The Quartz Hazard: A Variable Entity

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An IARC Working Group recently classified crystalline silica (quartz) into IARC's Group 1, i.e. a carcinogen. This classification is based on evidence of carcinogenicity in experimental animals and in humans. However, the evaluation stated that in making the overall evaluation, the Working Group noted that carcinogenicity to humans was not detected in all industrial circumstances studied and that carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity. The present review seeks to put the apparently conflicting findings of cancer incidence in quartz-exposed industries into a unifying thesis, based on mechanistic studies. These mechanistic studies have enabled the events leading from deposition of quartz to silicosis and cancer to be partially elucidated and have demonstrated that the biological effects of quartz can be understood in terms of surface reactivity. We particularly emphasise the ability of quartz to generate free radicals and cause oxidative stress and the fact that this could be modified by a range of substances that affect the quartz surface; some of these modifying substances could originate from other minerals. We therefore propose that the hazard posed by quartz is not a constant entity, but one that may vary dramatically depending on the origin of the silica sample or its contact with other chemicals/minerals within its complex constitution. The mechanistic data described here could assist in the interpretation of epidemiological studies and pose further hypotheses that could be tested in order to help resolve the quartz carcinogenesis anomaly. The data suggest that quartz cannot be dealt with as a single hazard entity, as is the case with most other chemicals.

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INTRODUCTION

In 1987 an IARC Working Group classified crystalline silica (quartz) into IARC's Group 2, i.e. a probable carcinogen, based on an evaluation that stated that there was sufficient evidence for carcinogenicity in experimental animals and limited evidence for carcinogenicity in humans (IARC Monograph, 1987). In 1997 a follow-up meeting was convened which re-evaluated quartz as a Group 1 carcinogen concluding that there was sufficient evidence for carcinogenicity in experimental animals and sufficient evidence for carcinogenicity in humans (IARC Monograph, 1997). This was mainly based on the epidemiological evidence published since 1987. The following section was inserted in the final evaluation:

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

There was not unanimous agreement for the classification amongst the working group (not an unusual situation in itself for an IARC working group) and disagreement was based largely on several issues, including (1) the strong association between silicosis and lung cancer, (2) the use of silicosis as an index of cumulative exposure and (3) the negative outcome of coal mine dust as a lung carcinogen, established at the same meeting. In previous reviews (Checkoway, 1995; McDonald, 1995) the first issue has been covered extensively and will not be addressed in this paper from the epidemiological point of view. The present review addresses the other two issues and thereby seeks to put the apparently conflicting findings of cancer incidence in quartz-exposed industries into a unifying thesis, based on mechanistic studies. These mechanistic studies demonstrate the following:

(1) The events leading from deposition of quartz to silicosis and cancer have been partially elucidated in experimental animal studies.
(2) The biological effects of quartz can be understood in terms of its surface reactivity and in particular its ability to generate free radicals and cause oxidative stress.

(3) The biological reactivity of quartz can be modified by a range of substances that affect the quartz surface, some of which originate from other minerals.

From these data we discuss in this paper the proposition that the hazard posed by quartz is not a constant entity, but one that may vary dramatically depending on the origin of the silica sample or its contact with other chemicals/minerals within its complex constitution. This review does not deal with amorphous silica.

**CRYSSTALLINE SILICA**

Silica exists in the earth's crust in 3 main crystalline forms: quartz, cristobalite and tridymite. Of these quartz is by far the most common and is in fact one of the most abundant minerals in the earth's crust. The vast majority of human exposures to crystalline silica are in fact exposures to quartz. These exposures arise in a large spectrum of industries (Table 1).

