SILICA DUST, CRYSTALLINE, IN THE FORM OF QUARTZ OR CRISTOBALITE

Silica was considered by previous IARC Working Groups in 1986, 1987, and 1996 (IARC, 1987a, b, 1997). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Silica, or silicon dioxide (SiO_2), is a group IV metal oxide, which naturally occurs in both crystalline and amorphous forms (i.e. polymorphic; NTP, 2005). The various forms of crystalline silica are: α-quartz, β-quartz, α-tridymite, β-tridymite, α-cristobalite, β-cristobalite, keatite, coesite, stishovite, and moganite (NIOSH, 2002). The most abundant form of silica is α-quartz, and the term quartz is often used in place of the general term crystalline silica (NIOSH, 2002).

1.1 Identification of the agent

α-Quartz is the thermodynamically stable form of crystalline silica in ambient conditions. The overwhelming majority of natural crystalline silica exists as α-quartz. The other forms exist in a metastable state. The nomenclature used is that of α for a lower-temperature phase, and β for a higher-temperature phase. Other notations exist and the prefixes low- and high- are also used (IARC, 1997). The classification and nomenclature of silica forms are summarized in Table 1.1. For more detailed information, refer to the previous *IARC Monograph* (IARC, 1997).

1.2 Chemical and physical properties of the agent

Selected chemical and physical properties of silica and certain crystalline polymorphs are summarized in Table 1.1. For a detailed discussion of the crystalline structure and morphology of silica particulates, and corresponding physical properties and domains of thermodynamic stability, refer to the previous *IARC Monograph* (IARC, 1997).

1.3 Use of the agent

The physical and chemical properties of silica make it suitable for many uses. Most silica in commercial use is obtained from naturally occurring sources, and is categorized by end-use or industry (IARC, 1997; NTP, 2005). The three predominant commercial silica product categories are: sand and gravel, quartz crystals, and diatomites.

Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties

Name	CAS No.	Basic Formula	Classification	Synonyms	Properties
Silica	7631-86-9	SiO_2	α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite		Structure: crystalline, amorphous, cryptocrystalline Molecular weight: 60.1 Solubility: poorly soluble in water at 20 °C and most acids; increases with temperature and pH Reactivity: reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol
Crystalline Silica					
Cristobalite	14464-46-1		α-cristobalite, β-cristobalite		
Quartz	14808-60-7		α-quartz, β-quartz	α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Solubility: 6–11 μg/cm^3 (6–11 ppm) at room temperature; slightly soluble in body fluids Thermodynamic properties: melts to a glass; coefficient of expansion by heat—lowest of any known substance
Tripoli	1317-95-9				
Tridymite	15468-32-3		α-tridymite, β1-tridymite, β2-tridymite		

From IARC (1997), NIOSH (2002), NTP (2005)

1.3.1 Sand and gravel

Although silica sand has been used for many different purposes throughout history, its most ancient and principal use has been in the manufacture of glass (e.g. containers, flat plate and window, and fibreglass). Sands are used in ceramics (e.g. pottery, brick, and tile), foundry (e.g. moulding and core, refractory), abrasive (e.g. blasting, scouring cleansers, sawing and sanding), hydraulic fracturing applications, and many other uses. Several uses require the material to be ground (e.g. scouring cleansers, some types of fibreglass, certain foundry applications). In some uses (e.g. sandblasting, abrasives), grinding also occurs during use. For a more complete list of end-uses, refer to Table 8 of the previous *IARC Monograph* (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 121 million metric tons (Dolley, 2009). The leading producers were the USA (30.4 million metric tons), Italy (13.8 million metric tons), Germany (8.2 million metric tons), the United Kingdom (5.6 million metric tons), Australia (5.3 million metric tons), France (5 million metric tons), Spain (5 million metric tons), and Japan (4.5 million metric tons).

1.3.2 Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine), and is used extensively in both the electronics and optical components industries. Electronic-grade quartz is used in electronic circuits, and optical-grade quartz is used in windows, and other specialized devices (e.g. lasers) (IARC, 1997).

1.3.3 Diatomites

Diatomites are used in filtration, as fillers (in paint, paper, synthetic rubber goods, laboratory absorbents, anti-caking agents, and scouring powders), and as carriers for pesticides. They impart abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. Other uses include: insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, and packing material (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 2.2 million metric tons. The USA accounted for 35% of total world production, followed by the People's Republic of China (20%), Denmark (11%), Japan (5%), Mexico (4%), and France (3%) (Crangle, 2009).

1.4 Environmental occurrence

Keatite, coesite, stishovite, and moganite are rarely found in nature. The most commonly occurring polymorphs are quartz, cristobalite and tridymite, which are found in rocks and soil. These forms of silica can be released to the environment via both natural and anthropogenic sources (e.g. foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth). Some of these anthropogenic activities may cause transformation of one polymorph into another (NIOSH, 2002).

1.4.1 Natural occurrence

α-Quartz is found in trace to major amounts in most rock types (e.g. igneous, sedimentary, metamorphic, argillaceous), sands, and soils. The average quartz composition of major igneous and sedimentary rocks is summarized in Table 10 of the previous *IARC Monograph* (IARC, 1997). Quartz is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. It is the primary matrix mineral in the metalliferous veins of ore deposits, and can also be found in semiprecious stones, such as amethyst, citrine, smoky quartz, morion, and tiger's eye (IARC, 1997).

Crystalline tridymite and cristobalite are found in acid volcanic rocks. Cristobalite also occurs in some bentonite clays, and as traces in diatomite. Although rarely found in nature, coesite and stishovite have been found in rocks that equilibrated in short-lived high-pressure environments (e.g. meteoritic impact craters), and keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources (IARC, 1997).

For a more detailed description of the natural occurrence of crystalline silica and its polymorphs in air, water and soil, refer to the previous *IARC Monograph* (IARC, 1997).

1.5 Human exposure

1.5.1 Exposure of the general population

Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar. No quantitative data on potential levels of exposurem during the use of these products were available at the time of

writing (WHO, 2000). The general population may also be exposed via ingestion of potable water containing quartz particles; however, quantitative data on concentrations of quartz in potable or other forms of drinking-water were again not available (IARC, 1997; WHO, 2000).

1.5.2 Occupational exposure

Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations (IARC, 1997). Table 1.2 lists the main industries and activities in which workers could be exposed to crystalline silica. Included in this table are activities that involve the movement of earth (e.g. mining, farming, construction, quarrying), disturbance of silica-containing products (e.g. demolition of masonry and concrete), handling or use of sand- and other silica-containing products (e.g. foundry processes, such as casting, furnace installation and repair; abrasive blasting; production of glass, ceramics, abrasives, cement, etc.).

Estimates of the number of workers potentially exposed to respirable crystalline silica have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupational Exposure Survey (NOES), conducted during 1981–83, and the *County Business Patterns 1986*, NIOSH estimated that about 1.7 million US workers were potentially exposed to respirable crystalline silica (NIOSH, 2002). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that more than 3.2 million workers in the then 15 Member States of the European Union during 1990–93 were considered as occupationally exposed to respirable crystalline silica above background level (Kauppinen *et al.*, 2000). Nearly 87% of these workers were employed in 'construction' (n = 2080000), 'manufacture of other non-metallic mineral products' (n = 191000), 'other mining' (n = 132000), 'manufacture of pottery, china and earthenware' (n = 96000), 'manufacture of machinery except electrical' (n = 78000), 'iron and steel basic industries' (n = 68000), 'manufacture of fabricated metal products, except machinery and equipment' (n = 68000), and 'metal ore mining' (n = 55000). The countries with the highest number of potentially exposed workers were: Germany (1 million workers), the United Kingdom (580000 workers), Spain (400000 workers), Italy (250000 workers), the Netherlands (170000 workers), France (110000 workers), and Austria (100000 workers) (Kauppinen *et al.*, 2000; Mirabelli & Kauppinen, 2005; Scarselli *et al.*, 2008).

For representative data in the main industries where quantitative exposure levels were available in the published literature and/or where major occupational health studies had been conducted, refer to the previous *IARC Monograph* (IARC, 1997). These main industries include mines and quarries, foundries and other metallurgical operations, ceramics and related industries, construction, granite, crushed stone and related industries, sandblasting of metal surfaces, agriculture, and miscellaneous other operations (IARC, 1997). Data from studies and reviews on crystalline silica exposure published since the previous *IARC Monograph* are summarized below.

(a) Levels of occupational exposure

To estimate the number of US workers potentially exposed to high levels of crystalline silica and to examine trends in exposure over time, Yassin *et al.* (2005) analysed data contained in the OSHA Integrated Management Information System (IMIS) database. After exclusion of duplicate bulk and area samples, a total of 7209 personal sample measurements collected during

Table 1.2 Main activities in which workers may be exposed to crystalline silica

Industry/activity	Specific operation/task	Source material
Agriculture	Ploughing, harvesting, use of machinery	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and non-metal, coal)	Ores and associated rock
Quarrying and related milling operations	Crushing stone, sand and gravel processing, monumental stone cutting and abrasive blasting, slate work, diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures, buildings Highway and tunnel construction Excavation and earth-moving Masonry, concrete work, demolition	Sand, concrete Rock Soil and rock Concrete, mortar, plaster
Glass, including fibreglass	Raw material processing Refractory installation and repair	Sand, crushed quartz Refractory materials
Cement	Raw materials processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production Abrasive products fabrication	Sand Tripoli, sandstone
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, moulding, glaze or enamel spraying, finishing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material
Silicon and ferro-silicon	Raw materials handling	Sand
Foundries (ferrous and non-ferrous)	Casting, shaking out Abrasive blasting, fettling Furnace installation and repair	Sand Sand Refractory material
Metal products including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand
Rubber and plastics	Raw material handling	Fillers (tripoli, diatomaceous earth)
Paint	Raw materials handling	Fillers (tripoli, diatomaceous earth, silica flour)
Soaps and cosmetics	Abrasive soaps, scouring powders	Silica flour
Asphalt and roofing felt	Filling and granule application	Sand and aggregate, diatomaceous earth
Agricultural chemicals	Raw material crushing, handling	Phosphate ores and rock
Jewellery	Cutting, grinding, polishing, buffing	Semiprecious gems or stones, abrasives
Dental material	Sandblasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concretions

From IARC, 1997

2512 OSHA inspections during 1988–2003 were analysed. The findings suggest that geometric mean crystalline silica exposure levels declined in some high-risk construction industries during the period under study, and revealed a significant decline when compared with silica exposure levels found in a previous study by Stewart & Rice (1990). Geometric mean airborne silica exposure levels among workers in the following industries were significantly lower in 1988–2003

than in 1979–87: general contractor industry (0.057 mg/m^3 versus 0.354 mg/m^3), bridge-tunnel construction industry (0.069 mg/m^3 versus 0.383 mg/m^3), and stonework masonry industry (0.065 mg/m^3 versus 0.619 mg/m^3). Silica exposures in the grey-iron industry also declined by up to 54% for some occupations (e.g. the geometric mean for "furnace operators" in 1979–87 was 0.142 mg/m^3 versus 0.066 mg/m^3 in 1988–2003). [The Working Group noted that exposure levels may not have decreased globally.]

Table 1.3 presents the more recent studies that assessed the levels of respirable crystalline silica in a range of industries and countries. Other recent exposure studies that did not measure the respirable crystalline silica components are presented below.

(b) Mines

As part of a cohort mortality study follow-up in four tin mines in China, Chen *et al.* (2006) developed quantitative exposure estimates of silica mixed dust. Workers in the original cohort were followed up from the beginning of 1972 to the end of 1994. Cumulative exposure estimates were calculated for each worker using their mine employment records and industrial hygiene measurements of airborne total dust, particle size, and free silica content collected since the 1950s. Total dust concentrations of the main job titles exposed were found to have declined from about 10–25 mg/m^3 in the beginning of the 1950s to about 1–4 mg/m^3 in the 1980s and 1990s. The respirable fraction of total dust was estimated to be 25 ± 4%, and the respirable crystalline silica concentration was estimated to be 4.3% of the total mixed mine dust

Tse *et al.* (2007) conducted a cross-sectional study to investigate the prevalence of accelerated silicosis among 574 gold miners in Jiangxi, China. Using occupational hygiene data abstracted from government documents and bulk dust data from a study in another gold mine in the region, the estimated mean concentration of respirable silica dust were reported as 89.5 mg/m^3 (range, 70.2–108.8 mg/m^3). According to government documents, the total dust concentration in underground gold mining was in the range of 102.6–159 mg/m^3 (average, 130.8 mg/m^3), and the fraction of silica in total dust was around 75.7–76.1%. No data on the proportion of respirable dust were available.

