinations were presented, but most subjects must have had at least one chest radiograph. The grading of silicosis was based on a Chinese diagnostic scale (grade 0, I, II or III), which has been shown to correspond well to the ILO scheme. Employment history was obtained from interview and from personnel records, deaths were identified from records of funeral allowances, and cause of death was obtained from death certificates or from medical records. Smoking information was only available as smoker, non-smoker or unknown. The authors calculated standardised rate ratios (SRR) for selected causes of deaths relative to a reference population of around 11 500 male workers from rolling steel mills (excluding those ever exposed to RCS or known lung carcinogens). No information was presented to assess how these steel workers were selected or how reliable the detection of lung cancer was likely to be in this population. There was no information provided in the paper concerning the nature or extent of exposures to RCS in the cohort. It is possible that in the kilns used to manufacture the refractory bricks, some conversion of quartz to cristobalite may have occurred in this industry, but this was not discussed by the authors. The potential for PAH release from the kilns, or whether asbestos may have been used to line the kilns, was not discussed. Furthermore, details such as age of entry into the cohort, age at death etc were not provided.

At the end of 1985, 4.2% were lost to follow-up; the proportion of subjects lost to follow-up was highest in those with first exposures in the period 1960-1962 (22%). Total mortality in the cohort was low at around 14% (871 deaths). Silicosis gradings were available for most (6003) subjects, indicating that there was a reasonably high prevalence of silicosis in the cohort (48, 21.6, 20, 7.4 and 3% with grades 0, 0-I, I, II or III, respectively). It is not known if these prevalences were determined from single radiographic examinations or were the maximum grades obtained in successive radiographs. Therefore, it is possible that these are under-estimates of the true prevalence of silicosis at the end of the study. The authors reported that, overall, there were 1827 silicotic men including those with simple silicosis and silicotuberculosis, and 4176 men classified as non-silicotic. The SRRs were calculated for the whole cohort and also stratified on silicosis status (silicotic, presuming grade 0-I and above, or non-silicotic). There were statistically significant excesses of mortality in the cohort from all causes (SRR 1.44; 871 deaths), lung cancer (SRR 1.49; 65 deaths), pulmonary tuberculosis (SRR 13.22; 237 deaths) and cardiorespiratory diseases. These excesses were all limited to those with silicosis; the all-cause SRR was 2.1 (481 deaths) compared with 1.04 (390 deaths) in non-silicotics. For lung cancer, the SRR in silicotics was 2.1 (35 deaths) compared with 1.11 (30 deaths) in non-silicotics. The SRR for 'pulmonary heart disease' was 3.08 (71 deaths) in silicotics compared with 0.74 (21 deaths) in non-silicotics. The risk of these diseases generally increased with category of silicosis. The SRRs for lung cancer in those with silicosis grade 0, I, II and III were 1.11 (30 deaths), 1.97 (21 deaths), 2.34 (10 deaths) and 2.55 (4 deaths), respectively. There was a very pronounced excess of deaths from tuberculosis among the silicotics, which increased with severity (SRR around 20, 40 and 70 at grade I, II and III, respectively), and this may have acted as a competing cause of death, reducing the true eventual risk of lung cancer.

When mortality was stratified on smoking status and silicosis status, the excess of deaths was still limited to silicotics, but there were similar excesses of lung cancer in smoking and non-smoking silicotics (SRR 2.34 and 2.13, respectively; 21 deaths in each case). In non-silicotics, there was a slightly higher but still non-significant increase in smokers compared to non-smokers (1.2 and 0.85, respectively).

An internal analysis was conducted based on stratification according to latency – although from the tabulated results, this seems to have been treated synonymously with duration of exposure. The results showed a trend of increasing mortality with duration of exposure (SRR 1.08, 1.44, 1.44 and 1.63 at 0-9, 10-19, 20-29 and $\geq$30 years, respectively). A similar trend was observed for lung cancer, but the excess was only statistically significant in the two longest duration categories (SRR 1.77 and 2.39, respectively). The risk of lung cancer was also reported to increase with latency within each category of silicosis severity (data not presented).

The cohort contained 'silica brick' and 'clay' brick workers. The details of the comparison of mortality experience between each group were only briefly presented. In both groups there was a similar excess of lung cancer which was confined to silicotics.