Crystalline silica has the general formula SiO$_2$ and comprises a stacked framework of tetrahedral units, i.e. single molecules of Si with four associated O atoms that impart the 3-dimensional structure to the quartz crystal. There are, however, low levels of contaminating elements such as iron and aluminium associated with the quartz structure (IARC Monograph, 1987; Fubini et al., 1995) and these may be important, as described below. Quartz may also exhibit small, specific crystal lattice and elemental differences. The variations in lattice parameters have been attributed to the presence of foreign ions, or lattice defects caused by temperature and pressure during crystallisation (Deer et al., 1971). The contaminating ions in the quartz lattice include Al, Fe, Ge, Li, Mg, Ca, Na and K (Bray, 1942; Keith and Tuttle, 1952). Quartz is also a constituent of many (mineral) dusts, such as coal mine dust or coal fly-ashes. In keeping with current views of the effects of insoluble mineral particles on the lung, it is the surface of the quartz that is of prime importance in determining biological effects, since this surface makes contact with biological molecules and cell surfaces. Previous theories regarding the toxicity of soluble material from quartz have been abandoned (King, 1947).

**MECHANISMS OF THE PATHOGENICITY OF QUARTZ**

The possible events leading to silicosis and lung cancer, based on animal and in vitro studies referred to below, are shown in Fig. 1. In brief, silica causes cell injury and also stimulates release of cytokines leading to inflammation. Both direct silica surface-derived oxidants and inflammatory leukocyte-derived active oxidant species (AOS) can contribute to oxidative stress which can cause mutations in epithelial cells and assist in expression of proinflammatory genes. Increased epithelial proliferation results from cell injury and local accumulation of growth factors released by inflammatory cells; epithelial proliferation leads to epithelial hyperplasia which is likely to contribute to development of cancer. Clearance of quartz is impaired in quartz-exposed lungs, causing the accumulation of particle dose, i.e. enhanced lung burden.

Inhalable respirable-sized silica deposits in the alveolar duct/terminal bronchiolar surfaces where the average size of the deposited silica particles was 1.4 μm (range 0.3-4.0 μm) (Brody et al., 1982). The particles then interact with macrophages and epithelial cells causing cell injury (e.g. Vallyathan et al., 1991) and stimulation of cytokine release (Driscoll et al., 1990), both of which lead to inflammation (Donaldson et al., 1988). This is accompanied by increased interstitial translocation of quartz and corresponding accumulation in the lymph nodes (Hemenway et al., 1990) with concomitant slowing down of clearance (Oberdorster et al., 1997) and accumulation of dose in the lung. Oxidative stress from radicals associated with the quartz itself (Fubini et al., 1995; Vallyathan et al., 1991) and from the inflammatory leukocytes recruited to the lungs (Castranova et al., 1996a, 1996b) contribute to oxidative stress observed in quartz-exposed lung (Janssen et al., 1992). Quartz also causes release of cytokines from macrophages and epithelial cells via oxidative stress-related pathways (Meyer et al., 1994; Howard et al., in press) and mesenchymal...
cell-stimulating cytokines will be a factor in leading to the increase in mesenchymal cells and products in the interstitium that are characteristic of silicosis (Brody, 1991). Results from in vivo/ex vivo studies indicate that AOS from the quartz-induced inflammatory cells are capable of causing mutations in the epithelial cells of the lung (Driscoll et al., 1995; Borm and Driscoll, 1996) and this very likely is a key event in leading to development of epithelial cancer. It is important to note that this pro-carcinogenic effect of particle-induced inflammatory cells is not unique to quartz but is found when the pulmonary defences are overwhelmed by very high exposure even with non-toxic dusts (overload) (Driscoll et al., 1996); nor can this mechanism necessarily be directly extrapolated to humans since quartz-exposed populations show much less severe pulmonary inflammation than has been shown in rat studies with quartz (IARC Monograph, 1997). Nevertheless, this caveats, considerable advance has been made in understanding the mechanisms whereby quartz has its pathological effects at the cellular and molecular level.

