Epidemiological Evidence on the Carcinogenicity of Silica: Factors in Scientific Judgement

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In view of the extended debate and differing opinions on whether crystalline silica is a human carcinogen, we have reviewed a selection of epidemiological reports, to identify the areas of uncertainty and disagreement. We have chosen to examine the papers which in a recent review were considered to provide the least confounded examinations of an association between silica exposure and cancer risk. We also refer to a study of the mortality of coalminers very recently reported by ourselves and colleagues.

We find that parts of the evidence are coherent but there are contradictions. On examination this resolves mostly into differences between types of studies. The three types of epidemiological study included are: (i) exposure-response studies, the most powerful for the confirmation of a relationship between a specific exposure and a health effect; (ii) descriptive studies in which incidence of disease in an exposed population is compared with that in a reference population; and (iii) studies of incidence of disease in subjects on silicosis case-registers.

Descriptive studies frequently though not invariably suggest an excess lung cancer risk in silica-exposed workers compared with the general population, but exposure-response studies consistently fail to confirm that the cause is exposure to quartz. A single exposure-response study of cristobalite suggests a positive relation. Both sets of evidence have weaknesses. There are uncertainties on whether the excess risks in the descriptive studies are related to silica exposure or to lifestyle, including smoking habits. There are doubts on whether the exposure estimates in some of the exposure-response studies were sufficiently reliable to detect a small risk or weak association, though they are unlikely to have missed a strong effect.

Studies of subjects on silicosis case registers consistently show an excess of lung cancer, but it is not clear to what extent these increased risks represent a direct effect of silica exposure, a secondary effect of the silicosis, preferential inclusion of subjects suffering from the effects of smoking, or bias in diagnostic accuracy.

This not unnaturally leads to differences in opinion, exacerbated by variations in the strength of proof required by different experts.

The main scientific uncertainties in the evidence are:

1. Whether, in the descriptive studies, the excess lung cancer rates in silica-exposed workers are explicable in terms of smoking habits, socio-economic class differences and inappropriate comparison populations. Better smoking information and more carefully chosen comparison populations are needed;

2. Whether the exposure–response studies could have missed a real relationship between silica exposure and lung cancer, if one exists. Many of the exposure–response studies were conducted with great care, but weaknesses, in the available data on which the exposure estimations were based, could have caused a real relationship of lung cancer and silica exposure to be missed. These studies were sufficiently powerful to demonstrate relationships of silica exposure with silicosis and silico-tuberculosis, so it is unlikely that they would have missed any but a small risk, or weak relationship, for lung cancer. Our own recent study of coalminers used uniquely detailed and reliable exposure data, and failed to demonstrate convincingly an increased risk. This negative finding, though, applies only to a dust in which...
the proportion of quartz in the dust is usually less than 10%. Exposure–response studies are needed, with high quality exposure estimates, in populations exposed to respirable dust of which crystalline silica comprises more than 10%;

3. Whether the excess cancer risks in subjects on silicosis registers are the result of selection and diagnostic bias. Given these difficulties, case-register studies may not be capable of giving a reliable answer to the central question, though they have been useful in pointing to the possibility of a cancer risk;

4. If silica exposure is associated with increased risks of lung cancer, whether or not the increased risk is found in subjects without silicosis; or is confined to subjects with silicosis, with the implication that such a secondary effect would be avoided by avoiding the exposures that cause silicosis. The limited evidence available suggests that any silica-related cancer risk may well be confined to subjects with silicosis. Studies of risks in silica exposed workers demonstrated not to have silicosis would be informative;

5. Whether it is justifiable to assume that quartz and cristobalite have similar health effects. Laboratory studies could complement epidemiological studies helpfully in this respect.

We have not sought in this review to give our opinion on what conclusions the evidence overall justifies, but hope that this discussion of the strengths, weaknesses and conflicts in the evidence will help to clarify the debate. © 2000 British Occupational Hygiene Society. Published by Elsevier Science Ltd. All rights reserved.

Keywords: silica; carcinogenicity; epidemiology; IARC classification; EU classification; quartz; cristobalite

INTRODUCTION

There has been an extended debate on the question of the human carcinogenicity of crystalline silica (IARC, 1987, 1997; Goldsmith, 1994; McDonald, 1989; Weill and McDonald, 1996; Pairon et al., 1991; Pilkington et al., 1996). The reasons for a continuing division of opinions on this work may include incomplete data and differing requirements for proof. We have attempted to analyse the areas of uncertainty and potential disagreement in a limited but key body of evidence, and to indicate where scientific investigation or policy clarification might help to resolve the issue.

