

FINAL

**Report on Carcinogens
Background Document for**

**Silica, Crystalline
(Respirable Size)**

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**Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee**

Prepared for the:
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Summary Statement

Carcinogenicity

Respirable crystalline silica (RCS) is *known to be a human carcinogen*, based on findings of increased lung cancer rates in occupational groups exposed to crystalline silica dust (IARC, 1997; Brown *et al.*, 1997; Hnizdo *et al.*, 1997), and supporting animal [IARC, 1997] and mechanistic data. Cancer risks are associated with exposure to quartz and crystabolite but not to amorphous silica. The overall relative risk is about 1.3 to 1.5. Higher risks are found in groups with greater exposure or longer latency. Silicosis, a marker for exposures to silica dust, is associated with elevated lung cancer rates, with relative risks of 2.0 to 4.0. Elevated risks have been seen in studies that accounted for smoking or asbestos exposure, so confounding is unlikely to explain these results.

Results of animal experiments have shown consistent increases in lung cancers in rats, but not hamsters, chronically exposed to RCS by inhalation. Single intrapleural or intraperitoneal injections of various forms of RCS to rats resulted in lymphomas.

Other Relevant Information

Crystalline silica is an abundant and commonly found natural material. Hazardous human exposure to RCS, primarily quartz dusts, occurs mainly in industrial and occupational settings. Respirable quartz levels exceeding 0.1 mg/m^3 are most frequently found in metal, nonmetal, and coal mines and mills; in granite quarrying and processing; in crushed stone and related industries; in foundries; in the ceramics industry; in construction; and in sandblasting operations.

RCS deposited in the lungs causes epithelial injury and macrophage activation, leading to inflammatory responses and cell proliferation of the epithelial and interstitial cells. In humans, RCS persists in the lungs, culminating in the development of chronic silicosis, emphysema, obstructive airways disease, and lymph node fibrosis. RCS stimulates (1) release of cytokines and growth factors from macrophages and epithelial cells; (2) release of reactive oxygen and nitrogen intermediates; and (3) oxidative stress in lungs. All these pathways contribute to lung disease. Marked and persistent inflammation, specifically inflammatory cell-derived oxidants, may provide a mechanism by which RCS exposure can result in genotoxic effects in the lung parenchyma. Humans exposed to RCS had increases in sister chromatid exchanges and chromosomal aberrations in peripheral blood lymphocytes. In vitro exposure to some quartz samples induced micronuclei or cell transformation in several cell types, including cells of human origin.

1 Physical and Chemical Properties

Crystalline Silica (CS) is the scientific name for a group of minerals composed of silicon (Si) and oxygen (O) (U.S. DOI 1992). The word crystalline implies that silicon and oxygen are arranged in a three dimensional repeating pattern. Silicon-oxygen tetrahedra (SiO₄) are the basic units of CS. In a tetrahedron, each Si atom is surrounded by four O atoms. Each O atom is shared by two tetrahedra. CS has seven polymorphs. Four of these polymorphs (Coesite, Keatite, Stishovite, and Moganite) are extremely rare. The other three (α and β Cristobalite, α and β Quartz, and α , β_1 and β_2 Tridymite) are the most commonly found forms of free CS. These forms are interrelated and change forms depending upon the temperature and pressure. In comparison to tridymite and cristobalite, the quartz structure is the most compact. Quartz, which melts to glass, has the lowest heat of expansion of any substance. CS (SiO₂, Mol. Wt. = 60.08) is also known as:

Silicon dioxide

Cristobalite (CASRN 14464-46-1)

Tridymite (CASRN 15468-32-3)

Quartz (CASRN 14808-60-7)

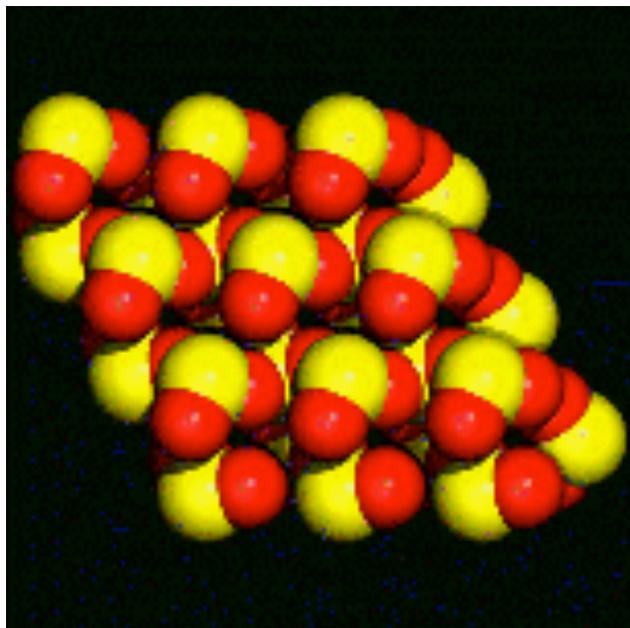
α -Quartz is the most stable form of CS under ambient conditions (α is the nomenclature for lower-temperature phase and β , the higher-temperature phase). Tridymite and cristobalite are formed at higher temperatures, while coesite and stishovite are formed at higher pressures. Keatite is not commonly found in nature. The physical and chemical properties and structure of α -Quartz are as follows:

Table 1-1. Industrial sand and gravel use Physical - Chemical Properties (α -Quartz)

Property	Information	Reference
Molecular Weight	60.08	Budavari <i>et al.</i> (1996)
Color	Transparent	Budavari <i>et al.</i> (1996)
Physical State	Transparent solid crystals (noncombustible)	Budavari <i>et al.</i> (1996)
Melting Point °C	573 transition to β -Quartz	CRC (1996)
Density, g/mL	2.648	Fron del (1962); Roberts <i>et al.</i> (1974); Smyth and Bish (1988)
Crystal system	Trigonal	Fron del (1962); Roberts <i>et al.</i> (1974); Smyth and Bish (1988)
Solubility:		
Water at 20°C	Insoluble	Iler (1979)
Acids	Insoluble	Budavari <i>et al.</i> (1996)
Hydrofluoric acids	Soluble (produces gaseous silicon tetrafluoride)	
Alkaline aqueous solutions	Soluble	

The α -Quartz structure is trigonal. Within it, the mean Si-O distance is 0.161-0.162 nm and the mean O-O distance is 0.264 nm (Florke and Martin 1993). It is stable up to 573°C and, above this temperature, converts to β -Quartz (Deer *et al.* 1966). The different polymorphs have different arrangements of tetrahedra, thus changing the density and distance between atoms. The structure of α -Quartz (3-D ball rendering) is shown in Figure 1.

Figure 1. 3-D ball rendering of α -Quartz



(<http://vanish.science.gmu.edu/~ccruz1/c80397/mvsio2.html>)

2 Human Exposure

2.1 Use

Owing to its unique physical and chemical properties, Crystalline Silica (CS) has many uses. Common, commercially produced silica products include quartzite, tripoli, gannister, chert, and novaculite. CS also occurs in nature as agate, amethyst, chalcedony, cristobalite, flint, quartz, tridymite, and, in its most common form, sand (IARC 1997).

2.1.1 Sand and Gravel

Sand has been used for many products throughout human history, but its most common use is in the production of glass. Table 2-1 summarizes other uses for sand and gravel. In some instances, grinding of sand or gravel is required, increasing levels of dust containing respirable crystalline silica (RSC) (IARC 1997).

Table 2-1. Industrial sand and gravel use

Product	Major End Use
Sand	
Glass Making	Containers, flat (plate and window), specialty, fiberglass (un-ground or ground)
Foundry	Molding and core, molding and core facing (ground) refractory
Metallurgical	Silicon carbide, flux for metal smelting
Abrasives	Blasting, scouring cleansers (ground), sawing and sanding, chemicals (ground and un-ground)
Fillers	Rubber, paints, putty, whole grain fillers/building products
Ceramic	Pottery, brick, tile, and refractory ceramics
Filtration	Water (municipal, county, local), swimming pool, others
Petroleum industry	Hydraulic fracturing, well packing, and cementing
Recreational	Golf courses, baseball, volleyball, play sands, beaches, traction (engine), roofing granules and fillers, other (ground silica or whole grain)
Gravel	Silica, ferrosilicon, filtration, nonmetallurgical flux, other

U.S. DOI (1994; cited by IARC 1997)

2.1.2 Quartz

Quartz was first used in crafting tools, weapons, and jewelry. It is the major component of the gemstones amethyst, tiger's eye, and onyx. Owing to its dielectric and piezoelectric properties, the electronic and optical components industries now use quartz. Electronic-grade quartz crystals are in demand because they can be used accurately to control frequency, timing, and filtering. High-purity, synthetic, and natural quartz crystals are used for special optical applications, such as fiber optics, and in the manufacture of watches, microcomputers, television equipment, and wireless communications equipment. Optical grade quartz is used to make lenses and windows in lasers and other devices (IARC 1997).

2.1.3 Diatomaceous Earth (DE)

DE, composed of fossilized diatoms, is used primarily as a substrate for filtration (60% of world production) because of their intricate microstructure and high pore-to-space volume. DE is amorphous silica, but becomes crystalline upon calcination. Calcined DE has been used to clarify or filter dry-cleaning solvents, pharmaceuticals, beer, wine, municipal and industrial water, fruit and vegetable juices, oils, and other chemical preparations. The next most important use of processed DE (25% of world production) is as fillers. It is used as a filler in paint, paper, and scouring powders. It is also used for their abrasive qualities in polishes, to provide flow and color qualities in paints, and to reinforce paper (Kadey 1975; cited by IARC 1987). DE is also used as a carrier for pesticides, fillers in synthetic rubber goods, laboratory absorbents, and in anti-caking agents (IARC 1997).

2.2 Production

Silica used in commercial products is obtained mainly from natural sources. U.S. production of silica sand was estimated at 25.8 million tons for 1990 and 27.9 million tons for 1994 (IARC 1997). The U.S. exports only about 4% of its production and, for the most part, does not import silica (IARC 1987). Quartz crystals are mined from the minor deposits found in the U.S. Synthetic quartz crystals (hydrothermally cultured quartz crystals) are becoming an increasingly important source of quartz production. The U.S. is one of three major countries (along with Russia and Japan) producing such crystals. The U.S. is also the major producing country of DE, with California being the most important commercial source (IARC 1997).

Fifteen suppliers for silicon/silicon dioxide have been identified: Quartz Unlimited, Inc.; 3M/Ceramic Fiber Products Division; Galtech, Inc.; TAM Ceramics, Inc.; Vesuvius McDanel Co.; Abar Ispen International, Inc.; C-E Minerals, Inc.; CEMCOM Corporation; Dentsply International, Inc.; Ferro Corp., Kyocera Industrial Ceramic Corp.; Malvern Minerals Co.; Oglebay Norton Industrial Sands; PPG Industries, Inc.; and PG Corporation (<http://www.corptech.com/FSP/Suppliers.cfm?RequestTimeout=900&ProductCode=MAT-CE-CH>).

2.3 Environmental Exposure

Silica-bearing deposits are found in every landmass and strata from every period of geologic time. Quartz, from which most silica deposits are derived, is hard, inert, and practically insoluble. Quartz survives numerous weathering processes and, as a result, constitutes approximately 12% of the continental landmass (IARC 1997). Granite may contain 25-30% silica, and shale, up to 30% silica. Sandstone is predominantly quartz, and limestone contains substantial amounts of silica. Silica is the major constituent of commercial sand. Metallic and nonmetallic ore bodies and fossil fuels may contain quartz (IARC 1987). Table 2-2 summarizes quartz concentration in different rocks.

Table 2-2. Average Quartz composition of major igneous and sedimentary rocks

Rock Type	Quartz-containing Rock	% Quartz (by weight)
Igneous	Rhyolites	33.2
	Alkali granites	32.2
	Alkali rhyolites	31.1
	Granites	29.2
	Quartz latites	26.1
	Quartz monzonites	24.8
	Quartz diorites	24.1
	Granodiorites	21.9
	Rhyodacites	20.8
	Dacites	19.6
	Latite andesites	7.2
	Andesites	5.7
	Syenites	2.0
	Monozodiorites	2.0
	Alkali syenites	1.7
	Diorites	0.3
Sedimentary	Sandstones	82
	Greywackes	37
	Shales	20

Carmichael (1989; cited by IARC 1997)

Owing to the ubiquity of silica in the natural environment and in various everyday products, environmental exposure is inevitable. Table 2-3 lists common products that could lead to human exposure to silica.

Table 2-3. Common products containing $\geq 0.1\%$ CS

At Home (as a consumer of the following items)		Everywhere (exposure could be on the job or at home)	
Product	Comment	Product	Comment
Art clays and glazes	Contain clay and sometimes RCS	Caulk and putty	Contain clay as a filler
Cleansers	Contain pumice and feldspar as abrasives	Dust (whether household or industrial)	Contain RCS
Cosmetics	Contain talc and clay	Fill dirt and topsoil	Contain sand
Pet litter	Composed primarily of clay	Foam in furniture and on rug backings	Contain talc and silica
Talcum powder	Contains talc	Paint	Contains clay, talc, sand, and diatomite
Unwashed root vegetables (such as potatoes and carrots)	Coated with soil, which has a high RCS content	Paper and paper dust	Contain kaolin and clay
Pharmaceuticals	Contain clays and talc as filler		
Sand	It is CS and amorphous silica		

U.S. DOI (1992)

2.4 Occupational Exposure

National Institute for Occupational Safety and Health (NIOSH) estimates that nearly two million workers are exposed to respirable silica, with over 100,000 of them being in high-risk environments. High-risk environments include sandblasters (including painters who sandblast), rock drillers, roof bolters, and high-risk foundry work (NIOSH 1994; cited by OSHA 1998: <http://www.osha.gov/oshinfo/priorities/silica.html>).

Respirable silica is so prevalent in the environment that, between 1980 and 1992, Occupational Safety and Health Administration (OSHA) found respirable quartz in 255 different industries, with 48% of these being above permissible exposure levels (PELs) (IARC 1997). NIOSH has compiled a list (summarized in Table 2-4) of industries for which respirable silica samples were found to be at least twice the PEL.

Table 2-4. Respirable Silica exposure in U.S. industries, 1979-1982

Industry	No. of Samples	Percentage of noncompliance (>Twice PEL)
Agriculture, Forestry, and Fishing	43	63
Mining	43	57
Construction		
Building Construction—general contractors	45	29
Construction other than building construction—general contractors	424	30
Construction—special trade contractors	289	10
Manufacturing		
Food and allied products	187	52
Textile mill products	52	27
Apparel and other finished products	16	0
Lumber and wood products, except furniture	13	8
Furniture and fixtures	31	0
Paper and allied products	82	13
Printing, publishing, and allied industries	31	0
Chemicals and allied products	640	013
Petroleum refining and related industries	214	11
Rubber and miscellaneous plastic products	269	9
Leather and leather products	14	0
Flat glass	82	9
Glassware, pressed or blown	229	11
Glass products from purchased glass	37	11
Hydraulic cement	65	0
Structured clay products	635	26
Pottery and related products	945	23
Concrete, gypsum, and plaster products	347	12
Cut stone and stone products	270	27
Abrasive, asbestos, and miscellaneous nonmetallic mineral products	558	16
Primary metal industries		
Blast furnace, steel works, rolling and finishing mills	639	32
Iron and steel foundries	10850	23
Primary smelting and refining of nonferrous metals	146	9
Secondary smelting and refining of nonferrous metals	39	0
Rolling, drawing, and extruding of nonferrous metals	23	22
Nonferrous foundries (casting)	2170	9
Miscellaneous primary metal product	68	46
Fabricated metal products, except machinery and transportation equipment	1265	22

Industry	No. of Samples	Percentage of noncompliance (>Twice PEL)
Machinery except electrical	1377	13
Electrical machinery and supplies	474	23
Transportation equipment	600	20
Measuring, analyzing, and controlling instruments and photographic and medical instruments	137	36
Miscellaneous manufacturing	211	9
Other industries	460	15

IARC (1987)

Table 2-5 summarizes occupational activities that lead to RCS exposure.

Table 2-5. Main activities in which workers may be exposed to RCS

Industry/Activity	Specific Operation/Task	Source Material
Agriculture	Plowing, harvesting, use of machinery	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal, nonmetal, coal)	Ores and associated rock
Quarry and related milling operations	Crushing stone, sand and gravel processing, monument 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 fiberglass and refractory ceramics	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	Sand
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, molding, 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 foundries (ferrous and nonferrous)	Casting, shaking out Abrasive blasting, fettling Furnace installation and repair	Sand Sand Sand
Metal products including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand

Industry/Activity	Specific Operation/Task	Source Material
Rubber and plastic	Raw materials 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
Jewelry	Cutting, grinding, polishing, buffing	Semi-precious gems or stones, abrasives
Dental material	Sand blasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concentrations

Kusnetz and Hutchison (1979); Corn (1980); Webster (1982); NIOSH (1983); Froines *et al.* (1986); Lauwerys (1990); U.S. Bureau of Mines (1992); Hilt (1993); Weill *et al.* (1994); and Burgess (1995); all cited by (IARC 1997)

2.5 RCS Analysis and Sampling

2.5.1 Air Sampling and Analysis

Air sampling involves collecting samples of air (by instruments such as the konimeter, thermal precipitator, or impinger) and analyzing these by light microscopy. One NIOSH approved method is to use X-ray diffraction to analyze air samples (another method uses infrared [IR] for analysis). The detection limit for X-ray diffraction is 5 µg for quartz (which translates to 0.01-0.02 mg/m³ for a 0.5 m³ air sample) (IARC 1997). Cost and time are other factors in this type of analysis. Collection is very time-consuming and expensive. Faster, cheaper methods have been suggested, but because they do not return consistent results, the X-ray diffraction method suggested by NIOSH presently appears to be the most useful (OSHA 1998: <http://www.osha-slc.gov/SLTC/silicacrystalline/smithdk/index.html>).

2.5.2 Bulk Analysis

Bulk analysis is used to analyze surfaces to determine silica concentrations. It does not seem to be effective in determining silica toxicity; instead, the exposed surface of silica is what predicts biological activity. Respirable silica concentrations may be determined by low-voltage scanning electron microscopy X-ray analysis. Laser microprobe mass analysis is also used to ionize a small volume of the material, which is analyzed by a time-of-flight mass spectrometer. There are other methods for analyzing bulk materials, however, these are too expensive and complicated for routine analysis. Certain physical properties of RCS have been found to be identical to the bulk properties (mostly surface properties such as hydrophilicity, surface radicals, and defects). Surface properties, therefore, can be obtained for smaller samples and applied to the bulk quantity (IARC 1997).

The major problems with bulk sampling are obtaining a representative sample and eliminating preferred orientation. Samples must be carefully extracted so that aliquots of samples have the same composition as the original material being observed. Particle separation, which is natural because of the different physical properties of the various phases, must be avoided. The side-

ripped method of loading sample holders can sometimes eliminate this orientation problem. Spheroidizing will eliminate the most severe orientation problems (Smith 1992: <http://www.osha-slc.gov/SLTC/silicacrystalline/smithdk/index.html>).

2.6 Regulations

RCS is federally regulated by EPA, FDA and OSHA as shown in the following tables:

Table 2-6. EPA Regulations

EPA Regulations	
40 CFR 411—PART 411—Cement Manufacturing Point Source Category. Promulgated: 39 FR 6591, 02/20/74. U.S. Codes: 33 U.S.C. 1251, 1311, 1314 (b) and (c), 1316 (b) and (c), and 1317(c); 86 Stat. 816 et seq., Pub. L., 92-500; 91 Stat. 1567, Pub. L. 95-217.	The provisions of this subpart are applicable to discharges resulting from the process in which several mineral ingredients (including silica) are used in the manufacturing of cement.
40 CFR 427—PART 427—Asbestos Manufacturing Point Source Category. Promulgated: 39 FR 7527, 02/26/74. U.S. Codes: 33 U.S.C. 1251, 1311, 1314 (b) and (c), 1316 (b) and (c), 1317(c); 86 Stat. 816 et seq.; Pub. L. 92-500.	The provisions of this subpart are applicable to discharges resulting from the process in which silica and other ingredients are used in the manufacturing of asbestos-cement pipe.
40 CFR 469—Subpart B—Electrical and Electronic Components Point Source Category. Promulgated: 48 FR 45250, 10/04/83. U.S. Codes: 33 U.S.C. 1311, 1314, 1316, 1317, 1318, and 1361; 86 Stat. 816, Pub. L. 92-500; 91 Stat. 1567, Pub. L. 95-217.	Any existing point source must achieve the following effluent limitations representing the degree of effluent reduction attainable by the application of the best practicable control technology currently available.

Table 2-7. OSHA Regulations

OSHA Regulations	
29 CFR 1910.1000—Subpart Z—Toxic and Hazardous Substances. Promulgated: 55 FR 9033 1/90. U.S. Codes: 29 U.S.C. 653, 655, and 657. PEL \leq 0.1 mg crystalline quartz (respirable dust)/m ³ 8-hr TWA; PEL \leq 0.05 mg crystalline cristobalite (respirable dust)/m ³ 8-hr TWA; PEL \leq 0.05 mg crystalline tridymite (respirable dust)/m ³ 8-hr TWA.	Limits employee exposure to RCS based on respiratory effects. Where administrative or engineering control is not feasible for compliance, protective equipment or protective measures approved for particular use by industrial hygienist or other technically qualified person shall be used to keep employee exposure within PEL.
29 CFR 1910.1450—Occupational exposure to hazardous chemicals in laboratories. Promulgated: 55 FR 3327, 01/31/90. U.S. Codes: 29 U.S.C. 653, 655, and 657. OSH Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As a select carcinogen (IARC Group 2A), RCS is included as a chemical hazard in laboratories. Employers are required to provide employee information and training and implement a Chemical Hygiene Plan.
29 CFR 1918—SUBPART I—General Working Conditions. Promulgated: 61 FR 5509, 02/13/96. Hazard Communication.	The purpose of this section is to ensure that the hazards of all chemicals produced or imported are evaluated, and that information concerning their hazards is transmitted to employers and employees. This transmittal of information is to be accomplished by means of comprehensive hazard communication programs, which are to include container labeling and other forms of warning, material safety data sheets, and employee

OSHA Regulations	
	training.

Table 2-8. FDA Regulations

FDA Regulations	
21 CFR 582—Substances Generally Recognized as Safe. Promulgated: 41 FR 38657, 10/10/76. U.S. Codes: 21 U.S.C. 321, 342, 348, 371.	Silica aerogel, a finely powdered microcellular silica foam having a minimum silica content of 89.5%, is generally recognized as safe when used as a component of an anti-foaming agent in accordance with good manufacturing or feeding practice.
21 CFR PART 872—Dental Devices. Promulgated: 52 FR 30097, 08/12/87. U.S. Codes: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	Porcelain powder for clinical use, a device consisting of a mixture of kaolin, felspar, quartz, or other substances intended for use in the production of artificial teeth in fixed or removable dentures, of jacket crowns, facings, and veneers, may be safely used in prosthetic dentistry.

3 Human Studies of Silica

Human cancer studies of silica before October 1996 were reviewed by International Agency for Research on Cancer (IARC) in Volume 68 (IARC 1997). Since the IARC review, seven studies of lung cancer and occupational exposures to silica dust have been published, as summarized in Table 3-1. Two of the cohort studies (Checkoway 1996b, 1997) and the nested case-control studies (Hnizdo 1997; de Klerk 1998) are extensions of earlier reports. Also, the association between silica and lung cancer was recently reviewed by Smith *et al.* (1995), Weill and McDonald (1996), Goldsmith (1997), and Steenland and Stayner (1997).

3.1 IARC (1997)

The IARC Working Group's 1996 evaluation divides silica into Crystalline Silica (CS) (quartz and cristobalite) and amorphous silica. For CS, the Working Group evaluated a large number of epidemiological studies. This evaluation included 13 cohort and five case-control studies of ore mining; six cohort studies of stone-cutters, quarry and granite production workers; 11 cohort (plus two that included nested-case-control analyses) and two case-control studies of the ceramic, pottery, refractory brick, and diatomaceous earth industries; and three cohort studies (plus one nested-case-control analysis) and one case-control study of foundry workers. There were also 23 studies evaluating cancer risk in cohorts of silicosis patients.

The IARC Working Group evaluated industry-based occupational cohorts and nested case-control studies, and one case-control study set in a pottery manufacturing region in central Italy. Community-based studies that relied on self-reported occupations and jobs were not included in the evaluation. The rationale for excluding these studies was that they would not add to the information on silica and cancer risks in the industry-based studies.

The IARC Working Group noted that the studies of miners and of foundry workers able to address the potential confounding effects of concurrent exposures (*e.g.*, radon, arsenic) and of smoking, provide only weak, inconsistent evidence of an association between silica dust exposure and lung cancer. However, based on the findings from the relatively large number of epidemiological studies of other exposures and populations (quarry and granite workers; ceramic, pottery, refractory brick, and diatomaceous earth industries; and silicosis patients from a variety of occupational settings), the IARC Working Group concluded that overall the epidemiological studies support increased lung cancer risk from inhaled CS resulting from occupational exposures. The IARC evaluation is that there is *sufficient* evidence in humans for the carcinogenicity of inhaled CS. The following studies were viewed by the IARC Working Group to be the least confounded:

1. Steenland and Brown (1995) followed a cohort study of 3,328 former gold miners in South Dakota. The standardized mortality ratio (SMR) for lung cancer, using the U.S. population rates as the reference, was 1.13 (95% CI [0.94-1.36]). For those with 30 years or more since first exposure the SMR was 1.27 (95% CI [1.02-1.55]), but there was no trend with duration or estimated cumulative dust exposure.
2. Guenel *et al.* (1989) reported on a cohort study of 2175 Danish stone workers. There were 2071 cancer cases identified through the Danish Cancer Registry from 1943-1984. The

standardized incidence ratio (SIR) for lung cancer was 1.38 (95% CI [1.00-1.89]) for skilled workers and 0.72 (95% CI [0.46-1.08]) for unskilled workers. Adjusting for region (to account for regional differences in smoking) potentiated the estimate for skilled workers (SIR 2.00, [1.49-2.69]) and substantially changed the estimate for unskilled workers (SIR 1.81, [1.16-2.70]).

3. Costello and Graham (1988) followed a cohort study of 5,414 male granite shed and quarry workers in Vermont. The risk of lung cancer mortality was increased among shed workers (SMR 1.27, 95% CI [1.03-1.55]) but not among quarry workers (SMR 0.82, 95% CI [0.50-1.27]). Risk increased with increasing number of years worked in the sheds and with year since first hire (latency).
4. Costello *et al.* (1995) reported a cohort study of 3,246 crushed stone workers in the U.S. Lung cancer mortality was increased with a SMR 1.19, 95% CI (0.85-1.62) for whites and SMR 1.85 95% CI (0.92-3.31) for nonwhites. Higher risks were seen among those with at least ten years of work and 20 or more years since first hire, particularly among granite workers (SMR 3.54, 95% CI [1.42-7.29]). There were also elevated values for limestone but not for traprock, SMR 1.50 95% CI (0.95-2.25) and 0.63 95% CI (0.13-1.84).
5. Checkoway *et al.* (1993, 1996a) studied a cohort study of 2,570 diatomaceous earth industry workers in California, but only 2,266 were included in the analyses that included asbestos exposure. Lung cancer mortality was increased (using U.S. population rates, SMR 1.43, 95% CI [1.09-1.84]; using local rates, SMR 1.59). There was evidence of increasing risk with increasing duration of employment and with a semiquantitative measure of cumulative dust exposure. This pattern was seen in the analysis that adjusted for asbestos exposure, and in the analysis, within the subgroup, without asbestos exposure.
6. Dong *et al.* (1995) reported a cohort study of 6,266 refractory brick workers in China (compared to 11,470 nonsilicotic steel workers). Lung cancer mortality risk was increased (Standardized Rate Ratios) (SRR 1.49 95% CI [1.15-1.90]), but this increased risk was only seen in workers with silicosis (SRR 2.10, 95% CI [1.46-2.92]). Smoking history did not affect the risk among silicotics (SRR 2.34, 95% CI [1.45-3.58] among smokers and 2.13, 95% CI [1.10-3.72] among nonsmokers).
7. Merlo *et al.* (1991) reported a cohort study of 1,022 refractory brick workers in Italy. Lung cancer mortality risk was increased (SMR 1.51, 95% CI [1.0-2.18]). The increased risk was seen in those employed before 1957, when exposures were higher (SMR 1.77, 95% CI [1.03-2.84]).
8. Winter *et al.* (1990), McDonald *et al.* (1995, 1997), Cherry *et al.* (1995a), and Burgess *et al.* (1997) presented cohort and nested case-control studies of pottery workers in the United Kingdom. There were 3,669 male and female workers under age 60 in 1970-1971 in the first cohort analysis through 1985 (Winter *et al.* 1990): the SMR was 1.40 (95% CI [1.07-1.80]) using national rates as the reference; 1.32 (95% CI [1.00-1.69]) using local rate comparisons. In another cohort of 5,115 pottery workers who had not worked in foundries or with asbestos or other dusts, the lung cancer SMR was 1.28 (95% CI [0.99-1.62 using local rates]) (Cherry

et al. 1995b). Intensity of exposure, rather than duration, appeared to have a stronger influence on risk.