To determine dose–response relationships between exposure to respirable dust and respiratory health outcomes, Naidoo *et al.* (2006) used historical data (n = 3645) and current measurements (n = 441) to characterize exposure to respirable coal mine dust in three South African coal mines. Jobs were classified into the following exposure zones: face (directly involved with coal extraction), underground backbye (away from the coal mining face), and work on the surface. Based on the 8-hour full-shift samples collected respectively, mean respirable dust concentrations in Mines 1, 2, and 3, were as follows: 0.91 mg/m^3 (GSD, 3.39; mean silica content, 2.3%; n = 102), 1.28 mg/m^3 (GSD, 2.11; mean silica content, 1.4%; n = 63), and 1.90 mg/m^3 (GSD, 2.23; mean silica content, 2.7%; n = 73) at the face; 0.48 mg/m^3 (GSD, 2.97; mean silica content, 1.48%; n = 30), 0.56 mg/m^3 (GSD, 3.71; mean silica content, 1.35%; n = 47), and 0.52 mg/m^3 (GSD, 4.06; mean silica content, 0.9%; n = 41) in the backbye zone; and, 0.31 mg/m^3 (GSD, 3.52; mean silica content, 0.95%; n = 8), 0.15 mg/m^3 (GSD, 3.56; n = 6), and 0.24 mg/m^3 (GSD, 7.69; mean silica content, 0.64%; n = 11) in the surface zone. Based on the historical data, overall geometric mean dust levels were 0.9 mg/m^3 (GSD, 4.9), 1.3 mg/m^3 (GSD, 3.3), and 0.5 mg/m^3 (GSD, 5.6) for Mines 1, 2, and 3, respectively.

(c) Granite-quarrying and -processing, crushed stone, and related industries

Bahrami *et al.* (2008) described the personal exposure to respirable dust and respirable quartz in stone-crushing units located in western Islamic Republic of Iran. A total of 40 personal samples

Table 1.3 Respirable crystalline silica concentrations in various industries worldwide

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Mines				
Hayumbu *et al.* (2008), copper mines, the Zambia		Arithmetic mean (SD; range)		Cross-sectional dust exposure assessment; bulk and personal respirable samples; NIOSH method 0600 for gravimetric analysis of respirable dust; NIOSH method 7500 for quartz analysis of bulk and respirable samples; mean personal sampling time: 307 minutes (Mine 1) and 312 minutes (Mine 2)
	Mine 1	0.14 (0.2; 0–1.3)	101	
	Mine 2	0.06 (0.06; 0–0.3)	102	
Weeks & Rose (2006), metal and non-metal mines, USA, 1998–2002		Arithmetic mean (GM)		Mine Safety and Health Administration compliance data from 4726 mines; 8-hour full-shift personal air samples; gravimetric analysis of respirable dust; NIOSH method 7500 for silica analysis; arithmetic and geometric mean exposure calculated and classified by occupation, mine, and state
	Strip and open pit mines	0.047 (0.027)	13702	
	Mills or preparation plants	0.045 (0.027)	1145	
	Underground mines	0.050 (0.029)	1360	
	Overall	0.047 (0.027)	16207	
Bråtveit *et al.* (2003) underground small-scale mining, United Republic of Tanzania, 2001		Geometric mean (GSD)		Personal dust sampling (respirable and total dust) on 3 consecutive day shifts; sampling time varied between 5 and 8 hours; gravimetric analysis of respirable and total dust; NIOSH method 7500 for silica analysis
	Drilling, blasting, and shovelling	2.0 (1.7)	6	
	Shovelling and loading of sacks	1.0 (1.5)	3	
	Overall	1.6 (1.8)	9	
Park *et al.* (2002) diatomaceous earth mining and milling, California, USA, 1942–94	Mines and mills	Arithmetic mean 0.29 Cumulative exposure (mg/m^3–yr) 2.16	NR	Re-analysis of data from a cohort of 2342 California diatomaceous earth workers; mean concentration of respirable crystalline silica averaged over years of employment of cohort; crystalline silica content of bulk samples varied from 1–25%, and depended on process location
Mamuya *et al.* (2006) underground coal mining, United Republic of Tanzania; June–August 2003 and July–August 2004		Geometric mean (GSD)		Personal dust samples collected during two periods in 2003 and 2004; 134 respirable dust samples collected and analysed gravimetrically; 125 samples analysed for quartz using NIOSH method 7500
	Development team	0.073 (11.1)	56	
	Mine team	0.013 (2.97)	45	
	Transport team	0.006 (1.84)	11	
	Maintenance team	0.016 (11.05)	13	
	Overall	0.027 (8.18)	125	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Granite-quarrying and -processing, crushed stone, and related industries				
Wickman & Middendorf (2002) Granite–quarrying, Georgia, USA; May 1993–February 1994	Granite sheds	Arithmetic mean (SD) 0.052 (0.047)	40	Exposure assessment surveys in 10 granite sheds to measure compliance; full-shift respirable dust samples in workers' breathing zone and area samples; gravimetric analysis of respirable dust; crystalline silica analysis using OSHA ID 142; TWA exposures calculated
Brown & Rushton (2005a) Industrial silica sand, United Kingdom, 1978–2000	Quarries	Unadjusted geometric mean (GSD) 0.09 (3.9)	2429 (personal) 583 (static)	Samples collected by companies as part of routine monitoring programme; gravimetric analysis; silica content measured by Fourier transform infrared spectrophotometry until 1997 and by X-ray diffraction thereafter; personal and static measurements combined into one data set
Gottesfeld *et al.* (2008) Stone–crushing mills, India, 2003 (initial phase), 2006 and 2007 (post-implementation of engineering controls)		Arithmetic mean (SD)		Bulk and personal air samples collected; silica analysis using NIOSH method 7500; NIOSH method 0500 for respirable particulates used in 2003
	Prior to water-spray controls (2003)	Cristobalite, 0.09 (0.08)	[5]	
		Quartz, 0.25 (0.12)	[5]	
	After water-spray controls			
	Monsoon season (winter 2007)	Cristobalite, 0.02 (0.01)	[18]	
		Quartz, 0.01 (0.01)	[18]	
	Dry season (summer 2006)	Cristobalite, 0.03 (0.03)	[27]	
		Quartz, 0.06 (0.12(	[27]	
Yingratanasuk *et al.* (2002) Stone carvers, Thailand, 1999–2000		Arithmetic mean	148 (total number of samples)	Cross-sectional study design; full-shift (8-hour) personal dust samples; respirable dust analysed gravimetrically; silica analysis by infrared spectrophotometry
	Carvers (Site 1)	0.22		
	Pestle makers (Site 1)	0.05		
	Mortar makers (Site 2)	0.05		
	Mortar makers (Site 3)	0.88		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Rando *et al.* (2001) Industrial sand industry, North America, 1974–98	Sand-processing plants	Geometic mean 0.042 (overall)	14249	Exposure estimates created for a longitudinal and case-referent analysis of a cohort of industrial sand workers; gravimetric analysis of total dust; silica analysis by X-ray diffraction spectroscopy
Yassin *et al.* (2005) Stonework masonry, USA, 1988–2003	All occupations	Geometric mean (GSD) 0.065 (0.732)	274	Analysis of personal silica measurements (n = 7209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
Foundries				
Andersson *et al.* (2009) Iron foundry, Sweden, April 2005–May 2006		Geometric mean (GSD)		Respirable dust, quartz, cristobalite, trydimite samples collected on 2 consecutive workdays for shift and daytime workers; gravimetric analysis conducted using modified NIOSH method; respirable quartz and cristobalite analysed using modified NIOSH method 7500
	Caster	0.020 (1.8)	22	
	Core Maker	0.016 (2.3)	55	
	Fettler	0.041 (2.9)	115	
	Furnace and ladle repair	0.052 (3.7)	33	
	Maintenance	0.021 (2.6)	26	
	Melter	0.022 (2.0)	49	
	Moulder	0.029 (2.6)	64	
	Sand mixer	0.020 (2.3)	14	
	Shake out	0.060 (1.7)	16	
	Transportation	0.017 (2.6)	13	
	Other	0.020 (2.0)	28	
	All occupations	0.028 (2.8)	435	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Yassin *et al.* (2005) Grey–iron foundry, USA 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Spruer	0.154 (0.100)	22	
	Hunter operator	0.093 (1.144)	10	
	Charger	0.091 (0.999)	8	
	Core maker	0.078 (1.033)	89	
	Grinder	0.075 (0.821)	371	
	Molder	0.073 (0.910)	308	
	Abrasive blast operator	0.070 (0.821)	56	
	Sorter	0.067 (0.827)	23	
	Reline cupola	0.067 (0.725)	29	
	Furnace operator	0.066 (0.766)	47	
	Core setter	0.066 (0.671)	23	
	Craneman	0.066 (0.815)	16	
	Cleaning department	0.060 (0.879)	36	
	Inspector	0.057 (1.298)	21	
	Ladle repair	0.055 (0.829)	30	
Other metallurgical operations				
Føreland *et al.* (2008) Silicon carbide industry, Norway, November 2002–December 2003		Geometric mean	720 (total)	Exposure survey conducted in 3 silicon carbide plants; measurements collected to improve previously developed job–exposure matrix; sampling duration close to full shift (6–8 hours); 2 sampling periods of 2 work weeks; gravimetric analysis of respirable dust; silica analysis using modified NIOSH method 7500
	Cleaning operators (Plant A)	0.020 (quartz)		
	Mix operators (Plants A and C), charger/ mix and charger operators (Plant C)	0.008–0.013 (quartz)		
	All other jobs (Plants A, B and C)	< 0.005 (quartz)		
	Charger/mix operators (Plant C)	0.038 (cristobalite)		
Construction				
Tjoe-Nij *et al.* (2003) Construction, the Netherlands		Geometric mean (GSD)		Cross-sectional study design; repeated dust measurements (n = 67) on 34 construction workers; full-shift (6–8 hours) personal respirable dust sampling; gravimetric analysis of respirable dust; silica analysis by infrared spectroscopy (NIOSH method 7602); 8-h TWA concentrations calculated
	Concrete drillers and grinders	0.42 (5.0)	14	
	Tuck pointers	0.35 (2.8)	10	
	Demolition workers	0.14 (2.7)	21	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Akbar-Khanzadeh & Brillhart (2002) Construction, USA	Concrete–finishing (grinding)	Arithmetic mean (SD) 1.16 (1.36)	49	Task-specific silica exposure assessment conducted as part of an OSHA Consultation Service in Ohio; gravimetric analysis of respirable samples using NIOSH method 0600; silica analysis using in-house method based on NIOSH method 7500 and OSHA ID 142
Verma *et al.* (2003)	Labourers Operating engineers Carpenters, iron workers, masons, painters, terrazzo workers	Range (min–max) 0.10–0.15 0.04–0.06 below detectable limits	 20 3 17	Task-based exposure assessment conducted as part of an epidemiological study of Ontario construction workers; personal dust sampling and direct-reading particulate monitoring; gravimetric analysis of respirable dust using modified NIOSH method 0600; respirable silica analysis using modified NIOSH method 7500
Woskie *et al.* (2002) Heavy and highway construction, USA	Labourers Miscellaneous trade Operating engineers	Geometric mean (GSD) 0.026 (5.9) 0.013 (2.8) 0.007 (2.8)	 146 26 88	Personal samples collected using the Construction Occupational Health Program sampling strategy; particulate samples analysed gravimetrically; quartz analysed by Fourier transform infrared spectrophotometry; duration of sampling—6 hours of an 8-hour working day
Flanagan *et al.* (2003) Construction, USA, August 2000–January 2001	Clean-up, demolition with hand-held tools, concrete cutting, concrete mixing, tuck-point grinding, surface grinding, sacking and patching concrete, and concrete-floor sanding	Geometric mean (GSD) 0.11 (5.21)	 113	Respirable samples analysed gravimetrically using NIOSH method 0600; silica analysed by Fourier transform infrared spectrophotometry using NIOSH method 7602
Lumens & Spee (2001) Construction, the Netherlands	Recess miller Demolition worker Inner wall constructor Overall	Geometric mean (GSD) 0.7 (3.3) 1.1 (4.0) 0.04 (2.6) 0.5 (5.6)	 53 82 36 171	Personal air samples collected during field study at 30 construction sites; duration of sampling 3 to 4 hours; gravimetric analysis of respirable dust samples; silica analysis using NIOSH method 7500

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Flanagan *et al.* (2006) Construction, USA, 1992–2002	Abrasive blasters, surface and tuck point grinders, jackhammers, rock drills	Geometric mean (GSD) 0.13 (5.9)	1374	Personal silica measurements collected as part of a silica-monitoring compilation project; data provided by 3 federal or state regulatory agencies (n = 827 samples), 6 university or research agencies (n = 491), and 4 private consultants or contractors (n = 134)
Akbar-Khanzadeh *et al.* (2007) Construction, USA	Uncontrolled conventional grinding Wet grinding Local exhaust ventilation grinding	Arithmetic mean 61.7 0.896 0.155	5 sessions 7 sessions 6 sessions	Personal samples collected during grinding operations in a controlled field laboratory to evaluate the effectiveness of wet grinding and local exhaust ventilation; samples collected and analysed using NIOSH methods 0600 and 7500
Bakke *et al.* (2002) Construction, Norway, 1996–99	Tunnel workers	Geometric mean (GSD) α-Quartz, 0.035 (5.0)	299	Personal samples collected as part of exposure survey; sampling duration: 5 to 8 h; respirable dust analysed gravimetrically; silica analysed by NIOSH method 7500
Linch (2002) Construction, USA, 1992–98	Abrasive blasting of concrete structures Drilling concrete highway pavement Concrete-wall grinding Concrete sawing Milling of asphalt	TWA (8-hour) 2.8 3.3 0.26 10.0 0.36		Personal samples collected as part of NIOSH effort to characterize respirable silica exposure in construction industry; respirable dust collected and analysed according to NIOSH method 0600; silica analysed by NIOSH method 7500
Meijer *et al.* (2001) Construction, USA, 1992–93	Concrete workers	Arithmetic mean 0.06	96	Personal samples of respirable dust and silica; gravimetric analysis of respirable dust; silica analysed by infrared spectrophotometry
Miscellaneous operations				
Hicks & Yager (2006) Coal-fired power plants, USA	Normal production activities	Arithmetic mean 0.048	108	Personal breathing zone samples collected during normal full shifts and analysed by NIOSH method 7500

