



---

CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE  
VICE PRESIDENT  
CHEMSTAR

March 10, 1998

**VIA FAX & FEDEX**

Dr. C. W. Jameson  
National Toxicology Program  
Report on Carcinogens (MD EC-14)  
P.O. Box 12233  
Research Triangle Park, NC 27709

**Re: NTP Review of Crystalline Silica**

Dear Dr. Jameson:

The Chemical Manufacturers Association (CMA) Crystalline Silica Panel is pleased to provide the National Toxicology Program (NTP) with information relevant to its consideration of the potential carcinogenicity of crystalline silica. We enclose a review of crystalline silica epidemiology studies recently completed by the Institute of Occupational Medicine (IOM). In addition, we will be sending shortly, upon its completion, another review of the epidemiology studies by Dr. John Gamble of Exxon Biomedical Sciences. We urge NTP's close consideration of both reviews, as we believe the epidemiology data do not provide sufficient evidence to support an NTP finding that crystalline silica is "known to be a human carcinogen."

**NTP BACKGROUND**

NTP listed respirable crystalline silica as a substance "reasonably anticipated" to be a carcinogen in its Sixth Annual Report, at pp. 357-64 (1991). NTP's Summary found "sufficient" evidence of the carcinogenicity of respirable silica in animals, but agreed with the 1987 International Agency for Research on Cancer (IARC) conclusion that the human evidence was "limited." NTP found the data limited (at p. 360) because "[o]nly rarely...were data obtained on smoking and on potential confounding exposures and the comparability of the referent population assured."

NTP's criteria for a listing as a "known human carcinogen" require a finding of "sufficient evidence from studies in humans which indicates a causal relationship between exposure to the...substance...and human cancer." "Sufficient" evidence is distinguished in the criteria from "limited" human evidence that does not warrant a "known" carcinogen listing; "limited" human evidence exists when a "causal interpretation is credible but...alternative explanations such as chance, bias or confounding factors could not adequately be excluded."



INNOVATION, TECHNOLOGY AND RESPONSIBLE CARE® AT WORK

1300 WILSON BLVD., ARLINGTON, VA 22209 • TELEPHONE 703-741-5600 • FAX 703-741-6091



By contrast, epidemiology studies reported to date on crystalline silica do not present "sufficient" evidence because:

- they are not consistent with a finding of an increased risk of lung cancer;
- risk estimates are generally low with standardized mortality ratios less than 150;
- the studies are confounded by other lung carcinogens, notably tobacco, which are not controlled adequately in the design of the studies; and,
- exposure response gradients have not been studied adequately and, where they have been studied, generally a monotonic increase risk of lung cancer with exposure is not seen.

The Panel believes that chance, bias and confounding factors cannot be excluded adequately and the epidemiology studies are not convincing to conclude that silica causes lung cancer in humans. Therefore, NTP should not change its current listing for crystalline silica.

NTP's plan to reconsider crystalline silica has been prompted by IARC's reclassification of silica last year to Group 1, "carcinogenic to humans." It is significant that the IARC reclassification occurred only after a sharply divided vote of its expert committee and that the reclassification was carefully (and in a manner unusual at IARC) circumscribed. Of the nineteen scientists on the IARC Working Group, only ten supported the reclassification (seven voted against the reclassification, one abstained, and one was not present). And, the reclassification was based on an evaluation (all emphases added) that found "sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the forms of quartz or cristobalite *from occupational sources*." That evaluation was based on assessment of "inhalation resulting *from workplace exposures*." The Working Group further limited its evaluation by noting:

In making the overall evaluation, the Working Group noted that carcinogenicity was *not detected in all industrial circumstances* studied. Carcinogenicity may be dependent on inherent characteristics of crystalline silica or external factors affecting its biological activity or distribution of its polymorphs.

Thus, even the far from unanimous IARC evaluation included qualifiers not typically found in the IARC's evaluations. It is, therefore, particularly important for NTP to conduct its own careful assessment and not merely rely on the IARC reclassification.

## **THE IOM REVIEW**

As noted above, the Panel has enclosed a recent review by the IOM. Drs. C.A. Soutar, A. Robertson, B.G. Miller and A. Searl of IOM and Dr. J. Bignon of the University of Paris, in their "Epidemiologic evidence on the carcinogenicity of silica: factors in scientific judgement," review the same epidemiologic studies reviewed by IARC (plus one more recently published

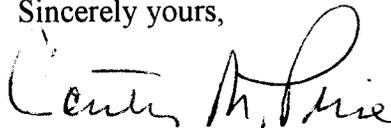
study of British coal miners). The IOM review (at pp. 12-13) presents both the evidence "for" and "against" a conclusion that silica is carcinogenic to humans.

The IOM authors do not present an overall conclusion (p. 14). They note (p. 13) that one reason why they do not reach a conclusion is that such decisions depend upon the "strength of proof required for attribution of human carcinogenicity." NTP criteria require "sufficient" evidence of a "causal relationship." The Panel believes that the epidemiology studies on crystalline silica do not provide "sufficient" evidence.

\* \* \* \* \*

The Panel will be sending to NTP shortly the review of the silica epidemiology studies by Dr. Gamble, who was an observer at the IARC Working Group meeting on silica. Further, the Panel requests that it be kept informed of the internal and external review process regarding crystalline silica as the Panel intends to take every opportunity to provide further input through written submissions and oral presentations. If we can provide any further information in the interim, or if you have updates to share with us, please contact Elizabeth Festa Watson, Panel Manager, at 703-741-5629, or [elizabeth\\_watson@mail.cmahq.com](mailto:elizabeth_watson@mail.cmahq.com).

Sincerely yours,



Courtney M. Price  
Vice President, CHEMSTAR

Enclosure

INSTITUTE OF  
OCCUPATIONAL  
MEDICINE



**IOM**

**TECHNICAL MEMORANDUM  
SERIES**

***Epidemiological evidence on the  
carcinogenicity of silica:  
factors in scientific judgement***

*CA Soutar, A Robertson, BG Miller, A Searl  
Institute of Occupational Medicine*

*J Bignon  
University Paris Val de Marne*

*December 1997  
IOM Report TM / 97 / 09*

Report No. TM/97/09

**INSTITUTE OF OCCUPATIONAL MEDICINE**

**Epidemiological evidence on the carcinogenicity of silica:  
factors in scientific judgement**

by

CA Soutar, A Robertson, BG Miller, A Searl, J Bignon

**FINAL REPORT ON RESEARCH CONTRACT**

**Institute of Occupational Medicine  
8 Roxburgh Place  
Edinburgh EH8 9SU**

**Tel: 0131 667 5131  
Fax: 0131 667 0136**

December 1997

## CONTENTS

	Page
<b>OVERVIEW</b>	(i)
<b>1. INTRODUCTION</b>	1
<b>2. LOGICAL FRAMEWORK FOR THIS REVIEW</b>	3
2.1 Degree of proof required	3
2.2 Evidential power of study design	3
2.2.1 Exposure-response studies	3
2.2.2 Ecological studies	3
2.2.3 Case register studies	4
2.2.4 An example	4
2.3 Secondary effects	4
2.4 Classification rules for carcinogens; contrasts Between the IARC and EU rules	5
2.5 Confounding	5
<b>3. REVIEW</b>	7
3.1 Exposure-response studies	7
3.2 Ecological studies	8
3.2.1 Suitability of comparative rates	9
3.2.2 Interpretation of higher SMRs in selected small subgroups	9
3.3 Case register studies	10
3.4 Evidence on whether any excess cancer risks are confined to those with silicosis	10
3.5 Dust composition	10
3.6 Presence of cristobalite	11
3.7 Mineral dust in general	11