INTER-SPECIES DIFFERENCES IN THE RESPONSE TO QUARTZ

Experimentally, quartz is clearly demonstrated to be carcinogenic in rats (e.g. Muhle et al., 1989), whilst mice and hamsters show much less, or no malignant tumour response to quartz (reviewed in IARC Monograph, 1997). Saffiotti and Stinson (1988) have investigated the time course of the histopathological response to instilled quartz in the 3 species and described inflammation, fibrosis and hyperplastic epithelial responses in the terminal airways of the rat in much greater amounts than was seen in mice or hamsters. Humans respond to quartz inhalation with much less inflammation than rats, alveolar lining, fibrosis and nodular tumours (Borm et al., 1989a, 1989b) whilst the charged products of heterolytic cleavage of the SiO bonds that make up the basic crystalline structure of the quartz (Fubini et al., 1995). Homolytic cleavage results in Si and Si-O radicals whereas heterolytic cleavage produces charged Si+ and Si-O- radicals. In solution, for instance in lung lining fluid or tissue fluid, these products of homolytic cleavage can give rise to OH and H2O2 (Castranova et al., 1996a, 1996b) whilst the charged products of heterolytic cleavage are involved in interactions with membranes (Fubini et al., 1995). Common contaminants such as iron and aluminium (Guthrie and Heaney, 1995) may lower the toxicity of quartz but Fenton chemistry-derived hydroxyl radicals may also be generated (Castranova et al., 1996a, 1996b), adding to the oxidative stress. A corollary of the fact that it is only the surface layer, a molecule or so thick, that interacts with lung cells and fluids is that a change in the chemical makeup of this layer could alter the reactivity of the particle, but might impact minimally on the bulk chemistry of the quartz (Wallace et al., 1996). To overcome this problem, Wallace et al. (1996) have developed a multiple voltage SEM-EDX technique which provides information on the elemental composition of the surface molecular layers of respirable particles. In a preliminary study the authors demonstrated substantial differences in the silicon composition of the surface layers of some particles collected from the air of coal mines (Wallace et al., 1996). These studies emphasise the importance of the quartz surface in mediating its toxic effects on the lungs and also highlight how the surface can be modified chemically.

THE QUARTZ SURFACE AND OXIDATIVE STRESS

The biological effects of silica are likely to be related to the surface reactivity of the particles, since the surface makes contact with lung lining fluid, biological molecules and cells. There are several ways in which the quartz surface can generate reactive species following interactions of the quartz particles with pulmonary cells or lung fluids. Silanol groups (Si–OH) and ionised silanol groups (Si–O–) on the surface are considered to play a major role in interaction with membranes (Nolan et al., 1981). The regular Si/O tetrahedra are interrupted when the quartz is com-minged, producing both homolytic and heterolytic cleavage of the SiO bonds that make up the basic crystalline structure of the quartz (Fubini et al., 1995). Homolytic cleavage results in Si and Si-O radicals whereas heterolytic cleavage produces charged Si+ and Si-O- groups. In solution, for instance in lung lining fluid or in tissue fluid, these products of homolytic cleavage can give rise to OH and H2O2 (Castranova et al., 1996a, 1996b) whilst the charged products of heterolytic cleavage are involved in interactions with membranes (Fubini et al., 1995). Common contaminants such as iron and aluminium (Guthrie and Heaney, 1995) may lower the toxicity of quartz but Fenton chemistry-derived hydroxyl radicals may also be generated (Castranova et al., 1996a, 1996b), adding to the oxidative stress. A corollary of the fact that it is only the surface layer, a molecule or so thick, that interacts with lung cells and fluids is that a change in the chemical makeup of this layer could alter the reactivity of the particle, but might impact minimally on the bulk chemistry of the quartz (Wallace et al., 1996). To overcome this problem, Wallace et al. (1996) have developed a multiple voltage SEM-EDX technique which provides information on the elemental composition of the surface molecular layers of respirable particles. In a preliminary study the authors demonstrated substantial differences in the silicon composition of the surface layers of some particles collected from the air of coal mines (Wallace et al., 1996). These studies emphasise the importance of the quartz surface in mediating its toxic effects on the lungs and also highlight how the surface can be modified chemically.