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Shih *et al.* (2008) Furnace relining, Taiwan, China		Arithmetic mean		Exposures measured in a municipal waste incinerator during annual furnace relining; respirable dust collected and analysed by NIOSH method 0600; silica analysed by NIOSH method 7500
	Sandblasting	0.578	7	
	Bottom-ash cleaning	0.386	8	
	Wall demolishing	0.116	8	
	Relining	0.041	10	
	Grid repairing	0.042	14	
	Scaffold establishing	0.040	8	
	Others	0.082	8	
Zhuang *et al.* (2001) Pottery factories and metal mines, China, 1988–89		Arithmetic mean		Special exposure survey conducted to compare results obtained from traditional Chinese samplers with nylon cyclones; gravimetric analysis of cyclone samples; silica analysis using X-ray diffraction
	Pottery factories	0.116	54	
	Iron/copper mines	0.017	23	
	Tin mines	0.097	10	
	Tungsten mines	0.101	56	
Yassin *et al.* (2005) Several industries, USA, 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Soap and other detergents	0.102 (0.757)	6	
	Testing laboratories services	0.099 (0.896)	53	
	Cut stone and stone products	0.091 (0.956)	405	
	General contractors	0.091 (0.900)	28	
	Coating engraving	0.075 (0.839)	75	
	Grey–iron foundries	0.073 (0.877)	1 760	
	Concrete work	0.073 (0.705)	94	
	Manufacturing explosives	0.070 (0.841)	9	
	Bridge-tunnel construction	0.070 (0.827)	91	
	Stonework masonry	0.065 (0.732)	274	
	Overall	0.073 (0.919)	7209	

GM, geometric mean; GSD, geometric standard deviation; IMIS, Integrated Management Information System; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA; SD, standard deviation

and 40 area samples were collected and analysed by X-ray diffraction. Personal samples were collected after the installation of local exhaust ventilation, and area samples were collected inside the industrial units before (n = 20) and after (n = 20) the installation of local exhaust ventilation. Personal samples were collected from process workers (n = 12), hopper workers (n = 8), drivers (n = 11), and office employees (n = 9). Personal concentrations of respirable dust were as follows: process workers, 0.21 mg/m^3; hopper workers, 0.45 mg/m^3; and, drivers, 0.20 mg/m^3. Personal concentrations of respirable quartz were as follows: process workers, 0.19 mg/m^3; hopper workers, 0.40 mg/m^3; and, drivers, 0.17 mg/m^3. Based on the area samples, the average levels of total dust and respirable dust were 9.46 mg/m^3 and 1.24 mg/m^3, respectively. The amount of free silica in the stone was 85–97%.

Golbabaei *et al.* (2004) measured TWA concentrations of total dust, respirable dust, and crystalline silica (α-quartz) in a marble stone quarry located in the north-eastern region of the Islamic Republic of Iran. Full-shift (2 × 4-hour samples) personal breathing zone samples were collected and analysed using gravimetric and X-ray diffraction methods. The highest levels of total and respirable dust exposure were observed for workers in the hammer drill process area (107.9 mg/m^3 and 11.2 mg/m^3, respectively), and the cutting machine workers had the lowest levels of exposure (9.3 mg/m^3 and 1.8 mg/m^3, respectively). The highest concentrations of α-quartz in total and respirable dust were measured in hammer drill process workers (0.670 mg/m^3 and 0.057 mg/m^3, respectively).

In a NIOSH-conducted cohort mortality study of workers from 18 silica sand plants, Sanderson *et al.* (2000) estimated historical quartz exposures using personal respirable quartz measurements (collected during 1974–96) and impinger dust samples (collected in 1946). During 1974–96, a total of 4269 respirable dust samples were collected from workers performing 143 jobs at these 18 plants. Respirable quartz concentrations ranged from less than 1 to 11700 μg/m^3, with a geometric mean concentration of 25.9 μg/m^3. Over one-third of the samples exceeded the Mine Safety and Health Administration permissible exposure limit value for quartz (PEL, 10 mg/m^3/(%quartz + 2)), and half of the samples exceeded the NIOSH recommended exposure limit [at the time] (REL, 0.050 mg/m^3). Quartz concentrations varied significantly by plant, job, and year and decreased over time, with concentrations measured in the 1970s being significantly greater than those measured later.

(d) Foundries

Lee (2009) reported on exposures to benzene and crystalline silica during the inspection of a foundry processing grey and ductile iron. The facility consisted of two buildings: the main foundry where moulding, core-making, metal pouring, and shakeout took place; and, the finishing part of the site where grinding and painting was done. Personal sampling for crystalline silica was conducted in the grinding area, in casting shakeout, and in both the mould- and core-making operations. Eight-hour TWA concentrations of crystalline silica were in the range of 2.11–4.38 mg/m^3 in the grinding area (n = 4), 1.18–2.14 mg/m^3 in the shakeout area (n = 2), and 1.15–1.63 mg/m^3 in the core-maker area (n = 2). The 8-hour TWA concentration in the mould area was 0.988 mg/m^3.

(e) Construction

In a study of cement masons at six commercial building sites in Seattle, WA, USA, Croteau *et al.* (2004) measured personal exposures to respirable dust and crystalline silica during concrete-grinding activities to assess the effectiveness of a commercially available local exhaust ventilation (LEV) system. Levels were measured with and without LEV, one sample directly after the other. A total of 28 paired

samples were collected. The results showed that the application of LEV resulted in a mean exposure reduction of 92%, with the overall geometric mean respirable dust exposure declining from 4.5 to 0.14 mg/m^3. However, approximately one quarter of the samples collected while LEV was being used were greater than the OSHA 8–hour TWA PEL (22% of samples), and the American Conference of Governmental Industrial Hygiene (ACGIH) threshold limit value (26%) for respirable crystalline silica.

Rappaport *et al.* (2003) investigated exposures to respirable dust and crystalline silica among 80 workers in four trades (bricklayers, painters (when abrasive blasting), operating engineers, and labourers) at 36 construction sites in the Eastern and Midwestern USA. A total of 151 personal respirable air samples were collected and analysed using gravimetric and X-ray diffraction methods. Painters had the highest median exposures for respirable dust and silica (13.5 and 1.28 mg/m^3, respectively), followed by labourers (2.46 and 0.350 mg/m^3), bricklayers (2.13 and 3.20 mg/m^3), and operating engineers (0.720 and 0.075 mg/m^3). The following engineering controls and workplace characteristics were found to significantly affect silica exposures: wet dust suppression reduced labourers' exposures by approximately 3-fold; the use of ventilated cabs reduced operating engineers' exposures by approximately 6-fold; and, working indoors resulted in a 4-fold increase in labourers' exposures.

(f) Agriculture

Archer *et al.* (2002) assessed the exposure to respirable silica of 27 farm workers at seven farms in eastern North Carolina, USA. Four-hour personal breathing zone samples (n = 37) were collected during various agricultural activities and analysed for respirable dust, respirable silica, and percentage silica using gravimetric and X-ray diffraction methods. The overall mean respirable dust, respirable silica, and percentage silica values were 1.31 mg/m^3 (n = 37), 0.66 mg/m^3 (n = 34), and 34.4% (n = 34), respectively. The highest respirable dust and respirable silica concentrations were measured during sweet potato transplanting (mean, 7.6 and 3.9 mg/m^3, respectively; n = 5), and during riding on or driving an uncabbed tractor (mean, 3.1 and 1.6 mg/m^3, respectively; n = 13).

Nieuwenhuijsen *et al.* (1999) measured personal exposure to dust, endotoxin, and crystalline silica during various agricultural operations at ten farms in California, USA, between April 1995 and June 1996. A total of 142 personal inhalable samples and 144 personal respirable samples were collected. The highest levels of inhalable dust exposure were measured during machine-harvesting of tree crops and vegetables (GM, 45.1 mg/m^3 and 7.9 mg/m^3, respectively), and during the cleaning of poultry houses (GM, 6.7 mg/m^3). Respirable dust levels were generally low, except for machine-harvesting of tree crops and vegetables (GM, 2.8 mg/m^3 and 0.9 mg/m^3, respectively). The percentage of crystalline silica was higher in the respirable dust samples (overall, 18.6%; range, 4.8–23.0%) than in the inhalable dust samples (overall, 7.4%; range, not detectable to 13.0%).

(g) Miscellaneous operations

Harrison *et al.* (2005) analysed respirable silica dust samples (n = 47) from several Chinese workplaces (three tungsten mines, three tin mines, and nine pottery mines) to determine the effect of surface occlusion by alumino-silicate on silica particles in respirable dust. The average sample percentages of respirable-sized silica particles indicating alumino-silicate occlusion of their surface were: 45% for potteries, 18% for tin mines, and 13% for tungsten mines.

To provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer, 't Mannetje *et al.* (2002) conducted a pooled analysis of existing quantitative exposure data for ten cohorts exposed to silica

(US diatomaceous earth workers; Finnish and US granite workers; US industrial sand workers; Chinese pottery workers, and tin and tungsten miners; and South African, Australian, and US gold miners). Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligrams per cubic metre (mg/m^3) respirable crystalline silica. The median of the average cumulative exposure to respirable crystalline silica ranged from 0.04 mg/m^3 for US industrial sand workers to 0.59 mg/m^3 for Finnish granite workers. The cohort-specific median of cumulative exposure ranged from 0.13 mg/m^3–years for US industrial sand workers to 11.37 mg/m^3–years for Australian gold miners.

In a cross-sectional survey, Hai *et al.* (2001) determined the levels of respirable nuisance and silica dusts to which refractory brickworkers were exposed at a company in Ha Noi, Viet Nam. Respirable dust levels were in the range of 2.2–14.4 mg/m^3 at nine sample sites. The estimated free silica content of dust was 3.5% for unfired materials at the powder collectors (n = 8 samples), and 11.4% in the brick-cleaning area following firing (n = 1 sample).

Burgess (1998) investigated processes associated with occupational exposure to respirable crystalline silica in the British pottery industry during 1930–1995, and developed a quantitative job–exposure matrix. Exposure estimates were derived from 1390 air samples, the published literature, and unpublished reports of dust control innovations and process changes. In the matrix, daily 8-hour TWA airborne concentrations of respirable crystalline silica ranged from 0.002 mg/m^3 for pottery-support activities performed in the 1990s to 0.8 mg/m^3 for firing activities in the 1930s. Although exposure estimates within decades varied, median concentrations for all process categories displayed an overall trend towards progressive reduction in exposure during the 65 year span.

2. Cancer in Humans

2.1 Cancer of the lung

In the previous *IARC Monograph* (IARC, 1997) not all studies reviewed demonstrated an excess of cancer of the lung and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results had been expected. However, overall, the epidemiological findings at the time supported an association between cancer of the lung and inhaled crystalline silica (α-quartz and cristobalite) resulting from occupational exposure.

The current evaluation has a primary focus on studies that employed quantitative data on occupational exposures to crystalline silica dust (α-quartz and cristobalite). The establishment of exposure–response relationships not only provides critical evidence of causation, but the availability of quantitative exposures on crystalline silica and other exposures of relevance facilitates the accurate assessment of exposure–response relationships in the presence of potential confounders. In addition to the focus on quantitative exposure–response relationships, a summary of findings from eight published meta-analyses of lung cancer was also elaborated. Of these, the seven meta-analyses involving absolute risk summarize the information from the many studies that did not consider quantitative exposure–response relationships, while the eighth is a meta-analysis of exposure-response.

Findings from cohort studies are given in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.1.pdf, and those for the case–control studies are provided in Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.2.pdf. Given that there was concern by the previous IARC Working Group that different exposure settings (including the nature of the industry and the crystalline silica polymorph) may give rise to different (or

no) cancer risks, this evaluation is divided into sections based on the industrial setting where exposure to silica occurs. As with other evaluations, data from community-based studies are not included, although studies of persons with silicosis are.

2.1.1 Diatomaceous earth

Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of US diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment (Checkoway *et al.*, 1993). Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed (Checkoway *et al.*, 1996). Those with uncertain asbestos exposures were omitted from the analysis leading to the loss of seven lung cancer deaths. Among those with no asbestos exposure, the lung cancer standardized mortality ratios (SMR) for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest exposure groups, although they were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue. Checkoway *et al.* (1997) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respirable crystalline silica exposures (Table 2.1 online). The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated. Trends for both unlagged and lagged exposure–response were of borderline significance. Rice *et al.* (2001) used the same cohort to examine risk, assessing the relationship between lung cancer mortality and respirable crystalline silica exposure using a variety of models. All except one model demonstrated statistical significance, and the trends of the predicted rate ratios with cumulative crystalline silica exposure were generally similar across models.

