WORKING FOR A HEALTHY FUTURE

HISTORICAL RESEARCH REPORT

Research Report TM/87/13
1987

The toxic effects of silica

Seaton A, Addison J, Davis JMG, Hurley JF, McGovern B, Miller BG

WORLD HEALTH ORGANISATION
COLLABORATING CENTRE
FOR OCCUPATIONAL HEALTH

HISTORICAL RESEARCH REPORT
Research Report TM/87/13
1987

The toxic effects of silca

Seaton A, Addison J, Davis JMG, Hurley JF, McGovern B, Miller BG

INSTITUTE OF OCCUPATIONAL MEDICINE
Research Avenue North, Riccarton, Edinburgh, EH14 4AP
Tel: +44 (0)870 850 5131 Fax: +44 (0)870 850 5132
e-mail publications@iomhq.org.uk

TM/87/13
UDC 615.9:549.514.51

THE TOXIC EFFECTS OF SILICA

by

Anthony Seaton
John Addison
J.M.G. Davis
J.F. Hurley
Brenda McGovern
B.G. Miller

August 1987

Price:
£40.00 (UK)
£45.00 (Overseas)

Report No: TM/87/13

THE TOXIC EFFECTS OF SILICA

BY

Anthony Seaton, John Addison, J.M.G. Davis
J.F. Hurley, Brenda McGovern, B.G. Miller

Institute of Occupational Medicine,
8 Roxburgh Place,
EDINBURGH EH8 9SU,
Scotland.

Telephone: 031-667 5131

August 1987

THE TOXIC EFFECTS OF SILICA

CONTENTS

PREFACE

The work reported in this paper was commissioned by the Health and Safety Executive in order to examine the published evidence which relates exposure to the different forms of silica to risks of silicosis and other non-neoplastic diseases. It specifically excludes consideration of the evidence concerning the relationship, if any, between silica exposure and carcinoma, which has been discussed in a separate HSE publication - Toxicity Review 15 : carcinogenic hazard of wood dusts and carcinogenicity of crystalline silica (London: HMSO, 1986).

This report is one of a series of Technical Memoranda (TM) published by the Institute of Occupational Medicine. Current and earlier lists of these reports, and of other Institute publications, are available from the Librarian/Technical Information Officer at the address overleaf.

For further information about the Institute's facilities for research, consultancy and teaching on occupational health and hygiene, please contact the Director.

THE TOXIC EFFECTS OF SILICA

SUMMARY

Quartz, a crystalline form of silicon dioxide, is one of the most abundant minerals in the earth's crust. Other minerals grouped under the term free silica include cristobalite, tridymite, coesite, keatite and stishovite (which are also crystalline) and amorphous silicas. Man may be exposed to quartz or, occasionally, other forms of silica, in many trades and industries, including mining, tunnelling, quarrying, masonry, metal foundry, pottery and production of silica flour and diatomaceous earths.

While there is some evidence that amorphous silicas may occasionally cause radiological changes in man, most silica-related disease described in human populations has been the result of inhalation of crystalline silica, usually quartz. Quartz has been shown in experimental studies to be toxic to phagocytic cells and to initiate, when inhaled, a process of nodular lung fibrosis. High doses in animals may also provoke the rapidly fatal condition of alveolar proteinosis. These effects are analogous to classical and acute silicosis occurring in human populations. Acute silicosis has been described relatively infrequently, in response to very high, uncontrolled exposures to quartz or cristobalite. It is always fatal. Classical silicosis ranges from small nodular opacities on the chest radiograph, unassociated with clinical disablement, to progressive massive fibrosis which may lead to premature death. The disease, once initiated, is usually progressive and it may occur for the first time after exposure has ceased.

There is evidence from studies of human populations and of individual patients that some diseases other than silicosis may result from the inhalation of quartz. In particular, an adverse effect on lung function leading to airflow obstruction has been related to quartz

exposure. The mean intensity of this effect at levels of dust exposure insufficient to cause clinically significant silicosis is likely to be small. High exposures to quartz, usually sufficient to cause silicosis as well, have been associated with an increased risk to the worker of tuberculosis, other mycobacterial infections, systemic sclerosis and renal disease.

Studies of the relation between exposure to quartz dust and the risk of radiological evidence of silicosis all suffer from deficiencies either in determining exposures or in measuring radiological response. Nevertheless, it is clear that a relation exists between exposure and disease. It is not possible to determine from the published literature whether or not there is a safe dose at which no disease occurs. However, at working lifetime exposures to respirable quartz dust of 100 $\mu g.m^{-3}$ or less (or its equivalent in particle counts) clinically significant silicosis appears to be rare or possibly absent. Nevertheless, exposures to lower levels of quartz in several industries have been associated with the development of radiological changes in a proportion of the workforce. The clinical significance of these changes remains undetermined. The variations in types, size distribution and properties of silica in mixed dusts in industry make it unlikely that a single standard would be appropriate to all circumstances in which silica exposures may occur.

THE TOXIC EFFECTS OF SILICA

1. IDENTITY OF SILICA

Silicon is the second most abundant element (after oxygen) in the earth's crust, where it is predominantly found in crystalline silicate minerals. Free silica is the term applied to silicon dioxide (SiO_2) which is not combined with other elements in silicate minerals but exists as a pure oxide. Most naturally occurring free silica is crystalline in that the SiO_2 units are arranged in large regular atomic lattices. The most common of these is the mineral quartz which is found in high proportions in a wide range of rock types but many others also occur naturally or have been made artificially. Crystalline types such as cristobalite and tridymite are formed at high temperatures in igneous rocks but are relatively rare in nature. They are however frequently formed where silica-rich materials are subjected to high temperature (e.g., silica bricks or aluminium silicate glass fibres in oven or furnace linings) or in the preparation of commercial products by calcination of other forms of silica. Keatite, coesite and stishovite are extremely rare both as natural or synthetic minerals, being the product of very high pressure and temperature alteration of silica. Indeed, the last two were only identified in trace quantities in a meteorite impact crater as recently as 1962.

Cryptocrystalline varieties of free silica, which can be considered as densely packed aggregates of microcrystalline quartz or cristobalite, are very common natural minerals in forms such as chalcedony, agate, flint, opal and sinter.

Amorphous silica is the term used to describe forms which have no regular crystal structure; it includes a very wide range of different types, many of which are commercially important. Diatomaceous earth (kieselguhr or tripolite), formed from the siliceous skeletons of animate aquatic organisms, is an important biogenic type of amorphous silica which has been in widespread industrial use for many years. While originally completely amorphous, it may be converted to crystalline forms over geological time or by calcination. Other biogenic silicas, for example the residues recovered after incineration of materials such as rice hulls, bamboo or even sugar cane are also amorphous. It is worth noting that several of these natural amorphous silicas may be found in fine fibrous form.

Artificial amorphous silicas are common commercial products with many industrial uses. Silica fumes, gels, sols and other fine powdered varieties are formed by precipitation from sodium silicate or other solutions or by high temperature volatilisation of other silica types. They are also frequent by-products in other processes such as the manufacture of silicon crystals for the electronics industry.

Frondel provides a good account of the systematic mineralogy of the silica minerals,[1] while Iler gives a comprehensive review of the silica phases in general.[2]

2. DEPOSITION OF SILICA IN THE LUNGS

Silica has the potential to harm lungs when it becomes suspended in the air in a particle size sufficiently small for inhalation. Thus man is at risk when cutting, drilling, polishing or carving rock, when using silica-containing materials as abrasives or as components in the manufacture of ceramics, bricks or refractory materials, or when polishing fused silica off the surface of metal castings. The hazard arises from generation of a dust of suspended particles of

silica. Dust particles may be inhaled and a proportion of them deposited in the lung. Their predominant site of deposition depends on their aerodynamic diameter determined by their size, shape and density.* In general, particles of large aerodynamic diameter fall in air under the influence of gravity more rapidly than particles of smaller aerodynamic size. Thus aerodynamically fine particles of silica may remain suspended in inhaled air until they reach the most peripheral, alveolated, part of the lung (the acinus), whereas aerodynamically larger particles are more likely to strike the airways as a result of gravitational and inertial forces. These size- and mass-dependent differences in deposition are important in that particles landing on airways may be readily and quickly cleared by entrapment in airway mucus and transported to the throat by ciliary activity, whereas particles reaching alveolar level are removed by a slower mechanism involving ingestion by phagocytic cells.

Epidemiological studies of the effects of dust inhalation, if they are to be of value in setting standards to prevent lung disease, need to include estimates of the amount of dust inhaled by individuals in the study population. If they take as their indication of disease radiological changes of pneumoconiosis, such studies must attempt to estimate the amount of dust reaching the lung acinus. On the other hand, studies concerned with bronchial symptoms (cough and sputum) may more appropriately attempt to measure dust likely to be deposited on larger airways. If the evidence of disease sought is a measurement of limitation of airflow within the lung, such as forced expiratory volume in one second (FEV_1), then again particles likely to be deposited in acini are probably of prime importance since emphysema and narrowing of the smallest airways are the major determinants of airflow limitation.

*Aerodynamic diameter is defined as the diameter (in microns) of a spherical particle of unit density (1g/ml) that settles at the same speed as in the particle in question.

This review is concerned primarily with the disease silicosis, a condition of fibrosis affecting the acinar part of the lung rather than the airways. The fraction of airborne dust of interest in causing this disease is therefore that portion of particle size sufficiently small in aerodynamic diameter to penetrate to acinar level, the so-called 'respirable' subfraction. Studies using radioisotope-labelled monodisperse aerosols have shown that the dust reaching this part of the lung is below approximately 10 μm in aerodynamic diameter, the proportion of particles of each size range reaching the acinus rising from about 5% at 8 μm to about 50% at 3 μm, then falling again at smaller diameters. Thus, in order to estimate risks of silicosis to human lungs from dust clouds an ideal dust sampler would mimic the way the acinar part of the lung itself traps particles. Such a perfect sampler is not feasible, so two alternative approaches have been used. Understanding of these is fundamental to interpretation of the results of the epidemiological studies discussed later.

3. MEASUREMENT OF SILICA - THE EXPOSURE VARIABLE

3.1 Sampling of respirable silica dust

Airborne silica dust in industry is polydisperse, that is it consists of particles of many different sizes. Such dust may be sampled so as to measure either the total mass in every cubic metre of air (total dust), the mass likely to be breathed in through the mouth or nose of a worker (inspirable dust) or sub-fractions of the inspired mass below certain aerodynamic diameters and therefore likely to reach the acinus (respirable dust).[3,4,5] It is with this last fraction that we are concerned here. Until the late 1960s this fraction could not be measured directly, but was assessed by collection of all the

dust in a known volume of air and by counting (by optical microscopy) the particles beneath a specified size, usually 5 μm. Such measurements correspond to the optical size (projected area diameter) as seen under the microscope and do not correspond directly to the aerodynamic diameters now used to define respirable dust. Many studies of silicosis risk in dusty industries report the results of dust measurement in million particles per cubic foot (mppcf), obtained by one such method. For example, the early studies of Vermont granite quarry workers used impingers, in which the dust was drawn through a small orifice under fluid and trapped by an impingement process; the suspension of dust particles was then able to be counted by microscopy. Such instruments were only able to measure dust on a static or area basis, that is they could not be used to measure the personal dust exposure of a worker as he moved about in the workplace. From the late 1960s it became possible to measure respirable dust by weight directly, due to the development of size selective samplers. These instruments mimic the process that occurs in the lung, in that they allow aerodynamically larger particles to fall out before collecting the finer particles, which may then be weighed. They make use of either an elutriator, a stack of horizontal plates between which the air is drawn, or a cyclone in which the aerodynamically larger particles are removed by inertia and sedimentation. In both instruments the remaining finer dust is then collected on a filter for weighing and analysis.

The design of these gravimetric respirable dust samplers is such that they collect dust selectively according to physical criteria that simulate the deposition of particles in the acinar region, though these criteria may differ from one type of instrument to another. In general their performances approximate either to the British Medical Research Council/ Johannesburg particle penetration curve[6] or to the slightly different United States Atomic Energy Commission curve.[7] For example, in the UK both the MRE Gravimetric horizontal

elutriator and the Simpleds cyclone samplers perform in accordance with the BMRC curve whereas the performance of the USAEC cyclone matches the USAEC curve. Different penetration curves have been used for instrument design in Germany.[8] These penetration curves inevitably overrepresent the very finest dust, below 1 μm, of which relatively little is retained in alveoli but which is all caught on the filters.

Gravimetric samplers are suitable for measurement of shift-long dust conditions. Moreover, cyclone samplers can be worn by a worker close to his face, thus allowing shift-long personal samples to be taken. Most recent studies of dust exposure in industries with a silicosis risk have used gravimetric methods, and particularly personal sampling.

A third approach to measuring respirable dust has also been used extensively in Germany, Sweden and Finland; this involves collection of total dust on a filter and, after weighing it, separation out of the finer particles by a liquid sedimentation method using ethyl alcohol. This technique gave figures approximately double those obtained by samplers based on the MRC/Johannesburg curve.[9]

For the purposes of epidemiology, it has been necessary to assess the dust exposures of individuals and groups of workers from whatever measurements have been made in the past. This has often meant conversion of mppcf to $mg.m^{-3}$ or vice versa. This has usually been done by comparing the results of side-by-side sampling over a period. However, it should be clear that such comparisons only give an approximate relationship and one that may only be true for the particular dust and conditions at the time of sampling. Care should be exercised when considering basing a standard, to be monitored by gravimetric sampling, on studies carried out using particle counting. Nevertheless, the availability of dust counts made by whatever method is certainly better than estimates of

"dustiness" by visual assessment. The problems and techniques of dust sampling have been reviewed by Dodgson.[10]

3.2 Measurement of the silica content of dust

A further possible source of confusion in considering the exposure of individuals to silica is the method of analysis of the collected sample of dust. Very few industrial dusts consist of pure forms of silica; indeed the percentage quartz content of respirable dusts in the quarrying industry may be very low in spite of the fact that quartz is often the most abundant component of the rock being worked. It is therefore essential to analyse the collected dust for its silica content, including both crystalline and amorphous types. The standard methods used for these analyses are infrared spectrophotometry (IR)[11,12] and X-ray diffractometry (XRD).[13] IR has both advantages and limitations. It also allows rapid direct analysis of the sample filter with sufficient sensitivity to measure concentrations below the occupational exposure limits in moderate sample volumes. It is necessary however to prepare calibrations with pure mineral standards which are closely matched by particle size with the minerals in the samples. This is usually achieved by loading calibration filters with pure mineral standards using the same type of dust sampling instrument as that used to collect the mixed respirable dust. Interference in the IR spectrum from other minerals, including other silica varieties, may also seriously hamper IR analysis of some types of sample.

XRD also allows quantitative analysis of silica in bulk dusts or on filter but it is applicable only to the crystalline varieties and gives no indication of any amorphous silica. Detection limits and sensitivity are similar to IR but it is less susceptible to particle size variations between samples and standard minerals and it differentiates more specifically between crystalline minerals. Since it is generally more

costly and time-consuming than IR, it would only be recommended for routine analysis where interferences were observed in IR or when crystalline silica is to be analysed in the presence of amorphous silica. Estimates of amorphous silica content may be obtained by combination of IR and XRD, though the accuracy of this procedure has not been fully evaluated. Both IR and XRD have been shown to give comparable results for quartz in a range of workplace dust samples.[14]

4. MEASUREMENT OF DISEASE - THE RESPONSE VARIABLE

4.1 Measurement of silicosis

Silicosis may be defined as pulmonary fibrosis due to the inhalation of free silica. This fibrotic lung reaction is almost always of a nodular type and may be diagnosed either radiographically or on pathological examination of the lungs. The clinical and pathological features have been reviewed by Seaton.[15] Either method of diagnosis may be used in a quantitative manner, though in the epidemiological studies with which this review is concerned the radiographic method has been used. Silicosis may therefore be regarded as a condition characterised by nodular radiological opacities on the chest radiograph occurring in people exposed to airborne free silica dust. These radiological appearances may be quantitated by use of a scale of profusion, perhaps combined with a categorisation describing size of individual opacities. The most widely used such scale is that published by the International Labour Organization, which depends on the use of standard radiographs with which the films under study are to be compared.[16] Not all studies, however, have used this method and in particular Swedish researchers have used a scale dependent on the size of the nodules, in which Stage 1 is defined as showing nodules of 1-3 mm, Stage 2, 4-10 mm and Stage 3 greater than 10 mm.[17] Stage 3 in this classification would be equivalent to progressive massive fibrosis (PMF), Stages A, B and C in the ILO scheme.

The prevalence of silicosis may be measured as the proportion of subjects in a population of exposed workers whose chest radiographs show evidence of nodular opacities according to an appropriate classification. It should be noted that there may be considerable variability between and within readers in deciding on the presence and category of nodular opacities; epidemiological methods used to reduce the uncertainty and possibilities of bias arising from this usually include having each radiograph read by several readers. The readings produced may then be combined to produce a summary reading, may be reviewed to produce a consensus reading or may be analysed individually. Progression of silicosis may be measured by comparing change in profusion or size of nodules (or both) over time. Again problems may arise with respect to reader variability and appropriate epidemiological steps need to be taken to allow for this. Studies of progression may be biased by the X-ray film readers knowing the order in which the films were made. This may be avoided by having them read separately without such knowledge (independent readings), though there is also a case for reading the films side-by-side and thereby allowing the reader to make allowance for technical differences between them; this side-by-side method is almost always associated with bias due to knowledge of the order in which the films were taken. This subject has been reviewed by Liddell and Morgan.[18] Whichever method is used should clearly be stated in papers describing the research.

4.2 Measurement of pulmonary dysfunction

The disease silicosis may have an adverse effect on pulmonary function. As discussed later, this usually becomes apparent when radiographic abnormalities are well marked and takes the form of a restrictive pattern, with reduction in lung volumes and transfer factor for carbon monoxide. It is thus not useful as a method of detecting early evidence of silicosis. However, exposure to dust containing silica may have an adverse effect on lung function separate from that whereby it causes

silicosis. Studies intended to investigate this might therefore relate measurements of exposure to measurements of function such as dynamic lung volumes or transfer factor. Reports of such studies require to show evidence of the use of standardised methods of measurement and the avoidance of bias due to systematic differences in technique between surveys in longitudinal studies.

5. EXPERIMENTAL STUDIES ON THE DEVELOPMENT OF SILICOSIS

5.1 Animal studies of the development of silicotic lesions

The development of silicotic lesions in the lungs of experimental animals has been observed by many workers and fibrotic nodules with many similarities to those of silicosis have been reported. Following the inhalation of quartz dusts the early lesions appear as collections of dust laden macrophages particularly adjacent to small blood vessels. The macrophages are joined by cells of epithelioid type and fibroblasts and a reticulin network develops. Reticulin is eventually replaced by collagen and the largest and oldest lesions may become hyalinised. Essentially similar findings have been demonstrated following quartz inhalation in rats[19-26] and in guinea pigs,[26] rabbits[27] and monkeys.[28,29] In addition to inhalation, intratracheal injection of quartz dust has been used as a simple test to examine the effects of various dust preparations on lung tissue and most studies report the development of silicotic nodules which in old animals may eventually become hyalinised with collagen arranged in a concentric form. It would appear that following intratracheal injection, the silicotic nodules tend to become larger than after dust inhalation and more likely to coalesce and involve large areas of lung tissue. Once again similar lesions have been found in a number of species including rats,[30-34] guinea pigs,[35] rabbits[36] and dogs.[37]

Lesions of a different type to the typical silicotic nodules were reported in rats by Heppleston,[38,39] In these studies, specific pathogen free (SPF) rats were treated with pure quartz dust by inhalation and the animals developed alveolar lipoproteinosis without typical fibrotic silicotic nodules. Alveoli over large areas of lung tissue were filled with eosinophilic granular material which gave a positive periodic acid Schiff (PAS) reaction. In this material birefringent particles were present as well as foamy macrophages containing PAS positive material and sometimes sudanophilic fat. This type of lesion is very similar to the alveolar proteinosis found in acute silicosis in man and its development in rats following the inhalation of large doses of pure quartz was confirmed by several workers.[40-43] It was reported, however, that guinea pigs and hamsters developed extensive desquamative pneumonitis rather than lipoproteinosis when treated with the same quartz dose.[41]

It appears that the lipoproteinaceous material is produced by hyperactive type II pneumocytes and may be related to pulmonary surfactant.[43-46] It was suggested that the inhalation of quartz into the clean lungs of SPF rats leads to alveolar lipoproteinosis while the presence of a more prolific bacterial flora in non SPF animals predisposes to the formation of silicotic nodules. This was confirmed for rats[47] using both SPF and non SPF rats of the same strain treated with quartz, but it is doubtful if the absence of infection is the only explanation for lipoproteinosis. In humans the condition is usually associated with acute exposure to very high levels of silica dust but, by human standards, all animal experiments would have been carried out at extremely high doses and in the earlier studies at least, typical silicotic nodules developed. It may be that one essential factor in lipoproteinosis is the inhalation of extremely toxic quartz dusts and only relatively recent animal experiments have been undertaken with dusts of this high level of purity. Even if sufficiently toxic quartz

is inhaled, the presence of low grade infection may predispose to pulmonary fibrosis with the formation of silicotic nodules.