USE OF SHORT-TERM ASSAYS TO UNDERSTAND THE ROLE OF SURFACE FACTORS IN CARCINOGENESIS OF QUARTZ

A hypothetical sequence of events that leads to production of cancer by quartz can be advanced and is shown in Fig. 1. It is therefore possible, by utilising suitably chosen endpoints, to explore the role of the quartz surface in the events leading to carcinogenesis without carrying experiments through to lifetime carcinogenesis studies, which are prohibitively expensive. Therefore the endpoints described below, membrane, cell damage, inflammation in the lung, col-
lagen accumulation, etc. are all generally relevant to the development of carcinogenesis by quartz.

A number of experimental toxicological studies have demonstrated that the quartz hazard for lung fibrosis can be altered. Since pathways to fibrosis and cancer are considered to be similar (Fig. 1), these studies are worthwhile in hazard and risk evaluation of quartz-containing dusts. Ross et al. (1962) exposed rats to inhaled dust compositions comprised of quartz to 5 or 10% in a very low quartz coal dust. The composed mixtures of quartz and coal dust were ground and mixed in electrically-driven mortars overnight. Rats were exposed to 60 mg/m$^3$ of total dust comprising an airborne mass concentration of 3 or 6 mg/m$^3$ of quartz, for 10–17 months at 16 h per day. Silica accumulated to high levels in the lungs of the rats inhaling these dust mixes (up to 15 mg per rat at the end of dusting) but despite this high lung dose of quartz, there was little fibrosis, indicating that silica in a coalmine dust mixture behaves differently from quartz alone.

A complementary experiment was carried out by Le Bouffant et al. (1982) who used naturally occurring coal dust mixtures containing approximately 5 and 15% quartz. The authors also composed mixtures of quartz and low-quartz coal to give the same percentages of quartz. Rats were exposed to 100 mg/m$^3$ for 5 h per day, 5 days a week for 12 months.

As shown in Table 2 there was a striking difference in the response to the natural or the composed dusts, with significantly more toxicity, as gauged by lung collagen analysis as an indicator of fibrosis, measured in rats exposed to the artificially composed dusts. It may be of importance to note that the dust mixtures in the LeBouffant study, were prepared by mixing, with no mention of grinding. These two studies suggest that quartz in coalmine dust has little activity up to about 10% if the quartz occurring naturally in association with the coal or if quartz is systematically ground as an admixture with coal dust. If, however, it is simply mixed with the coal dust then the toxic effect of the quartz can still be expressed.

In attempting to further dissect the role of coal-derived material in inhibiting quartz toxicity, Martin et al. (1972) placed quartz and coalmine dust in a dual chamber separated from each other by a filter that only allowed dissolved products to pass between the two dust samples; a control quartz sample was placed in an identical chamber separated by a filter from water. After 4 weeks the quartzes were retrieved and the quartz exposed to the soluble materials from coal was found to have much less ability to damage the rat lung than the control quartz following instillation of dust as shown in Table 3.

Several studies have shown that aluminium salts, ubiquitously present in some minerals that are found together with quartz, can lower the toxicity of quartz (Brown and Donaldson, 1996). In the study of Daniel et al. (1977), inhaled aluminium hydroxide or aluminium chlorhydrolallantoato for 30 min per day during a 12 month exposure to 300 mg/m$^3$ of quartz, attenuated the fibrogenic response compared to rats which did not receive the aluminium treatment. Accumulation of quartz was the similar in the aluminium-treated and control groups. In a sheep instillation model of silicosis (Begin et al., 1987) animals were exposed to quartz, aluminium lactate or quartz plus aluminium lactate at monthly intervals from month 4 to month 10. The lungs of sheep instilled with quartz showed severe inflammation and animals exposed to quartz concomitant with aluminium lactate demonstrated lower pathology scores and reduced cellular activity in bronchoalveolar lavage (BAL) fluid. In the study of Brown et al. (1990) aluminium lactate-coated quartz was substantially less inflammogenic to the rat lung than native quartz, as assessed by inflammatory cell recruitment and mediator release by the BAL cells.