Rather than review the entire relevant literature we have focused on those studies which a recent IARC working group (IARC, 1997) stated provide the least confounded examinations of an association between silica exposure and cancer risk. Examination of these studies is informative on how differences of scientific opinion can arise from the same body of data. The studies were: South Dakota gold miners; Danish stone industry workers; Vermont granite shed and quarry workers; United States crushed stone industry workers; United States diatomaceous earth industry workers; Chinese refractory brick workers; Italian refractory brick workers; United Kingdom pottery workers; Chinese pottery workers; Cohorts of registered silicotics from North Carolina and Finland.

We have also considered a report of a study of British coal miners, only recently prepared by our own colleagues (Miller et al., 1997) which is particularly informative because it is based on a large long-term retrospective study which included a uniquely detailed programme of measurements of exposures to dust and quartz.

METHODS

We constructed a logical framework for identifying areas of uncertainty which might give rise to differences of interpretation or opinion. The components of this framework included: the evidential power of study design; interpretation of causation when carcinogenesis may be secondary to fibrosis; judgements on the influence of technical defects in the studies; the weight given to the overall picture. even when individual studies are flawed; differences in the implications of the IARC and EU classification rules; and degree of proof required. We also outline cases for and against the carcinogenicity of silica, and point out where resolution could be assisted by further information.

We make below some background observations relevant to the key issues.

Degree of proof required

The IARC (1997) guidelines for classification of carcinogens state that sufficient evidence of carcinogenicity in humans is provided when the relevant Working Group considers that “a causal relationship has been established between exposure to the agent… and human cancer. That is a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence”.

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Where a working group considers that a causal interpretation is credible, but chance, bias or confounding cannot be ruled out with reasonable confidence, this represents "limited evidence of carcinogenicity". The interpretation of this wording may be critical to the conclusions drawn, and some further clarification by the regulators could be helpful. As an illustration, such phrases as "beyond reasonable doubt" or "on the balance of probabilities" would give further guidance on the degree of proof required.

Possibly some of the differences in scientific opinion are related to varying interpretations of the "reasonable confidence" with which chance, bias or confounding can be ruled out. Some experts may be using "balance of probabilities" as the criterion, others "beyond all reasonable doubt".

The EU guidelines (Commission of the European Communities, 1993) give less guidance on this matter. This is in contrast to the detailed and prescriptive guidance provided on the interpretation of animal studies.

Note that both classification systems are of hazard, not "risk", that is whether the substance can cause cancer, not how likely it is to do so.

**Evidential power of study design**

Partly, the strength of proof is determined by the design of a study. It is well recognised that epidemiology cannot prove causation, but it can demonstrate association, from which arguments can be developed for causation in some cases.

**Exposure–response studies.** The strongest case for association between exposure to silica and risk of lung cancer, since no designed experiments are possible, would be provided by a study which demonstrated an exposure–response relationship. These studies are typically of cohort or case-control design. The strength of the exposure–response study lies in the demonstration, over a gradient of exposure to the suspected agent, of a progressive increase in health risk not explained by confounding factors. In practice, the lack of detailed exposure information reduces the power of many studies to identify an association.

**Descriptive studies.** A lesser degree of certainty is provided by descriptive studies which seek to examine whether a disease is more frequent in a working population than in a comparable non-exposed population. This type of study does not, however, indicate what exposure factor(s) might be causing any observed excess of disease (EPA, 1996; CCCF, 1991), and confident attribution to one specific cause requires elimination of other potential causes. In practice, smoking is invariably present as a potential confounder.

**Case register studies.** Studies of silicosis case registers represent an indirect way of investigating associations between exposure to quartz and cancer risk. The difficulties of drawing conclusions from studies of silicosis case registers have been well described (McDonald, 1989; Pairon et al., 1991). People can be included in silicosis registers not only because they have silicosis, but also because they have smoking-related symptoms or other abnormalities as well as silicosis, or because they have smoking-related chest radiographic abnormalities, or other disease, which mimic silicosis. The presence of respiratory symptoms (Peto et al., 1983) or deficits of lung function (Miller et al., 1981) in smokers identifies subjects with subsequent increased risks of lung cancer, and any preferential inclusion of such subjects by virtue of these clinical features would be expected to increase the cancer rates. Additionally there are well described uncertainties about whether the diagnosis of lung cancer is as reliable in subjects not on case registers as it is in registered silicotics receiving regular medical examinations.