9. Chen *et al.* (1992) and McLaughlin *et al.* (1992) reported cohort and nested case-control studies of pottery workers in China. Lung cancer risk among 13,719 pottery workers was not increased (SMR 0.58 [$p < 0.05$]). In the nested case-control analyses, there were higher risks with the highest levels of cumulative dust (odds ratio [OR] adjusting for age and smoking, 1.5) or cumulative respirable silica (OR 2.1, [0.8-4.12]), but the dose-trends were not significant.
10. Amandus *et al.* (1991, 1992, 1995) presented studies of silicosis patients in North Carolina, and Partanen *et al.* (1994) presented studies of silicosis patients in Finland. Most studies of silicosis patients have reported increased risks of lung cancer (mortality or incidence), with risk ratios between 0.5 and 4.0. These studies are among those that address potential diagnostic and self-selection biases.

Three case-control studies considered the possible associations of amorphous silica from biogenic amorphous silica fiber exposures in the sugar cane industry.

Rothschild and Mulvey (1982) studied 284 lung cancer deaths and 284 controls in Southern Louisiana. An association with sugar cane farming was found only among smokers (OR 2.6 (95% CI [1.8-4.0]) but not in nonsmokers (OR 0.9 [95% CI (0.2-3.9)]. There was no suggestion of an association between lung cancer and silica fibers by the authors and no measurements of fiber concentrations were reported.

Brooks *et al.* (1992) studied 98 male lung cancer cases and 44 male mesothelioma cases and matched controls in Florida. No consistent association with either lung cancer or mesothelioma and residence near sugar cane fields was found. For employment in the sugar cane industry the odds ratio for lung cancer was 1.8 (95% CI [0.5-7.5]). There was one case of mesothelioma who worked in the industry but had previous asbestos exposures.

Sinks *et al.* (1994) compared work histories of 93 mesothelioma cases in Hawaii with matched controls. The odds ratio for employment as a sugar cane worker was 1.1 (95% CI [0.4-2.9]).

The IARC Working Group concluded that no association was detected with biogenic amorphous silica fibers in these three studies. The IARC evaluation is that there is *inadequate evidence* in humans for the carcinogenicity of amorphous silica.

3.2 Current Epidemiological Studies

Table 3-1 gives the details of seven studies (three occupational cohorts, two silicosis cohorts, and two nested-case control studies) published since the IARC Working Group meeting in October 1996 (IARC 1997). These studies concern occupational exposures to CS and lung cancer. There is no new information to add to the IARC report on amorphous silica.

The cohort study of workers in the diatomaceous earth industry has been extended by Checkoway *et al.* (1997) by an additional seven years of follow-up and quantitative dose-response analyses. Exposure assessments were based on air monitoring data that date back into

the 1940s. Asbestos exposures were also available and estimates were made for each cohort member. The relative risk for lung cancer was 2.15 (95% CI [1.08-4.28]) in the highest exposure category of $\geq 5 \text{ mg/m}^3$ -years of respirable CS. Among workers without asbestos exposure, the relative risk was 2.03 (95% CI [0.93-4.45]) in the highest exposure category.

Rafnsson and Gunnarsdottir (1997) reported a study of 1,346 diatomaceous earth workers in Iceland. Five lung cancers occurred, compared to an expected 4.4 (SIR 1.14, 95% CI [0.37-2.65]). The plant began operation in 1967, so the maximum time of follow-up (and exposure) was 25 years; < 20% had worked for five or more years. Smoking data were available and the workers had lower smoking rates than the general population.

Checkoway *et al.* (1996b) updated a follow-up study of 22,992 Florida phosphate industry workers. Among whites, the SMR was 1.19 (95% CI [1.07-1.32]) using national population rates as the reference, and 0.98 (95% CI [0.88-1.09]) using local rates. Among nonwhites, the SMR was 1.13 (95% CI [0.92-1.37]) using national rates and 0.94 (95% CI [0.77-1.13]) using local rates. There was no dose-related association with estimated cumulative exposure to silica.

A large cohort (n=11,224) of men with pneumoconiosis from the Polish National Registry of Occupational Diseases was studied by Starzynski *et al.* (1996). The study divided the workers into subcohorts: a) coal miners (n=7,065), b) underground workers (n=924), c) metallurgical industry workers (n=1,796), and d) refractory materials (china, ceramics, and quarry) workers (n=1,439). Silica exposures were lowest among coal miners and highest among refractory workers. Lung cancer mortality was increased among metallurgical workers (SMR 1.59, 95% CI [1.24-2.01]), but not among refractory workers (SMR 1.02, 95% CI [0.72-1.4]). The metallurgical workers had the more complex exposures (including to polycyclic aromatic hydrocarbons) and smoked at a higher rate than the general public.

Cancer incidence and mortality was examined in a cohort of 1,295 silicosis patients identified from hospitalization registries in Sweden and Denmark (Brown *et al.* 1997). Incidence of lung cancer was increased (SIR 3.1, 95% CI (2.1-4.2) in Sweden and 2.9, 95% CI [1.5-5.2] in Denmark). Mortality was only assessed in Sweden, and there was also an increased risk in this measure (SMR 2.9, 95% CI [2.1-3.9]).

Hnizdo *et al.* (1997) conducted a nested case-control study of lung cancer among a cohort of South African gold miners. Lung cancer risk was associated with smoking (RR 1.0, 3.5, 5.7, and 13.2 for < 6.5, 6.5-20, 21-30, and > 30 pack years) and with silicosis (RR 2.45, 95% CI [1.2-5.2]). There was some evidence of a multiplicative interaction between smoking and silicosis.

A nested-case control study among 2,297 gold miners (138 cases) in western Australia was reported by de Klerk *et al.* (1998). The relative risk for lung cancer and silicosis was 1.59 (95% CI 1.1-2.28), but there were no other significant associations with measures of silica exposure.

Two additional studies of other types of cancers and occupational silica exposure have recently been published. A case-control study of salivary gland cancer in Shanghai included 41 cases and 414 controls (Zheng *et al.* 1996). The association between occupational exposure to silica dust and salivary gland cancer was 2.5 (95% CI [1.1-5.8]). Occupational history was based on a standardized interview, but information on the methods used to classify silica exposure was not

presented. Parent *et al.* (1997) conducted a case-control study of gastric cancer in Montreal, with 250 male patients and 2,289 controls. Occupational silica dust exposure was based on an evaluation of a patient's work history obtained from participant interviews. The evaluation was conducted by a panel of chemists and industrial hygienists. They reported an increased risk across levels of exposure (OR 1.7, 95% CI [1.1-2.7]) for substantial and OR 1.4 (95% CI [1.0-1.9]) for nonsubstantial, compared to none. Risk also increased with increased frequency and concentration of exposure, but not with duration.

Table 3-1. Studies of Silica and Lung Cancer in Humans

Study Type	Population Group	Exposure	Effects	Potential Confounders and Modifiers	Comments	References
Cohort (mortality)	2,342 white male workers exposed to RCS in the diatomaceous earth industry during 1942-1994. Quantitative asbestos exposure was estimated for a sub-cohort of 2,266.	Estimated cumulative exposure to RCS (primarily cristobalite, asbestos, and chrysotile).	77 lung cancer deaths; SMR 1.29 (95% CI (1.01-1.61)) using US rates; SMR 1.43 using local rates. The SMR for the highest level of silica exposure was 2.15 (95% CI [1.08-4.28]). For those with no asbestos exposure (47 lung cancer deaths) the SMRs were 1.0 (referent), 0.73, 0.73, 1.00, and 2.03 for increasing levels of cumulative RCS.	Adjusted for and stratified by asbestos.	Smoking information was incomplete. The previous suggestion of a possible synergism between silica and asbestos was not observed in this updated analysis. The previous reports followed the cohort from 1942-1987.	Checkoway <i>et al.</i> (1996a, 1997, 1993)
Cohort (incidence)	920 men and 426 women from a diatomaceous plant in Iceland.	RCS with a high cristobalite content from heating diatomite.	Only five lung cancer cases were observed with 4.4 expected, SIR 1.14 (95% CI [0.37-2.65]). Among men with at least five years exposure there was an excess of lung cancer (three cases), SIR 2.34 (95% CI [0.48-6.85]).	Smoking was less than in the general population.	Small cohort, relatively short follow-up, and relatively short length of employment (< 20% had worked five or more years).	Rafnsson and Gunnarsdottir (1997)
Cohort (mortality)	18,446 white and 4,546 nonwhite male workers in the Florida phosphate industry. Follow-up period 1949-1992.	RCS exposure from mining and processing of phosphate ores.	Among whites, 354 lung cancer deaths, (SMR 1.19 (95% CI [1.07-1.32]) using national reference; 0.98 (95% CI [0.88-1.09]) using local rates. Among nonwhites, the SMR was 1.13 (95% CI [0.92-1.37]) using national rates and 0.94 (95% CI [0.77-1.13]) using local rates. There was no dose-related association with estimated cumulative exposure to silica		Lack of industrial hygiene and cigarette smoking data. Exposure to total dust, alpha and gamma radiation, and acid mists also assessed.	Checkoway <i>et al.</i> (1996b, 1985)

Study Type	Population Group	Exposure	Effects	Potential Confounders and Modifiers	Comments	References
			(relative risk 1.05 in highest compared to lowest category for whites, 0.68 for nonwhites).			
Cohort - silicotics (mortality)	11,224 men with pneumoconiosis from the Polish National Registry of Occupational Diseases.	Analysis divided by type of work (coal miners; other underground, metallurgical, and refractory material workers).	Significantly elevated lung cancer risk in metallurgical industry and nonferrous foundry workers (SMR 1.59, 95% CI [1.24-2.01]), but not in miners (SMR 1.04, 95% CI [0.88-1.22]), other underground workers, (SMR 1.30, 95% CI [0.85-1.90]) or refractory materials workers (SMR 1.02, 95% CI [0.72-1.40]).	Smoking rates were higher in metallurgy and foundry workers (85% compared to 75% in the general male population). These workers also have complex exposures including polycyclic aromatic hydrocarbons and carcinogenic metals.		Starzynski <i>et al.</i> (1996)
Cohort - silicotics (incidence and mortality)	1,295 silicosis patients in Sweden (n=1052) and Sweden (n=243).		Lung cancer incidence increased (SIR 3.1, 95% CI [2.1-4.2]) in Sweden and 2.9, (95% CI [1.5-5.2]) in Denmark; lung cancer mortality increased (SMR 2.9, 95% CI [2.1-3.9]).		Silicosis patients identified through hospital discharge diagnoses. Incident cases or deaths within 12 months of study entry excluded.	Brown <i>et al.</i> (1997)
Nested case-control	78 lung cancer cases and 386 controls among a cohort of 2,260 South African gold miners followed from 1970 to 1986.	Mining in rock composed of quartz (70-90%), silicates (10-30%).	Lung cancer risk was associated with smoking (RR 1.0, 3.5, 5.7, and 13.2 for < 6.5, 6.5-20, 21-30, and > 30 pack years) and with silicosis RR 2.45 (95% CI [1.2-5.2]). There was some evidence of a multiplication interaction between smoking and silicosis: among those without silicosis, the association (relative risk) between smoking (measured by three levels of pack-years) and	Uranium exposure was also present in this cohort, but no association with lung cancer mortality was seen with the measures of uranium available in this analysis.	Smoking habits ascertained by questionnaire during medical examination.	Hnizdo <i>et al.</i> (1991, 1997)

Study Type	Population Group	Exposure	Effects	Potential Confounders and Modifiers	Comments	References
			lung cancer was 1.0, 5.1, and 11.7; among silicosis patients, corresponding associations were 4.1, 7.9, and 48.9.			
Nested case-control	138 lung cancer cases among 2,297 western Australia gold miners (cases age-matched to controls).		Relative risk for lung cancer and silicosis was 1.59 (95% CI 1.1-2.28). No significant associations with measures of silica exposure.	Adjusted for smoking.		de Klerk <i>et al.</i> (1995, 1998)
Case-control	41 incident salivary gland cancers and 414 controls in Shanghai.	Occupational exposures to silica dust based on work histories.	Ten cases and 61 controls were exposed to silica dust for an OR=2.5 (1.1-5.8). For males 18 cases and OR=3.1 (1.1-8.9) and for females 23 cases and OR=1.5 (0.3-7.7).	np	Among males there were eight cases and 52 controls exposed to silica dust and for females two cases and nine controls exposed. Smoking habits were assessed and no association was found with smoking or other exposures such as asbestos, coal dust, textile dust, or wood dust. An association was found with head x-ray examinations and exposure to kerosene in cooking.	Zheng <i>et al.</i> (1996)
Case-control	250 male gastric cancer patents and	RCS from work as carpenters,	For nonsubstantial exposure OR=1.4 (1.0-1.9) and for	np	Exposures based on reviews of question-	Parent <i>et al.</i> (1997)

Study Type	Population Group	Exposure	Effects	Potential Confounders and Modifiers	Comments	References
	2,289 controls.	cabinet and furniture makers, and construction laborers.	substantial exposure OR=1.7 (1.1-2.7). For levels of exposure concentration; low OR=1.3 (0.9-1.9), medium OR=1.6 (1.0-2.4) and high OR=1.7 (0.8-3.6).		naires. 82 cases were associated with the silica occupations. There was not an association with duration of exposure.	

3.3 Discussion

Several review papers and meta-analyses have been published recently. Goldsmith (1997) reviewed those lung cancer studies that had dose-response associations. He compared the extrapolated risk based on animal studies with risk estimates from the worker studies. A factor of two difference was reported, with the animals being more sensitive.

Weill and McDonald (1996) reviewed the epidemiological literature on the relationship between silica, silicosis, and lung cancer. They considered work reported after 1985 and found papers by Merlo *et al.* (1991) and Checkoway *et al.* (1993) particularly compelling. They pointed out that for many of these studies there were important confounders such as polycyclic aromatic hydrocarbons (PAH) in foundries and radon and arsenic in mines. They also discussed the selection bias of using registries of silicosis patients. For example, for many of the compensated cases there were likely to be respiratory problems due to smoking. They believed that the study by Amandus *et al.* (1991, 1992) was free of this problem.

Smith *et al.* (1995) carried out a formal meta-analysis of lung cancer studies among silicotics. They considered 29 studies and were able to use 23 in their analysis. The pooled relative risk for lung cancer was RR=2.2 (95% CI [2.1-2.4]), with RR=2.0 for cohort studies, and RR=2.5 for case-control studies. The authors conclude that the association between silicosis and lung cancer was causal, either due to silicosis itself or due to the effect of exposure to silica.

Steenland and Stayner (1997) carried out a meta-analysis using cohort and case-control studies (for 16 silica exposed workers and 19 silicotics workers) of the largest and pertinent occupational studies. They calculated a pooled relative risk of RR=1.3 (95% CI [1.2-1.4]) for the meta analysis using 16 occupational studies. They noted that the relative risk was greatest and most consistent among 19 studies of silicotics with a RR=2.3 (95% CI [2.2-2.4]).

3.4 Summary of Epidemiological Studies

The quantity and quality of cancer epidemiology studies (primarily lung cancer) of silica exposure have increased substantially in the past decade. Generally, these have focused on either specific occupations with potentially high exposures to silica (*e.g.*, miners, quarry and stone workers) or on patients with silicosis. An important issue in evaluating these studies is the possibility of confounding or effect modification by smoking. Another issue for some of the occupational studies is the potential for confounding by other exposures. This is of particular concern for the studies of mining (*e.g.*, arsenic and radon exposures in gold mines) and foundries (polycyclic aromatic hydrocarbons exposure).

Most studies of miners and of foundry workers did not assess the potential confounding effects of other exposures. The studies that addressed this issue in the analysis provide only weak and inconsistent evidence of an association between silica dust exposure and lung cancer.

Confounding exposures are less likely to influence studies of stone, pottery, brick, and ceramic workers. These studies have shown an increased risk of lung cancer (incidence or mortality), with overall risk ratios around 1.3. Some studies have suggested a latency of at least 15 years, increased risks with increased duration of exposure, or that the increased risk is most evident in workers exposed before dust control measures were undertaken. It is difficult to separate these different effects given the exposure distributions in these studies.

An increased risk of lung cancer among silicosis patients has been reported in more than 20 studies, with risk ratios generally between 0.5 and 4.0. This increased risk is seen in studies that adjust for smoking and in stratified analyses of smokers and nonsmokers. It is also seen in studies in a variety of occupational settings, so it is unlikely that silicosis is only acting as a marker for exposure to other carcinogens (*e.g.*, radon). One criticism raised about some studies is the potential for biased assessment of cancer (*i.e.*, greater surveillance or reporting of lung cancer among silicosis patients because of compensation issues). However, results from the studies that addressed these issues are similar to earlier studies that were more likely to be influenced by these potential biases.

4 Experimental Carcinogenesis

International Agency for Research on Cancer (IARC) conducted two evaluative reviews of silica-induced carcinogenesis (IARC 1987, 1997). In its most recent review, the IARC Working Group noted numerous animal experiments tested the carcinogenic potential Crystalline Silica (CS) by a variety of routes. Those studies were judged to have provided sufficient evidence that CS is carcinogenic in experimental animals.

Various types of quartz (see previous sections), with particle sizes in the respirable range, have been studied in four studies each of exposure by inhalation and intratracheal instillation. In these eight rat experiments, Respirable Crystalline Silica (RCS) exposure was associated with increased incidences of pulmonary adenocarcinoma and squamous cell carcinoma. These lesions were accompanied by dense pulmonary fibrosis which was considered to be an important aspect of the overall biological response.

Although pulmonary tumor incidence was not increased in hamsters after repeated intratracheal instillation of quartz dust (three experiments), pulmonary granulomatous inflammation, and slight- to moderate fibrosis of the alveolar septa was observed.

Neither a mouse lung adenoma assay (A/J mice), nor a limited inhalation study of quartz in mice, produced increased incidences of lung tumors. Quartz exposure caused silicotic granulomas and lymphoid cuffing around airways, but pulmonary fibrosis was not observed in quartz-exposed mice.

RCS was administered either intrapleurally or intraperitoneally to rats in several experiments. This treatment caused thoracic and abdominal malignant lymphomas, primarily of the histiocytic type.

4.1 Previously Reviewed Studies (IARC 1997)

4.1.1 *Inhalationally administered RCS in rats*

Protocol outlines and results of inhalation studies, considered by IARC to be adequate for evaluation, are summarized in Table 4.1.

Table 4-1. Summary of inhalation experiments conducted on RCS and reviewed in IARC (1997)

Sex/ Species/ Strain	N/group		Concentration	Crystalline silica characteristics	Inhalation parameters	Duration of experiment	Interim sacrifice	Results	Reference (Cited in IARC 1987)
Male/female F 344 rats	Not reported but presumed to be 36 males and 36 females.		0 51.6 mg/m ³	Quartz, median aerodynamic. diam = 1.7-2.5 µm	Whole body, 6 h/d, 5 d/wk	24 mo. 10 rats/ group removed from exposure at 4, 8, 12, and 16 mo. and observed until 24 mo.	5 of each sex after 4, 8, 12, and 16 mo.	Epidermoid carcinoma in 10/53 males and 1/47 females. No lung tumors in controls. 3/5 females exposed for four mo. had tumors.	Dagle <i>et al.</i> (1986)
Female F344 rats		62	12±5 mg/m ³	Quartz, median aerodynamic. diam = 2.24±0.2 µm	Nose only, 6 h/d, 4 d/wk	Exposed for 83 weeks then observed until natural death.	No	18/60 exposed had squamous cell carcinoma, adenocarcinoma, and/or adenomas.	Holland <i>et al.</i> (1983, 1986)
Male/female SPF F 344 rats	50 50	50 50	0 1 mg/m ³	Silicon dioxide, aerodynamic. diam = 1.3µm	Whole body, 6 h/d, 5 d/wk	24 mo. then observed for additional 6 weeks.	No	7/50 male and 12/50 female had lung adenoma, adenocarcinoma, cystic keratinizing squamous cell tumors, adenosquamous carcinoma, and/or squamous cell carcinoma.	Muhle <i>et al.</i> (1989, 1991, 1995)
Female Wistar rats		90 90 90	0 6.1±0.36 mg/m ³ 30.6±1.59 mg/m ³	Quartz, aerodynamic. diam = 1.8 µm	Nose only, 6 h/d, 5 d/wk	34 mo., exposed for 29 days.	2-6 rats/ group at 6, 12, and 24 mo.	8/37 low-dose, 43/82 high-dose rats with bronchio-/alveolar adenoma or carcinoma, squamous cell carcinoma, and or anaplastic carcinoma. Distant metastases were seen.	Spiethoff <i>et al.</i> (1992)

Dagle *et al.* (1986; cited in IARC 1987) exposed male and female Fischer 344 rats to 0.0 or 51.6 mg/m³ quartz (mass median aerodynamic diameter, 1.7-2.5 µm; geometric standard deviation, 1.9-2.1) in inhalation chambers. Animals were exposed 6h/d, 5 d/wk, for up to 24 months. After 4, 8, 12 or 16 months, ten animals of each sex were removed from exposure and five were sacrificed. The remaining five were observed and survivors were sacrificed at 24 months. The incidence of epidermoid carcinomas of the lungs in rats surviving for 494 days (*i.e.*, roughly 16 months) when the first tumor was detected, was 10/53 (19%) in females and 1/47 (2%) in males. Three of five females that received no further exposure to quartz after four months had epidermoid carcinomas. No lung tumors were found in controls of either gender.

Holland *et al.* (1983) and Holland *et al.* (1986; both cited in IARC 1987) exposed female Fischer 344 rats to quartz (mass median aerodynamic diameter, 2.24±0.2 µm; geometric standard deviation, 1.75±0.3, all particles were <5.0 µm). Rats were exposed by a nose-only technique for 6 h/d, 4 d/wk, for 83 weeks (*i.e.*, approximately 21 months) and observed for the remainder of their lives. Quartz exposure was associated with squamous cell carcinomas, adenocarcinomas, and/or adenomas of the lung. There were no lung tumors in sham exposed rats. Most quartz exposed rats that survived more than 400 days had pronounced pulmonary fibrosis, granulomatous and silicotic nodules, often with emphysema and alveolar proteinosis.

Muhle *et al.* (1989, 1991, 1995; all cited in IARC 1997) studied groups of 50 male and 50 female viral antibody-free, SPF Fischer 344 rats, 8 weeks of age at the start of the experiment. The animals were exposed, in inhalation chambers, to 0.0 or 1.0 mg/m³ silica (silicon dioxide, mass median aerodynamic diameter about 1.3 µm, with a geometric standard deviation of 1.8). Animals were exposed 6 h/d, 5 d/wk, for 24 months. Animals that survived 24 months were maintained, without further exposure, for an additional six weeks. The incidences of primary lung tumors in RCS exposed rats were 7/50 in males and 12/50 in females. Lung tumors included adenoma, adenocarcinoma, benign cystic keratinizing squamous cell tumors, and adenosquamous carcinoma. Furthermore, nodular bronchoalveolar hyperplasia, interpreted as *borderline adenoma*, was found in 13/100 silica-exposed animals. No lung tumors were observed in controls. Non-neoplastic changes reported in silica-exposed animals included multifocal lipoproteinosis with adjacent fibrotic areas, fibrosis, and alveolar- and bronchiolar-type bronchoalveolar hyperplasia. The severity of these lesions was directly related to duration of exposure.

Spiethoff *et al.* (1992; cited in IARC 1997) exposed groups of female Wistar rats (6 to 8 weeks old) to 0.0, 6.1±0.36, or 30.6±1.59 mg/m³ quartz (mass median aerodynamic diameter, 1.8 µm) 6 h/d, 5 d/wk, for 29 days (nose-only exposure). Two to six animals per group were sacrificed at 29 days and at 6, 12, and 24 months. The study was terminated at 34 months, when all surviving animals were sacrificed. The overall incidence of lung tumors in the low- and high-dose groups after the 24-month sacrifice was 8/37 (22%) and 13/43 (30%), respectively. Total lung tumor incidences, at termination of the study, were 37/82 (45%) and 43/82 (52%) in the low- and high-dose groups, respectively. No lung tumors were observed in control rats. Many animals exhibited lung tumor multiplicity, sometimes with the same tumor type, and sometimes with different tumor types. Tumor types included bronchiolo-alveolar adenomas, bronchiolo-alveolar carcinomas, squamous cell carcinomas, and anaplastic carcinomas. Metastases were observed in

the tracheobronchial lymph nodes and, occasionally, in the kidneys and heart. Non-neoplastic pulmonary lesions included fibrosis and alveolar and bronchiolar epithelial proliferation.

4.1.2 Inhalationally administered RCS in mice

Wilson *et al.* (1986; cited in IARC 1997) exposed BALB/cBYJ mice to RCS (>96% quartz) for 8 h/d, 5 d/wk in inhalation chambers. Animals were exposed 150, 300, or 570 days. Average exposure concentrations were 1,475; 1,800; or 1,950 mg/m³ (diameter < 2.1 µm). Overall lung tumor incidences were 9/60 in exposed mice and 7/59 in controls. This difference was not statistically significant. In their review, the IARC working group noted small numbers of animals were used and that exposure and observation periods varied widely within the studies.

4.1.3 Intratracheal administration in rats

Holland *et al.* (1983; cited in IARC 1997) instilled 7 mg of quartz (mean particle size 1.71±1.86 µm; all particles < 5 µm) into the tracheas of Sprague-Dawley rats (gender not specified) once weekly for ten weeks. Animals were observed over their lifetimes. Lung tumors (adenomas or carcinomas) were observed in 6/36 (17%) of dosed animals, 0/40 saline controls, and 0/18 untreated controls. Focal and diffuse pulmonary fibrosis was observed in quartz dosed animals.

Male Fischer 344 rats were administered 20 mg of quartz (Min-U-Sil; particle size, 0.1% ≥ 5 µm; or novaculite, particle size, 2.2% ≥ 5 µm) as a single intratracheal/lung instillation. Interim sacrifices were conducted at 6, 12, and 18 months (ten animals at each interval) and terminal sacrifice was made at 22 months. The tumor incidences observed in this study are summarized in Table 4-2.

Table 4-2. Lung tumor incidences in F 344 rats that received intratracheal instillations of RCS

Material Tested	Incidences of lung tumors at various intervals				
	12 mo.	18 mo.	12-22 mo. spontaneous deaths	22 mo.	Total Lung tumors
Min-U-Sil	1/10	5/10	5/17	19/30	30/67 (45%)
Novaculite	1/10	2/10	2/17	16/35	21/72 (29%)

Holland *et al.* (1993)

Animals dosed with Min-U-Sil had larger lung tumors and more extensive granulomatous and fibrotic lung lesions than did the novaculite-dosed group (Groth *et al.* 1986; cited in IARC 1997).

Saffiotti (1990, 1992) and Saffiotti *et al.* (1996; all cited in IARC 1997) instilled single, intratracheal doses of 12 or 20 mg of quartz (Min-U-Sil, 99% pure with 0.1% iron and 99% pure with no iron, and a particle size distribution between 0.5 and 2.0 µm) into male and female F344/NCr rats. Additional groups received 20 mg of ferric oxide (Fe₂O₃, nonfibrogenic dust). Tumor incidences are summarized in Table 4-3.

Table 4-3. Incidence of lung tumors in F344/NCr rats after single intratracheal instillation of quartz

Treatment Material	Dose	Observation time	Lung tumors	
			Incidence	Types
Males				
Untreated	None	17-26 mo	0/32	
Ferric oxide	20 mg	11-26 mo	0/15	
Quartz w iron	12 mg	Killed at 11 mo	3/18 (17%)	Adenomas and adenocarcinomas Undiff carc., mixed carc. Epidermoid carc.
		Killed at 17 mo	6/19	
Quartz w/o iron	12 mg	17-26 mo	12/14	Adenomas, adenocarc., mixed carc.
		Killed at 11 mo	2/18 (11%)	
		Killed at 17 mo	7/19 (78%)	
		17-26 mo	7/9 (78%)	
Females				
Untreated	None	17-26 mo	1/20 (5%)	Adenoma
Ferric oxide	20 mg	11-26 mo	0/18 ()	
Quartz w iron	12 mg	Killed at 11 mo	8/19 (42%)	Adenomas, adenocarcinomas, undiff carc.
		Killed at 17 mo	10/17 (59%)	
Quartz w/o iron	20 mg	17-26 mo	8/9 (89%)	Mixed carc. Epidermoid carc. Adenoma, adenocarc. Mixed carc. Epidermoid carc.
		17-26 mo	6/8 (75%)	
		17-26 mo	6/8 (75%)	
Quartz w/o iron	12 mg	Killed at 11 mo	7/18 (39%)	Adenoma, adenocarc. Adenoma, adenocarcinoma, mixed carc., epidermoid carc.
		Killed at 17 mo	13/16 (81%)	
		17-26 mo	8/8 (100%)	

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

Non-neoplastic changes observed in this study included interstitial fibrosis, hyperplasia of peribronchial lymphoid tissue, silicotic granulomas, hypertrophy, and finally, hyperplasia and adenomatoid proliferation of alveolar epithelium.

In a study by Pott *et al.* (1994; cited in IARC 1997) six groups of female Wistar rats received either one (45 mg), or 15 (3 mg), intratracheal instillations of one of three quartz preparations (DQ 12, Min-U-Sil, or Quartz Sykron F 600) in saline. Two of the groups received subcutaneous injections of polyvinylpyridine-N-oxide (PVNO) (seven total injections administered at four-month intervals) to retard the development of silicosis. Animals died spontaneously, were killed when moribund, or were terminated at 131 weeks. Tumor incidences are summarized in Table 4-4.