Overall, this study demonstrated an excess of lung cancer in Chinese 'silica' and clay brick refractory workers. The excess was confined to those with radiographic silicosis and increased with grade of silicosis. The risk of lung cancer in silicotics was around two-fold higher than in non-silicotics. The cohort was identified from medical records, and if not all workers had attended medical examinations, then this could have introduced selection bias. The likelihood of this possibility is difficult to judge, but given the roughly equal number of deaths in silicotics and non-silicotics (481 and 390, respectively) in the cohort, it would not appear that silicotics were preferentially included. Although the influence of smoking was only crudely investigated in this study, smoking seems unlikely to be a major confounding factor given that the external referent population was comprised of steel workers, and it is unlikely that there would be great differences in the pattern of smoking between these two groups which are probably of similar socioeconomic status. There was a large excess of 'pulmonary heart disease' in silicotics, but it is not clear if this can be attributed to smoking. The study is limited by the lack of any quantitative exposure data and lack of internal analysis of lung cancer risk according to cumulative exposure category. Stratification according to silicosis status may be considered to act as a crude surrogate for cumulative exposure. However, the reliability of the silicosis diagnoses is uncertain, given that the time between death and the last chest radiograph is not known. The study was also quite briefly reported with no details of the industrial processes for the refractory brick workers or for the referent population. No information was presented concerning how mortality statistics were gathered for the referent population, and whether the age and employment profile for the referent population adequately matched the study cohort.

Overall, there are some limitations to the reporting of this study and the level of detail provided. However, there was a clear excess of lung cancer in the overall cohort of refractory brick workers compared to an external referent group of workers from steel rolling mills. Internal analyses showed that the excess of lung cancer was restricted to those with silicosis, and lung cancer risk showed a clearly increasing trend with increasing latency/duration of exposure. There was also a marked increase in deaths from tuberculosis and cardiorespiratory disease in the silicotics, which may have acted as competing causes of death obscuring the true eventual burden of lung cancer development. The results of this study support the view that RCS can cause lung cancer, and appear to suggest that heavy and prolonged exposures may be required for this to become manifest.

2.5.4 Italian refractory brick workers

2.5.4.1 Merlo et al (1991) conducted a retrospective cohort mortality study in Italian refractory brick workers. The results demonstrated increased mortality from lung cancer in those employed in the industry in earlier times when exposures to RCS were believed to have been higher, and with long latency.

Merlo et al (1991) conducted a retrospective cohort mortality study in 1022 male Italian refractory brick workers who had worked in the industry between 1954 and 1977, and were followed up to 1986. Vital status was determined from regional records (not described further). The only information on smoking derived from a questionnaire filled out by 285 workers actively employed in 1984, but it was not clear if these workers were included in the cohort studied.

Only limited exposure data were available from measurements of respirable dust made in 1973 and 1975. Geometric mean concentrations of respirable dust were 0.2-0.56 $mg.m^{-3}$, which contained variable but high proportions of crystalline silica (65, 54 and 30% in grounding, mixing and pressing areas, respectively). Measurable amounts of crystalline silica were reported to be detected in all work areas. The authors indicate that dust and RCS exposures were probably higher before 1950 before improvements in dust control. However, there was no information on sampling methodology for the limited exposure data available.

SMRs were calculated in the conventional manner using the Italian male population as the referent group. At the end of follow-up, there were 732 workers alive, 243 dead, and 47 lost to follow-up. There was no overall excess of deaths from all causes (SMR 1.1), but there was a significant excess of cancer of the lung (SMR 1.51 (95% CI 1-2.18)), respiratory tract (SMR 1.51 (95% CI 1.04-2.12)) and bladder (SMR 2.78 (95% CI 1.12-5.71, based on 7 deaths)). There were 40 deaths from respiratory diseases (SMR 2.41 (95% CI 1.72-3.28)); 7 of these deaths were attributed to silicosis, but the basis for these diagnoses was not explained.

SMRs were calculated for sub-cohorts stratified on the basis of time of first employment (either ≤1957 or >1957), tenure and latency. The excess of lung cancer was only statistically significantly increased in those first employed pre-1957 (SMR 1.77 (1.03-2.84); 17 deaths, compared to an SMR of 1.23 (95% CI 0.61-2.2); 11 deaths post-1957). A similar but more pronounced pattern was observed for deaths from respiratory diseases. There were no significant excesses of mortality from any cause in those first employed after 1957. Many of the workers employed after 1957 had very short follow-up periods, making comparison of those employed before and after 1957 questionable.

When mortality was analysed on length of latency and tenure (both stratified around 19 years), there were only statistically significant excesses of lung cancer (SMR 2.01 (1.07-3.44) with >19 years' tenure), bladder cancer (SMR 5.75 (1.57-14.74) with ≤19 years' tenure), and respiratory diseases (SMR 3.89 (2.59-5.63) with >19 years' tenure) in those with >19 years' latency. The largest SMR for lung cancer was observed in a sub-group of workers hired before 1957 and after a latency period of 19 years (SMR 2.24 (1.2-3.83)). There was no consistent pattern in mortality from these causes with length of tenure.

There was a slight trend of decreasing mortality from all causes and lung cancer with increasing age at first hire. It was noted that 6 of the 7 deaths from bladder cancer occurred in those over 40 years old at first hire (SMR 5.18 (1.9-11.27)), with no excess evident in those who were younger at first hire. This finding led the author to speculate that these workers might have been exposed to a bladder carcinogen in a previous occupation, but no information on past occupational histories was available.

