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HISTORICAL RESEARCH REPORT

Research Report TM/95/08
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WORLD HEALTH ORGANISATION
COLLABORATING CENTRE
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Scientific Opinion on the Health Effects of Airborne Crystalline Silica

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SCIENTIFIC OPINION ON THE HEALTH EFFECTS OF AIRBORNE CRYSTALLINE SILICA

by

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1. INTRODUCTION

1.1 Crystalline Silica and Quartz

By far the most common form of crystalline silica to which workers are exposed is quartz, and this review for the most part considers the evidence as it relates to quartz. Other forms of crystalline silica have differing surface properties and biological reactivities.

1.2 Aims

The aims of this study are to give an informed scientific opinion, supported by reference to the literature, on:

(a) The risk of silicosis in the range of control limits for airborne quartz currently under discussion (0.03-0.4mg/m^3); the confidence which can be placed in these estimates, and what evidence there may be of absence of an effect at low concentrations.

(b) Whether evidence from animal studies confirms that lung cancer from quartz occurs only in rats and whether lung fibrosis is a necessary precursor for lung cancer.

(c) Whether there is a risk of lung cancer directly attributable to exposure to quartz, and if so, whether this risk is confined to those with silicosis.

These questions have been considered not only in relation to the available epidemiological and animal studies, but also in relation to the EU conventions used for classification of possible carcinogens.

2. OPINION

In order to address the aims, consideration was given to data from animal studies, human exposure data and human studies of both silicosis and lung cancer in relation to exposure to quartz. Following a literature search papers were reviewed using the same framework. Details of methodology, selection criteria and the review framework are listed in Appendix 1.

Results and Discussions

When considering human exposure-response epidemiological studies, the reliability of the exposure information, health assessments, and potential bias and confounding factors must be taken into account.

2.1 Quality of exposure data

The exposure data for the key epidemiological studies raise a number of issues. Crystalline silica includes five minerals with differing surface properties and biological reactivities. Most workers exposed to crystalline silica are exposed to quartz, but those dealing with refractory products, diatomaceous earth and devitrified silicate glasses such as ceramic fibres, may be exposed to cristobalite (Checkoway *et al* 1993, Merlo *et al* 1991). None of the studies fully describes the mineralogical composition of respirable dust, or fully characterises all confounding co-exposures such as radon, diesel fumes and heavy metals (Hnizdo and Sluis-Cremer 1993, Amandus *et al* 1993), and this induces varying degrees of uncertainty in the published exposure-response relationships.

At low dust concentrations particle number or surface area concentrations may be more biologically relevant measures of exposure than mass concentrations (see Appendix 3). Particle numbers and surface areas per milligram of quartz will vary widely in dusts produced from different industrial processes using different source materials. It is also possible that freshly shattered surfaces may be much more toxic than aged surfaces (see Appendix 3). Exposure is often expressed in terms that cannot be readily converted to mass concentrations even when good exposure measurements do exist (Hnizdo and Sluis-Cremer 1993). The source references for exposure data often indicate a relatively limited database, suggesting that the exposure estimations are not soundly based.

None of the key studies consider exposure to low levels of quartz for periods greater than 25 years, important when interpreting the results as the latency for lung cancer is at least this long. Workers exposed for longer periods were initially exposed to very high dust levels prior to the introduction of modern hygiene measures, and this may have induced underestimation of exposures, and over estimation of risks. Also the degree of lung damage caused by short term high level exposure may not equate with that produced by the same dose of quartz over a longer period of time. Dust measurements made before the early 1960's were of number of particles per unit volume, whereas current control limits are expressed as gravimetric units. Only two of the key studies made an extensive side by side comparison of particle number concentrations versus gravimetric concentrations of respirable quartz (Davis *et al* 1983, Muir *et al* 1989). Other studies applied the conversion factor derived from one of these studies without considering whether particle size or relative quartz content of the dust would be similar.

Given these considerations, it is unlikely that many of the reported dose-response relationships relating quartz exposure to risks of silicosis, or lung cancer, will be reliable or consistent, and care is needed in evaluating each study on its merits.

2.2 Human studies - Silicosis

In an attempt to quantify the risks of silicosis at low exposure to quartz dust, a review of the literature on the toxic effects of silica published by the Institute of Occupational Medicine in 1987 (Seaton *et al*, 1987) was initially considered. The authors concluded that there was a definite exposure-response relation, but that it could not be described precisely due to imprecision in estimates of exposure, and to a lesser extent response, and uncertainties associated with extrapolation to low exposures. They also stated that a single occupational exposure standard for quartz would probably not be appropriate for different industries, because of variations in the type of quartz, particle size, and chemical properties. However, they concluded that if concentrations of respirable quartz were kept below 0.1 mg/m^3, the available evidence suggested that most serious cases of silicosis would be prevented.

As a result of the literature search the following relevant subsequent studies were considered: two cohort studies - of Ontario hard-rock miners (Muir *et al*, 1987a, 1987b, 1987c) and South African gold miners (Hnizdo and Sluis-Cremer, 1993); three cross-sectional studies, granite workers in Vermont (Graham *et al*, 1991) and in Hong-Kong (Ng and Chan, 1994), and a report of British heavy clay workers (Love *et al*, 1994). A cohort study of Scottish coal miners (Miller *et al*, 1995), published too recently to be identified in the literature search, is also considered. Brief summaries of these studies, and exposure-response relationships are given in Appendix 4.3.

After due consideration, we decided that the three cross-sectional studies did not provide reliable information regarding the risks of silicosis at low levels of exposure. The Vermont study gave an exposure-response relation in terms of years worked in granite, not cumulative exposure to quartz dust. For the Hong-Kong study, the exposure-response relation may have been affected by various biases, in particular non-response among workers with low exposure to dust, which may partly account for the probable over-estimation of risk in the low exposure groups (a prevalence of 9.9% category 1/1+ was predicted for 60 year old workers with zero cumulative exposure to quartz). In the study of Love *et al*, exposures could not be estimated with sufficient precision to allow accurate quantification of risk at very low levels, nor was reliable information on past exposures available. Thus, cumulative exposure estimates were based on one round of hygiene surveys at 18 sites carried out during 1990/91. The only factor taken account of in extrapolating dust concentrations backwards in time over periods up to 40 years, was change in kiln type. In particular, the effect of introducing local exhaust ventilation could not be allowed for.

Of the three cohort studies, the study of Scottish coal miners is of high quality as regards exposure estimation, identification of cases of pneumoconiosis, and methods of statistical analysis of exposure-response relationships. However, from the point of view of providing reliable estimates of risks of pneumoconiosis incurred over a working lifetime at low exposure to silica dust, the study's results (as published to date) are of limited usefulness. This is because the exposures of men in the cohort follow an unusual pattern, in that for a short interval of less than five years during the 1970's, some study members were exposed to extremely high levels of quartz, in some cases as high as 10 mg/m^3. The authors state in their summary: "Further work is needed to investigate in more detail the relationships between exposure, time, and the development of pneumoconiosis...". Until such further analyses have been carried out, the relationships and models presented in this report should not be used to predict risks at low mean concentrations of quartz in contexts such as standard setting, where precision of predictions is at a premium." A table of predicted prevalences is given in Appendix 4.3.2.

Of the two remaining cohort studies, we consider that from the point of view of exposure estimation, neither study is strong, but the study of Ontario hard rock miners (Muir *et al*. 1987[a,b,c]) is probably the stronger of the two. Cumulative exposures to respirable quartz were based on "a reasonably

complete set of konimeter counts" from 1959 onwards, by task and by mine, but prior to this date, sparser data obtained for engineering control purposes, when levels were high. (The authors noted that an over-estimation of exposure, and consequent under-estimation of risk could have resulted). Count data were translated into gravimetric units using a relation obtained from a side-by-side sampling exercise. The latter included an experiment to simulate high dust exposures which would have been encountered in the past. By contrast, in the South African study (Hnizdo and Sluis-Cremer, 1993), estimates of cumulative exposure to mixed respirable dust were based on a single study of exposure carried out in the early 1960's. Airborne quartz concentrations were not measured and in order to use the South African results to examine the relation with cumulative exposure to quartz, we transformed the dust exposures by multiplying by a factor of 0.3, quoted by the authors as representing the approximate quartz content of mixed respirable dust in South African gold mines. The authors noted that it was possible that the average quartz concentrations used in their study underetimated the actual exposure. Thus while the mixed dust exposure estimates were reasonably reliable, the translation of these into quartz exposures is relatively unreliable.

The Ontario study is also probably more reliable in respect of the identification of cases of silicosis. A three-stage reading strategy was used, involving five readers, whereas in the South African Study only 2 readers were involved, and in the analyses, results from only one of these were used.

However, from the point of view of choice of study population, the South African study appears to be less subject to bias, since it included miners who had left the industry (though even here, self selection among leavers could have induced a bias towards overstating prevalence). In the Ontario study, routine radiographs were taken only as long as miners worked in Ontario. To be included as a case, a miner had to develop silicosis while still employed as a miner in Ontario. This procedure may strongly underestimate the actual number of silicotics, as it is known that this disease usually progresses, even after cessation of exposure. Moreover selection of miners having been employed more than 60 months may have led to a healthy worker effect, thus underestimating the true incidence of silicosis in the whole cohort of workers.

The exposure response estimates based on either of these studies are likely to be unreliable, and since neither of the two studies is obviously superior to the other in every respect we have chosen to present estimates of risk from both of them. In calculating risk, we have purposely avoided extrapolating beyond the limits of the data as presented in the papers. Taking the study of Muir *et al* (1989) first, the various diagrams presented suggest that consideration of 15 years exposure to quartz concentrations of between 0.025 and 0.4mg/m^3, which corresponds to cumulative quartz exposures of between 0.375 and 6 mg/m^3. years, would not represent an extrapolation beyond the limits of the study data. We have calculated the cumulative risk separately for each reader, and then taken an arithmetic mean over readers.(Note that the model of Muir *et al* (1989) fits a distribution of cumulative exposure lagged by five years. That is, the predicted proportion of silicosis cases refers to five years later than the date at which the exposure was acquired). We have also calculated the predicted cumulative risk for a 40-year exposure, although some extrapolation beyond the data is necessary to do this. Thus, the longest duration of exposure for cases was 38 years. Furthermore, an exposure such as 4mg/m^3.years, if it arises from a lifetime exposure to 0.1mg/m^3, also represents an extrapolation beyond the study data, even though it apparently lies within the range of cumulative exposures of men in the study.

In the Hnizdo and Sluis-Cremer 1993 study, the average duration of dust exposure was 23.5 years, with a minimum of 8.7 years and a maximum of 37.9 years. Fifteen years exposure therefore lies well within the limits of the study data. Assuming a quartz content of 30%, the range of cumulative dust exposures corresponding to a range of cumulative quartz exposures of 0.375 to 6mg/m^3.years (see above) is 1.25 to 20mg/m^3 years, which fits the range of exposures actually experienced by men

in the study quite closely (1.2 to 1.87 mg/m^3 years). However, for 40-year exposures an extrapolation is necessary.

The predicted cumulative risks of category 1/1+ silicosis (%) are shown in the following table. If no entry is tabulated, the corresponding exposure is outside the range of cumulative exposures acquired by the men in the study.

Table 1 - Predicted cumulative risks* (per cent) of category 1/1 or greater silicosis.

Study	Period	Silica Concentration (mg/m^{-3})				
		0.025	0.05	0.1	0.2	0.4
		Cumulative risks (%)				
Muir *et al* 1989**	15 years	0.02	0.08	0.24	0.79	2.61
	40 years	0.12	0.39	1.29	4.29	---
Hnizdo and Sluis-Cremer 1993***	15 years	0.00	0.10	2.25	35.00	---
	40 years	0.36	7.86	66.52	---	---

* These estimates have been calculated using the estimated parameter values quoted by the authors. In the paper by Muir *et al*, different parameter values are given for each of five X-ray readers; the above table gives the arithmetic mean of the five separate predictions. See Appendix 4.3 for further details of these studies

** Miners employed >5 years (mean = 15.5 yrs). No follow up of leavers

*** Miners employed >10 years (mean = 24 years). Follow up until 1991. Only 1 x-ray reader (best correlated with autopsy findings).

The differences in predicted risk between the two studies, which are present over the range of concentrations considered, are consistent with our view that the exposure response estimates based on these studies are unreliable, and that reliable quantification of the risks of silicosis at low levels of exposure is not possible at present.

Nevertheless, if decisions on control limits have to be made, the Muir *et al* (1989) estimates could be used as the least unreliable approximate guide to the true risks. On this basis it is reasonable to conclude that the risk of category 1 or greater silicosis after a 40 year exposure to an average concentration of 0.1mg/m^3 respirable quartz is low. Category 1 represents mild or early silicosis, and the risks of more severe and clinically more important categories are likely to be much less. Risks of silicosis at average concentrations lower than 0.1mg/m^3 cannot be estimated with any confidence. We see no reason to differ from the view expressed by Seaton et al. (1987) that if concentrations of respirable quartz are kept below 0.1mg/m^3 most serious cases of silicosis would be prevented.

Note that these risk estimates are not numerically equivalent to control limits. The relationship between a control limit and average exposure is influenced by the variations in concentrations which occur, how the limit is applied, frequency of monitoring and whether monitoring is random or applied to typical or atypical circumstances, and what control actions are activated by exceeding the limit (or exceeding specified action levels).

Risk as a function of cumulative exposure

A statistical model such as that used by Muir *et al* (1989), which treats the effect of exposure in terms of cumulative exposure, assumes that exposures to short term high concentrations have the same biological effect as the equivalent cumulative exposure to low concentrations experienced over a longer period. This has the benefit of making a conservative estimate of safer levels of quartz, but is biologically insecure since high concentrations of quartz may induce disproportionately more severe and persistent inflammation than low concentrations (Tran *et al* 1994). As an analogy, a statistical exposure-risk model for benzene which weights exposure by concentration (concentration squared or cubed) has been claimed to explain benzene-related health risks better than the conventional un-weighted models (Crump, 1994). This aspect of risks associated with quartz exposure should be explored, since it could have important implications for estimated risks at high and low concentrations.

2.3 Animal studies (for full description and references, see appendix 4.1)

The experimental administration of quartz to rats has resulted in the development of pulmonary tumours including malignant carcinomas in several studies predominantly (though not exclusively) in female rats. Similar results are not found in mice or hamsters. Rat lung tissue appears very sensitive to heavy exposure to a number of types of mineral particle that do not appear hazardous to humans, for example titanium dioxide. For reasons not understood, female rats are also more susceptible to pulmonary carcinogenesis following dust inhalation than males, and it is possible that this sex difference may only be apparent with materials of relatively low carcinogenic potency. However, malignant tumours were also observed by one author in silica-treated male rats following exposure by inhalation (Mühle et al. 1991).

