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Recommendation from the Scientific Committee on
Occupational Exposure Limits
for Silica, Crystalline (respirable dust)

Substance:

Chemical name	silicon dioxide, crystalline		
SiO_2 modifications			
Synonyms	quartz, α-quartz, low quartz		
CAS number	14808-60-7		
Synonyms	cristobalite, α-cristobalite, low cristobalite		
CAS number	14464-46-1		
Synonyms	tridymite, α-tridymite, low tridymite		
CAS number	15468-32-3		
Molecular formula	SiO_2		
Molecular weight	60.09		
	Quartz	Cristobalite	Tridymite
Temperature at which the α-modification is transformed into the high-temperature β-modification	573°C	270°C	130°C
Melting point	1610°C	1713°C	--
Density at 20°C (g/m^3)	2.65 g/cm^3	2.33 g/cm^3	2.27 g/cm^3
Crystal form	trigonal	tetragonal	monoclinic

Occurrence/use

Silica (silicon dioxide (SiO_2)), occurs in either a crystalline or non-crystalline (amorphous) form. Crystalline silica may be found in more than one form (polymorphism), depending on the orientation and position of the tetrahedra (i.e., the three-dimensional basic unit of all forms of crystalline silica). The natural crystalline forms of silica are α-quartz, α-,β_1-, and β_2-tridymite, α- and β-cristobalite, coesite, stishovite, and moganite (IARC, 1997). The most common form of naturally occurring

crystalline silica are quartz (CAS No. 14808-60-7), Cristobalite (CAS No. 14464-46-1) and tridymite (CAS No. 15468-32-3), but they can also be created during industrial processes, such as the calcination of diatomaceous earth, ceramics manufacturing, foundry processes, silicon carbide manufacturing, and any other process in which quartz is heated to high temperature.

Quartz is a colourless, odourless, non-combustible solid and a component of many mineral dusts. It is insoluble in water. When quartz is cut, ground, or milled, the crystal is fractured, and Si and Si-O radicals may be generated on the cleavage surfaces. Trace metal impurities, such as iron and aluminium, can modify the surface reactivity of quartz.

Quartz is abundant in most rocks, sands, and soils. The extensive natural occurrence of quartz and the wide uses of the materials than contain quartz are directly related to potential occupational exposures to quartz for workers in many industries and occupations. Virtually any process that involves movement of earth (e.g., quarrying and tunnelling), disturbance of silica-containing products such as masonry or use of sand and other silica-containing products (e.g., foundry processes) may potentially expose a workers to quartz.

Health significance

Introduction

In humans the main effect of the exposure to respirable silica dust is silicosis. Silicosis has been detected by X-ray, lung-function testing and computed tomography. Other non-neoplastic pulmonary effects in humans are inflammation, lymph node fibrosis, chronic air flow limitation, emphysema and "extrapulmonary silicosis".

Epidemiological studies reveal an association between exposure to crystalline silica dust and an increased probability of developing lung cancer. Administration of crystalline silica to rats by inhalation or intratracheal instillation also led to the development of lung tumours. Therefore crystalline silica is classified by IARC as a Group 1 carcinogen to humans.

The epidemiological studies show that the incidence of lung cancer is increased especially in workers with silicosis. The first step in reducing the cancer risk, therefore, must be the prevention of silicosis.

Mechanism of crystalline silica toxicity

The mechanism for the development of silicosis and lung tumours in man and animals exposed to crystalline silica is still unclear.

The mechanism of the toxic action of crystalline silica and other SiO_2 modifications involves a direct interaction of the surface of the crystalline silica particles with cell membranes or cell fluids. Treatment of crystalline silica by heating, corrosion with chemicals or milling can alter the surface properties of the crystalline silica particles and therefore alter their toxicity (Fubini 1998, Fubini *et al.* 1995). The binding to trivalent ions such as Al^{3+} or Fe^{3+} can reduce the effects of crystalline silica on cell membranes (Nolan *et al.* 1981). The study of the physicochemical properties of the various SiO_2 modifications is a very complex area of research (reviewed by Fubini 1998, Fubini *et al.*

1989, 1995). The functional groups which have been suggested to be involved in interactions of the surface of crystalline silica particles confer a hydrophilic or hydrophobic character, or result in charged groups or the formation of reactive radicals on the particle surfaces and affect the facility with which hydrogen bonds are formed (Fubini 1998). This indicates that crystalline silica particles of different sources, age and preparation modes differ in their inflammatory potencies. Further research will help to better differentiate between the different crystalline silica species and the biological potencies.