	<b>Page</b>
<b>3.8</b> <b>Opposing cases for and against the carcinogenicity of silica</b>	11
<b>3.9</b> <b>Resolution of the uncertainties</b>	12
<b>4.</b> <b>NOTES ON THE PAPERS</b>	15
<b>4.1</b> <b>Gold miners in South Dakota</b>	15
4.1.1    Exposures	15
4.1.2    SMRs, comparisons with US rates	15
4.1.3    SMRs, comparisons with exposure and other historical indices	15
<b>4.2</b> <b>Danish stone industry workers</b>	16
<b>4.3</b> <b>Vermont granite shed and quarry workers</b>	17
<b>4.4</b> <b>US crushed stone industry workers</b>	18
<b>4.5</b> <b>Chinese refractory brick workers</b>	19
<b>4.6</b> <b>Italian refractory brick workers</b>	20
<b>4.7</b> <b>UK pottery workers</b>	20
<b>4.8</b> <b>US diatomaceous earth industry workers</b>	21
<b>4.9</b> <b>Chinese pottery workers</b>	23
<b>4.10</b> <b>Cohorts of registered silicotics in North Carolina and Finland</b>	24
<b>4.11.</b> <b>Mortality of coalminers in Britain</b>	24
 <b>ACKNOWLEDGEMENTS</b>	 27
 <b>REFERENCES</b>	 29

(i)

## OVERVIEW

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 review 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) ecological 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.

Ecological 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. An exposure-response study of cristobalite is suggestive of a positive relation. Both sets of evidence have weaknesses. There are uncertainties on whether the excess risks in the ecological 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 no doubt by variations between experts in the required strength of proof.

The main scientific uncertainties in the evidence are:

1. Whether, in the ecological 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,

(ii)

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 dust in which the proportion of quartz in the dust is usually less than 10%.

Exposure-response studies, with high quality exposure estimates, in populations exposed to respirable dust of which crystalline silica comprises more than 10% are needed;

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.

## 1. INTRODUCTION

The reasons for the extended debate and divided opinions on the question of the human carcinogenicity of crystalline silica (IARC, 1987; Goldsmith, 1994; McDonald, 1989; Weill and McDonald, 1996; Pairon, 1991; Pilkington *et al*, 1996) 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 data set, and indicate where scientific investigation or policy clarification might help to resolve the issue.

Rather than review the entire relevant literature (again, Pilkington *et al*, 1996) we focus on those studies which a recent IARC working group 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. They 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 very recently prepared by our own colleagues (Miller *et al*, 1997) which is particularly informative because it is based on a large long-term prospective study which included a uniquely detailed programme of measurements of exposures to dust and quartz.



## 2. LOGICAL FRAMEWORK FOR THIS REVIEW

We constructed a logical framework for identifying areas of uncertainty which give opportunities for differences of interpretation or opinion. The components of this framework included: differences in the implications of the IARC and EU classification rules; 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; 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.

### 2.1 Degree of proof required

Neither the IARC (1994) nor EU (1993) guidelines for classification of carcinogens specify the degree of proof required for conclusions from human studies. Advice is limited to 'where a causal relationship can be established between exposure and cancer in humans' (IARC), and 'sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer' (EU). This is in contrast to the detailed and prescriptive guidance provided on the interpretation of animal studies.

As an illustration, such phrases as 'beyond (all) reasonable doubt', or 'on the balance of probabilities' would give guidance on the degree of proof required.

### 2.2 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 prove association, from which arguments can be developed for causation in some cases.

#### 2.2.1 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 an exposure-response study design. These studies are 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.

#### 2.2.2 Ecological studies

A lesser degree of certainty is provided by ecological (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 (Environmental Protection Agency, 1996; HMSO, 1991), and confident attribution to one specific cause requires elimination of other potential causes. In practice, smoking is invariably present as a potential confounder.

### 2.2.3 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, 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 functional deficits (Miller *et al*, 1981) in smokers identify 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.

### 2.2.4 An example

An example illustrates some of these points well. Coalminers, obviously, have historically an excess of pneumoconiosis, and this is easily demonstrated by ecological 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).

## 2.3 Secondary effects

Inhalation of quartz results in chronic inflammation and fibrosis in the lungs (Donaldson *et al*, 1990; Donaldson *et al*, 1988; Donaldson *et al*, 1992), and these processes may result in an increased risk of cancer. Rats with silica-induced lung cancers appear always to have fibrosis (Muhle *et al*, 1989; Muhle *et al*, 1996). 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?

Apart from the philosophical argument on direct and indirect causation, one way of resolving this is to examine whether the risks of cancer in subjects without silicosis are demonstrably related to amount of exposure to quartz.

An additional 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.

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

The IARC (1994) and EU (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 (eg. 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.

#### 2.5 Confounding

Confounding is 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 studies in this review were chosen by the IARC working group for their relative absence of other known confounding occupational exposures, but background variations in lung cancer in the general population should be considered.

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. The table below shows standard 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 (HMSO, 1986). The social class classification is a grouping of men according to the work they perform, and the definitions are given at the foot of the table. 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 (OPCS, 1995) does not present this information).

Social class							
Region	All men	I	II	III N	III M	IV	V
Great Britain	100	43	62	78	117	125	171
Wales	89	43	60	74	92	111	202
North	131	54	74	90	147	164	237
Yorkshire and Humberside	108	38	71	91	119	138	178
East Midlands	90	36	61	76	98	116	160
East Anglia	80	44	57	66	95	92	136
South East	87	41	59	74	112	113	140
South West	77	38	53	65	94	100	137
West Midlands	107	45	62	81	130	128	187
North West	120	45	74	91	142	150	215
Scotland	122	58	73	98	152	142	210

Social class definitions; I professional etc., II intermediate, III N skilled non-manual, III M skilled manual, IV partially skilled, V unskilled.

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).

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, 1997).

Smoking habit varies by occupation (OPCS, 1995; Fox and Adelstein, 1978; Sterling and Weinkham, 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.

### 3. REVIEW

We reviewed the selected papers according to the above framework, and append brief notes on each paper in the Appendix. Here we present a review of the scientific issues.

#### 3.1 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 prospective studies have been conducted, and how weak are the exposure data in most study populations.

The only relevant prospective studies of which we are aware are those of the Vermont granite workers (Davis *et al*, 1983), which commenced in the 1930s, and a large study of coal miners in Britain (Miller *et al*, 1977) 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*, 1977) was also negative for a relationship between silica exposure and lung cancer. It included immensely detailed prospective 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.

Retrospective exposure-response studies 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 non-statistically significantly higher rate in exposed compared with non exposed workers, but there was no general trend with exposure).

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 non-statistically

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). This result is suggestive of a cancer risk associated with cristobalite. 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, 1997). The thoroughness of the coal miners study (Miller *et al*, 1977), is unlikely ever to be bettered. In these 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. The negative result for the coalminers applies to dust in which the proportion of quartz is generally less than 10%. Conceivably higher proportions of quartz in dust might represent a higher health hazard. Within this large population of coalminers is a colliery population in some members of which silicosis is known to have developed as a consequence of unusual exposures to dust with high concentrations of quartz (Seaton *et al*, 1981), but the duration of follow up at present is insufficient for any effects on mortality to be apparent.

### 3.2 Ecological studies

Ecological studies of ten silica exposed populations are reviewed here. Except for one (Dong *et al*, 1995) 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 (Amandus and Costello, 1991a), 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.

### 3.2.1 Suitability of comparative rates

We described earlier in this report 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 are at maximum about 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 an excess 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 in the Introduction.

