SZW

Ministry of Social Affairs
and Employment

Health-based recommended occupational exposure limits for crystalline forms of silicon dioxide (free silica)

Dutch expert committee en occupational standards
(met Nederlandse samenvatting)

RA 5/92

Labour Inspectorate

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This is a report of the Dutch Expert Committee on occupational standards (DECOS). The draft-document has been prepared by A.A.E. Wibowo.

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"This document is dedicated to a colleague and friend, Peter Joosting MD, who retired from being a member of the Dutch Expert Committee for Occupational Standards in 1991. His knowledge on the pathogenesis of toxic substances to the lungs is exceptional and his tenacity in completing the scientific value of the documents is praiseworthy."

Dutch Expert Committee for
Occupational Standard
August, 1991

NEDERLANDSTALIGE SAMENVATTING

KRISTALLIJNE VORMEN VAN SILICIUMDIOXIDE (KWARTS, CRISTOBALITE EN TRIDYMITE)

1. FYSISCHE EN CHEMISCHE EIGENSCHAPPEN

Kwarts komt voor als een wit poeder. De partikeldeeltjes hebben de structuur van hexagonale kristallen met een kleurloze, wit of variabele kleur. In de kristallen zijn de silicium- en zuurstofatomen gerangschikt volgens herkenbare geregelde patronen; dit in onderscheid met de amorfe vorm van siliciumdioxide. Kwarts heeft een hardheid van 7 Moh's eenheden en een relatieve dichtheid van 2,65 (water = 1).
Kwarts is een bestanddeel van o.a. zand, graniet, schuurpoeder en klei.

2. MONITORING

Ofschoon er meerdere technieken aanwezig zijn voor het analyseren van kwarts en voor de kwantitatieve bepaling in de arbeidssituatie hebben twee methoden de voorkeur, met name de infraroodspectrometrie en de röntgenstralings-diffractie-methode. Een andere techniek, de natte chemische methode, wordt in het algemeen gebruikt om het totale siliciumdioxide te meten, hierbij wordt geen onderscheid gemaakt tussen de amorfe en kristallijne vormen.
Conventionele biologische monitoring van werknemers die blootgesteld zijn aan deze stoffen is niet bekend.

3. GRENSWAARDEN

Nederland heeft een MAC-waarde van 0,15 mg/m^3, TGG-8 uur, voor respirabele kwartsdeeltjes. Voor cristobalite en tridymite geldt een MAC-waarde van 0,075 mg/m^3, TGG-8 uur.
In Duitsland geldt één MAK voor alle drie de stoffen, met name 0,15 mg/m^3 respirabele deeltjes. De ACGIH in de VS adviseerde een TLV van 0,10 mg/m^3 voor respirabel kwartsstof en 0,05 mg/m^3 voor cristobalite en tridymite.

4. TOXICOKINETIEK

De plaats van depositie van geïnhaleerde partikeldeeltjes is afhankelijk van de vorm, massa, aerodynamische eigenschappen en andere fysische factoren. De totale depositie

van partikeldeeltjes met een gemiddelde aerodynamische diameter van 5 µm kan oplopen tot 90 %.
Het grootste deel van de gedeponeerde partikeldeeltjes wordt uitgescheiden via de longen, sommigen via de mucociliaire stroom en de rest via het lymfesysteem. De lokale alveolaire macrofagen ingesteren de partikeltjes direct na de depositie. Vrij siliciumdioxide is matig oplosbaar in lichaamsvloeistoffen, dit kan tot de produktie van kiezelzuur en colloïdale suspensies leiden.
Er is geen informatie beschikbaar over de biotransformatie van kwarts, cristobalite, of tridymite.

5. EFFEKTEN

Bij blootstelling door inhalatie zijn de longen het doelorgaan. Blootstelling van proefdieren aan grote hoeveelheden gedurende een korte periode, veroorzaakt de stof alveolaire lipoproteinose. Onderzoeken bij proefdieren hebben aangetoond dat cellulaire en biochemische veranderingen in de uitwassingsvloeistof eerder vóórkomen dan andere afwijkingen van de longen, en dat de intensiteit van het silicoseproces meer afhankelijk is van de mate van retentie dan van de concentratie blootgestelde stof. In de symptomatologie veroorzaakt kwarts een vermindering van de luchtstroom, emfyseem en beschadiging van de smalle luchtwegen.
Langdurende blootstelling aan de stof door inhalatie of intratracheale instillatie bij ratten induceert een verhoging van de incidenties van adenocarcinomen en plaveiselcelcarcinomen in de longen. Dit soort effecten wordt niet gevonden bij muizen en hamsters. Kwarts is niet genotoxisch en de gegevens zijn te summier om effecten op de reproductie te kunnen evalueren.

Het is bekend dat kwarts bij de mens vier verschillende typen van silicose kan veroorzaken: nodulaire of "zuivere" silicose, gemengde fibrose, diatomie pneumoconiose en alveolaire lipoproteinose. Twee van de vijf case-control studies bij longkankerpatienten geven een verdubbeling aan van het risico bij personen blootgesteld aan kwarts. Het blijkt dat dit verhoogde risico alleen te vinden is bij personen met silicose. Ook neemt het risico op longkanker toe bij een verhoging van de blootstellingsconcentratie van kwarts. Een cohort morbiditeitsstudie rapporteert een toename van de gestandaardiseerde incidentie-ratio van longkanker. Het blijkt dat langdurende blootstelling aan ongeveer 0.16 mg/m^3 respirabel kwarts gerelateerd is aan een significante toename van de incidentie van longkanker, en dat bij een concentratie van 0.05 mg/m^3 dit niet meer het geval is. Men vond een dosis-respons relatie tussen de mate van blootstelling aan respirabele kwartspartikeltjes en het relatieve risico van silicose en tuberculose.

Men schat dat de NOAEL ligt bij een concentratie van 0.075 mg/m^3 respirabele kwarts-partikeldeeltjes.

6. EVALUATIE EN ADVIES

Aan te nemen is dat de drie soorten kristallijne vormen van siliciumdioxide (kwarts, cristobalite en tridymite) silicose kunnen veroorzaken. Bij proefdieren blijkt dat kwarts longkanker kan induceren en wel op basis van een epigenetisch werkingsmechanisme. Gegevens uit de epidemiologie hebben aangetoond dat de niet-nadelige concentratie voor silicose lager ligt dan die van longkanker; dit betekent dat preventie van silicose door begrenzing van de blootstelling aan de stof tegelijkertijd ook preventief werkt op de inductie van longkanker.

Hieruit concluderend heeft de WGD een advieswaarde voorgedragen van 0.075 mg/m^3, TGG-8 uur, voor alle drie de vormen van kristallijne partikels van siliciumdioxide. Deze advieswaarde geldt voor partikeldeeltjes met een respirabele aerodynamische diameter.

Datum van afsluiting: februari 1992.

1. INTRODUCTION

It is important to distinguish between the terms silicon (the element), silica (the minerals), silicates (the minerals), and silicone (a man-made synthetic polymer).

Silica or silicon dioxide (SiO_2) exists in nature in amorphous and crystalline forms. In amorphous silica the different molecules are in dissimilar spatial relationship one to another, with the result that there is no definite regular pattern between molecules some distance apart. Amorphous silica includes natural glasses, such as are found in volcanic tuff; synthetic glasses of commerce, including the glasses of mineral wool; and fume silica. In crystalline silica, the silicon and oxygen atoms are arranged in a definite regular pattern throughout the crystal. The characteristic crystal faces of a crystalline form of silica are the outward expression of this regular arrangement of the atoms. Crystalline silica forms in the earth's crust under conditions of increased heat and pressure. Free silica refers to pure crystalline silicon dioxide. It consists of silicon-oxygen tetrahedra in a number of polymorphic forms. The medically important crystalline phases of silicon dioxide are known as alpha quartz, cristobalite and tridymite (SSDC/NIOSH, 1988).

This document concerns the risk evaluation of workers occupationally exposed to the crystalline form of silicon dioxide (also called free silica) which may lead to the establishment of health-based occupational exposure limits of these compounds.

As background information the following review papers have been consulted:

- Silicosis and Silicate Disease Committee/NIOSH (1988): Diseases associated with exposure to silica and non-fibrous silicate minerals. Arch. Pathol. Lab. Med. 112, 673-720.
- IARC (1987): Silica. IARC monography on the evaluation of carcinogenic risk of chemicals to humans 42, 39-143.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, MONITORING

2.1. IDENTITY

2.1.1. Sctructure

The basic structural units of the silica minerals are tetrahedra. These are linked by sharing each of their four corners with another tetrahydron to form a three-dimensional framework. Differences in symmetry and cell parameters are designated by the prefixes α- and ß-. As shown in the introduction, "free silica" refers to pure crystalline silicon dioxide. The medically important crystalline phases of SiO_2 are known as α-quartz, cristobalite and tridymite. Among these, α-quartz is the most common mineral of commercial importance (SSDC/NIOSH, 1988). It is a major constituent of igneous rocks such as granite and pregmatite, but it is also found in sandstone and sedimentary deposits such as slate and shale. Cristobalite and tridymite are formed from quartz at high temperatures and have a restrictive geological distribution.

2.1.2. Chemical names and synonyms/registry numbers

Chem. Abstr. Name : Silica
CAS Registry No. : 7631-86-9

Synonyms for crystalline form: chalcedony; chert; coesite; cristobalite; cryptocrystalline silica; flint; jasper; microcrystalline silica; novaculite; quartz; quarzite; sandstone; silica sand; stishovite; tridymite and tripoli.

The overwhelming majority of natural crystalline SiO_2 exists as quartz, with CAS No. 14808-60-7. The CAS No. of cristobalite is 14464-46-1 and tridimyte 15468-32-3.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of selected silica forms are shown in Table 1.

Table 1. The chemical and physical properties of some selected silica forms as reported by IARC (1987)

Property	α-quartz	α-cristobalite	α-tridymite
Hardness (Moh's scale)	7	6.5	7
Density	2.65	2.33	2.26
Cleavage	poor	poor	poor
Twinning	(1) Twin plane $(10\bar{1}1)\mu$ (2) Twin plane $(01\bar{1}1)z$ (3) Twin plane $(10\bar{1}0)m$	spinel type twins on (111)	common on (110)
Colour	colourless, white or variable, black, purple, green	colourless, white, or yellowish	colourless or white
Description	occurs as hexagonal crystals; more commonly natural in an anhedral massive form	occurs as octahedral, rarely cubical, crystals; also in massive form	occurs as tabular, pseudohexagonal crystals; also in massive form

2.3. ANALYTICAL METHODS

2.3.1. Environmental monitoring

Silica can be analysed by a number of techniques, including optical microscopy, analytical electron microscopy, differential thermal analysis, infrared spectrometry, wet chemical techniques and X-ray diffraction. However, for quantitative evaluation of occupational exposure, infrared spectrometry and X-ray diffraction are the preferred techniques (IARC, 1987). Wet chemical techniques are generally used to determine total silica and do not distinguish amorphous and crystalline forms.

Infrared spectrometry

The NIOSH (1977) recommended this method for the determination of quartz in coal dust. The airborne coal dust is collected on mixed cellulose ester membrane

filters. For a 1 to 2 mg sample of coal dust, the analytical range extends from 10 to 100 µg of quartz. The sensitivity is 5 µg of quartz. The relative standard deviation is less than 15% at 30 µg of quartz. It should be pointed out that this method does not differentiate between quarts, cristobalite and tridymite.

X-ray diffraction

This method is based essentially upon mixing a known amount of reference standard dust with the unknown, and by determining the relative intensity of characteristic diffraction lines on passing an X-ray beam through the mixture. The diffraction pattern is photographed and the image intensity assessed, or the diffracted beam may be measured directly. The NIOSH (1977) recommendation for this method uses fluorite as the internal standard. The analytical range extends from 5 $\mu g/cm^2$ to 200 $\mu g/cm^2$ for each free silica species; the total athmospheric dust loading on the filter must not exceed 1 mg/cm^2. The sensitivity is 5 µg for each free silica species. The IARC (1987) reported that the detection limit in respirable dust is about 5 µg for quartz and 10 µg for cristobalite, which approximates an atmospheric level of 0.01 - 0.02 mg/m^3 for a 0.5 m^3 air sample.