Table 4-4. Incidence of lung tumors in female Wistar rats after intratracheal instillation of quartz

Test Material	No. of Instillations	Tumor Incidence
Quartz (DQ 12)	1 x 45 mg	9/40 (23%)
Quartz (DQ 12)	15 x 3 mg	14/37 (38%)
Quartz (DQ 12)+PVNO	5 x 3 mg	22/38 (58%)
Quartz Min-U-Sil	15 x 3 mg	21/39 (54%)
Quartz Min-U-Sil+PVNO	15 x 3 mg	20/35 (57%)
Quartz Sykron (F600)	15 x 3 mg	12/40 (30%)

Pott *et al.* (1994)

RCS produced a variety of tumors in these studies (adenomas, adenocarcinomas, squamous cell carcinomas and benign cystic, keratinizing, squamous cell tumors, fibrosarcoma, lymphosarcoma, and mesotheliomas). Animals dosed with DQ 12 developed severe silicosis and had a median survival time of about 15 months. Survival of PVNO-dosed rats was not specified, but those animals developed more lung tumors. The authors attributed this difference to the protective effect against silicosis (Pott *et al.* 1994; cited in IARC 1997).

4.1.4 Intratracheal administration in hamsters

Intratracheal instillation of RCS in hamsters has not produced increased incidences of lung tumors. Three studies were reviewed by IARC as summarized in Table 4-5.

Table 4-5. Summary of protocols and results of intratracheal RCS-instillation experiments conducted in hamsters

Material tested	Dose	Comments	Reference
Min-U-Sil	3 or 7 mg once weekly for 10 weeks	Incidence and severity of pulmonary fibrosis was minimal.	Holland <i>et al.</i> (1983; cited in IARC 1997)
Min-U-Sil	0.03, 0.33, 3.3 or 6.0 mg once weekly for 15 weeks	No animals developed nodular fibrosis or foci of dense fibrous tissue in lung.	Renne <i>et al.</i> (1985; cited in IARC 1997)
Sil-Co-Sil and Min-U-Sil	1.1 mg weekly for 15 weeks	Bronchiolo-alveolar hyperplasia occasionally seen but no fibrosis.	Niemeier <i>et al.</i> (1986; cited in IARC 1997)

Cited in IARC (1997)

4.1.5 Intrapulmonary deposition

Kahulau (1961; cited in IARC 1987) administered an unspecified amount of quartz (particle size about 2 μm) into the lung of seven rabbits. Two rabbits died after administration, but five survived for five to six years. Four of the survivors developed malignant lung tumors. Interpretation of this study is confounded by the absence of a vehicle control group.

4.1.6 Intrapleural and intrathoracic administration

Bryson *et al.* (1974; cited in IARC 1997) administered single, intrathoracic injections of 10 mg tridymite (20% of particles <3.3 µm) or 5 mg chrysotile (particle size not given) to mice. After 19 months (32-34 animals were surviving), one animal given tridymite had a lung adenocarcinoma and two had intrapleural lymphoid tumors. There were four lung adenocarcinomas and four lymphoid tumors in the chrysotile group. There was one lung adenocarcinoma and no lymphoid tumors in the control group.

Single, intrapleural, injections of 20 mg of quartz particles (<5µm) were carcinogenic in male and female SPF Wistar rats and standard Wistar rats. Malignant tumors of the reticuloendothelial system, involving the thoracic region, were observed in 39/95 (41%) SPF rats and in 31/94 (33%) standard rats (genders were combined in presentation of the data). These results were confirmed in a larger study involving groups of 80 male and 80 female SPF Wistar rats. The same studies were also conducted using other rat strains (Wagner and Berry 1969; Wagner 1970, 1976, Wagner *et al.* 1980; all cited in IARC 1997).

Jaurand *et al.* (1987; cited in IARC 1997) dosed Sprague-Dawley rats with 20 mg quartz (DQ 12) (in 1 mL saline) by intrapleural space injection. Animals were observed over their life spans and were sacrificed when moribund. Mean survival times were 769, 809 and 780 days for untreated controls, saline controls, and dosed animals, respectively. Six malignant histiocytic lymphomas and two malignant Schwannomas were found in RCS-dosed animals. Furthermore, one chronic lymphoid leukemia and one fibrosarcoma were observed in the saline and untreated controls groups, respectively.

4.1.7 Other routes of administration

When administered into the peritoneal cavity of male and female rats (single 20 mg injection), quartz (Min-U-Sil) increased the incidence of malignant lymphomas (Wagner 1976; cited in IARC 1997). Intravenous administration of 1 mg quartz (average particle size, 1.6 µm) to mice produced no evidence of carcinogenicity (Shimkin and Leiter 1940; cited in IARC 1997). In a later study, Wagner (1976; cited in IARC 1997) administered 20 mg quartz intravenously to groups of 16 male and 16 female SPF Wistar rats. Four animals (sexes not specified) developed thymomas/lymphosarcomas. Whether these results are indicative of a carcinogenic effect can not be ascertained since vehicle control groups were not included.

Two groups of 40 female (C57xBALB/ F₁) mice received single, subcutaneous injections of 4 mg of *d*-, or 4 mg of *l*-, quartz (synthetic *d*- and *l*-quartz). A control group of 60 mice were injected with only saline. Survivors were killed at 18 months. Incidences of lymphomas/leukemias were 0/60, 1/40, and 12/40 for saline, *d*-quartz, and *l*-quartz dosed mice, respectively. In addition, 1/40 *d*-quartz and 3/40 *l*-quartz-dosed mice had liver adenomas while none of the controls had liver tumors. Fibrotic nodules were observed at the injection sites in 17/40 *d*-quartz- and 27/40 *l*-quartz-injected mice, but not in controls (Ebbesen 1991; cited in IARC 1997).

4.1.8 Administration of RCS with known carcinogens

In an inhalation study using Wistar rats, quartz (DQ 12) produced a pronounced pulmonary carcinogenic interaction with Thorotrast, an α -particle emitting material (Spiethoff *et al.* 1992; cited in IARC 1997).

Intratracheal instillation of quartz (Sil-Co-Sil and Min-U-Sil, 50 mg/animal) enhanced the respiratory tract carcinogenesis of benzo[a]pyrene (5 mg/animal) in hamsters (Niemeier *et al.* 1986; cited in IARC 1997). In two studies that administered mixtures of quartz and ferric oxide (1:1) to hamsters by intratracheal instillation, there were no increases in pulmonary tumor incidence (Saffiotti 1990, 1992, 1996; all cited in IARC 1997) (see Table 4-2).

4.2 Interpretations by Earlier Review Groups

The IARC Working Group concluded there is *sufficient evidence* for the carcinogenicity of CS in experimental animals.

4.3 Pertinent Information Developed Since Earlier Reviews

Williams and Knapton (1996) administered quartz (suspended in Eagle's minimum essential medium) subcutaneously or intraperitoneally to nude mice and Syrian golden hamsters. Mice received 3.5 g/kg and hamsters received 1.6 g/kg. Animals were killed, serially, and these authors presented descriptions of pathological changes produced in the liver by the treatment. Quartz-exposure produced granulomas, fibrosis, and cirrhosis, reaching 100% at 12 and 3 months in mice and hamsters, respectively. Hyperplasia and hypertrophy of nonparenchymal cells and foci of hyperplastic liver nodules were also found. Two of six mice (given quartz subcutaneously) killed between 13 and 17 months had liver cell carcinomas. One of these animals had a 1 cm diameter carcinoma and coexisting microscopic adenoma with cytoplasmic inclusion bodies. Control animals were reported to have no hepatic lesions.

5 Genotoxicity

5.1 Prokaryotic Systems

No data found.

5.2 Lower Eukaryotic Systems

No data found.

5.3 Mammalian Systems *in vitro*

5.3.1 Induction of micronuclei

Several studies have demonstrated the ability of Respirable Crystalline Silica (RCS) to cause chromosomal damage in mammalian cells in culture. Hesterberg *et al.* (1986; cited by IARC 1997), treating Syrian hamster embryo cells with Min-U-Sil quartz, noted a significant increase in micronuclei. The same group (Oshimura *et al.* 1984; cited by IARC 1997), however, using another sample of quartz, failed to induce micronuclei, a modification of the number of chromosomal aberrations, aneuploid cells, or tetraploid cells.

Nagalakshmi *et al.* (1995), using Chinese hamster lung fibroblasts (V79) and human embryonic lung (Hel 299) cells, found a significant increase in micronuclei in both types of cells following treatment with Min-U-Sil 5 and Min-U-Sil 10 for 24 hours at several concentrations. However, the frequency of chromosome aberrations was not affected.

Liu *et al.* (1996) treated V79 cells with respirable silica particles. Two particle sizes of crystalline quartz and a noncrystalline form of silica were assayed for induction of micronuclei. Both forms of silica, dispersed in medium, induced micronuclei formation in dose-dependent manner. The RCS was more active, however, than the noncrystalline silica on a mass basis (as shown in Table 5-1). Treatment of cells with surfactant-coated silica was not significantly different from that of nontreated control cultures.

5.3.2 Direct interaction with DNA measured by infrared spectroscopy

Using Fourier transform infrared spectroscopy, Daniel *et al.* (1995) showed *distinct alterations* in the DNA spectra of fetal rat alveolar epithelial cells following *in vitro* exposure to quartz. By means of electron microscopy and energy dispersive X-ray spectroscopy, they also demonstrated localization of quartz particles in the nuclei and mitotic spindles of the cells and related changes to the quartz spectra. As discussed in Section 6, they speculated that RCS particles in aqueous buffer produce oxygen radicals that can mediate DNA strand breakage. Estimating a hydroxyl radical reaction distance of 15 Angstroms, they described the likely hydrogen bonding between surface silanol groups of the quartz and the phosphate-sugar backbone of DNA. Finally, they discussed the means by which direct interaction of RCS with DNA may trigger carcinogenesis by interfering with DNA mitotic processes, replication, or repair.

5.3.3 DNA damage measured by SCG assay

The single cell gel (SCG)/comet assay was used to compare DNA damage in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblasts (Hel 299 cells) exposed to RCS, amorphous silica, and glass fibers (Zhong *et al.* 1997). RCS and glass fibers

caused a significant increase in DNA migration, measured as tail length in both cell lines, at almost all concentrations tested. The increase was much higher in the Chinese hamster lung fibroblasts than in human embryonic lung fibroblasts for RCS. These results indicate that silica and glass fibers induce DNA damage in mammalian cells. RCS was found to have a higher DNA-damaging activity than amorphous silica.

5.4 Mammalian Systems *in vivo*

5.4.1 Induction of *hprt* mutations

Driscoll *et al.* (1995) were able to demonstrate that *in vivo* treatment of rats with α -quartz could induce mutations in the hypoxanthine guanine phosphoribosyl transferase (*hprt*) gene of alveolar epithelial lung cells. Seven months after exposure to 100 mg/kg body weight of intratracheally instilled α -quartz, female F344 rats were sacrificed and alveolar type II cells harvested and cultured to select for *hprt* mutants. Isolated cells showed a significant (greater than ten-fold) increase in *hprt* mutant frequency compared to cells isolated from saline instilled controls.

Table 5-1. Frequency of micronuclei induced by silica particles in V79 cells

Compound	Concentration ($\mu\text{g}/\text{cm}^2$)	Frequency of MN ($\bar{x} \pm \text{SE}$)
Min-U-Sil 5	0	6.67 \pm 0.33
	20	9.33 \pm 0.88
	40	15.67 \pm 0.88 ^b
	80	20.67 \pm 1.77 ^b
	160	25.67 \pm 0.33 ^b
Min-U-Sil 10	0	6.67 \pm 0.33
	20	9.67 \pm 0.67
	40	11.67 \pm 0.67 ^a
	80	17.00 \pm 1.00 ^b
	160	19.67 \pm 0.67 ^b
SSB1	0	7.67 \pm 2.33
	20	10.33 \pm 0.86
	40	8.67 \pm 2.41
	80	13.33 \pm 1.77 ^a
	160	18.00 \pm 2.08 ^b
MNNG ^c	1 ($\mu\text{g}/\text{ml}$)	96.67 \pm 9.53 ^b

Liu *et al.* (1996)

3000 cells were scored for each treatment group; frequencies are mean values per 1000 cells.

^aCompared with solvent control $p < 0.05$.

^bCompared with solvent control $p < 0.01$.

^cMNNG was used as a positive control in this experiment.

6 Other Information Relative to Evaluation of the Carcinogenicity RCS in Laboratory Animals

6.1 Particle Size, Deposition, and Disposition in the Respiratory Tract

The nature of the deposition of respired particles within the pulmonary system is a function of both species and the aerodynamic diameter of the particle in question.

In humans, large particles with aerodynamic diameters $\geq 10 \mu\text{m}$, generally deposit in the upper respiratory tract and only smaller particles will deposit in the tracheobronchial region. Deposition in the alveolar region begins to be substantial only when aerodynamic diameters are well below $10 \mu\text{m}$ (Task Force Group on Lung Dynamic 1966; cited in IARC 1997). In small laboratory animals, such as the rat, deposition of particles of aerodynamic diameter $> 6 \mu\text{m}$ is negligible. This species differential is attributable to differing modes of breathing (rodents are obligatory nose breathers, while humans are both mouth and nose breathers) and respiratory patterns, such as cycle period and tidal volume (Jones 1993; cited in IARC 1997).

Quartz particles with an aerodynamic diameter $< 6 \mu\text{m}$ are likely to be the most damaging to rats. Substantial deposition of quartz particles with a mean aerodynamic diameter of $1.4 \mu\text{m}$ (range, 0.3-4.0) was reported on alveolar duct/terminal bronchiolar surfaces (Brody *et al.* 1982; cited in IARC 1997). More than 80% of particles deposited peripherally in the lungs (on the alveolar ducts, particularly at their bifurcations, and on the distal terminal bronchioles) had an aerodynamic diameter of $3.7 \mu\text{m}$ (Warheit *et al.* 1991; cited in IARC 1997).

6.2 Distribution And Clearance Of Particles

After deposition of quartz on the surface of the respiratory tract, there is either rapid mucociliary clearance (from the upper airways), or phagocytosis by alveolar macrophages. Clearance tends to be slower if deposition is in the lung periphery (Brody *et al.* 1982; Warheit *et al.* 1991; both cited in IARC 1997). Clearance from the lungs of humans, dogs, and guinea pigs is slower than from the lungs of rats and hamsters (Oberdorster 1988; Jones 1993; both cited in IARC 1997). In general, clearance of particles by mucociliary mechanisms is considered to be efficient, while clearance from the lung periphery is slow and incomplete (Morgan 1984; Vacek *et al.* 1991; both cited in IARC 1997).

6.3 Quartz-Induced Inflammation

Exposure of rats to RCS results in a marked and persistent inflammatory response, characterized by a high percentage of neutrophils. This response has been repeatedly demonstrated after either inhalation or intratracheal instillation exposure (IARC 1997).

Henderson *et al.* (1995; cited in IARC 1997) exposed female Fischer 344 rats, by inhalation, to air or 0.1, 1.0, or 10 mg/m³ RCS (Min-U-Sil) 6 h/d, 5d/wk for 4 weeks. The mass median aerodynamic diameter of the aerosol was 1.3-2.0 μm . Lung responses were characterized by analysis of bronchoalveolar lavage (BAL) cell populations one, eight, and 24 weeks after exposure. Lung burdens of SiO₂ were determined one week after cessation of exposure. The results are summarized in Table 6-1.

Table 6-1. BAL cell populations in rats exposed to RCS for four weeks

Treatment	Route	Cell differential (%)		SiO ₂ Burden μg/mg ¹	Comments
		Macrophages	Neutrophils		
Air (control)	Inhalation	99	1		BAL results are for 24 weeks after cessation of either inhalation or intratracheal exposure.
0.1 mg/m ³	Inhalation	99.5	0.5	43	
1 mg/m ³	Inhalation	97	2.5	190	
10	Inhalation	59	41	720	
Saline (control)	Intratracheal	98	2	Not reported	
750μg	Intratracheal	38	62	Not reported	

¹Lung burdens of SiO₂ were determined one week after cessation of inhalation exposure Henderson *et al.* (1995)

Exposure to 10 mg/m³ RCS (Min-U-Sil) caused lung injury and inflammation as evidenced by the pronounced increase in percent of neutrophils among the BAL cells. The authors reported that the 1 mg/m³ dose caused a transient increase in BAL fluid neutrophils (however, no data were presented). Histopathological examination of lung tissues 24 weeks after exposure revealed an active-chronic inflammatory response in bronchial-associated lymphoid tissues, interstitium, and intrapleural regions of animals dosed with 10 mg/m³. Intratracheal instillation of 750 μg of RCS produced an unequivocal increase in BAL fluid neutrophils.

6.4 Quartz-Induced Epithelial Injury and Proliferation in the Lung

After intratracheal instillation of quartz in mice, a wave of type II cell proliferation to regenerate damaged type I cells was reported by Adamson and Bowden (1984; cited in IARC 1997). This was accompanied by increasing hydroxyproline levels and sustained interstitial proliferation, interpreted to be evidence of mesenchymal cell proliferation and fibrosis. Miller and Hook (1988; cited in IARC 1997) reported a nearly two-fold increase in the number of type II epithelial cells in Min-U-Sil quartz-exposed lungs. These cells were hypertrophic with increased numbers of lamellar bodies. Warheit *et al.* (1991; cited in IARC 1997) reported that inhalation of Min-U-Sil quartz (but not carbonyl-iron) particles, caused proliferation in the lung parenchyma of rats. Type II cells, isolated from Min-U-Sil-exposed lungs, were shown to synthesize DNA *in vitro*, but they did not divide (Panos *et al.* 1990; cited in IARC 1997).

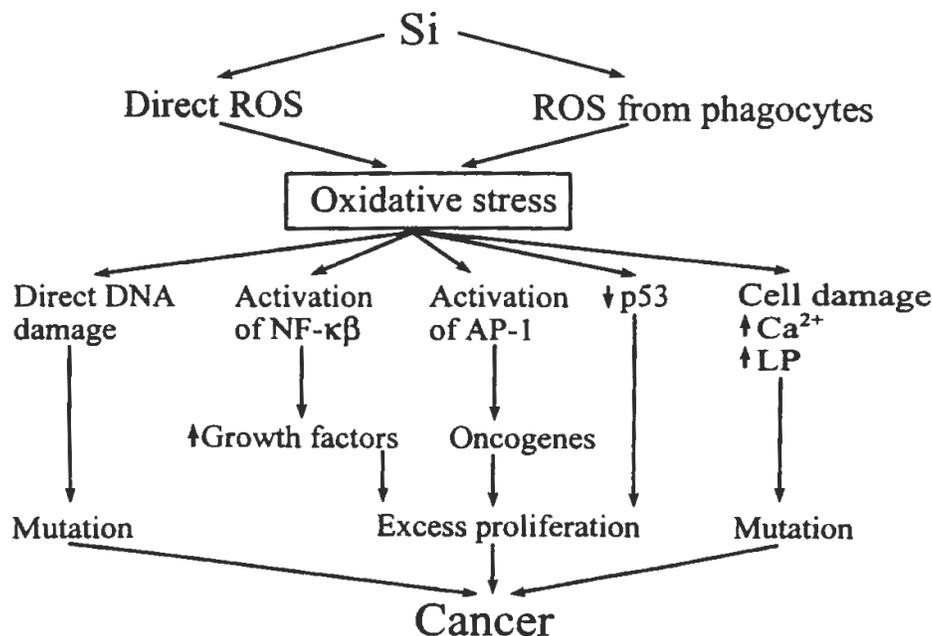
Lesur *et al.* (1992; cited in IARC 1997) reported that noncytotoxic concentrations of Min-U-Sil quartz caused proliferation and thymidine uptake in isolated rat epithelial cells. Macrophages, exposed to Min-U-Sil quartz *in vitro*, have been shown to release factors that stimulate growth of type II epithelial cells (Melloni *et al.* 1993; cited in IARC 1997). These results suggest that quartz may cause direct and indirect growth promotion of epithelial cells.

6.5 Oxidative Stress in Quartz-Exposed Lungs

Min-U-Sil quartz-exposed lungs have been shown to contain two- to three-fold more hydroxy radical activity than lungs exposed to either titanium dioxide or saline (Schapira *et al.* 1994; cited in IARC 1997). Both reactive oxygen and reactive nitrogen species (NO and peroxyxynitrite) are generated in Min-U-Sil quartz-induced inflammation (Blackford *et al.* 1994; Van Dyke *et al.* 1994; both cited in IARC 1997).

Shi *et al.* (1998) recently reviewed the scientific literature describing molecular level interactions between silica and biological materials. They have hypothesized that silica-mediated free radical reactions may cause oxidative stress in pulmonary tissue and thereby play a role in carcinogenesis. The Shi *et al.* model is presented schematically in Figure 2.

Figure 2. Schematic representation of (hypothesized) silica-induced generation of reactive oxygen species (ROS) and possible role in carcinogenesis.



Shi *et al.* (1998)

Fracturing silica crystals has been demonstrated to result in the generation of silicon-based free radicals which, upon reaction with water or H₂O₂, generate reactive oxygen species (ROS). ROS may also be generated from silica-stimulated phagocytes. It is hypothesized (Shi *et al.* 1998) that persistent oxidative stress possesses the potential to mediate carcinogenesis through mutations caused by direct DNA damage or via lipid peroxidation, activation of nuclear transcription and growth factors, oncogene expression, or inhibition of tumor suppressor genes.

6.6 Formation Of 8-Oxoguanine In Quartz-Exposed Rat Lungs

Nehls *et al.* (1997) exposed Wistar rats to quartz (DQ 12; 2.5 mg/rat) or corundum (2.5 mg/rat) suspended in saline, by intratracheal instillation. Animals were sacrificed 7, 21, or 90 days after dosing. Lung sections were examined for 8-Oxoguanine (8-oxoGua) level by immunocytological assay and proliferation was assessed by labeling with bromodeoxyuridine (doses administered two hours prior to sacrifice). The 8-oxoGua levels in quartz-exposed lung cells were markedly elevated, at all time intervals tested, relative to those saline- or corundum-exposed. Lung cell proliferation, in saline- or corundum-dosed animals, was unchanged, but exposure to quartz resulted in a three- to four-fold increase in cell proliferation at each of the time points.

These observations suggest that pulmonary inflammation (repeatedly demonstrated in rats), in conjunction with mutagenic DNA oxidation products in target cells (demonstrated by Nehls *et al.* 1997), and a quartz-induced proliferative response (demonstrated by earlier workers and Nehls *et al.* 1997), combine to play key roles in RCS-induced pulmonary carcinogenesis in rats. Nehls *et al.* (1997) further speculated that mutagenic events, triggered by ROS, may activate protooncogenes or inactivate tumor-suppressor genes to effect carcinogenesis. Shi *et al.* (1998) have suggested that differences in intra- and extracellular antioxidant levels between species may explain species' differences with respect to susceptibilities to silica-induced carcinogenesis.

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Silica, some silicates, coal dust and para-aramid fibrils. Lyon, France.

SILICA

Silica was considered by previous Working Groups in June 1986 and March 1987 (IARC, 1987a,b). New data have since become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Classification and nomenclature of silica forms

Chem. Abstr. Name: Silica

Chemical name: Silicon dioxide

Structure: Crystalline, amorphous or cryptocrystalline

Origin: Mineral, biogenic or synthetic

Classification:

(a) *Crystalline forms*

natural — α , β quartz; α , β_1 , β_2 tridymite; α , β cristobalite; coesite; stishovite; moganite

synthetic — keatite; silica W; porosils (zeosils and clathrasils)

(b) *Amorphous forms*

natural — opal; biogenic silica; diatomaceous earths; silica fibres (biogenic); vitreous silica

synthetic — fused silica; pyrogenic or fumed silica; precipitated silica; colloidal silica; silica gel

(c) *Silica rocks (> 90% SiO₂)*

quartzite, quartz arenite, diatomite, porcellanite, radiolarite, chert, geyselite (Fron del, 1962; Coyle, 1982; Flörke & Martin, 1993)

Varietal names

(a) *Crystalline forms*

natural — α -quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli

(b) *Amorphous forms*

natural — diatomaceous earths: diatomite, kieselguhr, tripolite (Benda & Paschen, 1993)

CAS Reg. Nos: See Table 1.

Table 1. Chemical Abstracts Registry numbers for various forms of silica

Type of silica	CAS Reg. No.
Silica	7631-86-9; deleted CAS Nos, 179046-03-8; 152787-33-2; 122985-48-2; 1340-09-6; 145686-91-5; 155575-05-6; 155552-25-3; 50813-13-3; 139074-73-0; 136881-80-6; 126879-30-9; 126879-14-9; 89493-21-0; 127689-16-1; 1133384-41-1; 62655-73-6; 83652-92-0; 55599-33-2; 97709-14-3; 108727-71-5; 87501-59-5; 39336-66-8; 83589-56-4; 70563-35-8; 97343-62-9; 78207-17-7; 70536-23-1; 12765-74-1; 12125-13-2; 56645-27-3; 53468-64-7; 50926-93-7; 61673-46-9; 67167-16-2; 52350-43-3; 60572-11-4; 51542-58-6; 51542-57-5; 50935-83-6; 56731-06-7; 39372-58-2; 39409-25-1; 37241-25-1; 12774-28-6; 9049-77-8; 11139-72-3; 11139-73-4; 12737-36-9; 12753-63-8; 37220-24-9; 37334-65-9; 37340-45-7; 37380-93-1; 39443-40-8; 39456-81-0
Crystalline silica	
Cristobalite	14464-46-1
Quartz	14808-60-7
Tripoli	1317-95-9; deleted CAS No., 12421-13-5
Tridymite	15468-32-3; deleted CAS Nos, 12414-70-9; 1317-94-8
Amorphous silica	
Pyrogenic (fumed) amorphous silica ^a	112945-52-5 (previously included under 7631-86-9)
Precipitated silica, including silica gel	112926-00-8 (previously included under 7631-86-9); deleted CAS No., 112945-53-6)
Diatomaceous earth (uncalcined)	61790-53-2; deleted CAS Nos, 53571-43-0; 77108-41-9; 61970-41-0; 37337-67-0; 56748-40-4; 54990-62-4; 54990-61-3; 57692-84-9; 81988-94-5; 67417-47-4; 39455-02-2; 54511-18-1; 37264-95-2; 50814-24-9; 73158-38-0; 12623-98-2; 55839-10-6; 51109-72-9; 68368-75-2; 67016-73-3; 12750-99-1; 64060-29-3; 39421-62-0; 37328-66-8; 11139-66-5; 57126-63-3; 29847-98-1
Vitreous silica, quartz glass, fused silica	60676-86-0; deleted CAS Nos, 55126-05-1; 1119573-97-6; 37224-35-4; 37224-34-3)
Flux-calcined diatomaceous earth	68855-54-9

^aDifferent from amorphous silica fume (CAS Reg. No., 69012-64-2)

Trade names(a) *Crystalline forms*

natural — *-quartz*: CSQZ, DQ 12 (Robock, 1973), Min-U-Sil, Sil-Co-Sil, Snowit, Sykron F300, Sykron F600 (Fu *et al.*, 1984)

(b) *Amorphous forms*

natural — *diatomaceous earths*: Celatom, Celite, Clarcel, Decalite, Fina/Optima, Skamol (Flörke & Martin, 1993)

synthetic — *fused silica*: Suprasil, TAFQ

pyrogenic or fumed silica: Aerosil, Cab-O-Sil, HDK, Reosil

precipitated silica: FK, Hi-Sil, Ketjensil, Neosyl, Nipsil, Sident, Sipernat, Spherosil, Tixosil, Ultrasil (Flörke & Martin, 1993)

colloidal silica: Baykisol, Bindzil, Hispacil, Ludox, Nalcoag, Nyacol, Seahostar, Snowtex, Syton (Flörke & Martin, 1993)

silica gel: Art Sorb, Britesorb, Diamantgel, Gasil, KC-Trockenperlen, Lucilite, Silcron, Silica-Perlen, Silica-Pulver, Sylobloc, Syloid, Sylopute, Trisyl (Flörke & Martin, 1993)

Description(a) *Crystalline forms*(i) *Natural*

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 (see Section 1.1.3). 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.

The large majority of the experiments reported in Sections 3 and 4 were carried out with Min-U-Sil or DQ 12 quartz. Min-U-Sil is a trade name under which ground quartz dust has been sold by different companies. The number that follows some Min-U-Sil preparations (e.g. Min-U-Sil 5) refers to the particle size of the sample (Min-U-Sil 5 is $\leq 5 \mu\text{m}$ in diameter). The purity is $> 99\%$ quartz. However, the mineral sources of the quartz crystals employed for the preparation of the ground dust have varied with time; consequently, the associated impurities may also have varied. In one case, a Min-U-Sil sample was analysed and the presence of trace amounts of iron ($< 0.1\%$) was reported (Saffiotti *et al.*, 1996).

DQ 12 $< 5 \mu\text{m}$ is a quartz sand with a content of 87% crystalline silica, the remainder being amorphous silica with small contaminations of kaolinite. DQ 12 was described and provided by Robock (1973) from a geological source in Dörentrup, Germany. All DQ 12 samples originate from the same source, but no other descriptions of composition or particle size have been reported in subsequent years.

(ii) *Synthetic*

Keatite is obtained under thermal conditions. *Silica W* is formed at about 1200°C from SiO as metastable fibrous woolly aggregates, unstable at ambient temperature

(Flörke & Martin, 1993). *Porosils (zeosils and clathrasils)* are crystalline porous silicas with a zeolitic structure made up from only silicon and oxygen (Gies, 1993).