A small cohort study among Icelandic diatomaceous earth workers (Rafnsson & Gunnarsdóttir, 1997) provided findings that supported an effect of crystalline silica on lung cancer risk (SIR, 2.34; 95%CI: 0.48–6.85 for those who had worked 5 or more years). Smoking habits among the workers were reported to be similar to the general population.

2.1.2 Ore mining

Steenland & Brown (1995) updated a cohort of US gold miners previously studied (McDonald *et al.*, 1978; Table 2.1 online). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure–response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated. In contrast, tuberculosis and silicosis mortality was elevated and exhibited an exposure–response relationship with crystalline silica exposure.

Gold miners were investigated in a South African cohort study (Hnizdo & Sluis-Cremer, 1991) and in case–control studies nested within that cohort study and within another South African gold miner cohort (Reid & Sluis-Cremer, 1996; Tables 2.1 and 2.2 online). In the Hnizdo & Sluis-Cremer, (1991) cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area–years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure–response in both case–control studies: RR, 1.12; 95%CI: 0.97–1.3 for Reid & Sluis-Cremer (1996),

and lung cancer mortality was elevated in the highest exposure group adjusting for smoking in the Hnizdo *et al.* (1997) study. [In this study, exposure to uranium did not confound the results.] [The Working Group noted the potential for confounding from radon, and also noted that the South African cohorts might overlap.]

McLaughlin *et al.* (1992) undertook a nested case–control study of lung cancer among the members of a prior cohort study by Chen *et al.* (1992) (Table 2.2 online). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure–response relationship with the quantitative measures of crystalline silica cumulative exposure. The tin miners underwent further follow-up in a cohort study (Chen *et al.*, 2006) and a nested case–control study (Chen & Chen, 2002). Although the cohort study findings provided some overall indication of elevated lung cancer exposure–response mortality with cumulative dust exposure (Table 2.1 online), the findings were much less clear when presented by mine and silicosis status. In the nested case–control study (Table 2.2 online), there was evidence of exposure–response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etiological factor unclear. The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by Cocco *et al.* (2001), and were confirmed by Chen *et al.* (2007) adjusting for smoking and other confounding factors. Here, no relationship of lung cancer mortality with cumulative crystalline silica exposure was noted for the tungsten mines, nor was any evidence for the iron and copper mines adjusting for radon. [The Working Group noted that crystalline silica exposures were very low in the iron and copper mines.] For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polyaromatic hydrocarbons (PAHs), and radon, no exposure–response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor. This was especially true when the iron/copper mines were removed for reason of having poorer data, when the trend tended towards lower risk with increasing crystalline silica exposure.

Carta *et al.* (2001) examined 724 compensated silicotics with radiographic indication of 1/0 or greater small opacities on the International Labor Organization scale who had worked at Sardinian lead and zinc mines, brown coal mines, and granite quarries. Using quantitative estimates of cumulative exposure to respirable crystalline silica dust and radon, the exposure–response was studied in a cohort study and a nested case–control study of 34 lung cancer cases (Tables 2.1 and 2.2 online). Little evidence of a trend with crystalline silica exposure was observed in either study component (after controlling for smoking, airflow obstruction, radon, and severity of silicosis in the case–control study). A clear relationship emerged with exposure to radon in the case–control study. [The Working Group noted that this study was small.]

2.1.3 Ceramics

A case–control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure–response was seen in the three higher exposure categories (McLaughlin *et al.*, 1992; Table 2.2 online). This study was nested within the cohort analysis by Chen *et al.* (1992). Although reported exposure to asbestos was to be minimal, the workers were exposed to PAHs, and in a separate analysis

there were non-significant elevations in lung cancer risk with increasing cumulative exposure to PAHs. This was confirmed in the follow-up analysis by Chen *et al.* (2007) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (95%CI: 1.02–1.12) dropping to 1.0 (95%CI: 0.96–1.09). [The Working Group noted that in the prior analysis of the Chinese ceramics data by McLaughlin *et al.* (1992), adjusting for PAHs slightly raised rather than reduced the crystalline silica exposure relative risks. The correlation between the crystalline silica and PAH exposures was reported as 0.56.]

Another case–control study of pottery workers with quantitative crystalline silica dust exposures was from the United Kingdom (Cherry *et al.*, 1998). This analysis, which was restricted to ever smokers but adjusted for smoking amount and ex-smoking, showed a significantly elevated risk of lung cancer mortality with increasing average intensity of exposure, but not with cumulative exposure. No confounders, apart from smoking, were noted in this report.

Ulm *et al.* (1999) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposure was seen in the ceramic worker subset nor overall. [The Working Group noted that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.]

2.1.4 Quarries

In an extension of the Vermont granite workers study by Costello & Graham (1988), Attfield & Costello (2004) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures (Table 2.1 online). The exposures were noteworthy for being developed from environmental surveys undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk of lung cancer mortality with increasing cumulative respirable crystalline silica exposure up until the penultimate exposure group. [The Working Group noted that the findings were heavily dependent on the final exposure group; when it was included, the models were no longer statistically significant.] Graham *et al.* (2004) undertook a parallel analysis of the same data as Attfield & Costello (2004), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1998 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different.

As noted above, Ulm *et al.* (1999) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry (Table 2.2 online). The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall. [The Working Group noted

that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.] Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure. [The Working Group noted that the cohort study included only 440 individuals with 16 lung cancer cases. It was also restricted to those with silicosis, which was likely to lead to a lack of low exposures, a consequent limited exposure range, and low study power.]

Among studies that did not use quantitative estimates of crystalline silica exposure, that by Koskela *et al.* (1994) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency ($P < 0.05$). Guénel *et al.* (1989) also found an excess of lung cancer among stone workers after adjustment for smoking, but this was not the case in a study of slate workers by Mehnert *et al.* (1990).

2.1.5 Sand and gravel

Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the McDonald *et al.* (2001) cohort study of nine North American sand and gravel workers, Hughes *et al.* (2001) reported significant exposure–response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices. McDonald *et al.* (2005) examined a slightly smaller subset of the cohort described by McDonald *et al.* (2001) based on an extended update at eight of the nine plants, and also undertook a nested case–control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure ($P = 0.011$), but 15-year lagged cumulative exposures provided a slightly better fit ($P = 0.006$) (Table 2.2 online). These findings were basically similar to those obtained by Hughes *et al.* (2001) using the larger cohort and shorter follow-up time. McDonald *et al.* (2005) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer risk ($P = 0.015$).

Steenland & Sanderson (2001) studied workers in 18 sand and gravel companies in the same trade organization as the nine included in the McDonald *et al.* (2001) study (Table 2.1 online). They, too, employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry ($P < 0.06$). Further analysis using a nested case–control approach found marginal evidence of exposure–response using quartiles of cumulative exposure ($P = 0.04$), but stronger evidence with average intensity ($P = 0.003$). [The Working Group noted that a sensitivity analysis of the effect of smoking in this cohort (Steenland & Greenland, 2004) led to an adjusted overall SMR estimate of 1.43 (95% Monte Carlo limits: 1.15–1.78) compared with the original SMR of 1.60 (95%CI: 1.31–1.93). The analysis did not deal with the exposure–response estimates.]

The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by Brown & Rushton (2005b). No overall excess of lung cancer was found (although there was a large, and highly significant, variation

in lung cancer SMRs between quarries; range: 0.27–1.61, both extremes $P < 0.01$. Relative risks rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected. [The Working Group noted that Steenland (2005) commented that the low exposures in the Brown & Rushton (2005b) study was likely to have impacted its power to detect a crystalline-silica effect.]

2.1.6 Other industries

Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by Watkins *et al.* (2002) was a small case–control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure (Table 2.2 online). The second study was a nested case–control analysis of Chinese iron and steel workers (Xu *et al.*, 1996). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although the relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not for benzo[*a*]pyrene exposures, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level.

2.1.7 Semiquantitative exposure and expert-opinion studies

The studies that follow used quantitative exposure measurements in deriving crystalline silica exposure estimates for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. Hessel *et al.* (1986) undertook a case–control study of lung cancer and cumulative crystalline silica exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure–response was detected. Neither was any evidence of exposure–response detected in the later necropsy study of South African gold miners (Hessel *et al.*, 1990) that used the same approach to code the exposure data. [The Working Group noted that the study methods in the case–control study may have led to overmatching for exposure in the case–control study, and that there may have been some selection bias and exposure misclassification in the second study.]

de Klerk & Musk (1998) undertook a nested case–control analysis of lung cancer within a cohort study of gold miners and showed exposure–response for log of cumulative exposure (exposure-score–years) but not for any other index of exposure. The analysis adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure. The study by Kauppinen *et al.* (2003) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposures to PAHs, diesel exhaust, and asbestos, nor smoking. Moulin *et al.* (2000) conducted a nested case–control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure.

Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures Brüske-Hohlfeld *et al.* (2000) and Pukkala *et al.* (2005) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjustment for smoking, and in the latter study, also for social class and exposure to asbestos.

2.1.8 Pooled analysis, meta-analyses, and other studies

Steenland *et al.* (2001) reported on a case–control analysis nested within a pooled study of data from ten cohorts from a variety of industries and countries (Table 2.2 online). It included information on diatomaceous, granite, industrial sand, and pottery workers, and workers in tungsten, tin, and gold mines. Results from all of the studies had been previously published, although not all had originally employed quantitative estimates of crystalline silica exposure; and for half, the duration of follow-up had been extended. All indices of cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P < 0.0001$), and average exposure demonstrated a less significant trend ($P < 0.05$). Of these indices, log cumulative exposure led to homogeneity in findings across the cohorts ($P = 0.08$ and 0.34 for unlagged and 15-year lag respectively). Findings were similar for the mining and non-mining subgroups. No adjustment was made for smoking and other confounders, although it was noted that smoking had previously been shown not to be a major confounder in five of the ten studies. Analyses of subsets of the data omitting cohorts with suspected other confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. [The Working Group noted that the robustness in the findings to exclusion of cohorts with potential confounders from other occupational exposures indicates that any confounding in the individual studies were unlikely to have had an impact on their findings related to crystalline silica.]

The presence of silicosis in an individual is a biomarker of high exposure to crystalline silica dust. Accordingly, studies of individuals with silicosis have the potential to provide useful information on the lung cancer risk associated with exposure to crystalline silica. Three meta-analyses have focused on the risk of lung cancer among individuals with silicosis (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Lacasse *et al.*, 2005). Erren *et al.* (2009) also provide summary information in an electronic supplement to their article. Four others have looked at crystalline silica exposure (including silicosis status unknown and those without silicosis; Steenland & Stayner, 1997; Kurihara & Wada, 2004; Pelucchi *et al.*, 2006; Erren *et al.*, 2009). The number of studies included ranged from 11 in a meta-analysis focused on individuals without silicosis (Erren *et al.*, 2009) to 43 (Pelucchi *et al.*, 2006) in a study of those with and without silicosis. Reasons for this variation included: the publication date, the time period of interest, whether the study was focused on those with or without silicosis, the originating country of the studies, and analysis-specific criteria. For example, Steenland & Stayner (1997) rejected studies of miners and foundry workers on the assumption that they had the greatest potential for confounding exposures, and Smith *et al.* (1995) rejected certain studies they deemed under or overestimated the risk of lung cancer. Overall, of the total of 112 publications included by one or more of the seven meta-analyses, none were common to all analyses.

The detailed results from the seven meta-analyses are shown in Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.3.pdf. In brief, all analyses except for those devoted to categories without silicosis found an elevated lung cancer risk, whether occurring among those with silicosis or among crystalline-silica-exposed workers, or arising from cohort or case–control studies. [The Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of crystalline silica exposure, because individuals with the highest exposures tend to be omitted. Limiting the range of exposure results in reduced power to detect associations.] Overall, the rate ratios were

very similar across studies (1.74–2.76 for those with silicosis, and 1.25–1.32 for workers exposed to crystalline silica). Results from case–control studies, where there is greater opportunity to control for smoking, revealed lower rate ratios than from cohort studies in two analyses, greater rate ratios in two, and about the same in the fifth (the sixth analysis did not break the results out separately by study type). Moreover, the supplementary materials of Erren *et al.* (2009) show equal risk for crystalline silica exposure in unadjusted and smoking-adjusted studies. The two available analyses providing results on workers exposed to crystalline silica by type of study reported larger rate ratios from the case–control studies.

A further meta-analysis examined exposure–response (Lacasse *et al.*, 2009) rather than overall risk, and for this reason its findings are reported separately. The analysis included findings from ten studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increasing risk of lung cancer was observed with increasing cumulative exposure to crystalline silica above a threshold of 1.84 mg/m^3 per year. Although the overall findings were heterogeneous, they were similar to those from a subset of seven more homogeneous studies.

Many of the meta-analyses noted that a lung cancer risk was apparent either after adjusting for smoking or among non-smokers (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Kurihara & Wada, 2004; Lacasse *et al.*, 2005). Yu & Tse (2007) further explored the issue of smoking on the interpretation of the published cohort and case–control studies of crystalline silica exposure and lung cancer. In this, they examined reported SMRs and standardized incidence ratios (SIR) for lung cancer reported in ten different published studies, and concluded that the risk had been systematically underreported for never smokers. After adjustment, five of the ten SMRs and SIRs showed significant lung cancer excesses among never smokers compared to two when unadjusted, and ranged from 2.60–11.93. The SMRs and SIRs for ever smokers were reduced after adjustment for smoking, but tended to retain their statistical significance.