Information from the smoking questionnaire revealed that the smoking habits of the subjects in the plant in 1984 were similar to the general Italian male population. The authors used an indirect method to estimate the excess mortality that could be attributed to smoking. It was assumed that the relative risk for non-smokers was 1, for ex-smokers was 5, and for those smoking ≤20 and >20 cigarettes a day was 6.5 and 13.7 respectively. On this basis, the authors calculated that the excess mortality that could be attributed to smoking was only 1.8%, suggesting that smoking could not account for all the observed excess in mortality.

In summary, the results of this study demonstrated an excess mortality from lung cancer in a cohort of workers involved in the production of refractory bricks. The findings showed that excess lung cancer was limited to those employed prior to 1957 for more than 19 years' tenure or latency, around the time when dust control measures were introduced. The excess lung mortality was seen in association with a relatively high mortality from non-malignant respiratory diseases in the cohort, including some deaths attributed to silicosis, suggesting that there had been substantial exposures to RCS in this cohort. However, the study is limited by the lack of reliable quantitative exposure data. The authors noted that confounding by exposure to PAHs was unlikely because measured levels of PAHs in the workplace were not raised above environmental levels. Furthermore, there were no deaths from mesothelioma in the cohort and asbestos was said never to have been used in the production processes. The potential influence of cigarette smoking on the observed lung cancer mortality is difficult to gauge. Although the authors attempted an indirect assessment of the role of smoking and concluded that it did not contribute substantially to mortality, the reliability of this conclusion is uncertain. The authors also noted that, as there was no excess mortality from heart disease or emphysema in this cohort, smoking was not likely to have been a major confounding factor. Overall, the results of this study are consistent with the view that long duration of exposure to RCS can lead to an increased risk of lung cancer, but it was a relatively small-scale study with a number of weaknesses, as noted above.

2.5.5 Dutch ceramic workers

2.5.5.1 Meijers et al (1996) conducted a retrospective cohort mortality study in Dutch ceramic workers. The results revealed an excess of lung cancer in workers with simple pneumoconiosis (ILO ≥1/1). However, the prevalence of smoking was high and the potential confounding effect of smoking could not be accounted for.

Meijers et al (1996) conducted a retrospective cohort mortality study in male Dutch ceramic workers. The cohort was selected from subjects identified in a nationwide cross-sectional silicosis survey. Most of the workers were drawn from two large mechanised companies, with the remainder coming from 76 small ceramic workshops. In this survey, subjects received a thorough medical examination which included a chest radiograph, and questionnaires on job history, respiratory symptoms and smoking habit. If the initial chest radiograph was suggestive of 'silicosis' (or, more accurately, pneumoconiosis), a second larger radiograph was taken and graded according to the ILO scale. In total, 1794 male workers were selected for the cohort who had worked in the ceramics industry between 1972 and 1982 for more than two years. The cohort was followed up to the end of 1991. SMRs were calculated using the Dutch male population as the referent group.

No quantitative information on exposure to RCS was available. However, the level of exposure was judged to be highly correlated to the stage of production of ceramic ware. This allowed the authors to assign each subject to a qualitative category of average exposure (none, low, moderate or high) based on job description. However, this categorisation was based on each subject's job at the time of the medical survey and took no account of possible movement between different jobs during their employment, which could potentially impact significantly on their cumulative exposure estimates over the period of the study. Indeed, subjects identified with simple pneumoconiosis were not allowed to work in jobs where RCS exposure occurred, and so a worker could have potentially been classified as having high exposure but could have spent much of their later employment time in a job with no exposure. This is a significant weakness in the study design and renders the exposure assessments very unreliable.

There was no information on the extent to which these subjects may have been exposed to cristobalite as distinct from quartz. The authors did not identify any problems with confounding exposures. There was limited use of talc to dust moulds, but exposure to talc was not considered to be significant.

The mean length of follow-up was 14 years, and mean age at the start of the follow-up period was 40 years. Follow-up was complete for virtually all (99.8%) subjects. Around half of the workers had worked for more than 10 years in the industry. Smoking details were only briefly presented but indicated that, at the time of the medical examination, 20% of subjects were non-smokers. There were 124 subjects (around 7% of the cohort) with radiographically apparent opacities (simple pneumoconiosis), but in all cases the ILO grading was no higher than 1/1. Smoking data suggested that around 80% of the cohort smoked, but the absence of a clear excess of lung cancer (SMR 0.88 based on 30 lung cancer deaths in the entire cohort) suggests that they may not have been heavy smokers. Smoking can also cause opacities on radiographs, and so there is some uncertainty as to whether these opacities can confidently be assigned to silicosis. The prevalence of workers with opacities in the different exposure categories was not stated.