5.2 Parameters of silica preparations that relate to pathogenicity

5.2.1 Crystalline structure and forms of silica

As stated previously, silica may exist in a number of forms both crystalline and amorphous, and many experimental studies have concentrated on determining whether or not all forms are equally pathogenic. It was reported in 1950[48] that both fused (amorphous) and unfused (crystalline) silica produced nodules in experimental animals but that the nodules produced by the crystalline quartz were larger. It appears that while crystalline quartz produced typical silicotic nodules in experimental animals, amorphous silica caused only a diffuse tissue reaction.[49] However, lesions in experimental animals, produced with amorphous silica, have been claimed to be identical to those produced with quartz dust.[50,51] Studies which examined the effects of a variety of silica preparations including molecular silica, silica gel and silica colloid administered by intraperitoneal injection, intratracheal injection and by inhalation were published in 1953.[52] It was reported that both the solution of molecular silica and silica gel were inert, that colloidal amorphous silica was toxic but not fibrogenic,while crystalline quartz produced a maximal fibrotic response. By now many workers have examined the harmful effects of various samples of silica which were either completely amorphous or had a low content of crystalline material.[53-68] In general it would appear that the relatively insoluble forms of amorphous free silica can be fibrogenic but less so than pure crystalline samples. The terminology of many of the silica preparations tested is, however, imprecise and this makes comparative evaluation of the results difficult. Diatomaceous earth (kieselguhr) has been contrasted with 'silica earth' which appears more fibrogenic. It is likely

that the silica earth samples represent aged diatomaceous deposits where an element of crystallization has occurred. Similarly the terms 'condensed', 'fume', 'gel' and 'precipitated' amorphous silica are all listed in the above publications and refer to samples produced by different techniques. Since the amorphous silica products of any manufacturer may differ considerably in their pathogenic potential it is unfortunate that standard 'control' preparations have not been available for inclusion in experimental studies.

Not all forms of crystalline silica are equally pathogenic. It was reported in 1953[30] that following the intratracheal injection into rats of a number of silica preparations, tridymite was the most fibrogenic followed by cristobalite, and then quartz. These findings have now been confirmed by a number of workers using either intratracheal injection in rats or intravenous injection in mice.[69-72] Not all forms of crystalline silica may be fibrogenic, however, since it has been demonstrated that following intratracheal injection stishovite is inert while coesite is fibrogenic but apparently less so than quartz.[73-75] One study in 1968[76] exposed dogs, guinea pigs and rats by inhalation to calcined diatomaceous earth (crystobalite content 61%) at dose levels approximating to the normal hygiene standards for humans. Relatively little pathological change was found in the lungs of any species but it must be emphasised that with dusts, animal experimentation cannot be used to validate threshold limit values for humans since fibrosis is a long-term progressive condition and animal lifespans are generally too short.

5.2.2 The importance of particle size in the pathogenicity of silica dusts

Many experimental studies have examined the importance of particle size on the pathogenicity of silica dusts. In

studies reported in 1933[77] two quartz preparations were injected into rabbits; it was found that the one with particles in the 1-3 μm size range caused much more liver fibrosis than that with particles in the 6-12 μm range. Later studies, using the same techniques, suggested that quartz pathogenicity increased with reducing particle size to well below 1 μm[78] and this has been confirmed by a number of workers.[79-81] When equal mass doses are injected, however, reducing particle size means increasing particle number. To counteract this, preparations with a constant surface area were used[80] and it was found that following intracheal injection into rats the maximum fibrosis was still obtained with particles 1-2 μm in diameter. Similar results were obtained following intratracheal injection into rats but following intravenous injection into mice the maximum liver fibrosis was obtained with quartz particles 0.2-0.5 μm in diameter.[31] There is now good agreement that the most fibrogenic size for quartz dust particles deposited in lung tissue is 1-2 μm.[82-84]

It appears likely that there is no lower size limit for the toxicity of amorphous silica although particles in the 1-2 μm range appear most fibrogenic. Intratracheal injections of amorphous silica particles 20A units in diameter into rats were found to be fatal within twelve hours[85] and similar findings were reported following the intravenous injection of colloidal silica into mice.[86] A number of workers have examined the effects of amorphous silica particles in the 100-200A size range.[87-91] The results of these studies have differed depending on dose and route of administration. In general high doses injected either intratracheally or intraperitoneally resulted in rapid death while lower doses, especially if administered by inhalation, produced fibrosis.

5.3 The effects of other minerals on the development of silicosis.

In humans, exposure to completely pure silica is rare and mixed dust exposure is much more usual. The development of silicotic lesions therefore depends to some extent on the ability of silica particles to retain their toxicity in the presence of other minerals. It has been reported that animals dusted with quartz to which 1% of metallic aluminium had been added developed no fibrosis although pure quartz produced typical silicotic lesions.[27] Following intratracheal injection of dust it was found that 2% of metallic aluminium failed to inhibit fibrosis when 100 g of quartz was administered[92] but it was found that the same preparation if administered by inhalation was not fibrogenic.[93] It has been claimed that hydrated aluminum is the most effective compound in reducing the fibrogenic properties of quartz[94] although some workers have found that both colloidal aluminium hydroxide and powdered aluminum hydrate were equally effective.[95] When rats were treated with a mixture of coal and quartz dusts (15% quartz) with and without aluminum powder, the aluminum-containing dust produced much smaller lesions.[96]

This last study was important in relation to the development of coal workers' pneumoconiosis. While some early experimental studies reported that pulmonary fibrosis increased with the proportion of quartz in coal dust,[97] human epidemiology has shown that the prevalence of pneumoconiosis does not relate closely to the quartz content of the dust; indeed some groups of workers exposed to dust containing as much as 20% of quartz have shown a relatively low prevalence of pneumoconiosis.[98,99] The reasons for this were examined in a series of experiments by Le Bouffant and his coworkers.[32,100,101] In inhalation and injection studies using rats these workers demonstrated that minerals present in some mine dusts are capable of reducing the pathogenic effect of quartz. This protective effect appears to be related mainly to clay minerals, illite being

particularly effective but kaolin less so. The authors suggested that this protective effect was at least partly due to release of aluminium by the clays but pointed out that other minerals not yet examined may be able to protect against quartz. Iron can certainly protect against quartz toxicity[102,103] and also some polymer compounds.[104-106] It appears that the amount of protective materials present in inhaled dust will determine the pathogenicity of any type of quartz exposure to humans and the harmfulness of any dust type should not be expected to correspond exactly to the quartz concentration inhaled.

5.4 The effects of pulmonary infections on the development of silicosis.

Following the observation that silica and tuberculosis were frequently associated in humans, animal studies were undertaken to confirm this relationship and to explore the conditions in which it was most likely to occur. Early experiments[107,108] confirmed the easier growth of tuberculosis in silicotic nodules and showed it was not due just to the presence of necrosis but needed the presence of silica dust. Later studies[109] using a variety of dust samples showed that silica was much the most effective in stimulating the growth of tubercular organisms. Another series of experiments used guinea pigs with healing tubercles in their lung tissue.[110] Following the inhalation of quartz it was found that these lesions were reactivated when dust was localised in the immediate vicinity of the tubercular foci. This study also demonstrated that the combined effects of tubercular infection and silicosis produced more fibrosis than either agent alone. Some studies[111] produced little fibrosis in experimental animals treated with silica alone but, in the presence of tubercle bacilli, a nodular fibrosis similar to human silicosis was produced. Many workers have now obtained experimental confirmation that silica dust exacerbates infection with

mycobacteria, often producing rapidly fatal disease when control animals treated with mycobacteria alone recovered completely.[112-117]

The exact mechanisms by which silica dust enhances the effect of mycobacteria remain uncertain. In 1930 it was suggested that quartz, by causing tissue necrosis, merely provided a suitable growth medium for tubercle bacilli.[118] Later it was reported that enhanced growth of tubercle bacilli was found in artificial media when silica was present[119] but this could not be substantiated.[120] Quite early Gardner suggested that silica altered the defence mechanism by injuring or killing phagocytic cells and therefore reducing the bactericidal activity of the tissues.[121] This is supported by the more recent observation that BCG organisms do not multiply in macrophages while those cells retain the capacity to phagocytose dust particles.[122] However, in 1959 an alternative hypothesis was put forward.[123] It was suggested that quartz dust could greatly increase the immune response to mycobacteria and the lesions of infectious silicosis were largely the result of a hypersensitivity reaction. Nevertheless, there is evidence that quartz dust, by its harmful effects on macrophages, can increase susceptibility to protozoon parasites,[124,125] bacteria[126,127] and viruses.[128]

It has recently been suggested that any type of pulmonary infection may exacerbate the effects of inhaled silica. It has been shown that SPF rats develop only small pulmonary lesions in response to inhaled tridymite while conventionally maintained animals develop large and sometimes confluent nodules.[47]

5.5 Short-term in vitro studies on the toxicity of silica

While long-term in vivo studies, especially with the dust administered by inhalation, offer the best chance of

determining the relative pathogenicity of dusts containing silica, these animal studies are time-consuming and costly to perform. With the realisation that many of the complex biological reactions that are involved in the development of silicosis result from the toxic effects of the dust on macrophages, many workers have studied this toxicity in vitro in an attempt to develop reliable short-term predictive tests for dust pathogenicity. Macrophages from all the main types of laboratory rodents have been used, usually collected from the peritoneal cavity following the injection of mildly irritant material, although some workers have obtained alveolar macrophages by pulmonary lavage techniques and others have used permanent lines of transformed macrophages. The parameters used to measure the toxic effects of dusts have also varied greatly and have included tests for macrophage viability with dye exclusion techniques, the release of cytoplasmic enzymes such as lactic acid dehydrogenase or aldalase, the release of lysosomal enzymes such as β-glucuronidase and the cells' ability to produce lactic acid, to consume oxygen or to reduce triphenyltetrazolium chloride (TTC).

Early studies[129] examined the effects on guinea pig peritoneal macrophage viability of tridymite, cristobalite, quartz and vitreous silica as well as a number of coal mine dusts containing varying amounts of quartz. Both tridymite and cristobalite were reported to be roughly eight times more toxic than quartz or vitreous silica. The coal dust samples all showed little or no toxicity. In contrast, it was reported that neither quartz nor tridymite caused morphological signs of toxicity in rat peritoneal macrophages although both these dusts reduced oxygen utilisation by the cultures.[130] The effects on rabbit peritoneal macrophages of tridymite and quartz either in its raw state or etched with hydrofluoric acid were examined in rabbit peritoneal macrophages.[131] Both the tridymite and etched quartz caused rapid cell death. Unetched quartz showed approximately one quarter of this toxicity.

Lactic acid production and oxygen utilisation in guinea pig peritoneal macrophages was found to be reduced more by tridymite, quartz and cristobalite etched by hydrofluoric acid than by unetched dusts or vitreous silica.[132] Rather different results were produced with alkali-etched crystalline silica and similarly treated amorphous silica.[133] In this study hamster peritoneal macrophages treated with the crystalline silica showed no morphological signs of toxicity but the amorphous variety killed 50% of cells within eighteen hours. It has been shown that some pure quartz samples reduce the viability of rat peritoneal macrophages and their ability to reduce TTC more than tridymite[134] and it has been demonstrated that samples of diatomaceous earth containing mainly amorphous silica can cause considerable release of lactic acid dehydrogenase from mouse peritoneal macrophages although they are less toxic than either quartz or cristobalite. The non-toxic dust magnetite has no effect on the cells.[135]

The greater sensitivity of modern biochemical techniques has enabled the in vitro examination and grading of quite large series of dust samples containing different proportion of quartz and other silica compounds. Both dusts from coal mining and metal mining have been examined. The effects on guinea pig peritoneal macrophages of a series of coal mine dust samples from the Ruhr and Saar coal fields have been examined.[98,136] Toxicity was estimated from changes in the TTC reduction activities of the cells. A wide range of dust toxicity was recorded but this was not closely related to the quartz content. Very similar findings were reported in studies involving the treatment of $P388D_1$ cells (a permanent macrophage line) with dusts from British collieries[137] and experiments using guinea pig alveolar macrophages and dusts from mines in West Germany.[138,139] In these studies the parameters of toxicity examined included cell viability, release of lactic acid dehydrogenase and β-glucuronidase and lactic acid production. The in vitro production of fibrogenic factor/s by

rat peritoneal macrophages treated with a series of European coal mine dusts and also artificial mixtures of coal with known amounts of quartz has also been examined.[140] Once again the biological effects of the dusts seemed unrelated to the quartz content. A further study[141] has examined the cytotoxic effects on guinea pig alveolar macrophages of two main samples of colliery mine dust. However, each was fractionated into five different size ranges. With one mine sample, the quartz content rose with the reduction of particle size in the subfractions and so did cytotoxicity as recorded by dye exclusion, LDH release and lactic acid production. In the other sample the quartz content remained very low in all subfractions and cytotoxicity was negligible. These findings indicate that dusts collected by samplers with different particle selection characteristics to the respiratory system may not be suitable for predictive tests on pathology.

Several attempts have been made to compare the in vitro cytotoxicity of dusts with their in vivo effects in experimental animals. Dust samples from three ore mines were tested on guinea pig peritoneal macrophages in vitro and the same dust samples were administered to rats by intratracheal injection.[142] The in vitro effects on TTC reductase activity showed little correlation with long-term fibrogenicity.

Another series of experiments[143] examined the TTC reductase activity of twenty seven West German coal mine dusts which were also injected into the peritoneal cavities of rats. The extent of "quartz typical areas" in the regional lymph nodes showed little correlation with the in vitro results.

Three coal mine dust samples from the same seam with quartz contents ranging between 6 and 25% had similar effects on the viability of $P388D_1$ cells.[144] Following long-term dust inhalation in rats however, the high quartz dusts had produced larger and more numerous pneumoconiotic nodules than the low.

When the dusts were treated with dithionite, however, the samples with the highest quartz levels now showed much greater in vitro cytotoxicity than the low quartz samples. This study confirms that in mixed dust samples the contamination of the quartz surface with other minerals can greatly influence the toxic effect of the dust. This protective contamination is unlikely to be removed during short-term in vitro tests but removal may occur during long-term in vivo studies.

Because it is recognised that the interaction between macrophages and silica dust plays a very important part in the development of pulmonary fibrosis most in vitro studies have concentrated on macrophages or closely related cells. Some workers have, however, examined the direct effect of quartz on primary cultures of human and rabbit lung fibroblasts.[145,146] It was found that quartz actually increased the thymidine uptake and hydroxyproline production of cultures as compared to controls although the effect was less marked than with asbestos. Other studies have also examined the effects of mineral dusts on non-phagocytic cells.[147,148] They have used Chinese hamster fibroblasts but also cultures of a permanent line of human alveolar type II cells. Quartz was found to have little effect on the cloning efficiency of fibroblasts or on the average diameter of type II pneumocytes in contrast to asbestos. Non-fibrous diatomaceous earth had similar effects to quartz but a fibrous variety did affect the cloning efficiency of fibroblast cultures indicating a similarity to carcinogenic fibrous dusts. The studies were refined[149] when it was shown that quartz in common with amosite asbestos did not affect the metabolic cooperation between cells of fibroblast cultures treated with 12-O-tetradecanoylphorbol-13-acetate (TPA). It has also been demonstrated that quartz is not toxic to primary cultures of mesothelial cells.[150]

It is now believed that the toxicity of silica dusts depends on their ability to damage cell membranes, especially the

membranes of macrophage phagosomes. Because of this, several workers have suggested that tests demonstrating membrane damage may predict long-term pathology and have used the simple test system of erythrocyte lysis. One study[151] compared the level of haemolysis obtained with four silica varieties and reported that while quartz, coesite and corundum in that order were very haemolytic, stishovite had little effect. Further work[152] confirmed that quartz is extremely haemolytic and demonstrated that its dose-dependent effect is more rapid than those of a series of other silicate compounds. Slate dusts have been shown to be haemolytic[153,154] and it has been suggested that this is due to the release of silicic acid although slate dust would be expected to contain significant amounts of crystalline quartz.

5.6 Experimental studies on the mechanisms by which silica particles damage tissue and initiate silicotic lesions

5.6.1 Physical and chemical theories

As early as 1866 Zenker[155] suggested that the ability of quartz to damage tissues depended on the sharp angularity of the dust particles. This theory persisted until it was demonstrated that carborundum dust, as hard and sharp as quartz, did not produce fibrosis.[156] Similarly, it was shown that the coating of quartz particles with aluminum hydroxide or iron oxide, which did not change the quartz angularity, nonetheless eliminated its fibrogenic potential.[27] Finally it was demonstrated that spherical submicron amorphous silica particles were able to cause silicosis in experimental animals.[157] Another suggestion has been put forward that freshly fractured silica particles have unsatisfied valencies on their surfaces which cause the biological activity of the dust.[158] It has been shown that dust nearly twenty years old can cause silicosis[159] but it is also maintained that the harmful effects of quartz on pulmonary tissue are due to the

presence of atomic oxygen at the freshly fractured surface.[160] It has been shown that inhaled silica becomes hydrated before reaching the alveoli[85] and that there is a highly soluble surface layer on quartz particles which is not discrete but blends smoothly into the less soluble core.[161] It has been reported that the removal of this layer with HF or NaOH increases the biological activity of quartz considerably but tridymite, the most fibrogenic form of quartz, appears to lack a high solubility surface layer and its activity is not increased by chemical treatment.[162] The maximum toxicity of silica dusts is always obtained when the SiO_2 surface is chemically clean.[163,164] It appears that surface components only a few atoms thick may have a considerable effect on quartz toxicity and this surface contamination is frequently found in mixed dusts where other minerals frequently exert a protective effect against quartz.[32,101,143] Because of this it has been suggested that the potential toxicity of a quartz-containing dust is best obtained by calculating the clean quartz surface area rather than the mass or particle numbers of the quartz.[164] Several workers have suggested that the piezoelectric properties of silica are the main factors in the development of silicosis and it has been claimed that fibrosis can be produced by such piezoelectric substances as tourmaline, barium titanate and synthetic berlinite.[165-167] This suggestion has been refuted[168] and it has been demonstrated that many piezoelectric substances do not produce fibrosis while the non-piezoelectric tridymite is the most fibrogenic variety of silica.