Thus it does not logically follow, unless these uncertainties can be eliminated or quantified, that an excess mortality from lung cancer in subjects on silicosis registers necessarily indicates that silica is the cause. Nevertheless such studies, when positive, generate a suspicion that quartz may be causing cancer in man, and have provided much of the impetus to further investigation, based on studies of less selected populations exposed to silica.

**An example.** An example illustrates some of these points well. Coalminers, obviously, have historically an excess of pneumoconiosis, and this is easily demonstrated by descriptive studies. The putative cause, exposure to coal mine dust, has been confirmed to be associated with risk of pneumoconiosis by many exposure–response studies, and coal dust is accepted as causative. On the other hand coalminers have repeatedly been shown also to have an excess frequency of stomach cancer. Exposure–response studies have failed to demonstrate a consistent association with exposure to coal mine dust. No other causes have seriously been suggested, and the finding remains unexplained. Coalmine dust is not considered to be a carcinogen (IARC, 1997).

**Secondary effects**

Inhalation of quartz results in chronic inflammation and fibrosis in the lungs (Donaldson et al., 1988, 1990, 1992) and these processes might result in an increased risk of cancer. Rats with silica-induced lung cancers appear always to have fibrosis (Muhle et al., 1989, 1995). If cancers arise as a secondary effect of the scarring process in subjects with silicosis, possibly by increasing susceptibility to other causes, to what extent should this be considered a result of exposure to silica, or the result of the fibrosis? This may seem an unimportant distinction, but in some cases regulatory toxicology interprets secondary carcinogenesis differently from carcinogenesis arising as a primary consequence of
exposure (Commission of the European Communities, 1993).

An examination of whether the risks of cancer in subjects without silicosis are demonstrably related to amount of exposure to quartz would determine whether or not quartz is a direct cause of cancer (we recognise the conceptual difficulty of defining the onset of silicosis, and added difficulty of detection). The practical consequence, of finding that any lung cancer risk is secondary to fibrosis, is that measures to prevent silicosis should also be sufficient to prevent any excess cancer risk.

Classification rules for carcinogens; contrasts between the IARC and EU rules

The IARC (1994) and EU (Commission of the European Communities, 1993) rules for judging the human evidence of carcinogenicity are very similar. The rules for interpreting animal studies differ to some degree. One difference relevant to consideration of the secondary nature of possible effects is that the EU rules argue that for animal studies "existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation)" is an argument for classifying as Category 3 ("substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment"). Similar considerations, logically, are relevant to the human evidence, though this is not stated explicitly. The IARC rules make no reference to secondary effects.

Confounding

Confounding occurs when an apparent relationship between exposure to an agent and risk of ill health is distorted by the influence of a second agent which itself influences health and is also associated with exposure to the first agent. The result is that it is not possible to assign all or part of the association unambiguously to one of the agents (depending on the extent of the confounding). The studies in this review were chosen by the IARC working group, being the least confounded examinations of a possible association between crystalline silica exposure and lung cancer.

In many countries lung cancer rates vary by geographical area, socioeconomic class, occupational group and smoking habit, and decade (Fox, 1989; OPCS, 1986; Williams and Horm, 1977; Pearce and Howard, 1986; Levi et al., 1988; Cohart, 1955; Horm and Kessler, 1986). The British Registrar General's decennial series of reports on occupational mortality are a rich source of information on these variations. Table 1 shows standardised mortality ratios (SMRs) for deaths in British men from malignant neoplasms of the lung in the period 1978-80 to 1982-83, according to region and social class (OPCS, 1986). The social class classification is a grouping of men according to the work they perform. The variations in lung cancer SMRs with social class and region are striking. In the more extreme cases, comparing the lung cancer mortality of a population of unskilled working men (social class V) in the North or North East of England or Scotland with national rates for all men would overestimate the SMR by a factor of two. These social class differentials have been progressively widening throughout this century (Logan, 1982) and continued to do so up to 1982 (the most recent report (Drever, 1995) does not present this information).

These social class differences do not appear simply to reflect the influence of exposures to harmful agents at work, for 80% of the variation of lung cancer SMRs between the major occupational groups is explained by social class (Fox and Adelstein, 1978).