2.2 Other cancers

2.2.1 Cancer of the stomach

In the 40 reports with information on cancer of the stomach, 18 had relative risks > 1.0 (including three significantly elevated), and 22 with relatives risks ≤ 1.0 (including two significantly reduced).

2.2.2 Digestive, gastro-intestinal, or intestinal cancers

In the 15 reports of digestive, gastro-intestinal, or intestinal cancer, seven had relative risks > 1.0 (including one significantly elevated), and eight with reltaive risks ≤ 1.0 (two significantly reduced).

2.2.3 Cancer of the oesophagus

In the 14 reports of oesophageal cancer, five had relative risks > 1.0 (including three significantly elevated), and nine with relative risks ≤ 1.0.

Wernli *et al.* (2006) reported a hazard ratio of 15.80 (95%CI: 3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. In Chinese refractory brick workers, Pan *et al.* (1999) found not only a significant elevation with being ever exposed to crystalline silica dust (RR, 2.75; 95%CI: 1.44–5.25), but also a clear exposure–response relationship with years of exposure, adjusting for smoking and other personal factors. [The Working Group noted that confounding from exposure to PAHs could not be ruled out in the above two studies.]

Yu *et al.* (2007) reported an overall SMR for cancer of the oesophagus of 2.22 (95%CI: 1.36–3.43), and an SMR of 4.21 (95%CI: 1.81–8.30)

among caisson workers (who were noted to have had higher exposures to crystalline silica dust than non-caisson workers). The relative risk of oesophageal cancer for caisson workers with silicosis was reduced to 2.34 after adjusting for smoking and alcohol drinking. No excess risk of oesophageal cancer was observed among the non-caisson workers with silicosis after adjustment.

2.2.4 Cancer of the kidney

In the eight reports on cancer of the kidney, five had relative risks > 1.0 (including two significantly elevated), and three with relative risks ≤ 1.0. The two with significantly elevated risks provided information on exposure–response relationships with crystalline silica exposure, although neither formally evaluated this. In US sand and gravel workers (McDonald *et al.*, 2005), a non-significant negative trend with increasing crystalline silica exposure was observed. However, in Vermont granite workers (Attfield & Costello, 2004), kidney cancer SMRs increased almost monotonically with increasing exposure (except for the last exposure group), and the SMR of 3.12 in the penultimate exposure group was significantly elevated.

2.2.5 Others

There have been isolated reports of excesses in other cancers but the evidence is, in general, too sparse for evaluation. Elci *et al.* (2002) reported an excess of cancer of the larynx in workers potentially exposed to crystalline silica dust, particularly for supraglottic cancer (OR, 1.8; 95%CI: 1.3–2.3), with a significant exposure–response relationship.

2.3 Synthesis

Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk. The findings are supported by studies in these industries that lack quantitative exposures. Results from the other industry segments generally added support although some studies had potential confounding from arsenic, radon, or PAHs. In one case among Chinese tin miners, the arsenic and crystalline silica exposures were virtually collinear, and no adjustment could be made for arsenic. In another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect, and in a third, among iron and copper miners, the crystalline silica effect disappeared after adjustment for radon. In these, the role of crystalline silica exposure must be regarded as unclear. Mixed findings were reported among gold, tungsten, and lead/zinc miners.

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure–response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusions.

Cancers other than that of the lung have not been as thoroughly researched. In many cases the findings were reported in passing, in analyses focused on lung cancer, and rarely have the data examined exposure–response with crystalline silica exposure or its surrogates.

3. Cancer in Experimental Animals

No additional relevant cancer bioassays have been conducted since the previous *IARC Monograph* (IARC, 1997) except for a study in hamsters by inhalation (Muhle *et al.*, 1998), and a study in mice by intratracheal instillation (Ishihara *et al.*, 2002). Studies from the previous evaluation considered adequate are summarized below together with the new studies published since.

3.1 Inhalation exposure

See Table 3.1

3.1.1 Mouse

Female BALB/cBYJ mice exposed to crystalline silica by inhalation (Wilson *et al.*, 1986) did not have an increase in lung tumours compared to controls. Pulmonary adenomas were observed in both the silica-exposed (9/60) and the control animals (7/59). [The Working Group noted that the study groups were small (6–16 mice).]

3.1.2 Rat

Male and female F344 rats were exposed to 0 or 52 mg/m^3 of crystalline silica (Min-U-Sil) over a 24-month period. Interim removals of ten males and ten females per group were made after 4, 8, 12, and 16 months of exposure. Half of those removed were necropsied, and half were held until the end of the 24 months. None of the controls developed a lung tumour. In the silica-exposed rats, the first pulmonary tumour appeared at 494 days, and the incidence was 10/53 in females and 1/47 in males (Dagle *et al.*, 1986).

One group of 62 female F344 rats was exposed by nose-only inhalation to 12 mg/m^3 crystalline silica (Min-U-Sil) for 83 weeks. An equal number of controls was sham-exposed to filtered air, and 15 rats were left untreated. The animals were observed for the duration of their lifespan. There were no lung tumours in the sham-exposed group, and 1/15 unexposed rats had an adenoma of the lung. In the quartz-exposed rats, the incidence of lung tumours was 18/60 (Holland *et al.*, 1983, 1986; Johnson *et al.*, 1987).

Groups of 50 male and 50 female viral antibody-free SPF F344 rats were exposed by inhalation to 0 or 1 mg/m^3 silica (DQ12; 87% crystallinity as quartz) for 24 months. The rats were then held for another 6 weeks without exposure. The incidence of lung tumours in the silica-exposed rats was 7/50 males and 12/50 in females. Only 3/100 controls had lung tumours (Muhle *et al.*, 1989, 1991, 1995).

Three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by nose-only inhalation to 6.1 or 30.6 mg/m^3 DQ12 quartz for 29 days. Interim sacrifices were made immediately after the exposure and at 6, 12, and 24 months, with the final sacrifice at 34 months after exposure. The total animals with lung tumours was 0 (controls), 37/82 (low dose), and 43/82 (high dose). Many animals had multiple tumours (Spiethoff *et al.*, 1992).

3.1.3 Hamster

Groups of 50 male and 50 female Syrian golden hamsters were exposed to 0 (control) or 3 mg/m^3 DQ12 quartz (mass median aerodynamic diameter, 1.3 µm) for 18 months. The experiment was terminated 5 months later. In the silica-exposed group, 91% of the animals developed very slight to slight fibrosis in the lung, but no significant increase of lung tumours was observed (Muhle *et al.*, 1998)

Table 3.1 Studies of cancer in experimental animals exposed to crystalline silica (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size, GSD	Incidence of tumours in respiratory tract	Significance	Comments
Mouse, BALB/c BYJ (F) 150, 300 or 570 d Wilson *et al.* (1986)	0, 1.5, 1.8 or 2.0 mg/m^3 8 h/d, 5 d/wk 6–16 animals Diameter < 2.1 µm	Lung (adenomas): 7/59 (control), 9/60 (all exposed)	[NS]	
Rat, F344 (M, F) 24 mo Dagle *et al.* (1986)	0, 52 mg/m^3 6 h/d, 5 d/wk 72/sex MMAD, 1.7–2.5 µm; GSD, 1.9–2.1	Lung (epidermoid carcinomas): M–0/42 (control), 1/47 F–0/47 (control), 10/53	[NS] [$P < 0.002$]	
Rat, F344 (F) Lifespan Holland *et al.* (1983, 1986); Johnson *et al.* (1987)	0, 12 mg/m^3 6 h/d, 5 d/wk for 83 wk 62 animals MMAD, 2.24 µm; GSD, 1.75	Lung (tumours): 0/54 (control), 18/60 (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas)	[$P < 0.001$]	Nose-only inhalation exposure. Age unspecified
Rat, SPF F344 (M, F) 30 mo Muhle *et al.* (1989, 1991, 1995)	0, 1 mg/m^3 6 h/d, 5 d/wk for 24 mo 50/sex MMAD, 1.3 µm; GSD, 1.8	Lung (tumours): 3/100 (control M, F), 7/50 (M), 12/50 (F) M–1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma F–2 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours	Unspecified (M) [$P < 0.05$] (F)	
Rat, Wistar (F) Up to 35 mo Spiethoff *et al.* (1992)	0, 6.1, 30.6 mg/m^3 6 h/d, 5 d/wk for 29 d 90 animals MMAD, 1.8 µm; GSD, 2.0	0/85 (control), 37/82 (low dose), 43/82 (high dose) Multiple tumours/rat: 21 bronchiolo-alveolar adenomas, 43 bronchiolo-alveolar carcinomas, 67 squamous cell carcinomas, 1 anaplastic carcinoma	[$P < 0.0001$] (both doses)	Nose-only inhalation exposure

d, day or days; F, female; GSD, geometric standard deviation; h, hour or hours; M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NS, not significant; wk, week or weeks

3.2 Intranasal administration

3.2.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single intranasal instillation of 4 mg of synthetic *d*- or *l*-quartz. A group of 60 females received an intranasal instillation of saline. Survivors were killed at 18 months after treatment, and the incidence of lymphomas and leukaemias combined was 0/60 (controls), 2/40 (*d*-quartz), and 6/40 (*l*-quartz) (Ebbesen, 1991). [The Working Group noted that the study was not designed to detect silica-induced lung tumours, and also noted the lack of information on quartz retention.]

3.3 Intratracheal administration

See Table 3.2

3.3.1 Mouse

A group of 30 male A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg quartz for 15 weeks. A group of 20 mice received instillations of vehicle [unspecified]. Animals were killed 20 weeks after the instillations. The incidences of lung adenomas were 9/29 in the controls, and 4/20 for the silica-instilled mice, values that were not statistically different (McNeill *et al.*, 1990).

Ishihara *et al.* (2002) administered a single dose (2 mg in saline/mouse) of crystalline silica to a group of four C57BL/6N mice by intratracheal instillation to study subsequent genotoxic effects. A control group of four animals was instilled saline only. Silicotic lesions were observed in the lungs of the exposed mice, but no pulmonary neoplasms were observed after 15 months.

3.3.2 Rat

A group of 40 Sprague Dawley rats [sex unspecified] received weekly instillations of 7 mg quartz (Min-U-Sil) in saline for 10 weeks. Another groups of 40 rats received instillations of saline alone, and 20 rats remained untreated. Animals were observed over their lifespan. The incidence of lung tumours in quartz-treated rats was 6/36, 0/40 in the saline controls, and 0/18 in the untreated rats (Holland *et al.*, 1983).

Groups of 85 male F344 rats received a single intratracheal instillation of 20 mg quartz in deionized water, Min-U-Sil or novaculite, into the left lung. Controls were instilled with vehicle only. Interim sacrifices of ten rats were made at 6, 12, and 18 months with a final sacrifice at 22 months. The incidence of lung tumours in the Min-U-Sil-instilled rats was 30/67, in the novaculite-treated rats 21/72, and in controls 1/75. All of the lung tumours were adenocarcinomas, except for one epidermoid carcinoma in the novaculite-treated rats (Groth *et al.*, 1986).

Groups of male and female F344/NCr rats [initial number unspecified] received one intratracheal instillation of 12 or 20 mg quartz in saline or 20 mg of ferric oxide (non-fibrogenic dust) in saline. Interim sacrifices were made at 11 and 17 months with a final sacrifice at 26 months. There was a group of untreated controls observed at unscheduled deaths after 17 months. No lung tumours were observed in the ferric-oxide-treated rats and only one adenoma was observed in the untreated controls. The high incidences of benign and mainly malignant lung tumours observed in the quartz-treated rats is summarized in Table 3.3 (Saffiotti, 1990, 1992; Saffiotti *et al.*, 1996).