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

Source	SMR
Amandus and Costello, 1991a	1.29 (3.35 in those with long tenure and long latency, but this group was extremely small)
Checkoway <i>et al</i> , 1996	1.34 (after exclusion of possibly asbestos-exposed workers)
Chen <i>et al</i> , 1992	0.58 and 0.78
Cherry <i>et al</i> , 1995	1.7 compared with national rates and 1.28 compared with local rates
Costello and Graham, 1988	1.15, 1.27 and 0.82
Dong <i>et al</i> , 1989	1.49 (risk ratio)
Guenel <i>et al</i> , 1989	1.38 (2.0 and 1.81 after crude regional adjustment) (Standardised Incidence Ratios)
Merlo <i>et al</i> , 1991	1.51 (1.77 to 2 in subjects with long tenure and long latency)
Steenland and Brown, 1995	1.13
Winder <i>et al</i> , 1990	1.3

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.

### 3.2.2 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 likely to be the result of occupation.

The SMR of 3.35 reported by Amandus and Costello (1991a) represented only seven lung cancer deaths in a small group selected by long tenure and long latency. Such small groups are open to chance events, particularly since long tenure and long latency are likely to have been associated with age. Smoking information was not available.

The study of Danish stone workers reported by Guenel *et al* (1989) found Standardised Incidence Ratios (SIR) for 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 socioeconomic status.

### 3.3 Case register studies

Of the two case register studies quoted, that of N. Carolina dusty trades workers (Amandus *et al*, 1995; 1991b; 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 reliability of 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 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 very 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. Possibly these kinds of studies may never be capable of confirming an increased risk beyond doubt.

### 3.4 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.

### 3.5 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. While in some of the ecological 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 ecological study and a negative exposure response study were found for the same, or almost the same, population. Thus we do not find evidence that the proportion of quartz in the dust has influenced the detection of risks.

### 3.6 Presence of cristobalite

Cristobalite is a high temperature polymorph of silica and is the first mineral formed as molten silica cools. In most geological melts cristobalite would be 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, in the diatomaceous earth industry and resulting from high temperature treatment of vegetable matter such as rice husks. 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.

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.

The carcinogenicity of cristobalite in animals has not been studied, to our knowledge. In rats, high doses of cristobalite injected into the lung cause fibrosis slightly more rapidly than quartz (Kind *et al*, 1953).

### 3.7 Mineral dust in general

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.

### 3.8 Opposing cases for and against the carcinogenicity of silica

1. **For:** silica is a carcinogen in rats (Pilkington *et al*, 1996);  
**Against:** silica may cause cancer in rats (less in males than females), but it does not in other species (Pilkington *et al*, 1996); 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.

### 3.9 Resolution of the uncertainties

- 3.9.1 It would be helpful if the regulatory bodies were to indicate the strength of proof required for attribution of human carcinogenicity.
- 3.9.2 Ecological 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.
- 3.9.3 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; Bagley *et al*, 1996) 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 prospective 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.
- 3.9.4 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.
- 3.9.5 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 any overall conclusions 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.

## 4. NOTES ON THE PAPERS

### 4.1 Gold miners in South Dakota

Steenland and Brown (1995) recently reported an extended follow-up study of the mortality of gold miners in South Dakota, who worked underground for at least one year between 1940 and 1965. The work extended and built upon several earlier studies of mortality and exposure estimation (McDonald *et al*, 1978; Gillam *et al*, 1976; Brown *et al*, 1986), and reasonably detailed estimates of individual exposures were possible (Gillam *et al*, 1976). The study compared cause-specific standardised mortality ratios (SMRs) with local and national rates, and with estimated exposure.

#### 4.1.1 Exposures

The authors describe the exposures to crystalline silica as high, especially prior to the 1950s. The silica content of respirable dust was estimated (very approximately) in the past to be 13% by mass (Gillam *et al*, 1976), but no information is given on variations between occupations or over time. Pre 1950 silica exposures were estimated to range from one to three times current standards, though still somewhat less than other occupational cohorts of the time. The method of conversion from particle counts to gravimetric measures of concentration is based on the Vermont study (see later). This introduced misclassification errors in the Vermont study and may be even less appropriate for conditions in these mines. Thus the exposure estimates are very approximate. Some exposure to 'non-asbestiform' fibrous minerals also occurred, but concentrations were said to be very low and confined to one mine. There appears to be some disagreement on the classification of these fibres. In earlier publications they were called asbestiform (Zumwalde *et al*, 1981), even called amosite (Gillam *et al*, 1976), and they look like asbestos in the photographs (Zumwalde *et al*, 1981). Exposures were, however, high by current standards, and, like the dust concentrations, may have been much higher in the 1940s. Exposures to arsenic and radon were noted, but concentrations were also low in the 1970s. No attempt is made to quantify these pre 1950. By analogy with silica, they may have been in excess of the OSHA limit.

#### 4.1.2 SMRs, comparisons with US rates

The authors discuss the possible unsuitability of local and South Dakota mortality rates for comparison, and choose to emphasise the comparisons with US rates. In their view conclusions about the findings on causation are best based on biological plausibility and disease trend with calendar time or estimated exposure rather than point estimates based on any set of referent rates. In comparison with US rates lung cancer SMR was 1.13, an excess which could have arisen by chance, and was within the range predicted by the smoking habits of the group.

#### 4.1.3 SMRs, comparisons with exposure and other historical indices

There was no consistent or statistically significant relationship between SMR for lung cancer and cumulative dust exposure. A marginally higher SMR in the highest exposure group

compared with the others was not supported by a general trend with exposure, and a nested case-control study showed no association of lung cancer with cumulative exposure.

The authors conclude that 'lung cancer rates showed some elevation but did not exhibit a positive exposure-response trend.....the association between cumulative silica exposure and lung cancer was generally negative.'

By contrast strong, and anticipated trends with exposure were shown for silico-tuberculosis and pneumoconiosis, confirming the reasonable reliability of the exposure estimates. In spite of this it must be noted that the exposure estimates were very approximate, and a weak association with lung cancer, if it existed, might have been missed.

No information is available on any differentials in smoking habit between the occupational groupings used to estimate exposure, and it is not possible to say whether smoking could have obscured any effect of occupation.

#### 4.2 Danish stone industry workers

Guenel *et al* (1989) reported a study of cancer incidence among 2071 Danish stone industry workers, including skilled stone cutters working with granite and sandstone, and unskilled workers in the stone cutting, roads and construction industries. Compared with national rates, the lung cancer standardised incidence ratio (SIR) was slightly raised at 1.38 for the skilled workers, on the border of statistical significance, but low (not significantly) at 0.72 for the unskilled workers. There were only 68 lung cancer deaths in total.

The authors recognised that as a standard of comparison national rates were not ideal, because the study population was predominantly from selected regions (Copenhagen and Bornholm). Local Bornholm rates were said to be too unstable to be reliable, and the national rates were therefore adjusted by factors derived from a study in the 1970s of regional variation of cancer incidence and smoking habit (Carstensen and Jensen, 1986). These adjustments resulted in some large changes to the estimated regional rates used for comparison, and the estimated SIRs for lung cancer derived from these were higher (2.0 for skilled and 1.81 for unskilled workers) and these differences were statistically significant.

Use of regional variation rates in this way assumes that regional variation in the 1970s adequately represents the variation throughout the period of the study (1943 to 1984). The predicted cancer rates show great regional variation, but the results of the study are only in part sensitive to the regional adjustments, and the results suggest an increased risk of lung cancer in stone workers.

The authors did not identify any other known or suspected carcinogen in the workplace. Roadstone plants in the UK have bitumen coating plants, previously tar plants, which might have been another source of exposure to carcinogens in the past for these workers but not for the skilled stone cutters.

The authors also attempted to investigate whether the adjustment for smoking habits by region introduced distortions of the SMRs for bladder cancer, and found this did not induce the striking differences seen for lung cancer. This is a suggestive argument that the lung cancer findings are not therefore the result of smoking differences, but not conclusive because the exposure-response relationship for lung and bladder cancers are not quantitatively the same

(Williams and Horm, 1977), in fact the bladder cancer rates were generally raised, though not statistically significantly, suggesting that smoking rates may have been high. There was no information on smoking habit.