Crystalline silica can accumulate in the lungs. With increasing levels of deposited crystalline silica the alveolar macrophages and epithelial cells become activated. This results in increased release of cytokines, bioactive lipids, growth factors, proteases and reactive oxygen and nitrogen oxide species. The sequel can be a chronic inflammatory reaction. Oxidative stress can induce mutations in epithelial cells. Activation of nuclear transcription factors, increased expression of proinflammatory genes and oncogenes and the induction of nuclear transcription factors and mutations in tumour suppresser genes can be caused by reactive oxygen species (Donaldson and Borm 1998, Fubini 1998, Hojo *et al.* 1998, Knaapen *et al.* 1999, Shi *et al.* 1998).

In vitro, crystalline silica induces DNA damage in cell-free systems and micronuclei and cell transformation in mammalian cells. It is, however, doubtful whether the DNA damage demonstrated with very high crystalline silica concentrations in unphysiological milieu *in vitro* also occurs *in vivo*. In an *in vivo* micronucleus test in the mouse, crystalline silica had no effects.

Toxicokinetics

Crystalline silica dust is practically insoluble in body fluids and can be deposited in the lungs. In addition, the macrophage-mediated mechanical clearance of crystalline silica particles can be disturbed because crystalline silica dust is cytotoxic for macrophages. Therefore, in the presence of high levels of crystalline silica dust, the transport of particles out of the lungs by this means is minimal. Cigarette smoking can reduce the clearance of crystalline silica . Autopsy reports for persons who had been exposed to crystalline silica revealed wide range of levels of crystalline silica retention in the lungs. For example, lung loads of 264 mg per lung were found in employees exposed during work with rock for per 14 to 36 years (Greim 1999). Crystalline silica dust has been detected in bronchoalveolar macrophages and in the saliva of persons suffering from silicosis.

Genotoxicity

Crystalline silica dust induced cell transforming activity *in vitro* in mammalian cells. High concentrations of crystalline silica induced DNA damage in cell-free systems and also micronuclei in mammalian cells *in vitro*. In contrast, after intraperitoneal injection into mice, no micronuclei were detected *in vivo*. The hprt mutations detected *in vitro* in the alveolar epithelial cells of rats exposed to crystalline silica dust are probably the result of indirect genotoxic effects. This could be explained by the production of reactive oxygen and nitrogen species which can be formed on reactive SiO_2 surfaces or by activation of alveolar macrophages (IARC 1997).

In the alkaline single cell gel/comet assay, crystalline silica (Min-U-Sil 5) induced DNA damage i.e., DNA migration) in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblasts (Hel 299 cells) at concentrations ranging from 17.2 to 103.4 μg/cm^2 (Zhong et al., 1997, Liu et al. 1996, 1998). Experimental conditions (i.e., Chinese hamster lung fibroblasts challenge with dusts pre-treated with a phospholipid surfactant) were applied recentes to simulate the condition of particles immediately after deposition on the pulmonary alveolar surface. Results of the experiments showed that untreated Min-U-Sil 5 and Min-U-Sil 10 induced micronucleus formation in a dose-dependent manner, but surfactant pre-treatment suppressed that activity (Liu et al., 1996). A subsequent experiment found that surfactant pre-treatment suppressed crystalline silica-induced DNA damage in lavaged rat pulmonary macrophages, but DNA-damaging activity was restored with time as the phospholipid surfactant was removed by intercellular digestion (Liu et al., 1998).

Recent *in vivo* studies found that crystalline silica induced micronuclei in pulmonary alveolar macrophages of male Wistar rats in a time-dependent (Leigh et al. 1998) and dose-dependent manner (Wang et al., 1997).

Fibrosis and tumour induction

It is not clear whether fibrosis is a precondition for the development of tumours. Fibrosis develops in different target cells (fibroblasts) than do the lung tumours (epithelial cells). It seems likely that the chronic inflammatory processes play an important role in the development of both fibrosis and lung tumours. A hypothetical mechanism for the development of tumours in a rat is shown in the documentation of the MAK-Commission (see Figure 2 in Greim, 2000; Donaldson and Borm 1998, Driscoll *et al.* 1998, IARC 1997, Shi *et al.* 1998, Vallyathan *et al.* 1998). It is not clear whether the same mechanism could also be responsible for the development of lung tumours in man because the inflammatory processes seen in persons exposed to crystalline silica are less severe.

There are numerous studies of persons with silicosis for whom this has been recognized as an occupational disease. In the IARC document (IARC 1997) most emphasis is placed on two studies (Amandus *et al.* 1991, Partanen *et al.* 1994) in each of which the causes of death in a cohort of persons with silicosis was studied.