Six groups of 37–50 female Wistar rats, 15 weeks old, received either a single or 15 weekly intratracheal instillation of one of three types of quartz preparations in saline (see Table 3.4). A control group received 15 weekly instillations of saline. To retard the development of silicosis,

Table 3.2 Studies of cancer in experimental animals exposed to silica (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size	Incidence of tumours	Significance
Mouse, A/J (M) 20 wk McNeill *et al.* (1990)	0, 2.9 mg Weekly for 15 wk 30, 20 (controls) 1–5 µm (size not further specified)	Lung (adenomas): 9/29 (control), 4/20 Tumour multiplicity: 0.31 ± 0.09 (control), 0.20 ± 0.09	[NS] [NS]
Rat, Sprague Dawley (NR) Lifespan Holland *et al.* (1983)	0 (saline), 7 mg Weekly for 10 wk 40 animals 1.71 ± 1.86 µm	Lung (1 adenoma, 5 carcinomas): 0/40 (control), 6/36	[P<0.05] (carcinomas)
Rat, F344 (M) 22 mo Groth *et al.* (1986)	0, 20 mg once only 85 animals < 5 µm	Lung (adenocarcinomas): 1/75 (control), 30/67	[P<0.001]
Rat, F344/NCr (M, F) 11, 17 or 26 mo Saffiotti (1990, 1992); Saffiotti *et al.* (1996)	0, 12, 20 mg quartz Once only Ferric oxide (20 mg) was negative control [Initial number of rats, NR] 0.5–2.0 µm	High incidences of benign and mainly malignant lung tumours in quartz-treated rats reported in Table 3.3 No tumours observed in ferric oxide group One adenoma in untreated controls	NR
Rat, Wistar Lifespan Pott *et al.* (1994)	0 (saline), one single or 15 weekly injections of one of 3 types of quartz Some rats received PVNO to protect against silicosis 37–50/group	Incidences of benign and malignant lung tumours in quartz-treated rats are shown in Table 3.4 No tumours observed in saline-treated rats	NR
Hamster Syrian Golden (NR) Lifespan Holland *et al.* (1983)	0 (saline), 3, 7 mg quartz (Min-U-Sil) Once a wk for 10 wk 48/group; 68 (controls) 1.71 ± 1.86 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) Lifespan Renne *et al.* (1985)	0 (saline), 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) weekly for 15 wk 25–27/group MMAD, 5.1 µm Geometric diameter, 1.0 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) 92 wk Niemeier *et al.* (1986)	0 (saline), 1.1 (Sil-Co-Sil) or 0.7 (Min-U-Sil) mg One group received 3 mg ferric oxide 50/group 5 µm (Min-U-Sil)	No tumours in saline controls or in Sil-Co-Sil groups 1 adenosquamous carcinoma of the bronchi and lung in Min-U-Sil group and 1 benign tumour of the larynx in ferric oxide group	

M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NR, not reported; NS, not significant; PVNO, polyvinylpyridine-*N*-oxide; wk, week or weeks

Table 3.3 Incidence, numbers, and histological types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz

Treatment		Observation time	Lung tumours	
Material	**Dose**[a]		**Incidence**	**Types**
Males				
Untreated	None	17–26 mo	0/32	
Ferric oxide	20 mg	11–26 mo	0/15	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	3/18 (17%)	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	6/19 (32%)	
		17–26 mo	12/14 (86%)	
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	2/18 (11%)	5 adenomas, 14 adenocarcinomas, 1 mixed carcinoma
		Killed at 17 mo	7/19 (37%)	
		17–26 mo	7/9 (78%)	
Females				
Untreated	None	17–26 mo	1/20 (5%)	1 adenoma
Ferric oxide	20 mg	11–26 mo	0/18	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	8/19 (42%)	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	10/17 (59%)	
		17–26 mo	8/9 (89%)	
	20 mg	17–26 mo	6/8 (75%)	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, 1 epidermoid carcinoma
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	7/18 (39%)	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, 5 epidermoid carcinomas
		Killed at 17 mo	13/16 (81%)	
		17–26 mo	8/8 (100%)	

[a] Suspended in 0.3 or 0.5 mL saline

HF, hydrogen fluoride; mo, month or months

From Saffiotti (1990, 1992), Saffiotti *et al.* (1996)

Table 3.4 Incidence, numbers, and histological types of lung tumours in female Wistar rats after intratracheal instillation of quartz

Material	Surface area	No. of instillations	No. of rats examined	No. and #% of rats with primary epithelial lung tumours[a]					Other tumours[b]
	(m^2/g)	(del # × mg)		Adenoma	Adenocarcinoma	Benign CKSCT	Squamous cell carcinoma	Total (%)	
Quartz (DQ 12)	9.4	15 × 3	37	0	1z	11	1 + 1y	38	1
Quartz (DQ 12) + PVNO	9.4	15 × 3	38	0	1 + 3z	8 + 1x	4+1x+3y+1z	58	2
Quartz (DQ 12)	9.4	1 × 45	40	0	1	7	1	23	2
Quartz (Min-U-Sil)	–	15 × 3	39	1	4 + 4z	6	1+2y+2z+1y,z	54	3
Quartz (Min-U-Sil) + PVNO	–	15 × 3	35	1	2 + 1x	8	5+1x+1y+1z	57	3
Quartz Sykron (F 600)	3.7	15 × 3	40	0	3	5	3 + 1z	30	1
0.9% Sodium chloride	–	15 × 0.4 mL	39	0	0	0	0	0	5

[a] If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows: [x]adenoma; [y]adenocarcinoma; [z]benign CKSCT.

[b] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

PVNO, polyvinylpyridine-*N*-oxide; CKSCT, cystic keratinizing squamous cell tumour

From Pott *et al.* (1994)

two of the groups received injections of polyvinylpyridine-*N*-oxide. All groups of quartz-exposed rats had a significant increase in lung tumours, and the rats protected against silicosis developed more pulmonary squamous cell carcinomas than rats that were not protected (Pott *et al.*, 1994).

3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil) in saline once a week for 10 weeks. A group of 68 hamsters received saline alone, and another group of 72 hamsters were untreated. All animals were observed for their lifespan. No lung tumours were observed in any of the groups (Holland *et al.*, 1983).

Groups of 25–27 male Syrian golden hamsters, 11–weeks old, received weekly intratracheal instillation of 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) in saline for 15 weeks. Groups of 27 saline-instilled hamsters and 25 untreated controls were used as controls. Animals were observed for their lifespan. No lung tumours were observed in any group (Renne *et al.*, 1985).

Three groups of 50 male Syrian golden hamsters received weekly instillations of 1.1 mg of quartz as Sil-Co-Sil, or 0.7 mg of quartz as Min-U-Sil, or 3 mg of ferric oxide (non-fibrogenic particle) in saline for 15 weeks. A group of 50 saline-instilled hamsters served as controls. Survivors were killed at 92 weeks after the beginning of the instillations. No respiratory tract tumours were observed in the hamsters exposed to Sil-Co-Sil or in the saline controls. One adenosquamous carcinoma of the bronchi and lung was observed in the Min-U-Sil group, and one benign tumour of the larynx in the ferric-oxide-exposed group (Niemeier *et al.*, 1986).

3.4 Intrapleural and intrathoracic administration

3.4.1 Mouse

One mouse study was reported in the previous *IARC Monograph* (IARC, 1997) in which the route of exposure was via a single intrathoracic injection of tridymite. The study was only reported as an abstract, and therefore is not described here (Bryson *et al.*, 1974).

3.4.2 Rat

Two groups of 48 male and 48 female standard Wistar rats and two groups 48 male and 48 female SPF Wistar rats were given a single intrapleural injection of 20 mg alkaline-washed quartz (size, < 5 µm) in saline, and observed for their lifespan. Control rats received injections of 0.4 mL saline alone. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats [$P < 0.001$] (23 histiocytic lymphomas, five Letterer-Siwe/Hand-Schüller-Christian disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas, and six spindle cell sarcomas), and in 31/94 quartz-treated standard rats [$P < 0.001$] (30 histiocytic lymphomas and one spindle-cell sarcoma). In the SPF control animals, 8/96 rats had tumours (three lymphoblastic lymphosarcomas, five reticulum cell sarcomas), 7/85 standard rat controls had tumours (one lymphoblastic lymphosarcoma, and six reticulum cell sarcomas) (Wagner & Berry, 1969; Wagner, 1970; Wagner & Wagner, 1972). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

In a second study, with the same dosing regimen and type of quartz, 23 rats developed malignant reticuloendothelial system tumours (21 malignant lymphomas of the histiocytic type [MLHT], two thymomas, and one lymphosarcoma/thymoma/spindle cell sarcoma) in 80 male

and 80 female SPF Wistar rats after 120 weeks. In another experiment, 16 male and 16 female SPF Wistar rats dosed similarly with Min-U-Sil quartz were observed until they were moribund. Eight of the 32 rats developed MLHT and three developed thymomas/lymphosarcomas. In a last experiment with the same experimental design, 18 of 32 SPF Wistar rats that had been injected with cristobalite developed malignant lymphomas (13 MLHT and five thymomas/lymphosarcomas). No MLHT and one thymoma/lymphosarcoma tumours were observed in 15 saline-injected control rats. (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified, and that no statistics were provided.]

In one experiment, groups of 16 male and 16 female Wistar rats were given intrapleural injections of 20 mg of four types of quartz (Min-U-Sil, D&D, Snowit, and DQ12). The animals were observed for their lifespan. For all but the group treated with DQ12 quartz, there was a statistically significant increase in MLHT over saline controls (Table 3.5). In a second experiment with the same experimental design, two other strains of rats were injected Min-U-Sil (12 male and 12 female PVG rats and 20 male and 20 female Agus rats). A non-significant increase in MLHT was observed in both strains, and there was no MLHT in the saline controls. In a third experiment with the same experimental design, cristobalite was injected, and 4/32 treated Wistar rats developed MLHT [not significant], but none of the 32 saline controls did. In a final experiment, 16 male and 16 female Wistar rats were injected triolymite (size, < 0.5 μm; 0.35×10^6 particle/μg), and observed for their lifespan. A total of 16/32 Wistar rats developed MLHT, whereas no such tumours were observed in the 32 saline controls (Wagner *et al.*, 1980). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

Two groups of 36 2-month-old male Sprague-Dawley rats, received a single intrapleural injection of 20 mg DQ12 quartz in saline or saline alone, and were observed for their lifespan. Twenty-seven male rats served as untreated controls. Six malignant histiocytic lymphomas and two malignant Schwannomas were observed in the quartz-treated group [not significant], and one chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline group and untreated controls, respectively (Jaurand *et al.*, 1987).

3.5 Intraperitoneal administration

3.5.1 Rat

Two groups of 16 male and 16 female SPF Wistar rats received a single intraperitoneal injection of 20 mg of Min-U-Sil quartz in saline, and were observed for their lifespan. There were 12 saline controls [sex unspecified]. A total of 9/64 quartz-exposed rats developed malignant lymphomas (two MLHT and seven thymoma/lymphosarcomas). None of the saline controls developed MLHT, but one thymoma/lymphosarcoma was noted (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

3.6 Subcutaneous administration

3.6.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single subcutaneous injection of 4 mg of *d*- or *l*-quartz. A group of 60 female mice served as saline controls. At 18 months after injection, there was an incidence of lymphomas/leukemias of 0/60, 1/40 and 12/40 ($P < 0.001$), and of liver adenomas of 0/60, 1/40 and 3/40 for the saline controls, *d*-quartz and *l*-quartz groups, respectively. No injection-site tumours were reported (Ebbesen, 1991).

Table 3.5 Incidences of malignant lymphoma of the histiocytic type (MLHT) in Wistar rats after an intrapleural injection of 20 mg quartz/animal

Sample	No. of particles × 10^6/µg	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%)[a]
		< 1 µm	1–2 µm	2–4.6 µm		
Min-U-Sil (a commercially prepared crystalline quartz probably 93% pure)	0.59	61.4	27.9	9.1	545	11/32 (34%)b
D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz)	0.30	48.4	33.2	18.4	633	8/32 (25%)b
Snowit (commercially prepared washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%)b
DQ12 (standard pure quartz)	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	–	–	–	–	717	0 [0/32] (0%)

[a] Sex unspecified
[b] [Significantly different from controls by Fisher Exact test, $P < 0.05$]
From Wagner *et al.* (1980)

3.7 Intravenous administration

3.7.1 Mouse

Groups of 25 male and 25 female strain A mice were injected in the tail vein with 1 mg quartz in 0.1 mL of saline, with a control group of 75 male and female untreated animals. Animals were killed 3, 4.5 or 6 months after injection. There was no difference in the incidences and multiplicities of pulmonary adenomas between treated and untreated animals (Shimkin & Leiter, 1940).

3.8 Administration with known carcinogens

3.8.1 Inhalation

(a) Rat

Studies have been completed to determine the effect of co-exposure to silica and Thorotrast, a known carcinogen (See Table 3.6). Two sets of three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by inhalation to 0, 6, or 31 mg/m^3 of DQ12 quartz (mass median diameter, 1.8 µm; GSD, 2.0) for 6 hours/day 5 days/week for 29 days. One week after the inhalation exposure, one group of quartz-exposed rats and one group of sham-exposed rats received an intravenous injection of Thorotrast (2960 Bq ^{228}Th/mL, 0.6 mL). Controls were only sham-exposed. In each of the six groups, interim sacrifices of three or six animals each were made 0, 6, 12 and 24 months after the end of exposure. The experiment was terminated 34 months after the end of exposure. In rats that were exposed to silica by inhalation and then given Thorotrast, there was a small increase in lung tumours compared to the already high incidence of benign and malignant tumours induced by silica alone (Spiethoff *et al.*, 1992).

3.8.2 Intratracheal administration

(a) Rat

Four groups of white rats (group sizes varied from 28 to 70, with approximately equal numbers of males and females) were given either no treatment or a single instillation of 5 mg benzo[*a*]pyrene or an instillation of 50 mg quartz (size, 82% < 2 µm) and 5 mg benzo[*a*]pyrene (Group A) or 50 mg quartz and a later (1 month) instillation of 5 mg benzo[*a*]pyrene (Group B). The rats were observed until death. There were no

Table 3.6 Incidence, numbers and histological types of lung tumours in female Wistar rats after inhalation exposure to quartz and/or Thorotrast

Treatment	Number of rats[a]	Lung tumours				
		Incidence	Total number	Histological type		
		Observed		Bronchiolo-alveolar adenoma	Bronchiolo-alveolar carcinoma	Squamous cell carcinoma
Controls	85	–	–	–	–	–
Low-dose quartz	82	37	62	8	17	37
High-dose quartz	82	43	69	13	26	30
Thorotrast (Tho)	87	3	6	–	5	1
Low-dose quartz + Tho	87	39	68	10	28	30
High-dose quartz + Tho	87	57	98	16	47	35

[a] Without the animals sacrificed 0 and 6 months after the end of inhalation exposure.
From Spiethoff *et al.* (1992)

lung tumours in the untreated rats (0/45), nor in those exposed to benzo[*a*]pyrene alone (0/19). In the combined exposures to benzo[*a*]pyrene and quartz, an increased incidence in lung tumours was observed (Group A, 14/31, 11 squamous cell carcinomas and three papillomas; Group B, 4/18, two papillomas and two carcinomas) (Pylev, 1980). [The Working Group noted the absence of a group exposed to quartz alone.]