Quartz has been clearly demonstrated to produce pulmonary tumours in rats following inhalation exposures as low as 1mg/m^3 and although other particulate dusts produce similar tumours in rats, they do so for the most part only at extremely high doses. From this evidence it is clear that quartz is a carcinogen in rats, and therefore would appear to have carcinogenic potential in other species including man. The translation into actual human risk is uncertain, and since quartz as an animal carcinogen appears possibly to be of relatively low potency (because of the difference in response between male and female rats), it is not clear whether this implies significant human cancer risks in response to the cumulative exposures which can be experienced in practice.

Two other factors must be taken into account. Firstly, the animal studies have all been conducted with specially produced quartz samples with high purity and toxicity. Most human exposures will be to material of lower potency and lower average concentrations; and accompanying minerals may reduce toxicity. Secondly, tumour production in rats has always been accompanied by the development of significant pulmonary fibrosis, in those animals where tumours have been found. The mechanism of tumour production could possibly be secondary to the fibrosis, although presently this is difficult to prove. Quartz does cause a chronic inflammation and continued stimulation of cell proliferation in the rat lung (Donaldson *et al* 1990), part of the process leading to fibrosis. The situation in humans is likely to be similar so that if exposures can be kept below the level at which

fibrosis (silicosis) develops, then an excess of pulmonary cancer is most unlikely to occur.

2.4 Human studies - Lung cancer

For the purposes of determining whether exposure to quartz *per se* is related to lung cancer in man, exposure-response studies are desirable, since reports of small differences in the mortality experience of occupational groups can be the result of factors other than dust exposure (smoking habits, other occupational exposures). Two exposure-response studies are claimed to show an exposure-response relationship for silica exposure and lung cancer.

Checkoway *et al* (1993), in a study of diatomaceous earth workers, consider exposure predominantly to cristobalite which is mineralogically distinct from quartz, therefore the conclusions of the study cannot be directly applied to quartz. There are also doubts about possible confounding with asbestos exposure. Although known asbestos workers were excluded on the basis of job history, it is possible that some other workers who participated in the study were also exposed.

Hnizdo and Sluis-Cremer (1991), in an exposure-response study of South African gold miners, do not take account of exposure to radon which would have been particularly high in gold mines prior to the mid 1950's. Radon daughters have been linked in several studies with small cell lung cancer. In this study this type of lung cancer was found at autopsy at double the normal rates, and cases were not associated with silicosis. Potential confounding may have occurred due to the presence of heavy metals. In both studies smoking data is poorly quantified, though it is unlikely that smoking could have influenced the exposure-response relationship substantially.

The other studies, detailed in Appendix 4.2, which suggest an elevated lung cancer risk (Amandus *et al* 1992, Koskela *et al* 1987, Merlo *et al* 1991), have either poor exposure data, limited consideration of confounders, or lack of data on the presence of silicosis. In addition to these problems the papers suggesting no association (Carta *et al* 1994, Davis *et al* 1983, Meijers *et al* 1990), often lack statistical power and, have short follow up periods, which do not adequately allow for the latency of silicosis and lung cancer.

Silicosis studies conducted following the introduction of improved industrial hygiene measures in the Vermont granite industry suggest a steady fall in the number of cases of silicosis, and no new cases reported allowing for latency. Cases of lung cancer have also fallen, and so far in those cases which have occurred , the individuals have been smokers (Costello, Graham *et al* 1988).

We withhold judgement on the Checkoway et al 1993 study pending further work on confounding with asbestos exposure. If confounding with asbestos exposure is confirmed, then the study may provide little information on the relations between cristobalite and lung cancer. If confounding with asbestos is excluded, or adequately taken into account, then this study may provide good evidence of a relationship with cristobalite exposure. However even if confirmed, these results do not apply to quartz, a different form of silica.

Studies of lung cancer in silicotics

When studying the relationship between exposure to silica and lung cancer, it appears important to consider studies performed in silicotics. We have reviewed studies published in peer review journals or IARC publications after 1985, excluding those performed in coal miners (coal worker pneumoconiosis is known to be different from silicosis) as well as those concerning foundries and iron miners (these workers have a significant excess of lung cancer in most of the studies, but they have

to be excluded because of frequent co-exposure to known carcinogens.)

Two main types of studies may be distinguished: case-control studies which specifically investigated the relationship of lung cancer with the existence of silicosis in a given industrial group; and mortality studies performed on national or regional registers of silicotics. Lung cancer frequency is then compared to that observed in the general national or regional population of the same age. This last group of studies generally includes silicotics from varying backgrounds, some of whom may obviously have been exposed to various agents known to have pulmonary carcinogenic potential, for example, polycyclic aromatic hydrocarbons, such as in foundry workers.

Most of these studies have concluded that there is a significant association between silicosis and an excess of lung cancer (see Appendix 4.4). This excess could not be explained by tobacco smoking alone (Forastiere *et al* 1986, Zambon *et al* 1987, Amandus *et al* 1991a, Hessel *et al* 1990, Hnizdo and Sluis-Cremer 1991, McLaughlin *et al* 1992, Hua *et al* 1994) after statistical adjustment for the percentage of smokers in the population studied.

However, it cannot be concluded reliably from these studies that quartz itself is the agent responsible for lung cancer. Registers of silicotics do not provide information on the level of exposure to quartz and thus do not allow assessment of a dose-response relationship. Moreover, it should be emphasized that subjects recorded in the registers and followed up may not be representative of all cases of silicosis. Indeed compensation depends on disability and one cannot exclude the fact that smoking related disability may have increased the probability of being compensated, as both diseases (smoking-related disease and silicosis) are often associated. Nevertheless, it is reasonable to consider that, even if silica *per se* is not the carcinogenic agent, the development of lung cancer is strongly dependent on exposures of crystalline silica high enough to induce a silicotic fibrogenic process, possibly in conjunction with other cofactors. Such a relationship suggesting a progression from pulmonary fibrosis to lung cancer has been suggested in man for other agents (eg. asbestos), although this remains controversial.

2.5 Opinion on classification of quartz as a carcinogen

The evidence from human studies at this time is inadequate to support a causal relationship between quartz and lung cancer, in the terms required by the IARC and EU Classification schemes, although this association is biologically plausible. Consequently, there is not Sufficient Evidence from human studies of the carcinogenicity of quartz; and the evidence from human studies at best fits the Limited or Inadequate Evidence categories as defined by the criteria discussed in Appendix 2.

The principal inadequacy of the evidence from human studies is the absence of studies showing increased risks of lung cancer associated with exposure to quartz in people without silicosis. (We have excluded cristobalite as this is mineralogically distinct from quartz). The reported excesses of lung cancer in many cohorts of subjects with silicosis do not establish a direct link with quartz exposure. The influence of confounders such as smoking are difficult to distinguish from quartz exposure, and a secondary effect of carcinogenesis associated with fibrosis (silicosis) is possible.

This human evidence together is equivalent to Limited or Inadequate Evidence. The distinction is not of great practical importance to the EU classification because, in the absence of sufficient evidence from human studies, the attribution to categories depends primarily on the evidence from animal studies.

The evidence from animal studies could be classified as EU Category 2 (May cause cancer) or Category 3 (Possible risk of irreversible effects), depending on interpretation.

The guidance notes to the EU classification (Commission 1993 and Appendix 2) indicate that placing of a substance into categories 2 and 3 is based primarily on animal experiments. For classification as a Category 2 carcinogen, either 'results in two animal species should be available' (they are not, in this case) or 'clear positive evidence in one species together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, indication of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association'. In this case a judgement has to be made on whether the cancer excesses, predominantly in female rats, represent clear positive evidence. In our view it is clear positive evidence that quartz is a carcinogen in rats, and therefore potentially in humans, but not clear positive evidence that there are significant risks in humans in response to the exposures which can be experienced in practice.

For distinction between categories 2 and 3 "various other arguments may be considered which reduce the significance of experimental tumour induction ....." (appendix 2), one of which is "the 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)". In the case of quartz, as has been discussed, it is quite possible that the lung cancers in exposed rats are a secondary response to the fibrosis or the fibrotic process. Chronic stimulation of cell proliferation, part of the continuing inflammation, has been demonstrated in rat lungs, in response to silica, indicating that a process which could lead to secondary carcinogenesis does occur. If the reported excesses of lung cancer in subjects with silicosis should in future be shown to be associated with exposure to quartz, carcinogenesis secondary to chronic inflammation and fibrosis, analogous to that which may occur in rats, may be an explanation.

Another argument listed by the EU which may distinguish between categories 2 and 3, is 'appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation'. In this case, the rat model has been developed because it is sensitive to inhaled dusts (more than the guinea pig or hamster, for example), but is less likely to show spontaneous tumour formation than the mouse. On balance we believe the rat model cannot be disregarded on the grounds of extreme oversensitivity or high spontaneous tumour rates, but the quantitative translation of risks from rats to man is not clearly established.

Another argument concerns the lack of genotoxicity in short term tests *in vivo* and *in vitro*. As discussed in Appendix 4.5, the evidence that quartz directly affects the genome (genes) is somewhat conflicting but mostly negative.

Other possible arguments listed by the EC do not apply in this case. We believe that regulators will wish to include the above elements of the scientific argument in their considerations.

We have attempted to discuss the above issues carefully to a degree which might appear pedantic. However, the issue is of great practical importance since the labelling requirement associated with a Category 2 classification is a skull and crossbones image, with the words "May cause cancer". In our view a major difficulty with the classification rules, and associated labelling requirements, interpreted literally, is that they take no account of the degree of carcinogenic potency.

Further animal studies may clarify the situation in terms of carcinogenic potency of silica, and the relationship with fibrosis. However, these studies should be performed to Good Laboratory Practice (GLP) type rules and investigate several doses, with an accurate grading of fibrosis.

Resolution of the uncertainties will be achieved by improved epidemiological studies, with better exposure estimates, taking adequate account (or avoidance) of confounders, and study of the quartz exposure/cancer risks separately in those with and without silicosis.

We are aware of one study population (Miller et al 1995) where historical quartz exposures are extremely well documented, and are unlikely ever to be bettered. Further study of this population and, if feasible the Ontario hard-rock miners (Muir *et al.* 1989), would usefully inform the decision-making process.

2.6 Conclusion

In addressing the aims of this study our review of current epidemiological evidence shows that reliable quantitative estimates of risk for silicosis are not possible at the low levels of exposure currently under consideration. The least unreliable estimate is probably that of Muir *et al* 1989, and this suggests that the frequency of category 1 or greater silicosis over a 40 year exposure to $0.1 mg/m^{-3}$ respirable silica is low. No reliable estimates of risk at lower concentrations can be made at present. The risks of greater, and more clinically important, categories of silicosis are likely to be much less than those of category 1.

The exposure data in the key epidemiological investigations are inadequate to determine whether crystalline silica polymorphs are carcinogenic in man. Evidence from epidemiological studies is insufficient to support a causal relationship between crystalline silica *per se* and lung cancer. Excesses of lung cancer in subjects with silicosis have been reported, though a direct role of silica has not been established.

Whether silica is classified according to EU rules as a category 2, or a category 3, carcinogen depends on the interpretation of the animal studies. On the one hand positive results in several independent animal studies could constitute sufficient evidence of carcinogenicity (Category 2). On the other hand the single animal species, demonstration of carcinogenicity predominantly in female rats, except in one study, making quantitative extrapolation to human health risks uncertain, lack of convincing evidence of genotoxicity, and possibly secondary mechanism of action, would argue for a category 3.

It is probable that exposure limits for quartz which prevent silicosis will prevent any related risks of cancer, if they exist for man.

Further work

The need for the protection of workers is to control quartz exposures to a level which prevents silicosis, and this will probably also prevent any associated risks of lung cancer. While existing knowledge indicates that the risks of silicosis can be contained by avoiding quartz concentrations on average greater than somewhere in the region of $0.1 mg/m^3$, the relative merits of levels below, at or above this level are unclear at present, and there is a research need for clarification of risks at these low levels.

This research need can best be addressed by epidemiological studies of a quartz exposed population, whose individual historical exposures to respirable quartz (gravimetric measurements) can be, or have been, quantified reliably, and who have been, or can be followed up, and chest radiographs performed. This should be after an interval since main exposure of at least one and preferably two or more decades, with minimally biased selection of individuals for follow-up. Confounding exposures (smoking, other minerals) are invariably present, but can be accounted for if adequate

exposure histories are available.

In this context another important issue for control limits to prevent silicosis is whether the present linear statistical model of exposure (concentrations multiplied by time) is accurate, for if the biological risk is in reality better related to a power of concentration weighted by time, then quite different risks at low concentrations may be estimated. These relationships can be modelled in data from rats exposed to low concentrations of quartz, and in epidemiological data such as in the kind of population described above.

The research needs for resolution of the regulatory debate include the above topics, and additionally include the question of differentiation between category 2 and category 3 carcinogenesis. Studies are necessary of whether the excess of lung cancer in rats, and possible excess in human silicotic subjects, is a direct effect of quartz or a secondary effect, of fibrosis. For this purpose, studies in both rats and man would be informative. In rats, studies of the effects of very low quartz concentrations could determine whether excess lung cancers are dependent on the presence of fibrosis. Rat studies may also provide useful tools for assessing the mechanism of silica-induced fibrosis at an early stage. Thus, they may allow a study of markers of early biological events which could contribute to the chronic stimulation leading to fibrosis and tumours. In man, a mortality study of a population similar to that described in the preceding paragraphs would indicate whether excesses of lung cancer occurred only in those with evidence of silicosis, or also were related to quartz exposure in subjects without silicosis. The question of whether silicosis could have developed in the interval between the last chest radiograph and development of lung cancer would need to be considered in the study design.

3. ACKNOWLEDGEMENTS

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APPENDIX 1

A1.1 Study Design

A1.2 Selection process

The source papers were selected by the following process.

(a) A literature search using criteria listed below

(b) Those papers listed in reviews by other authors

(c) Those papers used by Regulatory authorities of member states to set existing or proposed control limits.

A1.3 Selection criteria

The following criteria were used to select source papers.

(a) Studies which support both negative and positive associations between silica exposure and lung cancer in order to avoid bias in producing a final report.

(b) Those studies which use populations selected after the introduction of occupational hygiene controls, as exposure levels prior to this time are often poorly documented, extremely high and atypical of conditions which now exist.

(c) Studies using populations mainly from "first world" countries, to produce better correlation for European requirements.

(d) Studies produced since 1990 which have appropriate exposure data, and account for confounders, if applicable to allow more reliable estimates of risk.

(e) Those animal studies which enable the aims of the project to be met.

A1.4 Framework for review

This framework was used throughout the review.