Another suggestion is that silica particles are pathogenic because of negative charges on their surfaces and their interaction with the presumably positively charged protoplasm of the cell.[169,170] Negative charge may be the reason for the affinity that the quartz surface has for adsorbing proteins but it is uncertain whether or not this is involved in disease development.[171] Certainly some dusts such

as carborundum also adsorb proteins but are not pathogenic. It has been suggested that binding of the silica surface to cell membranes is by hydrogen bonds between the dust and the membrane's protein components.[172] It is postulated that these proteins are eventually extracted from the membrane onto the silica surface with resulting loss of membrane integrity. It has been claimed that contact between cell membranes and the SiO_4 tetrahedron groups and transferable hydroxyl groups attached to them is a prerequisite for fibrosis.[173] This has been supported by studies which showed that coesite and quartz glass which have a tetrahedral configuration of SiO_2 molecules were fibrogenic when injected intratracheally into experimental animals but that stishovite which has an octahedral configuration was not fibrogenic.[61,74,75]

Kettle in 1926[174] first suggested that tissue damage in silicosis resulted from soluble products of the dusts. He reported that a culodian bag containing silica produced fibrosis when implanted into the flank of a rabbit but that an empty bag did not. He also reported that quartz particles coated with iron oxide were inactive. Similar studies by other workers produced the same results. It was suggested that the soluble factor responsible for disease development was silicic acid and that the pathogenicity of quartz stone dust was roughly related to the rate at which it released silicic acid into the solution.[27,175] That silica solubility could be important in tissue damage has been confirmed[53,176] but it was demonstrated that while highly soluble silica compounds have a very toxic action, in contrast less soluble varieties of quartz are fibrogenic. In 1953 it was demonstrated that four silica types, fused silica, quartz, cristobalite and tridymite differed greatly in their fibrogenic properties despite having similar solubilities.[30] Later it was shown that different specimens of quartz of different solubility had the same fibrogenic effect in animal lungs[177] and also that silica particles placed in a diffusion chamber in the peritoneal

cavity stimulated no fibrosis.[178] This was confirmed[179] but it was suggested that colloidal silicic acid, the form that might be involved in silicotic fibrosis did not escape from the diffusion chambers used. In this connection it was reported that the biological activity of its silicic acid in solution depends on its degree of polymerisation.[180]

5.6.2 Biological responses to silica toxicity

Regardless of which physical and chemical parameters are important in silica toxicity, it is now believed that in order to promote disease silica particles must first be phagocytosed by macrophages. It was suggested by Allison[181,182] that the silica particles are first taken into the macrophage phagosome where they become associated with lysosomal enzymes. During even short residence in tissues, silica dust becomes coated with proteins. In this state the dust surface is non-pathogenic but the proteins are digested by the lysosomal enzymes which are mainly acid hydrolases, allowing the quartz to cause the rupture of the phagosome membrane. This liberates enzyme back into the cell cytoplasm and eventually, following cell necrosis, into the surrounding tissues where it can exacerbate the overall inflammatory response. While this process no doubt occurs to some extent, it has been demonstrated that mouse macrophages which have ingested small amounts of quartz may survive in culture for several weeks.[183] During this period of time macrophages can actively secrete a number of bioactive materials including neutral proteases such as collagenase and elastase[184] although it seems likely that neutrophils attracted to quartz-damaged lungs in large numbers may be also involved in the secretion of these products.[185-188]

Recently it has been suggested that the secretion by leucocytes of oxygen-derived free radicals and metabolites such as hydrogen peroxide, superoxide anion, hydroxyl radical and singlet oxygen may be important in the inflammatory response to a number of harmful agents.[189] Some studies have failed to demonstrate increased release of these reactive oxygen intermediates (ROI) from monocytes and neutrophils treated with pathogenic dusts, including quartz, compared to harmless minerals.[190] Neutrophils, however, have almost no phagocytic potential towards mineral particles and monocytes respond much less than fully activated macrophages, and an increase in ROI release from rabbit alveolar macrophages following treatment with quartz has been demonstrated.[191]

That macrophages damaged by quartz might liberate specific factors that could be involved directly in fibrogenesis was suggested by Heppleston and Styles in 1967.[192] These workers treated macrophages with quartz and found that a supernatant extract of these cells, when lysed, could stimulate collagen production in fibroblast cultures. By using related in vitro systems a number of workers have demonstrated similar factors that appear to be important in fibrogenesis.[193-196] These factors appear to have molecular weights of approximately 15,000 and are probably polypeptides. Some workers have failed to demonstrate fibroblast stimulation by extracts of quartz-treated macrophages[197,198] but this may be due to concentration effects since it has been reported that at low concentration macrophages produce factors that stimulate fibroblast proliferation,[199] while high concentrations cause inhibition.[200] It has been suggested that a time factor could be important in determining the effects of macrophage factors, with macrophages exposed to quartz in vitro for a short period producing a fibroblast inhibitor while macrophages exposed in vivo for several weeks produce a factor enhancing fibroblast proliferation.[201] Recently it has been suggested that one of the fibrogenic factors is identical to interleukin I, a material with important immunological functions.[202]

Vigliani et al in 1950[203] first suggested that immunological factors might be important in the development of silicotic lesions and many experimental studies have confirmed that some type of immunological reaction is involved. It has been claimed that autoantibodies are found in silicosis and that these arise from proteins modified by contact with quartz.[89,204] However, it has been reported that when serum gamma globulins are adsorbed onto quartz they retain their normal antigenic properties.[205] Large amounts of gamma globulins have been found in the hyaline tissue of silicotic nodules[206] and it has been reported that hypersensitised animals treated with silica produce larger and more clearly demarcated collagenous lesions than controls.[207] Some studies have been unable to demonstrate specific antibodies in animals during the development of experimental silicosis[208] but lung-reactive antibodies that appear specific for collagen and/or elastin have been found in the serum of patients with pneumoconiosis.[209]

More recent work has suggested that the immunological phenomena involved in silicosis result from soluble products of macrophages which have phagocytosed dust particles and the most important of these products appears to be interleukin I. This and/or other products can stimulate thymocyte proliferation and the proliferation of thymus derived cells (T lymphocytes) in the spleen.[210-213] In contrast, proliferation of splenocytes (B lymphocytes) is depressed.[127,210,214] One study has reported some reduction of mitogenesis in spleen T cells but this followed the intraperitoneal injection of quartz, and the transfer of dust to the spleen, with general toxicity to spleen cells, is likely to have occurred.[215] Antibody production in general can be shown to be stimulated by quartz[216-217] although it has been found that mice treated with quartz by inhalation show impaired ability to respond to inhaled E. coli antigens.[218] This impairment was much less marked, however, if the E. coli antigen was given intravenously.

From all these studies it appears likely that the production of interleukin I stimulates the production of T helper cells which in turn stimulate the transformation of primed B lymphocytes to plasma cells. This would enhance the production of immunoglobulins in general without the multiplication of B lymphocyte stem cells. The failure of animals to respond specifically to inhaled antigens after periods of quartz inhalation probably results from the impaired ability of the pulmonary macrophages to process these antigens for presentation to immunocompetent cells.

In conclusion it would appear that the development of silicotic lesions depends on the phagocytosis of silica particles by macrophages which are damaged by this process and which liberate factors possessing toxic, fibrogenic or immunomodulatory activity. The way in which this combination orchestrates the local tissue reaction will determine the type and severity of silicotic lesions that are produced.

6. EFFECTS OF SILICA ON MAN

6.1 Hazards associated with different types of silica

Almost all the silica to which workers are exposed in industry is quartz, usually mixed with other minerals. The proportion of quartz may vary from very low levels, as in some coal mine dust, to almost 100 %, as in silica flour. Many mineral dusts, such as granite and slate, contain a variable amount of quartz from workplace to workplace and within the same workplace. In general, it appears that the rapidity with which silicosis appears and progresses depends on the total amount of quartz to which workers are exposed and the time over which that exposure has taken place. Recent descriptions of rapidly progressive, fatal silicosis have been reported among men working in milling silica flour, drilling the overburden in surface coal mines, sandblasting and pottery. All these

episodes were characterised by a relatively short exposure to unmeasured but clearly high levels of quartz (Table 1).[219-225] Only one of these acute and fatal episodes has been reported in the United Kingdom[219] since the original paper by Middleton,[226] although the annual report of the Chief Inspector of Factories for 1948 noted 59 deaths from silicosis in sandblasters and a further 12 deaths in the manufacture of scouring powders.[227] Slightly less rapidly progressive silicosis, affecting a high proportion of the workforce and proving fatal in some after an exposure of about 10 years, has been reported in Indian slate pencil workers.[228-230] Levels of respirable quartz measured in the breathing zone of cutters in this trade were shown to range between about 2 and 10 $mg.m^{-3}$. Similar patterns of disease have been described amongst sandblasters in Louisiana,[231] whose mean levels of exposure to free silica have been recorded at about 5 $mg.m^{-3}$, amongst jade polishers in Hong Kong,[232] exposed to silica flour at about 0.7 $mg.m^{-3}$, and amongst workers making abrasive soaps and exposed to silica flour in Ontario.[233]

The clinical effects of exposures to other forms of silica are less well documented. Calcined or heated silica-containing minerals may be anticipated to contain cristobalite or tridymite; thus workers exposed to dust in fettling, where silica has become fused to the surface of castings, and in the production of diatomaceous earth may be exposed in part to these minerals. A study of workers exposed to diatomaceous earths has shown that silicosis occurred in some 25% of workers with more than 5 years' exposure in 1953; 10% of this population had PMF, indicating a severe and sometimes progressive form of the disease.[234] Follow-up surveys in 1974 and 1979, after the introduction of effective dust control measures, showed the prevalences of silicosis and PMF had been reduced considerably, all cases occurring in workers with greater than 15 years' exposure.[235,236] In all these surveys, disease occurred almost exclusively in workers exposed to

TABLE 1

CASE REPORTS OF ACUTE SILICOSIS

Author	Reference	Job	Exposure	Country	Onset to death
Scott 1964	219	4 flint crushers	3-6 yrs	N. Ireland	6m - 3 yrs
Buechner & Ansari 1969	220	4 sandblasters	3-6 yrs	USA	3-15 months
Suratt et al 1977	221	4 sandblasters	4-6 yrs	USA	4-11 months
Xippel et al 1977	222	quartz miller	7 yrs	Australia	3 yrs
Zimmerman & Sinclair 1977	223	abrasive manuf.	3 yrs	Australia	30 months
Roeslin et al 1980	224	pottery	?	France	1 yr
Banks et al 1983	225	rock driller	5 yrs	USA	2 yrs

calcined or flux-calcined diatomaceous earth, which contained up to 20 and 60% cristobalite respectively.

The effects of amorphous silica have been investigated in the diatomaceous earth industry as well as in the production of silicon metal and of submicron silica. In the former industry, workers in quarries have been and are exposed to uncalcined diatomaceous earth, though there is no good evidence in the literature of their exposure levels. Since the work is in open air, they may not be very great. Nevertheless, in a review of men who took part in the original study in 1953, low categories of pneumoconiosis were found in at least two quarry workers.[236] Similarly, a study of 26 Italian diatomaceous earth quarry workers has shown two with category 1 and one with category 2 simple pneumoconiosis.[237] These men were said to have been exposed to dust that contained less than 2.35% quartz and was primarily amorphous silica.

In the silicon metal industry, quartz is heated above its boiling point (2350°C). Workers may be exposed to a fume consisting of very small (0.05-0.75 μm) spherical particles of silica. Two papers in the last decade have reported changes consistent with pneumoconiosis in these workers. In 1977, 11 of 40 US men exposed to this process were said to have abnormal radiographs, and convincing evidence of radiographic abnormality was presented for three of these.[238] In two, lung biopsies had been carried out and showed a process of fibrosis and histiocytosis unlike classical silicosis and similar to that found in experimental studies with the dust to which these workers had been exposed. However, the authors noted that this dust contained unspecified amounts of crystalline silica and the experimental study indicates that it consisted of cristobalite surrounded by a layer of amorphous silica.[239]

The second paper, from France in 1980, records the finding of irregular and nodular radiological shadows in 10 patients

working in a silicon foundry.[240] Lung biopsies in two confirmed interstitial fibrosis associated with amorphous silica; fewer than 1% of the pulmonary particles were crystalline silica and analyses of the foundry dust were said to be similar.

A third paper in 1979 reported the absence of radiographic or functional abnormalities in 165 US workers exposed to 'precipitated amorphous silica'.[241] Analytical details are not given and lung function is expressed, unsatisfactorily, as the rate of change over a number of years, taking first and last readings. In spite of having data on cumulative exposures, smoking history, age and sequential lung function, the authors have missed the opportunity to carry out multiple regression analyses.

Clinical studies of workers exposed to submicron amorphous silica ('Hi-sil' and 'Silene') with particle sizes in the region of 0.02 μm have reported no radiological changes.[242,243] No details of mineralogy confirming the nature of the silica are given. Neither of these studies was planned as an epidemiological investigation and the radiology was a clinical reading by one observer. All subjects were currently exposed, and none had been exposed for more than 17 years. The results therefore can only be regarded as suggestive that this material is less harmful than crystalline silica and further follow-up studies are clearly needed.

In summary, there is no doubt that quartz and cristobalite are capable of causing silicosis in man, and there is no evidence that either is more toxic in this respect than the other. Diatomaceous earth in the calcined or flux calcined state is similarly harmful, and there is some evidence that it may cause pneumoconiosis in workers quarrying the raw material. Submicron sized amorphous silica has not clearly been implicated in causing silicosis, though there is evidence that

the disease may occur if the amorphous silica is contaminated by cristobalite, as may happen in the silicon metal industry. There is insufficient evidence in the literature to state with confidence that amorphous silica is non-toxic to the lungs. However, amorphous silica exists in different forms, and these may have different toxic potential; animal studies have shown, for example, that diatomaceous earth heated to 800°C but containing no crystalline silica is more fibrogenic than the unheated mineral.[81]

6.2 The clinical spectrum of silicosis

People are rarely exposed to pure silica; the dust they breathe in the workplace is usually composed of a mixture of quartz with other minerals. Moreover, the absolute amounts of quartz may vary considerably as may the time period over which exposure occurs. Thus the response of the lungs differs in different circumstances. For convenience, this spectrum of response from simple mixed dust pneumoconiosis to acute silicosis may be described in terms of typical distinct patterns. It should however be appreciated that these merge with each other and that the appearances in an individual depend largely on his personal exposure to dust.

Mixed dust pneumoconiosis is a name given to the radiological findings of nodular pneumoconiosis occurring as a response to the inhalation of dust containing a mixture of minerals, usually including quartz. Coalworkers' pneumoconiosis, in which inhaled carbon and silicates play an important role in the aetiology, foundryman's pneumoconiosis, related in part to the inhalation of oxides of iron, and oil shale pneumoconiosis, again caused by organic and silicate minerals, may all be regarded as forms of mixed dust pneumoconiosis. The radiographic appearances are of a simple multinodular pneumoconiosis, usually of p or q (<5mm in diameter) size. Progressive massive fibrosis may occur, sometimes long after

exposure has ceased. Further discussion of the mixed dust pneumoconioses is outside the scope of this review but may be found elsewhere.[244,245] However, it should be noted that the more quartz the inhaled dust has contained, the more the appearances approximate to those of silicosis, and that typical silicosis may occur in workers in industries which are normally associated with mixed dust pneumoconiosis. For example, coalminers working a seam which generated a dust with high levels of respirable quartz have been described as developing a rapidly progressive pneumoconiosis with all the characteristics of silicosis.[246] Necropsy studies of coalminers have shown the typical histological appearances of silicosis in association with high proportions of quartz in the lung dust.[247,248] Such appearances at necropsy relate most closely to the radiographic finding of r nodules (5-10 mm in diameter), suggesting that it may be possible to identify radiologically individuals who are showing silicotic responses to mixed dust exposures.

Simple silicosis is characterised by diffuse nodular shadows on the chest radiograph. They are often quite radiodense and may occasionally calcify. With increasing exposure to silica, their profusion increases;[249] individual opacities may also increase in size with time.[246] The hilar lymph nodes are commonly enlarged and typically calcify in a circumferential manner. This eggshell calcification is pathognomonic, in a worker exposed to dust, of silicosis.

The first appearance of nodules is usually in the upper zones of the lung and the nodules themselves are often quite small (2-3 mm). As the profusion increases, lesions appear throughout the lungs and a proportion increase in size to the typical r nodules. Progression of silicosis may also be marked by conglomeration of several nodules to form the early lesion of progressive massive fibrosis. Again, this typically occurs first in the upper part of a lung, and a single such

lesion is often followed later by the development of others. These lesions are classified according to the ILO (1980) scheme[16] on the basis of their size, A shadows being between 1 cm and 5 cm in greatest diameter, B being one or more lesions with a total diameter greater than 5 cm but occupying a total area less than that of one third of the right lung, and C being of greater total area than B.

The natural history of progressive massive fibrosis is that of a gradual increase in size, irrespective of further dust exposure.[250] The lesions may appear at any time after an appropriate exposure to silica, and not uncommonly occur first many years after dust exposure has ceased.[251] While in general the greater the profusion of small opacities, the greater the likelihood of an individual developing massive fibrosis, nevertheless isolated lesions may sometimes occur against a radiological background free of small nodules.

Symptoms occur late in the course of silicosis, when extensive massive fibrosis is present; at this stage the patient complains of shortness of breath. Cough and sputum production are usually due to bronchial disease and not to the pathological silicotic process. As discussed later, bronchial disease may result from exposure to industrial dusts as well as from exposure to cigarette smoke.

Accelerated silicosis may occur in occupations involving high exposures to silica over a relatively short period of a few years, as in sandblasting and silica flour, slate pencil and diatomaceous earth production. The small radiographic nodules may be less obvious and a more irregular upper zone fibrosis may occur leading to bilateral apical massive fibrosis. The condition typically occurs within a few years of first exposure and may progress to death within a decade.[15]

Acute silicosis occurs as a result of massive exposures to silica. Recent reports have been recorded in Table 1. The

nodular radiographic pattern is absent and the lungs show a diffuse ground glass appearance, similar to that of pulmonary oedema. The condition causes rapidly progressive dyspnoea and death, usually within months of onset.

6.3 Functional effects of silica exposure

Two important questions have been addressed by those who have investigated lung function in workers exposed to silica. The first concerns the effects of the disease silicosis, as demonstrated by radiographic changes, on lung function while the second concerns the effects of silica exposure on lung function. With respect to the first, it is well established that extensive progressive massive fibrosis is associated with impairment of function and this may be sufficiently severe to lead to cardiac failure and death. The pattern of dysfunction is usually a combination of restriction of lung volumes, reduction in gas transfer, and flow obstruction. Equally well established is the restrictive dysfunction associated with accelerated and acute silicosis.[252] There has been more debate about the effects, if any, of simple silicosis. Study of this has been complicated by a number of factors. First, the definition of silicosis is dependent upon interpretation of radiographs, and this has not always been carried out according to standard epidemiological practice. Secondly, silicosis has often been combined with mixed dust pneumoconiosis, which is usually characterised pathologically by less fibrosis and clinically by a less progressive nature. Thirdly, populations of silicotics almost always include a high proportion of cigarette smokers, who are thus exposed to a second potential cause of lung disease. Fourthly, the effects of silica inhalation may be twofold; first, induction of silicotic fibrosis and, secondly, induction of airflow obstruction either by a direct effect on bronchi or by promoting emphysema. Thus, in studying the lung function of silicotic subjects, it may be impossible to distinguish the effects of silicosis from the

independent effects of the silica exposure that led to the silicosis.

Two papers have addressed this last problem by estimating the exposures of their subjects to dust.[253,254] Both reported the results of studies of white gold miners in South Africa in whom it was possible to calculate total exposures to dust by summing the total duration of employment of each man in different occupations multiplied by the dust concentrations in these occupations. The first of these papers demonstrated a significant positive correlation between dust exposure and physiological evidence of airflow obstruction.[253] The second paper reported investigation of a subset of the population studied in the first paper, selected on the basis of age (45-54 years), at least 10 years underground experience in gold mines and less than 2 years in other mines.[254] Those subjects with silicosis (Cat. 1/0 or greater, as read by one experienced reader) had on average lower FEV_1 and FEF_{25-75} than those with normal radiographs. However, when the silicotics were compared with non-silicotic controls (matched on age, height, dust exposure and tobacco consumption), no significant differences in function were found. Investigation of the inter-relationships of age, height, dust exposure, smoking history and silicosis by analysis of covariance in the whole study group showed silicosis to have a significant effect only on FEF_{25-75}.

A study of English gypsum miners has shown changes of simple pneumoconiosis in a proportion of those with long service;[255] the authors suggested that these changes might have been related to quartz exposure, since they occurred largely in the mine in which quartz levels were likely to have been highest, and their prevalence showed a positive relationship to indices of dust exposure. Lung function tests, standardized for age and height, showed evidence of a deterioration in FEV_1, FEV_1/FVC and MEF_{50} in relation to length of mining service.