(b) *Amorphous forms*

(i) *Natural*

Opal is an amorphous hydrous silica that may contain cryptocrystalline cristobalite (Fron del, 1962). *Biogenic silica* is defined as any silica originating in living matter (known sources include bacteria, fungi, diatoms, sponges and plants); the two most relevant biogenic silicas are those associated with fossilized diatoms and crop plants (Rabovsky, 1995). *Diatomaceous earths* are the geological products of decayed unicellular organisms (algae) called diatoms. *Vitreous silicas* are volcanic glasses; lechatelierites are natural glasses produced by the fusion of siliceous material under the impact of meteorites (Fron del, 1962).

In commercial products, a large proportion of the amorphous silica in diatomaceous earths is converted into a crystalline form (cristobalite) during processing (Kadey, 1975; Benda & Paschen 1993). *Silica fibres* (of biogenic origin) are derived from plants such as sugar cane, canary grass and millet (Bhatt *et al.*, 1984).

(ii) *Synthetic*

Fused silica is silica heated up to a liquid phase and cooled down without allowing it to crystallize. *Pyrogenic or fumed silica* is silica prepared by the combustion of a volatile silicon compound (usually SiCl_4). *Precipitated silica* is silica precipitated from an aqueous solution. *Colloidal silica* is a stable dispersion of discrete, colloid-sized particles of amorphous silica in an aqueous solution. *Silica gel* is a coherent, rigid, continuous three-dimensional network of spherical particles of colloidal microporous silica (Flörke & Martin, 1993). The characteristics of synthetic silicas have been the subject of many reviews (e.g. Iler, 1979; Bergna, 1994). Characteristics of commercial synthetic silicas have been described recently (Ferch & Toussaint, 1996).

1.1.2 *Crystalline structure and morphology of silica particulates*

Molecular formula: SiO_2

Silicon–oxygen tetrahedra (SiO_4) are the basic units of all crystalline and amorphous forms reported in Section 1.1.1 (with the exception of stishovite, in which, under extreme pressure conditions, silicon is forced to bind to six oxygen atoms in an octahedral coordination). In each silicon–oxygen tetrahedron, each silicon atom is surrounded by four oxygen atoms; each oxygen atom is shared by two tetrahedra.

The three-dimensional framework of crystalline silicas is determined by the regular arrangement of the tetrahedra, which share each of their corners with another tetrahedron. Differences in the orientation and position of the tetrahedra create the differences in symmetry and cell parameters that give rise to the various polymorphs. In the case of quartz, the structural feature is a helix composed of tetrahedra along the c-axis. The helices have a repeat distance of three tetrahedra. The winding of the helices

can be left- or right-handed, which results in the enantiomorphism of quartz crystals (Fron del, 1962).

The phases of silica and their crystalline structures have been extensively studied and several surveys have been carried out (e.g. Fron del, 1962; Wycoff, 1963; Sosman, 1965). **Table 2** reports symmetry, lattice parameters (the unit cell dimensions *a*, *b*, *c*), density and the strongest lines (*d* values) obtained by X-ray diffraction of the various natural polymorphs stable or metastable at room temperature.

Table 2. Crystallographic data of silica polymorphs

Polymorph	α -Quartz	α -Tridymite	α -Cristobalite	Coesite	Stishovite
Crystal system	Trigonal	Orthorhombic	Tetragonal	Monoclinic	Tetragonal
Space group	P3 ₂ 1	C22 ₂	P4 ₂ 2 ₂	C2/c	P4/mnm
Cell parameters ^a					
<i>a</i>	4.9134	9.91	4.970	7.1464	4.1790
<i>b</i>	4.9134	17.18	4.970	12.3796	4.1790
<i>c</i>	5.4052	40.78	6.948	7.1829	2.6651
Density	2.648	2.269	2.318	2.909	4.287
Strongest diffraction lines ^b	3.343, 4.26, 1.817	4.30, 4.09, 3.80	4.05, 2.485, 2.841	3.098, 3.432, 2.77	2.959, 1.538, 1.981

From Fron del (1962); Roberts *et al.* (1974); Smyth & Bish (1988)

^a In Angstrom units

^b Source of X-ray: copper

The silicon–oxygen bond is regarded as partially ionic (that is, close to 1 : 1 ionic to covalent bond character). The mean Si–O distance in tetrahedral polymorphs is 0.161–0.162 nm and the mean O–O distance 0.264 nm. The variation in the Si–O–Si bond angles and the almost unrestricted rotation of adjacent tetrahedra around the bridging oxygen atom account for the variability of silica frameworks (Flörke & Martin, 1993).

The ²⁹Si nuclear magnetic resonance (NMR) peaks of the framework of silica polymorphs appear at the highest field of the ²⁹Si chemical shift range of silicates. The shifts observed for silica polymorphs range from –107 to –121 ppm. The chemical shift differences observed for the various polymorphs are due only to changes in the structural arrangement of the SiO₄ tetrahedra within the silica backbone. Quantitative correlations between the observed chemical shifts and several geometrical parameters, typically bond angles, have been established (Engelhardt & Michel, 1987). In this context, NMR appears to be a promising technique for a better insight into the crystal structure and for the identification of the various polymorphs.

The amorphous silica forms are also composed of tetrahedra sharing their oxygen atoms. However, in these silicas the orientation of the bonds is random and lacks any long-range periodicity. The lack of crystal structure is shown by the absence of sharp lines in an X-ray diffraction, although some short-range organization may still be present.

A large variety of amorphous silicas have been prepared for different uses (Section 1.1.1), the properties of which are described by Iler (1979) and Bergna (1994). These amorphous silicas differ in particle form and size, porous structure and residual water content.

The micromorphology of silica particulates to which people are exposed (respirable size range) depends not only upon crystallinity but also upon the way in which the silica particulates were formed. Ground samples — whether from crystalline or vitreous forms — have very acute edges and a marked heterogeneity in particle size; smaller particles are held at the surface of bigger ones by surface charges (Fubini *et al.*, 1990). Diatomaceous earths and even cristobalite particles derived from diatomaceous earths have an almost infinite variety of shapes; this variation has its origins in the living matter from which they originated (Iler, 1979). Pyrogenic amorphous silicas are aggregates of non-porous, smooth, round particles and are totally different from the forms found in diatomaceous earths (Ettlinger, 1993; Ferch & Toussaint, 1996). In precipitated silicas, the size of the particle morphology and the extent of the inherently porous structure are dependent upon the procedure used in their preparation.

The surface areas of ground samples of crystalline or vitreous silica depend on the grinding procedure and vary between 0.1 and 10–15 m²/g. Diatomites have a rather broad range of surface areas, which, after calcination, fall mostly into the range 2–20 m²/g. Pyrogenic amorphous silicas have surface areas ranging from 50 to 400 m²/g. Precipitated amorphous silicas have a very variable specific surface area ranging between 50 and nearly 1000 m²/g because of their porous structure and the small size of the particles.

Quartz particles often have a perturbed external amorphous layer (known as the Beilby layer; Fubini, 1997). Removal of this layer by etching improves the crystallinity and increases the fibrogenic potential of the dust (King & Nagelschmidt, 1960).

1.1.3 *Physical properties and domain of thermodynamic stability*

The stability of the polymorphs of silica is related to temperature and pressure (Klein & Hurlbut, 1993). α -Quartz is stable over most of the temperatures and pressures that characterize the earth's crust. Tridymite and cristobalite are formed at higher temperatures, while coesite and stishovite are formed at higher pressure. The conversion from one crystalline structure to another requires the rupture of silicon–oxygen bonds and the reconstruction of new ones. This process requires a very high activation energy. Although α -quartz is the only silica phase stable under ambient conditions, other silica polymorphs, namely α -tridymite, α -cristobalite, coesite and stishovite, exist with metastability at the earth's surface. Their conversion to α -quartz under ambient conditions is, in fact, immeasurably slow. In contrast, the $\alpha \rightleftharpoons \beta$ conversion in quartz, tridymite and cristobalite requires only the rotation of silicon bonds; this can occur rapidly at the interconversion temperature. Consequently, only the α (low) forms can exist in ambient conditions.

The temperature ranges of stability of the most important silica polymorphs are reported in **Table 3**.

Table 3. Domain of thermodynamic stability and metastability of silica polymorphs at ambient pressure^a

Polymorph	Stable	Metastable
α -Quartz	Up to 573 °C	–
β -Quartz	From 573 °C to 870 °C	Above 870 °C
α -Tridymite	–	Up to 117 °C
β_1 -Tridymite	–	From 117 °C to 163 °C
β_2 -Tridymite	From 870 °C to 1470 °C	Above 163 °C
α -Cristobalite	–	Up to 200–275 °C
β -Cristobalite	From 1470 °C to 1713 °C (melting-point)	Above 200–275 °C

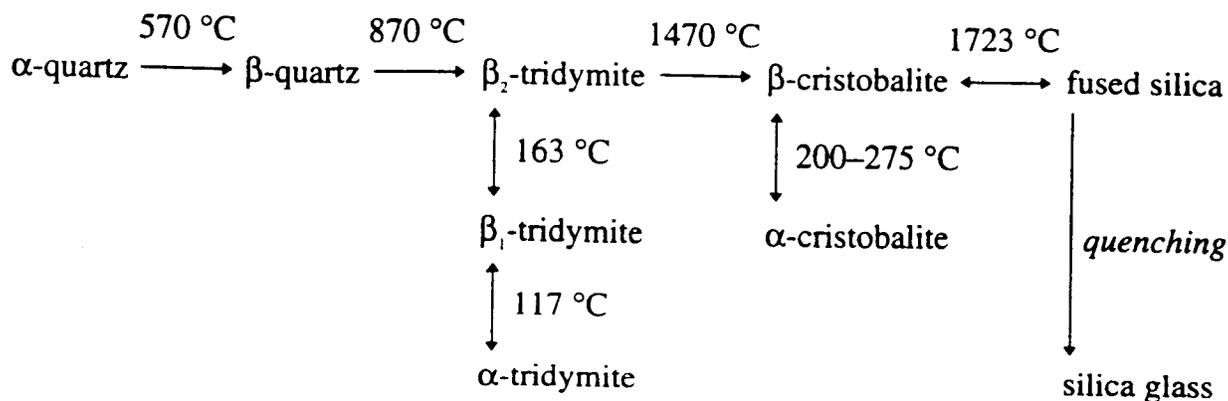
^a From Deer *et al.* (1966)

The following polymorphs are obtained at high pressure: coesite, produced at 450–800 °C and at 38 000 atmospheres (3.8×10^6 kPa), found in rocks subjected to the impact of large meteorites; keatite, synthesized at 380–585 °C and 330–1200 atmospheres ($33\text{--}121 \times 10^3$ kPa), not commonly found in nature; and stishovite, synthesized at temperatures above 1200 °C and at 130 000 atmospheres (13×10^6 kPa), detected in Meteor crater, Arizona, United States.

These forms of silica are metastable under ambient conditions and can be converted into other polymorphs upon heating (Cerrato *et al.*, 1995). Silica glass exists at room temperature up to about 1000 °C; the rate of crystallization rapidly increases as temperature increases beyond this point. Silica glass is unstable at temperatures below 1713 °C.

The interconversion from one polymorph to another upon heating or cooling may be schematized as follows (Frondel, 1962):

Double arrows indicate a rapid interconversion.



The different arrangements of tetrahedra in the various polymorphs and the presence of octahedrally coordinated silicon in stishovite imply remarkable differences in density and in the distance between the silicon and oxygen atoms. A relationship between these

parameters and some biological responses (i.e. hydroxyproline as a measure of fibrosis *in vivo* and percentage haemolysis as a measure of red blood cell membrane lysis) have been proposed (Wiessner *et al.*, 1988). Atom distances, bonding angles and percentage volume occupied by the atoms in the unit cell have been related to the biological responses elicited (Mandel & Mandel, 1996).

The general features of the formation and reversion of the amorphous phases of silica are reported by Sosman (1965). Conversion from the crystalline to amorphous form may occur by grinding (Steinicke *et al.*, 1982, 1987) or by melting and rapidly cooling down the melt. The vitreous phase is metastable and under ambient conditions remains in that state for long periods of time (years). Conversely, crystallization into various forms may take place during heating or under geothermal conditions. Biogenic silicas are readily converted into cristobalite under relatively mild temperature conditions (*c.* 800 °C), well below the temperature range of thermodynamic stability of cristobalite (Kadey, 1975; Jahr, 1981; Rabovsky, 1995).

The so-called cryptocrystalline forms of quartz — chalcedony, agate, flint, chert, novaculite — are the products of geological crystallization into fine-grained varieties of quartz (Fron del, 1962)

1.1.4 *Chemical properties*

(a) *Solubility in water*

Silica is rather poorly soluble in water and solubility is higher for the amorphous than for the crystalline morphologies. The solubility of the various phases of silicas is very complex and depends upon several factors (Iler, 1979). Solubility increases with temperature and pH and is affected by the presence of trace metals. Particle size influences the rate of solubility. The external amorphous layer in quartz (the Beilby layer) is more soluble than the crystalline underlying core.

(b) *Reactivity*

Silica is attacked by alkaline aqueous solutions, by hydrofluoric acid and by catechol (Iler, 1979). The rates of etching in hydrofluoric acid vary in the following sequence (King & Nagelschmidt, 1960; Flörke & Martin, 1993): stishovite < coesite < quartz < tridymite, cristobalite < vitreous silica (Coyle, 1982).

Etching in hydrofluoric acid eliminates the Beilby layer (Fubini *et al.*, 1995) on quartz (see Section 1.1.2). Stishovite is almost insoluble in hydrofluoric acid and coesite reacts at a much lower rate than quartz or vitreous silica. Hydrofluoric acid solutions can thus be used to separate the various polymorphs (Stalder & Stöber, 1965).

1.1.5 *Surface properties*

The major surface properties of silicas have been reported by Iler (1979) and have recently been reviewed by Legrand (1997). Surface properties are not only determined by the underlying crystalline structure but also by the origin and thermal and mechanical history of the dust and by the presence of contaminants.

(a) *Hydration and hydrophilicity*

The surface of silica reacts with water vapour from the ambient air to form an external layer of silanols (SiOH). This process may be extremely slow (smooth surfaces with stable siloxane bridges, Si–O–Si) or very fast (fresh defective surfaces, strained siloxane bridges). The part of the surface covered by a dense layer of silanols is hydrophobic (Bolis *et al.*, 1991). Under the same conditions of humidity, the various polymorphs show a different degree of hydrophilicity — quartz and stishovite being the most hydrophilic and pyrogenic amorphous silica the most hydrophobic (Cerrato *et al.*, 1995).

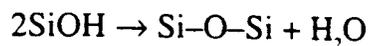
(b) *Mechanical fracture*

Cleavage seldom occurs on defined crystal planes and fractures are conchoidal. Dusts originated by quartz grinding have a peculiar reactivity arising from the homolytic and heterolytic rupture of the silicon–oxygen bonds, which leaves unsatisfied valencies as unpaired electrons (surface radicals) and surface charges (Antonini & Hochstrasser, 1972; Fubini *et al.*, 1989). A similar, even more pronounced effect takes place with tridymite and cristobalite (Fubini *et al.*, 1989, 1990). The effect is less pronounced with coesite and does not occur with stishovite (Fubini *et al.*, 1995). If grinding is performed in dry air, oxygen or hydrogen peroxide aqueous solutions, reactive oxygen species (ROS) — SiO_2^{\cdot} and $\text{Si}^{\cdot}\text{O}_2^-$ — are formed (Dalal *et al.*, 1989; Fubini *et al.*, 1989, 1990; Fubini, 1997). Conversely, if grinding takes place in a wet atmosphere, silanols are formed rather than surface radicals (Volante *et al.*, 1994).

In aqueous suspensions, freshly ground surfaces generate ROS (Vallyathan *et al.*, 1988). Whether the ROS arise from the silica itself or from certain impurities exposed at the surface during the grinding procedure is still under debate; acid washing decreases the radical yield (Miles *et al.*, 1994).

(c) *Thermal treatments*

The presence and extent of silanols at the surface of a silica sample determines its hydrophilicity. Upon heating, silanols condense into siloxanes with elimination of water:



This reaction progressively converts hydrophilic surfaces to hydrophobic ones (Fubini *et al.*, 1995). When cooling down under ambient conditions, some water uptake takes place, with partial reconversion of siloxanes into silanols. However, high temperature and prolonged heating stabilize surface siloxane with consequent inhibition of rehydroxylation. The surface is thus metastably hydrophobic and remains as such for very long periods of time.

The above reaction occurs more readily with amorphous silicas, in which the silicon tetrahedra are able to move more easily than in the crystalline forms where the silanols are stabilized in ordered arrays. As a consequence, crystalline particles are more hydrophilic than amorphous ones when submitted to the same heating procedure.

Heating also removes defects and radicals originated by grinding (Fubini *et al.*, 1989).

(d) *Etching*

Etching with hydrofluoric acid, alkaline hydroxides or catechol modifies the surface of silica samples (Iler, 1979). External layers are attacked with the progressive elimination of surface radicals (Costa *et al.*, 1991). With hydrofluoric acid, the external surface is smoothed out and the specific surface area decreases. This effect is due to the smoothing out of the fractal part of the surface and to the total dissolution of smaller particles rather than the simple reduction in the dimensions of each particle (Fubini *et al.*, 1995). As a consequence, the size distribution of an etched sample reveals a higher proportion of larger particles.

Etching also eliminates impurities that can modulate silica toxicity (King & Nagelschmidt, 1960; Nash *et al.*, 1966; Nolan *et al.*, 1981).

(e) *Metal contaminants*

Metal impurities modify the surface reactivity of silica samples. Aluminium decreases silica solubility (Iler, 1979). Transition metal ions (typically iron), adsorbed at the surface, activate the production of free radicals in aqueous suspensions (Vallyathan *et al.*, 1988).

1.1.6 *Impurities*

Major impurities in crystalline silica polymorphs include aluminium, iron, titanium, lithium, sodium, potassium and calcium (Frondel, 1962). The concentrations of these impurities vary from specimen to specimen but are generally below 1.0% in weight as oxide (Heaney & Banfield, 1993). Aluminium readily substitutes for silica in a tetrahedral framework. This substitution is generally coupled with the introduction of a monovalent or divalent cation into a vacant site. Alkali cations are too large to substitute for silicon but offset the charge imbalance created by other substitutions located in the open cavities within the framework. Iron may be present in silica polymorphs at either position up to a few tenths of a percentage by weight (Guthrie & Heaney, 1995). Very pure quartz is rare. Even the pure quartz dust with the trade name of Min-U-Sil, sold in different particle sizes, was found to contain iron in traces (Daniel *et al.*, 1993). Very pure samples can be obtained from purification of the melt.

Commercial products derived from silica sand, sandstone and quartzites are granular materials with a high silica content, mostly quartz. Impurities in this case may be up to 25% but are usually about 5%. Different particle sizes may be found among these products; those consisting of very fine grains are called silica flours.

Diatomaceous earths have a variable silica content usually between 86 and 94%. Being sedimentary rocks, other sediments are usually associated. The chemical composition of diatomite ores from different countries has been reported by Kadey (1975). All have been found to contain, albeit in different percentages, Al_2O_3 , Fe_2O_3 , TiO_2 and the following elements in ionic form: calcium, magnesium, sodium and potassium; some also contain phosphates. The crystalline silica content of uncalcined diatomaceous earth is 0.1–4.0%. Commercial products are calcined at temperatures far below those required for the conversion of quartz into the other polymorphs. Under these conditions, a large

proportion of the material is converted into cristobalite (Kadey, 1975; Fubini *et al.*, 1995; Rabovsky, 1995); traces of tridymite may also be produced (Eller & Cassinelli, 1994). The cristobalite content of straight-calcined flux products is typically 10–20% and that of flux-calcined products 40–60% (Champeix & Cetilina, 1983).

Synthetic amorphous silicas are generally of very high purity. Pyrogenic silica after drying is typically > 99.8% silica, with alkali and heavy metals in the low ppm range and the hydrochloric acid content < 100 ppm. Precipitated silicas initially contain residues from the salts formed in the production process and other metal oxides in trace amounts. Silica gels and special precipitated grades are subjected to washing steps, which reduce their contamination by metal oxides (such as Al_2O_3 , TiO_2 , Fe_2O_3) to the 100–1000 ppm level (Ferch & Toussaint, 1996).

1.1.7 Sampling and analysis

(a) Air sampling and analysis for silica

In the past, assessment strategies for airborne crystalline silica were generally based on particle count procedures. Using sampling instruments such as the konimeter, thermal precipitator or impinger, airborne dust samples were collected and then examined by light microscopy. In some cases, selective counting rules were used to reject particles not considered to be respirable (Hearl & Hewett, 1993) or, in the case of mixed dust, not considered to be silica (see Section 1.3.2 for further information on historical sampling methods for occupational exposure).

Currently, filter collection methods, coupled with X-ray diffraction or infrared spectrophotometry (IR) are favoured for the assessment of the silica concentration of airborne dusts. In the case of crystalline silica, most countries (e.g. the United States, the United Kingdom, Germany, Japan and Australia) require that the sample be restricted to the respirable fraction. In contrast, amorphous silica can also be assessed using a total dust sample. Based on the information available, it appears that, internationally, the X-ray diffraction and IR methods are equally acceptable, except in Sweden and Japan in which only the X-ray diffraction method is permitted (Madsen *et al.*, 1995).

One standard procedure in the United States for crystalline silica (NIOSH Method 7500) employs a sampling train fitted with a 10-mm nylon cyclone and a polyvinyl chloride (PVC) membrane filter, running at a 1.7 L/min flow rate. After sampling is complete, the filter is removed and subjected to low-temperature ashing or dissolution, and the resulting dust is assessed for crystalline silica using X-ray diffraction. NIOSH Method 7602 is similar, but uses IR for analysis.

In NIOSH Method 7501 for amorphous silica, the sample is subjected to X-ray diffraction analysis before and after heating to 1500 °C (fumed silica) or to 1100 °C (other amorphous silica). The concentration of amorphous silica is calculated from the difference in the two cristobalite concentrations (Eller & Cassinelli, 1994).

Quartz, tridymite and cristobalite can be distinguished by X-ray diffraction because their strongest reflections (i.e. peaks in the diffractograms) are different (see Section 1.1.2). The detection limit in respirable dust samples is about 5 µg for quartz and 10 µg

for cristobalite; these limits approximate to an atmospheric level of 0.01–0.02 mg/m³ for a 0.5 m³ air sample (Bye *et al.*, 1980; Bye, 1983).

(b) *Surface analysis*

In view of the most recent results, bulk analysis alone does not appear to be sufficient to predict the level of biological activity — it is largely the exposed surface of silica that determines its toxicity. Clay occlusion of respirable quartz particles may be detected by low-voltage scanning electron microscopy X-ray analysis (Wallace *et al.*, 1990). An alternative way is to determine the surface composition by laser microprobe mass analysis, which examines the outermost layers of individual particles (Tourmann & Kaufmann, 1994). The technique uses a laser to vaporize and ionize a small volume of material near the surface of a single particle. The ions generated are identified with a time-of-flight mass spectrometer.

Several techniques can be used to examine the various surface properties of particulate materials such as adsorption capacity, hydrophilicity and potential for free radical release; these techniques are described in Fubini (1997). Detailed surface analysis can be carried out with X-ray photoelectron spectroscopy, scanning electron microscopy with energy dispersion X-ray analysis, and several adsorption techniques. These techniques are too sophisticated for routine analysis.

Recent data reveal variation in the biological responses to crystalline silica samples that are identical in their bulk properties (Hemenway *et al.*, 1994; Daniel *et al.*, 1995; Fubini *et al.*, 1995). These differences must be related to surface properties — hydrophilicity, surface radicals, defects — or to different levels of surface impurities. In both hypotheses, surface analysis is required to define the potential hazard of a given dust.

1.2 Production and use

1.2.1 Production

Most silica in commercial use is obtained from naturally occurring sources. Several synthetic amorphous silicas (listed in Section 1.1.1) are, however, prepared for various purposes, and cultured quartz monocrystals are used in particular applications.

(a) *Sand and gravel*

Silica-bearing deposits are found on every continent and from every geological era. The majority of deposits that are mined for silica sands consist of free quartz, quartzites and sedimentary deposits, such as sandstone (Harben & Bates, 1984).

Industrial sand and gravel, often referred to as 'silica sand' and 'quartz sand', include high-silica-content sand and gravel (United States Department of the Interior, 1994). Table 4 summarizes recent data on the production of silica sand in major producing countries.

Processing operations depend both on the nature of the deposit and on the end product required. They generally include crushing and milling for refining particle size and wet/dry screening to separate very fine particles (Davis & Tepordei, 1985).

Table 4. Silica sand and gravel production^a

Region/country	Production (10 ⁶ tonnes)	
	1990	1994
Africa	2.6	2.6
Asia	8.2	8.2
Oceania	2.6	3.3
Europe		
Belgium	2.6	2.5
France	3.5	6.0
Germany	11.2	10.0
Italy	4.3	4.0
Netherlands	25.1	20.0
Spain	2.2	2.0
United Kingdom	4.3	3.6
North America		
Canada	2.1	1.6
Mexico	1.2	1.4
USA	25.8	27.9
South America		
Argentina	0.3	0.4
Brazil	2.7	2.7
Others	3.5	4.0

^a From United States Department of the Interior 1994)

(b) Quartz crystals

Two different kinds of production may be distinguished: (i) the processing of naturally occurring quartz; and (ii) the hydrothermal culturing of quartz.

The largest reserves of highly pure quartz occur in Brazil. Minor deposits are found in Angola, India, Madagascar and the United States.

Hydrothermally cultured quartz crystals are of major economic importance and their use is growing rapidly. Hydrothermal synthesis consists of crystal growth or reaction at high pressure and temperature in aqueous solution in sealed steel autoclaves (Flörke & Martin, 1993). Synthetic quartz crystal production is concentrated in Japan, Russia and the United States. Smaller production capacity exists in Belgium, Brazil, Bulgaria, China, France, Germany, the Republic of South Africa and the United Kingdom (United States Department of the Interior, 1994).

(c) Refractory silica

Silica bricks are manufactured from mixtures of ground quartz arenite and quartzite and are fired at 1450–1600 °C. They are used in certain high-temperature processes and are generally produced in batches. Silica used in refractories must contain > 93% in weight SiO₂. Quartz is mostly transformed into cristobalite, but tridymite is also formed under the action of mineralizers (mainly CaO). The brick consists of nearly equal

amounts of cristobalite, tridymite, residual quartz and a glass phase (Flörke & Martin, 1993).

(d) *Diatomite*

Diatomite is obtained from sedimentary rocks that are mainly composed of the skeletons of diatoms. These skeletons are composed of opal-like amorphous silica and exhibit a wide range of porous fine structures and shapes, which are altered upon calcination. Even the calcined and crystallized product, however, partially retains the original biogenic micromorphology (Iler, 1979). Particle-size distribution, shape and fine structure vary from one deposit to another (Benda & Paschen, 1993).

The most notable commercial source of diatomite is in California, United States, where there is a marine deposit of unusual purity over 300 m thick. Other major deposits that are mined occur in Algeria, Denmark, France, Iceland and Romania (Dickson, 1979; Reimarsson, 1981; Harben & Bates, 1984; Benda & Paschen, 1993).

Diatomite is mined almost exclusively by opencast methods, using bulldozers and other similar equipment to remove the material. Some diatomite is mined underground in Europe, Africa, South America and Asia. In one operation in Iceland, where the mineral lies under water, slurried material is transferred by a pipeline to a processing plant (Kadey, 1975). The processing methods for crude material are fairly uniform worldwide. The general procedure is described by Benda & Paschen (1993) and can be schematized as follows:

Preliminary size reduction → drying, grinding → dried, fine diatomite

Dried, fine diatomite → furnace, 800–1000 °C → grinding → calcined diatomite

Calcined diatomite → alkaline flux, 1000–1200 °C → grinding → flux-calcined diatomite

Calcination and, even more so, flux calcination yield a considerable amount (up to 65%) of crystalline material (cristobalite) (Benda & Paschen, 1993). During calcination, porosity area and specific surface strongly decrease. Some chemical and physical properties of commercially available diatomites used for filtering or as fillers are reported in **Table 5**.

The major producing country is the United States, followed by Denmark and France. Diatomite production by region during the years 1970–94 is presented in **Table 6**.

(e) *Synthetic amorphous silicas*

Commercial/synthetic amorphous silicas have been classified (Ferch & Toussaint, 1996) as 'wet process' silicas (including precipitated silicas and silica gels), pyrogenic ('fumed') silicas and surface-modified silicas. Surfaces of the modified silicas have been rendered hydrophobic, for example, by silylation with dimethyl dichlorosilane.

Worldwide production of synthetic amorphous silicas in 1995 was estimated at 1100 thousand tonnes, including 900 thousand tonnes precipitated silicas, 90 thousand tonnes silica gels and 110 thousand tonnes pyrogenic silicas (Ferch & Toussaint, 1996).