Que Hee (1989) in his X-ray diffraction method uses nickelous oxide as internal standard. Typically 200 mg of ash sample was mixed with 50 mg of NiO, and then scanned to identify α-quartz, cristobalite and tridymite in the presence of calcium carbonate and graphite. The detection limits for the free silica forms are less than one percent. Advances in the analytical methods for free silica using the X-ray diffraction technique have been reported recently [see Knight (1989) and Myers et al. (1989A)].

2.3.2. Biological monitoring

Conventional biological monitoring techniques are not applicable for exposure to free silica.

3. SOURCES OF EXPOSURE

3.1. NATURAL OCCURRENCE

Crystalline silica is the most widely occurring of all minerals and it is found in most rocks. The most commonly occurring form of silica is the sand found on beaches throughout the world. The sedimentary rock, sandstone, consists of grains of quartz cemented together with clays. The coarse-grained igneous rock, granite, consists of quartz, feldspar and mica in shapeless interlocking grains.

3.2. MAN-MADE SOURCES

3.2.1. Production

As far as known no free silica has been chemically produced, which is in accord with its worldwide abundance.

3.2.2. Uses

Silica is used extensively in the ceramic industry and is a constituent of most refractory bricks. Rock containing silica is used as common building materials. Flint, which is made of quartz, has been historically an important mineral to early man, which he used to make some of the first known tools and weapons.

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1. ENVIRONMENTAL LEVELS

4.1.1. Water and food

Quartz occurs as particles suspended in water at concentrations that are largely a function of rock type and the quartz content of the geological formation through which the water flows. Quartz is the most stable mineral in the geochemical environment of the earth's surface and is therefore among the most common minerals in detrital waterborne sediments (IARC, 1987).

There are no data on the level of silica in foodstuff, but it may be surmised that it may contain silica as an unintentional contaminant.

4.1.2. Air (occupational)

Exposure to free silica (SiO_2) outside of mines is at least as common as exposure in mines in recent years. The most important non-mining source of exposure is foundry work involving abrading and polishing surfaces of metal castings and replacing silica brick linings of furnaces. Recently Feigin (1989) cited eight categories of exposure to free silica: (1) mining, quarrying, and tunneling; (2) stonecutting and stone polishing, especially monumental masonry; (3) manufacturing of metal castings with adherent sand from molds; (4) manufacturing of glass; (5) foundry work involving sand molds and abrasive blasting; (6) manufacturing of pottery, porcelein and firebricks; (7) boiler scaling with pneumatic impact tools, and (8) vitreous enameling involving the use of high temperatures and air jets.

The IARC (1987) made an extensive report on the levels of unbound or free silica (quartz) in air in various industries of numerous countries. A summary of the data on industries in western Europe, supplemented with more recent information, is presented in Table 2a. A summary of the levels of quartz as found in some brickworks in the Netherlands is presented in Table 2b (Buringh et al., 1990).

Until approximately 1970, the monitoring method most commonly used to evalu-

ate occupational silica exposures was counting of particles by optical microscopy; the quartz content of the airborne dust was inferred from the analysis of product and settled dust samples. The method currently used by most occupational hygienists is sampling of the respirable mass combined with analysis for silica.

4.2. HUMAN EXPOSURE

4.2.1. General population

Local conditions, especially in deserts and areas around recent volcanic eruptions and mine dumps, can give rise to airborne silica-containing dust. Silica and its common forms are found in a large number of consumer products. Some, such as talcs, may be derived from crushed rocks. It should be stressed that exposure by way of digestive tract is not of great consequence.

4.2.2. Occupational population

Froines et al. (1986) conducted a quantitative evaluation of worker exposure to silica in nine Standard Industrial Classification (SIC) codes using data derived from OSHA compliance inspections in order to assess the silica exposure problem in the US. There were 696 inspections in which silica was identified, and a total of 3592 samples for silica were collected. It was estimated that 24889 workers employed in ferrous and non-ferrous foundries are at risk of silica-related pulmonary effects. Analysis of the relationship between exposure level, unionization patterns and basis of the inspection, i.e. complains initiated or general inspection, revealed that the mean and median severity levels were highest in inspections generated by complaint in unionized facilities in resins, soaps, cosmetics, pottery and non-ferrous foundries. These data may indicate either that unionized workers work in poorly controlled environments, or that they more readily identify uncontrolled exposures, or both.

Table 2a. The levels of quartz in ambient air of various industries in western Europe as reported by IARC (1987) and supplemented with more recent data (R = range; Md = median; M = mean)

Sort of industry	Country	Dust level (mg/m^3) in time average	Respirable quartz level of the dust (%)	Comments	References
Mining and quarrying industry	Sweden	R:4.5-8.4 (total dust)	R:7-46	No data on respirable dust	Gerhardson et al. (1974) - IARC
Iron ore mining	Norway	R:0.5-36 (total dust)	R:23-32	No data on respirable dust	Gylseth et al. (1981) - IARC
Graphite mining	Norway	R:17-57 (total dust)	R:4.0-7.7	No data on respirable dust	Hanoa (1985) - IARC
Metal mines	Italy	R:0.7-1.7 (respirable dust)	R:2.8-4.0	Including underground and surface operations	Casula et al. (1983) - IARC
Quarries producing non-metal materials (gravel, sand, clay, etc.)	U.K.	Md:6 (respirable dust)	15% of samples have > 30%		Magnire et al. (1975) - IARC
Collieries, coal mining	U.K.	R:3.6-11.5 (respirable dust)	R:1.5-10.3	In eight out of 274 collieries	Crawford et al. (1982) - IARC
Collieries, coal mining	U.K.	R:1.2-8.2 (respirable dust)	R:0.8-7.8		Dodgson et al. (1971) - IARC
Coal mining	FRG	R:5.6-23 (total dust)	R:1.5-3.7	Calculated respirable quartz concentration 0.21 - 0.37 mg/m^3	Reisner et al. (1982) - IARC

Stone industry	Sweden	M:18.9 (total dust)	M:18	High dust levels were found in flame cutting, drilling, chiselling, dry grinding and blasting.	Gerhardsson et al. (1974) - IARC
Stone industry	Switzer-land	R:0.5-16.3 (respir-able dust)	R:7-27	Measured during drilling, chiselling and grinding	Hodel (1975) - IARC
Stone industry Road material indu-stry	Denmark	Md:1.3 for flint Md:1.0 for gra-nite (respirable dust) Md:1.1	Md:23 (R:10-33) Md:13 (R:3-35) Md:13 (R:3-35)		Guenel et al. (1989A)
Construction indu-stry	Finland	Area samples M:12 (R:0.3-44) Personal samples M:25 (R:1.1-117) (Total dust)	M:0.19 (R:0.01-1.2) mg/m^3 M:0.45 (R:0.01-2.1) mg/m^3	Highest dust levels are found in dry sweeping. No data on respirable dust.	Riala (1988)
Pottery work	U.K.	M:0.80 (respirable dust)	M:15.1		Higgins et al. (1985) - IARC
Cement factory	Italy	Md:3 (respirable dust)	Md:<1		Pozzoli et al. (1979) - IARC
Refractory brick production	Italy	R:0.25-1.65 (res-pirable dust)	R:6-30		Puntoni et al. (1985) - IARC

Glass, porcelein and cement factory	Sweden	M:13.3, 7.1 and 61.2 resp. (total dust)	R:4-9	No data on respirable dust	Gerhardsson et al. (1974) - IARC
Diatomite mining and processing	Iceland	R:0.1-2.0 (respirable dust)	M:<5		Reimarsson (1981) - IARC
Diatomite production plant	Sweden	M:20.2 (respirable dust)	M:4		Gerhardsson et al. (1974) - IARC
Foundries, ferro-silicon production	FRG	R:2.1-26 (total dust)	R:5-21 (crystalline forms)	No data on respirable dust	Prohazka (1971) - IARC
Ferro alloy industry	Norway	M:2-64 (total dust) resp. dust 25-65%	Generally <2	During handling of raw material quartz content may reach 50%	Kjuus and Langard (1984) - IARC
Farming, during ploughing and harvesting	FRG	R:7-40 (total dust)	R:<1-25	No data on respirable dust	Batel (1979) - IARC

	Total dust concentration AM (range) (mg m^{-3})	Respirable dust concentration AM (range) (mg m^{-3})	N	Average % quartz in respirable dust
WORKS A				
Stationary sites				
(1) Clay processing	2.1 (1.0–2.9)	0.5 (0.3–0.7)	6	11 (1)
(2) Tracks finger cars	2.5 (1.7–3.9)	0.5 (0.3–0.7)	5	
(3) Near press	15.4 (11.2–21.8)	1.6 (1.3–1.9)	6	13.5 (6)
(4) Near track, point of turn over	6.3 (2.5–11.3)	0.8 (0.4–1.2)	6	11.5 (2)
(5) Near truck, deloading	4.8 (3.5–6.6)	0.6 (0.4–0.7)	6	12.5 (4)
Personal samples				
Cleaner		0.9 (0.5–1.3)	3	14 (4)
Shovel operator		0.8 (0.6–0.9)	5	12.5 (2)
Press operator		1.4 (1.0–1.8)	6	11.5 (6)
Finger-car driver		0.8 (0.6–0.9)	6	10.5 (1)
Maintenance man		2.1 (0.6–6.3)	4	9.5 (3)
Fork-lift truck driver		0.7 (0.4–1.1)	3	8.5 (2)
Loader		1.1 (0.6–2.5)	22	8 (12)
Crane driver		0.7	2	8 (1)
WORKS B				
Stationary sites				
(1) Clay processing	1.0 (0.6–1.4)	0.4 (0.2–0.7)	4	3 (1)
(2) Near press	4.3 (1.9–6.1)	0.4 (0.2–0.6)	4	17.5 (4)
(3) Near push-off/turn over of plates	2.2 (0.6–3.8)	0.3 (0.1–0.7)	4	10.5 (1)
(4) Near handling machine	0.7 (0.4–1.1)	0.3 (0.2–0.3)	4	11.5 (1)
(5) Near deloader	1.1 (0.2–1.9)	0.4 (0.3–0.5)	4	7 (3)
Personal samples				
Press operator		0.4	4	10 (1)
Handling machine operator		0.4 (0.3–0.5)	4	7 (1)
Clay processor		0.9 (0.5–1.5)	3	6 (2)
Loader		1.5 (0.4–3.8)	3	5 (2)
Maintenance		1.1 (0.8–1.5)	4	2 (3)
Technician (laboratory)		0.4 (0.1–0.6)	4	0 (1)
WORKS C				
Stationary sites				
(1) Plate turn over	6.7 (5.3–8.6)	1.7 (1.4–2.1)	6	17 (2)
(2) Clay processing	30 (21–42)	5.8 (3.3–8.0)	6	18 (2)
(3) Press sanding	15 (7.9–30)	4.0 (1.6–5.5)	6	12 (2)
(4) Near press operator	11.2 (8.0–14.6)	2.5 (1.8–3.6)	6	17 (6)
(5) Near handling machine	6.5 (4.2–8.8)	0.9 (0.8–1.1)	5	13.5 (5)
Personal samples				
Press operator		4.6 (3.0–6.7)	6	17 (5)
Press turn over/push off		6.8 (4.6–8.8)	4	16.5 (2)
Handling machine operator		2.1 (1.0–4.1)	4	16.5 (2)
Finger-car driver		2.6 (1.8–3.9)	6	16 (1)
Press sanding		5.2 (4.2–6.0)	6	15 (4)
Maintenance/electrician		2.8 (1.3–3.7)	6	13 (2)
Maintenance		4.1 (2.2–5.6)	5	9.5 (1)
Loader/lorry driver		0.8 (0.6–0.9)	6	7.5 (2)
WORKS D				
Stationary sites				
(1) Near tracks finger cars	1.1 (1.0–1.1)	0.4 (0.3–0.4)	4	
(2) Near extruder	0.9 (0.4–1.3)	0.4 (0.3–0.5)	4	13 (4)
(3) Near handling machine 1	1.4 (1.1–1.8)	0.3 (0.2–0.4)	4	
(4) Near handling machine 2	1.9 (1.1–2.8)	0.4 (0.2–0.5)	4	
(5) Near kiln	2.0 (1.3–3.0)	1.0 (0.4–2.2)	4	

Table 2 b. The levels of quartz respirable dusts in four Dutch brickworks as monitored by stationary and personal methods (Buringh et al., 1990). Major characteristics of the works are:

Works	Press	Sanding forms	Handling	Drying	Kiln type
A	Hand form	Yes	By hand	Chamber	Tunnel
B	Belt form	Yes	Mechanical	Tunnel	Tunnel
C	Hand form	Yes	Mechanical	Chamber	Tunnel
D	Extrusion	No	Mechanical	Chamber	Flame

5. GUIDELINES AND STANDARDS

5.1. GENERAL POPULATIONS

There are no standards for free silica (quartz) in ambient air levels.