A very high rate was found in Copenhagen sandstone skilled stonecutters (7 observed, 0.9 predicted), though this in a very small group. Some small earlier studies of skilled stone cutters in Copenhagen had shown very high frequencies of silicosis.

The highest risk was in skilled workers using granite and sandstone (mostly the former). Lower risks were found in skilled and unskilled workers using granite and flint, but past exposures were poorly characterised.

The results do seem to suggest an excess in these workers, but the major risks seem to have been before 1940, when possibly exposures might have been much higher, or conceivably to other agents, since these men would presumably have been working during the 1920s and 30s or earlier.

#### 4.3 Vermont granite shed and quarry workers

Costello and Graham (1988) studied the mortality of Vermont granite workers who had been employed between 1950 and 1982, extending the population studied by Davis *et al* (1983). The cohort included men who had been exposed to high levels of granite dust prior to 1938-1940. Overall, Costello and Graham found lung cancer rates to be within predicted limits (SMR 1.15), but slightly raised (SMR 1.27) in workers in the granite sheds, though not in quarry workers (SMR .82). There were too few quarry workers to act as a reliable comparison group. The excess in the shed workers was in men who had been exposed to high dust concentrations in the past, and who had long tenure and long latency, but such men could also have smoked longer.

Lung cancer did not occur in non-smokers in this population, and study of a non-random subset indicated that, among men hired before 1930, 68% had pre-mortem evidence of silicosis; of those hired between 1930 and 1939, 26%. Deaths from silicosis and tuberculosis were extremely high (SMRs of 9.99 and 8.94 respectively for workers hired before 1930). The smoking habits of these men in earlier years are not known, but it is known that granite workers active in the 1970s smoked slightly more than US white males in 1970 (Sterling and Weinkham, 1976; Graham *et al*, 1981).

The study confirmed the Davis *et al* (1983) findings on tuberculosis and silicosis, but the lung cancer findings had not been demonstrated by the earlier study. Nor did Davis *et al* (1983) demonstrate any consistent relationship between lung cancer and extremely detailed estimates of cumulative exposure (exposure-response study). However, conversion from historic particle count to gravimetric dust measurements was necessary, and the data presented demonstrate poor correlation overall between the two types of measurement when performed side-by side, which the conversion factors do not represent well. This introduced considerable misclassification errors into the exposure estimates. In our experience with studies of quarry workers, different occupations within the same quarry are exposed to dusts with different quartz contents. It might have been better to have used separate factors for each occupational group because of less variability of particle size distribution and composition within each occupation. The proportions of quartz may also vary with time. In addition to poor correlations between particle count and gravimetric estimates, some of the

data are very sparse, and many of the measurements are at or close to detection limits. Extrapolating back in time from these estimates to higher concentrations seems unreliable.

The quartz content of the dust was about 10% by mass, on average (Davis *et al*, 1983; Bagley *et al*, 1996), but we suspect that there was substantial variation between occupational groups.

Exposure-response relationships were not examined in the recent study. In view of this and the conflict with the results of the Davis *et al* (1983) study, it would be premature to conclude from this study that the increased lung cancer risk in granite shed workers is the result of exposure to quartz. A cohort exposure-response study of the population reported by Costello and Graham, if feasible, would be desirable, with particle count conversion factors separately for each occupational group.

Some supplementary evidence suggested that there may have been a high prevalence of silicosis among those who subsequently contracted lung cancer. Exposure was to granite dust only. Insufficient information on smoking was available to judge whether smoking differentials could explain the slight excess of lung cancer mortality in the granite shed workers overall. Excess in workers hired before 1930 has not been distinguished from an effect of smoking in these analyses.

#### 4.4 US crushed stone industry workers

Amandus and Costello (1991a) investigated the mortality of 3246 US workers employed in the crushed stone industry, including limestone, traprock and granite. Quartz was found to be a component of dusts to which workers were exposed in all three parts of the industry; comprising 37%, 11% and 15% by weight of the personal respirable samples collected at granite, limestone and traprock operations, respectively. Mean respirable concentrations of quartz were 0.06, 0.04 and 0.04 mg.m<sup>-3</sup>, respectively, based on a single round of dust measurements (Amandus and Costello, 1991a). Though the percentage of quartz in the respirable dust was highest in the granite operations, the highest maximum quartz concentration recorded was no greater than 0.28 mg.m<sup>-3</sup> (Kullman *et al*, 1995). Very limited use was made of the available exposure measurements (Kullman *et al*, 1995), though our inspection of the available data does not suggest any relationship between exposure and risk.

Compared with US national rates, lung cancer mortality overall was slightly elevated (SMR 1.29), but not statistically significantly. An increased risk was more apparent in those with more than 10 years tenure in the industry, and more than 20 years latency, though these differences did not reach statistical significance. These small excesses are not necessarily associated with occupation, since an excess of lung cancer from any cause could easily occur predominantly in older men, who would be expected to have longer tenure and longer latency on average. However there was a differential between the parts of the industry: the excess in workers with long latency was most marked in the granite workers (SMR 3.35, statistically significant; but only 7 deaths); was only suggestive in the limestone workers, and not apparent in the traprock workers. Smoking information was not available.

Deaths with pneumoconiosis were infrequent; four cases, three from limestone, and one traprock, operation. There were twenty deaths in the category 'pneumoconiosis and other respiratory disease', which on inspection included chronic obstructive lung disease (15), chronic interstitial pneumonia (2), lung abscess and empyema (1 each), but not

pneumoconiosis. Rates were elevated in granite workers with long latency (only three cases in this group), but these deaths were not related to long tenure.

These findings are hard to interpret. The association with work in granite, rather than limestone or traprock, possibly suggests an association with this work, but some features seem inconsistent with a causative association between exposure to granite dust and cancer. We interpret the average quartz concentrations which were reported (Kullman *et al*, 1995) to be relatively low in relation to other dusty industries historically, even though they sometimes breached more recent NIOSH recommended limits. The absence of deaths from silicosis in the granite workers would be consistent with reasonably low exposures. The increased risk of deaths from chronic airflow obstruction in granite workers, but lack of association with tenure, tend to suggest a cause other than dust (such as smoking), directly for obstructive lung disease, and by implication for lung cancer. On the other hand gastrointestinal and urinary cancers (stomach and bladder cancers were not studied specifically) were not unduly frequent. Information on smoking habits was not available.

Lack of smoking information and uncertainties about suitability of national rates as basis of comparison reduce power. A suggestive difference in lung cancer risk between granite and other stone workers might be the result of confounding with age, but provides some argument that the small excess in granite workers may be related to occupation. This is counterbalanced by lack of any deaths from pneumoconiosis in granite workers, and lack of relationship of chronic obstructive lung disease with tenure, suggesting low exposures and possibility of other reasons for cancer excess besides dust. Conclusion: mildly suggestive of greater risk in granite workers compared with limestone and traprock workers.

No information available which would enable a judgement on whether differences in smoking habits could account for findings, but magnitudes of the differences are within the range of smoking effects.

#### 4.5 Chinese refractory brick workers

Dong *et al* (1995) studied six thousand refractory brick workers who were subjects of periodic health examinations for silicosis between 1963 and 1985. Entry to the study was restricted to those employed before 1962 in manufacturing silica or clay brick. The authors do not describe how workers were selected for the periodic health examinations, or the completeness of response, or whether subject selection could have been influenced by the health of the individuals. Without this information it is not possible to reach a conclusion on whether the population selection was biased towards the inclusion of subjects with respiratory symptoms. Unlike the brick workers, the steel workers chosen as the comparison population were not stated to be receiving periodic medical examinations. There was therefore a potential for bias towards more sensitive diagnosis of lung cancer in the brick than in the steel workers (standardised risk ratio 1.49). The exposures are not described; there is a passing comment that exposure was to pure silica dust without the complications of other carcinogens as seen in other industries. They do look at relationship between cancers and time in terms of latency - but not obviously as a surrogate for exposure.