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Table 1. SMRs for deaths in British men aged 20–64 for malignant neoplasms of the trachea, bronchus and lung 1978–80 to 1982–83, according to geographical region and social class (OPCS, 1986). Social class definitions: I professional etc., II intermediate, III N skilled non-manual, III M skilled manual, IV partially skilled, V unskilled.

<table>
<thead>
<tr>
<th>Region</th>
<th>All men</th>
<th>I</th>
<th>II</th>
<th>III N</th>
<th>III M</th>
<th>IV</th>
<th>V</th>
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<tr>
<td>Great Britain</td>
<td>100</td>
<td>43</td>
<td>62</td>
<td>78</td>
<td>117</td>
<td>125</td>
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<tr>
<td>Wales</td>
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<td>43</td>
<td>60</td>
<td>74</td>
<td>92</td>
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<td>202</td>
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<tr>
<td>North</td>
<td>131</td>
<td>54</td>
<td>74</td>
<td>90</td>
<td>147</td>
<td>164</td>
<td>237</td>
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<tr>
<td>Yorkshire and Humberside</td>
<td>108</td>
<td>38</td>
<td>71</td>
<td>91</td>
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<td>138</td>
<td>178</td>
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<tr>
<td>East Midlands</td>
<td>90</td>
<td>36</td>
<td>61</td>
<td>76</td>
<td>98</td>
<td>116</td>
<td>160</td>
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<tr>
<td>East Anglia</td>
<td>80</td>
<td>44</td>
<td>57</td>
<td>66</td>
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<td>136</td>
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<tr>
<td>South East</td>
<td>87</td>
<td>41</td>
<td>59</td>
<td>74</td>
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<tr>
<td>South West</td>
<td>77</td>
<td>38</td>
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<tr>
<td>West Midlands</td>
<td>107</td>
<td>45</td>
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<tr>
<td>North West</td>
<td>120</td>
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<td>74</td>
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<tr>
<td>Scotland</td>
<td>122</td>
<td>58</td>
<td>73</td>
<td>98</td>
<td>152</td>
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<td>210</td>
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</tbody>
</table>
Social class differences include smoking habit. Smoking scores for occupational orders are highly correlated with lung cancer SMRs (Fox and Adelstein, 1978). Smoking does not appear to account for all the social class differences, however (Fox and Adelstein, 1978; Hein et al., 1992), and other way-of-life differences may play a part, including, possibly, nutrition (Byers, 1994).

Smoking habit varies by occupation (Drever, 1995; Fox and Adelstein, 1978; Sterling and Weinkharn, 1976), and the potential of differences in smoking habit to introduce differentials in lung cancer rates between occupational groups has been estimated (Axelson and Steenland, 1988). For example, Axelson (1988, 1978) estimated that a population with 60% smokers could have a risk ratio for lung cancer of 1.22 times that for an hypothetical population with 50% smokers; for 70% smokers, a 1.43 risk factor.

These variations apply internationally (Fox, 1989; Hakulinen et al., 1987; Mizuno et al., 1989), possibly to different extents. Silica exposed populations are likely to range in social class from unskilled to skilled manual workers, the very social levels which are associated with increased background rates of lung cancer. Thus there would be a tendency for selection of silica exposed populations to select those with other, social, high risk factors for lung cancer. Their influence should be taken into account in the interpretation of the generally small increases in mortality risks found in silica-exposed workers.

**REVIEW**

We reviewed the selected papers according to the above framework, and elsewhere have appended brief notes on each paper (Soutar et al., 1997). Here we present a review of the scientific issues.

**Exposure–response studies**

Exposure–response studies are preferred for confirmation of relationships between occupational agents and health effects (EPA, 1996; CCCF, 1991). Considering the importance of the health effects of silica, it is surprising how few exposure–response studies have been conducted, and the weakness of the exposure data in most study populations.

The only relevant exposure–response studies, in which exposures were measured longitudinally for research purposes, of which we are aware are those of the Vermont granite workers (Davis et al., 1983), which commenced in the 1920s, and a large study of coal miners in Britain (Miller et al., 1997) which commenced in the 1950s. The Vermont study included extremely detailed programmes of dust and quartz measurement, conducted as a series of cross-sectional surveys. The study was negative for any relationship between silica exposure and lung cancer. Unfortunately the necessity to convert from particle count to gravimetric measurements caused large errors in the exposure estimates, and this must have weakened the power of the study to detect modest risks. It is possible that the particle count/gravimetric conversions could be performed more reliably by using separate factors for each occupational group.