5.2. OCCUPATIONAL POPULATIONS

Country (years)	Standards (mg/m^3)	Comments
The Netherlands (1990)		
respirable dust of quartz	0.15	t.w.a.- 8 h
cristobalite	0.075	t.w.a.- 8 h
tridymite	0.075	t.w.a.- 8 h
USA-ACGIH (1990)		
respirable dust of quartz	0.10	t.w.a.- 8 h
cristobalite	0.05	t.w.a.- 8 h
tridymite	0.05	t.w.a.- 8 h
USA-NIOSH (1974)		
free silica	0.05	t.w.a.-10 h
Germany-DFG (1990)		
respirable dust of siliciumdioxide, cristallines (including quartz, cristobalite and tridymite)	0.15	t.w.a.- 8 h
Sweden (1989)		
respirable dust of quartz	0.10	t.w.a.- 8 h
cristobalite	0.05	t.w.a.- 8 h
tridymite	0.05	t.w.a.- 8 h

United Kingdom - HSE (1990)		
quartz, respirable dust	0.10	t.w.a.- 8 h
quartz, total inhalable dust	0.30	t.w.a.- 8 h
WHO (1986)		
free crystalline silica, as respirable dust	0.04	t.w.a.- 8 h

6. TOXICOKINETICS

6.1. UPTAKE

6.1.1. Inhalation

Dust deposition. The presence of free silica particles in the lung parenchyma at autopsy demonstrates that a fraction of such aerosols is respirable. Inhaled particles are deposited at various locations within the respiratory tract depending on their size, shape, mass, aerodynamic characteristics and other physical properties. The sites at which they land determine, in part, whether these particulates are rapidly cleared from the lung or remain to interact with pulmonary tissues, and the host defence mechanisms that protect them. Particles with mass median aerodynamic diameters (MMAD) greater than 10 μm are largely deposited against the turbinates of the nose and in the posterior oropharynx; particles with MMAD of 5-10 μm are deposited in the large and mediumsized airways, while particles with MMAD of 0.5-5 μm can reach the lower respiratory tract and are deposited in the smaller airways and alveoli. Very small particles, those of less than 0.5 μm MMAD may be carried away while still suspended in the exhaled airstream, or be deposited in the alveoli (Davis, 1986). Total deposition of particles of 5 μm diameter can reach a level as high as 90% (IARC, 1987).

In general, larger particles are deposited by inertial impaction at airway bifurcations. Smaller particles contact the respiratory membrane in small airways and alveolar units by sedimentation or from random Brownian motion as the airstream slows and the surface area increases relatively to the volume. Despite their small size and the apparently slow flow of the airstream in peripheral airways, silica particles deposit preferentially at alveolar duct bifurcations, rather than randomly on the alveolar wall. It is uncertain whether inertial impaction is responsible for deposition of particles in these small airways. This pattern focuses attention on the structure and sequence of events at these sites.

Particles that land on mucus pods in airways with ciliated epithelium are cleared from the lung within several hours of deposition. Particles deposited between islands of bronchial mucus, or which land on the nonciliated membrane of the lower respiratory tract, may be phagocytosed by macrophages or may penetrate

the respiratory epithelium directly to lodge in the interstitium. The penetration can occur within several hours of deposition, and thus potentially toxic particulates can gain access to structural lung matrix and cells quite rapidly after inhalation (Davis, 1986). The IARC (1987) reported an increased tracheobronchial deposition in patients with silicosis, but not in coal workers with simple pneumoconiosis.

Particle clearance. Most, but not all, silica is cleared from the lung after inhalation and deposition. The particles deposited may be removed by one of the following routes: the lymphatic system or the bronchial tree (Shi et al., 1989). Most of the particles deposited proximally to the respiratory bronchioles are removed by the effective mucociliary stream. It has been shown that some agents either inhibit or stimulate this clearing system. For example cigarette smoking inhibits the system, whereas SO_2 and NO_2 gases stimulate the system. The elimination of quartz particles from the lung continues for many years after the last exposure. Apparently locked particles in the area of fibrosis are detached from the tissue and cleared slowly.

Macrophages activity. At the alveolar level resident alveolar macrophages ingest dust particles soon after deposition. Similarly, interstitial macrophages probably ingest particles soon after they have penetrated the epithelium. It was noted that alveolar macrophages are randomly distributed on the alveolar surface before experimental animals were exposed briefly to an aerosol of silica, but within several hours after dust exposure the cells were concentrated at the alveolar dust bifurcations where particles were also found. Activation of complement present in the alveolar lining fluid, with generation of the powerful chemotactant C_{5a}, might account for this recruitment of macrophages to the sites of dust depositon. Chemotactins secreted by macrophages, and C_{5a} complement activation by proteinases released from macrophages, may amplify this recruitment (Davis, 1986).

Macrophages carrying particles gain access to the mucociliary escalator at bronchoalveolar junctions, travelling over the alveolar surface or along interstitial planes and lymphatic channels. Alveolar macrophages with particles are believed capable of penetrating the airspace epithelium, carrying these particles to intersti-

tial sites where they may remain for long periods of time. Clearance from the lung by means of these macrophages travelling to the mucociliary escalator appears to take place over several days after dust is deposited at the alveolar level.

Retention. Particles that gain access to the interstitial compartment may remain at that site, or may slowly be transported through interstitial planes and along lymphatic channels to regional lymphoid tissue, hillar lymph nodes, and subpleural lymphoid aggregates. Clearance from the lung by these pathways requires months for significant movement of dust; much of the material probably remains in the lung permanently. According to the IARC (1987) sixteen studies provide data on the mass of quartz and total dust retained in the lungs at autopsy from a total of some 1406 cases. The quartz contents was evenly distributed over the range of 0-5 g/both lungs, contrasting with the wide distribution of total dust contents which range from 0-100 g. Maximum lung storage probably depends on several factors, including the characteristics of exposure and the nature of the dust. Apparently, lungs do not accumulate more than 5 g of quartz, even in severe silicosis, but they can accumulate up to 100 g of carbon dust. In coal workers, the retention efficiency was higher among cases of progressive massive fibrosis and greater for quartz than for coal.

Absorption. Free silica particles are slightly soluble in body fluids, leading to the formation of silica acid and colloidal suspension (IARC, 1987). The absorption of dissolved silica is sufficient to increase its level in the blood and urine of exposed persons.

6.1.2. Skin contact

No data are available to indicate that free silica may be absorbed through the skin.

6.1.3. Ingestion

Due to its slight solubility in body fluids, small amounts of dissolved silica may be absorbed through the digestive tract, but no quantitative data are available.

6.2. DISTRIBUTION

There are no data available to indicate that crystalline silica is distributed to other organs of the body after penetration of the alveolar membrane, although it may be surmised that dissolved silica may do so. Traces amount have been found in blood and urine (Stolman and Stewart, 1985, cited by IARC, 1987). Of more importance is the distribution in the lung itself after being ingested by the macrophages. Dusts particles that gain access to the interstitial compartment may be transported through interstitial planes and along lymphatic channels to regional lymphoid tissue, hillar lymph nodes and subpleural lymphoid aggregates.

According to SSDC (1988) the uptake of quartz by cells of a variety of types in vitro and in vivo is followed by cytolysis. However, cytotoxicity in the acinus may be attenuated because of the changes in the surface properties of the particles and uptake of secretions and cell debris on their surfaces. The molecular basis of cell injury by silica has been the subject of considerable study. Binding of particles to cell membranes appears to be a surface phenomenon, and cytolysis is influenced by particle size since surface area increases in relation to mass as particles become smaller. The capacity of the crystal to bind hydrogen ions in the membranes of cells may be of critical importance.

6.3. BIOTRANSFORMATION

There are no data available on the biotransformation of quartz in the sense of common chemical compounds.

6.4. BIOLOGICAL MONITORING

There is no information of biological monitoring on workers occupationally exposed to free silica. A possibility is the use of biological effect monitoring (BEM). Quartz is toxic for the macrophage. This toxicity results in the release of cytoplasmic and lysosomal enzymes. Larivee et al. (1990) reported increased activities of cytotoxic enzymes in the Broncho Alveolar Lavage (BAL) of silica-exposed workers which apparently occur before the silicotic process is readily detected by the usual radiographic method. This observation was further confirmed in the animal model of the disease, in which increased LDH (Lactic dehydrogenase) activities in the BAL were seen at month 3 after initial exposure whereas radiographic changes occurred only at month 9 and after. Such early increases of LDH in BAL have been shown to occur within days of exposure (Bégin et al., 1986), which would support its primary relation to cytotoxicity of the dust toward the alveolar macrophage.

However, alveolar macrophages are not the only cellular source of the cytoplasmic and lysosomal enzymes. Alkaline phosphatase, which was also increased in the BAL of these workers, is an enzyme that may be derived primarily from type II pneumocytes. The development of the inflammatory process of silicosis may initiate the release by inflammatory leukocytes of products such as oxidants and enzymes that could damage and alter the function of other epithelial or interstitial lung cells.

It should be pointed out that this method of BEM is extremely intrusive to the worker, it can not be performed in the normal occupational health practice.

6.5. SUMMARY

Inhaled particles of respirable free silica are deposited at various locations within respiratory tract, depending on their shape, mass, aerodynamic characteristics and other physical properties. Total deposition of particles of 5 μm diameter can reach as high as 90%. Most, but not all silica are cleared from the lung after inhalation and deposition. The particles deposited may be cleared through the lymphatic systems on the bronchial tree. The elimination of quartz particles con-

tinues for many years after the last exposure.

Resident alveolar macrophages ingest dust particles soon after deposition, interstitial macrophages probably ingest after penetration of epithelium.

Free silica particles are slightly soluble in body fluids, leading to the formation of silicic acid and colloidal suspensions. The absorption of dissolved silica is sufficient to increase its level in the blood and urine of exposed persons.

Dusts particles that gain access to the interstitial compartment may be transported through interstitial planes and along lymphatic channels to regional lymphoid tissue, hillar lymph nodes and subpleural lymphoid aggregates.

There are no data on biotransformation of quartz in the sense of common chemical compounds.

There is no information of biological monitoring on workers occupationally exposed to quartz. A possibility is the use of biological effect monitoring (BEM). Increased activity of specific enzymes in the broncho-alveolar lavage may be detected. But this method is very intrusive to the worker.

7. EFFECTS

7.1. ANIMAL EXPERIMENTS

7.1.1. Non-oncogenic effects

The most important target organ in exposure by inhalation to free silica are the lungs. Silicosis is caused by the inhalation of crystalline silica in various forms. There is a cascade of inflammatory and fibrotic events involved in cell-mediated, and possibly humoral, immune responses to produce silicosis. The hypothesis rests on the central concept that interactions between silica and pulmonary macrophages are the pivotal events in the pathogenesis of silicosis. Resident and recruited pulmonary macrophages demonstrate intimate contact with silica from the moment of deposition, and throughout the time the particles remain in the lung. According to the current concepts (Davis, 1986) the silica probably exerts its effects on the macrophages that ingest it by altering their function while they are alive, rather than merely by disrupting them. The macrophage appears to be stimulated to secrete mediator substances, such as interleukin - 1 (IL-1), which alter the function and behavior of other cells. Lymphocytes and macrophages appear in close proximity to one another in developing silicotic nodules, and increased proportions of lymphocytes are found in broncho-alveolar lavage specimens from animals and humans with silica dust exposure.

Most animal experiments are performed to study the pathogenesis of silicosis and in itself not intended for the risk evaluation of workers exposure to silicon dioxide. Nevertheless, a summary will be given to present a better understanding on the early changes occurring in the lungs after exposure to the dust.