In spite of these defects some conclusions from the study are possible. A large number of the brick workers had silicosis, and lung cancer rates among them were higher than in the brick workers without silicosis. If the silicotics were receiving more regular medical surveillance, or had more ready access to medical diagnostic facilities than the non-silicotics,

a potential bias in diagnosis is present. No information is presented on the frequency of medical examinations according to silicosis status, for example. Lung cancer was twice as likely to be recorded as the cause of death in silicotics as in non-silicotics. Whether an excess of this size could result from differences in diagnostic accuracy would be influenced by the availability of medical resource, and diagnostic methods.

#### 4.6 Italian refractory brick workers

Merlo *et al* (1991) and Puntoni *et al* (1988), reported studies of a population of refractory brick workers in Italy. The more recent, and larger, study (Merlo *et al*, 1991) was of a thousand men working in the factory between 1954 and 1977. Mortality comparisons were made with Italian national rates. Lung cancer SMR was 1.51, on the borders of statistical significance. Higher, and statistically significant excess lung cancer rates were demonstrated when subgroups of men were examined, who had worked in earlier years, or with long employment or long latency (SMRs 1.77 to 2). This could reflect longer exposure to quartz, or to smoking or other agents.

Smoking histories were not generally available, but analysis of limited data indicated that these workers may have smoked more than the general population. A simulation performed by the authors suggested that the excess lung cancer mortality which could be attributed to smoking was at maximum 1.8%, averaging across all adult ages.

Some historical information on dust and silica concentrations was available. Puntoni *et al* (1988) reported that the silica in the raw material was in the form of amorphous silica and alpha quartz, and quartz was measured by X-ray diffraction from 1973. Respirable dust was collected by an elutriator. The main survey was in 1975 - 51, comprising respirable, fixed point dust samples from 45 locations, representing nine occupational groups. Crystalline silica concentrations (presumably quartz) were well in excess of  $0.1 \text{ mgm}^{-3}$ . The process description suggests that cristobalite might be formed, but no details of any measurements are given. PAH concentrations were the same as background, and there was no evidence of asbestos exposure. In the absence of job histories - men moved frequently between occupations - the Puntoni *et al* (1988) study compared relative risks for silicotics and non-silicotics only.

In the Merlo *et al* (1991) study the first measurements of respirable dust were in 1973 and 1975, silica concentrations  $0.2$  to  $0.5 \text{ mgm}^{-3}$  of dust - no details given, they therefore would appear to be same as the Puntoni *et al* (1988) measurements. These limited exposure data do not seem to have been used to any great extent, possibly since no occupational exposure histories were available (or estimated).

#### 4.7 UK pottery workers

Winter *et al* (1990) studied pottery workers who in 1970-1 had been included in a survey of respiratory disease in a stratified sample of the then current workforce of the pottery industry in Britain (Fox *et al*, 1975). In men under 60 at initial survey, lung cancer mortality was 30% greater than expected, even after adjusting for smoking habit. An index of exposure was derived from 1970-1 quartz concentrations, assuming unchanged concentrations historically, and from occupational histories.

In more detail, mean respirable quartz concentrations for workplace were available for most job/product combinations from the 1975 survey reported by Fox (1975), in which 280 jobs were sampled (624 samples) for respirable quartz and dust. 83% measurements showed less than  $0.1 \text{ mgm}^{-3}$  quartz, 0.4% greater than  $0.4 \text{ mgm}^{-3}$  quartz. The highest mean concentration in any occupational group in 1970-1 was  $0.17 \text{ mg.m}^{-3}$  respirable quartz. It was good information for that snapshot in time. 30% of those in the study had worked in dusty industries outside of the pottery industry. Winter *et al* (1990) grouped men into four groups by exposure level at time of survey and by cumulative exposure assuming exposure had remained constant ie no allowance for complicated job histories. No allowance was made for prior exposure to other hazardous dusts in other occupations.

Using these exposure indices, a relation between quartz exposure and lung cancer risk was indicated, even when expected rates were adjusted for smoking. Some doubts were expressed by the authors about the adequacy of tracing, and men over 60 were excluded for this reason. In view of the subsequent investigations described below, it is probable that the apparent exposure-response relation here was the result of confounding, by the location of the main pottery industry in an area with an unusually high background lung cancer mortality, and comparisons with national death rates.

More recently, in several related papers, Cherrie, Burgess and McDonald and colleagues (Cherry *et al*, 1995; McDonald *et al*, 1995; Burgess *et al*, 1997; Cherry *et al*, 1997; McDonald *et al*, 1997) reported the initial analyses of the results of a study of a population of pottery workers in a more restricted area in Britain. Lung cancer mortality overall was raised compared with national rates (SMR 1.7), but less so when compared with local rates (SMR 1.28) (Cherry *et al*, 1995). Detailed exposure histories were reconstructed (Burgess *et al*, 1997). Gravimetric personal samples were available from the late 1960s onwards and measured concentrations of respirable dust were  $< 0.8 \text{ mgm}^{-3}$  and largely between 0.1 and  $0.2 \text{ mgm}^{-3}$  (McDonald *et al*, 1995). Some earlier measurements dating back to the 1930s were also available as particle number counts. Burgess *et al* (1997) converted the particle counts to mass units using conversions from North Carolina dusty trades study. This seems less than ideal since they are very different materials and industries. There are no details of measurement or information about cristobalite concentrations.

Job titles were used to indicate similar exposure unless contrary information was available. They show a matrix of concentration versus calendar time periods for different occupations. Some judgements were required to fill gaps. Historically, the highest estimated mean concentration in any job was  $0.8 \text{ mg.m}^{-3}$  respirable quartz, with levels reducing steadily over successive decades. No relationship between lung cancer mortality and cumulative exposure could be demonstrated (Cherry *et al*, 1997). There was a slight excess in those who ever worked in firing and post firing operations. The authors pointed out that cristobalite would have been present in the dust in these occupations, as well as quartz.

#### 4.8 US diatomaceous earth industry workers

Checkoway and others (1993, 1996), studied the mortality of diatomaceous earth industry workers exposed to cristobalite, a variant of crystalline silica different from quartz, and to amorphous silica, and to low concentrations of quartz. While past measurements of concentrations of cristobalite were insufficient to permit estimation of fully quantitative cumulative exposures, detailed estimates of likely differences in concentrations between jobs were made, and together with information on respirator use, used to weight time in each job

to estimate a semiquantitative 'exposure' for each individual. Proportions by weight of cristobalite in the respirable dust from calcined diatomaceous earth ranged from 10 to 25%. It was not possible to estimate exposures to amorphous silica.

In more detail, estimates were based on qualitative observations of difference in dustiness between activities and estimated percentages of crystalline silica in respirable dust, plus a further factor for effectiveness of respirators. Jobs weighted at 0, 1, 3, and 6 (no, low, moderate, high exposure), time periods weighted as 12, 6, 2, 1.5, and 1. The cut off dates for early time periods would seem to be arbitrary. There is no mention of how the weightings for differences between occupations and time were arrived at, and whether they were based on any real measurement data. Final indices of exposure also utilised estimates (why not measurements) of the crystalline silica content of dusts at different points in the process.

The exposure assessments are reasonable, but would be more convincing if data were presented to show how the various weightings were derived, and what criteria were used to decide how dusty individual occupations were.