The British coal miners study (Miller et al., 1997) was also negative for a relationship between silica exposure and lung cancer. It included immensely detailed longitudinal and continuous dust measurement programmes, and could not demonstrate convincingly a relationship between silica exposure and lung cancer. While many of the exposures to quartz in this study were high, the quartz was mixed with even larger quantities of coal and other minerals. This negative result therefore applies to coalmines where the silica content of the respirable dust is generally less than 10%, but is not particularly informative about situations where silica proportions are often higher than this.

Exposure–response studies in which estimates of past exposure are constructed retrospectively tend to be technically weaker, usually because of the difficulties of reconstructing exposure histories based on incomplete dust concentration data. For quartz, these studies comprised goldminers in South Dakota (Steenland and Brown, 1995; McDonald et al., 1978; Gillam et al., 1976), for whom the same criticisms on particle count/gravimetric conversions apply as in the Vermont study, UK pottery workers (Winter et al., 1990; Cherry et al., 1995; McDonald et al., 1995; Burgess et al., 1997; Cherry et al., 1997; McDonald et al., 1997), and Chinese pottery workers (McLaughlin et al., 1992). In these studies the work to estimate past exposure was necessarily based on expert judgement and incomplete past measurement, and therefore subject to error. These studies all were essentially negative for a relationship between exposure to silica and lung cancer (the Chinese pottery workers exhibited a statistically non-significant higher rate in exposed compared with non exposed workers, but there was no general trend with exposure).

A subsequent report of a more detailed analysis of the results in the UK pottery workers, including a case-control study (Cherry et al., 1998), demonstrated an association between lung cancer risk and the mean concentration of crystalline silica to which subjects had been exposed. Curiously, risk was inversely related to duration of exposure and was not related to cumulative exposure. While this finding might indicate a causal association, a selection by social class into the dustier jobs cannot be ruled out. The cases smoked more than the controls, but adjustments for this were reported not to remove the association with silica concentration.
For cristobalite, the studies of diatomaceous earth workers Checkoway et al. (1993, 1996) relied on semiquantitative estimates of likely exposure, based mostly on expert judgement, and the results at present indicate, in workers not also exposed to asbestos, a statistically non-significant, suggestive, relationship between cristobalite exposure and lung cancer. In workers exposed to both asbestos and cristobalite, a relationship with cristobalite was still suggested after allowing for semiquantitative estimates of asbestos exposure (Checkoway et al., 1996). Possibly the new studies under way announced by Checkoway et al. (1996) will give a clearer result.

On the basis of the exposure-response studies alone, we do not think that there could be much disagreement that the evidence for an association between lung cancer and quartz exposure is not "beyond all reasonable doubt" and not "on the balance of probabilities"; not even suggestive. For cristobalite, there is a suggestion that there might be a relationship, subject to further investigation.

Could these studies have missed a genuine relationship? All exposure estimates include errors, more likely in retrospective studies, and it is recognised that errors in the estimates can obscure relationships (Heederik and Miller, 1988). In the above studies the estimates were reliable enough to demonstrate exposure-related risks of pneumoconiosis, silicosis and silicotuberculosis, but the detection of modest excess lung cancer risks would be expected to be more difficult than this, because of confounding with the high risks associated with smoking. This suggests that errors in the exposure estimates could have obscured a small risk or a weak relationship, if one existed. On the other hand the thoroughness of the coal miners study (Miller et al., 1997) is unlikely ever to be bettered. The negative result for these coal miners applies to a dust in which the proportion of quartz is generally less than 10% (though many of the cumulative exposures to quartz were high). Conceivably higher proportions of quartz in dust might represent a different health hazard, and study of a well defined subset of this population who experienced such conditions (Miller et al., 1998) may well be informative in the future.

Descriptive studies

Descriptive studies of ten silica exposed populations are reviewed here. Except for one (Dong et al., 1995) it is clear from the published reports that selection was relatively unbiased. Seven of the remaining nine studies showed raised SMRs for lung cancer, in the range of 1.27 overall to about 2 or 3 for selected subgroups. Studies of two other populations [goldminers in South Dakota (McDonald et al., 1978; Amandus et al., 1995) and Chinese pottery workers (Chen et al., 1992)] did not show statistically significant excesses, in comparison to the rates the authors thought appropriate.

The seven populations in which small excess risks of lung cancer were demonstrated were Danish stone (Guenel et al., 1989), Vermont granite (Davis et al., 1983), US crushed stone (Costello et al., 1995), Italian refractory brick (Merlo et al., 1991), and UK pottery workers (two populations) (Winter et al., 1990; Cherry et al., 1995; McDonald et al., 1995) and US diatomaceous earth workers (Checkoway et al., 1996).