There were only 161 deaths in total (around 9% of the cohort), which was significantly less than expected (SMR 0.7). There were 30 deaths from lung cancer (SMR 0.88). There were no statistically significant trends in mortality from all causes or lung cancer with duration of employment, smoking status or exposure category.

There was a statistically significant excess of lung cancer in subjects with simple pneumoconiosis (SMR 2.2 (10 deaths)) compared to a deficit in those without pneumoconiosis (SMR 0.68). There were more deaths from lung cancer among smokers than non-smokers, but the number of deaths were similar to or less than expected numbers (SMR 0.97 for smokers (27 deaths) and 0.49 for non-smokers (3 deaths)). This may suggest a healthy worker effect in this population. Around a third of lung cancer deaths in smokers and non-smokers had simple pneumoconiosis, suggesting no synergistic relationship between the presence of smoking and pneumoconiosis and development of lung cancer.

This study is limited by lack of quantitative exposure data, low overall mortality, a relatively short period of follow-up of only 14 years, and a relatively young age at start of follow-up (40 years). However, the results did reveal a significant excess of lung cancer in those with simple pneumoconiosis (based on 10 deaths). It did not appear that this excess could be clearly attributed to smoking, but the absence of reliable exposure data prevents these deaths from being confidently assigned to exposure to crystalline RCS.

2.6 Meta-analyses

In recent years, two meta-analyses of studies on the relationship between silicosis and lung cancer have been published (Smith et al, 1995; Tsuda et al, 1997). The aims of the meta-analyses were to calculate quantitative summary measures of risk and to describe the homogeneity among available studies.

Each analysis used standard methods. Briefly, relevant studies were identified from the published literature, most of which were detailed in the IARC (1997) monograph. Tsuda et al also included ten studies from the Japanese literature. These studies were critically assessed and a small number with significant flaws or unquantifiable biases were rejected, leaving 23 and 32 (including 6 Japanese) studies in Smith et al and Tsuda et al, respectively, in the final analysis. Each meta-analysis included more or less the same studies with a few exceptions, resulting from disagreement over inclusion and the Japanese studies which were unique to the Tsuda study. Each analysis presented summary measures for the whole body of studies and also calculated separately for different study designs.

The conclusions from each meta-analysis were consistent in showing a two-fold excess of lung cancer risk in silicotics. The estimated risk derived by Smith et al was 2.2 (95% CI 2.1-2.4) for all study designs, 2.0 (95% CI 1.8-2.3) for cohort studies, 2.5 (95% CI 1.8-3.3) for case-control studies and 2.0 (95% CI 1.7-2.4) for 'proportional mortality ratio' studies. Similarly, Tsuda et al estimated a rate ratio of 2.74 (95% CI 2.6-2.9) for all studies, 2.77 (95% CI 2.61-2.94) for cohort studies and 2.84 (95% CI 2.25-3.59) for case-control studies.

Each author addressed and tried to minimise the effects of biases from the analysis such as using regional mortality rates for reference when available and adjusting for control deaths due to silicosis, diagnosis and selection bias. The most significant sources of bias identified were smoking and co-exposure to other occupational carcinogens. Smith et al noted that in the four studies that controlled for smoking, the smoking-adjusted risk estimate was higher than the non-adjusted (Amandus and Costello, 1991; Amandus et al, 1991; Cocco et al, 1990; Lagorio et al, 1990). Also, six studies calculated lung cancer risks for non-smoking silicotics. Two of these studies showed excess lung cancer risk (SMR 8.6; 3.6-20.5 and 5.3; 0.5-43.5), whereas the other studies did not. Smith et al suggest that the use of the general population as referents in these studies resulted in an under-estimate of lung cancer risk for non-smoking silicotics and an over-estimate for smoking silicotics. Adjustment of the findings from each of these studies, assuming that 80% of lung cancers in the general population are due to smoking, indicated a relative risk greater than one in five of the six studies and a pooled SMR of 3.3. Potential exposures to other carcinogens cannot be ruled out with certainty. However, several studies in the granite and stone industries – industries generally regarded as not having significant confounding factors – all demonstrated excess risks, confirming the association with silicosis rather than confounding factors. Indeed, Tsuda calculated relative risks for four separate industry categories and found similar estimates for each (RR 2.68, 2.65, 2.61 and 2.6 for mining, quarrying, foundry and pottery/ceramic work, respectively).

Steenland and Staynor (1997) conducted a meta-analysis using 16 studies of lung cancer and RCS exposure that they regarded as the best available, including several of the studies included in this document. The methodology used was not presented, but they calculated a combined RR of 1.3 (95% CI 1.2-1.4) for RCS-exposed workers and 2.3 (95% CI 2.2-2.4) for silicotic workers.