(b) Hamster

Groups of 50 male Syrian golden hamsters received weekly intratracheal instillations for 15 weeks in saline of 3 mg benzo[*a*]pyrene or 3 mg ferric oxide or 3 mg ferric oxide plus 3 mg benzo[*a*]pyrene or 1.1 mg Sil-Co-Sil or 1.1 mg Sil-Co-Sil plus 3 mg benzo[*a*]pyrene or 0.7 mg Min-U-Sil or 0.7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene or 7 mg Min-U-Sil or 7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene. Fifty male controls received saline alone. Survivors were killed at 92 weeks after exposure. Co-exposures with silica caused an enhancement of the number of respiratory tract tumours induced by benzo[*a*]pyrene (mainly in the bronchus and lung) (Niemeier *et al.*, 1986; Table 3.7).

3.9 Synthesis

Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black (Mauderly *et al.*, 1994).

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induced lymphomas were observed in only a single experiment.

Table 3.7 Incidences of respiratory tract tumours in Syrian golden hamsters after intratracheal administration of quartz with or without benzo[*a*]pyrene

Treatment	No. of animals	No. of animals with respiratory tract tumours	No. of respiratory tract tumours[a] by site			Mean latency (wk)
			Larynx	Trachea	Bronchus and lung	
Saline control	48	0	0	0	0	–
BaP	47	22	5	3	32	72.6
Ferric oxide	50	1	1	0	0	62
Ferric oxide + BaP	48	35b,c	5	6	69	70.2
Sil-Co-Sil	50	0	0	0	0	–
Sil-Co-Sil + BaP	50	36b,c	13	13	72	66.5
Min-U-Sil	50	1	0	0	1	68
Min-U-Sil + BaP	50	44b,c	10	2	111	68.5
Min-U-Sil + ferric oxide	49	0	0	0	0	–
Min-U-Sil + ferric oxide + BaP	50	38b,c	10	4	81	66.7

[a] Types of tumours: polyps, adenomas, carcinomas, squamous cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas.
[b] Statistically significantly higher ($P < 0.00001$; two-tailed Fisher Exact test) compared with the corresponding group not treated with BaP.
[c] Statistically significantly higher ($P < 0.01$; two-tailed Fisher Exact test) compared with the BaP group.
BaP, benzo[*a*]pyrene
From Niemeier *et al.* (1986)

4. Other Relevant Data

4.1 Deposition and biopersistence

The inhalation of crystalline silica is associated with various lung diseases including acute silicosis or lipoproteinosis, chronic nodular silicosis, and lung cancer. Exposure to silica dust may also cause renal and autoimmune diseases (Steenland & Goldsmith, 1995; Stratta *et al.*, 2001; Cooper *et al.*, 2002; Otsuki *et al.*, 2007). In silicotic patients, alveolar macrophages collected by pulmonary lavage contain crystalline silica and at autopsy, elevated levels of quartz are found in the lungs and lymph nodes. Crystalline silica is poorly soluble and biopersistent; even after cessation of exposure, silicosis can progress and is a risk factor for the development of lung cancer (IARC, 1997).

Alveolar macrophages play a key role in silica-related toxicity, and therefore the cytotoxic potency of silica particles determine the degree of silica-related pathogenicity (IARC, 1997; Donaldson & Borm, 1998). The stronger the cytotoxicity of crystalline silica to alveolar macrophages, the higher the intensity of the inflammatory reaction, and the longer the residence time of the particle in the lung (Donaldson & Borm, 1998; Fenoglio *et al.*, 2000a).

Rodent inhalation studies have investigated the relationship between intrinsic particle toxicity, persistent inflammation, altered macrophage-mediated clearance, and biopersistence in the lung (Warheit *et al.*, 2007). Crystalline silica particles induce lung inflammation that persists even after cessation of exposure, with alveolar macrophages having reduced chemotactic responses and phagocytosis. Crystalline silica impairs macrophage-mediated clearance secondary to its cytotoxicity that allows these particles to accumulate and persist in the lungs (IARC, 1997). In humans, it is possible that co-exposure to tobacco smoke and crystalline silica may impair the clearance of these toxic particles (IARC, 2004).

4.2 Mechanisms of carcinogenicity

It is generally accepted that alveolar macrophages and neutrophils play a central role in diseases associated with exposure to crystalline silica (Hamilton *et al.*, 2008). An inflammation-based mechanism as described in IARC (1997) is a likely mechanism responsible for the induction of lung cancer associated with exposure to crystalline silica, although reactive oxygen species can be directly generated by crystalline silica polymorphs themselves, and can be taken up by epithelial cells. For this reason, a direct effect on lung epithelial cells cannot be excluded (Schins, 2002; Fubini & Hubbard, 2003; Knaapen *et al.* 2004).

4.2.1 Physicochemical features of crystalline silica dusts associated with carcinogenicity

The major forms or polymorphs of crystalline silica are the natural minerals quartz, tridymite, cristobalite, coesite, stishovite, and the artifical silica-based zeolites (porosils) (Fenoglio *et al.*, 2000a). Humans have been exposed only to quartz, tridymite, cristobalite, the other forms being very rare. Several amorphous forms of silica exist, some of which were classified in Group 3 (*not classifiable as to their carcinogenicity*) in the previous *IARC Monograph* (IARC, 1997). Also, it has been shown that this cytotoxicity is lowered with lowering hydrophilicity (Fubini *et al.*, 1999), which depends upon the circumstances under which the surface was created. For example, silica in fly ashes or volcanic dusts is generated at high temperatures, and is mostly hydrophobic.

The classification in Group 1 (*carcinogenic to humans*) of some silica polymorphs in the previous *IARC Monograph* (IARC, 1997) was preceded by a preamble indicating that crystalline silica did not show the same carcinogenic potency in all circumstances. Physicochemical features – polymorph characteristics, associated contaminants – may account for the differences found in humans and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called "variability of quartz hazard" have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle (Donaldson & Borm, 1998; Fubini, 1998a; Elias *et al.*, 2000; Donaldson *et al.*, 2001). The larger potency of freshly ground dusts (e.g. as in sandblasting) has been confirmed in several studies; Vallyathan *et al.*, 1995), as immediately after cleavage, a large number of surface-active radicals are formed that rapidly decay (Damm & Peukert, 2009). The association with clay or other aluminium-containing compounds inhibits most adverse effects (Duffin *et al.*, 2001; Schins *et al.*, 2002a), iron in traces may enhance the effects but an iron coverage inhibits cytotoxicity and cell transformation (Fubini *et al.*, 2001). One study on a large variety of commercial quartz dusts has shown a spectrum of variability in oxidative stress and inflammogenicity *in vitro* and *in vivo*, which exceeds the differences previously found among different polymorphs (Bruch *et al.*, 2004; Cakmak *et al.*, 2004; Fubini *et al.*, 2004; Seiler *et al.*, 2004). Subtle differences in the level of contaminants appear to determine such variability. New studies *in vitro* and *in vivo* on synthesized nanoparticles of quartz (Warheit *et al.*, 2007) indicate a variability of effects also at the nanoscale. These new data clearly show that more or less pathogenic materials are comprised under the term "crystalline silica dusts." However, most studies, so far, have failed to identify strict criteria to distinguish between potentially more or less hazardous forms of crystalline silica.

The pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the

grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron) (Fubini *et al.*, 2004).

The toxicity of silica dust from various sources may be related either to the kind of silica polymorph or to impurities.

The correlation between artificially pure crystalline silicas (porosils) with similar physicochemical properties, but different micromorphology, size and surface area, was investigated (Fenoglio *et al.*, 2000a). Surface area and aspect ratio (elongated crystals with a higher aspect ratio than more isometric crystals) of the particulates tested in a cellular system (mouse monocyte-macrophage tumour cell line) correlate best with inhibition of cell proliferation after 24–72 hours experimental time. From the natural crystalline silicas, only stishovite did not show a cytotoxic effect; all the other natural polymorphs were rather toxic. Stishovite is made up of smooth round particles (Cerrato *et al.*, 1995) whereas quartz, tridymite, and cristobalite consist of particles with very sharp edges caused by grinding (Fubini, 1998a; Fubini *et al.*, 1990, 1999). Stishovite, the only polymorph with silicon in octahedral coordination, has densely packed hydroxyl-silanols on its surface that interact with hydrogen bonds with each other; for this reason, the interaction of silanols with cell membranes, which normally does occur, is dramatically reduced (Cerrato *et al.*, 1995).

Pure silica-zeolites with different particle forms exhibit similar cytotoxicity *in vitro* if compared at equal surface area instead of equal mass. The extent of free radical generation did not show a significant correlation with cytotoxicity in this short-term in-vitro test (Fenoglio *et al.*, 2000a). Free radicals generated by the particle may play a role in later stages of toxicity related to crystalline silica (Ziemann *et al.*, 2009). Both silicon-based surface radicals and iron ions located at the particle surface may be active centres for free radical release in solution (Fubini *et al.*, 2001).

As has already been demonstrated with quartz and cristobalite (Brown & Donaldson, 1996; Bégin *et al.*, 1987), the cytotoxicity of artificially pure silica-zeolites can be decreased by aluminium ions adsorbed onto the particle surface (Fenoglio *et al.*, 2000a). Crystalline silica may occur naturally embedded in clays or may be mixed with other materials in some commercial products. It is possible that these materials may adsorb onto the silica surface, and modify its reactivity. However, the extent of surface coverage and the potency of these modified crystalline silica particles after long-term residence in the lungs have not been systematically assessed.

A quartz sample isolated from bentonite clay obtained from a 100 to 112 million-year-old formation in Wyoming, USA, exhibits a low degree of internal crystal organization, and the surface of this quartz particles are occluded by coatings of the clay. This "quartz isolate" was compared in respect to its toxic potency after intratracheal instillation in rats with the quartz sample DQ12. The "quartz isolate" showed a much lower toxicity than DQ12 quartz, in agreement with the much lower surface reactivity of "quartz isolate" compared to the DQ12 quartz (Creutzenberg *et al.*, 2008; Miles *et al.*, 2008).

4.2.2 Direct genotoxicity and cell transformation

Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic and epithelial cells exposed to quartz particles (Castranova *et al.*, 1991; Deshpande *et al.*, 2002). Oxidants generated by silica particles and by the respiratory burst of silica-activated phagocytic cells may cause cellular and lung injury, including DNA damage. Lung injury may be initiated and amplified by severe inflammation (Donaldson *et al.*, 2001; Castranova, 2004; Knaapen *et al.*, 2004). Various

products (chemotactic factors, cytokines, growth factors) released by activated (and also dying) alveolar macrophages will not only recruit more macrophages as well as polymorphonuclear leukocytes (PMNs) and lymphocytes, but may also affect and activate bronchiolar and alveolar epithelial cells.

Reactive oxygen species can directly induce DNA damage (Knaapen *et al.*, 2002; Schins *et al.*, 2002b), and morphological transformations observed in Syrian hamster embryo (SHE) cells correlate well with the amount of hydroxyl radicals generated (Elias *et al.*, 2000, 2006; Fubini *et al.*, 2001). Neoplastic transformation was observed in in-vitro assays in the absence of secondary inflammatory cells (Hersterberg *et al.*, 1986; Saffiotti & Ahmed, 1995; Elias *et al.*, 2000). There seems to be no correlation between the extent of cytotoxicity as assessed by colony-forming efficiency and transforming potency (SHE test) when various quartz samples were investigated (Elias *et al.*, 2000). In contrast to transforming potency, which was clearly related to hydroxyl radical generation, cytotoxicity was not affected by antioxidants. Partial reduction of transforming potency when deferoxamine-treated quartz was used points to the role of transitional metals, e.g. iron on the particle surface in generating hydroxyl radicals (Fubini *et al.*, 2001). The SHE test used in this study by Fubini *et al.* (2001) and by others is recommended by the Centre for the Validation of Alternative Methods (ECVAM) as an alternative method for investigating the potential carcinogenicity of particulates (Fubini, 1998b). In nude mice injected with these transformed cells, tumours could be initiated (Saffiotti & Ahmed, 1995).

Particle uptake by target cells is also relevant for direct genotoxicity (Schins, 2002). Crystalline silica particles were detected in type II lung epithelial cells (RLE-6TN) *in vitro*; these particles were located also in close proximity to the nuclei and mitochondria, but not within these organelles. An osteosarcoma cell line lacking functional mitochondria was investigated with respect to quartz-related DNA damage with an osteosarcoma cell line with normal mitochondria. Only the cell line with functioning mitochondria showed significantly increased DNA damage after exposure to DQ12 quartz (Li *et al.*, 2007).