No relationship to other indices of dust exposure was found.

A series of studies of Vermont granite workers has investigated the inter-relationships of lung function and dust exposure. The first was carried out in 1970. The estimates of dust exposure, while imperfect, are nevertheless based on the most detailed study of workers' occupational histories and associated dust levels so far reported in the literature.[256] Lung function was measured by spirometry (FEV_1, vital capacity) and radiology (total lung capacity). Multiple regression analysis suggested statistically significant decrements in FVC (1.0 ml), FEV_1 (1.6 ml) and TLC (1.8 ml) for every year of exposure to the average level of respirable granite dust of about 0.5 $mg.m^{-3}$.[257] Larger annual decrements of FVC (30 ml and 9 ml) occurred in relation to years of age and years of smoking, as expected. A later study (in 1974) of the same workers, using analyses of longitudinal loss of function, purported to show that real losses of FVC and FEV_1 were far greater than these.[258] However, a further follow-up in 1979 showed a rise in FEV_1 and FVC compared to the values obtained in 1974.[259] The mean FVC reported in 1979 was even greater than that reported in 1970. Thus doubt has been cast on the reliability of data from the two earlier studies, and particularly on that generated in the 1974 study. Incomplete expiration during the FVC manoeuvre, a leaking spirometer and different methods of measuring FEV_1 and FVC (best of three in 1979, mean of three in 1970 and 1974) have been identified as three possible reasons for these inconsistent results.

Moreover, the 1970 study produced plausible cross-sectional evidence that granite dust (and the quartz component of that dust) has a small but statistically significant effect on FEV_1, FVC and TLC. The effect concerned is an estimate of average response. This implies that some workers will suffer a greater effect (and equally, some a smaller) and that the magnitude of the effect will depend also on the individual's level of exposure to respirable dust.

The 1970 Vermont study also investigated the influence of radiographic changes on lung function.[260] The classifications were made by only one reader who recorded a relatively high prevalence (30%) of abnormalities in films of men with very little granite dust exposure. However, this included men with category 1 (presumably 1/0 and greater) of both rounded and irregular shadows and is consistent with findings in more recent studies of other dust-exposed workers.[261] It should not therefore be regarded as invalidating the study. The paper reported FVC to be lower in subjects with abnormal films, being inversely related to the profusion of opacities. Both ventilatory function and profusion of radiographic shadows showed a relationship to estimates of dust exposure.

Several other studies have investigated the inter-relationships between radiological change and lung function in workers exposed to silica, though without any useful information on the levels of exposure. Of these, the most informative was an investigation of lung function and the prevalence of pneumoconiosis among slate workers in North Wales.[262] Slate dust exposures were not measured, but the dust was said to contain 13 to 32% respirable quartz. The study differed from others reviewed here in that it was based on random samples of the populations of slate mining communities; more than half of the individuals thus selected were found to have worked in slate. The possibility of bias due to studying a relatively fit working population was therefore avoided. The prevalences of both simple pneumoconiosis and of large shadows (massive fibrosis and/or tuberculous scars) were related to years of work in slate and to likely intensity of exposure to dust. Both FVC and FEV_1 were shown to have declined more rapidly in men with pneumoconiosis (Categories 1 and 2) than in men without, both in smokers and non-smokers. When the effects of age and pneumoconiosis category had been taken into account, no further significant effect of years of work in slate could be detected. Nevertheless, these results are consistent with either a dust effect or a pneumoconiosis effect.

In a study of subjects with radiological signs of silicosis reported to the Finnish Occupational Disease Register, almost half were found to have FVC and transfer factor below 80% of predicted values.[263] Radiological readings were by consensus of two physicians, using the ILO (1980) classification.[16] Subjects with category 3 disease had, on average, lower values for transfer factor than did those with Categories 1 and 2, though three out of nine men with category 3 disease still had normal lung function. In a case-control study, matching 28 of the silicotic subjects with controls from the same workplace (on the basis of age, sex and duration of dust exposure) but with normal radiographs, the silicotic subjects were shown to have significantly lower FEV_1, FVC and transfer factor.

Other clinical studies have investigated the relationships of functional abnormalities to radiographic abnormality. A French paper has reported slight reductions in lung volumes and increases in lung recoil pressure in non-smoking, non-bronchitic men with category 2 and 3 silicosis, in comparison to non-dust-exposed controls.[264] A Romanian study, also of carefully selected non-smoking, non-bronchitic men with silicosis, showed that gas transfer factor was normal in the simple disease but reduced in Stage B and C massive fibrosis.[265]

In summary, there is clear evidence that silica exposure may affect lung function. Workers with advanced massive fibrosis, accelerated silicosis and acute silicosis may be expected to have a largely restrictive functional abnormality. Workers with simple silicosis may have completely normal lung function, even when the condition reaches radiological category 3. At this stage, however, a mixed restrictive and obstructive pattern may be present; this is probably related more closely to other effects of the dust exposure than those responsible for the nodular fibrotic change. There is strong evidence that dust exposure by itself may be responsible for

deterioration in lung function in the absence of radiological evidence of silicosis.

6.4 Other diseases related to silica exposure

Silicosis has long been known to predispose to tuberculosis,[266] and before the introduction of chemotherapy in the 1950s it is likely that most patients with silicosis sooner or later developed tuberculosis. The complication is still not infrequent in endemic areas; thus, in South African blacks necropsy evidence of tuberculosis is more frequent in silicotic subjects than in those without the disease.[267] In that country in the 1960s some 20% of silicotic gold miners had active tuberculosis.[268] At the same time in Northern Rhodesia, silicotic copper miners were shown to have tuberculosis thirty times more frequently than non-silicotic miners.[269] In Britain, 0.5% of slate miners were found to have active tuberculosis in the 1950s,[270] and, in a recent study of the population of Welsh slatemining villages, almost half of the miners had radiological changes indistinguishable from the signs of healed tuberculosis.[262] As tuberculosis has become a less prevalent disease, so infections with non-tuberculous mycobacteria have been reported more frequently amongst workers with silicosis. In a study of silicotic sandblasters in Louisiana, of 83 men 10 had tuberculosis, 9 M. kansasii and 3 M. avium-intracellulare infection.[271] Other opportunist infections, including nocardiosis, cryptococcosis and sporotrichosis, have also been noted in patients with silicosis.[271]

Collagen diseases appear to occur more frequently in silicotic subjects than in the general population. Systemic sclerosis, or scleroderma, was originally described as occurring more frequently (9 in 8 000) in South African gold miners than among other men (1 in 25 000).[272] A recent case-control study amongst these miners has confirmed that the risk of scleroderma

relates not to the presence of silicosis but to greater intensity of silica exposure.[273] This may be the explanation for the high prevalence found amongst men with accelerated silicosis, where some 10% of patients have been reported to have scleroderma or other collagen disease.[274] Caplan's syndrome seems to occur relatively uncommonly in patients with silicosis, but has been described.[275] The onset of collagen disease in a subject with silicosis may herald rapid progression of the lung disease.[276,277]

Renal disease has been described in workers exposed to high levels of silica. A series of case reports has suggested that there may be a relationship between quartz exposure and development of cellular necrotic changes in glomeruli and proximal tubules.[278-282] All of these patients seem to have been exposed to very high, but unmeasured, levels of quartz at their work, five of the seven reported also having had acute or 'advanced' silicosis (Table 2). In three patients high levels of elemental silicon were demonstrated in renal biopsies, though whether these levels were higher than those that would have been found in quartz-exposed workers without renal disease is not known. In some instances it has been suggested that there may have been an auto-immune basis for the renal lesions,[281,282] though immunoglobulin deposits in the kidneys have not been universal findings.

No studies of the prevalence of renal disease in workers exposed to silica appear to have been carried out. However, one study of 15 patients with silicosis has found normal renal function in all[283] while, in contrast, another study of 20 silicotics found four to have proteinuria and lipiduria.[284] These authors also found glomerular and tubular lesions in 23 of 45 patients who had died of advanced silicosis. Another study has also shown renal functional impairment in nine of 20 silicotic subjects.[285] The balance of the evidence thus seems to indicate that there is a relationship between heavy exposure

TABLE 2

RECENT REPORTS OF RENAL DISEASE IN QUARTZ-EXPOSED MEN

Author	Reference	Job	Clinical features	Renal biopsy
Saldanha et al 1975	278	furnace bricklayer	hypertension, albuminuria renal Si 220 ppm normal chest film	proximal tubular degeneration
Giles et al 1978	279	sandblaster	acute renal failure acute silicosis renal Si 264 ppm	hypercellular glomeruli proximal tubular degeneration
Hauglustaine et al 1980	280	tile manufacture	hypertension, albuminuria normal chest film renal Si 150 ppm	hypercellular glomeruli proximal tubular degeneration
Bolton et al 1981	281	1 sandblaster 1 sand grinder 1 foundryman	renal failure, collagen disease features acute & chronic silicosis	hypercellular glomeruli crescents and proximal tubular degeneration
Banks et al 1983	282	rock driller	proteinuria, scleroderma, acute silicosis	proliferative & necrotic changes in glomeruli & proximal tubules

to quartz and the development of renal failure characterized by minimal histological changes in glomeruli and proximal tubules on light microscopy. Whether this is mediated by an auto-immune or by a direct toxic effect is unclear; the latter mechanism seems more likely.

6.5 Radiological response in relation to silica exposure

6.5.1 Granite workers in Vermont, USA

Studies of granite workers in Vermont are the best known source of epidemiological results relating quartz exposure to effects on man. They highlight the two main questions regarding toxicity which this review of epidemiological studies seeks to answer. First, is there a safe or threshold level of concentration or exposure where the risk of silicosis is effectively zero? And second, what is the relation between exposure to quartz and the risk of developing silicosis? Of course, the two questions are related; any estimate of an exposure-response relation implies also an answer to the question of threshold.

An early investigation (in 1924-26) of 972 granite shed workers in Vermont reported a very high prevalence of silicosis, 100% among men working for 15 years or more in the dustiest jobs.[286] Silicosis was diagnosed on the basis of clinical and radiographic findings together with an appropriate history of exposure. A follow-up study in 1937-38 commented on the rapid progression of disease in workers exposed to the highest levels of dust, many of whom ultimately succumbed to tuberculosis.[287] All workers exposed to average concentrations of between 40 and 60 mppcf suffered progressive and severe silicosis. Some workers exposed to, on average, between 10 and 20 mppcf developed silicosis, though in the conditions of the period this was not regarded by the authors as serious disease. Nevertheless, there was evidence in some of progression after

moving to less dusty work, and these workers also had a high mortality from tuberculosis. In workers exposed to levels below 9 mppcf, the authors detected no serious disease. It was noted that risk of silicosis was related to length of service as well as to average dust levels. However, the numbers studied were too few to estimate general exposure-response relations. Moreover, loss to follow-up had been severe, implying that such estimates might in any case have been suspect.

Dust control measures were initiated in 1937, with a recommended limit of 10 mppcf. The outcome was apparently successful. An environmental survey in 1955 showed that the mean dust exposure from 223 samples in the granite sheds was just under 5 mppcf, with only 10% of the samples exceeding the 10 mppcf limit;[288] the quartz content of airborne samples was about 25%. Insofar as X-ray records showed, only one man appeared to have any silicosis (and the authors of the report state that in his case the diagnosis was questionable) among 1 134 men in the granite sheds who started work after dust controls were introduced in 1937. The remainder had been employed for only seven years on average, though 100 had 15 or more years experience. It should be noted that this was a study of active workers, and that ex-workers (who may have shown a higher prevalence of disease) were not included. These findings were confirmed when a later study reported no new occurrences of silicosis among 855 men who had worked for up to 26 years in controlled conditions.[289] The absence of new occurrences under controlled conditions in Vermont was the main reason why 5 mppcf, or its approximate gravimetric equivalent of 50 $\mu g.m^{-3}$, was recommended as a safe limit in the USA.[290] Difficulties in converting from particle count to mass units, and in extrapolating from granite sheds to other industries, were however noted in the discussion of standards.

The more recent studies of Vermont granite workers, carried out by the Harvard School of Public Health in the 1970s, have been discussed above in the context of lung function. The main results linking film readings to exposure concerned 784 granite shed workers.[260] Estimates of the cumulative exposures of individuals were obtained by linking detailed work histories, from company records, with results from a current (1972) gravimetric sampling programme.[256] Exposures were summarised in units of dust-year and quartz-year, defined as exposure of 40 hours per week for one year to dust and quartz concentrations of 523 $\mu g.m^{-3}$ and 50 $\mu g.m^{-3}$ respectively. (Per cent quartz in the respirable fraction was about 9%, lower than in earlier surveys.) Though yearly serial radiographs were available, one film per man was classified, by one reader, according to the UICC/Cincinnati elaboration of the ILO (1971) classification.[291] Some abnormality, mostly rounded rather than irregular opacities, was found in 233 of the 784 films. Presence of small rounded opacities was clearly dust-related, whereas irregular opacities seemed to be related to years of smoking and not to dust. The results showed that the risk of any abnormality increased clearly with exposures above 35 dust-years. The risk was estimated as constant, at 30%, in men with lower exposures.

Reliance on 1972 concentrations is clearly a defect when estimating exposures historically, and 784 samples seem few when estimates of concentrations in up to 637 occupational groups (13 groups in 49 sheds) are required.[256] Nevertheless, such imperfect estimates of individual exposures are almost surely better than simple summaries of years worked in particular jobs, a view which further analyses could verify. Radiographs were classified by only one reader, on one occasion. This is a limitation on the study's reliability and is a controversial one because of the relatively high levels of abnormality, recorded even at low exposures; these require explanation in view of earlier results.[288,289] The authors

say that a clinical radiologist would probably consider a diagnosis of silicosis in respect of 45 men in their study classified as showing profusion 2 or more small rounded opacities.[260] The 36 men with profusion 2 were on average aged just over 50 years; it is likely, therefore, that at least several were first employed after dust controls began, in 1937, 34 years prior to medical survey. Re-classification of the radiographs is therefore highly desirable, not only to substantiate the estimated exposure-response curve, but also to confirm continued absence of new occurrences of silicosis with mean quartz levels less than 5 mppcf. Note however that a recent mortality report of the Vermont study reiterates that "no cases of silicosis or silicotuberculosis have been reported among men who began employment after controls were initiated".[292]

The constant non-zero risk at low exposures, if true, is consistent with a threshold model together with a background level of opacities (not dust-related) which in turn may be real, or artefacts of the classification. However, aspects of the fitted curve appear questionable. For example, the estimated level of 30% abnormality at low exposures is identical to the prevalence (233/784) in the entire group, even though the exposure-response curve rises clearly from 35 dust-years onwards. A distribution of the numbers at risk in each dust-year would be helpful; at present it is unclear whether at low exposures these numbers are sufficient to differentiate reliably between models of constant or increasing risk.

Because these are uniquely important data, further analyses are highly desirable using film classifications by several readers and the latest ILO (1980) Classification.[16] On current evidence, the major strength of the Vermont data seems to be in the earlier, pre-1974, studies.

6.5.2 Dusty trades in North Carolina, USA

The State of North Carolina provides comprehensive occupational medical and hygiene services to companies and workers involved in dusty trades. The industries include granite quarries for crushed stone and dimension stone; stone sheds (monumental stone); foundries; and mining and processing of minerals such as tungsten, pyrophyllite and gold.[293] Pre-employment physical examinations along with occupational histories and annual examinations (including X-rays) of dusty trades' workers have been carried out since 1935. Hygiene surveys have also been carried out both on an ad hoc and routine basis using impinger and subsequently cyclone samplers, and yielding more than 10 000 samples in total.

Radiographs, mostly 100 mm rather than standard 6 ft postero-anterior views, referring to about 3 000 workers prior to 1955 and about 6 000 thereafter, were classified by a single reader, though without using a standard pneumoconiosis classification scheme. Data for healthy individuals are discarded five years after leaving the dusty trades.

Of the 785 male cases of silicosis diagnosed from 1935 through 1980, the 331 men still in their first job on 1 January 1935 or first employed 1 January 1930 or later formed the basis of a case-control study.[294] Of these, 216 were matched successfully by race, year of birth and year of joining with 672 controls, though a 1:4 matching ratio was intended. It was required that each control had spent at least as long in view in the study, from joining to final examination, as the corresponding case. Three distinct estimates of individuals' cumulative exposures to quartz were derived, involving conversion of gravimetric to particle count data, commodity- and location-specific estimates of per cent quartz, and detailed classifications of work histories.[294,295] Men were stratified into four exposure categories 0, 1, 2 and 3;

exposure category 1 was roughly equivalent to a mean exposure of 1 mppcf over a 40-year working lifetime.

The results showed that the risks of being a case were clearly higher in the higher exposure categories. The authors summarise their main finding as showing a statistically significant increase in relative risk among men with exposure equivalent to 2.5 or more mppcf over 40 years, but no statistically significant effect at quartz exposures averaging 1 mppcf. A history of cigarette smoking did not alter the results substantially.

This again is an important study, and the exposure-response relation is clearcut. Note that case-control methods yield estimates of relative risk only; estimates of the absolute risk require information on numbers at risk, which was not available. Clearly there are problems with using for epidemiological purposes radiological and environmental data collected for health and hygiene surveillance respectively. But errors of classification would be expected to reduce the chances of finding an exposure-response relation rather than generate one artifically. The inability to match all cases seems to have been dealt with sensibly, and is not a major flaw. Analyses showed a definite increase in risks with increase in exposure, an important finding which could have been estimated more precisely by appropriate analyses of ungrouped data. It may therefore have been misleading to summarise results by comparing separately the lowest exposure group with the other three and ignoring the unifying trend of increasing risk with increasing exposure which unifies the results. Their approach led the authors to conclude that the study showed no evidence of increased risks over a working lifetime at 1 mppcf, which was estimated as approximating to the current US standard; an alternative view, that all exposure including a working lifetime at lmppcf is associated with some real increase in relative risk of silicosis, seems to arise more naturally from the data.

6.5.3 English gypsum miners

In a cross-sectional study in 1976-77 of underground workers at four English gypsum mines,[255] radiographs from 221 men were classified independently by three readers according to the ILO (1971) scheme.[296] Exposures were estimated by linking work histories from pay records to results of a limited gravimetric personal sampling programme, carried out by the company and using 33 occupational groups. Results were ranked on a 20-point scale with approximate conversions to respirable dust and quartz ($\mu g.m^{-3}$). Estimates of quartz content were not considered wholly reliable by the authors. Nevertheless, radiographic abnormalities (mostly small rounded opacities) were associated with measurements of respirable quartz rather than dust. It was concluded that quartz, not gypsum, was responsible. Further analyses confirmed a relation between exposure and small opacities ($\geq$ 1/0).[297] They support a threshold model at approximately 35 $\mu g.m^{-3}$ rather than a non-threshold model, though the latter is not inconsistent with the data. The authors assess that, at 100 $\mu g.m^{-3}$, over 50 % of workers exposed for 20 years or more would develop small rounded opacities of category 1/0 or more. They comment that these estimates are unlikely to be associated with a greater than two-fold error either way; this implies a probability of occurrence between 33% and 67% if, as seems natural, the two-fold factor is applied to the odds rather than to the probability itself. This seems a well-balanced assessment of results from a careful study of limited data.

6.5.4 South African gold miners

Workers underground in gold mines in South Africa are exposed to dust containing about 30% free silica. A study was begun in 1959 of 1 200 white miners who were first employed underground between 1934 and 1938 and who had completed at least 3 000 shifts.[249] The study therefore did not include

any men with short lengths of exposure to either high or low dust levels. Serial annual films were classified by one reader according to the ILO (1971) scheme[296] and onset of silicosis was defined as the first appearance of opacities classifiable as being of at least category 1 (m) on that scale. Estimates of exposure to dust were derived from individual occupational histories and conversions to units of respirable surface area from a particle-count sampling scheme based on occupational groups within the mines. It was concluded that "a clear relationship has been obtained between dust exposure in these mines and the probability of developing radiological evidence of silicosis".[298] Given exposure, silicosis was not found to be related to age. The relationships obtained were expressed as a set of curves displaying increasing probability of developing silicosis as a function of increasing length of employment and mean daily dust level.[249,298,299] On close examination, however, it is difficult to reconcile the numbers labelling the axes of the graphs with the magnitudes of the data from which the curves appear to have been estimated.[249] This discrepancy between the two forms of presentation and the somewhat vague descriptions of the statistical methodology make it difficult to draw firm conclusions of a quantitative nature from the results of this study. Surprisingly, there does not appear to be available any analysis of films from this workforce taken later than around 1969; and no similar work has been published regarding more recent entrants to the industry.