Iron can also reduce the toxicity of quartz. This has been demonstrated as the ability of iron salts to protect against quartz-mediated damage to erythrocyte membranes (Nolan et al., 1981). In a recent study (Cullen et al., 1997) metallic iron was found to diminish the ability of quartz to cause inflammation

### Table 2. Summary of the study by Le Bouffant et al. (1982)

<table>
<thead>
<tr>
<th>Dust</th>
<th>% Quartz</th>
<th>Total dust in lung (mg)</th>
<th>Total quartz in lung (mg)</th>
<th>Approximate* lung collagen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturally-occurring coal dust</td>
<td>5.4</td>
<td>60.2</td>
<td>2.8</td>
<td>30</td>
</tr>
<tr>
<td>Composed coal dust</td>
<td>4.2</td>
<td>42.2</td>
<td>3.5</td>
<td>100</td>
</tr>
<tr>
<td>Naturally-occurring coal dust</td>
<td>13</td>
<td>61.6</td>
<td>8.0</td>
<td>50</td>
</tr>
<tr>
<td>Composed coal dust</td>
<td>16</td>
<td>38.1</td>
<td>8.9</td>
<td>150</td>
</tr>
</tbody>
</table>

*Data taken from a graph, levels at 24 months

### Table 3. Summary of the study by Martin et al. (1972)

<table>
<thead>
<tr>
<th>Dust</th>
<th>Lung weight (g/100 g rat weight)</th>
<th>Lung collagen (mg) at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control quartz</td>
<td>1.75</td>
<td>91.0</td>
</tr>
<tr>
<td>Quartz treated with water</td>
<td>1.83</td>
<td>91.5</td>
</tr>
<tr>
<td>Quartz treated with coal-derived material</td>
<td>0.76</td>
<td>5.6</td>
</tr>
</tbody>
</table>
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Table 4. Summary of the study by Cullen et al. (1997)

<table>
<thead>
<tr>
<th>Instillate</th>
<th>Mean numbers of neutrophils in lavage (×10⁶) 7 days after instillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9 mg quartz</td>
<td>30.19</td>
</tr>
<tr>
<td>50 mg iron carbonyl</td>
<td>1.77</td>
</tr>
<tr>
<td>3.9 mg Quartz + 46.1 mg iron carbonyl</td>
<td>2.89</td>
</tr>
</tbody>
</table>

in the lungs of rats, following instillation: all data as mean number of neutrophils in BAL at 7 days after instillation (Table 4).

However, the state of the iron is likely to be a most important factor in determining the activity of the surface. Whilst metallic iron can have the above inhibitory effects, ferrous or ferric iron contamination could lead to Fenton chemistry-mediated generation of hydroxyl radicals as has been suggested for some quartz samples (Castranova, 1996). The same authors reported that inhalation of a mixture of iron and freshly fractured quartz was more inflammmogen than quartz alone (Castranova et al., 1997). In this case inhalation of a mixture of iron and freshly fractured quartz was shown to be more pathogenic than the inhalation of freshly fractured quartz alone. The quantity of contaminating iron may also be important and trace amounts of iron may assist AOS generation, whilst a large excess may detoxify the quartz surface; more research is required to understand this phenomenon.

Various external agents, i.e. not in the dust, such as lipid and proteinaceous surfactant materials, the polymer polyvinyl-pyridine-n-oxide (PVPNO) and organosilane, have been shown to coat the surface of quartz and decrease its toxicity. Antonini and Reasor (1994) used Min-U-Sil quartz which was boiled in HCl prior to use and used it either in this form or coated with artificial lung surfactant (Survanta). Both the ability of the quartz to kill macrophages and ability to cause lung inflammation after instillation was dramatically attenuated by treatment of the quartz with surfactant. Wallace et al. (1985) used the lipid dipalmitoyl lecithin to treat Min-U-Sil quartz and then used both materials in in vitro assays of cellular toxicity. Both membranolytic activity against erythrocytes and toxicity to alveolar macrophages was dramatically attenuated by treatment of the quartz with this lipid material. In a similar study Vallyathan et al. (1991) demonstrated that freshly fractured quartz surface was more cell stimulatory and injurious than aged quartz and that this activity could be simply ameliorated with an organosilane coating on the quartz. The polymer PVPNO is a strong hydrogen bonding agent which binds to silanol groups at the quartz surface (Castranova et al., 1996a, 1996b). Nolan et al. (1981) demonstrated that treatment of quartz with PVPNO was a powerful attenuator of the haemolytic activity of quartz.