7.1.1.1. Exposure by inhalation

A summary on exposure by inhalation in experimental animals is presented in Table 3.

It may be conluded that exposure to huge amounts of silica dust to experimental animals in a relatively short period of duration resulted in effects which are similar to that found in humans. The experiments performed by

Table 3. Data on experimental animals exposed to free silica by inhalation

Species of animals	Levels of exposure	Duration	Effects and comments	Reference
rats	30000 part/ml (Ø 40% < 0.5 μm)	18 h/d 5 d/w 420 d	reticulin fibrosis at 220 d	King et al. (1950) - IARC
rats	40 mg/m^3 (98.7% pure quartz < 3 μm)	12 w	alveolar proteinosis	Heppleston et al. (1967) - IARC
rats	38 and 50 mg/m^3 pure α-quartz (Ø 1.4 μm, 73% respirable)	28 d, follow-up 1 y	4 w: foamy alveolar macrophages, with polymorph infiltration 17 w: perivascular and subpleural granuloma formation 34 w: focal pleural fibrosis, alveolar lipoproteinosis 56 w: focal squamous metaplasia	Bennett et al. (1988)
hamsters	300 mg/m^3 silica with 96% quartz Ø 80% < 2 μm	5 h/d 5 d/w 2 mo follow-up 7 mo	increased peroxidase activity in the BAL, accompanied by an influx of poly-morphonuclear neutrophils in airways	de Mendez et al. (1989)

Bennett et al. (1988) on rats exposed to 38 and 50 mg/m^3 pure quartz with 73% of respirable size for 28 days showed that at 34 w after first exposure signs of alveolar lipoproteinosis were found. There were even multiple foci of foamy alveolar macrophages with associated infiltration of polymorphonuclear leucocyts in groups of alveoli immediately after 4 weeks exposure. In humans, alveolar lipoproteinosis with fibrosing alveolitis develops rapidly in weeks or months (Parkes, 1982), they are even called "acute silicosis".

The data from this summary do not make it possible to derive the no-adverse-effect level of free silica. Equally it is difficult to extrapolate these huge levels of experimental exposures to animals to realistic situation in workroom environment in which workers are mostly undergoing long-term low level exposures.

7.1.1.2. Other ways of exposure

Only the more recent data will be reported in this chapter. These experiments have been performed with the objective of understanding more the mechanisms leading to silicosis.

According to Bégin et al. (1989) the cellular and biochemical alterations of the lung lavage precede other changes in the lung. They exposed sheep by repeated intratracheal infusion at 10-day intervals to 100 mg pure quartz in 100 ml saline and the animals were investigated at 3-months intervals by chest radiograph, lung function and lung lavage. An analysis of temporal trends demonstrated that the cellular and biochemical events preceded changes in the lung function and radiograph. It was shown that quartz exposure induced an expansion of all BAL cell populations, with sustained evidence of cell membrane damage (LDH accumulation), chronic activation of BAL cells (^{67}Ga accumulation), and excessive production of phospholipids (by pneumocytes), of fibronectin, and of fibroblast growth factors. These changes are paralleled by enhanced capacity of the lung inflammatory cells to release toxic oxigen radicals. The investigators also concluded that the quartz content in the BAL could be used as an index of alveolar dust retention and furthermore, the data suggest that the intensity of silicotic process in these animals is better related to the degree of quartz retained than to the external exposure dose. To study the relationship of macrophage damage

(cytotoxicity of quartz) Larivee et al. (1990) measured the release of LDH by sheep alveolar macrophage in 24 h cell culture under controlled conditions. It was shown that the LDH increase was dose-related during the exposure and the toxicity was attenuated by aluminium treatment of quartz. In an in vitro experiment Brown et al. (1988) demonstrated that supernatants of silica-stimulated human alveolar macrophages cause significantly greater amounts of fibroblast proliferation than do supernatants of macrophages stimulated with optimal amounts of endotoxin (LPS). These studies suggest that silica may be a very effective stimulus for fibroblast proliferation in vivo since it causes macrophages to release growth factors for fibroblasts without triggering the release of PGE_2, which is an inhibitor of fibroblast proliferation. Gulyar et al. (1988) also reported that quartz dust enhanced the release of elastase from activated rabbit alveolar macrophages in vitro. Increased elastase secretion suggests a possible risk for emphysema in workers handling this compound.

Changes in the function of lymphocytes after exposure to quartz were also reported. Bisonnette et al. (1989) studied rat splenic responsiveness to different mitogens (lipopolysaccharide, phytohemagglutinin and concanavalin A) in a murine model of pulmonary fibrosis. The fibrosis was induced by intratracheal administration of 5 mg silica particles. They found that stimulation of splenic cells with LPS was not affected, but stimulation with phytohemagglutinin and concanavalin A induced increased responses especially at 3 and 6 months after instillation. Struhar et al. (1989) examined the inflammatory cells and lymphocyte populations in the BAL fluid, lung tissues and peripheral blood from rats at various times after the intratracheal instillation of silica (10 mg, diameter less than 5 μm). In the BAL fluid a rapid increase of polymorphonuclear leukocytes was observed which slowly decreased during the course of experiment. There was also an increase of the lymphocytes throughout the 75 days of the experiment, with a predominance of the T-helper phenotype. In the peripheral blood of silicotic rats, T-helper cells were significantly increased until day-14 and then returned to normal values. The results of this experiment showed that T-helper cells may play an important role in the inflammatory fibrotic process in the lungs of rats with silicosis.

Direct effects on the alveolar epithelial cells by exposure to quartz are also reported. Merchant et al. (1990) measured paracellular permeability of rat alveolar epithelium after exposure to silica, in vitro, using markers of the extracellular space. They found that silica markedly increases the permeability in a dose- and time-dependent manner. This event was not the result of cytolytic injury, because lactate dehydrogenase release from monolayers exposed to silica was not increased. It may be surmised that an increase in epithelial permeability over a prolonged period of time may permit serum derived inflammatory mediators access to the alveolar surface. Under these conditions a variety of inflammatory cells might be attracted to the lung, which may have the potential to cause permanent injury to the alveolar - capillary membrane. Hypertrophy of type II cells from the lungs of silica treated rats was reported by Miller and Hook (1988). Their results suggest that the hypertrophy of the cells is responsible for the increases in the surfactant-associated phospholipids in the lungs.

The close proximity of lymphocytes and macrophages in developing silicotic granuloma in both animal model and human cases suggests the involvement of cellular immunologic process. Struhar et al. (1989) studied two important components of cell-mediated immune responses in the lungs of rats with silica induced lung disease, i.e. class II (Ia) antigen expression and IL-1 production. They found a three-fold increase of Ia expression on the alveolar macrophages and a two-fold increase in type II cells from rats with silicosis compared to normal rats. Szymaniec et al. (1989) studied the antibody producing cells in the spleens of mice treated with various pathogenic mineral dusts by intraperitoneal injection. They found that quartz caused one-third reduction of the plaque forming cells. The implications of this study are, of course, that inhaled dust causes important immunomodulation systematically which could be important for development of dust-related disease or responses to other substances, for instance infectious agents.

Quartz causes air-flow obstruction, emphysema and small airway lesions in the rat, as reported by Wright et al. (1988). They administered 10 or 30 mg of quartz to rats by intratracheal instillation. The animals were killed after 30 days and

pulmonary function and morphologic changes were examined. Both quartz-exposed groups showed evidence of air-flow obstruction, with more severe abnormalities in the high dose group. These findings correlated with morphometric observations of emphysema and thickening of airway walls, with changes again more severe in the high dose group. Early silicotic nodules were also present in the latter animals.

7.1.2. Long-term carcinogenicity studies

A summary of animal experiments as reported by the IARC and supplemented with more recent data is presented in Table 4. Only experiments in which the administration methods are performed by inhalation and intratracheal instillation are shown. Other methods, such as intrapulmonary deposition, intrapleural, intrathoraxic, intraperitoneal and intravenous administration are viewed to be of no consequence for the assessment of determining the health-based occupational exposure limit of free silica.

Different samples of quartz, with particle sizes in the respirable range, were tested for carcinogenicity in three experiments in rats and one experiment in mice by inhalation, and in two experiments in rats and three experiments in hamsters by intratracheal instillation. In all five experiments on rats, whether by inhalation or intratracheal instillation, there were significant increases in the incidences of adenocarcinomas and squamous cell carcinomas of the lung. No pulmonary tumours were observed in hamsters in three experiments using repeated intra-tracheal instillation of quartz dusts with observation periods between 77 w and life-span. In an experiment on mice by inhalation no significant increase of tumours of the lung was found, although it is speculated that the number of animals used in this experiment is too small, e.g. 6-16 animals per group. In the studies by inhalation and intratracheal administration, fibrosis was an important part of the biological response to crystalline silica.

Two studies by intratracheal administration, one on rats and the other one on hamsters, were performed to investigate possible interactions between quartz and known carcinogens in inducing tumours. Pylev (1980-IARC) used benzo(a)pyrene as the known carcinogen. The experiment was performed in rats

given single administration of both agents. The following protocol and its results were shown:

Groups	Dose	Observation	Incidence
Group 1 28 males 30 females	50 mg quartz + 5 mg BaP	survival ≥ 7 mo	3/11 lung tumours 11/20 lung tumours
Group 2 37 males 33 females	50 mg quartz + 4 mo later 5 mg BaP	survival ≥ 11.5 mo	4/11 lung tumours 0/7 lung tumours
Group 3 10 males 18 females	5 mg BaP	survival ≥ 9 mo	0/8 lung tumours 0/11 lung tumours
Group 4 39 males 30 females	no treatment	survival ≥ 16 mo	0/16 lung tumours 0/29 lung tumours

In this experiment a control group receiving quartz without BaP is absent. Therefore no conclusion can be made on the effect of quartz and on the interaction of BaP and quartz. Furthermore, the number of animals used in Group 3 is quite different from the other groups and a single administration of quartz does not conform with the usual long-term carcinogenicity test programs. Niemeier et al. (1986-IARC) studied the interaction between quartz and BaP on Syrian golden hamsters by weekly intratracheal administration for 15 weeks. The following results (incidences of respiratory tumour-bearing animals) with its associated treatment were attained: 0/48 (saline control), 22/47 (saline + BaP), 0/50 (Sil-CoSil), 36/50 (Sil-Co-Sil + BaP), 1/50 (Min-U-Sil), 44/50 (Min-U-Sil + BaP). From this experiment it may be concluded that quartz itself probably does not induce lung tumours in hamsters, but it may increase the incidences of lung tumours induced by BaP in this species of animals.