6.5.5 Pottery workers

An early and important study of silicosis was carried out among 1 627 men and 889 women employed in nine pottery factories in West Virginia, USA in 1936-37.[300] Diagnosis of silicosis was based on a combination of radiological and clinical criteria, but the overall definition included people with early radiological change and minimal symptoms. Length of

employment and dustiness of the jobs were both related to the prevalence of silicosis. Only two cases of silicosis were found among men exposed to less than 4mppcf, though only 39 subjects were at risk for more than 30 years in these conditions. The authors suggested that if dust levels could be brought below 4 mppcf, no new cases would be likely to develop. Petrographic analyses of the quartz content of 650 samples of dust which had settled on rafters (that is, collected at or above breathing level) suggested that about half of the workforce was exposed to dust with more than 20% quartz content. For the most part, the correlation between high quartz and high dust precluded distinguishing their effects, though limited comparisons did suggest a direct association between quartz and disease. This is certainly plausible in the light of more recent knowledge of the effects of such dusts.

Apart from a recent mortality study,[301] the long-term health effects of dust exposures in the pottery industry have not been evaluated in the USA. In Britain, however, an investigation into the respiratory health of pottery workers was reported in 1975.[302] Radiological readings by three readers, using the ILO (1971) scheme,[296] refer to 5 684 subjects; simple pneumoconiosis was defined as category 2 or 3. Data from 624 dust samples, representing 280 jobs, showed quartz contents of the respirable fractions ranging from 6 to 13% (mean 9%); in 18% of the samples the respirable quartz concentration exceeded 100 $\mu g.m^{-3}$. Radiological signs were age-related, with some evidence of smoking differences. Length of exposure was also important in the prediction of radiological signs, as was previous experience in coalmining. The authors state that current dust concentrations were related to radiological signs; that a crude measure of exposure was little better than current dust levels in explaining radiological signs; and that the main contributor to abnormality in the dust measurements was the respirable quartz concentration. This last conclusion was

derived from the finding of an association between radiological score, adjusted for other effects, and occupational groups ranked according to the quartz content of the dust to which they were exposed. Despite the absence of estimates of exposure clearly related to radiological signs, the study provides further evidence of an exposure-response relation. In general, detailed information relevant to a threshold is not given, though the conclusions state that, in the population of current workers studied, disease was observed principally in response to exposures 10, 15 or 20 years earlier.

6.5.6 Slate workers

Slate workers and ex-workers in North Wales have been studied and compared with men from the same area but not exposed to slate dust.[262] Although no measurements of dust levels were available, different occupations within the industry were grouped according to apparent dustiness and each man's occupational history was summarised as a set of times spent working in these occupational groups. Respirable slate dust contains between 13% and 32% of respirable quartz; the authors preferred to use the general description of pneumoconiosis for observed abnormalities rather than the more specific term silicosis. Films were read by three readers according to the ILO (1971) classification;[296] categories on the 4-point scale assigned to observed small opacities were averaged and transformed to a scale designed to approximate to the Normal distribution of random variations. Regression analyses showed relationships between increasing severity of opacities and time spent in the dustiest occupations; viz. miners, rockmen, and slate makers. Overall prevalences were high, one-third of all the slate workers showing signs of pneumoconiosis of category 1 or greater, and 10% showing category 2 or greater. From the analyses, it was estimated that men mining slate for 20-30 years would have a greater than 50% probability of reaching category 2 or higher. Had dust measurements for the various

occupations been available, this study would certainly have provided important evidence on quantitative risks in an industry where the respirable dust contained a significant proportion of silica.

Indian workers employed in the manufacture of slate pencils have been found to be exposed to respirable dust at concentrations between 4 and 18 $mg.m^{-3}$ in cutting the slate, and between 3 and 9 $mg.m^{-3}$ elsewhere in the factories.[229] The dust contained between 47% and 61% free silica. The median of three readers' assessments on the ILO (1980) classification[16] was analysed as a summary of radiological response. Of 403 cutters surveyed, 243 showed signs of silicosis at category 1 or worse, and 87 showed large opacities (massive fibrosis). Clear gradients in prevalence were found with length of employment in cutters and non-cutters; 100% of cutters employed for more than 15 years showed some sign of silicosis and 59% displayed massive fibrosis. A follow-up study 16 months later showed high mortality, many new cases, and rapid progression of existing cases.[230]

6.5.7 British coalminers

The proportion of silica in airborne dusts sampled in studies of the respiratory health of British coalminers has typically been below 10%. Coalworkers' pneumoconiosis, caused by exposure to mixed coal dust in coalmines, has generally been considered to present a different radiographic appearance from classical silicosis, and to be a less aggressive form of lung disease. In a study of 3 154 faceworkers from the National Coal Board's Pneumoconiosis Field Research programme, the probability of radiological progression on a 12-point scale elaboration of the ILO classification[303] was shown to increase, for exposure to a given mass of respirable dust, with decreasing mineral content.[304] The role of quartz in the mineral fraction was not clear, and appeared to depend on the

quantities of other minerals present in the dust. However, a routine survey in 1978 at one Scottish colliery yielded films for 623 men, and 21 of these showed unusually rapid progression of simple pneumoconiosis in spite of generally low exposures to coalmine dust.[246] The radiographic aspects of these films were considered to show similarities to silicosis. Analysis of the dust exposures of these cases in comparison with matched controls without radiographic progression showed a much higher mean proportion of quartz in the exposures of the cases (13%) than in those of the controls (8%). Airborne quartz concentrations at one face in this colliery reached unusually high levels for a period in the early 1970s; the radiographs from that period for all the miners at the colliery are currently being intensively studied together with the men's exposure histories to confirm and clarify these findings. A separate study matched 41 cases of rapid progression of simple pneumoconiosis during 10-year periods at nine collieries to controls of similar age, initial category of pneumoconiosis and dust exposure from the same collieries, who had not progressed over the same time period.[305] None of the coalminers studied had more than 18% quartz in his 10-year exposure to dust, but a disproportionately high number of the cases had exposures to quartz in the upper tail of the distribution; and the mean proportion of quartz in their exposures (6%) differed significantly from that recorded for the matched controls (5%). This quartz-related unusually rapid progression of small opacities was shown to be associated also with disproportionately frequent occurrence of progressive massive fibrosis. Further studies of radiographs of miners classified as showing large opacities (PMF) have suggested that these opacities may develop as different and identifiable types.[306] One type in particular was shown to occur with a frequency which related to exposure to coalmine dust containing relatively high proportions of quartz. Research on the effects of silica in mixed coal dust has been limited in the past by the low levels of silica present in the dust, but

investigations currently being carried out and further work arising may help to shed light on the problem.

6.5.8 Foundry workers

Silica sand is used in making moulds and cores for foundry castings. Earlier epidemiological studies of respiratory health in foundry workers were reviewed in 1950 in a report which also included new results showing a high prevalence of silicosis among steel fettlers in particular.[307] Studies since then, and especially recently, have focussed on mortality including lung cancer. Investigations of silicosis, with which this review is concerned, have generally been deficient but provide some useful information. For example, a large-scale prevalence study reported cases in light alloy foundries as well as in large iron foundries; no dust data were available.[308] A smaller subsequent study of cases at a Sheffield steel works recorded progression of silicosis in foundry workers after cessation of exposure.[309]

The most comprehensive recent survey[310] included independent classifications of radiographs by three readers of 2 142 men, including 321 controls, according to the NCB elaboration of the ILO scheme.[303] The prevalence of abnormalities was again found to be higher in fettlers than in other groups of men. Detailed analyses referred to 896 foundry floor men and 160 fettlers who did not report the syndrome of sputum and chest illness (i.e., a history of sputum for at least three months each year associated with one or more chest illnesses) and who had no other experience of dusty work. Both age and years as a foundry worker were related to the radiological score, with risks per year of exposure particularly high among fettlers. There were no data to permit estimates of individuals' exposures.

Presence of radiological change has been considered in relation

to estimates of previous exposure to respirable dust in a study of foundry workers in England which, after exclusions, referred to 172 men.[311] The study procedures seem deficient in several aspects, a problem compounded by the absence of relevant details of methods in what the authors acknowledge is a preliminary analysis. The main result was that none of the men whose estimated cumulative exposure to respirable dust (of which the quartz content was said to be low) was less than 40 $mg.year.m^{-3}$ was classified as having radiological abnormality. However, because of the small numbers of men at risk and other limitations of the study, this finding does not support the authors' views on safe levels of exposures to dust and quartz; indeed, there were no reasonable data on quartz exposures to support such an evaluation. The results of this modest and potentially interesting study appear to have been seriously over-interpreted.

It has also been clear for some time that silicosis has occurred among foundry workers in the USA. For example, a review of cases on record from 1950 through 1954 at official health and compensation agencies in 22 States reported 1 645 cases (16% of the total) among foundry workers.[312] More recent surveys in that country have shown that quartz levels in foundries may not infrequently exceed the OSHA permissible exposure limit.[313] The authors commented on the lack of epidemiological studies intended to relate exposure to radiological response in foundries and recommend strongly that such a study be undertaken. A small-scale recent study of respiratory health at an iron and steel foundry in Vancouver, Canada, did include environmental monitoring.[314] However, since only 78 workers were involved, estimation of exposure-response relations was not possible.

Several studies from mainland Europe are of interest primarily for reports of prevalence; those from Finland and Denmark merit special mention. A large scale study of the health of

foundry workers in Finland included environmental monitoring.[9] Crude exposure groups were defined but were not used in the study of pneumoconiosis, since they referred to current exposures only.[315] The prevalence of disease was lower than expected in view of the dust concentrations reported, but several difficulties were noted in the discussion, including the need to rely in part on 100 mm films. Measurements of concentrations were also unavailable in the Danish study, where a follow-up in 11 foundries was of particular interest.[316] Time worked by cases and controls is reported in detail by occupational group within foundry. The relation between presence of silicosis, identified radiologically, and time worked in the occupational groups is striking, leading to the conclusion that in this study non-environmental factors played only a minor role. It would, however, be unwise to generalise on the basis of one study only.

6.5.9 Other groups of workers

Other studies reported in the literature are of limited usefulness either because of lack of environmental measurements or poor definition of radiological response. Miners in the Cumbrian haematite mines were first surveyed in 1934.[317] Up to that time conditions had been very dusty, with the ore containing typically 8-12% silica and high levels of nitrous fumes being produced by blasting operations. A large proportion of the worforce displayed radiographic abnormalities, including massive fibrosis; this was particularly noted in those workers who had long employment histories. Haematite pneumoconiosis has been shown to resemble silicosis pathologically.[318,319] Measures were introduced to suppress dust and fumes, and by the early 1960s dust levels were relatively low (<2 mg.m^{-3} in drilling operations). The prevalence of radiographic abnormalities was greatly reduced, and no new case of haematite pneumoconiosis has been certified since 1967. Individual dust measurements

which might have permitted the estimation of exposure-response relationships were not made.

A prevalence survey of 192 long-term uranium miners in New Mexico yielded films for 143 men.[320] These films were read according to the ILO (1980) scheme[16] and ten films were classified as 1/0 or 1/1. A further two were classified as 2/2 and 2/3, both also exhibiting ill-defined large opacities. Opacities were described as of a silicotic type. Although years of employment was used as an exposure variable for analyses of lung function data, no results were published on any relationship between years of employment and risk of developing opacities.

Of 22 metal mines studied in Peru from 1949 to 1969, 13 had consistent data on occupational exposure, and significant numbers of workers with and without silicosis.[321] The definition of silicosis in these studies is not given, however. Men were grouped by the length of their exposures, and dust levels for different mines were based on particle counts. A "silicosis index", defined as the proportion of miners developing silicosis, was shown to relate to the free silica content of the rock worked after allowance for length of exposure and dust levels; regression calculations and conversion factors were applied to derive the formula

$$C = 70/(\%SiO_2 + 3)$$

for the maximum permissible dust concentration in air (C, in mppcf) as a function of the free silica content of the airborne dust ($\%SiO_2$), to achieve a maximum target prevalence of 1% for silicosis. The formula adopted by the ACGIH in the USA for an analogous purpose was

$$C = 250/(\%SiO_2 + 5);$$

it was suggested that differences in the formula derived from the Peruvian data could have been due to the very different atmospheric conditions in mines more than 3 000 metres above sea level, and to the longer (48 hours) working week in Peru.

However, the many uncertainties in deriving indices of both exposure and response in this and other studies make the development of such formulae somewhat speculative and follow-up studies are necessary to test their validity.

In a study of 469 monumental masonry workers employed in Aberdeen, Scotland, in 1970,[322] radiological signs were recorded independently by three readers according to the 12-point elaboration of the ILO scheme,[323] and were related to years worked in the industry. Category 1 simple silicosis was not seen in men with less than 20 years exposure, while category 2 disease only occurred after a minimum of 30 years. Dust measurements, insufficient for construction of exposure indices, showed variations in quartz content of the "granite" dust from zero to 20%. The authors pointed to the insecurity of conclusions to be drawn from such a survivor study.

7. CONCLUSIONS WITH RESPECT TO A SILICA STANDARD

The many studies reviewed support some simple qualitative generalisations about silicosis, identified radiologically, following exposure to silica dust. Silicosis has been shown repeatedly to be related to length of time employed in dusty jobs and, for given employment times, to respirable dust concentrations and their quartz content. This evidence, supported by results from the few studies which included credible estimates of the exposures of individuals, leaves little room for doubt that there is a definite relation between exposure and response. However, on the basis of the studies reviewed it is not at present possible to describe the relation reliably. The difficulties are due in part to inexactness in measuring exposure, and to a lesser extent in measuring response, issues which arose as problems in all the studies considered. Much could be gained by further analyses of existing data and by carrying out new studies. Nevertheless, imprecisions in estimates of historical exposures, and the need

to extrapolate results to low exposure levels, are likely to remain as continuing difficulties.

Assessing whether or not there is a safe or threshold level of exposure is a less ambitious task than that of estimating an entire exposure-response relation. But even with regard to a threshold, the exposure-response studies provide no uniform answer. Evidence regarding a threshold therefore still depends importantly on studies of prevalence in known dust conditions, and on case reports showing whether or not silicosis can occur under various circumstances. Thus there is clear evidence that levels above about 1 $mg.m^{-3}$ are associated with unacceptable risks of rapidly progressive disease in, for example, sandblasters and slate pencil workers. At the other end of the scale, there is evidence from the Vermont granite sheds, the US diatomite industry and the Cumbrian haematite mines that dust control can satisfactorily reduce the risk of silicosis and practically eliminate new occurrences of serious disease. Note, however, that the reported absence of new cases in these industries under controlled conditions does not necessarily mean that conditions are safe; it would be necessary to study more men, and for longer time periods, before the absence of new cases would justify such a strong conclusion.

Because of the size of the workforce, the stated absence of new cases of silicosis among Vermont granite workers with a recommended level of 10 mppcf is, in our view, still a most important piece of evidence regarding a threshold limit. Nevertheless, reservations remain about the reliability and clinical significance of the diagnosis of silicosis in this study and about the possible bias introduced by the absence of any investigation of retired workers, since silicosis may appear after dust exposure has ceased. These reservations are strengthened by exposure-response investigations of English gypsum workers, North Carolina dusty trades workers and the

Vermont study itself, all of which suggest that a limit of 100 $\mu g.m^{-3}$ may be associated with the occurrence of some radiological changes.

Thus the evidence from epidemiological studies on the likely incidence of silicosis under various conditions is far from clearcut. And there are additional considerations in moving from an evaluation of epidemiological evidence to the related but different task of assessing the likely usefulness of any particular standard in preventing silicosis. First, the scientific evidence is reported and interpretable primarily in terms of years worked in average dust concentrations, whereas standards refer to acceptable upper limits on these concentrations. Setting of standards to ensure average levels which may be considered safe therefore involves an important degree of uncertainty which we acknowledge and which merits investigation. The relationship of upper limit to average may well vary from industry to industry, highlighting a second area of difficulty. Silica is a component of respirable dust in a very wide range of processes. The particle size distributions of these dusts differ, complicating the task of relating to a future gravimetric standard the results from studies based on particle count measurements. Average per cent quartz in respirable dust also varies considerably within and between industries, and the non-quartz component of the dust is undoubtedly relevant, in that it may in itself be toxic or it may alter the toxicity of the quartz. It follows that it is unlikely that any one standard would be appropriate over the wide variety of industries where quartz is present in the airborne dust. Finally, the usefulness of any standard in preventing disease is of course highly dependent on whether it is adhered to, an issue which depends not only on goodwill but also on technological feasibility, availability of resources, and diligence in supervision and enforcement.

These are not trivial problems, and a scientific evaluation of them is not possible with current knowledge. However the evidence, as we find it, suggests that restricting exposures to concentrations of quartz not exceeding 100 $\mu g.m^{-3}$ might prevent most (or possibly even all) serious cases of silicosis, but such exposures may nevertheless be associated with the development of radiological changes in a proportion of the workforce. The potential of such radiological change to lead to serious disease and disablement is at present undetermined.

The various areas of indeterminancy outlined above may to some extent be reduced by obtaining additional information, and it is appropriate to note that there exist opportunities for doing this. Further analyses of existing data provide one relatively inexpensive way of obtaining better epidemiological information. Obvious examples include epidemiological re-readings of X-ray films of the Vermont granite shed workers and those in the North Carolina studies. More detailed information on the responses to exposure in these studies might then be determined in relation to detailed dust exposure data from those industries. In the UK, further studies could be undertaken of groups of coalminers exposed to dusts containing substantial proportions of quartz, for whom detailed exposure data have been collected as part of a long-term epidemiological research programme. Such studies would provide useful and reliable information on exposure and response, and could additionally be useful in drawing distinctions between radiological patterns associated with differing proportions of the mineral and coal fractions of mine dusts.

There are also good grounds for new epidemiological studies both in the UK and elsewhere. For example, the absence of recent work on the morbidity of pottery workers seems a serious omission. Finally, a comprehensive occupational hygiene study

of silica-related industries in the UK would be invaluable in assessing the likely impact of any proposed silica standard, both by relating maximum to average concentrations and by describing composition of airborne respirable dusts which contain silica.

REFERENCES

1 FRONDEL C. The system of mineralogy of Dana. Vol.3. Silica minerals. 7th ed. New York: Wiley, 1962.

2 ILER RK. The chemistry of silica. New York: Wiley, 1979.

3 INTERNATIONAL ORGANIZATION FOR STANDARDIZATION. Air quality - particle size fraction definitions for health-related sampling. Switzerland: ISO, 1983. (Technical Report ISO/TR 7708-1983)

4 AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS. Particle size-selective sampling in the workplace. Cincinnati (OH): ACGIH, 1985.

5 HEALTH AND SAFETY EXECUTIVE. General methods for the gravimetric determination of respirable and total dust. London: HSE, 1983. (MDHS 14)

6 ORENSTEIN AJ, ed. Recommendations adopted by the Pneumoconiosis Conference. In: Orenstein AJ, ed. Proceedings of the Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg, February 1959. London: Churchill, 1960: 617-21.

7 TASK GROUP ON LUNG DYNAMICS. Deposition and retention models for internal dosimetry of the human respiratory tract. Health Physics 1966; 12: 173.

8 BREUER H. Problems of gravimetric dust sampling. In: Walton WH, ed. Inhaled particles III. Old Woking (Surrey): Unwin Bros, 1971: 1031-43.

9 SILTANEN E, KOPONEN M, KOKKO A, ENGSTROM B, REPONEN J. Dust exposure in Finnish foundries. Scand J Work Environ Health 1976; 2(suppl.1): 19-31.