Each of these studies can be criticised, on the grounds of unsuitable comparison populations, and/or lack of information on smoking habits and silica exposures, and possible exposure to other carcinogens, but together the results appear to provide evidence that silica exposed workers in general have an excess of lung cancer in comparison to general population rates. If the selection criteria did not introduce some other systematic bias, this would provide support for the a priori hypothesis that silica causes lung cancer. In view of the lack of support for the hypothesis from the exposure-response studies, it is necessary to consider what other systematic bias or exposure might cause an apparent excess of lung cancer in silica-exposed workers.

Suitability of comparative rates. We described earlier how lung cancer rates vary according to geographical region, socioeconomic status and smoking habit. We recognise that there could still be debate on the relative importance of socioeconomic status and specific occupational exposures, though the weight of the evidence seems to us to favour the lifestyle factors associated with social status. The observed geographical and class-related variations in lung cancer SMRs in Britain range from half to twice the overall national average. Presumably the degree of such variations in other countries would be influenced by the extent of the lifestyle variations there. For example excesses of lung cancer in Finland compared with Norway (Hakulinen et al., 1987), and Britain compared with Japan (Mizuno et al., 1989), seem largely explicable by differences in smoking habit. We should consider the reported lung cancer risks in silica-exposed workers against the background variation described earlier.

The standardised risks of lung cancer observed in silica-exposed workers (irrespective of whether the authors considered the rates to represent significant increases) range mostly from 0.82 to 2. Table 2 shows the reported SMRs (or risk ratio) for these populations, and for some small selected subgroups.

Most of the rates are greater than 1, but, apart from some higher rates in selected small subgroups, are within the range of variation which can be related to lifestyle, including smoking, and geographical variations. By the nature of their work, silica exposed workers are likely to be members of those social groups which have the higher background risks, including heavier smoking. On this evidence
alone it is difficult to differentiate between lifestyle or silica as the cause of the excess risks.

Interpretation of higher SMRs in selected small subgroups. Occasionally higher rates have been found in selected small subgroups. For example, as above, Merlo et al. (1991) found rates of 1.77 to 2 in subjects selected for long tenure (>19 years) and or long latency (>19 years). These groups were relatively small. The authors estimated that the maximum excess likely to be due to smoking was 1.8, arguing that the excess was therefore likely to be the result of occupation.

The SMR of 3.35 reported by Costello et al. (1995) represented only seven lung cancer deaths in a small group of granite workers selected by long tenure and long latency (undefined, presumably time from first exposure). Such small groups are open to chance events and age-related influences such as smoking. Curiously, the limited information available suggested that exposures to respirable silica were relatively low compared with other quartz-exposed workers (Kullman et al., 1995), and deaths from silicosis did not occur in this exposed group. Deaths from a group of causes comprising mostly chronic obstructive lung disease were increased in this exposure group, suggesting the possibility of an effect of smoking, or of dust in general. Smoking information was not available.

The study of Danish stone workers reported by Guenel et al. (1989) found Standardised Incidence Ratios for incident cases of lung cancer of 1.38 (and 2.0 and 1.81 after crude regional adjustment). The picture was complicated by large regional differences and indirect methods of calculating regional rates, but the rates in many subgroups were raised, and were particularly high in one small subgroup (7 observed, 0.9 expected). A difference of this order is unlikely to be explained by smoking, social or regional differences, though with such a small group a chance event is possible. The majority of these deaths were before 1940, and the prevalence of silicosis in these groups of workers is known to have been extremely high. Evidence is not presented on the extent to which the lung cancers occurred among the silicotic subjects, nor is information available on whether exposure to known carcinogens might have occurred.

In most of the studies there was little information on whether the smoking habits of the populations were atypical. Steenland and Brown (1995), and Merlo et al. (1991) present information which suggests that the S. Dakota miners, and Italian brick makers, respectively, did smoke more than the average, and that this could have increased the lung cancer rates somewhat. This provides very limited evidence that silica exposed workers in general could smoke more than the average.

Resolution of the uncertainty over the interpretation of these suggestive excesses in small groups would require much better information on smoking and silica exposure for these populations, and adjustment for lifestyle in the SMR comparisons. In practice there may not be a perfect comparative population for detecting small excess risks reliably, and this confirms the need for exposure response studies within populations of comparable socio-economic status.