Table 5. Chemical and physical properties of some commercial diatomites^a

Property	Filter, dried, American	Filter, calcined, Danish	Filter, calcined, American	Filter, calcined, French	Filter, calcined, German	Filter, flux-calcined, American	Filter, flux-calcined, French	Filter, flux-calcined, Spanish	Filter, flux-calcined, German
Colour	White grey	Yellow brown	Pink	Yellow brown	Brown	White	White	White	Yellow brown
SiO ₂ (%)	89.0	72.5	90.7	87.5	86.0	89.5	90.7	91.5	90.2
Al ₂ O ₃ (%)	3.5	7.1	3.9	4.3	2.8	4.1	3.9	1.6	2.8
Fe ₂ O ₃ (%)	0.9	5.0	1.4	2.9	4.7	1.6	2.1	0.7	2.5
CaO (%)	1.1	1.2	0.5	1.9	0.6	0.5	1.0	4.4	0.7
Na ₂ O, K ₂ O (%)	0.8	1.4	0.9	0.8	0.7	3.6	3.5	1.9	0.9
Ignition loss (%)	2.0	4.7	0.5	0.7	0.3	0.2	0.1	0.1	0.4
Bulk density (g/L)	107	290	120	140	125	229	200	195	209
pH value	7.0	5.2	7.5	6.9	7.0	10.0	9.7	9.5	6.7
Water uptake (%)	255	200	250	205	201	156	160	200	196
Specific surface area (m ² /g)	19.2	25.4	15.2	13.0	16.1	1.9	1.6	3.0	10.6
Average particle size (μm)	14.2	19.3	15.9	14.1	13.9	22.5	30.1	6.5	14.7
Wet density (g/L)	228	280	271	255	209	297	290	350	357
Permeability (Darcy)	0.06	0.09	0.28	0.09	0.08	1.20	1.60	-	0.08
Crystalline content (%)	2.0	2.2	7.6	9.2	9.8	58.1	59.7	62.7	10.3

^a From Benda & Paschen (1993)

Table 6. World diatomite production 1970–94^a

Region	Major producer	Production (thousands of tonnes)				
		1970	1980	1990	1992	1994
Europe	France	778	733	854	757	611
North America	USA	578	686	692	655	671
Asia	Republic of Korea	8	27	60	87	79
South America	Peru	11	31	50	59	56
Africa	Algeria	12	7	8	5	6
Australia		3	3.6	10	11	11

^a From British Geological Survey (1995)

(i) *Silicas based on the 'wet process'*

This manufacturing process is based mainly on the precipitation of amorphous silicon dioxide particles from aqueous alkali metal silicate solution by acid neutralization. Usually, sulfuric acid is used, although carbon dioxide and hydrochloric acid can be used. Depending on the final pH of the solution, the following two different classes of synthetic amorphous silicas can be obtained: precipitated silicas — obtained in neutral or alkaline conditions; silica gels — obtained under acidic conditions. The main manufacturing steps include precipitation, filtration, washing, drying and grinding (Kerner *et al.*, 1993; Welsh *et al.*, 1993).

(ii) *Pyrogenic silicas*

The manufacturing process for pyrogenic silicas is based mainly on the combustion of volatile silanes, especially silicon tetrachloride, in an oxygen–hydrogen burner. Primary particles (7–50 nm particle size) of amorphous silica fuse together in the high-temperature flame to yield stable aggregates of between 100 and 500 nm in diameter. These aggregates form micron-sized agglomerates. The finely divided silica is separated from the hydrochloric acid-containing off-gas stream in filter stations. The hydrochloric acid content of the product is commonly reduced to less than 100 ppm by desorbing the hydrochloric acid with air in a fluid-bed reactor. Pyrogenic silica appears as a fluffy white powder (Ettliger, 1993; Ferch & Toussaint, 1996). Physico-chemical characteristics of pyrogenic and 'wet-process' silicas are given in **Table 7**.

(iii) *Surface-modified (after-treated) synthetic amorphous silicas*

All forms of synthetic amorphous silicas can be surface-modified either physically or chemically. Methods for chemical modification of the silica particle surface (e.g. silylation) are many and various. Most common treating agents are organosilicon compounds (Ferch & Toussaint, 1996). Less than 10% of the total production volume of synthetic amorphous silica is surface-modified.

Table 7. Characteristic properties of synthetic amorphous silicas

	Pyrogenic	Wet process	
		Precipitated	Silica gel
Specification properties			
Specific surface area (BET) ^a (m ² /g)	50–400	30–800	250–1000
Loss on drying ^b (%)	< 2.5	3–7	3–6
pH ^c	3.6–4.3	5–9	3–8
Tamped density ^d (g/L)	50–150	50–500	500–1000
Ignition loss ^e (%)	1–3	3–7	3–15
Typical (descriptive) properties			
Silanol group density (SiOH/nm ²)	2.5–3.5	5–6	5–6
Primary particle size ^f (nm)	7–50	5–100	3–20
Aggregate size (μm)	< 1	1–40	1–20
Agglomerate size (μm)	1–100	3–100	NA
Specific gravity ^g (g/mL)	2.2	1.9–2.1	2.0
DBP absorption ^h (mL/100 g)	250–350	175–320	100–350
Pore size (nm)	NA	> 30	2–20
Pore size distribution	NA	Very wide	Narrow

From Ferch & Toussaint (1996)

^aDIN 66131; ^bDIN ISO 727/2; ^cDIN ISO 787/9; ^dDIN ISO 787/11; ^eDIN 55921;

^fPrimary particles not existent as individual units; ^gDIN ISO 787/10; ^hDIN 53601

NA, not applicable; BET, Brunauer–Emmett–Teller

1.2.2 Use

(a) Sand and gravel

Silica sand has been used for many different purposes for many years; its most ancient and principal use throughout history has been in the manufacture of glass (Davis & Tepordei, 1985). Sands are used in ceramics, foundry, abrasive, hydraulic fracturing applications and many other uses (Table 8).

As illustrated in Table 8, several uses require the material to be ground. In some uses (e.g. sandblasting, abrasives), grinding also occurs during the use.

Refractory silica bricks, in which silica is converted by heat into cristobalite and tridymite are used in sprung arches of open-hearth furnaces, covers of electric furnaces, roofs of glass-tank furnaces, blast pre-heaters and coke and gas ovens (Flörke & Martin, 1993).

(b) Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine). Large quantities of pure crystals were required when the application of pure quartz in the electronics industry was discovered. At present, the major demand comes from both electronics and optical components industries.

Table 8. Industrial sand and gravel sold or used by United States producers in 1994, by major end use^a

Sand	
Glass-making	Containers, flat (plate and window), speciality, fibreglass (un-ground or ground)
Foundry	Moulding and core, moulding and core facing (ground), refractory
Metallurgical	Silicon carbide, flux for metal smelting
Abrasives	Blasting, scouring cleansers (ground), sawing and sanding, chemicals (ground and un-ground)
Fillers	Rubber, paints, putty, whole grain fillers/building products
Ceramic	Pottery, brick, tile
Filtration	Water (municipal, county, local), swimming pool, others
Petroleum industry	Hydraulic fracturing, well packing and cementing
Recreational	Golf course, baseball, volleyball, play sands, beaches, traction (engine), roofing granules and fillers, other (ground silica or whole grain)
Gravel	
	Silicon, ferrosilicon, filtration, non-metallurgical flux, other

^a From United States Department of the Interior (1994)

An electronic-grade quartz crystal is a single-crystal silica that is free from defects and has piezoelectric properties that permit its use in electronic circuits for accurate frequency control, timing and filtering. These uses generate most of the demand for electronic-grade quartz crystals. A smaller amount of optical-grade quartz crystal is used in windows and lenses in specialized devices, including some lasers. Cultured (synthetic) quartz has replaced natural crystal in most of these applications (United States Department of the Interior, 1994).

(c) *Diatomites*

The main uses of diatomites are in filtration (60% of world production), as fillers (25% of world production) and in other uses (insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, packing material) (Benda & Paschen, 1993).

The intricate microstructure and high pore-space volume of diatomite have made it a major substrate for filtration. Diatomite has been used to filter or clarify dry-cleaning solvents, pharmaceuticals, beer, wine, municipal and industrial water, fruit and vegetable juices, oils and other chemical preparations (Kadey, 1975).

The next most important application of diatomite is as a filler in paint, paper and scouring powders. It imparts abrasiveness to polishes, flow and colour qualities to paints and reinforcement to paper. It is also used as a carrier for pesticides, a filler in synthetic rubber goods, in laboratory absorbents and in anti-caking agents (Kadey, 1975; Sinha, 1982).

(d) Synthetic amorphous silicas

Consistent with their physico-chemical and morphological properties, the different classes of synthetic amorphous silicas find uses in very different areas of application. However, most of the applications are related to the reinforcement of various elastomers, the thickening of various liquid systems, the free-flow of powders or as a constituent of matting, absorbents and heat insulation material (Ferch & Toussaint, 1996). Table 9 lists the major applications of synthetic amorphous silicas.

Table 9. Major applications of finely divided synthetic amorphous silicas^a

Silica type	Application	Critical properties
Precipitated silica	Rubber reinforcement	Particle size, surface area
	Free-flow, anti-caking	Aggregate size, porosity
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
Silica gels	Paints: flattening	Aggregate size
	Desiccant, adsorbent	Porosity
	Paints: flattening	Aggregate size
Pyrogenic silica	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
	Silicone rubber reinforcement	Surface area, purity, structure
	Heat insulation	Aggregate size, purity
	Rheology control (numerous liquid systems)	Surface chemistry, aggregate/agglomerate size

^a From Ferch & Toussaint (1996)

1.3 Occurrence and exposure

1.3.1 Natural occurrence

Silicon is the second most abundant chemical element, after oxygen, in the earth's crust accounting for 28.15% of its mass (Carmichael, 1989). Silicate minerals (such as plagioclase, alkali feldspars, pyroxenes, amphiboles, micas and clays, excluding silica) comprise together 80% by volume of the earth's crust, while quartz, by far the most common form of silica in nature, comprises 12% by volume of the crust (Klein, 1993). Note that standard mineral composition tables often combine silica and silicates as percentage SiO₂ (or percentage silica).

Crystalline silica

Quartz in its α form is abundant in most rock types, sands and soils. Table 10 reports the average quartz composition of major igneous and sedimentary rocks. Important differences can be observed in the composition of the various rocks. In igneous rocks, quartz is a common component of acid (granitic) and intermediate (e.g. syenites, andesites) plutonic rocks. However, quartz occurs at very low levels or is absent from the basic and ultra-basic varieties (e.g. trachytes, gabbros, olivines, peridotite). Quartz may also be present in a variety of volcanic tuffs (United States Bureau of Mines, 1992).

Table 10. Average quartz composition of major igneous and sedimentary rocks^a

Rock type	Quartz-containing rock	% Quartz (by weight)
Igneous	Rhyolites	33.2
	Alkali granites	32.2
	Alkali rhyolites	31.1
	Granites	29.2
	Quartz latites	26.1
	Quartz monzonites	24.8
	Quartz diorites	24.1
	Granodiorites	21.9
	Rhyodacites	20.8
	Dacites	19.6
	Latite andesites	7.2
	Andesites	5.7
	Syenites	2.0
	Monzodiorites	2.0
	Alkali syenites	1.7
Diorites	0.3	
Sedimentary	Sandstones	82
	Greywackes	37
	Shales	20

^a From Carmichael (1989)

Quartz, being a hard, inert and insoluble mineral, endures through the various weathering processes and is found in trace to major amounts in a variety of sedimentary rocks. It is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. There are a variety of sandstones, including orthoquartzite in which the grains are 95% quartz and the cement is a precipitate or a film of clay. Greywacke is considered a variety of sandstone. Quartz is also common in siltstone. Sand is composed of quartz predominantly, while gravel is of variable composition. Argillaceous rocks, including shales, clays and mudstones, may contain substantial amounts of quartz, depending on the varieties. Wyoming bentonite, a valuable clay, contains up to 24% crystalline silica (quartz and cristobalite). In coal, quartz constitutes typically up to 20% of the mineral matter (Greskevitch *et al.*, 1992). Illinois coal has been reported to contain 1.2–3.1% quartz. Diatomaceous earth typically contains 0.1–4% quartz. Limestones may contain a small proportion of quartz (Atkinson & Atkinson, 1978; Harben & Bates, 1984; United States Bureau of Mines, 1992; Klein, 1993; Ross *et al.*, 1993; Parkes, 1994; Weill *et al.*, 1994).

In metamorphic rocks, quartz is a common constituent either an original constituent, as a product of the metamorphic process or by crystallization from silica-bearing fluids. It is an important constituent of metamorphic phyllites, mica schists, migmatites, gneiss and quartzites. It has been reported to comprise 31–45% of the mineral content of

Ardennes slate and 20–50% of taconite (Atkinson & Atkinson, 1978; United States Bureau of Mines, 1992; Heaney & Banfield, 1993; Ross *et al.*, 1993).

Quartz is the primary gangue (or matrix) mineral in the metalliferous veins of ore deposits. In nature, quartz can also be found in important colour varieties — amethyst, citrine, smoky quartz, morion, tiger's eye — which are valued as semi-precious stones. Quartz crystals are frequently found in cavities and also occur in hollow globular forms called geodes (Atkinson & Atkinson, 1978).

Tridymite and cristobalite, formed during the devitrification of siliceous volcanic glass, can be found as fine-grained crystals in acid volcanic rocks. Furthermore, cristobalite is present in some bentonite clays and may be present as traces in diatomite (Heaney & Banfield, 1993; Ross *et al.*, 1993; Parkes, 1994).

Coesite and stishovite have been found in rocks that equilibrated in short-lived high pressure environments, such as meteoritic impact craters. Keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources (Heaney & Banfield, 1993; Guthrie & Heaney, 1995).

Amorphous silica

Amorphous silica is widespread in nature as biogenic silica and non-biogenic silica glass.

Silica glass forms as volcanic glass (obsidian) from extrusive magmas, as lechatelierite within tektites associated with meteorite impact craters and as fulgurite resulting from lightning strikes on unconsolidated sand or soil (Heaney & Banfield, 1993).

Silica of biological origin is produced by diatoms, radiolarians and sponges which extract silica dissolved in water to form their structures or shells. Biogenic amorphous silica levels in diatoms vary with species and range from less than 1% to almost 50% by weight. Siliceous oozes on the sea floor, which derive from the skeletons of diatoms, solidify to form opaline deposits. Opaline materials characterize diatomaceous earth deposits and are also found in bentonite clays. Diatomaceous earth is typically 90% amorphous silica (Heaney & Banfield, 1993; Ross *et al.*, 1993; Rabovsky, 1995).

Biogenic silica is also produced by a variety of plants. Internal silicification of plant tissues promotes structural integrity and affords protection against plant pathogens and insects. The silica content is especially high in grasses, and silica can account for approximately 20% of the dry weight of rushes, rice and sugar cane. Amorphous silica in plants may be deposited as nodules or phytoliths — very tiny pure amorphous silica grains of a myriad of shapes and sizes — in many plants and trees (Heaney & Banfield, 1993). Some of the amorphous silica in plants (e.g. sugar cane, canary grass, wheat, rice, conifer needles) exists as fibres or spicules of various forms. Plant biogenic silica is released to the soil through burning or normal decay; soil concentrations are typically in the range of < 1 to 3% (Newman, 1986; Boeniger *et al.*, 1988; Lawson *et al.*, 1995).

1.3.2 Occupational exposure

Crystalline silica

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. Thus, between 1980 and 1992, compliance officers of the United States Occupational Safety and Health Administration found respirable quartz to be present in samples taken in 255 industries of differing Standard Industrial Classification codes, excluding mining. In 48% of those industries, average overall exposure exceeded permissible exposure levels (Freeman & Grossman, 1995).

Crystalline silica is probably one of the most documented workplace contaminants; the severity of its health effects and the widespread nature of exposure have been long recognized. Reviews on occupational exposures to crystalline silica can be found in a number of reports (United States National Institute for Occupational Safety and Health, 1974, 1983; World Health Organization, 1986; Hilt, 1993; Weill *et al.*, 1994). **Table 11** presents a number of industries, jobs or operations where occupational exposure to crystalline silica has been reported, together with the origin or source of the silica.

Table 11. Main activities in which workers may be exposed to crystalline silica^a

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	Sand, concrete
	Highway and tunnel construction	Rock
	Excavation and earth moving	Soil and rock
Glass, including fibreglass	Masonry, concrete work, demolition	Concrete, mortar, plaster
	Raw material processing	Sand, crushed quartz
Cement	Refractory installation and repair	Refractory materials
	Raw materials processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production	Sand
	Abrasive products fabrication	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

Table 11 (contd)

Industry/activity	Specific operation/task	Source material
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	Sand
	Abrasive blasting, fettling	Sand
	Furnace installation and repair	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	Semi-precious gems or stones, abrasives
Dental material	Sand blasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concretions

" From Kusnetz & Hutchison (1979); Corn (1980); Webster (1982); United States National Institute for Occupational Safety and Health (1983); Froines *et al.* (1986); Lauwerys (1990); United States Bureau of Mines (1992); Hilt (1993); Weill *et al.* (1994); Burgess (1995)

Although not exhaustive, the following section focuses on representative data in the main industries where quantitative exposure levels are available in the published literature and/or where major occupational health studies have been conducted. These 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.

The reporting of exposure levels to crystalline silica in the scientific literature has changed considerably over the years with the evolution of the various sampling techniques and strategies, the development of improved analytical methods and the formulation of occupational exposure limits reflecting advances in the understanding of particle penetration and effects in the respiratory system.

In the first half of the twentieth century, sampling techniques varied from country to country, and airborne particles were collected with a variety of devices, such as koni-

meters, Owen's jets, electrostatic or thermal precipitators, and impingers (Patty, 1958; Ayer, 1969; Harris & Lumsden, 1986). Exposure levels were usually reported as number of particles per unit volume, with particles counted by microscopy. No relationship could be established between the results of these various older methods.

In the United States, impinger methods (Greenburg-Smith or midget impingers) were commonly in use until the early 1970s. Dust levels, whether based on counts from an impinger or on mass collected on a filter, were associated frequently with data on the crystalline silica content of the dust. Considerable differences in estimates of crystalline silica content obtained by these methods may result, depending on the nature of interfering materials, on the analytical techniques used (whether chemical, petrographic or spectroscopic) and on the origin of the dust sample being analysed (Patty, 1958; Harris & Lumsden, 1986).

Crystalline silica content has been found to be usually smaller in airborne than in settled dust and in respirable than in total airborne dust (Ayer, 1969; Hearl & Hewett, 1993). However, there are exceptions to this general rule (Jorna *et al.*, 1994).

Various limitations of the impinger method led to its decreasing use; sampling times were too short (10–30 min), the complexity of the sampling procedure prevented personal samples being taken, the impinger could not trap particles $< c.$ 0.5–0.7 μm in size, and there was also found to be large inter-observer variability (Patty, 1958; Ayer, 1969; Hearl, 1996). On the other hand, however, total mass concentration, as collected on a filter, had the disadvantage of not being able to take into account particle size, which plays a major role in the hazards associated with crystalline silica inhalation (Ayer, 1969).

The introduction in the 1970s and the current generalized use of respirable mass sampling methods in most countries has made it possible to compare data realistically between various studies. In addition, conversion factors can be applied to filter-respirable mass concentration (in mg/m^3) and impinger-particle count levels (in million particles per cubic foot; mppcf) to integrate past and present evaluations. Conversion factors may differ, however, depending on the nature of the dust (Sheehy & McJilton, 1987; Montgomery *et al.*, 1991).

A number of factors remain to be taken into account when evaluating present data. There are uncertainties in the interpretation of analytical data for microcrystalline silica, or data taken in the presence of various interfering substances; in addition, in cases where the particle size distribution is widely different from that of the standards used, interpretation can be uncertain (Hearl & Hewett, 1993). More importantly, the representativeness of the data has to be evaluated in view of the sampling strategy used, recognizing that compliance inspection data usually have been obtained using a worst-case scenario strategy (Hearl & Hewett, 1993; Lippmann, 1995). A further complication results from the fact that respirable crystalline silica exposure levels are most often not reported directly in mg/m^3 but indirectly in terms of a total respirable mass concentration. This total respirable mass concentration has to be compared (e.g. in the form of a severity factor) with an occupational exposure limit that varies with the content of crystalline silica in the dust. Furthermore, the current practice of collecting only respirable dust has

been questioned by Lippmann (1995) who has argued that thoracic particles (i.e. those available for deposition within the airways of the thorax) may be more important for end-points such as lung and stomach cancer. Finally, it may be noted that industrial hygiene measurement practices do not take into account the surface area of particles, which may well be a relevant indicator of exposure. During the 1960s, crystalline silica dust exposure was measured in a study of South African gold mines as respirable surface area. This measurement was reported to be more strongly related to silicosis than the respirable particle count (Beadle, 1971).

(a) *Mines*

Occupational exposure to crystalline silica in mines originates from the dust generated from the ore being extracted or its associated rock. Mines are usually classified as surface or underground, coal, metal or non-metal; mines may be associated with various milling operations. In the United States, coal is the main mineral being mined primarily underground, together with antimony, lead, tungsten, molybdenum and silver. Surface mining accounts, however, for most of the metallic and non-metallic ores (Burgess, 1995). Exposure to crystalline silica in quarries, the crushed stone and related industries is detailed in a separate section. Exposure to silica in coal mines is covered in the monograph on coal dust in this volume.

The quartz content was determined in 2075 bulk settled dust samples collected from 1984 to 1989 in a representative sample of United States mines (491) from 66 different mineral commodities, including coal. Approximately 50% of all samples had a percentage of quartz above 5%; the overall average was 14%. Commodities with an average quartz percentage above 40% were sand/gravel and sandstone; those between 20 and 40% were copper, granite, lithium, mica, molybdenum, phosphate rock, shale, slate, stone, titanium and uranium–vanadium. For most commodities, wide variations were observed between the various samples. Labourers (surface) and bin pulley/truck loader workers were potentially exposed to bulk dust containing the highest percentage quartz. These data are only indicative of potential risk since settled dust composition may not be representative of inhalable or respirable dusts. Ninety-one per cent of samples analysed for cristobalite yielded non-detectable levels (< 0.75%) and only 4% contained more than 1% cristobalite, most of which came from diatomite calcining facilities (Greskevitch *et al.*, 1992).

Respirable quartz levels of nearly 22 000 samples taken by inspectors from 1988 to 1992 in United States mines are summarized by commodity in **Table 12**. Mean exposure levels were usually below 0.1 mg/m³ but a significant percentage of samples were found to exceed the compliance limit. Mean quartz content of samples by commodity was rarely greater than 15%. Occupations at greatest risk of overexposure were found to be scoop tram, crusher, jackleg stoper drill and load–haul–dump operators (underground occupations); jackhammer and pneumatic drill operators (surface occupations); and packing, packaging or loading, labourer and bullgang workers (milling occupations). The authors indicate various limitations to the representativeness of this data set, the main ones being the compliance sampling strategy and the exclusion of samples containing

less than 1% quartz or corresponding to less than 0.1 mg/m³ respirable dust. These effects would tend towards an overestimation of the exposure indicators (Watts & Parker, 1995).

Table 12. Respirable quartz exposures by commodity in United States mines (1988–92)

Commodity	No. of samples	Quartz (µg/m ³)		% > PEL	Mean % quartz
		GM	GSD		
Underground					
Silver	139	87	2	53.2	13.3
Copper	109	80	2	53.2	7.0
Uranium	67	64	2	43.3	9.7
Uranium and vanadium	73	64	2	41.1	7.5
Gold	238	51	3	31.1	9.0
Crushed limestone	256	42	2	28.5	3.4
Lead and zinc	78	40	2	25.6	6.1
Surface					
Dimension granite	477	78	3	44.0	13.5
Iron	180	45	3	27.8	13.0
Gold	547	52	3	26.1	12.6
Crushed traprock	159	42	3	25.8	10.7
Crushed stone	355	46	3	25.4	11.3
Crushed sandstone	412	51	3	24.3	19.5
Crushed granite	826	42	3	19.9	12.6
Sand and gravel	3843	40	3	17.4	13.1
Common clay	129	38	2	16.3	10.7
Crushed limestone	2684	32	3	15.1	7.0
Mill					
Non-metallic minerals NEC	151	107	3	55.6	42.7
Crushed sandstone	843	74	3	38.4	27.7
Gold	334	64	3	35.0	15.3
Crushed traprock	245	52	3	33.5	9.7
Crushed stone	306	51	3	30.7	13.2
Common clay	578	53	2	30.5	8.2
Crushed granite	529	50	2	25.5	13.4
Iron	360	47	3	24.7	13.7
Sand and gravel	3664	48	3	23.4	16.1
Crushed limestone	2094	39	3	22.4	7.3

From Watts & Parker (1995)

GM, geometric mean; GSD, geometric standard deviation; PEL, permissible exposure level; NEC, not elsewhere classified

Estimates of exposure to respirable crystalline silica during the period 1950–87 in 20 Chinese mines (10 tungsten, six iron–copper and four tin) have been derived from industrial hygiene data and other historical exposure information. A 10-fold decrease was found between the periods 1950–59 and 1981–87 and the following arithmetic mean levels of respirable silica dust in mg/m³ were estimated to be as follows (older and most

recent period, respectively): underground mining (4.89, 0.39), surface mining (1.75, 0.27), ore dressing (3.45, 0.42), tungsten mines (4.99, 0.64), iron and copper mines (0.75, 0.20) and tin mines (3.49, 0.45). In the surface mining operations, transport and service occupations generally had higher levels of exposure than mine production occupations; the opposite pattern was true in underground mining occupations, while the ore preparation workers were generally more exposed than ore separation or service workers in ore-dressing operations (Dosemeci *et al.*, 1995).

Indications of past and present exposure levels of gold miners have been reported in a number of epidemiological studies. In South Africa, a high crystalline silica content of 30% in respirable dust at the Witwatersrand mine was reported. The levels of dust exposure were reduced during the 1930s to a level ranging from 0.05 to 0.84 mg/m³ for respirable quartz in underground dust (Beadle & Bradley, 1970). At the Homestake gold mine (South Dakota, United States), respirable dust contained 13% crystalline silica and, since engineering improvements in the early 1950s, levels of respirable silica have decreased substantially to within legal limits (Brown *et al.*, 1986). In Ontario (Canada) gold mines, crystalline silica content in hard rock has been reported to vary from 4 to 12% and, based on konimeter data, past levels could have been significantly above current exposure limits (Kabir & Bilgi, 1993).

In two Sardinian mines (one for lead ore and the other for zinc ore), similar concentrations of respirable dust were estimated to be 3–5 mg/m³ in 1945–60 and 1.6–1.7 mg/m³ in 1981–88. However, quartz content differed significantly between the two mines (median values of 1.2% and 12.8%, respectively) because of differing wall rock composition (Carta *et al.*, 1994). In a copper mine in Finland, respirable dust contained on average 18.3% quartz; the mean concentration of respirable quartz in the general mine air decreased from about 0.16 mg/m³ before 1965 to 0.08 mg/m³ after 1981 and the mean concentration where loading operations took place decreased from 0.8 before 1965 to 0.15 mg/m³ since 1975. In an old copper mine, respirable quartz was estimated to be above 2 mg/m³ during dry-drilling operations before 1940 (Ahlman *et al.*, 1991). The mining and milling of diatomaceous earth may entail exposures to crystalline silica, notably to cristobalite formed from amorphous silica during the calcination process. Further details on occupational exposures in the diatomaceous earth industry may be found in the section on amorphous silica.

Beside crystalline silica, several other toxic hazards can be found in mines, such as carbon monoxide and nitrogen dioxide from blasting and engine exhausts, nickel and arsenic, depending on rock composition, aldehydes and polycyclic aromatic hydrocarbons from diesel engine exhausts, various metallic and non-metallic compounds such as asbestos, and ionizing radiation from radon daughters (Burgess, 1995). The extent of such exposures is strongly dependent on work practices and varies with commodity and specific vein composition. In the gold mines in the United States and Canada (Ontario) and the Sardinian lead and zinc mines mentioned above, and in a tin mine in south-east China, average working levels of radon daughters have been reported as ranging up to 0.3, which is within the accepted standard; substantial levels of radon daughters have been observed in Chinese copper mines and in some South African gold mines (Brown

et al., 1986; Hnizdo & Sluis-Cremer, 1991; Wu *et al.*, 1992; Kabir & Bilgi, 1993; Carta *et al.*, 1994; Fu *et al.*, 1994). Arsenic has been measured at average levels of a few $\mu\text{g}/\text{m}^3$ in the United States and Canadian gold mines; at the United States gold mine, amphibole asbestos fibres have been measured at mean levels of 0.44 and 1.16 fibres/mL for miners and surface crushers, respectively (Brown *et al.*, 1986).

(b) *Granite quarrying and processing, crushed stone and related industries*

Granite rock, containing from 10 to about 30% quartz, is obtained in quarries and further processed into structural (dimensional) stone or crushed for road materials. Other rocks rich in crystalline silica such as sandstone, flint and slate are also subjected to various quarrying, milling and processing operations to produce building or road materials (Weill *et al.*, 1994; Burgess, 1995). Respirable quartz exposure levels measured in various countries for various jobs in the granite quarrying and processing industries as well as the crushed stone and related industries are summarized in **Table 13**. Exposure data collected by inspectors in the United States appear in **Table 12**.

Respirable crystalline silica levels are related to the crystalline silica content of the rock being quarried or milled; for example, levels have been found to be higher with flint than with granite (Guénel *et al.*, 1989a), and with granite or sandstone than with limestone or traprock (Davies *et al.*, 1994; Kullman *et al.*, 1995). The higher exposure levels have usually been associated with the following jobs or operations: rock and stone drilling and cutting in quarries; dimensional stone cutting and finishing in sheds usually outside quarries; rock crushing, sieving and transport within or outside quarries. In three Russian quarries producing sand and gravel mixtures, the average respirable quartz levels in 1990 ranged from [0.44 to 4.46 mg/m^3] for various stone crusher locations in cold periods of the year and from [0.77 to 1.87 mg/m^3] in hot periods (Kiselev, 1990). In Hong Kong quarries producing crushed stone, average respirable quartz levels in 1982 were measured at 0.93 mg/m^3 for rock drillers, from 0.10 to 0.42 mg/m^3 for various crusher locations and from 0.11 to 0.19 mg/m^3 for screening locations (Ng *et al.*, 1987a). In United States granite quarries and sheds, control measures put in place during the late 1930s and the 1940s resulted in 10–100-fold reductions in what were very elevated dust levels (Davis *et al.*, 1983). Granite stone-cutting is now usually associated with mean levels of respirable quartz below 0.1 mg/m^3 . In the industry as a whole, present control measures include water-mist injection during drilling, local exhaust ventilation, wet methods for cutting granite and the use of control cabins (Health and Safety Executive, 1992a; Davies *et al.*, 1994; Burgess, 1995).