10 DODGSON J. The measurement of dust and fumes. In: Morgan WKC, Seaton A, ed. Occupational lung diseases. 2nd ed. Philadelphia: Saunders, 1984: 212-38.

11 DODGSON J, WHITTAKER W. The determination of quartz in respirable dust samples by infrared spectrometry - I. The potassium bromide disc method. Ann Occup Hyg 1973; 16: 373-387.

12 DODGSON J, WHITTAKER W. The determination of quartz in respirable dust samples by infrared spectrometry - II. The direct analysis of quartz deposited on filters. Ann Occup Hyg 1973; 16: 389-395.

13 ALTREE-WILLIAMS S, LEE J, MEZIN NV. Quantitative X-ray diffractometry on respirable dust collected on Nuclepore filters. Ann Occup Hyg 1977; 20: 109-26.

14 PICKARD KJ, WALKER RF, WEST NG. A comparison of X-ray diffraction and infra-red spectrophotometric methods for the analysis of alpha-quartz in airborne dusts. Ann Occup Hyg 1985; 29: 149-67.

15 SEATON A. Silicosis. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 2nd ed. Philadelphia: Saunders, 1984: 250-94.

16 INTERNATIONAL LABOUR ORGANISATION. Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconioses. Geneva: International Labour Office, 1980. (ILO Occupational Safety and Health Series no. 22 (rev. 80))

17 OHMAN KHG. Prevention of silica exposure and elimination of silicosis. Am Ind Hyg Ass J 1978; 39: 847-859.

18 LIDDELL FDK, MORGAN WKC. Methods of assessing serial films of the pneumoconioses: a review. J Soc Occup Med 1978; 28: 6-15.

19 KING EJ, RAY SC, HARRISON CV, NAGELSCHMIDT G. The effects of granite on the lungs of rats. Br J Ind Med 1950; 7: 37-41.

20 MARENGHI B, ROTA L. Effeti del cortisone sulla silicosi sperimentale del ratto. Med Lav 1953; 44: 383-97.

21 WATANABE K. The influence of X-ray on experimental pneumoconiosis. I. On the development of fibrogenic nodules produced by inhalation of quartz dust. Tohoku J Exp Med 1956; 63: 251-58

22 LEVIS F, OLIVIERI A, CAPPA PM, PERNIS B. [Morphological studies on silicosis as immunological disease. I - Experimental and histochemical studies on the evolution of lesions induced by quartz.] Med Lav 1958; 49: 735-59.

23 LEVIS F, CARBONARA A, OLIVIERI A. [Morphological studies on silicosis as immunological disease. II - Experimental and histochemical studies on the evolution of lesions induced by mixed dusts (coal mine dust with low quartz content).] Med Lav 1958; 49: 760-86.

24 HEPPLESTON AG. The disposal of dust in the lungs of silicotic rats. Am J Pathol 1962; 40: 493-506.

25 HEPPLESTON AG. The disposal of inhaled particulate matter; a unifying hypothesis. Am J Pathol 1963; 42: 119-35.

26 GARDNER LU. The experimental production of silicosis. US Public Health Rep 1935; 50: 695-702

27 DENNY JJ, ROBSON WD, IRWIN DA. The prevention of silicosis by metallic aluminum. II. Can Med Assoc J 1939; 40: 213-28.

28 CAUER H, NEYMANN N. Die inhalieranlage nach Barthel-Küster auf der Zeche Hannibal und die Inhalierung von Kalziumsole gegen Silikosebeschwerden. Glückauf 1951; 87: 1011-7.

29 CAUER H, NEYMANN N. Neue Untersuchungen auf dem Gebiete der Elektro-aerosol Inhalation. Staub 1953; 33: 293-307.

30 KING EJ, MOHANTY GP, HARRISON CV, NAGELESCHMIDT G. The action of different forms of pure silica on the lungs of rats. Br J Ind Med 1953; 10: 9-17.

31 ZAIDI SH, KING EJ, HARRISON CV, NAGELSCHMIDT G. Fibrogenic activity of free silica of different particle sizes. Tissue reactions in lungs of rats and livers of mice to different doses of ground flint of constant surface area. AMA Arch Ind Health 1956; 13: 122-32.

32 LE BOUFFANT L, DANIEL H, MARTIN JC, BRUYERE S. [Toxicology - variation in the toxic effect of certain silicas in relation to their residence time in the organism.] C R Acad Sci (D) 1977; 285: 599-602. (HSE Translation no. 9773)

33 LE BOUFFANT L, DANIEL H, MARTIN JC. Données nouvelles concernant la nocivité pulmonaire des poussières de silice. Arch Mal Prof 1979; 40: 59-62 (HSE Translation no. 8486)

34 REISER KM, HESTERBERG TW, HASCHEK WM, LAST JA. Experimental silicosis. I. Acute effects of intratracheally instilled quartz on collagen metabolism and morphologic characteristics of rat lungs. Am J Pathol 1982; 107: 176-85.

35 GROSS P, WESTRICK ML, McNERNEY JM. Tuberculosilicosis: a study of its synergistic mechanisms. J Occup Med 1960; 2: 571-5.

36 NAESLUND C. Ein Beitrag zur Frage der Technik bei experimenteller Silikose sowie eine Untersuchung über den Wert der Trachealsonde für das Studium der Staubwirkung in der Lunge. Arch Gewerbepath Gewerbehyg 1938; 9: 414-25.

37 MOSINGER M, FIORENTINI H, GRAS A, GARCIN C, EL FEKI M, CARTOUZOU G. [Studies of experimental pneumoconiosis in dogs.] Arch Mal Prof 1961; 22: 5-39.

38 HEPPLESTON AG. Atypical reaction to inhaled silica. Letter. Nature 1967; 213: 199.

39 HEPPLESTON AG, WRIGHT NA, STEWART JA. Experimental alveolar lipo-proteinosis following the inhalation of silica. J Pathol 1970; 101: 293-307.

40 GROSS P, deTREVILLE RTP. Experimental 'acute' silicosis. Arch Environ Health 1968; 17: 720-5.

41 GROSS P, deTREVILLE RTP. Alveolar proteinosis: its experimental production in rodents. Arch Pathol 1968; 86: 255-61.

42 CORRIN B, KING E. Experimental endogenous lipid pneumonia and silicosis. J Pathol 1969; 97: 325-30.

43 CORRIN B, KING E. Pathogenesis of experimental pulmonary alveolar proteinosis. Thorax 1970; 25: 230-6.

44 HEPPLESTON AG, FLETCHER K, WYATT I. Changes in the composition of lung lipids and the 'turnover' of dipalmitoyl lecithin in experimental alveolar lipo-proteinosis induced by inhaled quartz. Br J Exp Pathol 1974; 55: 384-95.

45 HEPPLESTON AG, McDERMOTT M, COLLINS MM. The surface properties of the lung in rats with alveolar lipoproteinosis. Br J Exp Pathol 1975; 56: 444-53.

46 McDERMOTT M, WAGNER JC, TETLEY T, HARWOOD J, RICHARDS RJ. The effects of inhaled silica and chrysotile on the elastic properties of rat lungs; physiological, physical and biochemical studies of the lung surfactant. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 415-27.

47 CHIAPPINO G, VIGLIANI EC. Role of infective, immunological, and chronic irritative factors in the development of silicosis. Br J Ind Med 1982; 39: 253-8.

48 SILVERMAN L, MORITZ AR. Peritoneal reaction to injected fused (spherical) and unfused (spiculate) quartz. Pathologic studies. AMA Arch Ind Hyg Occup Med 1950; 1: 499-505.

49 GARTNER H. Untersuchungen über die Wirkung feinkörniger, amorpher Kieselsäure in der Lunge von Kaninchen. Arch Hyg Bakt 1952; 136: 451-67.

50 OSANAI H. The fibrogenic activity of amorphous silica. J Sci Labour 1957; 33: 611-6.

51 POLICARD A, COLLET A. Etude expérimentale sur les réactions pathologiques consécutives a l'introduction dans l'organisme de silices amorphes en particules inframicroscopiques. Arch Mal Prof 1957; 18: 508-10.

52 KLOSTERKOTTER W, JOTTEN KW. [The action of different forms of silica in animal experiments.] Arch Hyg Bakt 1953; 137: 625-36.

53 KLOSTERKOTTER W. [A contribution by animal experiments to the problem of the toxic action of molecularly dissolved silica.] Arch Hyg Bakt 1952; 136: 188-94.

54 KLOSTERKOTTER W. [Studies of animals experimentally inflicted with silicosis through inhalation of amorphous arc silicic acid.] Arch Hyg Bakt 1966; 150: 542-57.

55 TEBBENS BD, BEARD RR. Experiments on diatomaceous earth pneumoconiosis. 1. Natural diatomaceous earth in guinea pigs. AMA Arch Ind Health 1957; 16: 55-63.

56 SCHEPERS GWH, DURKAN TM, DELAHANT AB, CREEDON FT, REDLIN AJ. The biological action of Degussa submicron amorphous silica dust (Dow Corning silica). I. Inhalation studies on rats. AMA Arch Ind Health 1957; 16: 125-46.

57 SCHEPERS GWH, DURKAN TM, DELAHANT AB, CREEDON FT, REDLIN AJ. The biological action of inhaled Degussa submicron amorphous silica dust (Dow Corning silica). II. The pulmonary reaction in uninfected guinea pigs. AMA Arch Ind Health 1957; 16: 203-24.

58 SCHEPERS GWH, DELAHANT AB, SCHMIDT JG, von WECHELN JC, CREEDON FT, CLARK RW. The biological action of Degussa submicron amorphous silica dust (Dow Corning silica). III. Inhalation studies on rabbits. AMA Arch Ind Health 1957; 16: 280-301.

59 FURUYA Y. Tissue reaction by amorphous fine silica and quartz with different sizes. Bull Inst Public Health 1958; 7: 29-36.

60 SWENSSON A. Tissue reaction to different types of amorphous silica. In: Davies CN, ed. Inhaled particles and vapours II. Oxford: *Pergamon Press*, 1967: 95-104

61 BRIEGER H, GROSS P. On the theory of silicosis. II. Quartz glass. Arch Environ Health 1967; 14: 299-303.

62 BELOBRAGINA GV, ELNICHNYKH LN. [*Lipid distribution in the lungs in* experimental silicosis caused by condensed silicon dioxide.] Gig Sanit 1972; 50(8): 45-9.

63 PODGAIKO GA, KATSNELSON BA, LEMIASEV MF et al. [Experimental silicosis in rats chronically exposed to a colloidal solution of silicic acid by inhalation.] Gig Tr Prof Zabol 1980; (7): 24-7.

64 GROTH DH, MOORMAN WJ, LYNCH DW, STETTLER LE, WAGNER WD, HORNUNG RW. Chronic effects of inhaled amorphous silicas in animals. In: Dunnom DD, ed. Health effects of synthetic silica particulates. Philadelphia (Pa): American Society for Testing and Materials, 1981: 118-43. (ASTM Special Publication 732).

65 WELLER W. Effects of unmodified natural and coated silicious earth in a long-term intraperitoneal test in rats. In: Dunnom DD, ed. Health effects of synthetic silica particulates. Philadelphia (Pa): American Society for Testing and Materials, 1981: 174-84. (ASTM Special Publication 732).

66 SCHEPERS GWH. Biological action of precipitation-process submicron amorphous silica (HI-SIL 233). In: Dunnom DD, ed. Health effects of synthetic silica particulates. Philadelphia (Pa): American Society for Testing and Materials, 1981: 144-73. (ASTM Special Publication 732).

67 WOZNIAK H. [Comparative studies on fibrogenic properties of diatomites and other silica dusts.] Med Pr 1983; 34: 427-34.

68 PRATT PC. Lung dust content and response in guinea pigs inhaling three forms of silica. Arch Environ Health 1983; 38: 197-204.

69 SCHMIDT KG, LUCHTRATH H. [Comparison of the effects of quartz, cristobalite and tridymite dust in intratracheal studies in rats.] Beitr Silikose-Forsch 1955; 37: 1-43.

70 ZAIDI SH, KING EJ, HARRISON CV, NAGELSCHMIDT G. Fibrogenic activity of different forms of free silica. The action of fused silica, quartz, cristobalite, and tridymite on the livers of mice. AMA Arch Ind Health 1956; 13: 112-21.

71 SAFFIOTTI U, DEGNA AT, MAYER L. The histogenesis of experimental silicosis. II - Cellular and tissue reactions in the histogenesis of pulmonary lesions. Med Lav 1960; 51: 518-22.

72 SAFFIOTTI U. The histogenesis of experimental silicosis. III - Early cellular reactions and the role of necrosis. Med Lav 1962; 53: 5-18.

73 THOMAS K. Grundfragen aus der Silikoseforschung. Schweiz Med Wochenschr 1964; 94: 213-7.

74 BRIEGER H, GROSS P. On the theory of silicosis. I. Coesite. Arch Environ Health 1966; 13: 38-43.

75 BRIEGER H, GROSS P. On the theory of silicosis. III. Stishovite. Arch Environ Health 1967; 15: 751-7.

76 WAGNER WD, FRASER DA, WRIGHT PG, DOBROGORSKI OJ, STOKINGER HE. Experimental evaluation of the threshold limit of cristobalite - calcined diatomaceous earth. Am Ind Hyg Ass J 1968; 29: 211-21.

77 GARDNER LU, CUMMINGS DE. The reaction to fine and medium sized quartz and aluminum oxide particles. Silicotic cirrhosis of the liver. Am J Pathol 1933; 9: 752-64.

78 TEBBENS BD, SCHULTZ RZ, DRINKER P. The potency of silica particles of different size. J Ind Hyg Toxicol 1945; 27: 199-200.

79 HATCH T, HEMEON WCL. Influence of particle size in dust exposure. J Ind Hyg Toxicol 1948; 30: 172-80.

80 KING EJ, MOHANTY GP, HARRISON CV, NAGELSCHMIDT G. The action of flint of variable size injected at constant weight and constant surface into the lungs of rats. Br J Ind Med 1953; 76-92.

81 SWENSSON A, GLOMME J, BLOOM G. On the toxicity of silica particles. AMA Arch Ind Health 1956; 14: 482-6.

82 GOLDSTEIN B. Animal experiments on important parameters of dust in relation to the production of fibrosis. In: Orenstein AJ, ed. Proceedings of the Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg, Februrary 1959. London: Churchill, 1960: 94-108.

83 KING EJ, NAGELSCHMIDT G. The physical and chemical properties of silica, silicates and modified forms of these in relation to pathogenic effects. In: Orenstein AJ, ed. Proceedings of the Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg, Februrary 1959. London: Churchill, 1960: 78-83.

84 GOLDSTEIN B, WEBSTER I. Intratracheal injection into rats of size-graded silica particles. Br J Ind Med 1966; 23: 71-4.

85 KING EJ. Solubility theory of silicosis. A critical study. Occup Med 1947; 4: 26-49.

86 DALE JC, KING EJ. Acute toxicity of mineral dusts. AMA Arch Ind Hyg Occup Med 1953; 7: 478-83.

87 JOTTEN KW, KLOSTERKOTTER W. Die Bedeutung der Löslichkeit der Kieselsäure für das Zustandekommen der Pneumokoniosen. Arch Hyg Bakt 1952; 136: 1-4.

88 POLICARD A, COLLET A. Toxic and fibrosing action of submicroscopic particles of amorphous silica. AMA Arch Ind Health 1954; 9: 389-95.

89 SCHLIPKOTTER HW, ROTHES I, DEFESCHE AJ. Einfluss des Dispersionsgrades einer feinkörnigen (200A) amorphen Kieselsäure auf die biologische Wirkung bei intratrachealen Rattenversuchen. Ein Beitrag zur Pathogenese der Silikose. Z Hyg 1957; 143: 533-42.

90 SCHEPERS GWH. Hypertension due to inhaled submicron amorphous silica. Toxicol Appl Pharmacol 1959; 1: 487-506.

91 VORWALD AJ. Inhaled submicroscopic particles in the pathogenesis and pathology of silicosis. In: Orenstein AJ, ed. Proceedings of the Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg, Februrary 1959. London: Churchill, 1960: 137-42.

92 BELT T, KING EJ. Failure of aluminium to prevent experimental silicosis. J Pathol Bacteriol 1943; 55: 69-73.

93 KING EJ, RAY SC, HARRISON CV. Inhibitory action of aluminium on quartz in experimental silicosis. In: International Labour Organisation. Third International Conference of Experts on Pneumoconiosis, Sydney, 1950. Vol.II. Record of proceedings. Geneva: International Labour Office, 1953: 140-5

94 GARDNER LU, DWORSKI M, DELAHANT AB. Aluminum therapy in silicosis. An experimental study. J Ind Hyg Toxicol 1944; 26: 211-23.

95 DWORSKI M. Prophylaxis and treatment of experimental silicosis by means of aluminum. An experimental study. Arch Ind Health 1955; 12: 229-46.

96 ULMER WT. Prophylaxis of silicosis by aluminum - preliminary report on experimental investigations. Ind Med Surg 1964; 33: 52-6.

97 RAY SC, KING EJ, HARRISON CV. The action of anthracite and bituminous coal dusts mixed with quartz on the lungs of rats. Br J Ind Med 1951; 8: 74-6.

98 REISNER MTR, ROBOCK K. Results of epidemiological, mineralogical and cytotoxicological studies on the pathogenicity of coal-mine dusts. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 703-15.

99 CRAWFORD NP, BODSWORTH PL, HADDEN GG, DODGSON J. A study of apparent anomalies between dust levels and pneumoconiosis at British collieries. Ann Occup Hyg 1982; 26: 725-44.

100 MARTIN JC, DANIEL H, LE BOUFFANT L. Short- and long-term experimental study of the toxicity of coal-mine dust and of some of its constituents. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 361-71.

101 LE BOUFFANT L, DANIEL H, MARTIN JC, BRUYERE S. Effect of impurities and associated minerals on quartz toxicity. In: Walton WH, ed. Inhaled particles V. Oxford: Pergamon Press, 1982: 625-34. (Ann Occup Hyg 1982; 26)

102 KETTLE EH. The interstitial reactions caused by various dusts and their influence on tuberculous infections. J Pathol Bacteriol 1932; 35: 395-405.

103 GROSS P, WESTRICK ML, McNERNEY JM. Experimental silicosis: the inhibitory effect of iron. Dis Chest 1960; 37: 35-41.

104 SCHLIPKOTER HW, BECK EG. Observations on the relationship between quartz cytotoxicity and fibrogenicity while testing the biological activity of synthetic polymers. Med Lav 1965; 56: 485-93.

105 HENNIES H, EGER K, EGER W. Präventive und kurative silikotrope Wirkung des Polyvinylpyridin-N-Oxid im Leber- und Milz-Test. Beitr Silikose-Forsch 1967; 93: 15-31.

106 WELLER W. Long-term test on rhesus monkeys for the PVNO-therapy of anthraco-silicosis. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 379-87.

107 GYE WE, KETTLE EH. Silicosis and miners' phthisis. Br J Exp Pathol 1922; 3: 241-51.

108 KETTLE EH. The demonstration by the fixation abcess of the influence of silica in determining B. tuberculosis infections. Br J Exp Pathol 1924; 5: 158-64.

109 VORWALD AJ, LANDAU A. Influence of dusts on tuberculous infection. Susceptibility of subcutaneous lesions produced by dusts to infection by tubercle bacilli injected intravenously. Arch Pathol 1937; 24: 8-18.

110 GARDNER LU. Will the inhalation of siliceous dusts activate a partially healed focus of tuberculous infection? An experimental study. US Public Health Rep 1930; 45: 282-8.

111 POLICARD A, DUFOURT A. Recherches expérimentales sur les pneumoconio-tuberculoses. Ann Med 1937; 41: 183-209.

112 DE BALSAC HFH, FERNBACH E, RULLIER G. La silice exerce-t-elle une influence sur le développement et la virulence du bacille tuberculeux. Bull Acad Med 1940; 123: 365-8.

113 SEN PK. Pneumoconiosis with special reference to silicosis, anthracosis and tuberculosis. Indian Med Gazette 1939; 14: 547.