The idea that there is "uncontaminated" quartz surface that has biological activity and that this activity is reduced following coating with less toxic or inert substances has been investigated by Kreigseis et al. (1987). In their studies the removal of "impurities" from the quartz surface with phosphoric acid or HCl was accompanied by increases in cytotoxicity. Thus a range of different studies have emphasised the importance of the quartz surface in pathogenicity and demonstrated that modification of the surface can lead to dramatic change in the pathogenic potential of quartz.

EFFECTS OF QUARTZ IN HUMAN POPULATIONS:
IMPLICATIONS FOR RISK ASSESSMENT

The IARC monograph on quartz (IARC Monograph, 1997) summarises several notable studies where, in the absence of confounding factors, no increase in lung cancer was found in industries where there was substantial quartz exposure:

Noteworthy instances where a relationship between lung cancer and crystalline silica was not detected include two independent studies of gold miners in South Dakota, United States, a study of miners in one lead and one zinc mine in Sardinia, Italy, and a study of tungsten miners in China.

However, we will restrict detailed discussion of epidemiological data relating to the hypothesis that the quartz risk is subject to considerable variation, to the coalmining experience. It is well known that the incidence of simple coal workers' pneumoconiosis (sCWP) and progressive massive fibrosis (PMF) varies between countries, regions and even within seams of mine-pits (Reisner, 1971; Heppleston, 1988; Gautrin et al., 1994). German epidemiological studies (Reisner, 1971) showed that the risk of contracting sCWP between coal fields varied between 2 and 40%, although miners had comparable levels of exposure. Neither mineral content nor percentage of quartz could account for these differences and in fact a low prevalence of sCWP sometimes occurred in collieries with higher gravimetric concentrations of quartz. Similar findings were made in France: approximately 40% of retired miners in Nord-Pas de Calais region and 10% of retired Lorraine miners were compensated for CWP, whereas no miners were compensated in the Provence region (Gautrin et al., 1994). Although American observations do show differences in coalworkers pneumoconiosis (CWP) and PMF between bituminous and anthracite coal mining, only coal rank played a significant role, with the higher ranked coals being more fibrogenic (Attfield and Morring, 1992). The fact that the slope of the dose–response curve between cumulative exposure (dose) and incidence of CWP (response) is so different, despite similar quartz content also has implications for the recent IARC hazard assessment as well as risk assessment; this will be discussed in the paragraph below. In an attempt
to explain these differences many studies have been conducted comparing quartz content, biological activity of the dust and incidence of CWP or PMF. In a large European-wide study (Davis et al., 1982; Robock and Reisner, 1982) no consistent relation was observed between any test of biological activity (toxicity to alveolar macrophages, haemolysis, etc.) and quartz content or epidemiological outcomes. In the latter study 120 dust samples from 43 coal faces of the Ruhr and Saar district were assessed and the biological effects in cell and animal experiments compared with studies of the mineral, chemical and physical properties of each of these samples.