One cohort was made up of 655 dusty trade workers in whom silicosis was diagnosed after 1940 in North Carolina (Amandus *et al.* 1991). The SMR for lung carcinoma for these persons with silicosis compared with the population of the USA was 2.56. In this publication it is stated that 18 of the 33 persons who died with lung carcinoma were smokers (SMR 3.4) and 5 were non-smokers (SMR 1.7). For the remaining 10 persons who died (SMR 2.2) there were no data for smoking habits. The authors suggested that their results be interpreted with caution because the calculation of the SMR values was based on official statistics which did not differentiate between smokers and non-smokers. In this study it is conspicuous that the proportion of non-smokers among the cases of lung carcinoma is relatively high (at least 5 of 33, i.e. 15 %). In this study the SMR did not increase with the time after the diagnosis of silicosis.

Among 811 Finnish workers for whom silicosis had been diagnosed, the incidence of lung carcinoma was increased (SIR 2.89) (Partanen *et al.* 1994). The smoking habits were known for 41 of the 101 cases of lung carcinoma. One patient said he had never smoked, 25 were active smokers (SIR 6.67) and 15 were ex-smokers (SIR 1.89). In this

study, unlike in that of Amandus *et al.* (1991), the SMR increased with the time after the diagnosis of silicosis. During the first two years, the disease was diagnosed in one patient. In the years 2–9, 32 cases were observed (SIR 2.73) and after 10 years another 68 cases had been diagnosed (SIR 3.27).

In a meta-analysis of the question of a relationship between silicosis and lung carcinoma, a total of 23 studies were analysed (Smith *et al.* 1995). The two studies described above from the USA and Finland were among these 23. In the studies a total of 882 cases of lung carcinoma were included. The relative overall risk was given as 2.2; the relative risk for the cohort studies was 2.0 and for the case-control studies 2.5.

Seen as a whole, the data indicate that the relative lung cancer risk is increased for persons with silicosis. At present there are no studies available which provide an explanation of the mechanism by which lung tumours develop and the possible role of silicosis.

Dose-response relationship for the carcinogenic activity of crystalline silica dust

It was shown that lung cancer risk tended to increase with:

- cumulative exposure to respirable silica (i.e., Checkoway et al., 1993, 1996)
- duration of exposure (i.e., Costello & Graham, 1988; Merlo et al., 1991, Partenen et al., 1994; Costello et al., 1995; Dong et al., 1995)
- peak intensity of exposure (Burgess et al., 1997; Cherry et al., 1997; McDonald et al., 1997)
- the presence of radiographically defined silicosis (Amandus et al., 1992; Dong et al., 1995)
- length of follow-up time from date of silicosis diagnosis (Partanen et al., 1994)

The existence of dose-response relationship was studied in three investigations. While the study of gold miners in the USA (Steenland and Brown 1995) and the study of English ceramics workers (Winter et al., 1990) did not reveal any dose-response for lung cancer mortality and different classes of exposure, Checkoway et al., (1997, 1999) revealed a statistically significant dose-response relationship with relative lung cancer risks of 1.0, 0.96, 0.77, 1.26 and 2.15 for cumulative exposure of < 0.5, 0.5-1.1, 1.1-2.1, 2.1-5.0, ≥ 5.0 mg/m^3 x years for the diatomaceous earth industry workers.

Further analysis of the dose-response relationship yielded an increased relative risk for lung cancer per 1000 particle years or per 0.06 mg respirable crystalline silica dust m^3 x year of 1.023 (95% CI: 1.005-1.042) for South African gold miners (Hnizdo and Sluis-Cremer, 1993).

In a case-control study was shown that the lung cancer risk was increased with increasing exposure (Meijers et al., 1990).

In another case-control study the OR for lung cancer increased with exposure to crystalline silica (McLanghlin et al., 1992).

No relationship between the exposure level and the risk of developing lung cancer could be demonstrated in a case-control study of employers without silicosis who worked in quarries and in the ceramics industry (Ulm et al., 1999).

In summary there is evidence that the incidence of lung cancer increases with increasing cumulative exposure to respirable crystalline silica dust and that the relative lung cancer risk is increased for persons with silicosis.. It is not clear from which exposure value the relative lung cancer risk is increased. The studies differ with respect to exposure levels and durations, with respect to the type of crystalline silica and also the occupational cofounders such as simultaneous exposure to radon.