(a) *Exposure*

- (i) What type of silica or quartz?
- (ii) Aerodynamic particle size?
- (iii) Naturally fine or ground?
- (iv) Effects from mixtures of other substances, especially where data is historical?
- (v) How reliable is exposure data, especially if historical?
- (vi) Is proper account taken of improved industrial hygiene measures, and changes in measuring instruments?
- (vii) How reliable are measures of exposure levels, or concentrations in relation to duration of exposure?
- (viii) How relevant are the levels stated to the aims of this study?

(b) *Study population*

(i) How has the study population been selected?
(ii) How great are the effects of selection and detection bias, and are these taken into account?
(iii) Is there a control group, or is it a study of degrees of exposure, or do both occur?

(c) *Confounders*

(i) Have all confounding factors been identified, considered and quantified?
(ii) How reliable is the data on smoking in relation to lung cancer. Is this based on individual, next of kin or pack/year estimates?

(d) *Medical measurement*

(i) Is silicosis defined? How is it defined?
(ii) Is it possible that there is fibrosis other than silicosis?
(iii) Have X-rays been read using the ILO classification?
(iv) How many trained readers have been used?
(v) Are the main testing instruments sensitive enough for reliable data interpretation?
(vi) How is lung cancer diagnosed?
(vii) Are specific types of lung cancer differentiated?
(viii) Is pathological confirmation available in mortality studies?

(e) *Animal studies*

(i) Has the study genuinely proved that silica is carcinogenic to rats?
(ii) Considering the experimental conditions what is the relevance of the findings to humans?

(f) *Analysis*

(i) What models have been used for data analysis and do these have biological relevance in humans?
(ii) Is it possible to demonstrate a dose-response effect?
(iii) Is it possible to demonstrate absence of effect at low concentrations?
(iv) Is consideration given to latency?
(v) Are specific periods of exposure in a working lifetime more relevant than others?
(vi) Is it possible to obtain a quantitative risk assessment?
(vii) Are confidence intervals quoted for relative risks (RR) and standardised mortality ratios (SMR)?
(viii) What are the aspects of uncertainty not quantified by confidence intervals?

A1.5 Pilot review

In considering the human studies both on silicosis and lung cancer, two studies were selected on each subject and reviewed in detail using the framework listed. The studies selected were those most likely to be included in the list of key papers, and the experience gained from this process will be used to limit the detail required for the review of source papers. Source papers scoring highly on aspects of

the framework review judged to be most critical in achieving the aims of the study were included in the list of key papers.

A1.6 Review of other selected papers

A subset of key papers were reviewed by all team members and the reliability of risk estimates and suggested control limits will be assessed on the basis of the review framework.

The data from animal studies were reviewed using a similar process, the key papers being summarised in Appendix 4.1.

APPENDIX 2

A2.1 Classification Systems

In the case of a suspected carcinogen the EU classification represents a qualitative estimate of hazard. No recommendation is given with regard to regulation or legislation which are the responsibility of individual governments or other international organisations.

The categories listed refer only to the strength of evidence that a substance is carcinogenic and not to its potency as a carcinogen nor to the mechanisms involved. The classification may change as new information becomes available. The evaluation is focused as narrowly as the available data permit. Results of animal, genetic and human studies are considered together with existing occupational exposure data. The following classification is used by the International Agency for Research on Cancer (IARC, 1994); all other classifications tend to be based upon this.

IARC Classification

(a) Sufficient evidence

From human studies - where a causal relationship can be established between exposure and cancer in humans.

From animal studies - where a causal relationship can be established between an agent and an increased incidence of malignant neoplasms, or an appropriate combination of benign and malignant neoplasms in:

(i) two or more species, or
(ii) two or more independent studies of one species carried out at different times, in different laboratories or under different protocols. Exceptionally a single study in one species may be sufficient if malignant neoplasms occur to an unusual degree.

(b) Limited evidence

From human studies - where causality is feasible but confounding cannot be ruled out with sufficient confidence.

From animal studies - where causality is feasible but at least one of the following applies:

(i) evidence of carcinogenicity is restricted to a single experiment

(ii) there are uncertainties regarding the adequacy of the design, conduct or interpretation of the study

(iii) the agent increases the incidence only of benign neoplasms, or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains

(c) Inadequate evidence

From human studies - where causality is not established as the available studies lack power and

consistency.

From animal studies - where available studies have major qualitative or quantitative limitations or no data on cancer in experimental animals is available.

(d) Evidence suggests lack of carcinogenicity

From human studies - adequate consistent studies are available covering the full range of human exposure levels.

From animal studies - adequate studies involving at least two separate species are available which show that within the limits of the tests used the agent is not carcinogenic. The conclusion is inevitably limited to the species, tumour sites and levels of exposure studied.

A2.2 The EU Classification and Labelling of Carcinogens

The *EU classification of carcinogens* (Commission 1993) follows the principles listed below.

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1

Substances known to be carcinogenic to humans. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2

Substances which should be regarded as if they are carcinogenic to humans. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

(a). appropriate long-term animal studies,
(b). other relevant information

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. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

Comments regarding the categorization of carcinogenic substances:

'The placing of a substance into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.'

For classification as a category 2 carcinogen, either results in two animal species should be available

or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 subcategories:

Category 3a - Substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

Category 3b - Substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For distinction between categories 2 and 3 the arguments listed below are relevant. These arguments, especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals:

(i) carcinogenic effects only at very high dose level exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;

(ii) appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation;

(iii) appearance of tumours, only at the site of application, in very sensitive test systems (eg. intraperitoneal or subcutaneous application of certain locally active compounds), if the particular target is not relevant to man;

(iv) lack of genotoxicity in short-term tests *in vivo* and *in vitro*;

(v) 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);

(vi) existence of a species-specific mechanism of tumour formation (eg. by specific metabolic pathways) irrelevant for man.

For a distinction between category 3 and no classification (category 4) arguments are relevant which exclude a concern for man.

(i) a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;

(ii) if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;

(iii) particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

The following symbols and specific risk phrases also apply to potential carcinogens.

Categories 1 and 2

T; R45 - May cause cancer

However, for substances and preparations which present a carcinogenic risk only when inhaled, for example as dust, vapour or fumes (other routes of exposure, eg. swallowing or contact with the skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 - May cause cancer by inhalation

The phrase 'may cause cancer by inhalation' was introduced into national legislation in 1991, to indicate a special subcategory of carcinogens that only cause cancer by inhalation.

Category 3

Xn; R40 - Possible risk of irreversible effects

The labelling guide also includes comments regarding the categorization of carcinogenic substances:

'The placing of a substance into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.'

For classification as a category 2 carcinogen, either results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Just as the final responsibility for the classification of carcinogens rests with individual governments, similarly, *EU Occupational Exposure Limits* (OEL's) are only recommendations which have no binding value and are based on an evaluation of existing criteria documents. These include an assessment of:

(i) the physical and chemical properties of a substance
(ii) its occurrence, production and use
(iii) quantitative information on exposure and most likely routes of uptake
(iv) toxicology and toxicodynamics
(v) existing OEL's
(vi) consideration of groups at special risk

Data from both human and animal studies is considered, and in setting limit values for man there is:

(i) determination of health-effects to organs or biological systems including a range of effect-related concentrations and if possible numerical values for dose-response relationships

(ii) definition of the most relevant and sensitive target organs including any evidence of a "no observed adverse effect level".

Other factors such as carcinogenicity are considered separately.

APPENDIX 3

A3.1 Measurement of exposure in key epidemiological studies

The exposure data in the key epidemiological investigations into the effects of crystalline silica are inadequate to determine whether quartz, in particular, or other crystalline silica polymorphs including cristobalite are carcinogenic. As discussed in more detail below, the data are not always specific as to which silica polymorph workers were exposed, how much workers were exposed to and to what other substances workers were co-exposed. In addition, there are several aspects of the determination of quartz exposures and cumulative dose that suggest that it would be very difficult to establish unique relationships linking the risk of silicosis or of lung cancer with cumulative quartz exposure.

Crystalline silica includes five different minerals with differing surface properties and hence chemical and biological reactivities. Quartz is the stable crystalline silica phase at the earth's surface and workers in quarries, brickworks, construction sites, aggregates and most other industries employing silica are exposed to quartz. Cristobalite is a high temperature phase that forms during the devitrification of amorphous silica including silicate glasses. Exposure occurs in industries that make and use refractory products such as calcined diatomaceous earth and ceramic fibres. Cristobalite is generally believed to be much more toxic than quartz. The silica phase in the study by Checkoway *et al* (1993), relating crystalline silica to lung cancer, is cristobalite and the results of this study cannot be used to assess the carcinogenicity of quartz. Similarly, the crystalline silica phase in the study by Merlo *et al* (1991) is probably cristobalite, although the nature of the exposure is not described.

Exposure to respirable quartz is measured as mg/m^3, as this is the easiest of the various measures of concentration to reliably quantify. Many toxic substances, such as metal salts, are relatively soluble, and inhaled particles are absorbed by the bloodstream leading to accumulation of the substance in target organs outside of the lung. In terms of toxic activity quartz is virtually insoluble and largely accumulates within the lung. The interaction between lung and quartz occurs at the surfaces of individual particles rather than throughout the mass of each quartz particle. Given that each individual quartz particle has to be dealt with individually by the lung's defence system, the total mass of quartz entering the lung at any instant may not be the most biologically relevant measure of exposure. At low dust concentrations, measures of particle number or surface area might be more likely to show a relationship with disease outcome. Beadle (1971), for example, found a relationship between risk of onset of silicosis in goldminers and cumulative exposure as particle surface area per cubic centimetre years. At higher dust concentrations, cells within the lung are likely to become more heavily loaded with particles, and less likely to clear particles from the lung. Given that the total loading per cell will affect that cell's viability, the total mass of dust (rather than just quartz) within the lung at any instant might be of more biological relevance at high concentrations than at low concentrations. Jacobsen *et al* (1971), for example, found a convincing relationship between the risk of pneumoconiosis and total dust concentrations as measured by mass, in British coal mines. The dust levels in their study were however very much higher than would be acceptable under modern hygiene measures, and quartz formed only a small proportion of the total dust. More generally, in any one study, if dust compositions are fairly similar throughout the study, mass concentrations of quartz may be a good proxy for particle number or surface area, and it may be difficult to determine whether mass is the most relevant measure of exposure. Quartz from different sources will have different particle size distributions and therefore different numbers of particles and surface areas per unit mass.

Dust measurements made before the early 1960s were of numbers of particles per unit volume with no specific measurements of silica. Extensive side by side comparisons of the particle number

concentrations versus gravimetric concentrations were made for the Vermont Granite workers (Davis *et al*, 1983) and the Ontario Hardrock miners (Muir *et al*, 1989). A similar smaller study was conducted in South Africa (Beadle, 1969). Other studies, for example Ng and Chan (1994) have used the conversion factor derived from the Vermont granite workers' study without any discussion of whether particle size distributions and relative quartz contents of dust were likely to be similar.

None of the studies that we have examined describes the full mineralogical composition of respirable dust or fully characterises all confounding co-exposures such as radon, diesel fumes and heavy metals. It is thought that some minerals, such as clay, may reduce quartz toxicity, whereas other substances may themselves be toxic and might effectively enhance quartz toxicity. Studies generally underestimate the number of likely confounding factors: for example, the probable exposure of quarry workers to diesel fumes is often not considered (eg Koskela *et al*, 1987). Radon is a serious confounder in various studies of metal miners, and the excess lung cancer in the Hnizdo and Sluis Cremer (1991) study of South African Goldminers could be entirely explained by radon exposure. None of the studies of metal miners (Hnizdo and Sluis-Cremer, 1991, 1993; Amandus and Costello, 1991; Carta *et al*, 1994; Muir *et al*, 1987) describe the metal content of mineral dusts. Many metals are known to cause lung disease and cancer. Most of the studies have included a token amount of smoking data, usually based on one or two surveys and extrapolated to the rest of the population and time period. None of the studies included a comprehensive assessment of exposure to tobacco smoke including the effects of secondary exposure. In Koskela *et al*'s (1987) study of granite workers in Finland, for example, it is assumed that the exposures to tobacco smoke would be the same as for the general population. In practice, workers might have huddled into poorly ventilated huts at breaktime to escape from the cold and had very much greater exposures to tobacco smoke than the general population.

The key studies that report dose-response relationships linking cumulative exposure to silica to the prevalence of silicosis do not fully describe levels of exposure in terms that can be readily converted into mg m^{-3}. Exposure is frequently described in purely qualitative terms, sometimes with the establishment of qualitative indexes (very high, high, medium, low) for different occupations within an industry, as, for example, in the study of Dutch ceramic workers by Meijers *et al* (1990). Other studies have used a similar weighting for time to allow for improved occupational hygiene (Checkoway *et al*, 1993). Numerical weightings are then assigned to different exposure categories with no discussion as to how these weightings were calculated, or whether identified time periods bore any relationship to major changes in occupational hygiene. Davis *et al* (1983) use a similar broad ranking of dose categories for the purpose of analysis, but have at least based their categorization on actual measured levels of exposure in particles per cubic foot times years of exposure (the slight overlap in classes is presumably a misprint). Davis *et al* also provide a useful compilation of dust concentrations by occupation but did not investigate quartz concentrations by occupation.

Other studies, such as those reported by Graham *et al* (1991) for Vermont Granite workers and for the US metal miners (Amandus and Costello, 1991), use cumulative length of service as a proxy for silica exposure, but with no allowance for the different dustiness of different occupations or through time. Graham *et al* (1991) do describe average levels of exposure, but the data is insufficient to judge the effectiveness of the current 0.1mg/m^3 limit on respirable quartz concentrations.

Studies which have used measures of respirable quartz concentrations in mg/m^3, for example, the Ontario Hardrock miners (Muir *et al*, 1989) and South African goldminers (Hnizdo and Sluis-Cremer, 1993) only report cumulative exposures. Although it is possible to use these to calculate mean levels of exposure, no information is available about maximum levels of exposure and how exposure might vary through time. Some limited information about the likely range of quartz exposures in the South African mines can be obtained from a source reference (Beadle, 1969, 1971) cited by Hnizdo and

Sluis-Cremer (1991, 1993). Beadle (1969) however, reported that the maximum concentration of respirable quartz in his survey of one group of mines was 0.33mg/m^3 whereas the maximum concentration that can be inferred from the Sluis-Cremer study (1993) is only 0.13mg/m^3. The earlier Sluis-Cremer lung cancer study (1991) suggested quartz concentrations had ranged up to 0.84mg/m^3. For the purposes of analysis, this paper described exposure in terms of particle-years, which might be particles per cubic centimetre- years or particle-surface area per cubic centimetre-years, but, as with the 1993 paper, the calculated doses are difficult to reconcile with the source reference (Beadle, 1971).