The presence of cristobalite has been reported in a limited number of samples in the road materials industry in Denmark (Guénel *et al.*, 1989a) and traprock crushing operations in the United States (Kullman *et al.*, 1995). Asbestos fibres and other fibrous minerals were found in one of 19 stone crushing facilities investigated in the United States (Kullman *et al.*, 1995). Other constituents of the dusts would depend on the mineral being mined or milled (e.g. silicates, carbonates) (Kullman *et al.*, 1995) and could include abrasives such as silicon carbide and aluminium oxides (Eisen *et al.*, 1984).

Table 13. Occupational exposure to crystalline silica in the granite quarrying and processing industries and the crushed stone and related industries in various countries

Country, year of survey (no. of plants)	Industry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > OEL ^a (%)	Reference
				Mean	Range		
Finland, 1970-72 (32)	Granite quarries, processing yards and crushing plants	Drilling	NR	1.47 GM	0.3-4.2		Koskela <i>et al.</i> (1987)
		Block surfacing	NR	0.82 GM	0.2-4.9		
		Other	NR	(0.12-1.44) GM ^b	0.02-3.6		
Sweden, 1976-88 (NR)	Granite crushing plants	Crushers	42 workers	0.16 ^c		71	Malmberg <i>et al.</i> (1993)
Denmark, 1968-80 (NR)	Road and building material (1968-77)	Drilling, crushing, sieving, granite, flint	80	2.1 ^c (severity) ^d	0.2-135 (severity) ^d	75	Guénel <i>et al.</i> (1989b)
		Stone-cutting (1977-80)	21	0.6 ^c (severity) ^d	0.3-6.3 (severity) ^d	45	
USA, Vermont, 1973-74 (5)	Granite processing	Various	220	(0.055-0.088) GM ^e	0.011-0.210	[35.9]	Donaldson <i>et al.</i> (1982)
USA, Georgia, 1973-74 (12)	Granite processing	Various	255	(0.027-0.063) GM ^e	0.004-0.83	[18.3]	
USA, Vermont, 1970, 1976 (NR)	Granite processing	Various, 1970	467	0.034 GM	0.003 GSD		Eisen <i>et al.</i> (1984)
		Various, 1976	535	0.043 GM	0.003 GSD		
USA, 1979-82 (19)	Crushed stone mining and milling	Various, limestone	295	0.04	ND-0.43	10	Kullman <i>et al.</i> (1995)
		Granite	143	0.06	ND-0.28	22	
		Traprock	121	0.04	ND-0.48	7	
UK, Scotland, 1989-91 (1)	Quarrying and crushing sandstone	Overall	119	0.04 GM	4.0 GSD		Davies <i>et al.</i> (1994)
		Crushers, screens	19	0.09 GM	2.2 GSD		

NR, not reported; GM, geometric mean; ND, not detected; GSD, geometric standard deviation

^aOEL, occupational exposure limit, defined as 0.1 mg/m³ of quartz or calculated with the following formula for respirable quartz dust: 10 mg/m³/(% SiO₂ + 2)

^bRange of geometric means for various jobs

^cAverage of individual assessments for each worker based on yearly dust measurements

^dMedian

^eSeverity defined as the concentration of respirable dust divided by the threshold limit value for quartz

Slate-pencil workers in India are exposed to respirable crystalline silica originating from the sawing of silica-rich [c. 40–50%] slate slabs. A survey of five plants in 1991 found personal respirable dust levels of 0.06–1.12 mg/m³ (average, 0.61 mg/m³; mean free silica content, 15%). Previous surveys in 1982 and 1971, before control measures were implemented, had found levels 10–100-fold higher (Fulekar & Alam Khan, 1995).

(c) *Foundries*

Occupational exposure to crystalline silica in foundries originates mainly in the use of sands in the making of moulds and cores. These sands have quartz contents of 5 to nearly 100%. Quartz and cristobalite, the latter being formed from quartz during the pouring of metal, may further contaminate the work environment during the knocking-out or shaking-out operations and during the removal of adherent sand from the castings by grinding or abrasive blasting operations. Other potential sources of crystalline silica are parting powders such as silica flour applied on the moulds as well as the maintenance and repair of silica-rich refractory materials used in furnaces and ladles (Weill *et al.*, 1994; Burgess, 1995). Detailed descriptions of metal founding operations can be found in McBain & Strange (1983), IARC (1984) and Burgess (1995).

Respirable quartz exposure levels measured for various jobs in foundries of various countries are summarized in **Table 14**. In general, the various studies concur in identifying high-exposure jobs as being related to sand preparation and reclamation, knocking-out or shaking-out, cleaning of castings (fettling, grinding, sandblasting), furnace and ladle refractory relining and repair. In two United States foundries where mullite sand was used as a refractory in moulds, personal respirable dust samples contained cristobalite up to 41% and the occupational exposure limit was exceeded 10 to 20 times in several operations, depending on the plant, notably during dipping, grinding and shaking-out. Cristobalite was present in the original mullite refractory and was also generated by heating the colloidal silica binder used in mould making (Janko *et al.*, 1989). Lower levels usually found in non-ferrous foundries compared to iron and steel foundries have been explained by the lower pouring temperatures of the metal, which results in lower sand contamination of the castings. Other factors may be related to the size of foundries, the size of castings and production rates (Oudiz *et al.*, 1983).

Improvement in plant ventilation and work practices have been credited in a 10–20-fold lowering in respirable crystalline silica exposure levels of fettlers and coremakers between 1977 and 1983 in a United States grey iron foundry (Landrigan *et al.*, 1986). Effective controls include well-designed and maintained local ventilation, baffles and air jets on the ventilation equipment of grinding machines, good housekeeping, use of vacuum systems and of wet sweeping, as well as isolation to prevent cross-contamination (Ayalp & Myroniuk, 1982; United States National Institute for Occupational Safety and Health, 1983; O'Brien *et al.*, 1987, 1992; Health and Safety Executive, 1992b). The substitution of siliceous sands with olivine (olivine is a magnesium iron silicate that contains almost no free silica; Davis, 1979) sands results in decreased exposure levels (Gerhardsson, 1976; O'Brien *et al.*, 1992), but contamination from processes using silica sand must be controlled (Davis, 1979). Silica flour parting powders can be replaced by

Table 14. Occupational exposure to crystalline silica in foundries in various countries

Country, year of survey (no. of plants)	Type of foundry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > 1.2 PEL ^a (%)	Reference
				Mean	Range		
Sweden, 1968-71 (87)	Iron	Various	821	[0.63]	[0.20-4.21] ^b		Gerhardsson (1976)
	Steel	Various, quartz sand		[0.275]	[0.18-0.38]		
Finland, 1972-74 (60)	Iron	Various, olivine sand	1073	[0.130]	[0.0-0.38]		Siltanen <i>et al.</i> (1976)
	Steel	Various	342	[0.19-2.25] ^b		41	
USA, 1976-81 (205)	Iron	Various	1149	[0.19-5.26] ^b		54.4	Oudiz <i>et al.</i> (1983) ^c
	Steel	Various	287			29.8	
	Aluminium	Various	171			23	
	Brass	Various	115			35	
	Other non-ferrous	Various	20			56.4	
	All combined	Melting	55			29.9	
		Pouring	52			45.8	
		Sand system	202			14.6	
		Coremaking	89			29.7	
		Moulding	397			49.0	
Canada (Alberta), 1978-80 (9)	Ferrous	Cleaning	779			35.5	Ayalp & Myroniuk (1982)
		Miscellaneous	166				
		Shaking-out with control	17		0.63-2.60		
		no control	10		0.40-21.3		
		Moulding with control	32		0.35-3.40		
		no control	47		0.95-6.13		
		Sand preparation with control	16		0.74-16.80		
		no control	11		2.44-16.70		

Table 14 (contd)

Country, year of survey (no. of plants)	Type of foundry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > 1.2 PEL ^a (%)	Reference
				Mean	Range		
Canada (Ontario) 1983-88 (2)	Iron	Various	1038	0.086	< 0.01-1.36		Oudyk (1995)
USA, NR (1)	Steel	Hand-grinding	15		ND ^b -0.097 quartz ND ^b -0.094 cristobalite	None	O'Brien <i>et al.</i> (1992)

NR, not reported

^a PEL, permissible exposure limit, defined as 0.1 mg/m³ or calculated with following formula for respirable quartz dust: 10 mg/m³ (%SiO₂ + 2)

^b Range of means for various jobs

^c Government inspection data

^d ND, lower than the limit of detection of 0.015 mg per sample

^e One sample exceeded the PEL for cristobalite of 0.05 mg/m³ by a factor of 2

low-silica powders such as those containing olivine or zircon (Landrigan *et al.*, 1986; Weill *et al.*, 1994).

Although crystalline silica represents a major potential air contaminant, the foundry environment is complex and several other exposures have been documented. For example, polycyclic aromatic hydrocarbons may originate from the thermal decomposition of organic material (such as coal-tar pitch, coal, mineral oils, synthetic resins, vegetable matter) present as additives or binders in sands. Other exposures include various metal fumes and dusts depending on type of metal or alloy produced, carbon monoxide, sulfur dioxide, nitrogen oxides, formaldehyde, amines, phenols, furfuryl alcohol and aliphatic and aromatic hydrocarbons (e.g. benzene) (IARC, 1984; Palmer & Scott, 1986; Burgess, 1995).

(d) *Other metallurgical operations*

In iron and steel mills, occupational exposure to crystalline silica may occur during the installation and repair of refractory material in the lining of furnaces, ovens, troughs and runners (Webster, 1982). In a Canadian electric arc steel making plant, whole-shift personal respirable crystalline silica levels were at or below 0.03 mg/m^3 , except for those associated with the tundish conditioner which were at 0.08 mg/m^3 (Finkelstein & Wilk, 1990). In the production of silicon, ferrosilicon and various silicon-containing alloys, quartz-containing materials are charged and melted in electric arc furnaces. Crystalline silica has been reported in proportions of 1–20% in airborne dust (Corsi & Piazza, 1970; Prochazka, 1971). In a United States ferroalloy plant, respirable crystalline silica levels were highest in the mix house (up to 0.223 mg/m^3) while little or no exposure was found in other departments, except for a ladle worker involved in spraying sand (0.065 mg/m^3) (Cherniak & Boiano, 1983).

(e) *Ceramics, cement and glass industries*

In the manufacture of structural clay products (bricks, pipes, tiles), exposure to crystalline silica depends mainly on the quartz content of the clay or shale that is the principal raw material. Refractory bricks are made with minerals of very high quartz content. In the case of pottery and sanitary ware, flint (100% quartz) is added to clay as a raw material going into the manufacture of the slip. Sand, which may be used as dusting powder, may also contribute to airborne silica in the ceramics industry, as well as the decorative material (glaze) that may be added to the surface (Weill *et al.*, 1994; Burgess, 1995).

Respirable quartz exposure levels measured for various jobs in the ceramics industry of various countries are summarized in **Table 15**. Mixing, moulding, glaze spraying and finishing jobs have been associated with the higher exposure levels, often in the range of $0.1\text{--}0.3 \text{ mg/m}^3$. Successful reduction of exposure levels has been accomplished by simple control measures such as enclosure, use of moisture or water mist, use of non-siliceous dusting compounds, better housekeeping and ventilation (Buringh *et al.*, 1990; Health and Safety Executive, 1992c; Cooper *et al.*, 1993; Burgess, 1995). It has been estimated that silica dust exposure 20–30 years ago in Italian ceramics factories was three- to five-fold higher than in the early 1990s (Cavariani *et al.*, 1995). Cristobalite may be released

Table 15. Occupational exposure to crystalline silica in the ceramics industry in various countries

Country, year of survey (no. of plants)	Industry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > OEL ^a (%)	Reference			
				Mean	Range					
Italy, 1989-92 (10)	Sanitary ware	Moulder	40	0.18 GM	0.02-0.67		Cavariani <i>et al.</i> (1995)			
		Inspection	22	0.26 GM	0.13-0.60					
		Mixer	19	0.12 GM	0.05-0.24					
		Sprinkler	23	0.24 GM	0.06-0.89					
		Warehouse man	13	0.01 GM	0.01-0.02					
		Furnace operator	15	0.44 GM	0.26-0.73					
		Moulder	28	0.02 GM	0.01-0.06					
		Mixer	21	0.04 GM	0.01-1.14					
		Painter	37	0.01 GM	0.01-0.06					
		Warehouse man	17	0.02 GM	0.01-0.04					
		Furnace operator	16	0.02 GM	0.01-0.04					
		USA, NR (1)	Sanitary ware	Casting	15	0.13 GM			95	Cooper <i>et al.</i> (1993)
				Glaze spray	18	0.22 GM			100	
				Glaze preparation	6	0.15 GM			83	
				Casting	24	0.027 GM			8	
Glaze spray	20			0.034 GM		5				
Glaze preparation	6			0.179 GM		50				
South Africa, NR (1)	Wall tiles, bathroom fittings	Various jobs or sections	38	(0.06-0.27) ^b median			Rees <i>et al.</i> (1992)			
							Rees <i>et al.</i> (1992)			
South Africa 1973 (NR) 1974 (NR) 1974 (NR) 1986 (NR) 1987 (NR) 1989 (NR)	Sanitary ware Tiles Sanitary ware Sanitary ware Tiles Sanitary ware	Various Various Various Various Various Various	15			100				
			24			88				
			24			63				
			43			93				
			6			17				
			9			89				

Table 15 (contd)

Country, year of survey (no. of plants)	Industry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > OEL ^a (%)	Reference
				Mean	Range		
United Kingdom, NR (1)	Sanitary ware	Fettlers	19	0.135 GM	2.44 GSD		Higgins <i>et al.</i> (1985)
United Kingdom, NR (4)	Sanitary ware	Casters	58		[0.01-0.187]	[10]	Bloor <i>et al.</i> (1971)
United Kingdom, (NR)	12 sectors of the pottery industry	Various	280 (jobs)	0.085		18	Fox <i>et al.</i> (1975)
USA, 1974-75 (4)	Building bricks	Mixing	21	0.113 GM	0.024-0.427		Anderson <i>et al.</i> (1980)
USA, 1974-75 (2)	Clay pipes	Various other	132	(0.021-0.072) ^c GM	0.0004-0.692		Anderson
South Africa, NR (3)	Brickworks	Various	47	(0.014-0.043) ^c GM	0.008-0.200		Anderson <i>et al.</i> (1980)
Netherlands, 1986-88 (4)	Brickworks	Various	29		0-0.230		Myers <i>et al.</i> (1989)
USA, 1980 (2)	Refractory bricks	Various	30		0-1.120		Buringh <i>et al.</i> (1990)
			8		< 0.004-0.143		Salisbury & Mellius (1982)

Table 15 (contd)

Country, year of survey (no. of plants)	Industry	Job	No. of samples	Air concentration in personal breathing zone (mg/m ³)		Proportion of samples > OEL ^a (%)	Reference
				Mean	Range		
China, 1950-87 (9)	Pottery ^d	All jobs	770 ^e	0.71			Dosemeci <i>et al.</i> (1995)
		Mud preparation workers	131 ^e	(0.45-4.70) ^f			
		Mud forming workers	135 ^e	(0.46-0.63) ^f			
		Finishing workers Service workers	395 ^e 109 ^e	(0.37-0.69) ^f (0.32-0.38) ^f			

NR, not reported; GM, geometric mean; GSD, geometric standard deviation

^a OEL, occupational exposure limit, defined as 0.1 mg/m³ or calculated with following formula for respirable quartz dust: 10 mg/m³/(%SiO₂ + 2)

^b Range of medians for various jobs

^c Range of geometric means for various jobs

^d Historical estimates developed using industrial hygiene data and other historical exposure information

^e Number of historical estimates

^f Range of arithmetic means for various job titles

during repair of refractory materials used in the fabric of kilns (Health and Safety Executive, 1992c).

Even though crystalline silica constitutes the main health hazard in the ceramics industry, other exposures may be found in certain operations. For example, talc is sometimes used in the body of clay products and as a parting compound in sanitary ware manufacture; various metal compounds, such as chromates and lead compounds, are used as pigments in glazes (Thomas *et al.*, 1986; Burgess, 1995).

In the cement industry, crystalline silica exposure may occur during the handling of raw materials that may contain some quartz, such as clay and volcanic tuff, as well as the sand dust may be added in the process. However, once manufactured, normal Portland cement contains little crystalline silica (Prodan, 1983). In a Swedish plant, the quartz content of dust was generally $< 5\%$ and respirable quartz concentrations in areas where raw materials were handled was generally less than 0.1 mg/m^3 . Substantially lower concentrations are reported for workers handling clinker and finished cement (Jakobsson *et al.*, 1993).

In a survey of 17 Italian cement factories, median respirable dust concentrations varied from 0.9 to 7 mg/m^3 depending on sites, but most samples contained $< 1\%$ crystalline silica (Pozzoli *et al.*, 1979).

Sand is a major raw material in the manufacture of glass (IARC, 1993), including fibreglass. When washed sand is used, airborne dust from the mixed batch commonly contains only $1\text{--}5\%$ crystalline silica. In the manufacture of fibreglass, the silica is added to the batch as a finely divided powdered sand of 98.5% or higher silica content (Powell, 1982). In the glass industry in general, the manual unloading of dry sand and the use of crushed quartz are considered to be hazardous procedures. Hazards associated with hand filling of pots in the pot process, more common in the past, have been eliminated in the more modern tank process. Refractory blocks and bricks used in the construction of furnaces and tanks contain crystalline silica including cristobalite and tridymite and exposure may occur during their cutting, sawing and chipping to size (Cameron & Hill, 1983).

Respirable quartz and cristobalite have been measured in the range of $0.004\text{--}0.71 \text{ mg/m}^3$ and $0.1\text{--}0.25 \text{ mg/m}^3$, respectively, in United States man-made mineral fibre plants (Manville, CertainTeed and Owens-Corning Fiberglass companies, 1962–87).

In seven European ceramic fibre plants, respirable crystalline silica was detected in eight of 17 groups where samples were collected. In general the levels were low — individual measurements ranged from 0.01 to 0.25 mg/m^3 . Cristobalite was found in a single sample collected from a bricklayer dismantling de-vitrified ceramic fibre insulation (Cherrie *et al.*, 1989). Exposures to man-made mineral fibres in the glass manufacturing industry have been covered previously in the *IARC Monographs* series (IARC, 1988, 1993).

(f) Construction

In the construction industry, rock drilling, sandblasting and the ubiquitous use of concrete are associated with opportunities for high-intensity silica exposure. In the

United States, some 700 000 construction workers have been estimated to be exposed to crystalline silica from various operations (Lofgren, 1993; Linch & Cocalis, 1994; Centers for Disease Control and Prevention, 1996).

Concrete finishers and masons in the United States involved in operations such as drilling holes through concrete walls, grinding concrete or mortar surfaces, cutting through concrete floors, blocks, walls or pipe and power cleaning concrete forms have been shown to be exposed to respirable quartz levels far exceeding the permissible exposure limit of 0.1 mg/m^3 . The worst exposures were found for dry grinding or cutting in enclosed areas, which presented the potential for exposure to exceed 50 times the permissible exposure limit. The nature of the data — inspections targeting the worst-case scenarios — renders these levels only indicative (Lofgren, 1993).

Hong-Kong caisson workers involved in pneumatic drilling and manual excavation of a granite-rich soil were found to be exposed to respirable silica levels exceeding the threshold limit value (TLV) in 65% of 87 air samples (average sampling time of 4 h) taken both inside and at the surface of the caisson, with a median severity factor of 4.2. Dry pneumatic drilling inside the caisson was associated with the highest exposure levels (median severity factor of 71) (Ng *et al.*, 1987b).

Construction site cleaners in Finland have been shown to be exposed to high concentrations of respirable quartz (mean level and range, $0.45, 0.01\text{--}2.1 \text{ mg/m}^3$; mean sampling time, 91 min) especially in dry sweeping operations and in some assisting work phases (Riala, 1988).

(g) *Sandblasting of metal surfaces*

Siliceous sands have been used in the past as abrasives in sandblasting operations designed to remove surface coatings, scale, rust and fused sand from metal surfaces in preparation for subsequent finishing operations. This includes indoor operations in metal fabrication facilities as well as outdoor operations on large equipment such as ships, trucks, trains, bridges, towers and water tanks (Burgess, 1995). This practice is still current in some industries in several countries including the United States and Canada.

Occupational exposure to respirable crystalline silica dust was determined in United States steel fabrication yards. In one study, the average external exposure level was 4.8 mg/m^3 for sandblasters (63 samples); when measured inside non-air-supplied hoods, average levels exceeded the occupational exposure limit by four to 80 times depending on the rate of work; for sandblasters using air-supplied hoods average concentrations still exceeded the occupational exposure limit by three to 34 times. Suspended dust generated by sandblasting resulted in crystalline silica exposure levels of helpers, abrasive-pot handlers, painters, welders and other jobs, all unprotected, exceeding the occupational exposure limit by 7.4, 5.8, 2.2, 1.9, and 1.4 times, respectively (Samimi *et al.*, 1974). In another study, respirable sandblasting dust was shown to spread to such an extent that risk may be unacceptable without some sort of respiratory protection as far away as approximately 700 m from the blasting site. Isolation, personal protection, substitution and recycling of abrasives as well as cleaning/coating of steel before fabrication have

been cited as possible control measures (Centers for Disease Control, 1992; Brantley & Reist, 1994).

(h) *Agriculture*

It is recognized that farming operations may produce large quantities of dust, especially in dry and windy conditions and during the use of machinery. Dust samples obtained from tractor cab filters in rural Alberta (Canada) contained 1–17% quartz (Green *et al.*, 1990), while in North Carolina (United States) quartz levels in the respirable fraction of sandy soils were consistently higher than in clay soils (29% versus 2%) (Stopford & Stopford, 1995).

In California (United States), median concentrations of respirable particulates ranging from 0.50 to 0.95 mg/m³, depending on crop, with a quartz content of 1–12% have been reported for fruit harvesters and from 0.007–0.07 mg/m³ as respirable quartz for rice farming activities; levels of up to approximately 1 mg/m³ of respirable silica have been reported during certain crop processing operations (Popendorf *et al.*, 1982, 1985; Lawson *et al.*, 1995; Stopford & Stopford, 1995). Exposure to biogenic silica fibres during farming operations is presented in the section on amorphous silica.

(i) *Miscellaneous operations*

In denture manufacturing workshops, crystalline silica may originate from refractory coatings, sanding products, polishing pastes and pumice. Eighteen percent of 66 whole-shift personal exposure levels to crystalline silica measured in 32 workshops in France were above the occupational exposure limit (Peltier *et al.*, 1991). In Hong Kong gemstone workers, mean respirable quartz levels for grinder-polishers and buffers of 0.10 ($n = 7$) and 0.16 mg/m³ ($n = 19$), respectively, resulted mainly from the use of silica flour as an abrasive (Ng *et al.*, 1987c). In India, agate workers have been found to be heavily exposed to respirable dust during grinding activities (186 mg/m³, with 70% of free silica [duration not stated]) (Rastogi *et al.*, 1988).

Refractory plasters containing high proportions of quartz and/or cristobalite resulted in two out of four personal crystalline silica levels measured in jewellery manufacturing workshops in France to exceed the occupational exposure limit (Peltier *et al.*, 1994). In the United States, refuse burning, transfer and landfill activities were shown to result in personal respirable quartz levels of up to 0.20 mg/m³ (Mozzon *et al.*, 1987). In another study of waste incinerator workers in the United States, respirable quartz levels were shown to be low (only two of 27 samples contained respirable silica: 0.018 and 0.036 mg/m³) (Bresnitz *et al.*, 1992). In two reports on wildland fire-fighters, personal respirable quartz exposure levels were shown to be usually well below 0.1 mg/m³ (Kelly, 1992; Materna *et al.*, 1992).

The concentrations of quartz and cristobalite were determined in personal samples in two Canadian silicon carbide manufacturing plants using high-purity crystalline silica as raw material charged into the furnace. Mean quartz levels ranged from not detected to 0.112 mg/m³, while cristobalite ranged from not detected to 0.036 mg/m³. Tridymite was shown to be absent from these two plants (Dufresne *et al.*, 1987).

Airborne respirable dust collected in grain elevators in Canada was found to range up to 76 mg/m^3 , depending on work area, and to contain an average of 1.2–6.5% quartz, depending on grain type and stage of treatment. The origin of the quartz is unknown, but its content in the dust seems to be affected by the extent to which the grain has been cleaned (Farant & Moore, 1978).

During the biennial stoppage of a major chemical plant in France, outside contractors' employees were exposed to crystalline silica originating from the removal of refractory brick in a sulfuric acid concentration shop. Personal respirable dust contained up to 3% quartz and 13% cristobalite, resulting in overall crystalline silica levels exceeding the occupational exposure limit in 10 of 14 samples and reaching up to 70 and 80 times that limit (Héry *et al.*, 1995).

Personal respirable crystalline silica exposure levels of maintenance-of-way railroad workers using granite-based ballast has been evaluated in the United States. For broom operators and ballast regulators, 15 and 23% of samples respectively exceeded the permissible exposure limit of 0.1 mg/m^3 (Tucker *et al.*, 1995).

Amorphous silica

Even though it may be present in a variety of work environments, exposure to amorphous silica has been the object of only a few quantitative published reports. This can be explained in good part by the fact that most varieties of amorphous silica have been considered to be of low toxicity compared to other occupational contaminants such as crystalline silica. Also, amorphous silicas have often not been reported specifically, being part of 'nuisance dusts' measured by non-specific gravimetric methods. Dust levels reported in a few studies, including a large compilation of data from the synthetic amorphous silica industry, can be found in **Table 16**.

(a) Diatomaceous earth

Occupational exposure to amorphous silica dust contained in diatomaceous earth may occur during its extraction, its treatment by calcination and through the handling of the calcined product in a variety of end-use industries as filtration agent, mineral charge, refractory, abrasive, carrier or adsorbent. Additionally, small amounts of quartz originating from sand may be present, but this rarely exceeds the level of 4% (Champeix & Catilina, 1983; Anon., 1986). Furthermore, cristobalite formed from amorphous silica during calcining operations has been reported to represent 10–20% of the respirable fraction of the dust of the calcined product and 20–25% in the case of the flux-calcined product (Checkoway *et al.*, 1993).

Bagging and bulk handling occupations are considered the dustiest; mechanization, the use of respiratory protection and dust control by local ventilation and application of water serve to reduce worker exposure.

(b) Synthetic amorphous silica

Occupational exposure to the various forms of synthetic amorphous silica may occur during their production and use as fillers and carriers in a variety of industries. The

Table 16. Occupational exposure to different types of amorphous silica

Type of amorphous silica	Industry, occupation	Level	Remarks on nature of dust	Reference, country
Diatomaceous earth	Production plant	28.2 mg/m ³ respirable dust	4% quartz content	Gerhardsson <i>et al.</i> (1974) Sweden
	Mining and processing	0.1–2.0 mg/m ³ respirable dust	< 5% quartz in respirable dust, up to 75% cristobalite in some calcined products	Reimarsson (1981) Iceland
	Mining and processing	< 1.05 mg/m ³ respirable dust	Natural product (< 1% cristobalite)	Cooper & Jacobson (1977) USA
		< 0.21 mg/m ³ respirable dust	Calcined (10–20% cristobalite)	
		< 0.14 mg/m ³ respirable dust	Flux-calcined (40–60% cristobalite)	
Synthetic amorphous silica	Chemical plant, production of amino-acids and vitamins 2 plants	0–10.5 mg/m ³ total dust 0–3.4 mg/m ³ respirable dust < 1.0–10 mg/m ³ total dust	Precipitated amorphous silica	Choudat <i>et al.</i> (1990) France
	Manufacture of pyrogenic (fumed) silica, 9 plants, filling, packing, bagging, mixing	0.61–6.5 mg/m ³ , range of medians, total dust, personal samples (1991–96) 0.2–2.1 mg/m ³ , range of medians, respirable dust, personal samples	Precipitated amorphous silica Particle size: primary (7–50 nm) aggregate (< 1 µm) agglomerate (1–100 µm)	Wilson <i>et al.</i> (1979) USA CEFIC (1996) Europe

Table 16 (contd)

Type of amorphous silica	Industry, occupation	Level	Remarks on nature of dust	Reference, country
Synthetic amorphous silica (contd)	Manufacture of wet process silica (precipitated silica and silica gel), 10 plants, filling, packing, cleaning, blending	1.0-8.8 mg/m ³ , range of medians, total dust, personal samples (1982-96) 0.5-2.1 mg/m ³ , range of medians, respirable dust, personal samples	Precipitated silica particle size: primary (5-100 nm), aggregate (1-40 µm), agglomerate (3-100 µm) Silica gel particle size: primary (3-20 nm), aggregate (1-20 µm)	CEFIC (1996) Europe
Fused silica	Manufacture of fumed silica	2-7 mg/m ³ total dust		Volk (1960) Germany Tharr (1991) USA
Fused silica	Fused quartz laser cutting	Up to 2.2 mg/m ³ (2 h) respirable dust, personal samples up to 0.9 mg/m ³ (8 h), respirable dust, area samples		
Silica fume	Ferrosilicon industry	7.3 mg/m ³ , median, total dust	Diameter < 1.5 µm, 22.3% silica (amorphous + crystalline)	Corsi & Piazza (1970) Italy
	Ferrosilicon and silicon industry Maintenance (tappers)	0.27-2.24 mg/m ³ , respirable dust	Amorphous silica	Cherniak & Boaino (1983) USA

Table 16 (contd)

Type of amorphous silica	Industry, occupation	Level	Remarks on nature of dust	Reference, country	
Biogenic silica fibres	Manual harvesting of sugar-cane				
	Burning	ND-58 000 fibres/m ³	Inorganic fibres, length: 3.5-65 µm, diameter: 0.3-1.5 µm	Boeniger <i>et al.</i> (1988) USA (Florida)	
	Cutting	ND-300 000 fibres/m ³			
	Area	ND-9300 fibres/m ³			
	Mechanical harvesting of sugar cane and sugar milling				
	Burning (area)			Inorganic fibres, length: 10-40 µm, diameter: 0.5-2 µm	Boeniger <i>et al.</i> (1991) USA (Hawaii)
	Harvesting	ND-6200 fibres/m ³			
	Sugarmill	ND-56 300 fibres/m ³ ND-8350 fibres/m ³			
	Rice farming				
	Interior of harvester		0.13 fibres/mL average	Levels reported for respirable silica fibres > 5 µm Actual length: 0.5-20 µm Width: 0.2-7 µm	Lawson <i>et al.</i> (1995) USA (California)
Bank out wagon		0.3 fibres/mL, average			
Burning by foot		< 0.1 fibres/mL, average			
Field preparation		1 fibres/mL, average			

NA, not available

substance is usually present as a dust of high purity. Comprehensive exposure data from 19 synthetic amorphous silica plants in Europe and the United States are summarized in a recent report (CEFIC, 1996). Exposure levels are highest in job categories involved with packing, weighing, reprocessing and cleaning (see also **Table 16**).