Overall, the meta-analyses indicate an increased risk of lung cancer among silicotics about twofold higher than in non-silicotics that did not appear to be explained by bias or confounding. It is unlikely that a risk of this magnitude could be explained fully by socioeconomic factors or any systematic bias. Smith et al (1995) indicated that the chance of this number of independent studies all producing a relative risk greater than 1.0 was very remote, and both Smith et al and Tsuda et al did not regard publication bias to be a significant problem. Silicotics represent a population who have had relatively high RCS exposure. These findings provide support for the contention that RCS poses a carcinogenic hazard. However, the findings do not inform on whether a lung cancer risk might occur in non-silicotics.

Section 3 - Experimental and animal data

The toxicity of silica has been the subject of a considerable amount of research over the last few decades. This work has elucidated many aspects of the interaction of silica particles with cells and tissues and has led to a widely accepted view on the mode of action of silica toxicity (IARC, 1997; Donaldson and Borm, 1998).

This section focuses on experimental findings that provide information pertinent to the questions being addressed, that is, the evidence for carcinogenicity in animals, genotoxicity, and relation of fibrosis/silicosis to cancer.

3.1 Animal evidence for carcinogenicity

The carcinogenic potential of crystalline silica in the lung has been investigated in studies in rodents exposed by inhalation and intra-tracheal instillation. However, most studies only employed single doses, which does not allow an exploration of dose-response relationships.

The available carcinogenicity studies are described in detail in other reviews (IARC, 1997; Soutar et al, 2000), and only the key aspects are presented here. In a study by Muhle et al (1991), male and female F344 rats were exposed to 1 $mg.m^{-3}$ DQ12 (87% quartz; MMAD 1.4 µm; 74% of particles respirable) for 24 months. There was an overall increase in lung tumours (19/100 against 3/100 in controls). The lung tumours were more prominent in females (12/50, 2 keratinising cystic squamous cell tumours, two adenomas and eight adenocarcinomas) than in males (6/50, two keratinising cystic cell tumours, two adenocarcinomas, one adenosquamous carcinoma and one epidermoid carcinoma). The minimal latency for tumour development was 21 months. The animals developed subpleural and peribronchiolar fibrosis, which the authors reported as being unlike the nodular fibrosis seen in human silicosis.

In a study by Holland et al (1986), female F344 rats were exposed to 12.4 $mg.m^{-3}$ Min-U-Sil (96% quartz; mean geometric size 5 µm; 70% of particles respirable) for 24 months. There was an increase in lung tumours (18/60, including 11 adenocarcinomas, 3 squamous cell carcinomas and 6 adenomas, against 0/54 in controls). The adenocarcinomas developed from type II alveolar cells.The minimum latency for development of tumours was 17 months. Extensive non-tumour

pathology was observed in most animals living beyond 400 days, including lipoproteinosis, granulomas and granulomatous plaques and interstitial and discrete nodular fibrosis.

In a study by Dagle et al (1986), male and female F344 rats were exposed to 51.6 $mg.m^{-3}$ Min-USil (96% quartz; MMAD 1.7-2.5 µm) for up to 24 months, with serial sacrifice or removal to recovery groups at 4, 8, 12 and 16 months. There was an overall increase in the frequency of lung tumours, with the increase being more prominent in females (10/53 epidermoid carcinomas against in 0/47 in controls; three of these rats were only exposed for four months) than in males (1/47 epidermoid carcinomas against 0/42 in controls). The minimum latency for tumour development was 16.5 months. The authors noted lipoproteinosis, metaplasia of the alveolar epithelium, thickening of the interalveolar septa and nodular fibrosis in most of the exposed animals.

In a study by Spiethoff et al (1992), female Wistar rats were exposed to 6 or 30 $mg.m^{-3}$ DQ12 for 29 days followed by lifetime observation. There was a similar increase in tumour incidence at each dose (62/82, including 8 adenomas, 17 bronchioalveolar carcinomas and 37 squamous carcinomas, at 6 $mg.m^{-3}$ and 69/82, including 3 adenomas, 26 bronchioalveolar carcinomas and 30 squamous carcinomas, at 30 $mg.m^{-3}$ against 0/85 in controls). In another study in Wistar rats, there was no increase in lung tumours after exposure to 58.5 $mg.m^{-3}$ quartz (Sikron F300; only a small fraction was respirable) for 13 weeks (1/70 squamous cell carcinoma against 0/70 in control; Reuzel et al, 1991). However, this study must be interpreted cautiously. The particle size was not respirable for rats, and so the actual dose reaching the lower lung would have been low (not quantified), and there was no information provided in the report on survival times, so it is unknown how many animals survived long enough to develop tumours. Similar findings were noted in rats dosed by intra-tracheal instillation (Holland et al, 1983; Groth et al, 1986), but these will not be discussed further in this document.