The South African goldminers' studies are typical of most of the studies that have considered real exposure data, in that data from a relatively limited hygiene survey (or in other studies' surveys) are extrapolated to cover the whole exposed population and exposure period. The Beadle surveys were of a limited number of mines during the early 1960s, but Hnizdo and Sluis-Cremer (1991, 1993) have extrapolated to calculate cumulative exposure in their much longer term epidemiological studies (1940-86). The study of Hong Kong granite workers includes a limited number of exposure data for the 1950s and 1960s and a final survey in 1982 (Ng *et al*, 1987). There is no information about the intervening time period. Exposure assessments for the Finnish granite workers' study were based on a single hygiene survey (Koskela *et al*, 1987).

Some of the key studies do not describe exposure at all, even though a large amount of exposure data was probably available to the authors (eg North Caroline Dusty Trades study, Amandus *et al*, 1991). There is a general assumption that the introduction of occupational exposure limits for quartz has limited workers' exposure. A major hygiene survey of the Danish Stone Industry (Guenel *et al*, 1989), however, suggests that many workers are exposed to much greater concentrations of respirable quartz than are allowed under the Danish occupational exposure limits.

The levels of dustiness in industry have been hugely reduced during the last half century. As a result, the key studies of workers who were exposed to the low levels of silica typical of more recent years (eg Carta *et al*, 1993) have relatively short exposures and follow-up times (less than about 25 years). Workers with longer exposure to silica (ie up to the typical working lifetime of forty years) were all initially exposed to very high dust levels prior to the introduction of more stringent hygiene measures. Damage to lung tissue, caused by a short term exposure to high levels of silica, may not equate to that caused by the same dose over a longer time period.

There is little discussion in the key epidemiological studies as to how the toxicity of quartz from different sources might vary. A number of studies have suggested that the toxicity of quartz is modified by the presence of other dust components and that quartz from different geological environments shows differing levels of biological activity. In particular freshly shattered quartz surfaces are thought to be more reactive and more toxic that those of aged surfaces. Clay-coated surfaces are even less reactive. One would anticipate that quartz in dust from quarries in igneous and metamorphic lithologies would be much more biologically active than that from quarries in most sedimentary lithologies or from bricks or other bulk materials based on clays. Similarly the quartz in dust from sawing a well cemented sandstone block, which is likely to include shattered sand grains, is likely to be more biologically active than that from breaking a poorly lithified sandstone, in which any liberated quartz would have been fine-grained in the original rock. The toxicity of quartz in dusts is therefore probably dependent on both the source material of the dust and the way the dust has been generated.

Some final aspects of exposure not covered by the epidemiological studies are; the definition of respirable, the performance of dust sampling instruments and the reliability of quartz determinations for airborne dust samples. Slight differences in the efficiency with which different particle sizes in

the respirable range are sampled by different instruments, could affect the apparent concentrations of respirable quartz present. At present there is no internationally accepted methodology for the analysis of airborne quartz samples, and considerable evidence of the poor comparability of quartz analyses performed in different laboratories following different methodologies (Addison, 1991; Madsen *et al*, 1994).

APPENDIX 4

A4.1 Animal Studies Relating to the Carcinogenicity of Quartz

The experimental administration of quartz to rats has resulted in the development of pulmonary tumours including malignant carcinomas. Positive results have been obtained both in inhalation studies (Dagle *et al* 1986; Holland *et al* 1986; Muhle *et al* 1991; Spiethoff *et al* 1992) and following intratracheal injection (Holland *et al* 1983; Groth *et al* 1986; Saffiotti, 1990). Mice on the other hand did not develop pulmonary tumours following long-term inhalation of quartz (Wilson *et al* 1986) or following intratracheal injection (Saffiotti, 1990). Hamsters have also failed to develop pulmonary tumours following the intratracheal injection of quartz (Holland *et al* 1983; Saffiotti, 1990).

The very clear evidence that quartz can produce pulmonary tumours in rats needs careful consideration in respect of whether or not these findings can be extrapolated to humans. Rat lung tissue appears very sensitive to the heavy accumulation of a number of types of mineral particle that do not appear hazardous to humans and both fibrosis and pulmonary tumours have been reported from the exposure of rats to titanium dioxide, often chosen in experimental studies as a completely inert material (Lee *et al* 1985), pure talc (National Toxicology Programme, 1992) or pure coal (Martin *et al* 1977). Extremely high doses were obviously a factor in some of these studies with titanium dioxide only producing tumours at the excessive inhalation exposure of 250mg/m^3. Similarly the tumours reported with pure coal developed following the exposure of 200mg/m^3. In contrast pure talc produced a significantly raised incidence of pulmonary tumours in rats exposed to only 18mg/m^3.

With rats the sex of the animals is an additional factor. For reasons not understood female rats are more susceptible to pulmonary carcinogenesis following dust inhalation than males. This was demonstrated in both the studies with titanium dioxide and talc where significant increases in pulmonary tumour production were found only in females and not in males. It is unfortunate that most of the positive experimental inhalation studies with quartz have used only females but where both sexes were exposed, the proportion of pulmonary tumours in females was much more marked (Dagle *et al* 1986; Muhle *et al* 1991). With asbestos, which is a well known human carcinogen, both male and female rats respond equally to dust inhalation producing large numbers of pulmonary tumours (Wagner *et al* 1974). It is likely that the sex difference in rats may only be apparent following treatment with materials of relatively low carcinogenic potency. Most of the positive rat studies have been conducted with just two samples of quartz (Min-U-Sil and DQ-12) that have been especially prepared for experimental work with a very small particle size and extremely high toxicity. Where another quartz sample (Novaculite) was compared to Min-U-Sil it was found to be less carcinogenic possibly because of its larger particle size, and therefore fewer particles per unit mass (Groth *et al* 1986). Few human exposures are to really pure quartz and there is considerable evidence that other materials inhaled with quartz can reduce its harmful effects (Le Bouffant *et al* 1977).

One factor appears clear from the published animal experiments. Quartz and other dusts only produce pulmonary tumours when they also produce severe pulmonary fibrosis. The typical round acellular fibrotic nodule that is the classical picture of human silicosis does not develop in rats but this may be a factor of time since the rat lesions must develop and mature during the period of at most 2 years. The rat response is initially alveolar lipoproteinosis which is similar to that found in human acute silicosis. Later small cellular nodular lesions develop around lymphatic channels in the peribronchiolar region and these can grow to a size of 1-2mm in diameter although they always remain cellular. Within the nodules a network of reticulin fibres can be demonstrated at an early

stage with later occurrence of collagen. Apart from nodular fibrosis areas of lung may be consolidated with granulation tissue which develops loose fibrosis. These areas can contain cholesterol clefts and areas of alveolar cell hyperplasia from which pulmonary tumours may develop. In the other species which has been tested with quartz, mice and hamsters, the pulmonary response appears to be limited to a widespread macrophage reaction with little or no pulmonary consolidation or fibrosis, and without alveolar lipoproteinosis.

A4.2 Summary of animal studies considered

One hundred and forty four rats of the Fischer F344 strain (72 males, 72 females) were exposed by inhalation to quartz dust (Min-U-Sil 5) at a dose level of 50mg/m^3 for 6 hours a day, 5 days a week, for as long as 24 months. Similar numbers of rats were maintained as controls. Subgroups of 10 rats (5 males, 5 females) were moved from quartz exposure at 4 month intervals up to 16 months to examine the development of pulmonary pathology. The remainder were exposed to quartz for their full life span. Widespread alveolar lipoproteinosis with marked peribronchiolar fibrosis was recorded and of those animals that survived for more than 494 days, 11 out of 100 developed squamous carcinomas. None of 89 control animals developed these tumours. There was marked difference in response between the sexes of those animals treated with quartz. Of the 11 carcinomas, 10 developed in female rats and only 1 in a male animal (Dagle *et al* 1986).

Sixty two female rats of the Fischer F344 strain were exposed by inhalation to quartz dust (Min-U-Sil) at a dose level of 12mg/m^3 for 6 hours a day, 5 days a week, for 83 weeks. One group of 62 female rats were subjected to the same confinement in the inhalation chambers but received only pure air to breathe. Another group of 15 female rats were maintained without any manipulation. Most of the animals exposed to quartz had developed "silicotic nodules" and "pleural plaques" by the end of exposure. Twenty out of 62 rats treated with quartz developed pulmonary tumours (6 benign, 14 malignant). (Holland *et al* 1986).

One hundred rats of the F344 strain (50 males, 50 females) were treated by inhalation to quartz dust (DQ-12) at a dose level of 1mg/m^3 for 6 hours a day, 5 days a week, for 24 months. Parallel groups of rats were exposed to titanium dioxide dust or air only. Fibrotic foci developed in most of the quartz-treated animals (99%), and 19 developed pulmonary tumours (7 developed benign, 12 malignant and 1 other had both benign and malignant tumours) (Muhle *et al* 1991). However, while 3 benign and 5 malignant pulmonary tumours occurred in seven male rats, (one animal with one of each), 4 benign and 8 malignant tumours developed in 12 female rats (Muhle, *et al*, in press). In the other groups 3 tumours were observed in air only treated rats (2 benign, 1 malignant) and 2 tumours in the titanium dioxide treated (1 benign, 1 malignant). No statistical evaluation of the data is given.

Groups of 90 female rats of the Wistar strain were treated by inhalation to doses of quartz (DQ-12) of either 6mg/m^3 or 30mg/m^3 for a period of only 29 days. Nineteen female rats were exposed in inhalation chambers to pure air as controls. Treated animals, especially the high dose group, showed marked alveolar lipoproteinosis and fibrosis. By the end of the study at 34 months, 8 rats from the low quartz treatment group and 13 rats from the high dose group had developed pulmonary tumours. Tumour types were not specified in detail but some were reported to be malignant (Spiethoff *et al* 1992).

A total of 60 female mice of the Balb/C BYJ strain were exposed to silica (Min-U-Sil) by inhalation for periods of between 150 and 570 days. Fifty nine mice were maintained as untreated controls. The dose level for silica treatment was approximately 1.5-2.0mg/m^3. Dosing was for 8 hours a day, 5 days each week. The occurrence of fibrosis was not recorded. Pulmonary tumours were all benign

adenomas and developed in similar numbers in both exposed and control mice (Wilson *et al* 1986).

Thirty six rats (sex unspecified) of the Sprague Dawley strain and 72 Syrian hamsters (sex unspecified) were treated with quartz (Min-U-Sil) by intratracheal injection. Ten weekly injections were given of either 3mg or 7mg (hamsters) or 7mg (rats). Forty rats and 58 hamsters received the same number of injections of saline only and 18 rats and 36 hamsters were maintained as untreated controls. None of the quartz-treated hamsters developed either fibrosis or pulmonary tumours. In the quartz-treated rats fibrosis was widespread and 6 animals developed pulmonary tumours (1 benign, 5 malignant). No pulmonary tumours were reported in control animals. (Holland *et al* 1983).

Two groups of 85 male rats of the Fischer 344 strain were given quartz by intratracheal instillation. Two varieties of quartz were used, Min-U-Sil or Novaculite. The dose was 20mg administered by a single injection. Eighty five rats received a single injection of saline as controls. Many treated rats developed pulmonary fibrosis including some with dense collagenised "silicotic nodules". Thirty rats exposed to Min-U-Sil developed pulmonary tumours compared to 21 exposed to Novaculite. All pulmonary tumours were described as malignant. A single malignant pulmonary tumour was found in a control animal. (Groth *et al* 1986).

Fifty three male and 49 female rats of the Fischer 344 strain were given a single intratracheal injection of quartz Min-U-Sil. Control animals were not mentioned. Widespread pulmonary fibrosis was recorded in the rats and 21 males and 27 females developed pulmonary tumours. In the same study mice and hamsters also received intratracheal injections of quartz. Neither the numbers of animals nor the dose administered was recorded. (Saffiotti, 1990).

Ninety seven female Sprague Dawley rats were exposed by inhalation to coal dust containing 10% of quartz for either 18 or 24 months. The dose level was 200mg/m^3 and dosing was for 5 hours per day, 5 days each week. Forty five were similarly exposed to pure coal dust and data was available for 485 untreated controls. Twenty eight rats exposed to coal plus quartz developed pulmonary tumours (mostly carcinomas). Three rats treated with pure coal dust developed similar pulmonary tumours but none occurred in the large control group. (Martin *et al* 1977).

Groups of 100 male and 100 female CD rats were treated by inhalation to titanium dioxide at dose levels of 10, 50, or 250mg/m^3. Exposure was for 6 hours per day, 5 days per week for 24 months. Similar sized groups were exposed to air only as controls. The incidence of pulmonary tumours in the two lower dose groups was at control levels (one or two tumours per group). At the 250mg dose, however, a total of 25 pulmonary adenomas and 14 pulmonary carcinomas occurred. The adenomas developed similarly in both sexes but 13 of the 14 carcinomas occurred in female rats. (Lee *et al* 1985).

Groups of 50 male and 50 female rats of the Fischer 344 strain were treated by inhalation to pure talc at dose levels of either 6 or 18mg/m^3 for over 2 years. Similar sized groups of male and female mice of the B6C3F strain were given the same treatment. The same sized groups of rats and mice of both sexes were maintained as controls. In the male rats a single pulmonary adenocarcinoma and 1 benign adenoma developed at each dose level. In the female rats, no pulmonary tumours were found in the low dose treatment group but 8 adenomas and 8 pulmonary carcinomas developed in the high dose group. In male control rats no pulmonary tumours were found but in females 1 adenoma and 1 carcinoma were reported. In the male and female mice, pulmonary tumours were relatively common but similar numbers were found in control animals. (US National Toxicology Programme, 1992).

A4.3 Human studies

Silica and Lung Cancer
Checkoway *et al* (1993)

This study is a retrospective cohort study of 2570 white men exposed to a mixture of silica phases, dominated by cristobalite at 2 Californian plants. The men had a minimum of 12 months cumulative service and were followed up between 1942 and 1987. Vital status was available for only 91% of the study population, and death certificate information for 94% of the identified deaths. The control group was restricted to white males chosen from the US population.

The workers in this study were exposed for an average of 8.8 years. Diatomaceous earth in the raw state comprises largely amorphous silica with small amounts of quartz (up to 4%). This material is calcined (kiln-treated) before use and this treatment causes a proportion of the originally amorphous silica to crystallise to cristobalite (rather than quartz). Respirable dusts generated from calcined diatomaceous earth have cristobalite contents of up to 25%. The other components of the dust are not described, but the volumetrically most important component of the dust is probably amorphous silica. The levels of exposure are not described within this paper and the exposure assessments are expressed in relative rather than absolute terms. Relative weightings are given to different occupations and for time allowing for progressive improvements in industrial hygiene.

Death certificate data were coded by one nosologist using the 5th to the 9th revisions of the ICD dependent on which was in effect when the death occurred.