(c) *Silica fume and fly ash*

Silica fume, generated unintentionally and emitted from electric arc furnaces may contaminate work environments in silicon, ferrosilicon and other silicon-containing alloy production. Particles collected in this industry often contain crystalline silica as well as various metals (American Conference of Governmental Industrial Hygienists, 1991).

Fly ash from power stations and various manufacturing facilities (e.g., silicon, silicon carbide, silicon nitride, ferrosilicon industries) may contain significant amounts of amorphous and crystalline silica (Rühl *et al.*, 1990). The estimated combined 'production' of silica fume and fly ash in 1995 worldwide was 2000 thousand tonnes (Ferch & Toussaint, 1996).

(d) *Biogenic silica fibres*

Occupational exposure to silica fibres originating from biogenic processes within a variety of crop plants has been measured for sugar cane and rice farming operations. Sampling and analytical methods vary from one study to another, namely in sampling times, in respirable particle selection, in fibre-counting techniques and conventions, and in the specific identification of amorphous silica versus silicate fibres (Scales *et al.*, 1995).

1.3.3 *Environmental occurrence*

(a) *Air*

Quartz is a major mineral component of desert dust, which consists of fine particles smaller in size than 10 μm that can be transported by winds over thousands of kilometres and brought down by rainfall onto water or land surfaces (Klein *et al.*, 1993). Exposure to quartz from dust storms has been suggested as a cause of non-occupational pneumoconioses reported in certain regions of the world (Weill *et al.*, 1994). In the western Himalayas, 80% of the dust collected during dust storms was respirable and its silica content ranged between 60 and 70% (Saiyed *et al.*, 1991). Levels of exposure to quartz attained during dust storms have not been documented. Dust samples collected in the windy season in two communes in a sandy area of Gansu Province in China ranged from 8.35 to 22 mg/m^3 . Deposited dust in these places consisted mainly in fine particles (< 5 μm) and had a free silica content of 15–26% (Xu *et al.*, 1996).

Crystalline silica has been reported as a possible important constituent of volcanic ash collected at high altitude or as settled dust at ground level. Cristobalite and keatite are reported to constitute 35% of El Chichón (Mexico) ash collected at 34–36 km altitude (Klein *et al.*, 1993); crystalline silica has been identified as present at levels of 3–7% in Mount St Helens (Washington State, United States) settled ash samples (Dollberg *et al.*, 1986).

There is no extensive data set on levels of silica in ambient air. Ambient levels of quartz, based on inhalable particulate measurements taken in 1980 in 22 United States cities have been reported. Fine quartz levels (particles $< 2.5 \mu\text{m}$ aerodynamic diameter) were from 0 to $1.9 \mu\text{g}/\text{m}^3$, while coarse levels (from 2.5 to $15 \mu\text{m}$) went from 1.0 to $8.0 \mu\text{g}/\text{m}^3$. Quartz represented on average 4.9% of the coarse particle mass and 0.4% of the fine particle mass (Davis *et al.*, 1984). It has been estimated that crystalline silica concentrations in the range of $1\text{--}10 \mu\text{g}/\text{m}^3$ are common in urban and rural settings (Hardy & Weill, 1995).

No data are available for ambient levels of amorphous silica, except for some measurements of silica fibres taken in the vicinity of farming operations. Thus, amorphous silica fibres were identified as smoke constituents in three of seven area samples located near burning sugar cane fields in Hawaii (Boeniger *et al.*, 1991). Amorphous silica fibres were observed at 0.02 fibres/mL in one of 11 samples collected upwind of rice farming operations in California, in one of two 1.5-km downwind samples and in two of four field-edge downwind samples; a mean level of 0.004 fibres/mL was detected for all downwind samples. For community samples collected in neighbouring towns on days when there was rice burning, fibres were detected in four of 14 samples; the mean level for all samples was < 0.004 fibres/mL (Lawson *et al.*, 1995).

Non-occupational inhalation of crystalline silica may also occur during the use of a variety of consumer or hobby products, such as cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk and putty, paint, mortar and cement (United States Bureau of Mines, 1992). In a study on the possible contamination of homes with crystalline silica on work clothing, no difference was found between the levels of cristobalite in outside ambient air and in the laundry areas of three homes investigated (Versen & Bunn, 1989).

(b) Water

Silica may be present in water as quartz particles and diatom fragments. No quantitative data on levels of quartz or other silica forms in potable or other forms of water were available to the Working Group. Silica dissolves to a small extent in water as monomeric silicic acid. Levels range from 1 ppm to almost 100 ppm (mg/L) depending on the climate, the petrographic nature of the aquifer, the depth and the activity of various biological processes (Siever, 1978).

(c) Food

Amorphous silica (such as fumed silica) is incorporated in a variety of food products as anti-caking agent at levels up to 2% by weight (such foods include beverage mixes, salad dressings, sauces, gravy mixes, seasoning mixes, soups, spices, snack foods, sugar substitutes, desserts). Amorphous silica is also used as an anti-caking agent and as an excipient in pharmaceuticals for various drug and vitamin preparations. Other possible uses include the following: retention of volatiles, microencapsulation, dispersion agent, clarification of beverages, viscosity control, anti-foaming agent and dough modifier (Villota & Hawkes, 1985).

1.4 Regulations and guidelines

Regulations and guidelines for occupational exposures to various forms of silica differ from one country to the other, and new limits are under consideration in some countries (see **Tables 17 and 18**). A general tendency is to set separate limits for the various crystalline polymorphs and for the various kinds of amorphous silicas.

2. Studies of Cancer in Humans

Epidemiological studies that were considered relevant to assess the carcinogenic risk of crystalline silica for humans include studies on ore miners, quarry workers, granite and slate industry workers, workers in the ceramics, pottery, refractory brick and diatomaceous earth processing industries, and in foundry workers. In addition, epidemiological studies were available on silicotic patients, many of whom had been employed in the industries listed above. In some of these industries, there are concomitant exposures to established carcinogens, such as radon decay products in ore-mining. Special weight was given to studies that were relatively free from confounders and that addressed exposure-response.

2.1 Ore mining

2.1.1 *Record-linkage studies*

Lynge *et al.* (1990) followed the 1960 census population of Sweden and the 1970 census populations of the other Nordic countries for mortality or cancer incidence. The follow-up was through to 1980. Linkage was made between the mortality and cancer incidence registers. Rate ratios for lung cancer were calculated for industries and occupational codes with known exposure to silica. Codes reported to the census were used. Expected numbers were calculated from five-year age-specific rates and calendar year-specific rates from all economically active men at the time of census. The rate ratios estimated for the Nordic countries and industries were as follows: for Norway, iron ore mining (5 observed; rate ratio, 1.36; 95% CI, 0.44–3.17) and other metal mining (5 observed; rate ratio, 1.00; 95% CI, 0.33–2.34); for Sweden, iron ore mining (124 observed; rate ratio, 3.19; 95% CI, 2.92–3.49) and other ore mining (31 observed; rate ratio, 3.71; 95% CI, 3.10–4.44); for Finland, iron ore mining (2 observed; rate ratio, 1.78; 95% CI, 0.22–6.45) and non-ferrous ore mining (21 observed; rate ratio, 5.02; 95% CI, 3.11–7.68).

2.1.2 *Cohort studies* (see also **Table 19**)

Gold ore miners

McDonald *et al.* (1978) conducted a study of a cohort of 1321 miners from one gold mine in South Dakota (United States) who had at least 21 years' employment at the mine. SMRs based on South Dakota mortality rates showed excess mortality from all

Table 17. Occupational exposure levels for amorphous silica

Country	Substance	Concentration (mg/m ³)	Interpretation	Date of publication/ implementation
Canada				
Québec	Silica, amorphous (gel) (total dust)	6	TWA	1995
	Silica, amorphous (precipitated) (total dust)	6	TWA	1995
	Silica, amorphous (non-calcinated diatomaceous earth (total dust)	6	TWA	1995
Ontario	Diatomaceous earth, uncalcinated (total dust)	4	TWA	1994
	Precipitated silica (total dust)	4	TWA	1994
	Silica gel (total dust)	4	TWA	1994
UK	Total dust	6	OES	1996
	Fine dust	3	OES	1996
USA				
NIOSH	Silica, amorphous	6	REL	1994
ACGIH	Diatomaceous earth (uncalcined)		TWA	
	Inhalable particulate ^a	10		1986
	Respirable particulate ^a	3		1995
	Precipitated silica	10		1987
	Silica, fused (respirable fraction)	0.1		1992
	Silica gel	10		1987
	Silica, fume (respirable fraction)	2		1992
OSHA	Total dust	6	PEL	1996
France	Total dust	10	VME	1996
	Respirable dust	5		

Table 17 (contd)

Country	Substance	Concentration (mg/m ³)	Interpretation	Date of publication/implementation
Germany	Pyrogenic and wet process silica, diatomaceous earth (uncalcined)	4 (inhalable fraction)	MAK	1996
	Quartz glass, fused silica, flux-calcined diatomaceous earth	0.3 (respirable fraction)	MAK	

TWA, time-weighted average; OES, Occupational exposure standard; OSHA, Occupational Safety and Health Administration; REL, recommended exposure limit; PEL, permissible exposure limit; VME, mean exposure value (valeur moyenne d'exposition); MAK, maximum workplace concentration

* The value is for inhalable (total) particulate matter containing no asbestos and < 1% crystalline silica

From American Conference of Governmental Industrial Hygienists (ACGIH) (1995); Anon. (1994); United States National Institute for Occupational Safety and Health (NIOSH) (1994); Anon. (1995); IMA-Europe (1995); CEFIC (1996); Deutsche Forschungsgemeinschaft (1996)

SILICA

Table 18. Occupational exposure limits for crystalline silica

Country	Substance	Interpretation	Nature of dust	Concentration (mg/m ³)	Measure duration	Date of publication/ implementation
Argentina	Quartz	MPC	RD	0.1	8-h TWA	1991
	Tridymite		RD	0.05	8-h TWA	1991
	Cristobalite		RD	0.05	8-h TWA	1991
Austria	Quartz, cristobalite, tridymite	MAK	FD	0.15	8 h daily and 40 h weekly	1992
	Quartz containing dust		FD	4		
Belgium	Quartz		RD	0.1	Average values over 15 mn, 8 h daily	1995
	Cristobalite, tridymite		RD	0.05		
Canada Québec	Quartz, fused silica, tripoli	TWA	RD	0.1	8 h	1996
	Tridymite	TWA	RD	0.05	8 h	1996
	Cristobalite	TWA	RD	0.05	8 h	1996
	Crystalline silica, respirable	TWA	RD	0.1	8 h	1993
Denmark	Quartz	TLV	RD	0.1	8 h	1988
	Cristobalite, tridymite		TD	0.3		
			RD	0.05		
			TD	0.15		
Finland	Quartz	OES	FD	0.2	8 h TWA	1993
	Cristobalite, tridymite		FD	0.1		
France	Quartz	VME	RD	0.1	8 h	1996
	Cristobalite, tridymite		RD	0.05		
Germany	Quartz, cristobalite, tridymite	MAK	RF	0.15	8 h, 40 h weekly: average work shift value	1996

Table 18 (contd)

Country	Substance	Interpretation	Nature of dust	Concentration (mg/m ³)	Measure duration	Date of publication/ implementation
Italy	Quartz	TLV-TWA	RD	0.1	8 h TWA, 40 h weekly	Adoption, 1982
	Cristobalite, tridymite	TLV	RD	0.05		Implementation, 1991
Netherlands	Quartz, cristobalite, tridymite	MAK	RD	0.075	8 h TWA	1 May 1996
Norway	Quartz	TLV	RD	0.1	8 h	1994
	Cristobalite, tridymite		TD	0.3		
Portugal	Quartz	Recommended norms	RD	0.05	8 h TWA daily, 40 h weekly	1988
			TD	0.15		
	Cristobalite, tridymite	RD	0.1			
		TD	0.3			
Russia	Cristobalite		RD	0.05		1990
			TD	0.15		
	Quartz	Aerosol	1			
		Aerosol with silica content > 70%	1			
South Africa	Quartz	TWA	Aerosol with 10-70% silica	2		
			Aerosol with silica content < 10%	4		
Spain	< 5% free silica quartz	Limit value	RD	0.1	8-h TWA	1996
			RD	6	8 h	1991
Sweden	Quartz		RD	0.1	8 h	10 June 1993
			RD	0.05		

Table 18 (contd)

Country	Substance	Interpretation	Nature of dust	Concentration (mg/m ³)	Measure duration	Date of publication/implementation
Switzerland	Q/C/T containing dust	VME	FD (1-5% Q/C/T)	4		
	Quartz, cristobalite, tridymite		FD	0.15		
United Kingdom	Quartz, cristobalite, tridymite	MEL	RD	0.4	8 h	1988
USA	Quartz	PEL	RD	10/(% SiO ₂ + 2)	8 h TWA	OSHA 1971
	Quartz		TD	30/(% SiO ₂ + 2)		MSHA 1978
	Quartz in coal mines		RD	2		MSHA 1978
	> 5% quartz in coal mines		RD	10/(% Q)		OSHA 1971
	Cristobalite, tridymite			Half the value for quartz		MSHA 1978
ACGIH	Cristobalite			0.05		
	Quartz	TWA	RF of particulate matter	0.1		1986
	Tridymite			0.05		
	Tripoli			0.1, of contained respirable quartz		
NIOSH	Fused silica, cristobalite, quartz, tridymite, tripoli	REL	RD	0.05		1994

RD, respirable dust; RF, respirable fraction; TD, total dust; OEL, occupational exposure limit; OES, occupational exposure standard; PEL, permissible exposure limit; TLV, threshold limit value; TWA, time weighted average; FD, fine dust; VME, mean exposure value (valeur moyenne d'exposition); REL, recommended exposure limit; Q/C/T, quartz/cristobalite/tridymite; MAK, maximal workplace concentration; MAC, maximal allowed concentration; MEL, maximum exposure limit; MSHA, Mine Safety and Health Administration

Anon. (1994); Anon. (1995); United States National Institute for Occupational Health (NIOSH) (1994); United States American Conference of Governmental Industrial Hygienists (ACGIH) (1995); United States Occupational Safety and Health Administration (OSHA) (1995); IMA-Europe (1995); UNEP (1996)

causes (631 observed; SMR, 1.15 [95% CI, 1.06–1.24]); there were 37 cases of pneumoconiosis (none expected) and 39 of tuberculosis (3.6 expected). There was no overall excess of respiratory cancer (17 observed; SMR, 1.03 [95% CI, 0.60–1.65]), although, in the first half of the follow-up period (1937–55), six deaths from lung cancer were observed against 3.4 expected. Using dust exposure data from company midget impinger samples and the estimated average silica content of 39%, the authors examined the mortality risks in five categories of dustiness; they showed clear linear relationships for tuberculosis and pneumoconiosis (McDonald & Oakes, 1984). Using five categories of dustiness, no correlation with respiratory cancer was found (McDonald *et al.*, 1978).

In a cohort previously followed by Brown *et al.* (1986), Steenland and Brown (1995) followed up 3328 white male United States gold miners from South Dakota who worked underground for at least one year between 1940 and 1965. The follow-up was through to 1990. Primary exposures were to (non-asbestiform) amphibole minerals in the cummingtonite–grunerite series and to silica. The silica content of respirable dust in the mid-1970s was estimated to be 13%. The median respirable silica decreased from 0.15 mg/m³ in 1930 to 0.05 mg/m³ after 1950. Exposure to arsenic and radon were below United States Occupational Safety and Health Administration standards (radon daughters, 0–0.17 WL). Yearly measurements from 1937 to 1975 were used to calculate exposure levels for five job categories and to calculate cumulative dust (dust-days). Smoking data (never/occasional, current and ex-smoker) were volunteered by 602 of the men in a 1960 Public Health Service Silicosis Survey. Compatible age- and race-specific data on smoking from a 1955 survey of a sample of the United States population were used to estimate the effect of smoking differences on SMR for lung cancer. Of the cohort, 2% was lost to follow-up. Mortality from all causes was elevated (1551 observed; SMR, 1.13; 95% CI, 1.07–1.19). The SMR for all cancers was not elevated (303 observed; SMR, 1.01; 95% CI, 0.90–1.13). None of the cancer sites had a greatly elevated SMR. The SMR for lung cancer was 1.13 (115 observed; 95% CI, 0.94–1.36) when the United States population was used for comparison. However, the SMR for lung cancer was elevated for person-years for those workers whose first exposure (first job underground) was more than 30 years before (90 observed; SMR, 1.27; 95% CI, 1.02–1.55). The SMR for lung cancer was also elevated in the highest exposure category (28 observed; SMR, 1.31 [95% CI, 0.87–1.89]), but the trend with duration of exposure was inconsistent: SMRs, 1.02 [95% CI, 0.79–1.30], 1.55 [95% CI, 1.08–2.16] and 1.01 [95% CI, 0.56–1.67] for < 10 years, 10–20 years and ≥ 20 years of exposure, based on 65, 35, 15 observed deaths, respectively. The SMR for lung cancer was increased mainly in men hired before 1930 (21 observed; SMR, 1.30 [95% CI, 0.80–1.99]). However, the smoking-adjusted SMR using the United States population was 1.07 [95% CI, 0.88–1.28]). Mortality was increased for non-malignant respiratory disease (170 observed; SMR, 1.86; 95% CI, 1.58–2.16), asthma (7 observed; SMR, 2.61; 95% CI, 1.09–5.61) and pneumoconiosis and other respiratory diseases (92 observed; SMR, 2.61; 95% CI, 2.11–3.20). Mortality was also increased for non-Hodgkin's lymphoma (13 observed; SMR, 1.63; 95% CI, 0.86–2.78).

Hnizdo and Sluis-Cremer (1991) followed up a cohort of 2209 white South African gold miners whose exposure started during 1936–43 and who were studied for

respiratory disorders during 1968–71, when 45–54 years of age. The mortality follow-up was through 1986. Vital status was established from the Gold Miners' Provident Fund records, medical files and the Department of Interior; miners not reported dead were assumed to be alive. The cause of death was established independently by two medical doctors from the best available evidence (death certificates, medical files and autopsy reports available on 84% of dead miners). The average level of respirable dust in the gold mine in 1968 was 0.3 mg/m³ of which approximately 30% was crystalline silica. Uranium was mined in some gold mines as a main product or as a by-product. Levels of radon daughters ranged from 0.1 to 3.0 working levels (WL) in most deep mines (average, 0.4 WL); in a few shallow mines, up to 6 WL was measured. Cumulative dust exposure was evaluated in terms of respirable surface area (RSA)-years (Beadle & Bradley, 1970) and the duration of dust exposure were calculated from personal records of dusty shifts. Smoking history was obtained in 1968–71 and pack-years were calculated. There were 77 cases of primary lung cancer. The estimated excess risk of lung cancer for every 1000 RSA-years, standardized for smoking, year of birth and age (estimated from the proportionate hazards model), was 2.3% (95% CI, 0.5%–4.2%). For miners in the highest exposure category ($\geq 41\ 000$ RSA-years), the estimated relative risk of lung cancer was 2.92 (95% CI, 1.02–8.4). No association between lung cancer and silicosis of the parenchyma or pleura at autopsy was found, but a significant association with hilar gland fibrosis was observed (adjusted odds ratio, 3.9; 95% CI, 1.2–12.7). [The Working Group noted that arsenic is not known to be present in the dust of South African gold mines but that radon was a potential confounding factor.]

In an extended follow-up of a study reported by Wyndham *et al.* (1986), Reid and Sluis-Cremer (1996) followed up a cohort of 4925 white South African gold miners. These miners were born in 1916–30, were working in gold mines in the vicinity of Johannesburg on 1 January 1970 and were then aged 39–54 years. The follow-up was through 1989. Daily cigarette consumption was obtained from medical files. Exposure to mining was measured as duration of dusty exposure obtained from a record of dusty shifts, and as cumulative dust exposure (duration weighted by an average dust level for an occupational category measured in the late 1960s, in years-mg/m³). Vital status was established for 4875 miners. The age- and year-specific mortality rates for white South African men were applied to calculate standardized mortality ratios (SMRs). The SMR was increased for all deaths (2032 observed; SMR, 1.30; 95% CI, 1.24–1.35). There was no increased risk for all cancers (341 observed; SMR, 1.10; 95% CI, 0.99–1.23), but the SMR for lung cancer was increased (143 observed; SMR, 1.40; 95% CI, 1.18–1.65). SMRs were also increased for pulmonary tuberculosis (20 observed; SMR, 2.95; 95% CI, 1.81–4.58), pneumonia (68 observed; SMR, 1.46; 95% CI, 1.13–1.85), pneumoconiosis (16 observed; SMR, 21.3; 95% CI, 12.2–34.7) and chronic obstructive pulmonary disease (i.e. emphysema, bronchitis, asthma) (176 observed; SMR, 1.89; 95% CI, 1.62–2.19). The relative risk for lung cancer and cumulative dust exposure for five years before death, adjusted for smoking, estimated from a nested case-control study was 1.12 (95% CI, 0.97–1.3) (mg/m³)-years and that for chronic obstructive pulmonary disease and cumulative dust exposure was 1.20 (95% CI, 1.0–1.4) (mg/m³)-years. [The Working

Group noted the possible overlap with the study of Hnizdo and Sluis-Cremer (1991). The Working Group considered that radon is a potential confounding factor for this study.]

Kusiak *et al.* (1991) followed up a cohort of 13 603 male non-uranium gold miners who worked in Ontario, Canada. This cohort consisted of all who had been examined in chest clinics in Ontario in 1955 or later and who had been employed for at least two weeks in dusty jobs in Ontario mines after 1954 and for at least 60 months in dusty jobs in the mining industry anywhere. Deaths that occurred between 1955 and 1986 were identified from a national mortality database (about 6% of deaths up to 1977 were missing). Miners who reported that they had worked in asbestos mines were excluded. Before 1950, dust concentrations were often above 1000 particles/mL; by 1959 they had dropped to 400 particles/mL by 1959 and by 1967 to 200 particles/mL. The percentage of silica in respirable dust measured in 1978 survey ranged from 4.3 to 11.8% in different mines. Arsenic was present in most gold mines and was also associated with gold specks. Measurements of radon decay products (all post 1961) ranged from 0.001 to 0.335 WL. Smoking data were obtained from a random sample of miners. Expected deaths were calculated from Ontario male death rates. The overall SMR for lung cancer in gold miners was increased (SMR, 1.29; 95% CI, 1.15–1.45). The SMR was increased among miners who started gold mining before 1946 and never mined nickel was 1.40 (95% CI, 1.22–1.59). No increase in lung cancer risk was observed in gold miners who started mining after 1945. The authors attributed the increased risk of lung cancer in Ontario gold miners to the duration of underground mining and the associated exposure to arsenic and radon decay products. In a nested case-control study, Kusiak *et al.* (1993) reported an increased mortality from stomach cancer in this cohort of gold miners (104 observed; SMR, 1.52; 95% CI, 1.25–1.85), which was attributed to exposure to chromium. [The Working Group noted the lack of cumulative exposure measurements to silica.]

Iron ore miners

Lawler *et al.* (1983) examined the mortality of 10 403 white male employees of a Minnesota (USA) haematite ore mining company (1937–1978) and contrasted it with that of US white males. Chemical analyses of the ore showed an average silica content of 8% in 1943 but 20–25% in the ore being mined in the late 1970s. For the total cohort (underground and above-ground miners), the SMR for all causes was 0.93 (4699 observed [95% CI, 0.90–0.96]). Mortality from tuberculosis (33 observed, SMR 0.45 [95% CI, 0.31–0.63]) and respiratory disease (234 observed, SMR 0.79 [95% CI, 0.69–0.90]) was lower than expected; no elevated risk from these two causes of death was seen for underground miners. For stomach cancer, underground miners had an SMR of 1.67 (77 observed [95% CI, 1.32–2.09]) and above-ground miners had an SMR of 1.81 (49 observed [95% CI, 1.34–2.40]). For lung cancer, the SMR was 1.00 for underground miners (117 observed [95% CI, 0.82–1.19]) and 0.88 for above-ground miners (95 observed [95% CI, 0.71–1.07]). No data on smoking habits or exposure to radon daughters were obtained. [The Working Group noted that exposures in the Minnesota iron ore mines were complex and included fibrous amphiboles as well as silica.]

A group of 1173 iron miners in Lorraine (France) was observed for five years following clinical examinations and lung function tests (Pham *et al.*, 1983). During this period, there were 40 deaths versus 39 expected on the basis of rates for the general male population of Lorraine. There were 13 deaths from lung cancer (SMR, 3.5; 95% CI, 1.9–6.0). All the lung cancer cases were found among underground workers; they were all smokers and they had had a longer mean length of employment underground (23.6 years) than the whole underground group (16.7 years). Measured levels of radon daughters were approximately 0.03 WL in the mine and 0.07 WL in the return air. The prevalence of smoking was higher (66%) in the study population than in a general population sample (52%). [The Working Group noted that the methods for ascertaining causes of death for cases and controls were not comparable.]

Kinlen and Willows (1988) followed a cohort of 1947 iron ore miners in Cumbria (United Kingdom) from 1939 to 1982. Miners were compared with men of a similar social class from England and Wales. Mortality data were analysed by proportional mortality. Radon levels measured in the mines in 1969 in the closed area ranged from 0.4–3.2 WLs (median 2.0). There were 1604 deaths. The proportionate mortality ratios (PMR) were increased for tuberculosis (88 observed; PMR, 3.55; [95% CI, 2.85–4.37]) and non-malignant respiratory disease (292 observed; PMR, 1.62; [95% CI, 1.44–1.82]). There was an elevated increase for cancer of the stomach (49 observed; PMR, 1.24; [95% CI, 0.82–1.64]). There was no elevated increase for lung cancer (84 observed; PMR, 0.97; [95% CI, 0.77–1.20]). Risk of lung cancer was increased when population rates for the rural population were used (PMR, 1.59; [95% CI, 1.27–1.97]).

Chen *et al.* (1990) followed a cohort of 6444 men employed on 1 January 1970 in two iron ore mines in Longyan and Taochong in China through to 1982. Vital status was ascertained in 8534 of 8641 (99%) miners; 2090 miners with exposure for less than one year were excluded. Occupational history and smoking habits were assessed retrospectively by a questionnaire. Job titles were used to assign exposure level. Mechanical ventilation was introduced in 1955 in the Longyan mine and in 1963 in the Taochong mine, reducing total dust from several hundred mg/m³ to 3.8 mg/m³ (23–28% of settled dust was iron). Traces of 3,4-benzo[*a*]pyrene, titanium, arsenic, chromium, nickel, cobalt, cadmium and beryllium were found in the dust. Levels of radon daughters found in 1984 at the working face were higher (0.2 WL) than at other workplaces (0.1 WL). With improvements in ventilation, there were parallel reductions in the radon and dust concentrations over the years. The expected deaths were based on sex- and age-specific death rates for China for the years 1973–75. Diagnosis of silicosis was obtained from routine X-ray examinations carried out on a periodical basis and read by a panel. There were 550 deaths. The SMR for total cancer mortality (98 cancers) was 1.1 (95% CI, 0.9–1.3). The SMR for lung cancer was increased (29 observed; SMR, 3.7; 95% CI, 2.5–5.3) and was higher in those who worked prior to usage of mechanical ventilation (20 observed; SMR, 4.8; 95% CI, 2.9–7.4) than in those who started after it was introduced (9 observed; SMR, 2.4; 95% CI, 1.1–4.6). There was an increasing trend with low, medium and heavy exposure (SMRs, 2.6, 2.6 and 4.2, respectively), mainly in smokers. [The Working Group noted that the exposure–response analysis was based on cumulative exposure estimates generated from single job titles, which may not reflect complete job

history.] A high proportion of deaths (41%) was due to non-malignant respiratory disease (227 observed). A total of 1226 silicotics, diagnosed at routine periodic examinations, had an SMR for lung cancer of 5.3 (14 deaths; 95% CI, 2.9–8.8) and for non-silicotics the SMR was 2.9 (15 deaths; 95% CI, 1.6–4.7). In current smokers, subjects with silicosis ($n = 962$) were at higher risk for lung cancer (13 observed; SMR, 6.7; 95% CI, 3.6–11.5) than subjects without silicosis ($n = 3123$) (12 observed; SMR, 3.0; 95% CI, 1.6–5.3). Subjects with silicotuberculosis ($n = 389$) were also at higher risk for lung cancer (7 observed; SMR, 9.3; 95% CI, 3.8–19.2).