In contrast, no evidence for the ability of RCS to cause cancer has been observed in other laboratory rodents other than the rat. In a study by Wilson et al (1986), female BALB/c BYJ mice were exposed to 1.475, 1.8 and 1.95 $mg.m^{-3}$ Min-U-Sil (96% quartz; MMAD <1.2 µm) for around two years, with serial sacrifices at 6 or 12 months. There were no exposure-related lung tumours or pulmonary fibrosis, although there was some alveolar macrophage accumulation and pulmonary granuloma formation. In a study by Mermelstein et al (1992), male and female Syrian golden hamsters were exposed to 3 $mg.m^{-3}$ DQ12 (87% quartz; MMAD 1.4 µm; 74% of particles respirable) whole body for 18 months, with 5 months' recovery. There was chronic inflammation and slight fibrosis in the lungs and interstitial inflammatory cell infiltration. There was no increase in tumour incidence, but it is possible that the high premature mortality (50% at 5 months) may have reduced the ability of the study to detect carcinogenicity.

Overall, the available inhalation carcinogenicity studies provide limited information. It is clear that RCS causes lung cancer in rats. The findings suggest that female rats are more sensitive to the carcinogenic activity of RCS than males. The available studies provide little information on the temporal relationships between RCS-induced fibrosis and lung cancer. In rats, significant fibrosis and lung inflammatory response was always present at carcinogenic doses, and Dagle et al demonstrated that it occurred many months before the appearance of tumours. In hamsters, there was no evidence of carcinogenicity even in the presence of slight fibrosis, suggesting that minimal fibrosis, at least, does not lead to cancer.

There is very little information on the dose-response relationship for tumours. Most of the available studies only used single doses and differed in several ways, making direct comparison difficult. However, taken together, these studies examined a reasonably large range of doses (1-52 $mg.m^{-3}$) and gave no indication of a relationship between dose and tumour incidence. The only study to use more than one dose demonstrated similar tumour incidences at two widely spaced doses. The species- and, to some extent, the sex-specific carcinogenicity and long latency, approaching the normal lifespan of the animals, are all consistent with the possibility of a non-genotoxic mechanism.

The findings with crystalline silica of tumours in rats and not in mice and hamsters, and more prominent tumour response in females than males, is consistent with findings from studies with other dusts, such as carbon black and titanium dioxide. The relevance of lung tumours in rats to human health is uncertain. Experimental evidence suggests that the rat may be the most sensitive species (of those commonly used in experimental studies) to the effects of dust accumulation in the lungs. Rats generally show a more aggressive inflammatory response to lung overload (ie impairment of dust clearance rates) than do mice and hamsters, and develop tumours under these conditions when other species do not. It seems possible that the rat lies at the extreme sensitive end of a spectrum of relative sensitivities to the effects of particulate accumulation in the lungs, especially with regard to carcinogenicity, with hamsters and mice some way towards the opposite end. It is uncertain where the human lung would lie within this spectrum. Regardless, if carcinogenicity was mediated by some aspect of lung inflammatory response, this would argue for a threshold for carcinogenicity, although one cannot be identified from the available data.

3.2 Genotoxicity

The genotoxicity of silica has been studied quite extensively in relatively standard tests (for detailed reviews see IARC, 1997; Hessel et al, 2000; CICAD, 2000; HSE, 1995). However, the solid form of silica makes it difficult to test. There is microscopic evidence from work with Syrian hamster embryo (SHE) cells that crystalline silica particles can be internalised by cells and gain access to the genetic material in the cell nuclei (Hesterberg et al, 1986). This suggests that any mutagenic activity of crystalline silica particles is likely to be detected by in vitro mutagenicity tests. Crystalline silica can cause strand breaks when incubated with isolated DNA at high particle doses (IARC, 1997). However, given the non-physiological nature of the test system, together with the very high particle numbers used, the relevance of such tests to in vivo exposure is questionable. A more recent study using the comet assay in Chinese hamster lung fibroblasts and human embryonic lung fibroblasts cells demonstrated the ability of crystalline silica to cause DNA strand breaks (Zhong et al, 1997). In in vitro test systems for sister chromatid exchange, chromosomal aberrations, aneuploidy and gene mutations at the HPRT locus, crystalline silica has consistently tested negative. Crystalline silica has been shown to cause micronuclei in a number of in vitro studies, although it has been suggested that the fragments of DNA previously interpreted as chromosomal fragments are possibly evidence of apoptosis caused by cytotoxicity (Hessel et al, 2000). In two studies by the same group, crystalline silica caused a dose-related increase in micronuclei in Chinese hamster lung fibroblasts and pulmonary macrophages, and this activity was reversibly inhibited by pre-treatment of the dust with a phospholipid surfactant, to simulate the coating of the particles after initial deposition in the lung (Liu et al, 1996 and 1998). The ability of silica to cause cell transformation has been demonstrated in a number of studies in SHE and mouse embryo BALB/c-3T3 cells. However, given that cell transformation can result from genotoxic or non-genotoxic mechanisms, these results are not particularly informative. There was no increase in bone marrow micronuclei in mice dosed intra-peritoneally (Vanchugova et al,

1985); given the physical nature of silica, it is possible that the target tissue was not exposed, although the authors did report an increased frequency of micronuclei when testing asbestos fibres. Overall, evidence for genotoxicity is limited to the induction of micronuclei in in vitro studies.