Studies among coal miners also generate an interesting paradox. CWP and PMF are highly correlated to estimates of cumulative dust exposure and dust components mainly in the lung (Rivers et al., 1960; Rossiter, 1972; Ruckley et al., 1984). Several classic postmortem studies have been done in which the whole lung is digested or ashed and the total or specific dust in the lung is measured (Rivers et al., 1960; Carberg et al., 1971). These studies show that in coal workers, 40–60 g of total dust may be found in the lungs, with an accumulation rate of 0.4–1.7 g of dust retained each year. The retained free silica load is usually a reflection of its content of respirable dust but is “concentrated” in lymph nodes compared to the lung tissue. Carberg et al. (1971) studied the lymph node/lung concentration ratios in post-mortem samples of 65 West Virginia bituminous coal miners. They observed that this ratio for total dust and coal were 0.88 and 0.92, whereas for free silica this ratio was 3.6 (P < 0.001). Similar findings were presented from an examination of 180 specimens of British coal miners (Chapman and Ruckley, 1985), showing a mean quartz content of 20.3% in lymph node dust as compared to 6.1% in lung dust. If quartz has a carcinogenic potency and is “concentrated” in lymph nodes up to 20% at a total load of 6 grams, one would expect lymphatic carcinomas in the lungs of coal miners. However, no excess mortality to lung or any specific cancer in coal miners is shown despite numerous reports (IARC Monograph, 1997). Actually, only increased mortality due to chronic non-specific respiratory diseases and occasionally gastric cancer are significant among coal miners (Swaen et al., 1996). Quartz in coalmine dust appears to have lost its ability to cause lung cancer.

INTERPRETATION AND USE OF TOXICOLOGICAL DATA ON THE QUARTZ HAZARD

There are three points that are important in considering the quartz hazard in relation to risk assessment. The first point is that, as demonstrated extensively in the above studies, quartz can be relatively easily modified in its ability to cause biological effects relevant to carcinogenesis of quartz. Apparently, quartz in coal mine dust or coal fly-ash (Borm, 1997) is not as biologically active compared to equivalent doses of pure samples of quartz in vivo or in vitro. Also coating, grinding and addition of metals significantly alters its biological activity.

The second point is that none of the studies described above to investigate the quartz hazard and its modulation utilised quartz that is representative of the kinds of quartz used in the majority of the industries where there is occupational exposure to quartz. In fact up to 80% of the studies on the quartz hazard which are included here and in the relevant section of IARC Monograph (1997) on crystalline silica, utilised Min-U-Sil or DQ12 quartz samples. The remainder used other finely ground pure quartz from a variety of sources. It is well known that a vast amount of the exposures to quartz are exposures to quartz in mixed dusts where, as we have seen in the above studies, it is relatively likely that modification of the surface could occur when substances such as iron or aluminium are present.

As is appropriate, much emphasis is placed on epidemiological studies, which confirm suspected associations between exposure and response in relevant populations. However, accurate exposure data are seldom available and confounders such as smoking are present. For this reason the incidence of fibrosis or CWP, scored by chest X-ray analysis, is often used as a surrogate for cumulative dose.

This brings us to the third point that should be considered in future risk assessment. Apart from inadequate or uncontrolled reading of most X-rays, there are clear differences in the slope of the dose–response curve, when incidence of CWP is plotted against years of exposure for groups of miners in different regions (Reisner, 1971), despite minor differences in quartz content. This means that at the same endpoint (a specific incidence of CWP) different cumulative doses of quartz are inhaled. Therefore the use of fibrosis as a dose estimate should be avoided, since it is not a reliable exposure index. Furthermore, we have suggested that the pathways to fibrosis and cancer are partly the same (Fig. 1), which probably explains the higher incidence of lung cancer among those with lung fibrosis (McDonald, 1995). There is uncertainty as to whether the hypothetical mechanism described in Fig. 1 for cancer caused by quartz in rats is relevant to humans and more research is required to elucidate this question. However, in both rats and humans, fibrosis appears to be a prerequisite for the development of quartz-associated cancer.

In conclusion, considering the above arguments and the difficulties encountered in epidemiological studies, we suggest that data from mechanistic studies may provide an explanation that could assist in the interpretation of epidemiological studies. We submit that this is indeed the case with quartz, where the mechanistic data described here provide an opportunity to assist in the interpretation of the epidemiological studies and pose further hypotheses that could be tested in order to help resolve the quartz carcinogenesis anomaly. These data suggest that
quartz cannot be dealt with as a single hazard entity, as is the case with most other chemicals.

REFERENCES