Mortality in the study population was compared with US rates, the suitability of which was supported by limited comparisons with local rates. Additionally SMRs were studied in subgroups of the population classified by exposure, and a multiple regression analysis was conducted to study risks associated with exposure after adjusting for the effects of age, year of death, duration of follow-up and ethnic group.

The first of these studies appeared to show that, compared with the US population, risks of lung cancer (SMR 1.43), and non malignant respiratory disease (SMR 2.27) were significantly increased. Internal regression analyses appeared to show a clear trend towards a modest increase in risks of lung cancer associated with cumulative exposure, after allowing for other factors, including age. Subsequently, however, it was discovered that more subjects had been exposed to asbestos than was at first realised, and this led to further exposure estimation and revised analyses.

The second, revised, analysis (Checkoway, 1996), of a subset of the population for whom asbestos exposures could be quantified approximately (details are not provided), indicated that some of the lung cancer deaths could have been the result of exposure to asbestos. After allowing for this and other factors by multiple regression analyses, there remained a suggestive trend of frequency of lung cancer with cumulative exposure to cristobalite, but these differences could have arisen by chance. A further study of this population is reported to be underway, to try to provide a more precise characterisation of the independent and joint effects of exposures to cristobalite and asbestos on mortality from lung cancer.

High risks of silicosis in the study population, so secondary effects possible. No information on relations between silicosis and lung cancer.

Cristobalite is not quartz, and its human and animal toxicity is less well established. Comparative toxicological studies of cristobalite and quartz would be informative.

#### 4.9 Chinese pottery workers

Chen *et al* (1992) and McLaughlin *et al* (1992) studied approximately 68,000 people employed in metal mines and pottery factories in China.

In Chen *et al* (1992) total dust, percent free silica and dust size were measured monthly from the 1950s to 1980s at 29 different places of work, and these data used to estimate exposure for every dust-exposed job over several calendar periods. The exposure data were used to divide workers into groupings of high, medium, low and no dust exposure. Workers were classified by the highest dust exposure occupation that they had undertaken over any 12 month period of their employment.

These estimates may not directly inform about the dose of respirable silica. There is no indication that the measurements were used to calculate cumulative exposure. No allowance was made for the effects of cumulative exposure or for succession of short term placements, some of which may have been very dusty. Exposure seems to have been considered solely in terms of total dust, not respirable. There is an implication that dustiness was associated solely with job title with no differentiation between different mines or factories - one would expect some variation in dustiness with location as well as occupation. Quite a lot of averaging was performed, but this may not be very important as the authors were not trying to establish dose-response. Silica polymorphs were not identified. Total dust exposures were probably high by UK standards (mine means were about 6 to 8 mgm<sup>-3</sup>).

The usual uncertainties in death certification were compounded by obtaining information from multiple sources, not of uniform reliability. Mortality from pneumoconiosis was high, but lung cancer risks were not increased except among tin miners (Chen *et al*, 1992).

A case-control study examined exposures in detail. McLaughlin *et al* (Mehnert, 1990) describe subjects (from 29 mines and factories) in terms of cumulative exposure to silica dust as well as to known lung carcinogens such as cigarette smoke, inorganic arsenic, PAHS and radon (Dosemeci *et al*, Applied Occupational and Environmental Hygiene). The study utilised historical information dating back to 1950s - total dust and percent silica, recent measurements of respirable dust and possible confounding carcinogens. Exposures to asbestos, Nickel, talc, and Cadmium were minimal. 148 job titles for 29 job sites were ignored out of a total of 659 facility and job combinations. The exposure assessments appear to have been fairly thorough, although measurements of respirable silica appear to be indirect.

For tin miners, exposure-response relationships for lung cancer were demonstrated for exposures to both silica and arsenic, but the effects could not be separated. For pottery workers a suggestive trend of lung cancer risk with silica exposure was suggested but was not statistically significant. Some exposure to PAHs also occurred, but appeared not to have increased the apparent (non-significant) risks associated with silica exposure. Over 90% of subjects smoked, which may have contributed to the lung cancer rates.

Workplace registries were kept of subjects with silicosis, and these subjects had regular chest radiographs. Risks of lung cancer were higher in iron-copper and tin miners with silicosis than in those without silicosis, but not in pottery workers with silicosis.

In spite of the high frequency of silicosis, no evidence of increased lung cancer risks were found among silicotics in pottery workers. There were higher risks in some miners with silicosis, but this was confounded with other exposures.

#### 4.10 Cohorts of registered silicotics in North Carolina and Finland

##### N. Carolina

Amandus *et al* (1995, 1991b, 1992) conducted a series of studies of silicotic subjects who had worked in North Carolina dusty trades. Lung cancer rates were over twice that expected for the United States, and higher compared with local rates. SMRs were about two and a half. The analysis partly either controlled or analysed possible confounding by age, smoking, exposure to other occupational carcinogens, and selection bias, providing some reassurance on most concerns about the reliability of the result. Curiously, these subjects had raised mortality also from several other causes not expected to be associated with silicosis, as well as the expected excesses of tuberculosis and pneumoconiosis.

No information is given on completeness of response to this voluntary surveillance programme. If it was significantly incomplete, there was an opportunity for bias to arise as a result of preferential recruitment of subjects suffering adverse effects (not malignant at this time) from their smoking habit (Peto *et al*, 1983; Miller *et al*, 1981).

This is probable but not conclusive evidence that silicosis predisposes to lung cancer. Relevance to the question of silica and lung cancer is indirect.

##### Finland

Partanen *et al* (1994) and Kurppa *et al* (1986) reported an approximately three-fold increase in lung cancer in silicotic subjects, compared with the normal population. Information on exposure was not available. It was concluded that smoking was unlikely to have influenced the result substantially, because other smoking related cancers were not in excess. Other occupational exposures were minimal, and, if recruitment bias had occurred, it was not because men entered the register with early lung cancer already present. This does not exclude recruitment bias influenced by symptoms of other disease, such as non-specific symptoms in response to some external or internal insult. Preferential diagnosis is not excluded.

The study is suggestive that silicosis predisposes to lung cancer.

#### 4.11 Mortality of coalminers in Britain

Very recently our colleagues have reported (Miller *et al*, 1977) the results of a mortality study of eighteen thousand coalminers, representing four hundred thousand man-years of follow-up. Exposures to respirable dust and quartz were measured in an extremely detailed prospective measurement programme linked to employment records, which commenced in 1953. Follow-up was to 1992. Information was available on exposures to radon and to diesel exhaust fumes, and from individuals on their smoking habits.

In comparison with regional mortality, rates for lung cancer were low. Higher risks for smokers, and in relation to amount smoked, were easily demonstrated. In some statistical models relationships between exposure to quartz and lung cancer risk were suggested, when allowing for regional differences, but these relationships became non-significant when differences between collieries were allowed for. Comparisons of pneumoconiosis mortality with quartz and dust exposure confirmed the effect of dust, and provided support for the

reliability of the exposure estimates. The statistical models which included colliery differences best demonstrated the non-contributory influence of quartz shown by previous studies.

By virtue of the detailed exposure measurement programme, and population size, this is the most powerful study to date, though refers only to conditions where quartz comprises generally less than 10% of the respirable dust. The study provides no definite evidence of an influence of quartz exposure on risks of lung cancer.



**ACKNOWLEDGEMENTS**

We gratefully acknowledge the support of EUROSIL for this work.