There is an increasing body of evidence demonstrating that marked and persistent inflammation provides a mechanism by which dusts, including RCS, can result in genotoxic effects in the lung. A series of studies by the same workers investigated the production of 8-hydroxydeoxyguanosine (8-OHdG), an oxidised DNA base, in the lung tissue of female Wistar rats at up to 90 days following a single intra-tracheal dose of 0.15 to 7.5 mg DQ12/quartz (Nehls et al, 1997; Bruch et al, 2000; Seiler et al, 2001). Lung inflammatory response was assessed using standard broncho-alveolar lavage (BAL) parameters and fibrosis by the ratio of phosphatidylglycerol to phosphatidylinositol (PG/PI; a lower ratio indicating more fibrosis), said to be an accepted marker for pulmonary fibrosis.

The results of these studies showed a time- and dose-related increase in the severity of lung inflammation as evidenced by an increase in total cells and neutrophils in broncho-alveolar lavage (BAL) fluid. Similarly, there was a dose-related increase in the severity of fibrosis when assessed at 90 days post-dose and a pronounced increase in the percentage of proliferating cells in the lung tissue. There was a time- and dose-related increase in 8-OHdG. The levels of 8-OHdG were only statistically significantly increased over control values at doses above 0.6 mg/lung consistent with a threshold mechanism. The amount of 8-OHdG was found to be same in all lung cell types studied (no more information presented). Both studies investigating the time-course of production of 8-OHdG demonstrated that the presence of the oxidised base was persistent over a 90-day period. The levels of 8-OHdG increased with the proportion of neutrophils in BAL fluid. These studies have demonstrated that crystalline silica causes oxidative DNA damage in vivo. The correlation between the levels of 8-OHdG with inflammation and proportion of neutrophils suggests that the adducts were caused by neutrophil-derived oxidants. There was evidence for a threshold, of around 0.3 mg/lung, for the increase in 8-OHdG production. No threshold for fibrosis was identified.

Studies by Driscoll and co-workers have investigated the ability of crystalline silica to induce mutations in rat alveolar epithelial cells. In one study, female rats received a single intra-tracheal dose of 10 or 100 mg/kg quartz, and at 15 months post-dose, effects on the HPRT gene locus in alveolar type II cells, and also the ex vivo mutagenicity of BAL cells were assessed (Driscoll et al, 1997). Examination of BAL fluid at 15 months post-dose suggested that there was a pronounced inflammatory response, evidenced by significant increases in total and differential cell counts at both doses. There was also clear histopathological evidence of inflammation, interstitial fibrosis and type II cell hyperplasia in the bronchoalveolar region, as well as squamous metaplasia of alveolar epithelial cells. There was a dose-related increase in the HPRT mutation frequency in alveolar type II cells isolated from BAL fluid (reaching approximately 180 mutants/10^6 cells at 100 mg/kg). The number of mutations was related to the severity of the inflammatory response, as indicated by the proportion of neutrophils in the BAL fluid (approximately 30 and 180 mutations/10^6 cells when BAL contained around 40 and 65% neutrophils, respectively). These results were paralleled by the in vitro findings. Cells from BAL fluid from animals treated as described above were cultured in vitro with a rat lung epithelial cell line, RLE-6TN cells, at a 10:1 or 50:1 (BAL cells:RLE-6TN cells) ratio. There was an increase in the number of mutations at the HPRT locus when the BAL cells were present in a 50-fold excess, but not when present in a 10-fold excess. This response was completely eliminated in the presence of catalase.

When RLE-6TN cells were cultured with specific BAL cell types, neutrophils caused a greater number of mutations than macrophages (around 0, 8 and 22 mutations/106 cells for control, macrophages and neutrophils, respectively). Culturing RLE-6TN cells directly with up to 100 mg/cm^2 quartz did not increase the frequency of mutations, suggesting that quartz did not cause the mutations directly.