Analysis of SMR's was carried out separately for four study groups (2570 white men, 37 black men, 242 white women, 104 white men exposed to asbestos) using US rates for years 1942 to 1987. In the main study cohort of 2570 white men, there were 628 deaths compared with 563 expected, an SMR of 1.12 (96% confidence interval [CI] 1.03 - 1.21). Cause-specific excesses were observed for lung cancer (59 observed, 41.4 expected, SMR 1.43, 95% CI 1.09 - 1.84), and non-malignant respiratory diseases excluding pneumonia and infectious diseases (NMRD) (56 observed, 21.6 expected, SMR 2.59, 95% CI 1.96 - 3.36). Analysis of lung cancer by year of hire showed the largest (and the only statistically significant) SMR in men hired before 1930 (8 observed, SMR 2.63, 95% CI 1.12 - 5.15). Analysis by year since first employment showed an increasing trend in lung cancer SMR apart from an SMR of 2.10 in the lowest category (< 10 years), which was however based on only 3 deaths. These results suggest the presence of a work-related lung cancer hazard, strongest prior to 1930.

Comparison of death rates for lung cancer and NMRD within the group of 2570 white men was made by multiple regression analysis. Person-years and observed deaths were tabulated by age at risk, calendar time, duration of follow-up, ethnicity (Hispanic versus non-Hispanic), and exposure category. Two exposure indices were used: duration of employment in dust-exposed jobs and a semi-quantitative index of exposure to crystalline silica. Although the semi-quantitative index considers occupation and improved hygiene conditions there is no discussion of how these weightings were arrived at. Numbers of deaths were assumed to follow a Poisson distribution. The mathematical form of the regression equation is not stated, but relative risks are quoted for three exposure categories in relation to the lowest category. Four analyses were carried out using exposure lags of 0, 5, 10, 15 years respectively. Only the main results for lung cancer are summarized here.

Analysis by duration of employment showed increasing trends in relative risk over the four exposure

categories, adjusted for age, calendar time, duration of follow-up, and ethnicity, for each of the four lags used. The strongest gradient occurred with a 15-year lag: men with 20 or more years employment in dust related jobs had a risk of lung cancer 2.88 times that of men with less than five years (95% CI 1.13 - 7.33). Increasing trends in relative risk with the semi-quantitative exposure index were also apparent for each lag, but were subject to some fluctuation. The strongest trend again occurred for a lag of 15 years.

Smoking data were available for 1113 of the 2570 men, but were not regarded as sufficiently complete for purposes of statistical adjustment. Using an assumed value of the proportion of smokers in the lowest category of the semi-quantitative exposure index, and a relative risk of 10 for smokers relative to non-smokers, the proportions of smokers in the higher exposure categories were calculated which would account for the observed trend in relative risk, assuming that dust exposure had no effect. For the highest exposure category it was found that even if all of the men smoked, the observed increases in risk could not be accounted for. A slightly lower proportion of smokers was documented in the lowest exposure category compared to the other categories, but otherwise there was no evidence of correlation with exposure. Apart from lung cancer, there were no overall excesses of the major cancers usually associated with smoking, suggesting that the cohort's smoking habit did not differ greatly from that of the general population.

Although known asbestos workers were excluded from the cohort, it appears likely that other occupational groups may have included asbestos exposed individuals, which may alter the interpretation of results. With this reservation, the study's results suggest that dust exposure in the diatomaceous earth industry is associated with increased risk of lung cancer. The lack of adjustment for smoking means that the magnitude of the exposure-response gradient is uncertain. The exposure indices used in the analysis are not appropriate for use in a regulatory context, and the question of lung cancer risks in the absence of silicosis is not investigated.

This study is of limited application for determining the risks associated with silica exposure, largely because of the absence of quantitative exposure data. In addition, most workers exposed to silica are exposed to quartz, rather than cristobalite which is relatively rare. Cristobalite occurs in products manufactured from diatomaceous earth and in some degraded refractory products. Cristobalite and quartz are two distinct mineral species with distinct properties and surface characteristics despite having the same chemical composition. The surface characteristics of a mineral govern how it interacts with cells and chemical species in the lung. The toxicity of distinct mineral species with the same chemistry can be quite different. For example, the toxicity of crocidolite asbestos is very much greater than that of the equivalent nonasbestiform mineral riebeckite. Various in-vitro and in-vivo tests with different silica polymorphs have highlighted probable differences in toxicity (Davis, 1993; Driscoll, 1993).

Hnizdo and Sluis Cremer (1991)

This paper considers a retrospective cohort of 2209 white South African gold miners who had at least 10 years cumulative service, and who had participated in a survey of respiratory impairment between 1968 and 1971. Mortality was followed up until the end of 1986.

South African gold miners are occupationally exposed to silica-rich mineral dusts, radon and diesel fumes. Respirable dusts contain up to 30% free crystalline silica (most probably as quartz). Radon exposures are over 100WLM (working level months) for miners with over 20 years of gold mining experience. The miners in the study worked for an average of 23.5 years and were exposed to dusts containing variable amounts of quartz (from 14 to 57% of respirable dust) and with quartz concentrations that ranged from 0.05 to 0.58mg/m^3 (Beadle, 1969). The exposure data for quartz in

the study are expressed in particle-years which are not formally defined by the authors. The exposure data was supposedly taken from Beadle (1971), although Beadle defined a smaller number of occupational groups than Hnizdo and Sluis Cremer. Particle years might mean particles per cubic centimetre per working year, although the numbers do not quite match those in Beadle's (1971) study. The numbers are slightly closer for surface area (μm^2) per cubic centimetre. It is probable that quartz particles in these mine dusts have freshly shattered reactive surfaces, in contrast to the aged surfaces that would be more typical of quartz from other geological environments, for example, clay pits and coal mines. No information is given by Beadle about the other dust components which may well include heavy metals such as uranium rare earth elements and diesel particulates. There is likely to be a direct relationship between particle concentration and exposure to radon daughters absorbed on dust particles. Although the nature of the dust exposures is not well characterised, the exposure assessments, in terms of particle years, for individuals within the study have been more carefully calculated than in other comparable studies.

Lung function and smoking data were available for only the period of the survey. Autopsy results were available for 84% of the dead miners, and results were scrutinized by a further 2 physicians. Death certificates were coded according to the 9th revision of the ICD.

Statistical analyses comprised: (i) a Cox regression analysis of lung cancer mortality in relation to age at the start of follow-up, four indices of exposure to tobacco smoke, examined singly,and five indices of exposure to gold mining dust, again examined singly; (ii) Poisson regression analysis of death rates derived by grouping person-years and deaths according to age, calendar time, cigarette-equivalent pack-years, and particle-years to the start of follow-up. In these analyses, the relative risk function included a "mixture parameter" between zero and one, which determined the shape of the function and the form of the interaction between smoking and dust exposure; (iii) logistic regression analysis of lung cancer mortality (yes/no) on age at death, four categories of silicosis (none, slight, moderate, marked), dust particle- years to the start of follow-up, and cigarette equivalent particle-years, restricted to 794 men on whom necropsies were performed.

The Cox regressions were carried out to select the smoking and gold mining dust exposure variables most strongly related to lung cancer risk. Those selected were: cigarette-equivalent pack-years, and particle-years/1000. This analysis gave a relative risk for lung cancer mortality of 1.023 (95% CI 1.005 - 1.042) per 1000 particle-years. The Poisson analysis gave adjusted relative risks of 1.54 (95% CI 0.6 - 4.3), 2.07 (0.7 - 6.0), and 2.92 (1.02 - 8.4) for three increasing categories of exposure: 16-30, 31-40 and >40 particle-years/1000, respectively, relative to a baseline category of <10 particle-years/1000. The estimated relative risk from the Poisson analysis was 1.028 per 1000 particle years (95% CI 1.009 - 1.048). Finally, the logistic analysis of the probability of lung cancer death showed a statistically significant relationship with the presence of silicosis of the hilar gland, the odds ratio being 3.9 (95% CI 1.2 - 12.7), adjusted for age at death, smoking, and exposure to gold mining dust.

The Cox analysis and the Poisson analysis both show statistically significant relationships with the index of exposure to gold mining dust. The relationships with cumulative exposure to gold mining dust are probably partly confounded with exposure to radon daughters, a fact noted by the authors. Logistic regression analysis establishes that silicosis of the hilar gland is associated with lung cancer mortality, but the effect of dust in silicotics and non-silicotics is not reported. An excess of small cell lung cancer was present at almost double the normal rates. This type has been associated with radon daughter exposure. Radon daughters have a short half-life, and their carcinogenic effect is likely to be based on a 'first hit' principle within lung tissue, which may also affect the distribution of tumours found at autopsy.

Due to the level of radon daughters to which some of these workers were exposed, it is more likely

that the dose-response relationship suggested in this study is primarily between radon exposure and lung cancer. However, other factors were present, for example heavy metals and diesel fumes, which could also contribute to the excess.

Koskela *et al* (1987)

These papers consider mortality and disability among Finnish granite workers. A cohort of 1026 men from three different areas of Finland, who were hired between 1940 and 1971 were followed up until 1981. This formed part of a Finnish Occupational Health Institute field study. Vital status was ascertained for all the cohort. The granite workers were exposed to mineral dusts containing quartz and probably also feldspars, and by inference, mica for a mean period of 12 years. Respirable quartz particles are likely to have had freshly shattered reactive, rather than aged surfaces. The authors claim that there would have been no co-exposure to other agents. It seems likely, however, that some of those involved in quarrying would have been exposed to diesel particulates and studies of granite workers in Vermont (Davis *et al*) have suggested that there may be a lung cancer risk associated with some of the abrasives used during the preparation of masonry stone. The levels of dust exposure were relatively high, up to 116mg/m^3 total dust and 4.9mg/m^3 quartz. Quartz constitutes between 25 and 35% of typical granite compositions, but may form a smaller proportion of the respirable fraction of dusts generated from granites, which may be dominated by micas. Exposure data was only available for the early seventies and the study does not include any assessment of any individual's cumulative dust or silica exposure.

Analyses were of mortality and incidence and prevalence rates of disability, the latter being defined in two ways; by the granting of a disability pension, and the granting of free medication. Both responses were analysed using a person-years approach. Comparisons of mortality rates were with Finnish national rates; rates for comparison of disability were obtained from the Finnish Social Insurance Institution. Mortality results were reported for three follow-up periods: to 1972, 1975 and 1981. The standard rates used in comparison for these periods were for single years only: 1965, 1969 and 1972 respectively. By the end of 1981, 20165 person-years had accumulated, an average of 19.6 per man.

Both primary and secondary causes of death were coded from death certificate data using the 8th revision of the ICD. It is assumed that data was available for all the cohort. A slight excess of lung cancer was found for the follow-up to 1981, which was not statistically significant (22 observed, 17.1 expected, SMR 1.29, 95% CI 0.80 - 1.95). Results for the two earlier follow-up periods showed a deficit of lung cancer (observed 4 and 8, expected 9.0 and 10.8 respectively). There was a statistically significant excess of mortality from "respiratory diseases" (28 observed, 13.9 expected, SMR 2.01, 95% CI 1.34 - 2.91). Analysis of lung cancer mortality by years since entry into granite work showed an increasing trend in SMR, with a notable excess in men with between 25 and 30 years elapsed (8 observed, 2.1 expected, SMR 3.81, $P<0.01$). Silicosis was recorded as the primary cause of death in 4.3% and a secondary cause in 2.6%.

The authors conclude that their results suggest that silica exposure per se influences the development of lung cancer. In support of this, they state that the cohort were not exposed to confounders such as radon daughters, PAH's or heavy metals, and further, that only one case where the primary cause of death was listed as lung cancer was silicosis listed as a secondary cause.

Data on smoking habits were collected by questionnaire in 1970-72. The numbers of study group members with smoking data is not given, but the authors state that the smoking habits of the granite workers were similar to those of other Finnish groups of active male workers of the same age. The authors argue that the high SMR's in different "years since entry groups" could not be explained by

differences in smoking habits.

The study is limited in its value for determining the risks associated with silica, as the exposures are poorly characterised and there is no quantification of the relative risks associated with differing levels of exposure. The authors' conclusion should also be regarded cautiously since smoking has not been allowed for in analysis. There is also the potential for geographical variation in disease prevalence. Further, it is difficult to assess what the effect on expected numbers of deaths of using only a single year's rates would be. Absence of radiological data means that the existence of silicosis in the cohort may be underestimated. There is also an unexplained deficiency of cancers at other anatomic sites.

Koskela *et al* (1994)

This paper follows up mortality until 1989 of the cohort of 1026 granite workers employed in the 3 main granite areas of Finland; Vehmaa (red granite), Kuru (grey granite), Viitasaari (black granite). Comparisons are made with mortality rates of census based target populations from the same regions.

Lung cancer risk increased with the length of exposure and latency. There were also regional differences in lung cancer risk; a 1.3 fold risk for workers in Vehmaa (red granite, 36% quartz), and a 2.1 fold risk for workers in Kuru (grey granite, 31% quartz). There were no cancer cases of any kind reported amongst workers in Viitasaari (black granite, no quartz content in the mineral): the word 'granite' was used by the authors in its building stone quality, rather than in the mineralogical sense. Comparison of lifelong exposure showed that the cases from Kuru were statistically significantly less exposed than the cases from Vehmaa. No remarkable exposure to other potential carcinogens was noted, and the differences could not be explained by differences in smoking habit.

As inflammation and carcinogenic potential of mineral dusts has been linked to the ability of dust to cause cell death (cytotoxicity), or to generate reactive oxygen species able to induce oxidative damage to DNA of target tissue, the mineral fractions from the three areas were analysed for ability to produce these changes. Cytotoxicity was estimated by the ability of 1mg/ml of dust to cause release of lactic dehydrogenase (LDH) from rat macrophages. The capacity of the dusts to generate reactive oxygen species in human leucocytes was estimated by a chemiluminescent method. In the cytotoxicity tests, the highest quartz containing fractions of red and grey caused the strongest LDH release. However, similar reactive oxygen species production was also seen with the quartz-free fraction of black granite. This activity was caused by the almost pure plagioclase fraction (calcium containing feldspar). It is not therefore possible to relate with enough confidence these in vitro biological responses to the incidence of lung cancer according simply to the silica content of the dust. The role of quartz in modification of host immunological response however remains interesting, particularly in the light of several studies showing increased rates of autoimmune disease, and disease of blood and blood forming organs in association with silica exposure.

Davis *et al* (1983)

This paper is a proportional mortality study of 969 deceased white male Vermont granite workers employed between 1952 and 1978 .The Department of Industrial Hygiene ran a voluntary X-ray programme from 1937 and 98% of the cohort had been X-rayed at least once by 1964. Retirement dates were not available for all men which may affect the estimates of duration of exposure. The granite workers were exposed to mineral dusts containing quartz and probably also feldspars, and by inference mica, for a mean period of 31 years. Free silica constitutes about 30% of the respirable fraction of dusts generated from the Vermont granites. The main dust component is probably mica.