Table 4. Data on carcinogenicity studies as reported by IARC (1987) and supplemented with recent information

Species of animals (number per group)	Dose and method of administration	Duration of exposure	Results	Comments	Reference
BALB/c BYC female mice (6-16)	1475 mg/m^3 1800 mg/m^3 1950 mg/m^3 (diameter <1.2 µm), by inhalation	8 h/d, 5 d/w, 150 d 8 h/d, 5 d/w, 300 d 8 h/d, 5 d/w, 570 d	Pulmonary adenoma in exposed and control groups. No significant difference.	Small numbers in each group.	Wilson et al. (1986) - IARC
F344 rats, both sex (72/sex)	51.6 mg/m^3 (MMAD 1.7-2.5 µm) by inhalation	6 h/d, 5 d/w, 24 mo	High incidence of epidermoid carcinoma of the lungs in treated rats. None in control.	Only one dose.	Dagle et al. (1986) - IARC
F344 female rats (62)	12 mg/m^3 (diameter <5 µm) by inhalation, nose only	6 h/d, 4 d/w, 83 w life span observation	18/60 incidence of lung tumours (squamous-cell car, adenocar and adenomas). None in sham exp. controls.	Only one dose. Most exp. rats develop silicosis.	Holland et al. (1983, 1986) - IARC Johnson et al. (1987) - IARC
F344 rats both sex (50/sex)	1 mg/m^3 (87% α-quartz) (MMAD 1.3 µm) by inhalation	6 h/d, 5 d/w, 24 mo life span observation	18/100 primary lung tumours 10/100 malignant tumours (adenocar., adenosquamous car., squamous cell car.)	61/100 lipoproteinosis	Muhle et al. (1989)

SD rats, sex unspecified (40)	7 mg/0.2 ml (diameter 1.7 μm) intratracheal	1/w, 10 w life span observation	6/36 incidence of lung tumours (carcinomas and adenomas). None in controls.	Fibrotic lesions in exposed rats.	Holland et al. (1983) - IARC
F344 male rats (85)	20 mg Min-U-Sil (0.1% ≥5 μm) Novaculite (2.2% ≥5 μm) intratracheal	Single exposure observation 22 mo	Incidences: 30/67 with lung carcinomas 21/72 with lung carcinomas In the control group 1/75		Groth et al. (1986) - IARC
Syrian golden hamsters sex unspecified (48)	3 mg/0.2 ml 7 mg/0.2 ml Min-U-Sil (diameter 1.7 μm) intratracheal	1/w, 10 w 1/w, 10 w life span observation	No lung tumours in both dose groups as well as controls.	Minimal severity of pulmonary fibrosis.	Holland et al. (1983) - IARC
Syrian golden hamsters, male (25-27)	0.03 mg 0.33 mg 3.3 mg 6.0 mg Min-U-Sil (diameter 1.06 μm) intratracheal	1/w, 15 w observatons 24.5 mo	No tumours were observed in any of the groups.	There are dose-related alveolar septal fibrosis, granulomatous inflammation and alveolar proteinosis observed.	Renne et al. (1985) - IARC

Syrian golden hamsters, male (50)	0.7 mg/0.2 ml Min-U-Sil (respirable) 1.1 mg/0.2 ml Sil-Co-Sil intratracheal	1/w, 15 w observation 77 w (total 92 w)	1/35 adenosquamous car. no tumours no tumours in the control group		Niemeier et al. (1986) - IARC

7.1.3. Mutagenic and genotoxic activity

The following experiments were reported by IARC (1987) on the mutagenic and genotoxic activity of silica:

Silica (physical form unspecified) was reported to be inactive in the Bacillus subtilis rec assay when tested at concentrations of 0.005-0.5 M.

Silica (physical form not specified) was not mutagenic to Salmonella typhimurium TA1535, TA1537, TA1538, TA98 or TA100 or to Escherichia coli WP2uvrA when tested at 0.3-10000 µg/plate in the presence or absence of a metabolic activation system from Aroclor-induced rat-liver homogenate.

Concentrations of 1-15 µg/ml quartz (Min-U-Sil) did not induce sister chromatid exchanges in Chinese hamster V79-4 cells, but 20 µg/cm^2 Min-U-Sil induced micronuclei in Syrian hamster embryo cells.

α-Quartz (2 µg/cm^2) did not induce chromosomal aberrations or aneuploidy in Syrian hamster embryo cells.

Concentrations of > 2 µg/cm^2 Min-U-Sil and > 10 µg/cm^2 α-quartz induced dose-dependent increases in the number of morphologically transformed Syrian hamster cells.

DQ12 quartz (500 mg/kg b.w.) did not induce micronuclei in polychromatophilic erythrocytes of mouse bone marrow.

Quartz did not inhibit functional intercellular communications as measured by metabolic cooperation between Chinese hamster hprt$^{+/-}$ cells.

7.1.4. Effects on reproduction

There are no data available to indicate that quartz has effects on the reproduction of experimental animals. The IARC (1987) cited some effects of colloidal silica on chick embryos, but it was concluded that the effect was due to the colloidal nature of the test materials rather than to their chemical type. Furthermore the effect on reproduction is not relevant in exposure to quartz since it is not the target system.

7.2. OBSERVATIONS IN MAN

Lung disease caused by silica may occur in four different types of silicosis which are best treated separately (Parkes, 1982):

(1) Nodular silicosis or "pure" silicosis which has characteristic hyaline and collagenous nodular lesions due to dusts having a substantial content of quartz. It should be pointed out that pure, or nearly pure airborne free silica dust is hardly encountered, as it is accompanied by variable amounts of other constituents. Strictly, therefore, all inhaled siliceous dusts are "mixed". Nodular silicosis occurs when the proportion of free silica in the dust is relatively high.

(2) Mixed dust fibrosis (Mischstaubpneumokoniosen) is an ill-defined, irregular, stellate fibrotic lesion due to the combined effect of dusts consisting of a mixture of free silica and an inert mineral, most commonly iron oxide.

(3) Diatomite pneumoconiosis is a predominantly fibrosing alveolitis often with a well developed cellular component caused by calcined diatomaceous earth.

(4) Alveolar lipoproteinosis with fibrosing alveolitis. Unlike the other three, disease in this group develops rapidly in weeks or months and can therefore be called "acute silicosis", although this term has sometimes been used to denote nodular silicosis of unusually quick development following heavy dust exposure.

Initial concern about pulmonary cancer arose from the observation of Paracelsus and Agricola in the 16th century that Schneeberg metal ore miners were dying of lung diseases later thought to be respiratory cancer, of which radium ore decay products were the probable cause (IARC, 1987). An extensive assessment has been made by the IARC and they concluded that there is limited evidence for the carcinogenicity of crystalline silica to humans.

7.2.1. Case-control studies

A summary of case-control studies is presented in Table 5.

One of the methodological problems in applying this type of studies is how to

Table 5. Case-control studies on lung diseases caused by exposure to free silica, recent data

Case determinant (number of cases)	Controls (number)	Industry of concern	Results (Relative Risk and 95% CI)	Comments	Reference
deceased lung cancer (72)	deceased referent (314) match on smoking habit, age and period of death	pottery	RR workers: 2.0(1.1.-3.5) RR silicotic individuals: 3.9(1.8-8.3) RR non-silicotic workers: 1.4(0.7-2.8) RR smokers >20 cig/d: 3.9(1.9-7.9)	Lung cancer may be associated indirectly with the silicotic process. Study performed by using death certificates with clinical validation. Smoking habit taken into account.	Forastiere et al. (1986) - Italy
deceased lung cancer (231) - white miners - pathology confirmed	deceased referent (318) - matched on year of birth - exposed to silica	gold mines	Cumulative dust exposure was calculated and comparable between cases and controls. Average exposure 0.2 mg/m^3 RR silicosis of parenchyma: 1.10(0.79-1.60).	No association between lung cancer and either silica dust exposure or silicosis. Smoking habit taken into account.	Hessel et al. (1990) - South Africa

patients with lung cancer (309)	patient referent (309) admitted to the same hospital)	quarry, tunnels and mines	RR silicotic non-smoker: 5.3(0.5-43.5) RR non-silicotic non-smoker: 1.3(0.0-13.8) RR silicotic smoker: 19.7-(5.1-89.7) RR non-silicotic smoker: 10.4(2.9-44.4) RR non-exposed smokers: 11.9(4.2-46.5)	In both smokers and non-smokers, exposure to silica without silicosis does not increase the risk of lung cancer, while a two-fold increase is discernible in workers with silicosis. Number of cases and referents for non-smokers is very small.	Mastrangelo et al. (1988) - Italy
male patients primary lung cancer (381) - histologically verified	patient referents (381) - matched on birth and diagnosis year - same register	coal mines	RR workers: 0.95(0.65-1.38) RR workers with history of underground mining: 0.96(0.56-1.65)	No information on smoking habits. No quantitative data on exposure.	Meijers et al. (1988) - Netherlands
patients lung cancer (414) -histological verified	patient referents (414) - matched on birth and diagnosis year - match on sex	fine ceramic industry	RR workers: 1.11(0.77-1.61) (only for the males) Based on exposure index RR tends to increase with increasing silica exposure.	The number of women workers is too small, analysis is restricted to males (762 matched males). No relation between specific tumour types and working in ceramic industry.	Meijers et al. (1990) - Netherlands

patients with simple pneumoconiosis (40) - radiology confirmed	referents with normal radiograph (80) - matched for age, smoking and date of entry into the workforce	iron ore surface mining	Exposure indices were calculated for each worker. Comparison between cases (ILO cat. I) and controls show significant values for peak respirable quartz, cumulative respirable dust and peak respirable dust.	Quartz exposure is the major contribution to radiographic changes in ILO cat. 2 and 3.	Moore et al. (1987) - Canada
deceased lung cancer (40); deceased chronic resp. disease (26)	for each case four referents, matched for age, same occupation	gold mine	RR for lung cancer: 1.77(0.94-3.31). RR for chronic resp. disease: 2.48(1.03-6.00).	Cigarette smoking is a major risk factor, but cumulative dust exposure has an additional effect on the risk in chronic resp. disease.	Wyndham et al. (1986) - South Africa

choose the right method for selection of cases and referents; various methods are known. Sometimes, investigation select cases from one source and referent subjects from a variety of sources, permitting comparisons with different control groups. Consistency of findings among different types of control groups compared to cases increases the strength of inferences derived from the findings.

Lung cancer as case determinant

From the seven case-control studies, 6 studies use lung cancer as the end-point. And from the latter only one study shows a significantly increased relative risk for lung cancer in workers occupationally exposed to free silica (Forastiere et al., 1986). This study was performed in Central Italy where the pottery industry has a long tradition and the municipal registers of deaths were utilized as source of subjects. A clinical validation of the lung cancer diagnosis had been performed, although it is not known whether pathological examination had taken place. Questionnaire on post employment and smoking habits were administered blindly to the next-of-kin of the deceased subjects. This study showed that a lung cancer risk for the ceramic workers was doubled in comparison to the unexposed workers, and this increased risk mainly occurred in silicotic individuals.

The other five studies reporting on workers in the gold mines (Hessel et al., 1990; Wyndham et al., 1986), coal mines (Meijers et al., 1988) and fine ceramic industry (Meijers et al., 1990) did not show a significant increased relative risk of lung cancer. Nevertheless, the study by Mastrangelo et al. (1988) showed that the risk for lung cancer in exposed subjects with silicosis was significantly higher, almost doubled, when compared to the non-exposed subjects, after being stratified for the smoking habits. From this study it may be concluded that the existence of silicosis is probably an important factor in the induction of lung cancer.

As is common in this kind of retrospective study the most difficult part is in attaining insight on the quantitative and qualitative past exposure. Meijers et al. (1990) in their study on ceramic workers in the Netherlands were able to make an estimate of exposure for every individual worker by using a panel of occupational hygienists. Although the total relative risk of lung cancer among workers regardless of the duration of employment, or the relative silica exposure, was not significantly increased (RR = 1.1 with 95% CI of 0.77-1.61), they found that the

relative risks tend to increase with increasing silica exposure. Despite the fact that no information was gathered on the smoking habits of cases and controls, there is no evidence for a different smoking pattern in ceramic workers in this study compared with general population in the Netherlands.

Simple pneumoconiosis as case determinant

Only the study from Moore et al. (1987) uses pneumoconiosis as the case determinant. They investigated the association between indices of dust exposure and the development of radiologic pneumoconiosis. The result showed that the association between dust composition and ILO radiologic catagory for simple pneumoconiosis was consistent, with respirable quartz being the best differentiating index between the case and control groups.

7.2.2. Cross-sectional studies

There are numerous cross-sectional studies on workers exposed to free silica, a summary is presented in Table 6.

There is no doubt that silicosis is a chronic inflammatory and fibrotic disease caused by the inhalation of crystalline silica in various forms. The clinical and epidemiological features of silicosis provide clues to the factors that govern the disease; the histopathologic characteristics of silicosis presents the cast of participants in its development.

The data from these studies indicate a number of factors that determine the severity and timing of the disease. The following factors may be summarised:

(a) the silica dose, e.g. airborne level, job type, hygiene
(b) duration of exposure, e.g. years of employment
(c) nature of the dust, percentage of quartz
(d) composition of the dust, e.g. contaminants
(e) additional factors, e.g. smoking habits
(f) complicating factors, e.g. tuberculosis, rheumatoid arthritis.

The importance of these factors can be assessed in very general terms, but only a few has been studied in great detail in human population.