Recently, Steenland et al. (2001) performed dose-response analyses and risk assessment for lung cancer in a pooled cohort of 65 980 silica-exposed workers (44 610 miners and 21 820 non miners) with 1 972 lung cancer deaths observed (663 in miners and 409 in non miners). Categorical analyses by quintile of cumulative exposure showed for miners and not miners the odds ratios and 95% confidence intervals reported in the table.

Quintiles of cumulative exposure (mg/m^3)	**Odds ratio, (95%CI)** Miners	**Odds ratio, (95%CI)** Non-miners	**Odds ratio, (95%CI)** Total
<0.07	1.0	1.0	1.0
0.07-0.21	0.90 (0.66-1.2)	1.2 (0.92-1.6)	1.0 (0.85-1.3)
0.21-0.41	0.81 (0.59-1.1)	2.1 (1.6-2.8)	1.3 (1.1-1.7)
0.41-1.36	1.2 (0.86-1.6)	1.7 (1.2-2,4)	1.5 (1.2-1.9)
>1.36 (median 3.75)	1.4 (1.0-1.9)	1.5 (0.97-2.4)	1.6 (1.3-2.1)

They also estimated excess lifetime (through age 75) risk of lung cancer death for workers exposed to various concentrations of respirable crystalline silica for 45 years (age 20-65). For a US worker, at 0.10 mg/m^3, resulting in a cumulative exposure of 3.0mg/m^3 by age 65, the excess risk above background was 1.7% (95%CI 0.2%-3.6%).The lifetime excess risk at 0.05 mg/m^3 (Steenland, 2002), using US rates after 45 years, assuming a 15 year exposure lag, is 1.5% (95% CI 0.2-3.7%), above a background US rate for the non-exposed of 6%.

Exposure limits to reduce silicosis

It is widely accepted that a reduction in the prevalence of silicosis can contribute to reducing the cancer risk. In a review of the results of epidemiological studies of silicosis prevalence (WHO 1986) the threshold value suggested for the avoidance of silicosis was a time-weighted average concentration of respirable crystalline silica dust of 0.04 mg/m^3 for an 8-hour shift, 40-hour week and 35-year working life.

From the results of the studies reviewed by the MAK Commission (Greim 2000), a NOAEL for the respirable crystalline silica dust concentration can be derived, at best in the range below 0.020 mg/m^3. This concentration, which is in the range of the detection limit of the currently used analytical method with personal sampling, was obtained mathematically by extrapolation from higher concentrations for shorter exposure periods to a working lifetime of 45 years. Use of a mathematical model without a threshold value predicts that reduction of the concentration of respirable crystalline

silica dust to 0.05 mg/m^3, measured as the average concentration during 40 years, corresponding to a cumulative exposure level of 2 mg/m^3 × years, could reduce the cumulative silicosis risk below that resulting from higher level exposures. The findings of the three extensive studies of cohorts from gold mining (Hnizdo and Sluis-Cremer 1993, Muir *et al.* 1989a, 1989b, Steenland and Brown 1995a, 1995b) and from the ceramics industry (Cherry *et al.* 1998) are considered to be particularly meaningful. According to these studies, at a respirable crystalline silica dust concentration of 0.05 mg/m^3 the silicosis risk could be kept to about 5 % to 10 %, whereby two of these studies (Hnizdo and Sluis-Cremer 1993, Muir *et al.* 1989a, 1989b) apply the restrictive exclusion criterion ILO ≥ 1/1. However, in mortality studies (Davis *et al.* 1983, McDonald and Oakes 1984 – only gold mines), at this concentration up to 1 % deaths from silicosis were found in each case. The estimated threshold limit values are based on working lifetime doses and thus on long-term exposure values. Therefore, the derived values for risk remain valid when the long-term exposure values are used as shift-related thresholds for which deviations above the threshold up to a factor of 2 are permissible for occasional shifts (DFG 1998).

Similar to MAK-Commission, Finkelstein (2000 s. table 1) evaluated the results of a number of studies that investigated silicosis. They showed that the risk of silicosis (ILO category 1/1 or more) following a lifetime of exposure at the current OSHA standard of 0.1 is likely to be at least 5-10%. The exposure–response relation for silicosis looks nonlinear (Hnizdo and Sluis-Cremer 1993), and is probably sigmoidal, as it is for asbestosis (Finkelstein 1982). Lifetime exposure at 0.1 mg/m^3 appears to put workers on the supra-linear portion of the exposure–response curve. Reduction of dust exposures would thus have a greater than linear benefit in terms of risk reduction. This evaluation suggests that 30 years exposure at 0.1 mg/m^3 might lead to a lifetime silicosis risk of about 25%, whereas reduction of the exposure to 0.05 mg/m^3 might reduce the risk to fewer than 5% (Hnizdo and Sluis-Cremer 1993).