## REFERENCES

- Amandus H, Costello J. (1991a). Silicosis and lung cancer in US metal miners. *Archives of Environmental Health*; 46: 82-89.
- Amandus HE, Shy C, Wing S, Blair A. (1991b). Silicosis and lung cancer in North Carolina dusty trade workers. *American Journal of Industrial Medicine*; 20: 57-70.
- Amandus HE, Castellan RM, Shy C, Heineman EF, Blair A. (1992). Re-evaluation of silicosis and lung cancer in North Carolina dusty trade workers. *American Journal of Industrial Medicine*; 22: 147-153.
- Amandus HE, Shy C, Castellan RM, Blair A, Heineman EF. (1995). Silicosis and lung cancer among workers in North Carolina dusty trades. *Scandinavian Journal of Work Environment Health*; 21 (Suppl 2): 81-83.
- Axelson O. (1978). Aspects of confounding in occupational health epidemiology. *Scandinavian Journal of Work, Environment and Health*; 4: 85-89.
- Axelson O, Steenland K. (1988). Indirect methods of assessing the effects of tobacco use in occupational studies. *American Journal of Industrial Medicine*; 13: 105-118.
- Bagley ST, Baumgard KJ, Gratz LD, Johnson JH, Leddy DG. (1996). Characterisation of Fuel and Aftertreatment Device Effects on Diesel Emissions. Cambridge (MA): Health Effects Institute. (Research Report No 76).
- Brown DP, Kaplan SD, Zumwalde RD, Kaplowitz M, Archer VE. (1986). Retrospective cohort mortality study of underground gold mine workers. In: Goldsmith DF, Winn DM, Shy CM, eds. *Silica, silicosis and lung cancer*. New York: Praeger: 335-350.
- Buechner HA, Ansari A. (1969). Acute silico-proteinosis: a new pathologic variant of acute silicosis in a sandbaster, characterised by histologic features resembling alveolar proteinosis. *Diseases of the Chest*; 55: 274-284.
- Burgess GL, Turner S, McDonald JC, Cherry NM. (1997). Cohort mortality study of Staffordshire pottery workers (I): radiographic validation of an exposure matrix for respirable crystalline silica. *Annals of Occupational Hygiene*; 41 (Suppl 1) (In press).
- Byers T. (1997). Diet as a factor in the etiology and prevention of lung cancer. In: Samet JM, ed. *Epidemiology of lung cancer*. New York: Marcel Dekker: 335-352. (*Lung Biology in Health and Disease* Vol. 74).
- Carstensen B, Jensen OM. (1986). *Atlas of cancer incidence in Denmark*. Copenhagen: Danish Cancer Registry and Environmental Protection Agency.
- Checkoway H, Heyer NJ, Demers PJ, Breslow NE. (1993). Mortality among workers in the diatomaceous earth industry. *British Journal of Industrial Medicine*; 50: 586-597.

- Checkoway H, Heyer NJ, Demers PJ, Gibbs GW. (1996). Reanalysis of mortality from lung cancer among diatomaceous earth industry workers, with consideration of potential confounding by asbestos exposure. *Occupational and Environmental Medicine*; 53: 645-647.
- Chen J, McLaughlin JK, Zhang J, Stone BJ, Luo J, Chen RA, Dosernecki M, Rexing SH, Wu Z, Hearl FJ, McCawley MA, Blot WJ. (1992). Mortality among dust-exposed Chinese mine and pottery workers. *Journal of Occupational Medicine*; 34: 311-316.
- Cherry NM, Burgess GL, McNamee R, Turner S, McDonald JC. (1995). Initial finding from a cohort mortality study of British pottery workers. *Applied Occupational and Environmental Hygiene*; 10: 1042-1045.
- Cherry NM, Burgess GL, Turner S, McDonald JC. (1997). Cohort study of Staffordshire pottery workers (II): nested case referent analysis of lung cancer. *Annals of Occupational Hygiene*; 41 (Suppl 1). (In press).
- Cohart EM. (1955). Socioeconomic distribution of cancer of the lung in New Haven. *Cancer*; 8: 1126-1129.
- Committee on Carcinogenicity of Chemicals in Food. (1991). Guidelines for the evaluation of chemicals for carcinogenicity. London: HMSO.
- Costello J, Graham WGB. (1988). Vermont granite workers mortality study. *American Journal of Industrial Medicine*; 13: 483-497.
- Davis LK, Wegman DH, Monson RR, Froines J. (1983). Mortality experience of Vermont granite workers. *American Journal of Industrial Medicine*; 4: 705-723.
- Donaldson K, Bolton RE, Brown DM, Brown GM, Cowie HA, Jones AD, Robertson MD, Slight J, Davies JMG. (1988). Studies on the cellular response in lung tissue to the inhalation of mineral dust. Edinburgh: Institute of Occupational Medicine. (IOM Report TM/88/01).
- Donaldson K, Brown GM, Brown DM, Robertson MD, Slight J, Cowie H, Jones AD, Bolton RE, Davis JMG. (1990). Contrasting bronchoalveolar leucocyte responses in rats inhaling coal mine dust, quartz, or titanium dioxide: effects of coal rank, airborne mass concentration, and cessation of exposure. *Environmental Research*; 52: 62-76.
- Donaldson K, Brown GM, Brown DM, Slight J, Li XY. (1992). Epithelial and extracellular matrix injury in quartz-inflamed lung; role of alveolar macrophages. *Environmental Health Perspectives*; 97: 221-224.
- Dong D, Xu G, Sun Y, Hu P. (1995). Lung cancer among workers exposed to silica dust in Chinese refractory plants. *Scandinavian Journal of Work Environment Health*; 21 (Suppl 2): 69-72.
- Commission of the European Communities. (1993). Annexes I, II, III and IV to Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities*; 36 (L110A).

Environmental Protection Agency. (1996). Risk assessment forum technical panel for cancer guidelines. Proposed guidelines for carcinogen risk assessment. Washington (DC): US Office of Research and Development. (EPA/600/P-92/003C).

Fox AJ, Greenberg M, Ritchie GL, Barraclough RNJ. (1975). A survey of respiratory disease in the pottery industry. London: HMSO.

Fox AJ, Adelstein AM. (1978). Occupational mortality: work or way of life? *Journal of epidemiology and public health*; 32: 73-78.

Fox J, ed. Health inequalities in European countries. Aldershot: Gower.

Gillam J, Dement J, Lemen R, Wagoner J, Archer V, Blejer H. (1976). Mortality patterns among hard rock gold miners exposed to an asbestiform material. *Annals of the New York Academy of Sciences*; 271: 336-344.

Goldsmith DF. (1994). Silica exposure and pulmonary cancer. In: Samet JM, ed. *Epidemiology of lung cancer*. New York: Marcel Dekker: 245-298. (*Lung Biology in Health and Disease Vol. 74*).

Graham WGB, O'Grady RV, Dubuc B. (1981). Pulmonary function loss in Vermont granite workers: a long term follow-up and critical reappraisal. *American Review of Respiratory Disease*; 123: 25-28.

Guenel P, Hojberg G, Lynge E. (1989). Cancer incidence among Danish stone workers. *Scandinavian Journal of Work Environment Health*; 15: 265-270.

Hakulinen T, Magnus K, Tenkanen L. (1987). Is smoking sufficient to explain the large difference in lung cancer incidence between Finland and Norway? *Scandinavian Journal of Social Medicine*; 15: 3-10.

Heederik D, Miller BG. (1997). Weak associations in occupational epidemiology: adjustment for exposure estimation error. *International Journal of Epidemiology*; 17: 970-974.

Hein HO, Suadicani P, Gyntelberg F. (1992). Lung cancer risk and social class. *Danish Medical Bulletin*; 39: 173-176.

Horm JW, Kessler LG. (1986). Falling rates of lung cancer in men in the United States. *Lancet*; I: 425-426.

IARC Working Group. (1987). Silica and some silicates. Lyon: International Agency for Research on Cancer. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. No. 42).

IARC. (1994). The evaluation of carcinogenic risks to humans. Lyon: International Agency for Research on Cancer. (IARC Monographs. No. 60).