Duration of exposure played an important role in the prevalence of silicosis (Amandus et al., 1989; Meijers et al., 1990; Swaen et al., 1988). Meijers et al. (1990) performed a cross sectional study on workers in the Dutch fine ceramic industry in Gouda and Maastricht. 520 Ceramic workers from Gouda, in which unmechanized ceramic shops prevail, were medically examined by Valk (1981). In Maastricht 1975 workers were examined, they were from two large mechanized fine ceramic companies. The medical examinations consisted of chest x-ray and a questionnaire. The following prevalences of silicosis were found, related to their duration of exposure:

Duration of exposure (years)	Prevalence in Gouda (%)	Prevalence in Maastricht (%)	Combined (%)
≤ 3	1.0	0.0	0.2
4 to 9	1.7	0.0	0.2
10 to 19	13.4	0.5	
20 to 24	15.5	2.0	
25 to 29	27.3	5.1	
≥ 30	30.1	13.0	19.9

Martin et al. (1988) reported that the seriousness of silicosis as expressed in the ILO-categories is related to age, duration of current exposure and the cumulative respirable dust and quartz levels in air. In their study on 1859 workers in iron-ore surface mining operations they found a dose-effect relationship between the estimated cumulative quartz level and the chest-film diagnosis of ILO-categories 0 to 3.

7.2.3. Retrospective cohort mortality/morbidity studies

A summary of various retrospective cohort mortality/morbidity studies is presented in Table 7.

There are various retrospective cohort studies carried out with morbidity or mortality as the end-point. One of the methods to express the morbidity is the incidence rate. The incidence rate is a direct estimate of the probability of develo-

ping a disease during a specified period of time. The relative risk (RR) permits to determine whether the probability of developing a disease differs in different populations or time periods or in relation to suspected etiologic factors. This relative risk can be made specific for age, sex and for any other personal characteristics. In addition to direct standardisation there is also the indirect standardisation method. The use of Standardised Mortality Ratio (SMR) or the Standardised Incidence Ratio (SIR) is sample of the indirect method. One of the difficulties in the methodology of determining Standardised Incidence Ratio's with lung cancer as pathological end-point is the collection of data of "new cases". Obligatory for the credibility of the method is the existence of a body which registers all new cases of cancer existing in the country. There are very few countries which have a national center for cancer registry, with the exception of Scandinavia.

The two cohort morbidity studies in the summary are performed in Denmark, one with lung cancer and the other with pulmonary tuberculosis as the pathological end-points. Guénel et al. (1989 B) found a significant increased SIR of lung cancer in a cohort of skilled Danish stone workers after adjustment for region. The highest ratio seemed to come from the cohort of workers originating from Copenhagen (SIR: 306 with 95% CI of 181-482). When further analysed according to the type of stone material the workers were exposed to, the SIR for sandstone workers was about two times higher than for granite workers (SIR of 808 vs 404). For the unskilled workers the SIR of lung cancer was also significantly increased when compared to national incidence rates adjusted for region. Further specification of this group of workers showed that stonecutting industry workers had a SIR of 111(95% CI of 45-229) and the road material industry workers a SIR of 246(95% CI of 143-394) for lung cancer. Silicosis was found in 56% of the sandstone cutters, in 14% of the granite cutters and in 23% of the men cutting both materials. Tobacco consumption could not be controlled for in the analysis, therefore the bladder cancer incidence was taken along in parallel to that of lung cancer. The fact that the ratio for the total cohort cancer was 193 and that of bladder cancer was 92, makes it plausible that an excess use of tobacco alone is unlikely. Research on the level of exposure to respirable quartz dust indicated a

Table 6. Cross-sectional studies on workers exposed to free silica, effects on the lungs

Industry of concern	Characteristic of workers	Level of exposure	Results	Comments	Reference
31 coal cleaning plants and strips coal mines Pennsylvania, US	1061 white males	no environmental monitoring, but work duration noted	In 516 men who had never been employed in dusty work other than surface mining, the prevalence of ILO Cat. I and higher was 4.5%. The prevalence increases with tenure as high wall drill operator.	Duration of exposure after controlled by age, height, smoking and exposure in dusty jobs other than drilling is related to radiographic evidence and decrease of FEV_1, FVC and peak flow.	Amadus et al. (1989)
granite industry and foundries, or gold mines Quebec, Canada	94 workers, work duration 14-42 y, 90% smokers	most of them are exposed to 1-4 mg/m^3 quartz	Subjects with aberrations in their chest röntgenogram and/or computerized tomograms showed reductions in various lung function parameters: lung volumes, lung compliance, diffusion capacity, expiratory flow rates.	From the 94 examined workers only 21 subjects showed no anomalies in their chest röntgenogram and CT-scan.	Bégin et al. (1988)

granite stone cutting industry Quebec, Canada	22 workers, age range: 35-71 y, non-smokers, 22 matched controls	range of exp. level: 1-4 mg/m^3 quartz	From the group of exposed workers: 7 are without disease; 9 had silicosis without conglomeration; the progress of the disease is clearly reflected in the biologic characterization of the BAL fluid: increase of IgM, fibronectin, procollagen 3.	This study supports the concept that in silica-exposed workers, airflow limitation progresses with the severity of the disease.	Bégin et al. (1987)
pyrite mine Tuscany, Italy	366 male workers, 322 control group from same area	0.60 mg/m^3 resp. dust, with quartz <1.5% others: 6.0 ppm CO 0.22 ppm NO_2 0.09 PPM SO_2	In the exposed group of workers there is an increased prevalence of simple chronic bronchitis and this condition is not associated with functional impairment of obstructive nature. Chest X-ray revealed 14 cases of pneumoconiosis.	The workers are exposed to mixed exposure, it is difficult to relate it directly to quartz.	Franzinelli et al. (1989)
granite industry Quebec, Canada	24 workers, exposure duration: 18-40 y, 25 matched controls, non-smokers >2 y	no data on airborne levels	Examination of the BAL fluid shows significant increase of LDH, ß-glucuromidase and alkaline-phosphatase in the exposed group compared to the control group.	Increased lung lavage enzyme activities may signify cytotoxic damage to the cells of the lung. This process occurred before silicosis is detected by radiographic method.	Larivée et al. (1990)

tiron ore surface mining Labrador, Canada	1859 workers, mean age 34 y, current smokers: 73%, non-smokers: 27%	estimated cumulative quartz level: 3.85 mg/m^3 9.27 mg/m^3 16.07 mg/m^3	chest film diagnosis: ILO category 0 (n=1817) ILO category 1 (n=30) ILO category 2-3 (n=12)	ILO category was related to age, duration of current employment and cumulative respirable dust and quartz levels as well as decrement in ventilatory function.	Martin et al. (1988)
fine ceramic industry Gouda, Maastricht, the Netherlands	520 workers from Gouda and 1975 workers from Maastricht	no data on airborne particle levels	Study by röntgenogram and questionnaire: Gouda: 13.3% had silicosis Maastricht: 1.7% had silicosis (Diagnosis according ILO class.)	The prevalence of silicosis is strongly associated with the duration of exposure to quartz containing airborne dust.	Meijers et al. (1990)
brickworks Cape Town, South Africa	268 male workers mean age: 29.6 y mean duration of work: 4.9 y migrant workers	<0.5 mg/m^3 - >5 mg mg/m^3 respirable dust	The prevalence of respiratory symptoms ranged from 7% for chronic bronchitis to 52% for morning cough to 27% for both chest tightness and wheeze and 9% for dyspnoea at effort. Effects of dust shown in FVC and FEV_1.	The symptoms are significantly predicted by combinations of smoking and exposure to dust. The percentage of quartz in dust is not noted.	Myers and Cornell (1989) Myers (1989)

quartz crushing industry Gurajat, India	19 workers, 3 male and 16 female, age 18-35, mean duration of exposure: 5 y 19 matched controls	no data on airborne levels	Of the 19 workers, 7 showed radiological evidence of silicosis. In this group an increase of IgG and IgA in serum was noted.	It is suggested of an important role of immunologic reaction in the pathogenesis of this disease.	Nigam et al. (1990)
pottery industry United Kingdom	276 present and former workers, recipient of pneumoconiosis disability pension (136 male, 140 female)	no data on airborne levels	The FEV_1 declines with increasing X-ray category of silicosis irrespective of smoking habit and was marked with symptomatic chronic bronchitis. Patients with conglomerate disease much higher decrease of FEV_1 than subjects with simple silicosis.	Highly selective subjects and probably a survivor population.	Prowse et al. (1989)
fine ceramic industry Gouda, Maastricht, the Netherlands	2495 workers	TWA of 0.15 mg/m^3 of quartz in respirable range is exceeded in many instances, at the time of the study	From 2495 subjects, 102 workers were diagnosed as cases of silicosis of the simple type.	The prevalence of silicosis is strongly associated with duration of exposure. Smoking was a risk factor for silicosis. Heavy smoking favors the clinical manifestation of silicosis after 20 years or more exposure to quartz containing dust.	Swaen et al. (1988)

Table 7. Retrospective cohort epidemiological studies of workers exposed to free silica

Authors, year (country)	Industry	Exposure data	Examined population	End-point of concern and results	Comments
Guénel et al. (1989 B) Denmark	stone cutting and road material industry	median and range of resp. quartz: 0.05(0.02-0.57) mg/m^3 for stone cutting and 0.16(0.02-12.7) for road material (current and past levels)	1081 skilled workers + 990 unskilled workers. Follow-up 24-30 y. Expected number from national rates, adjusted for regions.	Lung cancer incidence SIR skilled workers: 200(95% CI 149-269) for whole Denmark, or 306(95% CI 181-482) for Copenhagen; SIR for unskilled workers: 181(95% CI 116-270)	No data on smoking habits. Specification of SIR by type of stone material indicated sandstone to have higher risk than granite.
Sherson and Lander (1990) Denmark	metal foundry	no data available	5424 male foundry workers, including silicotic and non-silicotic subjects. Follow-up 18 y. Expected number from national rates.	Pulmonary tuberculosis morbidity SIR for silocotic subjects (n=155): 1000(95% CI 272-2561). SIR for non-silicotic subjects: employment <25 y: not sign; employment ≥25 y: 353(95% CI 130-768). For entire cohort the SIR: 201(95% CI 125-307).	Risk of tuberculosis is not only restricted to silicotic subjects, but also possible in non-silicotic foundry workers.

Davis et al. (1983) U.S.	granite industry	life time exposure is classified into very high (>0.15 mg/m^3); high (0.075-0.15 mg/m^3) medium (0.04-0.075 mg/m^3) low (<0.04 mg/m^3) resp. free silica	969 deceased white male workers, employed at least one year. Work during 1952-1978 compared with US white males.	Proportional mortality experience: O/E lung cancer: 1.2(95% CI 0.9-1.5) O/E total respiratory cancer: 1.3(95% CI 1.0-1.6) O/E all respiratory diseases: 1.2(95% CI 0.9-1.5) (all ratio's excluded silicosis death and tuberculosis deaths)	Other potential health hazards: noise, vibration and other abrasives. There is a dose-response relationship in the silicosis and tuberculosis deaths.
Costello and Graham (1988) U.S.	granite industry	exposure before 1940: 0.3 mg/m^3 and after 1940: 0.075 mg/m^3 respirable quartz (In 1940 started dust control activity.)	1527 deceased workers, employed during 1950-1982. 57% worked ≥15 y; 31% worked ≥30 y. Standard population all white US males. Follow up: 33 y.	Standard mortality ratio SMR lung cancer: 116(95% CI 96-139) SMR tuberculosis: 586(95% CI 468-699) SMR silicosis: 636(95% CI 456-862). A significant decrease in the SMR when workers before dust control are compared with after this activity.	100% of those dying from lung cancer had been smokers. Possible NOAEL of 0.075 mg/m^3 respirable quartz.

Finkelstein and Wilk (1990) Canada	electric arc steelmaking operation, melt shop	no data available for past exposure; current exposure: 0.1 mg/m^3 quartz, also detectable As and Cr	131 deceased workers with death certificates and work histories. Reference group from general population in Ontario.	Proportional mortality ratio PMR of workers employed in melt shop for 6 mo or more (n=23): PMR lung cancer = 361; PMR of workers never worked in the melt shop (n=108) for lung cancer is 70.	The number of participants is very small. No data on smoking habits. Possible commitment of carcinogenic metals.
Koskela et al. (1987) Finland	granite industry	quartz concentrations: drilling: 0.3-4.2 mg/m^3; block surfacing: 0.2-4.9 mg/m^3; other phases: 0.02-3.6 mg/m^3. Mean exposure time to quartz: 12 y.	1026 workers hired between 1940-1971 number of death: 235; ages: 15-72 y at time entry into cohort. Mean exposure time to quartz: 12 y. Follow-up until 1982. Comparison was made with general population.	Standardised mortality ratio For total workers: mortality to all tumors the same as in general populations (SMR=102). For lung tumors SMR = 129. Mortality for lung cancer was excessive for workers with at least 15 y since entry into granite work (O/E = 21/9.5), being highest during follow-up period of 25-29 y (O/E = 8/2.1, P <0.01).	The smoking habits are similar with other national groups at same age level. The study showed excess lung cancer in workers exposed to silica.