114 VORWALD AJ, DWORSKI M, PRATT PC, DELAHANT AB. BCG vaccination in silicosis. Am Rev Tuberc 1950; 62: 455-74.

115 KING EJ, HARRISON CV, MOHANTY GP, MITCHISON DA. Experimental infective pneumoconiosis. Arch Hig Rada 1953; 4: 289-300.

116 SCHEPERS GWH, DELAHANT AB, FEAR EJ, SCHMIDT JG. The biological action of Degussa submicron amorphous silica dust (Dow Corning silica). IV. Studies on guinea pigs infected with tuberculosis. AMA Arch Ind Health 1957; 16: 363-79.

117 GROSS P, WESTRICK ML, McNERNEY JM. Experimental *tuberculopneumoconiosis*. *AMA Arch Ind Health* 1959; 19: 320-34.

118 KETTLE EH. The relation of dust to infection. Proc R Soc Med 1930; 24: 79-94.

119 PRICE RM. Effect of silica on the growth of the tubercle bacillus. Proc Soc Exp Biol Med 1931; 28: 819-20.

120 VORWALD AJ, DWORSKI M, PRATT PC, DELAHANT AB. BCG vaccination in silicosis. II. An experimental study of the influence of inhaled quartz dust upon infection by BCG (Aronson), H37Ra, and M. marinum strains of tubercle bacilli. Am Rev Tuberc 1954; 69: 766-89.

121 GARDNER LU. Tuberculous infection and tuberculosis as modified by experimental pneumokoniosis. (Two parts). Tubercle 1924/25; 6: 336-41, 443-53.

122 EBINA T, TAKAHASHI Y, HASUIKE T. Effect of quartz powder on tubercle bacilli and phagocytes. Am Rev Respir Dis 1960; 82: 516-27.

123 VIGLIANI EC, PERNIS B. An immunologic approach to silicosis. J Occup Med 1959; 1: 319-28.

124 TAKEYA K, SHIMOTORI S, TANIGUCHI T, NOMOTO K. Cellular mechanisms in the protection against infection by Listeria monocytogenes in mice. J Gen Microbiol 1977; 100: 373-9.

125 TRISCHMANN T, TANOWITZ H, WITTNER M, BLOOM B. Trypanosoma cruzi: role of the immune response in the natural resistance of inbred mice. Exp Parasitol 1978; 45: 160-8.

126 FRIEDMAN, RL, MOON RJ. Hepatic clearance of Salmonella typhimurium in silica-treated mice. Infect Immun 1977; 16: 1005-12.

127 O'BRIEN AD, SCHER I, FORMAL SB. Effect of silica on the innate resistance of inbred mice to Salmonella typhimurium infection. Infect Immun 1979; 25: 513-20.

128 MORAHAN PS, KERN ER, GLASGOW LA. Immunomodulator-induced resistance against Herpes simplex virus. Proc Soc Exp Biol Med 1977; 154: 615-20.

129 MARKS J, MASON MA, NAGELSCHMIDT G. A study of dust toxicity using a quantitative tissue culture technique. Br J Ind Med 1956; 13: 187-91.

130 KOSHI K, KAWAI K, SAKABE H. Studies on the pathogenesis of silicosis. Effect of silica dusts on the phagocytic cells in vitro. Bull Natl Inst Ind Health 1959; 2: 29-39.

131 VIGLIANI EC, PERNIS B, MONACO LA. A study of the action of quartz particles on macrophages in vitro. In: Davies CN, ed. Inhaled particles and vapours. Oxford: Pergamon Press, 1961: 348-55.

132 KESSEL RWI, MONACO L, MARCHISIO MA. The specificity of the cytotoxic action of silica - a study in vitro. Br J Exp Pathol 1963; 44: 351-64.

133 BEY E, HARINGTON JS. Cytotoxic effects of some mineral dusts on Syrian hamster peritoneal macrophages. J Exp Med 1971; 133: 1149-69.

134 KATSNELSON BA, PRIVALOVA LI, KISLITSINA NS, PODGAIKO GA. Correlation between cytotoxicity and fibrogenicity of silicosis-inducing dusts. Med Lav 1984; 75: 450-62

135 BYE E, DAVIES R, GRIFFITHS DM, GYLSETH B, MONCRIEFF CB. In vitro cytotoxicity and quantitative silica analysis of diatomaceous earth products. Br J Ind Med 1984: 41: 228-34.

136 ROBOCK K, KLOSTERKOTTER W. The cytotoxic action and the semiconductor properties of mine dust. In Walton WH, ed. Inhaled particles III. Old Woking (Surrey): Unwin Bros, 1971: 453-60.

137 GORMLEY IP, BROWN GM, COLLINGS PL, DAVIS JMG, OTTERY J. The cytotoxicity of respirable dusts from collieries. In: Brown RC, Gormley IP, Chamberlain M, Davies R, eds. The in vitro effects of mineral dusts. London: Academic Press, 1980: 19-24.

138 SEEMAYER NH, MANOJLOVIC N. Biologic effects of coal mine dusts on macrophages. In: Brown RC, Gormley IP, Chamberlain M, Davies R, eds. The in vitro effects of mineral dusts. London: Academic Press, 1980: 5-12.

139 TILKES F, BECK EG. Macrophage functions after exposure to nonfibrous mineral dusts. Environ Health Perspect 1983; 51: 167-71.

140 HEPPLESTON AG, KULONEN E, POTILA M. In vitro assessment of the fibrogenicity of mineral dusts. Am J Ind Med 1984; 6: 373-86.

141 SEEMAYER NH. Biological effects of coal mine dusts on macrophages in vitro: importance of grain size and mineral content. In: VI International Pneumoconiosis Conference 1983. Bochum: Bergbau-Berufsgenossenschaft, 1984: 513-28.

142 DAVID A, HURYCH J, EFFENBERGEROVA E, HOLUSA R, SIMECEK J. Laboratory testing of biological activity of ore mine dust: fibrogenicity, cytotoxicity and hemolytic activity. Environ Res 1981; 24: 140-51.

143 BRUCH J, JOOS MR, REISNER MTR, ROSMANITH J. [Investigations into the specific harmfulness of respirable coal mine dusts. XVII. Comparison of the results from animal- and cell-tests.] Ergeb Untersuch Geb Staub-Silikosebekampf Steinkohlenbergbau 1983; 14: 241-55.

144 ROBERTSON A, BOLTON RE, CHAPMAN JS et al. Animal inhalation experiments to investigate the significance of high and low percentage concentrations of quartz in coalmine dusts in relation to epidemiology and other biological tests. Final report on CEC Contract 7256-32/019/08. Edinburgh: Institute of Occup Med, 1984. (IOM Report TM/84/5)

145 LEMAIRE I, GINGRAS D, LEMAIRE S. Thymidine incorporation by lung fibroblasts as a sensitive assay for biological activity of asbestos. Environ Res 1982; 28: 399-409.

146 RICHARDS RJ, HUNT J. Reaction of mineral dusts with primary lung fibroblast cultures. Environ Health Perspect 1983; 51: 61-5.

147 CHAMBERLAIN M, BROWN RC. The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines. Br J Exp Pathol 1978; 59: 183-9.

148 CHAMBERLAIN M, DAVIES R, BROWN RC, GRIFFITHS DM. In vitro tests for the pathogenicity of mineral dusts. Ann Occup Hyg 1982; 26: 583-92.

149 CHAMBERLAIN M. Effect of mineral dusts on metabolic cooperation between Chinese hamster V79 cells in vitro. Environ Health Perspect 1983; 51: 5-9.

150 JAURAND MC, BASTIE-SIGEAC I, RENIER A, BIGNON J. Comparative toxicities of different forms of asbestos on rat pleural mesothelial cells. Environ Health Perspect 1983; 51: 153-8.

151 STALDER K, STOBER W. Haemolytic activity of suspensions of different silica modifications and inert dusts. Nature 1965; 207: 874-5.

152 HEFNER RE, GEHRING PJ. A comparison of the relative rates of hemolysis induced by various fibrogenic and non-fibrogenic particles with washed rat erythrocytes in vitro. Am Ind Hyg Ass J 1975; 36: 734-40.

153 SINGH SV, DAS B, RAHMAN Q. Relationship between solubility and hemolytic effects of toxic dusts. J Appl Toxicol 1983; 3: 14-7.

154 SINGH SV, VISWANATHAN PN, RAHMAN Q. Interaction between erythrocyte plasma membrane and silicate dusts. Environ Health Perspect 1983; 51: 55-60.

155 ZENKER FA. Über Staubinhalationskrankheiten der Lungen. Dtsch Arch Klin Med 1866/7; 2: 116-72.

156 GARDNER LU. Studies on the relation of mineral dusts to tuberculosis. III. The relatively early lesions in experimental pneumokoniosis produced by carborundum inhalation and their influence on pulmonary tuberculosis. Am Rev Tuberc 1923; 7: 344-57.

157 SCHEPERS GWH. Theories of the causes of silicosis - part I. Ind Med Surg 1960; 29: 326-33.

158 HEFFERNAN P. What is silicosis? Tubercle 1935; 16: 397-406.

159 GARDNER LU. Studies on experimental pneumonokoniosis - VIII. Inhalation of quartz dust. J Ind Hyg 1932; 18-38.

160 WEYL WA. Active oxygen formed at surface of silica and clay as possible cause of silicosis. Am Ceram Soc Bull 1949; 28: 362.

161 DEMPSTER PB, RITCHIE PD. Surface of finely ground silica. Letter. Nature 1952; 169: 538-9.

162 ENGELBRECHT FM, YOGANATHAN M, KING EJ, NAGELSCHMIDT G. Fibrosis and collagen in rats' lungs produced by etched and unetched free silica dusts. AMA Arch Ind Health 1958; 17: 287-94.

163 KRIEGSEIS W, SCHARMANN A, SERAFIN J, BECK EG, TILKES F, BRUCH J. [Dependence of the cytotoxicity of SiO_2-containing dusts on their surface cleanliness.] Ergeb Untersuch Geb Staub- Silikosebekampf Steinkohlenbergbau 1983; 14: 281-99.

164 KRIEGSEIS W, SCHARMANN A. Determination of free quartz surfaces in coal mine dust. Ann Occup Hyg 1985; 29: 91-9.

165 VELICOGNA A. Teorie sulla patogenesi della silicosi. Med Lav 1946; 37: 107-12.

166 EVANS SM. Tissue responses to physical forces. I. The pathogenesis of silicosis. A preliminary report. J Ind Hyg Toxicol 1948; 30: 353-7.

167 EVANS SM, ZEIT W. Tissue responses to physical forces. II. The response of connective tissue to piezoelectrically active crystals. J Lab Clin Med 1949; 34: 592-609.

168 PRATT PC, BAILEY D, DELAHANT AB, VORWALD AJ. Relationship between the piezoelectric property and the fibrogenic capacity of dust. AMA Arch Ind Hyg Occup Med 1953; 8: 109-18.

169 HOUNAM RF. Some colloidal properties of inert dusts. AMA Arch Ind Hyg Occup Health 1952; 5: 375-86.

170 HOUNAM RF. Some reactions between inert dusts and proteins. AMA Arch Ind Health 1954; 9: 284-90.

171 WHEATLEY K. Surface properties of silica in relation to silicosis. Letter. Research 1957; 10: 76-7.

172 SUMMERTON J, HOENIG S, BUTLER C, CHVAPIL M. The mechanism of hemolysis by silica and its bearing on silicosis. Exp Mol Pathol 1977; 26: 113-28.

173 THOMAS K. [Biological effects of stable silica modifications.] Beitr Silikose-Forsch. Sonderband: Grundfr Silikoseforsch 1965; 6: 21-5.

174 KETTLE EH. Experimental silicosis. J Ind Hyg Toxicol 1926; 8: 491-5.

175 KING EJ, BELT TH. The physiological and pathological aspects of silica. Physiol Rev 1938; 18: 329-65.

176 KLOSTERKOTTER W. [Further investigations on the tissue action of silica in molecular and colloidal dispersion.] Arch Hyg Bakt 1953; 137: 307-16.

177 KING EJ, ZAIDI SH, NAGELSCHMIDT G. The silica-solubility theory of silicosis. AMA Arch Ind Health 1956; 13: 133-8.

178 CURRAN RC, ROWSELL EV. The application of the diffusion-chamber technique to the study of silicosis. J Pathol Bacteriol 1958; 76: 561-8.

179 HEPPLESTON AG, AHLQUIST KA, WILLIAMS D. Observations on the pathogenesis of silicosis by means of the diffusion chamber technique. Br J Ind Med 1961; 18: 143-7.

180 SIEHOFF F, ANTWEILER H. Zur Frage der biologischen Wirksamkeit von Poly-Kieselsäuren unterschiedlichen Polymerisationsgrades. Untersuchen zur Silikosepathogenese. Arch Gewerbepath Gewerbehyg 1956; 15: 158-70.

181 ALLISON AC, HARINGTON JS, BIRBECK M. An examination of the cytotoxic effects of silica on macrophages. J Exp Med 1966; 124: 141-53.

182 ALLISON AC, HARINGTON JS, BIRBECK M, NASH T. Observations on the cytotoxic action of silica on macrophages. In: Davies CN, ed. Inhaled particles and vapours II. Oxford: Pergamon Press, 1967: 121-8.

183 ALLISON AC, HART PD'A. Potentiation by silica of the growth of Mycobacterium tuberculosis in macrophage cultures. Br J Exp Pathol 1968; 49: 465-76.

184 DAVIES P, ALLISON AC. The macrophage as a secretory cell in chronic inflammation. Agents and Actions 1976; 6: 60-74.

185 SYKES SE, MORGAN A, MOORES SR, HOLMES A, DAVISON W. Dose-dependent effects in the subacute response of the rat lung to quartz. I. The cellular response and the activity of lactate dehydrogenase in the airways. Exp Lung Res 1983; 5: 229-43.

186 SYKES SE, MOORES SR, JONES ST. Dose-dependent effects in the subacute response of the rat lung to quartz. II. Protease activities and levels of soluble hydroxyproline in lung lavage. Exp Lung Res 1983; 5: 245-57.

187 SYKES SE, MORGAN A, MOORES SR, JONES ST, HOLMES A, DAVISON W. Evidence for a dose-dependent inflammatory response to quartz in the rat lung and its significance in early changes in collagen metabolism. Environ Health Perspect 1983; 51: 141-6.

188 ADAMSON IYR, BOWDEN DH. Role of polymorphonuclear leukocytes in silica-induced pulmonary fibrosis. Am J Pathol 1984; 117: 37-43.

189 FANTONE JC, WARD PA. Role of oxygen-derived free radicals and metabolites in leukocyte-dependent inflammatory reactions. Am J Pathol 1982; 107: 397-418.

190 GORMLEY IP, KOWOLIK MJ, CULLEN RT. The chemiluminescent response of human phagocyte cells to mineral dusts. Br J Exp Pathol 1985; 66: 409-16.

191 VILIM V, WILHELM J, BRZAK P, HURYCH J. The chemiluminescence of rabbit alveolar macrophages induced by quartz dust particles. Immunol Lett 1984; 8: 69-73.

192 HEPPLESTON AG, STYLES JA. Activity of a macrophage factor in collagen formation by silica. Letter. Nature 1967; 214: 521-2.

193 BURRELL R, ANDERSON M. The induction of fibrogenesis by silica-treated alveolar macrophages. Environ Res 1973; 6: 389-94.

194 AALTO M, POTILA M, KULONEN E. The effect of silica-treated macrophages on the synthesis of collagen and other proteins in vitro. Exp Cell Res 1976; 97: 193-202

195 AALTO M, VILJANEN M, KULONEN E. Neutralization of the fibrogenic silica-released macrophage factor by antiserum. Exp Pathol 1982; 22: 181-4.

196 KILROE-SMITH TA, WEBSTER I, VAN DRIMMELEN M, MARASAS L. An insoluble fibrogenic factor in macrophages from guinea pigs exposed to silica. Environ Res 1973; 6: 298-305.

197 HARINGTON JS, RITCHIE M, KING PC, MILLER K. The in vitro effects of silica-treated hamster macrophages on collagen production by hamster fibroblasts. J Pathol 1973; 109: 21-37.

198 BROWN GM, GORMLEY IP. An attempt to detect a macrophage fibrogenic factor in vitro. Ann Occup Hyg 1983; 27: 323-6.

199 LEIBOVICH SJ, ROSS R. A macrophage-dependent factor that stimulates the proliferation of fibroblasts in vitro. Am J Pathol 1976; 84: 501-13

200 CALDERON J, WILLIAMS RT, UNANUE ER. An inhibitor of cell proliferation released by cultures of macrophages. Proc Natl Acad Sci USA 1974; 71: 4273-7.

201 LUGANO EM, DAUBER JH, ELIAS JA, BASHEY RI, JIMENEZ SA, DANIELE RP. The regulation of lung fibroblast proliferation by alveolar macrophages in experimental silicosis. Am Rev Respir Dis 1984; 129: 767-71.

202 SCHMIDT JA, OLIVER CH, LEPE-ZUNIGA JL, GREEN I, GERY I. Silica-stimulated monocytes release fibroblast proliferation factors identical to interleukin 1. A potential role for interleukine 1 in the pathogenesis of silicosis. J Clin Invest 1984; 73: 1462-72.

203 VIGLIANI EC, BOSELLI A, PECCHIAI L. Studi sulla componente emoplasmopatica della silicosi. Med Lav 1950; 41: 33-48.

204 KALMAN E. [Experiments to prove autoimmunisation in silicosis.] Egeszsegtudomany 1957; 1: 43-59. (Abstract in Bull Hyg 1958; 33:134)

205 PERNIS B, CLERICI E, GHEZZI I. [Immunological study of serum proteins adsorbed on crystalline silica.] Med Lav 1959; 50: 405-11.

206 PERNIS B, CEPPELLINI R, GHEZZI I. [Immunological analysis of the silicotic nodule.] Med Lav 1957; 48: 380-6.

207 POWELL DEB, GOUGH J. The effect on experimental silicosis of hypersensitivity induced by horse serum. Br J Exp Pathol 1959; 40: 40-3.

208 ANTWEILER H, HIRSCH E. Animal experiment studies on the problem of the origin of antibodies in the development of silicosis. Arch Gewerbepath Gewerbehyg 1956; 14: 678-85.

209 ESBER HJ, BURRELL R. Further characterization of the specificity of lung-reactive antibodies in human serum. Arch Environ Health 1970; 21: 502-7.

210 MILLER SD, ZARKOWER A. Alterations of murine immunologic responses after silica dust inhalation. J Immunol 1974; 113: 1533-1543.

211 SCHMIDT JA, MIZEL SB, COHEN D, GREEN I. Interleukin 1, a potential regulator of fibroblast proliferation. J Immunol 1982; 128: 2177-82.

212 PERNIS BP, VIGLIANI EC. The role of macrophages and immunocytes in the pathogenesis of pulmonary diseases due to mineral dusts. Am J Ind Med 1982; 3: 133-7.

213 HANNANT D, DONALDSON K, BOLTON RE. Immunological consequences of mineral dust inhalation. In: Inhaled particles VI. Oxford: Pergamon Press (In press)

214 MILLER SD, ZARKOWER A. Silica-induced alterations of murine lymphocyte immunocompetence and suppression of B lymphocyte immunocompetence: a possible mechanism. Journal of the Reticuloendothelial Society 1976; 19: 47-61.

215 HANNANT D, DONALDSON K, BOLTON RE. Immunomodulatory effects of mineral dust. I. Effects of intraperitoneal dust inoculation on splenic lymphocyte function and humoral immune responses in vivo. J Clin Lab Immunol 1985; 16: 81-5.

216 MANCINO D, BEVILACQUA N. Persistent and boosterable IgE antibody production in mice injected with low doses of ovalbumin and silica. Int Arch Allergy Appl Immunol 1978; 57: 155-8.

217 MANCINO D, BUONO G, CUSANO M, MINUCCI M. Adjuvant effects of a crystalline silica on IgE and IgG1 antibody production in mice and their prevention by the macrophage stabilizer poly-2-vinylpyridine N-oxide. Int Arch Allergy Appl Immunol 1983; 71: 279-281.

218 BURNS CA, ZARKOWER A, FERGUSON FG. Murine immunological and histological changes in response to chronic silica exposure. Environ Res 1980; 21: 298-307.