Case register studies

Of the two case register studies quoted, that of N. Carolina dusty trades workers (Amandus et al., 1995, 1991, 1992) seems to us to be the stronger, though not flawless since misdiagnosis was frequent, and the representativeness of the study population is not established. The Finnish study does not inform the reader about the reliability of the diagnosis of silicosis (Partanen et al., 1994; Kurppa et al., 1986). Increased risks of lung cancer in subjects with silicosis could represent a direct effect of the silica exposure; a direct or indirect effect of silicosis; subjects with smoking related symptoms or lung functional defects may preferentially be included, and both these factors are associated with an increased risk of subsequent lung cancer (Peto et al., 1983; Miller et al., 1981).

There is insufficient evidence to distinguish between these mechanisms at present. The frequency of reports of excess lung cancer in these kinds of studies argues for an increased risk, at least as a secondary response to silicosis, but the possibility of selection bias remains as an opposing argument.
Evidence on whether any excess cancer risks are confined to those with silicosis

Only one of these epidemiological studies provided information on whether excess cancer risks were found only in subjects with silicosis. In the study of Chinese refractory brick workers (Dong et al., 1995) the excess cancer risks were indeed found principally in those with silicosis. Two other studies may be able to provide information on this question. The Vermont granite workers had chest radiographs, which if still available would enable a study. Chest radiographs, and readings, for the British coal miners are available. Some further studies of diatomaceous earth industry workers (Checkoway et al., 1999) appear to show that lung cancer risks might be related to silica exposure in the absence of silicosis, but the associations were suggestive only. Another recent report (Ulm et al., 1999) found no evidence of an excess lung cancer risk in silica-exposed workers without silicosis.

Dust composition

The mineralogical composition of workplace dusts that contain silica is typically very variable between and even within individual industries. In many industries, such as the quarry and mining industry, crystalline silica typically forms only a small proportion of workplace respirable dust. The proportions of quartz in the respirable dust in the reviewed studies would have been variable, and the non-quartz component differed greatly in composition, depending on the materials handled and the processing of these materials. In a number of the reviewed studies the incidence of disease has been examined in the context of dust exposure rather than specifically silica exposure. While in some of the descriptive studies (insofar as judgements can be made from the summary information provided) proportions of quartz were higher than in all the populations in whom exposure–response studies were performed, this was not so in every case. In some industries a positive descriptive study and a negative exposure response study were found for the same, or almost the same, population. There appears to be no evidence that the proportion of quartz in the dust has influenced the detection of risks.

Crystalline silica phase present

Silica can occur as one of several different crystalline polymorphs of which quartz is the most common on the earth’s surface. Cristobalite is a high temperature polymorph of silica and is the first mineral formed as molten silica cools. In most geological melts cristobalite is transformed to tridymite and then quartz on cooling, unless cooling is extremely rapid as in some volcanic rocks. Cristobalite also forms at Earth surface temperature during the transformation of amorphous biogenic silica (for example, diatomaceous earth) to crystalline silica. The mineral structure of quartz and cristobalite are very different and consequently the inversion of cristobalite to quartz only occurs over periods of millions of years.

Cristobalite is formed at high temperatures in workplace environments as a devitrification product of refractory ceramic fibres, in the refractory brick industry, during high temperature firing of pottery, and in the diatomaceous earth industry. Cristobalite is not a major constituent of the earth’s crust and would not be present in quarry or mine dusts or in dusts associated with stone cutting or crushing or in aggregate.

Cristobalite is widely considered to be more toxic than quartz, although there are relatively little data to allow comparison. The carcinogenicity of cristobalite in animals has not been extensively studied, to our knowledge. In rats, high doses of cristobalite injected into the lung cause fibrosis slightly more rapidly than quartz (King et al., 1953).

In the context of the studies under review, workers in the US diatomaceous earth and UK and other pottery industries may have been exposed to cristobalite. Workers in the US crushed rock, Vermont granite and Danish stone industries are very unlikely to have been exposed to cristobalite.

Particle toxicity

There is growing evidence that inhaled particles can have adverse health effects irrespective of chemical composition. Very large doses by inhalation of the low toxicity insoluble dust titanium dioxide in rats causes failure of lung clearance, chronic inflammation and fibrosis, and a few lung cancers (Lee et al., 1985). It is not known whether humans are equally susceptible to the effects of dust inhalation, but occupational exposure to a wide range of dusts is associated with the development of pneumoconiosis. Coal mine dust, for example, causes inflammation and fibrosis in man, but not lung cancer. Little other information is available which would distinguish between the effects of dust in general and its components.