Respirable quartz particles are likely to have had freshly shattered reactive, rather than aged surfaces. Some of the workers involved in quarrying would have been exposed to diesel particulates and cutters and polishers were exposed to abrasives used during the preparation of masonry stone.

The levels of exposure to respirable quartz prior to the introduction of modern hygiene practices in the 1950s ranged from about 1.0 to 4.9mg/m^3 in "shed" jobs, such as cutting and polishing and from about 8.7 to 14.2mg/m^3 in quarry jobs. Subsequently the levels of respirable silica have dropped below 0.9mg/m^3. The exposure data is expressed only in terms of very high, high, medium and low lifetime exposure but categories are well defined in terms of million particle per cubic foot years (>800, 399-800, 199-400, <200). It is not clear whether the slight overlap between these classes is due to a typographic error or was intended. Six major dust surveys had been performed during the fifty year period covered by the study and the relative levels of exposure associated with different occupations is well established. Simultaneous sampling in the Vermont granite sheds established a conversion factor by which the earlier readings in mppcf can be translated into mg/m^3 of respirable quartz (or vice versa). It appears that the exposures of the individuals in the cohort has been well established, although these data were only used to attribute individuals to an exposure group.

Death certificates were available for 95% of the identified deaths and coded by state nosologists according to the 7th revision of the ICD. Mobile X-ray units were used and films were read by 5 different readers. The diagnosis on the last X-ray was taken as evidence of silicosis status. The standard against which X-rays were read does not appear to have been consistent throughout the study and X-rays were mainly used to confirm the diagnosis listed on the death certificate.

In a proportional mortality analysis, observed numbers of deaths from specific causes of interest (within five-year age and calendar-time intervals) were compared to expected numbers calculated from the proportions of cause-specific deaths in the US white male population. Observed divided by expected gave what the authors call an "observed to expected ratio" or OER. Two sets of expected numbers of deaths were calculated: first, including deaths from tuberculosis and silicosis in the total number of deaths, and secondly, excluding these deaths from the study group total. These expected numbers yielded two sets of OER's, denoted OER I and II respectively. Notable excess mortality occurred from tuberculosis (65 observed, 6.5 expected (I)), laryngeal cancer (5 observed, 3.0 expected (I), 2.3 expected (II)), emphysema (22 observed, 16.9 expected (I), 15.2 expected(II)), diseases of skin and cellular tissue (3 observed, 0.7 expected (I), 0.6 expected (II)), suicide (34 observed, 19.0 expected (I), 18.3 expected (II)). There were 28 deaths from silicosis (expected number not calculated). A slight excess was observed for lung cancer (62 observed, 57.9 expected (I), 52.6 expected (II)); The OER (II) was 1.2 (95% CI 0.9 - 1.5). An analysis, in which deaths were grouped according to whether the subject had begun work before or after the introduction of dust controls, showed little difference in lung cancer OER (II) between the two groups: pre-control group OER 1.1, post-control OER 1.4).

A different form of analysis was used to compare the proportions of deaths from specific causes between exposure groups. As described above, estimates of lifetime exposure to granite dust were calculated for all subjects who were then grouped for exposure. For each exposure group, numbers of cause-specific deaths were expressed as a proportion of total deaths, using direct age-standardization, with the entire study group as the standard. For tuberculosis and silicosis, there were increasing trends in the standardized proportions by exposure category, but for lung cancer, there was no evidence of any trend. Directly standardized proportions were as follows (very high to low exposure): 5.8%, 6.5%, 8.6%, 7.2%.

The purity of the silica exposures in the Vermont granite industry is given as a possible reason for the finding of no association between lung cancer and dust exposure in the present study. Smoking

was not taken account of in the analysis, but information on granite shed workers indicates that granite workers smoked slightly more than US white males in 1970.

Guenel *et al* (1989)

This study considers a survey to assess exposure to silica dust in the Danish Stone Industry between 1948 and 1980. Records of 197 personal air samplers were considered from the Archives of the Danish Institute of Occupational Hygiene. Concentrations of respirable dust range from 0.1 to 39.7mg/m^3 and the quartz content of respirable dusts from granite ranged from 3-35% and from flint, 10-33%. Cristobalite was found within a small percentage of samples. Comparison is drawn between the stone-cutting and road material industries and in addition each of these industries was monitored in three distinct areas of Denmark. The levels of dust exposure in the road materials industry is higher than in the stone-cutting industry. Individual tasks were also compared increasing levels of quartz being associated with cutting, sieving, drilling and crushing.

No information is given on disease outcome and, no data is available for smoking or other exposures. This study is not informative regarding exposure-response for lung cancer and silica, and is therefore not helpful to the regulatory debate.

Carta *et al* (1994)

This is a study comparing mortality of two cohorts of Sardinian metal miners following a cross-sectional survey in 1973. Vital status was ascertained as of December 1988, for all subjects. The survey considered 1741 miners, accounting for over 98% of the workforce at both mines (906 mine A, 835 mine B) located in similar geographical areas. The miners in two mines were both exposed to mineral dusts containing quartz, radon and, during the latter part of the study period, diesel fumes.

The mean length of exposure was about 26 years. The respirable dust levels in both mines were similar: about 2.5mg/m^3 in the 1960s, 1.7mg/m^3 in the 1970s and 80s. The pre-1960s dust levels are believed to have been of the order of 3-5mg/m^3. Quartz levels in the two mines were quite different with median values of 1.2% of respirable dust in mine A and 12.8% in mine B. The radon levels were also quite different with miners in mine A experiencing a mean annual exposure of about 1.4WLM and in mine B about 0.12WLM. From information presented on the composition of the wall rocks, it may be assumed that the other dust components in mine A were probably calcite and dolomite (CaMg(CO3)2) whereas at mine B they were probably micas and possibly siderite (FeCO3). The quartz in both mines was probably dominated by freshly shattered, uncoated surfaces. The exposures to both quartz and radon have been relatively well characterised for the populations as a whole, but not for individual miners. There is little information about exposure to diesel fumes.

Although the same population was followed up in 1978, 1981, and 1988 the data are not yet available. The study therefore considers results of standard chest X-rays and lung function taken at the 1973 survey. The X-rays were reviewed independently by two radiologists using 1981 ILO criteria. Silicosis was classified as 1/1 or more on the ILO scale. Spirometry results were available for 98.9% of the cohort and, were reviewed according to American Thoracic Society criteria. Death certificates were available for all deceased subjects and, causes of death recoded according to the 9th revision of the ICD by three physicians.

Expected numbers of deaths were calculated from regional rates, and SMR's calculated for the complete study group, and within various sub-cohorts. A nested case-control study of lung cancer in relation to work underground (yes/no) and presence of airways obstruction, smoking, and age, was

carried out at 1 of the mines. Smoking and occupational histories were obtained at survey. All-causes SMR's at the mines were 0.82 and 0.90; lung cancer SMR's were 1.28 (95% CI 0.75 - 2.05) and 0.85 (95% CI 0.34 - 1.75). The higher lung cancer SMR was observed at the mine with higher radon daughter levels and lower quartz levels. Underground workers at this mine showed an upward trend in lung cancer SMR with years underground; there was no such trend at the other mine. The case-control study showed a statistically significant effect of airways obstruction, but not of having worked underground. This negative study suggests that quartz exposure is not an important risk factor in the development of lung cancer. The authors make the point that follow-up time is relatively short.

The authors' conclusion is that crystalline silica *per se* does not appear to affect lung cancer mortality, although they concede that the small sample size and short follow-up time reduces the power of this study.

Amandus *et al* (1991,1992) (Dusty trades)

These papers consider cases of silicosis diagnosed as part of the North Carolina (NC) Industrial Commission's pneumoconiosis surveillance programme for dusty trades. Voluntary medicals had been performed 1 to 2 yearly since 1935. Vital status was ascertained for 714 men at 1983. Medical records for non-silicotics were not retained. Work history and smoking data were available from the Industrial Commission's files. Expected deaths were computed using US rates from 1940 to 1983, and North Carolina rates from 1950 as rates were unavailable prior to this date. Other external referents included a nationwide sample of non-silicotic metal miners, and current and ex-Appalachian coal miners with pneumoconiosis. Bias is a potential problem in this study both in selection and disease detection.

Neither of the journal papers describes the details of exposure, although some consideration had been made of possible confounding factors. This was done through the use of work histories to determine whether members of the cohort had been exposed to asbestos: talc and olivine mining, insulation work and foundries were all considered to be potential sources of carcinogens. The paper by Shy *et al* describes the existence of a large amount of data, both as particle counts and cyclone samples. The mean exposure to crystalline silica is said to be 10mg/m^3. years, but there are no details as to how the levels of exposure vary between industries and through time.

Initial chest X-rays were classified by one reader according to the 1930 Johannesburg Conference report, and by the 1959 ILO classification for referents. Survey films were 4x4", but standard films were obtained if silicosis was suspected and were read by three readers. The small films are unsatisfactory for the recognition of pneumoconiosis. All X-rays were later re-evaluated against the ILO 1980 standard. Death certificate information was available for 99% of identified deaths and was coded against the ICD 1968 edition.

The lung cancer SMR for 655 white silicotics was 2.6 (95% CI 1.8 - 3.6) based on US rates, and 3.0 (2.0 - 4.2) based on NC rates. The age- and smoking-adjusted rate ratio for white NC silicotics with no exposure to known occupational carcinogens compared to the non-silicotic metal miners was 3.9 (2.4 - 6.4). Compared to the Appalachian miners and ex-miners, the age-adjusted lung cancer rate ratio for the same subgroup of silicotics was 1.5 (0.8 - 2.9). As the authors state, their results are consistent with an association between silicosis and lung cancer, but do not examine directly the role of silica exposure.

On re-classifying the X-rays, 477 films were available and read by 3 readers (370 silicotics, 107 non-silicotics). The percentage of the silicotic films re-classified as: category 0; categories 1,2,3; PMF

(progressive massive fibrosis) or unreadable, were 28, 44, 22, and 6 respectively. 97% of the non-silicotic films were re-classified as category 0. Analysis of lung-cancer mortality was restricted to 655 white silicotics. SMR's for men reclassified as category 0, categories 1+2+3, were 1.0 (95%CI 0.1 - 3.5) and 2.5 (1.1 - 4.9) respectively. SMR's for men with no exposure to potential carcinogens, other than silica, for men re-classified as category 0, 1.2 (0.2 - 0.4) and for men re-classified as categories 1+2+3, 2.4 (1.0 - 5.0). Corresponding SMR's for smokers were 1.3 (0.03 - 7.1) and 3.4 (1.1 - 7.9). It is of interest that SMR's were lower in those men whose X-rays were re-classified as category 0.

The study includes a range of industries within which exposure was probably predominantly to quartz. The other dust components and the surface characteristics, and therefore biological activity of quartz, are likely to differ greatly between different industries. These factors are not considered in the study.

Amandus *et al* (1991) (Metal miners)

This study considers a retrospective cohort of 9912 white male metal miners who attended Public Health medicals between 1959 and 1961. The cohort comprised 369 silicotics and 9543 non-silicotics. Information collected included chest X-ray, smoking habit, and occupational history. Deaths in the group were ascertained up to 1975. Lung cancer death rates in silicotics were compared to rates for white US males, and to rates for non-silicotics in the study group.
The miners were exposed to mineral dusts that contained quartz and probably a variety of other minerals. Dusts may also have contained small proportions of some heavy metals. The number of years individual miners had spent underground were taken to be a surrogate estimate of cumulative dust exposure. Radon exposures were estimated from measurements in 28 in the 38 study mines and in other nearby facilities. For the purposes of this study, the mines were divided into high and low radon groups. Individuals who had underground exposure to diesel fumes were excluded from the study. The quartz in these mine dusts was probably dominated by freshly shattered surfaces. The actual levels of exposure are not described.

Results of standard chest X-rays and spirometry were available from the medicals performed between 1959 and 1961. X-rays were classified by three radiologists using the 1959 ILO classification. Silicosis was defined as radiographic evidence of categories 1, 2, or 3 small rounded opacities or large opacities. Cause of death prior to 1975 was identified by death certificate information, although the coding system used is not stated.

A regression model was fitted to lung cancer death rates, using age, cigarette smoking and silicosis status as categorical explanatory variables. Lung cancer SMR's were 1.73 (95% CI 0.94 - 2.90) and 1.18 (0.98 - 1.42) for silicotics and non-silicotics respectively. The SMR for silicotics was higher in most subgroups defined by cigarette smoking, type of ore, years underground, low or high radon exposure, and year of hire. The age-adjusted lung cancer rate ratio (silicotics versus non-silicotics) was 1.56 (0.91 - 2.68), and, adjusted for age and smoking, 1.96 (1.19 - 3.23). Elevated rate ratios were present when mercury miners were excluded, and also in mines with low radon levels. The regression analysis showed a significant effect of smoking, but not of silicosis status (adjusted relative risk, 1.57 (0.94 - 2.64)). The study shows an increased lung cancer death rate in silicotics, but the effect of silica exposure is not examined directly.

Merlo *et al* (1991)

This is a retrospective cohort study of 1022 refractory brick workers at a factory in Genoa, employed

for at least six months between 1954 and 1977. Vital status was ascertained by demographic register at the end of 1986. Smoking data was based only on 285 workers employed in 1984 and there is lack of information on occupational history.

Workers were exposed to mean respirable dust concentrations of between 0.2 and 0.5mg/m^3 for a minimum period of six months. The maximum levels of crystalline silica in dust were 64.6% and were much lower elsewhere in the plant. The details of exposure are not reported in this paper. In particular it is not clear which silica polymorphs were present in the dust. It is likely that the dust contained cristobalite and possibly tridymite, either instead of, or in addition to quartz. No asbestos has ever been used at the plant and concentrations of polycyclic aromatic hydrocarbons within the plant are within the range of the local area.

Mortality was compared against the Italian male population. Death certificates were coded against the 9th revision of the ICD by a trained nosologist, although the completeness of follow-up is not recorded. From the available data it is not possible to identify those suffering from silicosis, which limits the usefulness of this study.

Expected numbers of deaths were calculated using Italian rates. SMR's were examined, for various causes of death, by year of first employment, years since first exposure, length of employment, age at hire. The all-causes SMR was 1.10, the lung cancer SMR, 1.51 (95% CI 1.00 - 2.18). In men with at least 19 years service, the lung cancer SMR was 2.01 (95% CI 1.07 - 3.44). Smoking habits of the 285 surveyed men were close to those of Italian males. Adjustment for smoking (using assumed relative risks) suggested that very little of the excess lung cancer mortality was due to smoking. There is no information on exposure-response given in this study.