ACGIH (2000) recommended a TLW-TWA for the alpha-crystalline silica from of crystalline silica of 0.05 mg/m^3 as respirable dust on the basis of the data shown in table 2.

An appropriate model for the effects of crystalline silica exposure on mortality from "Lung diseases other than cancer" (LDOC) was found to be the linear relative rate model, although the power model using log-transformed cumulative silica exposure performed almost as well (Park et al in press). It was estimated that based on the linear relative rate model, the excess lifetime risk at approximately 0.05 mg/m^3 for the cristobalite form of silica was estimated to be over 5 percent. Even exposures at 0.01 mg/m^3 may pose a risk, > 1 per 1000. This "Lung disease other than cancer" (LDOC) risk is in addition to the relative risk of lung cancer which has been shown to be increased for workers exposed to this form of silica (Park et al. in press).

HSE (2001) based its assessment for risk of developing silicosis on the study of Buchanan et al (2001) s. table 3. The results of this study show a steeply rising non-linear exposure response curve for silicosis, and indicate that periods of average exposure to concentrations ≥ 2 mg/m^3 even for a few months incur high risks of silicosis. A 15 years exposure to 0.02 mg/m^3 respirable crystalline silica results in 0.25% risk of developing silicosis (Category 2/1) 15 years past exposure.

Recommendation:

The main effect in human of the inhalation of respirable silica dust is silicosis. There is sufficient information to conclude that the relative lung cancer risk is increased in persons with silicosis (and, apparently, not in employees without silicosis exposed to silica dust in quarries and in the ceramic industry). Therefore, preventing the onset of silicosis will also reduce the cancer risk. Since a clear threshold for silicosis development cannot be identified, any reduction of exposure will reduce the risk of silicosis.

It was observed that the dose-response curve for silicosis appears to be sigmoidal and that maintenance of exposure below 0.05 mg/m^3 would avoid being on the steeper part of the dose-response curve, in the region where relatively small increases in exposure entail significant increases in silicosis risk.

The reduction of exposure to 0.05 mg/m^3 of crystalline silica is expected to reduce the prevalence of silicosis, ILO category 1/1, to about or less than 5% whereas an average respirable silica concentration of 0.02 mg/m^3 reduces prevalence of silicosis to about 0.25 % or less.

It arises that an OEL should lie below 0.05 mg/m^3 of respirable silica dust.

No STEL or skin notation are needed.

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Silicosis Risk

Table 1: Summary of Findings from the Silicosis Studies (Finkelstein 2000)

Study (and endpoint)	Silicosis Risk at 2 mg/m^3–years cumulative exposure (%)	Silicosis risk at 4 mg/m^3 –years cumulative exposure (%)
Muir (ILO ≥ 1/1)	0.4	12
Hnizdo (ILO ≥ 1/1)	5	52
Ng (ILO ≥ 1/1)	6 (at least 2 readers)	15
Steenland (Death certificate)	8	53
Kreiss (ILO ≥ 1/1)	11	53
Rosenman (ILO ≥ 1/0)	2	10
Miller (ILO ≥ 2/1)	6	30
Hughes (ILO ≥ 1/0)	1.1 (low intensity <0.5 mg/m^3) 3.7 (High intensity)	4 (Low intensity) 12 (High intensity)

Table 2: Relationship between respiratory silica exposure and risk of silicosis (ACGIH 2000)

Study	Length of Follow-up Since 1st Exposure	Average Respirable Silica Concentration in mg/m^3	Risk of Silicosis	ILO Category Used
Muir et al. (1989)	No follow-up after retirement	0.1	1.2%	1/1
Graham et al. (1991)	No follow-up after retirement	0.06	0.7%	1/0
Hnizdo and Sluis-Cremer (1993)	Yes; Follow-up after retirement	0.05	5%	• 1/1
Steenland & Brown (1995)	Yes; Follow-up after retirement	0.01	1%	• 1/1
Kreis and Zhen (1996)	Yes; Follow-up after retirement	0.025 to 0.05	13%	• 1/0

Table 3: Relationship between respiratory silica exposure and risk of silicosis (Buchanan et al 2001)

15 years exposure to respirable crystalline silica mg/m^{-3} (8-hr TWA)	Cumulative exposure mg/m^{-3} years	Risk of developing silicosis (Category 2/1) 15 years post-exposure
0.02	0.3	0.25%
0.04	0.6	0.5%
0.1	1.5	2.5%
0.3	4.5	20%