A similar study to the one above was conducted to compare the lung response to crystalline and amorphous silica (Johnston et al, 2000). Male rats were exposed by inhalation to 3 mg.m^{-3} crystalline cristobalite (MMAD 1.3 µm) or 50 mg.m^{-3} amorphous silica (MMAD 0.81 µm; primary particle size 12 nm; 200 m^2/g surface area) for up to 13 weeks, followed by up to 8 months' recovery. The lung burden of crystalline silica increased throughout exposure (336 and 819 mg/lung after 6.5 and 13 weeks' exposure, respectively), and there was no substantial clearance during recovery (658 and 743 mg/lung after 12 and 32 weeks' recovery, respectively). In contrast, for amorphous silica, lung burdens were similar to those found with crystalline silica immediately after exposure (756 and 883 mg/lung after 6.5 and 13 weeks' exposure, respectively) but decreased substantially during recovery (156 and 93 after 12 and 32 weeks' recovery, respectively), demonstrating a greater rate of clearance than for crystalline silica. BAL findings demonstrated a pronounced inflammatory response with crystalline silica throughout the exposure and recovery period, whereas with amorphous silica there was an inflammatory response of similar severity to crystalline silica during exposure which rapidly disappeared after three months' recovery. Immediately after exposure, the total number and proportion of neutrophils in BAL were higher for amorphous silica than for crystalline silica (around 55 and 47%, respectively, giving around 93 and 65 million cells, respectively). Similarly, LDH, a biochemical marker of cytotoxicity, was clearly higher in the amorphous group than in the crystalline silica group (1808 and 799 nmol/min/ml, respectively). The frequency of HPRT mutations in alveolar epithelial cells from BAL immediately after exposure was around 8, 32 and 4 mutants/106 cells for control, crystalline silica and amorphous silica, respectively. There was a proliferative response in lung tissue, observed earlier with amorphous silica (first observed at 45 days and at 90 days with crystalline silica), which only persisted through to the end of recovery with crystalline silica. Using a cell staining technique, there was evidence of apoptosis or necrosis throughout the terminal bronchiolar epithelium and parenchyma of rats exposed to amorphous silica for 90 days, but this was not evident in rats exposed to crystalline silica. This study demonstrated that both amorphous and crystalline silica caused a pronounced inflammatory response. The severity of the response appeared to be greater with amorphous silica than with crystalline silica in terms of inflammatory response and extent of cytotoxicity and cell death. It is generally considered that the total surface area of dust particles deposited in the lung is an important determinant of toxicity. It is uncertain whether the surface areas of the amorphous and crystalline silica deposited in the lungs in this study were the same, although the initial lung mass burdens were similar. The response with amorphous silica was less persistent than with crystalline silica as a result of the faster clearance of amorphous silica. Mutations of the HPRT gene were only evident for crystalline silica, despite pronounced inflammation and presence of neutrophils with amorphous silica. This finding suggests that other factors are important in this mutagenic response. It could be speculated that the lower level of cell death and apoptosis with crystalline silica may indicate a lower direct toxicity towards cells, which allows a greater population to survive and express the mutations.

In summary, the genotoxicity of silica has been studied relatively thoroughly using standard and non-standard tests. In most standard tests, the results are negative. Recent research has shown that the process of inflammation may cause genotoxicity as a result of increased production of oxidant species leading to oxidative DNA damage. It has been demonstrated that the extent of genotoxicity, in terms of gene mutation at the HPRT locus or production of 8-OHdG, is directly related to the severity of inflammation, particularly the number of neutrophils, present in the lung. It therefore seems most likely that RCS is not a direct-acting genotoxicant. However, in some circumstances it could lead indirectly to genotoxicity as a secondary consequence of inflammation. The pattern of evidence is consistent with the concept of a threshold related to the severity of inflammation.

3.3 Mechanisms of lung cancer induction by crystalline silica

The in vitro and in vivo evidence relating to the mechanism of toxicity of crystalline silica has been reviewed extensively (IARC, 1997; Donaldson and Borm, 1998). These data have led to a widely accepted mechanism of toxicity involving chronic inflammation and oxidative stress.

Single and repeated exposures to quartz are associated with the development of a lung inflammatory response, characterised by an influx of white blood cells into the lung. The most notable response to silica deposition in the lung is an accumulation of phagocytic cells, mainly alveolar macrophages (AM) and polymorphonuclear neutrophils (PMN), within a relatively short time following exposure at the sites of particle deposition. These cells phagocytose the silica particles and in the process produce a variety of reactive chemicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), during the so-called respiratory burst. In addition to their phagocytic role, these cells are also important effector cells, producing an elaborate spectrum of cytokines and other biologically active products. These products include substances which are mitogenic for epithelial cells or fibroblasts and cytokines such as tumour necrosis factor (TNF) and macrophage inflammatory proteins (MIP) which are involved in the inflammatory process (Driscoll et al, 1990; Donaldson et al, 1988). The combined effects of local tissue damage and mitogenic factors lead to proliferation and hyperplasia in epithelial cells, the progenitors of lung tumours. The induction of lung toxicity and proliferative changes and genotoxicity are related to the relative severity of inflammation. These findings are consistent with a threshold mechanism of carcinogenicity.

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