SMRs are based on national rates not on those of north west Italy which may have introduced some bias. The study found the highest risk associated with those employed for 20 years prior to the mid 1950's, which would be likely to include those exposed to dust before the introduction of improved industrial hygiene measures.

Meijers *et al* (1990, 1991)

The Netherlands Labour Inspectorate conducted a nationwide health survey among ceramics workers in the 1970's to determine the risk of pneumoconiosis. In phase 1, 520 workers from 76 companies in the Gouda region were medically examined. In phase 2, 1975 workers from 2 large ceramics companies in Maastricht, and 763 from other small ceramic industries were surveyed. A case-control study of 381 cases of lung cancer was also conducted in Maastricht, to analyse the relation between dust exposure and lung cancer.

Exposure for a number of occupations in the ceramic industry were ranked by a panel of occupational hygienists in terms of their relative exposure levels to respirable silica. An exposure index was calculated for individual workers based on their work history, the relative rankings of different occupations and taking into account vastly improved hygiene measures introduced in the 1960s. Actual levels of exposure are not reported and the average length of employment in the industry was less than ten years. The nature of other components in the dusts that workers were exposed to, would have varied depending on which stage of the process was considered. Dusts probably a significant proportion of clays and much of the quartz may have been original sedimentary particles rather than freshly shattered quartz particles. Clays in coalmine dusts are often thought to be protective of the effects of silica.

Chest X-rays (8x8cm) were taken for a study on the prevalence of silicosis in quartz exposed ceramic workers and were classified according to the 1971 ILO classification. If silicosis was expected a larger X- ray was made and evaluated by a panel. The cut-off point for defining silicosis is not stated. Lung cancer was diagnosed from tissue obtained at bronchoscopical examinations between 1972 and 1988, and all cases were histologically verified. The controls were age-matched from the same pathology register regardless of diagnosis except for primary lung cancer. 19% of controls had been employed in the Dutch ceramics industry, compared with 21% of cases.

Silicosis prevalences from the cross-sectional study were 13.3% in Gouda and 1.7% in Maastricht. The odds ratio for those who had ever worked in coal mining was 0.95. For subjects who worked in the coal industry, the odds ratio for underground work was 0.96. Analysis of 152 males who had at some time worked in the ceramics industry showed elevated, but non-significant, effects of duration of employment, and exposure level. Quantitative data on past exposures to silica were not available. Years worked in the exposure categories (high, moderate,low or none) multiplied by arbitrary scorings of 3,2,1,0 gave a semi-quantitative index of cumulative exposure. Analysis showed an increasing trend in odds ratio with this index, reaching a statistically significant value of 9.88 in the highest category. There is no smoking data available for the cases and controls.

The authors note that the hypothesis that silicosis is an essential step in the development of silica-related lung cancer could not be tested in this study. The study is also uninformative regarding exposure-response, since cumulative exposures were not available.

A4.4 Silica and Silicosis

Muir *et al*, Verma *et al* (1989)

This paper considers an epidemiological investigation to determine the relationship between silicosis in hardrock miners in Ontario and cumulative exposure to silica dust. The cohort comprised 2109 men who started work between 1940 and 1959, and who were followed up until the end of 1982, or the end of their dust exposure if this occurred first. The men selected had spent at least 80% of their mining work in one or more of 21 gold and uranium mines with adequate dust exposure records. Employment records giving details of work histories were available from the Workers' Compensation Board (WCB) master file of miners. Criteria for being on the WCB file were: at least 60 months in dusty jobs, X-ray category 1/0 or greater, uranium miners with at least 2 weeks exposure. There was no follow-up of leavers and small mines were excluded.

An extensive side by side sampling programme was undertaken in order to derive factors by which historical dust measurements in mppcf could be converted to gravimetric quantities of respirable silica. Cumulative dust exposure in terms of mg/m^3.years appears to have been carefully established. More than half the cohort was exposed to less than $0.5mg/m^3$.years over a mean period of about 12 years. About 3% of the cohort was exposed to more than $2.0mg/m^3$.years over a mean period of about 20 years. There are no details of how exposure has varied through time or whether there were major changes in industrial hygiene during the study. It is probable that exposures were highest during the early part of the study. Little information is given about the nature of the dust to which miners were exposed. The silica mineral in the dusts was quartz and it probably largely had freshly shattered, reactive surfaces. Other dust components may have included metals and co-exposure to radon is possible. Work histories for each miner in the study were combined with estimates of gravimetric concentrations, to give an estimate of cumulative exposure to silica.

Full sized chest X-rays were taken annually from 1927, and these were obtained from government

and Ministry of Labour Archives. In total 17,000 X-rays were considered. Films for 62 miners were only available on microfiche. Silicosis was diagnosed where the radiological category for small rounded opacities, whether or not combined with irregular opacities, was 1/1 or greater. The two most recent films were read by 4 readers independently. Based on the initial screening, the films of 650 miners required further scrutiny. Each reader separately classified all 6 lung zones according to 1980 ILO criteria. If 2 or more readers classified any of the zones as 1/1 or greater, then all films of that miner were selected for further evaluation. This resulted in the films of 48 miners being selected for the final step. All these films were presented to each reader and categorized in the normal manner, and 32 were considered by one or more readers to have silicosis as defined. Using a criterion of at least 3 readers agreeing, 15 showed silicosis.

From boxplots showing the distribution of years of dust exposure, by groups defined by cumulative exposure to quartz (mg/m^3 year), the approximate average duration of exposure is about 15.5 years, the approximate average level of quartz exposure is between 0.03 and 0.04 mg/m^3. The incidence data were analysed using a Weibull model, and lagged cumulative exposure as the time variable. The five-year lag gave the best fit to the data. Each reader's results were analysed separately. Also, silicosis defined by different degrees of reader agreement was analysed (from one reader only through to agreement between all five readers) using the earliest date of onset. Assuming 40 years exposure, the predicted cumulative risk of silicosis (% 1/1+, 3 or more readers agreeing) at quartz concentrations of 0.05, 0.1, 0.15, 0.2 mg m-3 are 0.4 (95% CI 0.2 - 0.8), 1.2 (0.7 - 2.1), 2.4 (1.4 - 3.9), 3.8 (2.2 - 6.5) respectively.

It had been practice in these mines for miners to inhale fine aluminium dust prior to underground work as this was thought to be a prophylactic measure. The affect of this intervention on the prevalence of silicosis cannot be assessed, as retired miners were not followed up.

Ng *et al* (1994)

This study estimated the risks of radiological opacities in relation to cumulative silica exposure in 338 male granite workers from two quarries in Hong Kong. This cohort represented 91% of those currently employed and 49%of all past workers who had worked at the quarries for at least one year between 1967 and 1985. Details of work history were obtained from personal interview, and both groups examined radiologically according to standard techniques as recommended by 1981 ILO guidelines.

The workers were exposed to dust with a mean quartz content of 27% (1982 survey). The mean length of exposure was 17.4 years to quartz concentrations of 0.3mg m^{-3}. The exposure assessments were based on a limited number of hygiene surveys performed between 1953 and 1969 and more recently in 1982. These surveys suggest that a marked improvement in industrial hygiene occurred during the mid 1950s followed by little subsequent improvement (Ng *et al*, 1987). Quartz concentrations in the early 1950s were of the order of 0.31-1.8mg m^{-3}. More recent measurements are in the range 0.03-0.42mg m^{-3}. The exposure data for the pre-1980s surveys was measured as particles per cubic foot. The conversion factor from particle number concentrations to mg m^{-3} of quartz was derived from surveys of the Vermont granite quarries. There is no discussion of how appropriate this conversion factor might be for the Hong Kong quarries. The total mineralogical composition of dust from the Hong Kong quarries is not described. The effects of smoking were considered but no information is given on how the smoking data was obtained. Other possible confounding co-exposures are not described.

Information on times worked in various locations was combined with quartz concentrations to give estimates of cumulative exposure to respirable quartz. The average quartz exposure was 5.38 mg/m^3

years, corresponding to an average of 17.4 years exposure. Radiological abnormality was defined as rounded or irregular small opacities of profusion 1/1 or greater, as agreed by at least two out of three experienced readers. Regular and irregular opacities were considered separately in the final analysis. The prevalence of category 1/1+ small rounded opacities was 10.6%, and of small irregular, 16.0% (based on agreement of at least 2 readers). A logistic regression analysis of 1/1+ small rounded opacities showed a statistically significant relation with cumulative exposure to quartz, allowing for age. Estimated prevalences (%) at exposures of 2, 4, 6, 8 mg/m^3 years were 10.7, 11.6, 12.6, 13.6, respectively.

Hnzido *et al* (1993)

In this study the risk of silicosis was investigated in a cohort of 2235 white South African gold miners who had on average 24 years net service between 1940 to the early 1970's. The men were selected based on attendance at a compulsory medical between 1968 and 1971, were aged between 45 and 54, and had at least 10 years of underground service. Those with greater than 2 years service in mines other than gold mines were excluded. At follow up in 1991, 948 had died and had an autopsy, and of the 1251 still living, 657 were receiving compensation for occupational lung disease. Silicosis is compensatable when the profusion of rounded opacities reaches ILO category 1/0.

The exposure data is based on the same limited survey performed in 20 mines during the 1960s (Beadle, 1971) as used in the earlier lung cancer paper. The X-rays were read independently by two readers, in chronological order, starting with the most recent. The onset of silicosis was defined as the year when rounded opacities of ILO category 1/1 or greater were first read. Only the reader whose readings best correlated with the autopsy results was used for further analysis.

The miners who died were also included in a study to assess the correlation between autopsy and radiological findings of silicosis. All those who had significant silicosis found at autopsy were included, and a systematic sample of those who had an insignificant number of silicotic nodules. The radiographs of 557, out of the 561 individuals selected, were obtained and read in random order.

Cumulative exposures to dust (mg/m^3. years) were calculated by combining dust concentrations and information on times worked in occupational categories. A log-logistic distribution was fitted to the cumulative exposure to dust up to the onset of silicosis. There were 313 cases of silicosis (14%). Cumulative risks of silicosis are presented graphically, for a range of cumulative dust exposures from 1 to 15 mg/m^3. years. Using parameter estimates provided, we calculate the following cumulative risks (%) for exposures of 1, 3, 5, 7, 9, 11, 13 and 15 mg/m^3. years, namely, 0.0, 0.2, 2.2, 9.6, 25.0, 45.3, 64.0 and 77.3, respectively. An estimate of the exposure-response relation with cumulative exposure to quartz may be obtained by applying a figure of 30% quartz in dust (quoted by the authors), to the cumulative dust exposures.

Graham *et al* (1991)

This is a cross-sectional study which considers radiographic abnormalities in workers exposed to low levels of granite dust. All workers employed in the Vermont granite industry in 1983 were offered 14 x 17" chest X-rays taken by a mobile unit. This group included quarry and stone shed workers who had been exposed to low dust levels prevailing in the industry since 1938 to 1940. Strict dust controls were not implemented in all quarries however, until 1950. Out of a total workforce of 1,400, 972 workers were X-rayed, including 31 women. As part of the survey, previously obtained work histories were updated, and complete occupational histories taken for workers not previously

seen. Smoking histories were also recorded. A survey of dust levels was carried out using a statistical sampling plan, and personal dust samples were collected.

Three certified 'B' readers interpreted the films independently without knowledge of work history using the 1980 ILO classification. X-rays were classified as abnormal where at least two readers assigned profusion of round or irregular opacities as 1/0 or greater. The final reading was the average of the abnormal profusion scores. The reader reliability was assessed by re-reading a stratified random sample of 98 films. Twenty-eight films showed 1/0+ small rounded or irregular opacities, according to two or more readers. Seven of these showed rounded opacities. The average total dust concentration was 0.601 mg/m^3. The authors use a previously published estimate of 10% quartz in granite shed dust, to arrive at an estimate of 0.06 mg/m^3 average quartz exposure. A multiple logistic regression analysis showed that years worked in the granite industry, pack-years of smoking, and their interaction, were statistically significantly associated with 1/0+ rounded or irregular opacities. Predicted prevalences (%) at 7.5, 10, 20, 30, 40 years worked were 0.4, 0.5, 1.4, 3.9, 10.4, respectively, assuming 20 pack-years of cigarette smoking.

Love *et al* (1994)

A survey was carried out of 1925 workers at 18 heavy clay sites in Britain, during 1990/91. Chest x-rays were taken, questionnaires on smoking and respiratory symptoms administered, and lifetime occupational histories obtained. 1407 personal dust samples were gathered in a hygiene survey carried out at the same time. These were later analysed for quartz content. The average dust concentration was 1.3 mg/m^3; the average quartz concentration, 0.11 mg/m^3.

Cumulative exposures to mixed respirable dust and to quartz were calculated by combining estimates of dust and quartz concentrations within occupational groups, and time worked in these groups. For 1831 men, in whom exposure-response was investigated, the mean of cumulative exposure to quartz was 1.51 mg/m^3. years. 120 men had 4.0mg/m^3. years exposure or higher.

X-rays were read by 3 physicians, and an average category of radiological abnormality was derived by using the median of the three readings. The prevalence of category 1/0+ small rounded opacities was 1.4%. A multiple logistic regression analysis showed a statistically significant relation between radiological abnormality (1/0+) and cumulative exposure to quartz, allowing for age and smoking. Predicted prevalences (%) in non-smoking workers, initially aged 20, exposed to a respirable quartz concentration of 0.1 mg/m^3 for 10 and 20 years respectively, were 0.2 (95%CI 0.1 -0.8) and 0.9 (0.4 -2.1).

Miller *et al* (1995)

In 1980 the IOM reported that quartz concentrations in certain faces of a Scottish colliery reached unusually high levels for a period in the 1970's, due to unusual geological conditions. This report describes a follow-up study of men who worked and were surveyed by the Pneumoconiosis Field Research (PFR) programme in this colliery during the 1970's.

A total of 551 men (53% of the surviving population) were seen between late 1990 and Spring 1991. In addition to chest X-rays and lung function tests, respiratory questionnaires were completed and details obtained of smoking habits and employment history since leaving the colliery. Extensive PFR data were available on these men's exposures to respirable dust and quartz throughout their work at the colliery. A wide range of quartz concentrations was observed, but for some periods, certain face

occupations experienced concentrations of respirable quartz over 10mg/m^3. The X-rays were examined and classified according to the 1980 ILO scheme by three experienced readers, profusion of small opacities were summarised by the median of the three readings. The observed prevalence of small opacities 2/1 or greater was 8.6% overall, but reached 20 to 40% in the groups with the highest quartz exposures.