OPPOSING CASES FOR AND AGAINST THE CARCINOGENICITY OF SILICA

1. For: silica is a carcinogen in rats (summarised by Pilkinson et al., 1996);

Against: silica may cause cancer in rats (less in males than females), but it does not in other species; the rat generates lung cancers from over-loading doses even of a low toxicity dust such as
titanium dioxide; so the rat may not be a good model for human risks.

2. For: subjects with silicosis have increased risks of lung cancer;

   Against: the findings may be the result of selection and diagnostic biases; also an excess of lung cancer in silicotics, if accepted, does not necessarily mean that silica is the direct cause: it may be a secondary effect.

3. For: many silica-exposed populations have increased lung cancer rates, and it is unlikely that in all cases this is the result of social differences or smoking habit;

   Against: social differences and smoking could easily be the cause of many of the excess risks. The larger excess risk in the Danish stone workers might be the result of a statistically unusual chance, and needs confirmation by other studies. It could also indicate a secondary effect in those with silicosis, or there may have been exposures before the 1940s not taken into account.

4. For: an association with exposure to an agent should not be rejected merely because exposure-response studies are negative, since errors in exposure estimates can weaken the power of such studies to detect effects. In most of these studies the exposure estimates are unreliable, and the British coalminers study, though reliable, is relevant only to dusts with low proportions of quartz;

   Against: the exposure-response studies were powerful enough to demonstrate effects of silica on pneumoconiosis and silico-tuberculosis, so the negative results for lung cancer are probably correct, or at least can have missed only a weak association or small risk.

5. For: the US diatomaceous earth industry worker study did suggest an exposure-response relationship with cristobalite, and asbestos exposure does not appear to have influenced this result much;

   Against: it should not be assumed that cristobalite has the same biological activity as quartz, since its crystalline structure, surface properties and fibrogenicity are different; also the epidemiological study result did not reach statistical significance.

   **RESOLUTION OF THE UNCERTAINTIES**

1. It would be helpful if the regulatory bodies were to seek conformity on the strength of proof required for attribution of human carcinogenicity, and to clarify what matters should be considered to rule out chance, bias and confounding with reasonable confidence.

2. Descriptive studies of silica-exposed populations must include data on the distribution of smoking habit, and comparisons must be with populations of similar smoking habit (or in which smoking habits are known and can be compared), socioeconomic status and geographical area.

3. Exposure–response studies are needed, in which the exposure estimates are reliable, in populations exposed to quartz comprising relatively high proportions by mass in the respirable dust, say, greater than 10%, and without confounding exposures (or with good data on these). Smoking information for individuals is important. Possibly this could be addressed by a cohort study of the expanded population of Vermont workers described by Costello and Graham (1988), with improvement of the exposure estimates by applying particle count/gravimetric conversion factors separately by occupational group. The average proportion of quartz in the dust was about 10% (Davis et al., 1983; Eisen et al., 1984) but some occupations are likely to have had much higher proportions than this. There may be other populations with adequate exposure data where a part retrospective, part retrospective study would give the best opportunity for a good study. Of course, controlling quartz concentrations to current accepted safe limits (designed to prevent silicosis) may eliminate any future risks, and while this would make risk estimation for future exposures impossible, in terms of risk prevention this would be a highly desirable outcome. We recently reported (Miller et al., 1998) excess respiratory morbidity (silicosis) in one colliery population exposed to unusually high proportions of quartz in the coalmine dust. Future study of mortality patterns of this population will be informative.

4. Exposure–response studies of exposed populations, with reliable exposure estimates, if chest radiological surveillance has been conducted regularly, would enable any exposure-related risks to be examined in subjects without evidence of silicosis.

5. Quantitative comparisons in rats of the possible carcinogenicity of cristobalite with that of quartz, could assist the interpretation of the relevance of the epidemiological studies of workers exposed to cristobalite, to human risks of exposure to quartz.

   **CONCLUSION**

We have chosen not to give an opinion in this paper on the carcinogenicity of quartz, but hope
that the reader will find this review of the strengths, weaknesses and conflicts in the evidence helpful in reaching such conclusions as the evidence justifies.

Acknowledgements—We gratefully acknowledge the support of EUROSIL for this independent review.

REFERENCES


gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of follow-up. American Journal of Industrial Medicine 27, 217–229.