The relationship between genotoxic effects (formation of DNA strand breaks) and the uptake of quartz particles was investigated *in vitro* with A549 human lung epithelial cells (Schins *et al.*, 2002a). The percentage of A549 cells containing particles was clearly lower after exposure to quartz coated with polyvinylpynidine-*N*-oxide or aluminum lactate compared to uncoated quartz (DQ12). In this experiment, DNA strand breaks measured (Comet assay) in the exposed cells correlated very well with the number of particles absorbed by the cells. It could also be demonstrated that the generation of reactive oxygen species was closely related to the formation of DNA strand breaks (Schins, 2002). However, in other in-vitro studies using different quartz species, DNA strand breaks in epithelial cells could be observed only at particle concentrations that caused cytotoxicity (Cakmak *et al.*, 2004).

Rats were exposed to crystalline silica for 3 hours and sacrificed at different time points after exposure, and lungs were examined by electron microscopy. The lungs were fixed by vascular perfusion through the right ventricle. In these investigations, silica crystals were found within the cytoplasm of type I lung epithelial cells (Brody *et al.*, 1982). Although type I cells are not the target cell for tumour formation, these data show that the uptake of quartz particles in epithelial lung cells *in vivo* is in principle possible. Other particles including titanium dioxide, carbon black, or metallic particles have occasionally been found in type I lung epithelial cells in rats after inhalation exposure (Anttila, 1986; Anttila *et al.*, 1988; Nolte *et al.*, 1994).

After intratracheal instillation of DQ12 quartz, DNA strand breaks could be observed in lung epithelial cells isolated from quartz-treated rats. This effect was not found when the quartz dust was treated with either polyvinylpyridine-*N*-oxide or aluminium lactate. This finding suggests an important role of the reactive surface of quartz-induced DNA damage *in vivo*. No increase in alkaline phosphatase was found in the bronchiolo-alveolar lavage fluid of quartz-treated rats, and therefore, as alkaline phosphatase is an enzyme specifically present in type II epithelial cells, it can be assumed that there was no obvious cytotoxicity in these lung cells. These data support the current view of the important role of inflammatory cells in quartz-induced genotoxic effects (Knaapen *et al.*, 2002).

4.2.3 Depletion of antioxidant defences

Substantial amounts of ascorbic acid (Fenoglio *et al.*, 2000b) and glutathione (Fenoglio *et al.*, 2003) are consumed in the presence of quartz in cell-free tests via two different surface reactions. Both reactions may deplete antioxidant defences in the lung-lining fluid, thereby enhancing the extent of oxidative damage.

Incubation of murine alveolar MH-S macrophages with quartz particles (80 µg/cm^2) for 24 hours inhibited glucose 6-phosphate dehydrogenase (G6PD)-1 activity by 70%, and the pentose phosphate pathway by 30%. Such effects were accompanied by a 50% decrease in intracellular glutathione. Quartz inhibits G6PD but not other oxidoreductases, and this inhibition is prevented by glutathione, suggesting that silica contributes to oxidative stress also by inhibiting the pentose phosphate pathway, which is critical for the regeneration of reduced glutathione (Polimeni *et al.*, 2008).

4.2.4 Indirect mechanisms

After 13 weeks of inhalation exposure to 3 mg/m^3 crystalline silica (mass median aerodynamic diameter, 1.3 µm) or 50 mg/m^3 amorphous silica (mass median aerodynamic diameter, 0.81 µm), the percentage of PMNs in the lung of the exposed rats was similar after each exposure. However, HPRT mutation frequency of the alveolar epithelial cells was significantly increased only in rats exposed to crystalline silica. Other factors including toxic effects to epithelial cells, solubility, and biopersistence may also be important for the induction of these mutagenic effects (Johnston *et al.*, 2000). A specific finding in rats treated intratracheally with amorphous silica (Aerosil®150, pyrogenic silica with primary particle size of 14 nm) was a severe granulomatous alveolitis which over time progressed to "scar-like" interstitial fibrotic granulomas not seen after crystalline silica exposure in rats (Ernst *et al.*, 2002). Lung tumours were found in rats also after the repeated intratracheal instillation of the same amorphous silica (Kolling *et al.*, 2008).

Toxic mineral dusts, especially crystalline silica, have unique, potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (silicosis) and lung cancer (Hamilton *et al.*, 2008). Macrophages express a variety of cell-surface receptors that bind to mineral dusts leading to phagocytosis, macrophage apoptosis, or macrophage activation. The major macrophage receptor that recognizes and binds inhaled particles as well as unopsonized bacteria is MARCO (Arredouani *et al.*, 2004, 2005). Additional members of the macrophage-scavenger receptor family responsible for binding mineral particles as well as a wide range of other ligands include SR-AI and SR-AII (Murphy *et al.*, 2005). Although SR-AI/II and MARCO bind both toxic and non-toxic particles, only crystalline silica triggers macrophage apoptosis following

binding to these scavenger receptors (Hamilton *et al.*, 2008). Other receptors expressed by macrophages and other target cells in the lung that bind mineral dusts include complement receptor and mannose receptors (Gordon, 2002). The pathological consequences of silica-induced injury to alveolar macrophages followed by apoptosis is impaired alveolar-macrophage-mediated clearance of crystalline silica as discussed in Section 4.1. Lysosomal membrane permeabilization following phagocytosis of crystalline silica particles has been hypothesized to enhance IL-1β secretion (Hornung *et al.*, 2008), and to trigger the release of cathepsin D, leading to mitochondrial damage, and the apoptosis of alveolar macrophages (Thibodeau *et al.*, 2004). Macrophage injury and apoptosis may be responsible for the increased susceptibility of workers exposed to silica to develop autoimmune disease (Pfau *et al.*, 2004; Brown *et al.*, 2005), and pulmonary tuberculosis (IARC, 1997; Huaux, 2007).

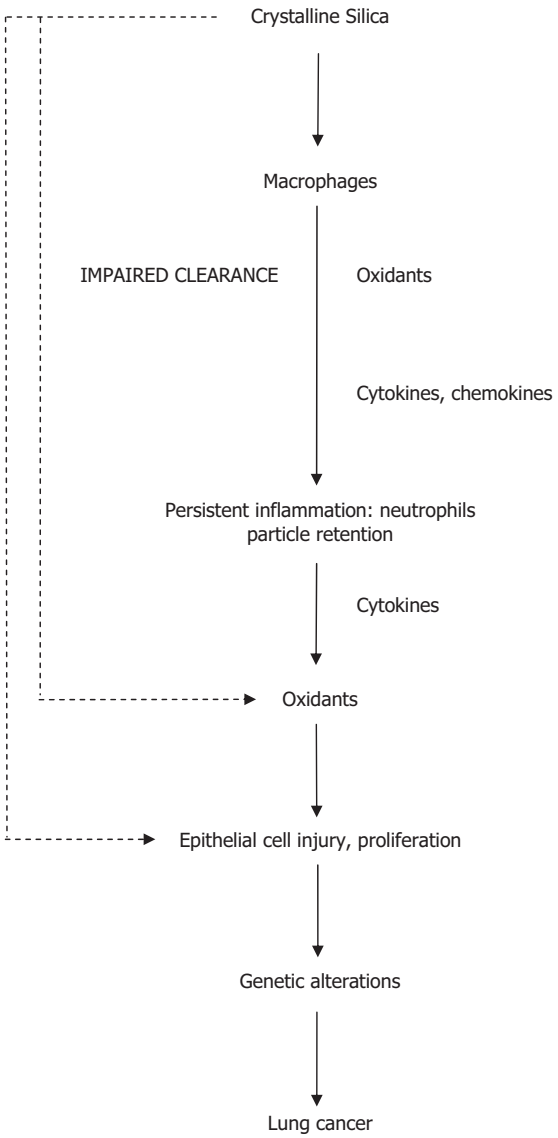
Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats, see Fig. 4.1 (IARC, 1997). Rats exposed to crystalline silica develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumours (Driscoll *et al.*, 1997). These persistent inflammatory and epithelial proliferative responses are less intense in mice and hamsters, and these species do not develop lung tumours following exposure to crystalline silica or other poorly soluble particles (IARC, 1997). There has been considerable discussion of whether the response of rats to inhaled particles is an appropriate model for the exposed response of humans (ILSI, 2000). Comparative histopathological studies of rats and humans exposed to the same particulate stimuli reveal more severe inflammation, alveolar lipoproteinosis, and alveolar epithelial hyperplasia in rats than in humans (Green *et al.*, 2007). These studies suggest that rats are more susceptible to develop persistent lung inflammation in response to particle inhalation than other species (ILSI, 2000).

Chronic exposure of rats to crystalline silica also leads to pulmonary fibrosis (Oberdörster, 1996), and workers with silicosis have an elevated risk of developing lung cancer (Pelucchi *et al.*, 2006). The causal association between chronic inflammation, fibrosis, and lung cancer was reviewed by IARC (2002). These associations provide a biological plausible mechanism between inflammation and the development of fibrosis and/or lung cancer (Balkwill & Mantovani, 2001).

4.3 Molecular pathogenesis of cancer of the lung

Acquired molecular alterations in oncogenes and tumour-suppressor genes characterize the multistage development of lung cancer (Sato *et al.*, 2007). Somatic alterations, such as DNA adducts, develop in the respiratory tract of smokers during the early stages of carcinogenesis (Wiencke *et al.*, 1999). Specific point mutations in in the *K-RAS* oncogene and the *p53* tumour-suppressor gene are considered as biomarkers of exposure to chemical carcinogens in tobacco smoke (Pfeifer *et al.*, 2002). Only one study has investigated the mutational spectrum of these genes that may be used as biomarkers for exposure to crystalline silica. Liu *et al.* (2000) analysed the mutation spectra in the *K-RAS* and *p53* genes in lung cancers that developed in workers with silicosis [smoking status unknown]. In a series of 36 cases, 16 mutations in exons 5, 7 and 8 of the *p53* gene were found. In contrast to non-occupational lung cancers, seven of these mutations clustered in exon 8. Most of the *K-RAS* gene mutations in non-small cell lung carcinomas occur at codon 12. Liu *et al.* (2000) did not detect this mutation in their case series of silicotics. Six mutations were found at codon 15 in exon 1 as well as additional mutations in codons 7, 15, 20, and

Fig. 4.1 Proposed mechanisms for the carcinogenicity of crystalline silica in rats



21. Most of these mutations were G→C transversions in contrast to G→T transversions at codon 12, which are characteristic of non-small cell lung cancers associated with tobacco smoking. If these specific mutations are confirmed in a larger series of lung cancers in silicotics, these could provide early biomarkers for the development of lung cancer in workers exposed to crystalline silica.

In a rat model of silica-induced lung cancer, a low frequency of *p53* gene mutations and no mutations in *K-RAS, N-RAS,* or *c-H-RAS* oncogenes were observed (Blanco *et al.*, 2007). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to crystalline silica.

The epigenetic silencing of the $p16^{INK4a}$ (Belinsky *et al.*, 2002), *CDH13,* and *APC* genes has also been found in a rat model of lung cancer induced by intratracheal instillation of crystalline silica (Blanco *et al.*, 2007). In this rodent model, the increased expression of iNOS

(inducible nitric oxide synthase) was also found in preneoplastic lesions, which is consistent with a role for reactive nitrogen species in silicosis (Porter *et al.*, 2006).

4.4 Species differences and susceptible populations

In rat chronic inhalation studies using crystalline silica or granular, poorly soluble particles, female rats are more susceptible than males to the induction of lung tumours. Overall, rats are susceptible to the induction of lung cancer following the exposure to crystalline silica or granular, poorly soluble particles, but hamsters and mice are more resistant. The mechanistic basis for these sex and species differences is unknown. Mice exposed to crystalline silica by intranasal instillation or subcutaneous injection, as well as rats injected intrapleurally or intraperitoneally develop lymphomas. Following inhalation exposure to crystalline silica, lymphomas have not been observed in any species (see Section 3).

In some workers exposed to crystalline silica, cytokine gene polymorphisms have been linked with silicosis (Yucesoy *et al.*, 2002). Specific polymorphisms in genes encoding in *TNF-α* and *IL-1RA* (interleukin-1 receptor antagonist) have been associated with an increased risk for the development of silicosis (Yucesoy & Luster, 2007). Gene–linkage analyses might reveal additional markers for susceptibility to the development of silicosis and lung cancer in workers exposed to crystalline silica.

4.5 Synthesis

Three mechanisms have been proposed for the carcinogenicity of crystalline silica in rats (Fig. 4.1). First, exposure to crystalline silica impairs alveolar-macrophage-mediated particle clearance thereby increasing persistence of silica in the lungs, which results in macrophage activation, and the sustained release of chemokines and cytokines. In rats, persistent inflammation is characterized by neutrophils that generate oxidants that induce genotoxicity, injury, and proliferation of lung epithelial cells leading to the development of lung cancer. Second, extracellular generation of free radicals by crystalline silica depletes antioxidants in the lung-lining fluid, and induces epithelial cell injury followed by epithelial cell proliferation. Third, crystalline silica particles are taken up by epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity.

The Working Group considers the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The mechanism responsible for the induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of quartz dust.

There is *limited evidence* in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.

Crystalline silica in the form of quartz or cristobalite dust is *carcinogenic to humans (Group 1).*

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