Neuberger et al. (1988) Austria	metal, ceramic, brick, glass and stone industry	no data available	1630 male workers born before 1930, examined in 1950-1960 and follow-up until 1980. Matched group of 1630 unexposed workers were selected from the same files.	Relative Risk of mortality Higher mortality and shorter survival for dust exposed compared to unexposed. RR lung cancer: 1.6 (exposed: 123 and unexposed 87 cases, P <0.001) RR respiratory diseases: 1.8 (P <0.0001)	No exposure data are examined. Most of the workers work in the metal industry. Possible role of carcinogenic metals.
Ng et al. (1990) Hongkong	underground workers: mine, tunnel and caison workers; surface workers: quarry and granite and crushing	no data available	1419 men from the silicosis register. Lung cancer mortality from 1980-1986 was studied. Comparison is made with male from general population.	Standard mortality ratio SMR all causes: 3.02(95% CI 2.71-3.35) SMR tuberculosis: 3.83(95% CI 1.84-7.04) SMR lung cancer: 2.03(95% CI 1.35-2.93). Risk of lung cancer deaths is related to number of years since first silica exposure and number of years worked. The highest risk occurs >30 y since first exposure.	The study is intended to examine possible risk of lung cancer in silicotic subjects. All cancer deaths were smokers. There is a dose-response relationship when the dose is expressed as duration of exposure.

median of 0.16 mg/m^3 (range 0.02-12.7) in the road and building material industry and a median of 0.05 mg/m^3 (range 0.02-0.57) in the stonecutting industry. From this study it may be concluded that long-term exposure at estimated 0.16 mg/m^3 respirable quartz dust is associated with significant increased SIR for lung cancer (as found in the road material industry workers) and at an estimated level of 0.05 mg/m^3 the SIR is not significantly increased (as found in stonecutting industry workers). There also seems to be a relationship between the SIR's due to sandstone or granite materials and the percentage of silicosis in workers, as can be observed in the following data:

	SIR	% silicosis
sandstone material	808(95% CI 323-1657)	56 (10/18)
granite material	404(95% CI 202-723)	14 (9/65)

Sandstone workers had higher SIR and also higher percentage of workers with silicosis. Sherson and Lander (1990) recently reported an increased incidence of pulmonary tuberculosis among cohorts of metal foundry workers in Denmark. No data on exposure levels were reported, but it was found that silicotic subjects had higher rates for tuberculosis of the lungs than non-silicotic subjects.

In a proportional mortality study of workers in the US granite industry (Davis et al., 1983) the authors were able to construct a dose-response relationship between exposure to respirable quartz dust and the relative risk of attaining tuberculosis or silicosis and lung cancer. The following results were presented for the relative risks:

Levels of exposure of respirable quartz (mg/m^3)*	RR of tuberculosis	RR of silicosis	RR of lung cancer

* Calculated from respectively 20, 10-20 and 5-10 mppcf.

>0.15	7.4	12.8	0.8
0.075-0.15	3.4	4.4	0.9
0.04-0.075	1.0	1.0	1.0-1.2

The results of this study make it plausible to suggest that the cut-off point lies at 0.075 mg/m^3 respirable quartz level and should be designated as the NOAEL for these effects.

Five years later the cut-off point of 0.075 mg/m^3 respirable quartz level has been further confirmed in a mortality study by Costello and Graham (1988) on Vermont granite workers, the same population as studied by Davis et al. (1983), but with the difference that they now calculated the SMR instead of the PMR and an additional 558 death certificates were found for the analysis. Adjustments were made for race, sex, age, geographic area and calender time and all white male in US were used as the standard population. There was no increased mortality related to lung cancer but the SMR's were increased for tuberculosis and silicosis (respectively 586 and 635). Important is when the SMR's were specified according to hire date, then the following was found:

	before 1930	1930-1939	1940-1949
tuberculosis	894	174	60
silicosis	999	430	95

It should be known that in 1938 hygienic control measures had been taken which lowered the level of workplace air of respirable quartz from 0.3 to 0.075 mg/m^3. This means that no increased mortality due to silicosis and lung tuberculosis was observed anymore at exposure level of 0.075 mg/m^3.

An increased mortality from lung cancer was reported by Koskela et al. (1987) in a cohort study on granite industry workers in Finland. The study comprised of 1026 workers hired between 1940 and 1971, the number of person-years was

20165 and the number of deaths 235. During the total follow-up (until year 1982) 46 tumours were observed and 44.9 were expected. An excess mortality from tumours was observed for workers followed for 20 years or more, the greatest excess occurring during the follow-up period of 25-29 years (O/E = 11/5.2, $P < 0.05$). The excess was mainly caused by lung tumours (O/E = 8/2.1, $P < 0.01$). Data on smoking habits collected during health screening in 1970-1972 indicated similarity to those of other Finnish groups of active male workers of the same age. Data on levels of respirable quartz in workroom air indicated that the concentrations ranged from 0.02 to 4.9 mg/m^3. An increased mortality from lung cancer was also reported by other authors (Neuberger et al., 1988; Ng et al., 1990) but the level of exposure to quartz was not reported in these studies.

Of interest is the study performed by Ng et al. (1990) who were trying to relate silicotic disease to lung cancer. The lung cancer mortality from 1980 to 1986 was studied in a cohort of 1419 men taken from the silicotic register who had no previous exposure to asbestos and PAH. The 28 deaths from lung cancer were statistically in excess of the expected number (SMR 2.03, 95% CI 1.35-2.93). All lung cancer deaths were smokers. The risk of lung cancer mortality is related to the number of years since first silica exposure and the number of years worked. A prudent conclusion should be that the most of excess lung cancer mortality in silicotics is due to smoking, but a synergistic effect between smoking and silica/silicosis on the risk of lung cancer is also likely. These facts have been substantiated in a recent study (Hnizdo and Sluis-Cremer, 1991). They studied the effects of exposure to gold mining dust with high concentration of free silica and tobacco smoking on mortality from lung cancer as assessed in a sample of 2209 white South African gold miners who started mining exposure during 1936-1943, and were selected for a study of respiratory disorders in 1968-1971 when they were aged 45-54. The mortality follow up was from 1968-1971 to 1986. The concentration of respirable silica considered representative of the mining industry ranges from 0.05 to 0.84 mg/m^3 and these concentrations remained more or less unchanged since the 1930's. By means of logistic regression analysis it was estimated that the relative risk for lung cancer increased with 0.023 for each cumulative exposure of 1000 particle-years. The combined effect of dust and tobacco

smoking was better fitted by the multiplicative model than the additive model, suggesting that the two exposures act synergistically. They also found a positive association between silicosis of the hilar glands and lung cancer.

Recently Tschakert and Mühler (1990) performed a radiological study of 1200 patients with irradiated bronchogenic carcinomas, 487 of them worked as coal miners and were exposed to quartz. Of these 212 patients showed radiological signs of pulmonary silicosis. The patients with bronchogenic carcinoma and silicosis showed no significant dependence upon the grade of silicosis or working time underground concerning histology, age at disease onset, or location in comparison to people with a bronchogenic carcinoma but without silicosis.

7.3. SUMMARY

- The most important target organ in exposure to free silica by inhalation are the lungs. Exposure of experimental animals to huge amounts of silica dust in a relatively short period of duration resulted in alveolar lipoproteinosis, which indicates some similarity in effects as found in humans.
  The data from experimental animals do not give the possibility to determine the no-adverse-effect level of free silica for short-term exposure.

- Experimental animal data show that cellular and biochemical alterations in the lung lavage fluid precede other changes in the lung, and also that the intensity of silicotic process in animals is better related to the degree of quartz retention rather than to the exposure dose.
  Quartz has direct effect on the alveolar epithelial cells, it increases its permiability and causes hypertrophy of the cells. Possible involvement of cellular immunity is reported. Quartz causes airflow obstruction, emphysema and small airway lesions.

- In all long-term exposure studies on rats, whether by inhalation or intratracheal instillation, there are significant increases in the incidences of adenocarcinomas and squamous-cell carcinomas of the lung. Intratracheal instillation of quartz dust into hamsters does not induce pulmonary tumours. Inhalatory

exposure of quartz to mice does not induce tumours of the lung, although the number of animals used in the experiment is inadequate.

- Quartz is not mutagenic in Salmonella typhimurium or Escherichia coli. Quartz induces micronuclei but no sister chromatid exchanges in mammalian cells in vitro. Two samples of quartz induce transformation in Syrian hamster embryo cells in culture. Quartz does not induce micronuclei in mice in vivo.

- The available data are not adequate to evaluate the effects on reproduction of experimental animals.

- It is recognized that silica caused four different types of silicosis in humans: nodular or "pure" silicosis, mixed dust fibrosis, diatomite pneumoconiosis and alveolar lipoproteinosis.

- From the 5 case-control studies using lung cancer as the pathological end-point two studies show a statistical significant increase of the relative risk for this disease, which is about doubled the risk found in unexposed workers. This increased risk is mainly restricted to individuals with silicosis.
  A study in the Netherlands showed that although the total relative risk of lung cancer among ceramic workers regardless of the duration of employment, or the relative silica exposure, was not significantly increased, they found that the relative risks tend to increase with increasing silica exposure.

- The severity and timing of silicosis depends on a few factors, e.g. the free silica level, duration of exposure, nature of the dust, composition of the dust, additional factors like smoking habits, and complicating factors like tuberculosis and rheumatoid arthritis.

- Much information can be obtained from the retrospective cohort morbidity/mortality studies of workers occupationally exposed to free silica. There are two cohort morbidity studies and one of them shows a significant increase of the SIR for lung cancer. An analysis on the type of material to which the wor-

kers were exposed shows that the incidence ratio after exposure to sandstone is about twice that of granite. When related to the exposure level of respirable quartz, it shows that long-term exposure at estimated 0.16 mg/m^3 is associated with significantly increased incidence ratio for lung cancer and at the level of 0.05 mg/m^3 the incidence ratio is not increased anymore.

- There is a dose-response relationship between exposure to repirable quartz and the relative risk in attaining silicosis and tuberculosis, as found in a proportional cohort mortality study. The results of this study make it plausible to suggest that the cut-off point of exposure lies at 0.075 mg/m^3 and should be designated as the NOAEL for these effects. The result of this study has been further confirmed in a different study calculating the standardized mortality ratio. There is no increased mortality related to lung cancer in this cohort.

- Other cohort mortality studies reported increased mortality due to lung cancer. A study in Finland indicated exposures to quartz at levels ranging from 0.02 to 4.9 mg/m^3. The smoking habits of the cohort was similar with other groups of male workers of the same age.

- A study on the risk of lung cancer mortality in men registered as silicotic comes to the conclusion that the excess of lung cancer risk in silicotis is due to smoking, but a synergistic effect between smoking and silica/silicosis on the risk of lung cancer is also likely.

8. PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

The present MAC for quartz in the Netherlands is 0.15 mg/m^3 in the respirable range, t.w.a.-8 hours. For cristobalite and tridymite the same MAC of 0.075 mg/m^3 in the respirable range is applied. No documentation is available on the motivation behind these occupational exposure limits, the standard is probably adopted from that of the (past) ACGIH recommendation.

The ACGIH (1986) recommended a TLV of 0.10 mg/m^3 for respirable quartz, t.w.a.-8 h. The recommended limit is based on a study in 1929 in which at 9 mppcf (million particles per cubic foot) was found to be the upper limit of exposure of a group of granite workers found without silicosis. Comparison of impinger-count concentration and respirable-mass concentration shows that 9-10 mppcf of granite dust contains 0.1 mg/m^3 of respirable quartz. Accordingly a TLV of 0.1 mg/m^3 is recommended. For cristobalite as well as tridymite a TLV of 0.05 mg/m^3 in the respirable range is recommended. They are based on analogy with the threshold limit for quartz and it is also reported that the responses of these minerals to experimental animals are more severe than quartz.