IARC. (1997). Silica, some silicates, coal dust and para-aramid fibrils. Lyon: International Agency for Research on Cancer. (IARC monographs on the evaluation of carcinogenic risks to humans. No. 68).

Jacobsen M, Smith TA, Hurley JF, Robertson A, Roscrow R. (1988). Respiratory infections in coalminers exposed to nitrogen oxides. Cambridge MA: Health Effects Institute. (HEI Research Report No. 18).

King EJ, Mohanty GP, Harrison CV, Nagelschmidt G. The action of different forms of pure silica on the lungs of rats. *British Journal of Industrial Medicine*; 10: 9-17.

Kullman GJ, Greife AL, Costello J, Hearl FJ. (1995). Occupational exposures to fibers and quartz at 19 crushed stone mining and milling operations. *American Journal of Industrial Medicine*; 27: 641-660.

Kurppa K, Gudbergsson H, Hannunkari I, Koskinen H, Hernberg S, Koskela R-S, Ahlman K. (1986). Lung cancer among silicotics in Finland. In: Goldsmith DF, Winn DM, Shy CM, eds. *Silica, silicosis and cancer*. New York: Praeger: 311-319.

Lee KP, Trochimowicz HJ, Reinhardt CF. (1985). Pulmonary response of rats exposed to titanium dioxide (TiO<sub>2</sub>) by inhalation for two years. *Toxicology and Applied Pharmacology*; 79: 179-192.

Levi F, Negri E, la Vecchia C, Tev C. (1988). Socioeconomic groups and cancer risk at death in the Swiss Canton of Vaud. *International Journal of Epidemiology*; 17: 711-717.

Logan WPD. (1982). *Cancer mortality by occupation and social class 1851-1971*. London, Lyon: HMSO, IARC. (Studies on Medical and Population Subjects No. 44).

McDonald JC, Gibbs G, Liddell W, McDonald A. (1978). Mortality after long exposure to Cummingtonite-Grunerite. *American Review of Respiratory Disease*; 118: 271-277.

McDonald JC. (1989). Silica, silicosis and lung cancer. *British Journal of Industrial Medicine*; 46: 289-291.

McDonald JC, Cherry NM, McNamee R, Burgess GL, Turner S. (1995). Preliminary analysis of proportional mortality in a cohort of British pottery workers exposed to crystalline silica. *Scandinavian Journal of Work Environment Health*; 21 (Suppl 2): 63-65.

McDonald JC, Burgess GL, Turner S, Cherry NM. (1997). Cohort study of Staffordshire pottery workers (III): lung cancer, radiographic changes, silica exposure and smoking habit. *Annals of Occupational Hygiene*; 41. (In press).

McLaughlin JK, Jing-Qiong C, Dosemeci M, Rong-An C, Rexing SH, Zhien W, Hearl FJ, McCawley MA, Blot WJ. (1992). A nested case-control study of lung cancer among silica exposed workers in China. *British Journal of Industrial Medicine*; 49: 167-171.

Mehnert WH, Staneczek W, Mohner M, Konetzke G, Muller W, Ahlendorf W, Beck B, Winkelmann R, Simonato L. (1990). A mortality study of a cohort of slate quarry workers in the German Democratic Republic. In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. *Occupational Exposure to Silica and Cancer Risk*. Lyon: International Agency for Research on Cancer; 55-64. (IARC Scientific Publications No. 97).

Merlo F, Constantini M, Reggiardo G, Ceppi M, Puntoni R. (1991). Lung cancer risk in refractory brick workers exposed to crystalline silica: a retrospective cohort study. *Epidemiology*; 2: 299-305.

Miller BG, Jacobsen M, Steele RC. (1981). Coalminers' mortality in relation to radiological category, lung function and exposure to airborne dust. Edinburgh: Institute of Occupational Medicine. (IOM Report TM/81/10).

Miller BG, Buchanan D, Hurley JF, Robertson A, Hutchison PA, Kidd MW, Pilkington AD, Soutar CA. (1997). The effects of exposure to diesel fumes, low-level radiation, and respirable dust and quartz, on cancer mortality in coalminers. Edinburgh: Institute of Occupational Medicine. (IOM Report TM/97/04).

Mizuno S, Akiba S, Hirayama T. (1989). Lung cancer risk comparison among male smokers between the "Six-prefecture Cohort" in Japan and the British physicians cohort. *Japanese Journal of Cancer Research*; 80: 1165-1170.

Muhle H, Takenaka S, Mohr U, Dasenbrock C, Mermelstein R. (1989). Lung tumour induction upon long-term low-level inhalation of crystalline silica. *American Journal of Industrial Medicine*; 15: 343-346.

Muhle H, Kittel B, Ernst H, Mohr U, Mermelstein R. (1995). Neoplastic lung lesions in rat after chronic exposure to crystalline silica. *Scandinavian Journal of Work, Environment and Health*; 21: 27-29.

Office of Population Censuses and Surveys. (1986). Occupational mortality. The Registrar General's decennial supplement for Great Britain, 1979-80, 1982-83. London: HMSO.

Drever F, ed. Office of Population Censuses and Surveys & Health and Safety Executive. (1995). Occupational Health. Decennial Supplement. The Registrar General's decennial supplement for England and Wales. London: HMSO.

Pairon JC, Brochard P, Jaurand MC, Bignon J. (1991). Silica and lung cancer: a controversial issue. *European Respiratory Journal* 4; 6: 730-744.

Partanen T, Pukkala E, Vainio H, Kurppa K, Koskinen H. (1994). Increased incidence of lung and skin cancer in Finnish silicotic patients. *Journal of Occupational Medicine*; 36: 616-622.

Pearce NE, Howard JK. (1986). Occupation, social class and male cancer mortality in New Zealand, 1974-78. *International Journal of Epidemiology*; 456-461.

Peto R, Speizer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM, Higgins ITT, Gray RG, Richards SM, Gilliland J, Norman-Smith B. (1983). The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. *American Review of Respiratory Disease*; 128: 491-500.

Pilkington A, Maclaren W, Searl A, Davies JMG, Hurley JF, Soutar CA. (1996). Scientific Opinion on the Health Effects of Airborne Crystalline Silica. Edinburgh: Institute of Occupational Medicine. (IOM Report TM/95/08).

Puntoni R, Goldsmith DF, Valerio F *et al.* (1988). A cohort study of workers employed in a refractory brick plant. *Tumori*; 74: 27-33.

Seaton A, Dick JA, Dodgson J, Jacobsen M. (1981). Quartz and pneumoconiosis in coalminers. *Lancet*; II: 1272-1275.

Steenland K, Brown D. (1995). Mortality study of 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.

Sterling TD, Weinkham JJ. (1976). Smoking characteristics by type of employment. *Journal of Occupational Medicine*; 18: 743-754.

Tran CL, Jones AD, Donaldson K. (1994). Development of a dosimetric model for assessing the health risks associated with inhaling coalmine dusts. Final report on CEC Contract 7280/07/015. Edinburgh: Institute of Occupational Medicine. (IOM Report TM/94/01).

Weill H, McDonald JC. (1996). Exposure to crystalline silica and risk of lung cancer: the epidemiological evidence. *Thorax*; 51: 97-102.

Williams RR, Horm JW. (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the third national cancer survey. *Journal of the National Cancer Institute*; 58: 525-547.

Winter PD, Gardner MJ, Fletcher AC, Jones RD. (1990). In: Simonato L, Fletcher AC, Saracci R, Thomas TL, eds. Occupational exposure to silica and cancer risk. Lyon: International Agency for Research into Cancer: 83-94. (IARC Scientific Publications No. 97).

Zumwalde R, Ludvig H, Dement J. (1981). Industrial hygiene report- Homestake Mining Company, Lead, South Dakota. Cincinnati (OH): IWSB, DHSEFS, NIOSH.