219 SCOTT GA. Acute silicosis. Ulster Med J 1964; 33: 116-21.

220 BUECHNER HA, ANSARI A. Acute silico-proteinosis. A new pathologic variant of acute silicosis in sandblasters, characterised by histologic features resembling alveolar proteinosis. Dis Chest 1969; 55: 274-84.

221 SURATT PM, WINN WC, BRODY AR, BOLTON WK, GILES RD. Acute silicosis in tombstone sandblasters. Am Rev Respir Dis 1977; 115: 521-9.

222 XIPELL JM, HAM KN, PRICE CG, THOMAS DP. Acute silicoproteinosis. Thorax 1977; 32: 104-11.

223 ZIMMERMAN PV, SINCLAIR RA. Rapidly progressive fatal silicosis in a young man. Med J Aust 1977; 2: 704-6.

224 ROESLIN N, LASSABE-ROTH C, MORAND G, BATZENSCHLAGER A. [Acute silico-proteinosis.] Arch Mal Prof 1980; 41: 15-8.

225 BANKS DE, BAUER MA, CASTELLAN RM, LAPP NL. Silicosis in surface coalmine drillers. Thorax 1983; 38: 275-8.

226 MIDDLETON EL. The present position of silicosis in industry in Britain. Br Med J 1929; ii: 485-9.

227 MINISTRY OF LABOUR AND NATIONAL SERVICE. Annual report of the Chief Inspector of Factories, 1948. London: HM Stationery Office, 1949. (Cmd.7839)

228 JAIN SM, SEPAHA GC, KHARE KC, DUBEY VS. Silicosis in slate pencil workers - A clinicoradiologic study. Chest 1977; 71: 423-6.

229 SAIYED HN, PARIKH DJ, GHODASARA NB et al. Silicosis in slate pencil workers: I. An environmental and medical study. Am J Ind Med 1985; 8: 127-33.

230 SAIYED HN, CHATTERJEE BB. Rapid progression of silicosis in slate pencil workers: II. A follow-up study. Am J Ind Med 1985; 8: 135-42.

231 SAMIMI B, ZISKIND M, WEILL H. The relation of silica dust to accelerated silicosis. Ecotoxicol Environ Safety 1978; 1: 429-36.

232 NG TP, ALLAN WGL, TSIN TW, O'KELLY FJ. Silicosis in jade workers. Br J Ind Med 1985; 42: 761-4.

233 NELSON HM, RAJHANS GS, MORTON S, BROWN JR. Silica flour exposures in Ontario. Am Ind Hyg Ass J 1978; 39: 261-9.

234 COOPER WC, CRALLEY LJ. Pneumoconiosis in diatomite mining and processing. Washington (DC): US Department of Health, Education and Welfare, Public Health Service, 1958. (PHS Publication No. 601)

235 COOPER WC, JACOBSON G. A 21-year radiographic follow-up of workers in the diatomite industry. J Occup Med 1977; 19: 563-6.

236 COOPER WC, SARGENT EN. A 26-year radiographic follow-up of workers in a diatomite mine and mill. J Occup Med 1984; 26: 456-60.

237 FRANZINELLI A, SARTORELLI E, LO MARTIRE N, CARINI R. [A contribution to the study of fossil flour pneumoconiosis. Med Lav 1971; 62: 258-71.

238 VITUMS VC, EDWARDS MJ, NILES NR, BORMAN JO, LOWRY RD. Pulmonary fibrosis from amorphous silica dust, a product of silica vapour. Arch Environ Health 1977; 32: 62-8.

239 JOHNSON GT, LEWIS TR, GROTH DH. Evaluation of health hazard of amorphous silica-coated cristobalite following intratracheal injection in rats. Cincinnati (OH): US Department of Health, Education and Welfare: National Institute for Occupational Safety and Health, 1973. (SR-35)

240 BRAMBILLA C, BRAMBILLA E, RIGAUD D, PERDRIX A, PARAMELLE B, FOURCY A. [Pneumoconiosis due to amorphous silica fume - Mineralogical and ultrastructural study of 6 cases.] Rev Fr Mal Respir 1980; 8: 383-91.

241 WILSON RK, STEVENS PM, LOVEJOY HB, BELL ZG, RICHIE RC. Effects of chronic amorphous silica exposure on sequential pulmonary function. J Occup Med 1979; 21: 399-402.

242 VOLK H. The health of workers in a plant making highly dispersed silica. Arch Environ Health 1960; 1: 125-8.

243 PLUNKETT ER, DeWITT BJ. Occupational exposure to Hi-Sil and Silene. Report of an 18-year study. Arch Environ Health 1962; 5: 469-72.

244 PARKES WR. Occupational lung disorders. 2nd ed. London: Butterworths, 1982.

245 MORGAN WKC, SEATON A. Occupational lung diseases. 2nd ed. Philadelphia: Saunders, 1984.

246 SEATON A, DICK JA, DODGSON J, JACOBSEN M. Quartz and pneumoconiosis in coal miners. Lancet 1981; ii: 1272-5. (Correspondence: 1982; i: 46)

247 RUCKLEY VA, FERNIE JM, CHAPMAN JS et al. Comparison of radiographic appearances with associated pathology and lung dust content in a group of coalworkers. Br J Ind Med 1984; 41: 459-67.

248 DAVIS JMG, CHAPMAN J, COLLINGS P et al. Variations in the histological patterns of the lesions of coal workers' pneumoconiosis in Britain and their relationship to lung dust content. Am Rev Respir Dis 1983; 128: 118-24.

249 BEADLE DG. The relationship between the amount of dust breathed and the development of radiological signs of silicosis: an epidemiological study in South African gold miners. In: Walton WH. Inhaled particles III. Old Woking (Surrey): Unwin Bros, 1971: 953-66.

250 HUGHES JM, JONES RN, GILSON JC et al. Determinants of progression in sandblasters' silicosis. Ann Occup Hyg 1982; 26: 701-12.

251 SOLOMON A. Massive fibrosis in gold miners - a radiological evaluation. Environ Res 1977; 13: 47-55.

252 JONES RN, WEILL H, ZISKIND M. Pulmonary function in sandblasters' silicosis. Bull Physiopathol Respir 1975; 11: 589-95.

253 WILES FJ, FAURE MH. Chronic obstructive lung disease in gold miners. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 727-35.

254 IRWIG LM, ROCKS P. Lung function and respiratory symptoms in silicotic and nonsilicotic gold miners. Am Rev Respir Dis 1978; 117: 429-35.

255 OAKES D, DOUGLAS R, KNIGHT K, WUSTEMAN M, McDONALD JC. Respiratory effects of prolonged exposure to gypsum dust. Ann Occup Hyg 1982; 26: 833-40.

256 THERIAULT GP, BURGESS WA, DIBERARDINIS LJ, PETERS JM. Dust exposure in the Vermont granite sheds. Arch Environ Health 1974; 28: 12-7.

257 THERIAULT GP, PETERS JM, FINE LJ. Pulmonary function in granite shed workers of Vermont. Arch Environ Health 1974; 28: 18-22.

258 MUSK AW, PETERS JM, WEGMAN DH, FINE LJ. Pulmonary function in granite dust exposure: A four-year follow-up. Am Rev Respir Dis 1977; 115: 769-76.

259 GRAHAM WGB, O'GRADY RV, DUBUC B. Pulmonary function loss in Vermont granite workers. A long-term follow-up and critical reappraisal. Am Rev Respir Dis 1981; 123: 25-8.

260 THERIAULT GP, PETERS JM, JOHNSON WM. Pulmonary function and roentgenographic changes in granite dust exposure. Arch Environ Health 1974; 28: 23-7.

261 SEATON A, LOUW SJ, COWIE HA. Epidemiologic studies of Scottish oil shale workers: 1. Prevalence of skin disease and pneumoconiosis. Am J Ind Med 1986; 9: 409-21.

262 GLOVER JR, BEVAN C, COTES JE et al. Effects of exposure to slate dust in North Wales. Br J Ind Med 1980; 37: 152-62.

263 KOSKINEN H. Symptoms and clinical findings in patients with silicosis. Scand J Work Environ Health 1985; 11: 101-6.

264 BOHADANA AB, PESLIN R, PONCELET B, HANNHART B. Lung mechanical properties in silicosis and silicoanthracosis. Bull Eur Physiopathol Respir 1980; 16: 521-32.

265 TECULESCU DB, STANESCU DC. Carbon monoxide transfer factor for the lung in silicosis. Scand J Respir Dis 1970; 51: 150-9.

266 SNIDER DE. The relationship between tuberculosis and silicosis. Am Rev Respir Dis 1978; 118: 455-60.

267 SLUIS-CREMER GK. Active pulmonary tuberculosis discovered at post-mortem examination of the lungs of black miners. Br J Dis Chest 1980; 74: 374-8.

268 CHATGIDAKIS CB. Silicosis in South African white gold miners. A comparative study of the disease in its different stages. Med Proc 1963; 9: 383-92.

269 PAUL R. Silicosis in Northern Rhodesia copper miners. Arch Environ Health 1961; 2: 96-109.

270 JARMAN TF, JONES JG, PHILLIPS JH, SEINGRY HE. Radiological surveys of working quarrymen and quarrying communities in Caernarvonshire. Br J Ind Med 1957; 14: 95-104.

271 BAILEY WC, BROWN M, BUECHNER HA, WEILL H, ICHINOSE H, ZISKIND M. Silico-mycobacterial disease in sandblasters. Am Rev Respir Dis 1974; 110: 115-25.

272 ERASMUS LD. Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations. S Afr J Lab Clin Med 1957; 3: 209-31.

273 SLUIS-CREMER GK, HESSEL PA, NIZDO EH, CHURCHILL AR, ZEISS EA. Silica, silicosis, and progressive systemic sclerosis. Br J Ind Med 1985; 42: 838-43.

274 ZISKIND M, JONES RN, WEILL H. Silicosis. Am Rev Respir Dis 1976; 113: 643-65.

275 GAMBINI G, AGNOLETTO A, MAGISTRETTI M. Tre casi di sindrome di Caplan. Med Lav 1964; 55: 261-71.

276 DEVULDER B, PLOUVIER B, MARTIN JC, LENOIR L. [The combination scleroderma-silicosis (Erasmus' syndrome) - clinical and physiopathological aspects.] Nouv Presse Med 1977; 6: 2877-9.

277 FRENEAUX B, FRENEAUX J, BUYSE N, LE VAN QUYEN H. [Association between silicosis and scleroderma.] Nouv Presse Med 1975; 4: 2087-90.

278 SALDANHA LF, ROSEN VJ, GONICK HC. Silicon nephropathy. Am J Med 1975; 59: 95-103.

279 GILES RD, STURGILL BC, SURATT PM, BOLTON WK. Massive proteinuria and acute renal failure in a patient with acute silicoproteinosis. Am J Med 1978; 64: 336-42.

280 HAUGLUSTAINE D, VAN DAMME B, DAENENS P, MICHIELSEN P. Silicon nephropathy: a possible occupational hazard. Nephron 1980; 26: 219-24.

281 BOLTON WK, SURATT PM, STURGILL BC. Rapidly progressive silicon nephropathy. Am J Med 1981; 71: 823-8.

282 BANKS DE, MILUTINOVIC J, DESNICK RJ, GRABOWSKI GA, LAPP NL, BOEHLECKE BA. Silicon nephropathy mimicking Fabry's disease. Am J Nephrol 1983; 3: 279-84.

283 CAPEZZUTO A. La funzionalita' renale nei silicotici. Folia Med 1963; 46: 697-705.

284 KOLEV K, DOITSCHINOV D, TODOROV D. Morphologic alterations in the kidneys by silicosis. Med Lav 1970; 61: 205-10.

285 SAITA G, ZAVAGLIA O. [Renal function in silicosis.] Med Lav 1951; 42: 41-8.

286 RUSSELL AE, BRITTEN RH, THOMPSON RL, BLOOMFIELD JJ. The health of workers in dusty trades. II. Exposure to siliceous dust. Washington (DC): US Treasury Department, Public Health Service, 1929: 1-28. (Public Health Bull No.187)

287 RUSSELL AE. The health of workers in dusty trades. VII. Restudy of a group of granite workers. Washington (DC): US Federal Security Agency, Public Health Service, 1941. (Public Health Bull 269)

288 HOSEY AD, ASHE HB, TRASKO VM. Control of silicosis in Vermont granite industry. Progress report. Washington(DC): US Department of Health, Education and Welfare, Public Health Service, 1957. (Public Health Service Bull No. 557)

289 ASHE HB, BERGSTROM DE. Twenty six years' experience with dust control in the Vermont granite industry. Ind Med Surg 1964; 33: 73-8.

290 NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH/OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION. Occupational health guideline for crystalline silica (1978). In: Occupational health guidelines for chemical hazards. Cincinnati(OH): NIOSH, 1981. (DHHS(NIOSH) Publication No. 81-123)

291 UICC COMMITTEE. A cooperative study by the UICC Committee: UICC/Cincinnati classification of the radiographic appearances of pneumoconiosis. Chest 1970; 58: 57-67.

292 DAVIS LK, WEGMAN DH, MONSON RR, FROINES J. Mortality experience of Vermont granite workers. Am J Ind Med 1983; 4: 705-23

293 BAUCOM CD. History of silicosis and the North Carolina Dusty Trades File. In: Goldsmith DF, Winn DM, Shy CM, eds. Silica, silicosis and cancer. Controversy in occupational medicine. New York: Praeger, 1986: 57-65. (Cancer Research Monographs Vol.2)

294 RICE CH, HARRIS RL, CHECKOWAY H, SYMONS MJ. Dose-response relationships for silicosis from a case-control study of North Carolina dusty trades workers. In: Goldsmith DF, Winn DM, Shy CM, eds. Silica, silicosis and cancer. Controversy in occupational medicine. New York: Praeger, 1986: 77-90. (Cancer Research Monographs Vol.2)

295 RICE C, HARRIS RL, LUMSDEN JC, SYMONS MJ. Reconstruction of silica exposure in the North Carolina dusty trades. Am Ind Hyg Ass J 1984; 45: 689-96.

296 INTERNATIONAL LABOUR OFFICE. ILO U/C International classification of radiographs of pneumoconioses 1971. Geneva, ILO: 1972. (ILO Occupational Safety and Health Series No.22 (rev.))

297 MCDONALD JC, OAKES D. Exposure-response in miners exposed to silica. In: VI International Pneumoconiosis Conference 1983. Bochum: Bergbau-Berufsgenossenschaft, 1984: 114-23.

298 BEADLE DG, HARRIS E, SLUIS-CREMER GK. The relationship between the amount of dust breathed and the incidence of silicosis. In: Shapiro HA, ed. Pneumoconiosis: proceedings of the International Conference, Johannesburg 1969. Cape Town: Oxford University Press, 1970: 473-7.

299 SLUIS-CREMER GK. Silica exposure and silicosis in Witwatersrand gold miners in South Africa. In: Goldsmith DF, Winn DM, Shy CM, eds. Silica, silicosis and cancer. Controversy in occupational medicine. New York: Praeger, 1986: 67-70. (Cancer Research Monographs Vol.2)

300 FLINN RH, DREESSEN WC, EDWARDS TI, RILEY EC, BLOOMFIELD JJ, SAYERS RR. Silicosis and lead poisoning among pottery workers. Washington (DC): US Treasury Dept, Public Health Service, 1939. (Public Health Bull No. 244)

301 THOMAS TL. A preliminary investigation of mortality among workers in the pottery industry. Int J Epidemiol 1982; 11: 175-80.

302 FOX AJ, GREENBERG M, RITCHIE GL, BARRACLOUGH RNJ. A survey of respiratory disease in the pottery industry. London: HM Stationery Office, 1975.

303 LIDDELL FDK, LINDARS DC. An elaboration of the ILO classification of simple pneumoconiosis. Br J Ind Med 1969; 26: 89-100.

304 WALTON WH, DODGSON J, HADDEN GG, JACOBSEN M. The effect of quartz and other non-coal dusts in coalworkers' pneumoconiosis. Part I. Epidemiological studies. In: Walton WH, ed. Inhaled particles IV. Oxford: Pergamon Press, 1977: 669-90.

305 JACOBSEN M, MACLAREN WM. Unusual pulmonary observations and exposure to coalmine dust: a case-control study. In: Walton WH, ed. Inhaled particles V. Oxford: Pergamon Press, 1982: 753-65. (Annals of Occupational Hygiene 1982; 26)

306 SOUTAR CA, COLLINS HPR. Classification of progressive massive fibrosis of coalminers by type of radiographic appearance. Br J Ind Med 1984; 41: 334-9.

307 MCLAUGHLIN AIG. Industrial lung disease of iron and steel workers. London: HM Stationery Office, 1950.

308 MACBAIN G, COLE CWD, SHEPHERD RD. Pneumoconiosis in a group of large iron and light alloy foundries. Trans Soc Ind Med Off 1962; 12: 17-28.

309 GREGORY J. A survey of pneumoconiosis at a Sheffield steel foundry. Arch Ind Health 1970; 20: 385-99.

310 LLOYD DAVIES TA. Respiratory disease in foundrymen. Report of a survey. London HM Stationery Office, 1971.

311 HIGGINS RI, DEWELL P. Medical and environmental studies in an ironfoundry - with special reference to pneumoconiosis. Birmingham: BCIRA, 1977. (Report 1252)

312 TRASKO VM. Some facts on the prevalence of silicosis in the United States. AMA Arch Ind Health 1956; 14: 379-86.

313 OUDIZ J, BROWN JW, AYER HE, SAMUELS S. A report on silica exposure levels in United States foundries. American Indusrial Hygiene Association Journal 1983; 44: 374-6.

314 JOHNSON A, CHAN-YEUNG M, MACLEAN L et al. Respiratory abnormalities among workers in an iron and steel foundry. Br J Ind Med 1985; 42: 94-100.

315 KARAVA R, HERNBERG S, KOSKELA R, LUOMA K. Prevalence of pneumoconiosis and chronic bronchitis in foundry workers. Scand J Work Environ Health 1976; 2(suppl. 1): 64-72.

316 BONNEVIE A. Silicosis and individual susceptibility - fact or myth? Ann Occup Hyg 1977; 20: 101-8

317 CRAW J. Pneumoconiosis in the haematite iron ore mines of West Cumbria. A study of 45 years of control. J Soc Occup Med 1982; 32: 53-65.

318 STEWART MJ, FAULDS JS. The pulmonary fibrosis of haematite miners. J Path Bact 1934; 39: 233-53.

319 HEATH D, MOOI W, SMITH P. The pulmonary vasculature in haematite lung. Br J Dis Chest 1978; 2: 88-94.

320 SAMET JM, YOUNG RA, MORGAN MV, HUMBLE CG. Prevalence survey of respiratory abnormalities in New Mexico uranium miners. Health Phys 1984; 46: 361-70.

321 PARETTO LA. Study of silicosis in Peruvian mines and permissible dust concentrations. Am Ind Hyg Ass J 1971; 32: 463-7.

322 LLOYD DAVIES TA, DOIG AT, FOX AJ, GREENBERG M. A radiographic survey of monumental masonry workers in Aberdeen. Br J Ind Med 1973; 30: 227-31.

323 LIDDELL FDK. An experiment in film reading. Br J Ind Med 1963; 20: 300-12.

HEAD OFFICE:

Research Avenue North,
Riccarton,
Edinburgh, EH14 4AP,
United Kingdom
Telephone: +44 (0)870 850 5131
Facsimile: +44 (0)870 850 5132

Tapton Park Innovation Centre,
Brimington Road, Tapton,
Chesterfield, Derbyshire, S41 0TZ,
United Kingdom
Telephone: +44 (0)1246 557866
Facsimile: +44 (0)1246 551212

Research House Business Centre,
Fraser Road,
Perivale, Middlesex, UB6 7AQ,
United Kingdom
Telephone: +44 (0)208 537 3491/2
Facsimile: +44 (0)208 537 3493

Brookside Business Park,
Cold Meece,
Stone, Staffs, ST15 0RZ,
United Kingdom
Telephone: +44 (0)1785 764810
Facsimile: +44 (0)1785 764811

Email: iom@iom-world.org