The NIOSH (1974) advised an occupational exposure limit of 0.05 mg/m^3 for free silica as determined by a full-shift sample for up to a 10-hour workday, 40 hours workweek. In "free silica" are included quartz, tridymite and cristobalite. This limit is based on the same study in 1929 on granite workers as reported by ACGIH, but had been revised by the same author in 1941. Exposure control-measures resulting in lowering of airborne exposure so that only a few granite sheds exceeded 5 mppcf brings about a reduction in the prevalence of silicosis from 45% in 1937 to 15% in 1956. Confirmation of the safety limit of 5 mppcf was found in 1964, 26 years after dust control began, no cases of silicosis were found in workers employed after it. Extrapolation of the 5 mppcf impinger-count measurement into size-selective mass concentration brings about 0.05 mg/m^3 free silica in the respirable range. It is believed that free silica concentration of 0.05 mg/m^3 in air is sufficiently low to protect workers exposed to cristobalite, tridymite or microcrystalline free silica against development of silicosis, thus no separate standard for these forms of free silica is recommended.

The National Swedish Board of Occupational Standard (1987) endorsed a limit value of 0.1 mg/m^3 for quartz respirable dust and 0.05 mg/m^3 for both cristobalite and tridymite. There is no documentation for these values.

The WHO (1986) recommended a health-based occupational exposure limit of 0.04 mg/m^3 for free crystalline silica, and it should be considered as tentative. In the assessment it is declared that only the relationship between dust exposure and pneumoconiosis has to be used in determining the recommended exposure limit. The WHO explicitly maintained that a deterioration in lung function was felt to exceed the Study Group's terms of reference. The level of 0.04 mg/m^3 of the limit is based on data which indicate that no cases of silicosis occurred at average exposure to 0.03 mg/m^3 in the Vermont granite sheds.

9. EVALUATION OF HUMAN HEALTH RISKS

9.1. GROUPS AT EXTRA RISK

No specific groups at extra risk are mentioned in the literature. Taking into account the lungs as the target organ in inhalation exposure to free silica, it may be presumed that subjects suffering from chronic non-specific lung disease and people with acquired hyperreactivity of the airways should be classified as groups at extra risk.

9.2 ASSESSMENT OF HEALTH RISK

An understanding of the pathogenesis of silicosis is a prerequisite for the assessment of health risk. Silicosis is basically a nodular fibrosis of the lung. It is caused by long-term inhalation of free silica. In nature free silica is found in a variety of forms, the most important and widespread being quartz. Even in its normal state, quartz is highly silicogenic, but when heated to temperatures in excess of 1000°C it is converted into tridymite and cristobalite

The severity and manifestation of silicosis depends on a few factors, e.g. the free silica level, duration of exposure, nature of the dust, composition of the dust, additional factors like smoking habits, and complicating factors like tuberculosis and rheumatoid arthritis. The dangerous free silica particles are those with an aerodynamic diameter of less than 5 µm (also called in the respirable range), since these particles can reach the alveoli, penetrate the interstitial tissue of the lung and be phagocytosed by the lung macrophage, which collect in foci at the beginning of the lymphatic vessels of the lung. Free silica particles have a marked selective toxic effect on macrophages, which autolyse after phagocytisis. A continuous accumulation and destruction of macrophages takes place in foci of dust collection, leading to the formation of collagenous fibres and to the deposit of hyaline substance on the fibres. Most of the above mentioned data are attained from animal experimentation. On the other hand these data do not give the opportunity to determine the no-adverse-effect level of free silica.

In animal experimentation it is also shown that long-term exposure to quartz dust by inhalation or intratracheal instillation induces lung cancer in rats, but not in hamsters and probably also not in mice. It is interesting to know the difference between rats and hamsters in the induction of lung cancer after exposure to quartz. As shown in Table 4 by the experiments performed by Holland et al. (1983), exposure by intratracheal instillation at the same dose and duration produced fibrotic lesions in the exposed rats, but only minimal severity of pulmonary fibrosis was found on hamsters. Quartz is not genotoxic. It may be concluded that free silica is an epigenetic carcinogen to rats.

In the health risk assessment of exposure to free silica in humans two pathological end-points are critical, which are silicosis and lung tumour. Increased incidences of silicosis have been reported frequently and there are various data indicating increased mortality due to lung cancer in groups of workers exposed to free silica. Since both diseases affect the same organ and the fact that quartz is known to be not genotoxic, a possible link between silicosis and the lung tumour may be surmised. Three hypothesis may be proposed:

(1) free silica directly induces lung cancer
(2) free silica causes silicosis, which may be an intermediate pathologic state leading to lung cancer
(3) free silica, linked with PAH either from smoking or from the ambient working environment, acting as a co-carcinogen.

As of this moment the answer to the question is still open.

When the accumulated data on humans are stratified according to the level of exposure, then the dose-response relationship may be presented as on the next page.

The following conclusions can be made from these data:

(1) The cut-off point for silicosis lies around an exposure level of 0.075 mg/m^3 respirable quartz
(2) The cut-off point for lung cancer lies probably about 0.16 mg/m^3 respirable quartz or higher.

Level of exposure to respirable quartz (mg/m^3)	Response
0.16	Significant increased SIR for lung cancer in road material industry workers (Guénel et al., 1989)
0.02-4.9	Increased SMR for lung cancer in granite industry workers (Koskela et al., 1987)
0.05-0.84	The RR for lung cancer is 1.023 for gold mine workers (Hnizdo and Sluis-Cremer, 1991)
>0.15	The RR for silicosis is 12.8 and for lung cancer 0.8 in granite industry workers (Davis et al., 1983)
0.05	No increased SIR for lung cancer in stone cutting industry workers (Guénel et al., 1989)
0.075-0.15	The RR for silicosis is 4.4 and for lung cancer 0.9 in granite industry workers (Davis et al., 1983)
0.04-0.075	The RR for silicosis is 1.0 and for lung cancer is 1.0-1.2 in granite industry workers (Davis et al., 1983)

This means that preventive action in controlling excessive exposure to respirable quartz dust to prevent silicosis probably also prevents the induction of lung cancer caused by quartz dust.

Taking into account that the no-observed-adverse effect level of respirable quartz dust is higher than 0.075 mg/m^3 the WGD recommended a health-based occupational exposure limit of 0.075 mg/m^3 for respirable quartz, t.w.a.-8 hours. There are no epidemiological data on cristobalite and tridymite, although it is reported that the responses in experimental animals are more severe than quartz. The Dutch expert Committee on Occupational Standards has the opinion that the data are too limited to differentiate between quartz, cristobalite and tridymite.

The Committee recommends to use the same limit of 0.075 mg/m^3 for all three substances.

Referring to lung cancer as the pathological end-point and the possibility of an interaction between exposure to quartz and PAH in the induction of it, it would be presumtive to assume that smoking habits and other sources of PAH should form an extra health risk for the worker.

9.3. RECOMMENDED OCCUPATIONAL EXPOSURE LIMIT

Crystalline forms of silicon dioxide (quartz, including cristobalite and tridymite)	0.075 mg/m^3 in respirable range, TWA-8 h

10. RECOMMENDATIONS FOR RESEARCH

- Research into the interaction between smoking habits and silicosis.

- Solutions to the hypotheses whether free silica directly induces lung cancer or whether free silica causes silicosis may be an intermediate pathologic state leading to lung cancer.

- Epidemiological research on effects of cristobalite and tridymite.

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Code		*Prijs*
RA 1/80	Fosfine	*f.* 12,=
RA 2/80	Anorganisch Lood	*f.* 18,=
RA 3/80	Carcinogene stoffen	*f.* 16,=
RA 4/80	Tolueen Diisocyanaat	*f.* 7,=
RA 5/80	Cadmium	*f.* 16,=
RA 6/80	Chloor	*f.* 13,=
RA 1/81	n-Heptaan	*f.* 11,=
RA 2/81	Pentaan	*f.* 9,=
RA 3/81	1,1,1-Trichloorethaan	*f.* 18,=
RA 4/81	Formaldehyde niet meer verkrijgbaar (zie RA 3/87)	
RA 5/81	Metallisch Kwik	*f.* 13,=
RA 1/82	Mangaan	*f.* 17,=
RA 2/82	Monochloorethaan	*f.* 11,=
RA 3/82	Anorganische Kwikzouten	*f.* 15,=
RA 4/82	Organische Kwikverbindingen *(Uitsluitend phenylkwik en alkoxyalkylverb.)*	*f.* 13,=
RA 5/82	Kwikalkylverbindingen - Korte keten *(Uitsluitend methylkwik en ethylkwik)*	*f.* 18,=
RA 1/83	Methyleenchloride	*f.* 17,=
RA 2/83	Triethylamine	*f.* 16,=
RA 3/83	Trichloorethyleen	*f.* 18,=
RA 1/84	Asbest	*f.* 28,=
RA 2/84	Anorganische Arseenverbindingen *(Exclusief Arseenwaterstof)*	*f.* 20,=
RA 4/84	Caprolactam	*f.* 17,=
RA 1/85	2-Nitropropaan	*f.* 12,=
RA 2/85	Lachgas	*f.* 21,=

Code		*Prijs*
RA 3/85	Nikkel en nikkelverbindingen	*f.* 21,=
RA 4/85	Zwaveldioxide	*f.* 17,=
RA 5/85	Stikstofdioxide	*f.* 15,=
RA 6/85	Chroom en chroomverbindingen	*f.* 20,=
RA 1/86	Epichloorhydrine	*f.* 19,=
RA 1/87	1,4-Dioxaan	*f.* 13,=
RA 2/87	Hydrazine, dimethylhydrazine, hydroxyethyl-hydrazine en fenylhydrazine	*f.* 21,=
RA 3/87	Formaldehyde *(Engelse uitgave)*	*f.* 22,=
RA 4/87	4,6-Dinitro-ortho-cresol	*f.* 13,=
RA 5/87	Dibroomethaan	*f.* 13,=
RA 6/87	Aflatoxine B1, B2, G1 en G2	*f.* 16,=
RA 7/87	Chloroform	*f.* 18,=
RA 8/87	1,1-Dichloorethaan	*f.* 9,=
RA 9/87	Trimethylamine	*f.* 13,=
RA 10/87	Vanadium metaal en anorganische verbindingen	*f.* 16,=
RA 11/87	n-Hexaan	*f.* 21,=
RA 12/87	2-Propoxyethanol, 2-Propoxyethylacetate, 2-Isopropoxyethanol *(Engelse uitgave)*	*f.* 9,=
RA 13/87	Acrilaten	*f.* 13,=
RA 14/87	Trichlorofluoromethane *(Engelse uitgave)*	*f.* 16,=
RA 15/87	Fluorcarbons(except FC11) *(Engelse uitgave)*	*f.* 21,=
RA 1/88	Para-Dichloorbenzeen	*f.* 15,=
*** RA 2/88	Hexachlorobenzene	*f.* 24,=
RA 3/88	Carbonylfluoride and PTFE Pyrolysis products	*f.* 11,=
RA 4/88	Beryllium and Beryllium compounds	*f.* 22,=
RA 1/89	Fluorine, Hydrogenfluorine and Inorganic fluorine compounds	*f.* 22,=
RA 2/89	Aniline	*f.* 17,=

Code		*Prijs*
RA 3/89	Phtalic anhydride	*f.* 12,=
RA 4/89	Ethyl Methanesulphonate (EMS) Methyl Methanesulphonate (MMS)	*f.* 22,=
RA 5/89	Benzeen *	*f.* 10,=
RA 6/89	Ethyleenoxide *	*f.* 13,=
RA 7/89	Selenium en verbindingen *	*f.* 18,=
RA 8/89	Styreen *	*f.* 17,=
RA 9/89	Evaluatie van risico op kanker bij beroepshalve blootstelling aan asbest (aanvullend op RA 1/84) *	*f.* 12,=
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RA 2/90	2-Hexanone	*f.* 17,=
RA 3/90	Cyclohexanol	*f.* 16,=
RA 4/90	Amyl acetate	*f.* 11,=
RA 5/90	1,3-Butadiene	*f.* 17,=
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RA 2/92	Nitrous oxide (Lachgas)	*f*.
RA 3/92	Gasoline	*f*.
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