Logistic regression analyses showed strong evidence of association between the risk of pneumoconiotic abnormalities and exposures during work at the colliery, this was most apparent for the period in the 1970's and with quartz exposure in particular. The results of the analyses were used to calculate preliminary risk estimates. Model 1+/F/17 (see Table 6.5 of Miller *et al*) predicts the probability of category 1/0+ small opacities in terms of age and cumulative exposure to quartz. Exposure is split into three periods: 1964-70, 1970-74, 1974-78, and response is considered at 1990/91. Assuming a uniform concentration over the 15-year period, and an age of 60 in 1990/91, predicted percent prevalences at concentrations 0.025, 0.05, 0.1, 0.2, 0.4 mg/m^3 quartz are,respectively, 12.9, 15.6, 22.3, 40.7, 79.7.

The rapid progression of radiological abnormalities and their relationship with quartz exposure estimates suggests that the effects of this unusual exposure are more similar to those of classical silicosis than to the patterns of pneumoconiosis observed in coalworkers.

A4.4.1 Exposure-response relations compared

In this section, the exposure-response relations quoted in the preceding summaries have been brought together in Figure A4.4.1. It should be noted that the response is not necessarily the same for each study. In the first place, Muir *et al*, Hnizdo and Sluis-Cremer, and Ng and Chan reported risks of small rounded opacities category 1/1+, whereas Graham *et al*, Love *et al*, and Miller *et al* reported risks of small opacities (rounded or irregular) category 1/0+. Secondly, Muir *et al*, and Hnizdo and Sluis-Cremer studied incidence of silicosis using a life-table method with cumulative exposure acting as the "time" variable, whereas the other authors modelled the prevalence of silicosis at a single time point, using logistic regression. Other points which may be borne in mind when comparing the relationships are:

(i) Graham *et al* examined prevalence in relation to "years in granite", which we have transformed into a cumulative quartz exposure by assuming a constant quartz concentration of 0.06 mg/m^3

(ii) The same authors found a statistically significant smoking effect in their data; the particular relationship chosen for Figure A4.3 assumes 20 pack-years cigarette consumption

(iii) Hnizdo and Sluis-Cremer examined incidence of silicosis in relation to cumulative exposure to goldmine dust; we have transformed this exposure into cumulative exposure to quartz by assuming a figure of 30% quartz in dust (which the authors state applies to South African gold mines).

Figure A4.4.1 therefore rests on a number of simplifications and unverifiable assumptions; but as long as these are borne in mind, the display is a useful one, in that it highlights the difficulty of setting standards for quartz exposure.

The most striking feature of Figure A4.4.1 is the extent to which the studies of Miller *et al*, and Hnizdo and Sluis-Cremer differ from the others. The study group of Miller *et al* are known to have been exposed to extremely high doses of quartz dust (up to 10mg/m^3) over periods of less than five years. One might therefore speculate whether the South African gold miners experienced a similar pattern of exposure. A statistical analysis which made appropriate allowance for variation in the temporal pattern of exposure (assuming that the relevant data were available), might remove some of the disagreement between studies.

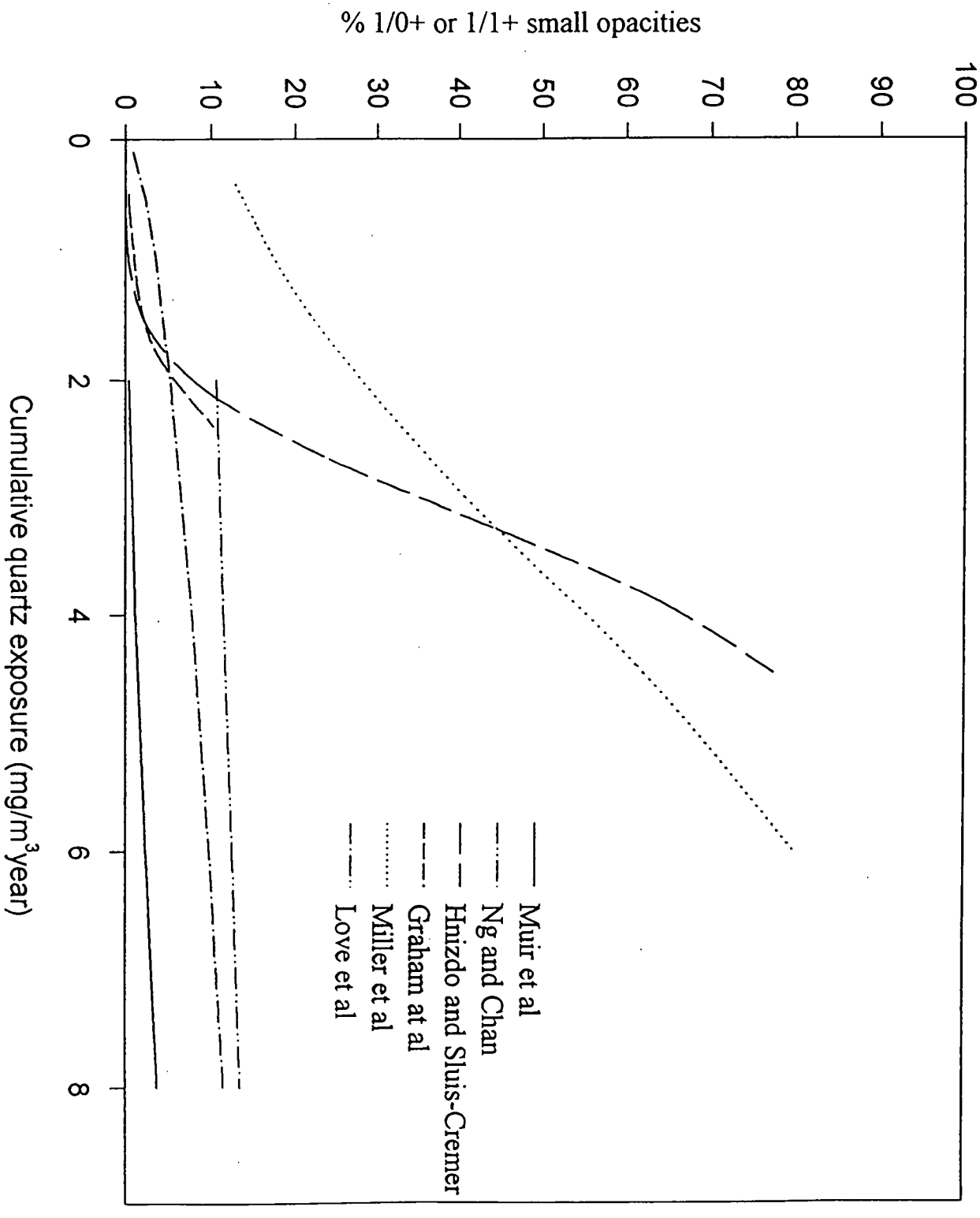

Figure A4.4.1 Risks of silicosis in relation to cumulative exposure to quartz, for six studies

Note that the estimate from Miller *et al.* is based on category 1/0 or greater small opacities

A4.5 Human studies - Silicosis and lung cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Steenland (USA)	1986	Case-control in a cohort	Granite cutters	3.16	*	no	8 other cancers[1]	not studied	volunteers (members of the Granite cutters Union)
Forastiere (Italy) Lagorio (Italy)	1986 1990	Case-control in "general" population	Mainly ceramic industry in the region	3.9	*	yes	regional population	duration:no	- exclusion of chronic bronchitis and pneumoconiosis from referent group - talc ? chromates ?
Mastrangelo (Italy)	1988	Case-control in general population	various	1.8	*	no[2]	regional population	not studied in silicotics	- exclusion of chronic bronchitis from referent group - hospital-based study
Mehnert (Germany)	1990	Sub-group of a cohort	Slate quarries	1.83	ns	no	national population	level:no duration:yes?	- exclusion of chronic bronchitis from referent group - hospital-based study

ns = not significant
* $p < 0.05$
[1] Site of cancers: stomach, colon, rectum, pancreas, liver, bladder, brain.
[2] Excess of lung cancer in both smokers and non-smokers, but wide confidence intervals

Silicosis and Lung Cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Hessel (South Africa)	1990	Case-control in a cohort	Gold mine	1.1[3] 1.3[4] 0.8[5]	ns	yes	-	not studied	- radon, asbestos, diesel emission - assessment of silicosis from necropsy report
Hnizdo (South Africa)	1991	Case-control in a cohort	Gold mine	0.9[3] 3.9[4] 1.2[5]	ns * ns	yes	-	not studied	idem Hessel (1990)
McLaughlin (China)	1992	Case-control in various cohorts (registry of silicotics)	Potteries Tungsten mines iron/copper mines tin mines	0.5 0.8 3.1 2.0	ns ns * *	yes	-	not studied in silicotics	- exposure to PAH, radon - exposure to arsenic, radon
Hua (China)	1994	Case-control in a cohort	Tin mine	2.04	*	yes	-	no[6]	- arsenic, cadmium[6]

[3] Silicosis of the parenchyma
[4] Silicosis of hilar glands
[5] Silicosis of the pleura

[6] Years spent drilling underground and cumulative smoking index explain the excess of lung cancer, silicosis is not an independent contributing factor

Silicosis and Lung Cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Finkelstein (Canada)	1987	Register	Various	2.3[7] 3.02[8]	*	no	General population (Ontario)	not studied	- various (depending on the industry)
Zambon (Italy)	1987	Register	Various	2.39 1.88	* *	yes	National population Regional population	duration: ? level: ? time since first exposure	- various (depending on the industry) - excess of lung cancer in the Veneto region
Forastiere (Italy)	1989	Register	Various	1.5	*	no	Regional population	not studied	- various (depending on the industry)
Infante-Rivard (Canada)	1989	Register	Various	3.47	*	no (RR due to smoking: 1.12)	Quebec population	duration: no	- various (depending on the industry)

[7] Miners
[8] Surface workers

Silicosis and Lung Cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Ng (Hong Kong)	1990	Register	Various	2.03[9]	*	no	General population	duration, time since first exposure	- exclusion of past or concomitant exposure to asbestos or polyaromatic hydrocarbons - high local prevalence of tuberculosis
Chiyotani (Japan)	1990	Register	Various	6.03 1.88	* *	no (some data available)	General population	duration: no	- various (depending on the industry) - hospital based study
Merlo (Italy)	1990	Register	Various	6.85	*	no	National population	not studied in silicotics	- hospitalised cases of silicosis
Tornling (Sweden)	1990	Register	Ceramic industry	1.88	ns[10]	no	National population	time since diagnosis of silicosis	

[9] OR underground workers = 3.41, $p<0.05$; OR surface workers = 1.87, $p<0.05$

[10] Result based on a small number of cases

Silicosis and Lung Cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Amandus (USA)	1991[a] 1992	Mortality of silicotics (routine diagnosis)	Various	1.5 to 3.9[11] 2.6	* *	yes no (some data available)	3 groups[12] "silicotics" with x-ray classified "0" (ILO)	not studied	confounders controlled for various[13]
Amandus (USA)	1991[b]	Silicotics in a cohort	Metal miners	1.96	ns	yes	non-silicotics	not studied	radon
Carta (Italy)	1991	Register	Various	1.29	ns	no (some data available)	Regional population	not studied in silicotics	various (depending on the industry)
Chia (Singapore)	1991	Register	Mainly granite workers	2.01	ns	no	National population	duration: ns	small population

11 depending on controls

12 coal miners without coal miner pneumoconiosis, non silicotic metal miners, metal miners

13 However, SMR = 2.4 in subjects with simple silicosis and no exposure to other known occupational carcinogens

Silicosis and Lung Cancer

Authors (Country)	Date	Type of Study	Industry	Relative risk or odds ratio	p	Results adjusted for smoking	Reference population	Dose-response relationship	Potential bias/ confounding factors/ comments
Partanen (Finland)	1994	Register	Various	2.89[14]	*	no[15]	National population	not studied	various (depending on the industry)

[14] SIR = 2.93 in stone quarrying, cutting, shaping, dressing, $p<0.05$; SIR = 4.46 in the ceramic industry, $p<0.05$

[15] RR due to smoking: less than 1.5

APPENDIX 5

A5.1 Mechanistic considerations

It is currently suggested that silica may generate chemical reactions capable of producing reactive oxygen species (ROS), as measured by electron spin resonance (ESR) on freshly crushed silica (Vallyathan *et al*, 1988). This release of ROS due to the surface activity of silica particles is capable of inducing oxidative DNA damage (Daniel *et al*,1993). Recently Koskela *et al* (1994) could not find any consistent pattern of *in vitro* biological responses (cytotoxicity, ROS production) when comparing three different dusts. Although the 2 quartz containing fractions of granite appeared consistently more active than the one which did not contain quartz, it was not possible to relate with enough confidence these *in vitro* biological responses to the incidence of lung cancer according to the silica content of the dust. Thus linking oxidative events to the carcinogenic potential of silica remains questionable.

Chromosomal aberrations have been observed in SHE (Syrian hamster epithelial) cells treated with α-quartz (Oshimura *et al*, 1984). The data on sister chromatid exchanges (SCE), are more complex. No increase of SCEs have been observed in Chinese hamster cells exposed to Min-U-Sil quartz (Price-Jones *et al*, 1980). Pairon *et al* (1990) have observed an increase of SCE's in human lymphocytes at the highest doses of trydimite, but only in a context of co-culture with monocytes. However another variety of silica (quartz Min-U-Sil) gave less clear-cut results, even at the highest dose. By contrast, both quartz and trydimite samples failed to induce SCE's in purified lymphocytes, which suggests that the release of a soluble clastogenic factor by stimulated monocytes is a necessary step. This role of monocytes (cells of histiocytic lines) might be linked with the excess of malignant lymphoma of the histiocytic type reported in the rat following intrapleural injection of various quartz samples (Wagner 1976; Wagner et al. 1980; Jaurand et al. 1987). This phenomenon should be considered in the context of a significant excess of systemic diseases of immunological origin, and also an excess of other diseases of blood forming organs.

In relation to silica exposure, the usual association of lung cancer to lung fibrosis in all experimental animals, as well as in most human studies, suggests that carcinogenesis is induced in the context of a fibrotic inflammatory reaction. This link between lung fibrosis and lung cancer is intriguing. The release of many growth factors and various cytokines following the inhalation of silica dust in animals is well documented (Donaldson *et al* 1990, Yang L-X *et al* 1994). Silica causes a chronic stimulation of cell proliferation in the rat lung (Donaldson *et al* 1990). Also, exposure of alveolar macrophages *in vitro* to silica has illustrated some of the biological events capable of inducing or promoting transformation of alveolar cells (Donaldson *et al* 1992, Driscoll *et al* 1990, Miller and Hook 1990, Panos *et al* 1990, Melloni *et al* 1993). As silicosis is related to cumulative dose of silica, if silicosis is a pre-requisite for lung cancer, this relationship should have a strong implication in risk assessment of silica-related lung cancer. However, further mechanistic research is necessary in order to gain better understanding of the biological events involved in such a relationship.

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