Other ore miners

Hodgson and Jones (1990) followed up a cohort of 3010 miners who had at least 12 months' mining experience between 1941 and 1984 in two tin ore mines in Cornwall, United Kingdom. The follow-up was through 1986. SMRs were calculated using the national age- and year-specific death rates. Radon daughter levels had been monitored since 1967 and the average exposure was estimated as 8–12 working level months (WLM)/year in mine A and 9–19 WLM/year in mine B. Arsenic was also mined in mine A. The SMR for all causes of death was increased (851 observed; SMR, 1.27; [95% CI, 1.18–1.35]) and that for lung cancer was significantly increased (105 observed; SMR, 1.58; [95% CI, 1.29–1.91]). There was a strong dose-response trend with duration of underground exposure; the SMRs increased as follows: 0.91 [95% CI, 0.51–1.50] for 1–5 years; 1.72 [95% CI, 0.94–2.88] for 5–10 years; 1.76 [95% CI, 1.09–2.7] for 10–20 years; 3.55 [95% CI, 2.07–5.69] for 20–30 years; and 4.47 ([95% CI, 2.50–7.37]) for more than 30 years. There were 49 deaths from silicosis and 33 deaths from silico-tuberculosis. Smoking and radon daughters were considered to be the main risk factors for lung cancer. [The Working Group noted the high exposure to radon.]

Ahlman *et al.* (1991) followed up a cohort of 597 miners employed between 1954 and 1973 for at least three years either in a copper ore mine ($n = 398$) or zinc ore mine ($n = 199$) in eastern Finland. The follow-up was through to 1986 (person-years, 14 782). Vital status was obtained via the Population Data Register. Regional age-specific data rates were used for comparison. Occupational histories and smoking data were obtained through a questionnaire. In the copper mine, mean respirable silica dust concentrations decreased from 0.16 to 0.08 mg/m³ over the years and average radon daughter levels decreased from 1.7 to 0.7 WL. In the zinc mine, the highest concentration measured was 11 WL and the mean concentration was 0.4 WL. Diesel-powered machines were introduced in the 1960s. Overall mortality was increased [SMR, 1.04; 95% CI, 0.85–1.27]; 102 observed; 97.8 expected based on regional rates). Mortality from lung cancer was increased (10 observed, 4.3 expected; 6.9 expected based on regional rates). Five of the lung cancer deaths (SMR, 2.94; [95% CI, 0.96–6.86]) came from the zinc mine (1.7 expected). [The Working Group noted the high exposure to radon.]

A total of 9912 (369 silicotics and 9543 non-silicotics) white male metal ore miners in the United States who volunteered for a standard medical examination during 1959–61 were followed up for lung cancer mortality through 1975 (Amandus & Costello, 1991). The ores that were mined consisted of copper, lead-zinc, iron, mercury, lead silver, gold

and gold-silver, tungsten and molybdenum. Miners who were employed in non-uranium mines and had not been exposed to diesel exhausts were studied. Silicosis was diagnosed from radiograms taken at the examination according to the ILO 1959 classification (1, 2, 3 small rounded opacities and large opacities). Lung cancer was increased in silicotics (14 deaths; SMR, 1.73; 95% CI, 0.94–2.90) in comparison with non-silicotics (118 deaths; SMR, 1.18; 95% CI, 0.98–1.42). Age- and smoking-adjusted lung cancer risk in silicotics was 1.96 (95% CI, 1.19–3.23) times that in non-silicotics. In those who had smoked cigarettes for over 25 years, SMRs were 2.69 in silicotics (8 deaths; 95% CI, 1.16–5.30) and 1.76 in non-silicotics (64 deaths; 95% CI, 1.36–2.26). The SMR for lung cancer was increased mainly in silicotics in lead-zinc mines (4 observed; SMR, 2.42; 95% CI, 0.66–6.21) and in mercury mines (3 observed; SMR, 14.03; 95% CI, 2.89–40.99). SMRs were significantly increased in non-silicotics who had worked for over 20 years in an underground metal mine (SMR, 1.52; 95% CI, 1.10–2.03); and who had been employed at a mercury mine (SMR, 2.66; 95% CI, 1.15–5.24). After excluding mercury miners, the SMR for lung cancer was 1.39 in silicotics and 1.14 in non-silicotics. Among those who had worked in mines with low radon exposure, age- and smoking-adjusted lung cancer risk ratio between silicotics and non-silicotics was 2.59 (95% CI, 1.44–4.68). [The Working Group noted that this is a cohort of volunteers based on a medical survey of 50 underground mines. Participation rate was not discussed nor was percentage follow-up defined.]

Chen *et al.* (1992) identified a cohort of 70 179 workers employed from 1972 through 1974 for at least one year in one of four industrial groups: (i) 10 tungsten ore mines, (ii) six copper-iron ore mines, (iii) four tin ore mines and (iv) eight pottery factories and one clay mine all in south central China. Mortality follow-up was through 1989. Silica dust exposure was estimated by merging individual job titles and time of exposure against job-time-specific measurements of total dust and percentage of free silica collected, mostly on a monthly basis for most dust-exposed jobs. Subjects were classified into four exposure levels according to the job title with the highest dust level in which the subject worked for at least one year. The average annual total dust levels were 6.1 mg/m³ (range, 2.0–26.3 mg/m³) for tungsten ore mines, 5.6 mg/m³ (range, 3.8–16.1 mg/m³) for copper and iron ore mines, and 7.7 mg/m³ (range, 3.4–29.7 mg/m³) for tin ore mines. The lower ranges represent more recent levels. Confounding factors studied were arsenic and polycyclic aromatic hydrocarbons. Vital status and cause of death were obtained from employment registers, accident records, medical records and personal contact. Cause of death was coded according to the Chinese coding system. For subjects who died of primary lung cancer, medical reports and X-rays were sought. Silica-exposed workers had yearly radiograms and cases of silicosis (Chinese categories: suspected, 1, 2 or 3) were reported to factory registries. [The Working Group noted that this system is very close to the ILO system.] Silicotics had more frequent medical examinations. The expected deaths for selected causes were based on age- and sex-specific rates computed as the average rates obtained from national mortality surveys carried out during 1973–75 and in 1987. Vital status was identified for 68 241 (97.2%) of the subjects (28 442 in tungsten mines, 18 231 in copper-iron mines, 7849 in tin mines). Mortality from all causes was slightly increased (6192 observed; SMR, 1.06; 95% CI, 1.04–1.09). Mortality

from all cancers was decreased (1572 observed; SMR, 0.86; 95% CI, 0.81–0.90). However, increased mortality was found for cancer of the nasopharynx (78 observed; SMR, 1.54; 95% CI, 1.22–1.93), due to a significant increase in tungsten ore and tin ore mines, and for liver cancer (474 observed; SMR, 1.15; 95% CI, 1.05–1.26), due to a significant increase in copper-iron ore and tin ore mines. Cancer sites with significantly decreased mortality were the oesophagus, stomach, colorectum and lung. The overall SMR for lung cancer was decreased (330 observed; SMR, 0.79; 95% CI, 0.71–0.88), although it was increased in tin ore miners (SMR, 1.98; 95% CI excludes 1.0) and in silicotic workers (SMR, 1.22; 95% CI, 0.9–1.6, compared to non-silicotics). Other causes of death with increased mortality were other respiratory diseases (925 observed; SMR, 1.48; 95% CI, 1.39–1.58), due to an increase in tungsten ore miners and pottery workers, and pulmonary heart disease (695 observed; SMR, 5.81; 95% CI, 5.38–6.26). Mortality from pulmonary tuberculosis was decreased in all groups (overall 312 observed; SMR, 0.77; 95% CI, 0.69–0.86) and that from pneumoconiosis was increased in all groups (overall 199 observed; SMR, 36.25 [95% CI, 31.4–41.7]). Relative risks, adjusted for decade of birth, sex, factory type and age, that showed a statistically significant trend with low, medium and high dust exposure levels ($p < 0.01$) were for respiratory disease (relative risks: low, 1.0; medium, 2.39 (95% CI, 1.9–3.0); and high, 3.65 (95% CI, 3.0–4.5), pneumoconiosis (relative risks, 1.0; 7.29 (95% CI, 4.5–11.8); and 13.57 (95% CI, 8.9–21.0), respectively) and pulmonary heart disease (relative risks, 1.0; 1.27 (95% CI, 1.0–1.6); and 1.93 (95% CI, 1.6–2.4). For lung cancer the respective relative risks were 1.0, 1.38 (95% CI, 1.0–1.9) and 1.10 (95% CI, 0.9–1.4).

McLaughlin *et al.* (1992) conducted a nested case-control study of this same cohort. Using 316 male lung cancer cases and 1352 controls, these investigators found an increasing trend in the age- and smoking-adjusted odds ratios for lung cancer with cumulative dust ($p = 0.02$) and cumulative respirable silica ($p = 0.004$) in tin ore miners only: the odds ratio in the highest level of cumulative silica dust was 3.10. A trend with increasing arsenic levels ($p = 0.0004$) was also observed in tin miners. Exposure to arsenic and to polycyclic aromatic hydrocarbons was highly correlated with exposure to silica dust. Subjects with silicosis had an increased risk of lung cancer in iron-copper ore miners (15 observed; odds ratio, 3.1) and in tin ore miners (37 observed; odds ratio, 2.0) but not in tungsten ore miners where a significant decreasing trend for lung cancer and respirable dust and respirable silica dust was observed ($p < 0.05$). [The Working Group noted that exposure to arsenic confounded the potential dose-response relationship between silica exposure and lung cancer risk in tin miners.]

In an update of previous studies (e.g. Higgins *et al.*, 1983), Cooper *et al.* (1992) followed a cohort of 3431 men who had worked prior to 1959 for at least three months in 'taconite' surface mines and the mill in a Minnesota (United States) iron ore mine through 1988. A total of 1058 subjects were found to be dead through employment records, Social Security Administration records (contributing to or receiving pension), from the National Death Index and from previous searches. Those not found were assumed to be alive. Death certificates were obtained from state offices of vital statistics in the State of residence or death. Death certificates were obtained for 1039 (98.2%) subjects known to be dead. The United States white male population was used as a

reference. Up to 28–40% of free silica in air samples was reported and subjects were exposed to elongated dust particle fragments of non-asbestiform amphibole minerals. There was no underground mining. SMRs were significantly decreased for all causes (1058 observed; SMR, 0.83; 95% CI, 0.78–0.88), all cancers (232 observed; SMR, 0.87; 95% CI 0.76–0.99) and all respiratory system cancers (65 observed; SMR, 0.67; 95% CI, 0.52–0.85) and lung cancers (62 observed; SMR, 0.67; 95% CI, 0.52–0.86). The SMR for respiratory cancers displayed a significant negative trend with duration of employment. The SMR for non-malignant respiratory disease was significantly decreased (55 observed; SMR, 0.71; 95% CI, 0.54–0.93). The use of Minnesota death rates increased the above SMRs, but not above 1.00. [The Working Group noted that the absence of an increase in mortality from non-malignant respiratory disease in this cohort suggests low worker exposure to free silica. In the first study of this cohort (Higgins *et al.*, 1983), the investigators also noted relatively low silica exposures in this study population.]

Cocco *et al.* (1994a) and Carta *et al.* (1994) followed up a cohort of 4740 male workers who had at least one year of employment between 1932 and 1971 and were working during 1960–71 in a lead ore (A) and a zinc ore (B) mine in Sardinia. The mortality follow-up was through 1988. Vital status was ascertained for 99.5% of the cohort. SMRs were based on the regional five-year age- and year-specific death rates. The average respirable dust concentrations in underground workplaces in the two mines were similar — 2.5–2.6 mg/m³ in 1962–70 and they decreased to 1.6–1.8 mg/m³ in 1981–88 (with median quartz concentration of 1.2% and 12.8%, respectively) in mines A and B. Surface workers were exposed to less than 1 mg/m³ in both mines from the 1970s. The mean exposure to radon daughters was higher in mine A (0.13 WL) than in mine B (0.011 WL) among underground miners. Smoking habits were comparable between the two mines. Of the cohort, 2096 worked in mine A and 2603 in mine B, and 41 in both. In underground workers from mine A, the SMR for all causes of death was not increased (325 observed; SMR, 1.03; 95% CI, 0.92–1.14) nor was that for all cancers (84 observed; SMR, 0.99; 95% CI, 0.80–1.23) nor that for lung cancer (28 observed; SMR, 1.15; 95% CI, 0.77–1.67); the SMRs for cancer of the peritoneum and retroperitoneum (4 observed; SMR, 9.17; 95% CI, 2.50–23.47) and for respiratory diseases (68 observed; SMR, 2.46; 95% CI, 1.91–3.12) were increased. In underground miners from mine B, the SMR for all causes of death was increased (472 observed; SMR, 1.20; 95% CI, 1.09–1.31). Mortality from all cancers (101 observed; SMR, 0.92; 95% CI, 0.76–1.12) and lung cancer (26 observed; SMR, 0.79; 95% CI, 0.52–1.16) were not increased. Increases were SMRs for infectious and parasitic diseases (29 observed; SMR, 4.16; 95% CI, 2.79–5.97), pulmonary tuberculosis (29 observed; SMR, 7.06; 95% CI, 4.73–10.14) and respiratory disease (156 observed; SMR, 5.18; 95% CI, 4.40–6.06). Death from silicosis was included under non-malignant respiratory disease. Surface workers from both mines had a similar pattern of SMRs. SMRs for lung cancer did not show a systematic increasing trend with increasing duration of underground employment in any of the mines.

A cohort of 310 women employed in surface jobs (belt pickers) in the two mines (reported above) and 173 women not exposed to silica were also studied for lung cancer

risk (Cocco *et al.*, 1994b). There were 163 deaths in the total cohort and the risk of lung cancer was elevated in the exposed (5 cases; SMR, 2.83; 95% CI, 0.91–6.60) and in the unexposed women (1 case; SMR, 1.22; 95% CI, 0.02–6.78). [The Working Group noted the small number of cancer cases.]

2.1.3 Case-control studies (see also Table 19)

Mastrangelo *et al.* (1988) studied 309 male cases of lung cancer and 309 male controls from Belluno in a Northern province of the Venetian region in Italy that has a high rate of compensation for silicosis. The main silica exposures came from tunnelling, mining and quarrying. Cases were newly diagnosed primary lung cancer in the Belluno city hospital chest clinic from 1973 through 1980. Controls were patients admitted to the same chest clinic and matched on year of birth, residence in the province of Belluno and date of admission to the clinic. Patients with chronic bronchitis were excluded from the controls. Information collected at the time of admission included the following: occupation, type of industry, length of exposure to silica, presence of compensated silicosis, the average number of cigarettes smoked per day in current smokers, and time since cessation of smoking in ex-smokers. When compared to non-exposed subjects, the relative risk adjusted for smoking, estimated from matched analysis, was increased for exposed subjects with silicosis (50 cases, 30 controls; OR, 1.9, 95% CI, 1.1–3.2), but was not increased for exposed subjects without silicosis (86 cases, 95 controls; OR, 0.9; 95% CI, 0.7–1.6). There was an increasing trend between risk for lung cancer and duration of exposure to silica dust, with the highest OR of 1.6 for workers employed for ≥ 15 years versus unexposed workers (p for trend < 0.05). There was an apparent synergistic effect between silicosis and smoking. The OR lung cancer in non-smoking silicotics exposed to silica was 5.3 (95% CI, 0.5–43.5); in smoking non-silicotics not exposed to silica, 11.9 (95% CI, 4.2–46.5); in smoking non-silicotics exposed to silica, 10.4 (95% CI, 2.9–44.4); and in smoking silicotics exposed to silica, 19.7 (95% CI, 5.1–89.7). Risk, estimated by type of occupational exposure, was highest for tunnelling. [The Working Group noted that potential biases may have occurred due to the use of chest-clinic controls.]

Hessel *et al.* (1990) selected 571 white South African gold miners who had a diagnosis of lung cancer at an autopsy conducted for compensation purposes during 1974–78 and 1983–86 by the mining medical bureau. After exclusion of secondary cancers, those with low exposure (less than 1000 shifts) and missing information, 231 cases remained. Cases were matched to 318 controls by age at death. Cumulative exposure to silica dust was calculated from detailed work histories and a relative index for dust levels assigned to occupational categories. Tobacco consumption was obtained from medical files and used to create smoking categories. The assessment of silicosis was obtained from necropsy reports. The degree of silicosis was diagnosed at autopsy on the basis of macroscopic and microscopic examination. There were no significant case-control differences in dust exposure. The adjusted odds ratio for lung cancer and silicosis were close to 1.0. Odds ratios for lung cancer were 1.1 (124 cases; 95% CI, 0.77–1.58) for silicosis of parenchyma and 1.29 (192 cases; 95% CI, 0.83–2.08) for silicosis of the hilar glands. These figures were adjusted for cumulative dust exposure. [The Working

Group noted that the elimination of cases and controls with low exposure may have biased the results against finding an exposure effect. It was also noted that workers in South African gold mines were exposed to radon.]

Fu *et al.* (1994) conducted a case-control study of lung cancer in male workers employed at the Dachang tin ore mine in the Guangxi province of south-eastern China. The cases and controls were selected from all miners resident in the area for at least 10 years. The 79 lung cancer cases were all cases identified from health records and death certificates filed at the Anti-epidemic Station during 1973-89 (9 alive at the end of sampling period). The 188 controls were stratified by decade of birth and survival of the oldest case. Years of exposure were calculated up to the year when cancer was diagnosed. The average dust levels prior to 1955 were 25 mg/m³; dry drilling during 1955-57 increased the levels as high as 128 mg/m³; after 1957, improved ventilation and wet drilling resulted in decrease to 2-5 mg/m³. The ore contained 23.6% silicon (as silica), 0.08% lead, 0.08% arsenic, 0.008% cadmium and other metals. Exposure to radon daughters was low (0.3 WLM per year). Smoking data were obtained retrospectively by questionnaire and occupational history was obtained from interview and employment records. Diagnosis of silicosis was obtained from medical records, but age of diagnosis could not be determined, so it was not possible to exclude controls who developed silicosis after the death of a corresponding case. The crude odds ratio for lung cancer was increased for years of underground exposure to dust (odds ratio, 2.13; 95% CI, 1.27-3.60) and the presence of silicosis (odds ratio, 2.03; 95% CI, 1.25-3.29) and there was a statistically significant trend with years of underground exposure to dust (odds ratios, 1.0, 1.69, 2.18 and 3.21 ($p < 0.002$), for 0, < 10, > 10 and > 20 years, respectively). The smoking-adjusted odds ratio for lung cancer and year of underground dust exposure was 1.05 (95% CI, 1.03-1.07) per year. [The Working Group noted that the apparent association of lung cancer risk with silica is potentially confounded by concomitant exposures to arsenic, cadmium and radon.]

A case-control study of radiographic silicosis and lung cancer was conducted among underground uranium ore miners in New Mexico, United States (Samet *et al.*, 1994). The study included 65 lung cancer cases and 216 matched controls, for whom chest radiographs were located and interpreted by two 'B' readers (two chest radiographs were available for 58 cases and 181 controls). The odds ratio for any type of opacity indicative of pneumoconiosis in the radiograph closest in time to the start of employment was 1.33 (95% CI, 0.31-5.72); for the second radiograph, it was 1.16 (95% CI, 0.35-3.84). Both odds ratios were adjusted for exposure to radon daughters. The findings were unchanged when both radiographs were entered into a logistic model, or for radiographs 0/1 or higher profusion, or just profusion of rounded opacities.

Armstrong *et al.* (1979) studied a cohort of 1974 miners who worked in gold mines in Kalgoorlie, Western Australia, and who were studied for respiratory symptoms in 1961-62 when 40-59 years old. Mortality follow-up was from 1969 to December 1975 (Armstrong *et al.*, 1979) and later updated to 1991 (de Klerk *et al.*, 1995). Exposure to silica dust was assessed in terms of duration of underground employment (7 categories). Smoking habits were assessed individually in 1961 as never smoked, current cigarette

smoker < 15 cigarettes/day, 15–24/day, ≥ 25 /day, current pipe or cigar smoker, ex-cigarette smoker and ex-pipe and cigar smoker. Maximal radon daughter concentration in the mines was 0.045 WL. In the first mortality follow-up by Armstrong *et al.* (1979), the OR for respiratory cancers (ICD-8 161–163) was slightly increased (59 observed; OR, 1.4 [95% CI, 1.11–1.87]). A synergistic effect between smoking and duration of underground exposure was observed. Tobacco consumption of the miners was given as a possible cause for the increased SMR. In the extended follow-up (de Klerk *et al.*, 1994), dead cases with lung cancer ($n = 98$) were compared with dead controls ($n = 744$). Deaths from tuberculosis, other respiratory disease and cancer of the larynx or unknown primary sites were excluded. The odds ratio (OR) for lung cancer for the longest duration of exposure (≥ 40 years) was elevated (OR, 2.3; 95% CI, 0.8–6.5). No elevated risks were found for shorter periods of employment underground and there was no trend in RR with duration. [The Working Group noted that the primary limitation of this study is the lack of any quantitative measurement of exposure. Exposure–response analysis depended upon the duration of underground employment.]

2.2 Workers exposed in quarries and granite production

2.2.1 Record-linkage studies

In the record-linkage study in four Nordic countries described in Section 2.1.1, Lyngé *et al.* (1990) reported results for lung cancer risk among stone-cutters in Norway (3 cases; rate ratio, 0.83; 95% CI, 0.17–2.44), Sweden (37 cases; rate ratio, 0.98; 95% CI, 0.83–1.16), Finland (15 cases; rate ratio, 1.75; 95% CI, 0.98–2.89), and Denmark (13 cases; rate ratio, 1.98 [95% CI, 1.06–3.39]). In an extended analysis of Finnish 1970 census records and 1971–1985 Cancer Registry records, stone-cutters had a social-class-adjusted standardized incidence ratio (SIR) for lung cancer of 1.68 (20 cases; 95% CI, 1.03–2.60) (Pukkala, 1995).

2.2.2 Cohort studies (see also Table 20)

Five cohort studies of workers employed in quarries and granite processing and one study of stone-cutters were available.

A proportionate mortality analysis, based on 969 deceased male granite workers from Vermont, who had died during 1952–78, was published by Davis *et al.* (1983). This population is included in the cohort study by Costello and Graham (1988). The PMR for lung cancer was 1.18 [95% CI, 0.90–1.51]; in an internal comparison analysis, lung cancer risk was 1.2, 0.9, 0.8 for the categories of medium (199–400 million particles per cubic foot (mppcf)-years), high (399–800 mppcf years) and very high (≥ 800 mppcf-years) cumulative exposure as compared with low cumulative exposure (< 199 mppcf-years).

Costello and Graham (1988) studied a cohort of 5414 workers employed in granite manufacturing plants (sheds) or quarries in Vermont (United States) during 1950–82 and who had had at least one X-ray (98% had X-rays). Dust concentrations were high up to 1940 and the average exposure for a cutter was 48.8 mppcf (Thériault *et al.*, 1974). Death

Table 19. Ore mining: cohort, case-control and proportionate mortality studies of silica

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Cohort studies				
<i>Gold ore miners</i>				
McDonald <i>et al.</i> (1978) United States	1321 former employees of Homestake Gold Mine, South Dakota; follow-up through 1973	All causes Respiratory cancer Dust exposure category Low Moderate High Very high Gastrointestinal cancer	SMR, 1.15 (641; [1.06-1.24]) 1.03 (17; [0.60-1.65]) 1.11 (7) 1.30 (3) 1.85 (5) 0.65 (2) 1.11 (39; [0.8-1.5])	Adjusted for smoking, year of birth, and age. Arsenic was not present in the dust. Uranium was mined in some gold mines. Interaction between smoking and dust was overadditive. Radon exposure was 0.1-3.0 WL.
Hnizdo & Sluis-Cremer (1991) South Africa	2209 gold miners (WM); mortality follow-up 1968-1986; internal proportional hazards analysis	Lung cancer Cumulative dust exposure per 1000 respirable surface area-years Exposure-response (per 1000 respirable surface area-years) ≤ 15 16-30 31-40 ≥ 41	RR 1.02 (1.01-1.04) 1.0 (4) 1.5 (30; 0.6-4.3) 2.07 (20; 0.7-6.0) 2.92 (23; 1.02-8.4)	
Kusiak <i>et al.</i> (1991, 1993) Canada	13 603 non-uranium gold miners (M) without exposure to asbestos; mortality follow-up 1955-86	Lung cancer Miners starting before 1946 (never nickel) Stomach cancer	SMR, 1.29 (1.15-1.45) 1.40 (236; 1.22-1.59) 1.52 (104; 1.25-1.85)	Adjusted for measurements for arsenic and radon decay products and duration of years of underground mining. Dust concentrations (particles/mL): before 1940s often above 1000; 1959, 400; 1967, 200

Table 19 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Cohort studies (contd)				
<i>Gold ore miners (contd)</i>				
Steenland & Brown (1995) United States	3328 gold miners (WM); mortality follow-up 1940-90	All causes All cancers Lung cancer Dust days (one day with an exposure of 1 mppcf) < 8000 8000-32 000 32 000-48 000 ≥ 48 000 Digestive system cancers	SMR, 1.13 (1551; 1.07-1.19) 1.01 (303; 0.90-1.13) 1.13 (115; 0.94-1.36) 1.17 (44; [0.84-1.55]) 1.01 (35; [0.71-1.41]) 0.97 (8; [0.41-1.85]) 1.31 (28; [0.87-1.89]) 0.85 (69; 0.66-1.07)	Cumulative exposure
Reid & Sluis-Cremer (1996) South Africa	4925 gold miners (WM) born between 1916 and 1930 and alive in 1970; mortality follow-up 1970-89	All causes Lung cancer Cumulative dust exposure 5 years before case death (year-mg/m ³) Stomach cancer	SMR, 1.30 (2032; 1.24-1.35) 1.40 (143; 1.18-1.65) 1.12 (0.97-1.3)	Adjusted for average cigarette consumption per day. Arsenic was not present in the dust.
<i>Iron ore miners</i>				
Chen <i>et al.</i> (1990) China	6444 iron ore miners (M) employed on 1 January 1970; follow-up through 31 December 1982	All cancers Lung cancer Unexposed Low exposure Medium exposure Heavy exposure Nonsmokers Silicotics Medium dust exposure Heavy dust exposure Stomach cancer	SMR, 1.1 (98; 0.9-1.3) 3.7 (29; 2.5-5.3) 1.2 (2; 0.1-4.2) 2.6 (3; 0.5-7.6) 2.6 (4; 0.7-6.6) 4.2 (22; 2.7-6.4) 0.6 (1; 0.0-3.3) 5.3 (14; 2.9-8.8) 11.1 (2; 1.3-40.1) 5.0 (12; 2.6-8.7) 0.8 (18; 0.5-1.3)	Traces of carcinogenic metals were detected in dust of iron ore mine. Radon daughters were measured in 1984.

Table 19 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Cohort studies (contd)				
<i>Other ore miners</i>				
Ahlman <i>et al.</i> (1991) Finland	597 copper and zinc ore miners employed between 1954 and 1973; follow-up through 1986	All causes All cancers Lung cancer	SMR, [1.04] (102; [0.85-1.27]) [0.99] (16; [0.6-1.6]) [1.45] (10; [0.7-2.7])	
Amandus & Costello (1991) United States	Metal miners (WM): 369 silicotics and 9543 non-silicotics from medical examination records 1959-61; mortality follow-up through 1975	Lung cancer Lung cancer Silicotics < 20 years underground > 20 years underground Non-silicotics < 20 years underground > 20 years underground Lung cancer Silicotics/non-silicotics	SMR 1.73 (14; 0.94-2.90) 1.78 (5; 0.56-4.16) 1.70 (9; 0.78-3.23) 1.18 (118; 1.98-1.42) 1.05 (74; 0.82-1.31) 1.52 (44; 1.10-2.03) RR 1.96 (1.19-3.23) 2.59 (1.44-4.68)	Adjusted for age and smoking Adjusted for smoking and restricted to subjects with low radon exposure
Chen <i>et al.</i> (1992) China	68 241 metal mine and pottery workers (M, F); mortality follow-up through 1989	All causes All cancers Lung cancer Dust exposure Low Medium High Stomach cancer Dust exposure Low Medium High	SMR, 1.06 (6192; 1.04-1.09) 0.86 (1572; 0.81-0.90) 0.79 (330; 0.71-0.88) 1.0 1.38 (1.0-1.9) 1.10 (0.9-1.4) 0.64 (225; 0.56-0.73) 1.0 1.14 (0.8-1.7) 1.00 (0.7-1.4)	

Table 19 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Cohort studies (contd)				
<i>Other ore miners (contd)</i>				
Cocco <i>et al.</i> (1994a) Italy	4740 workers (M) in lead (A) and zinc (B) mines; mortality follow-up 1960-88	All causes All cancers Lung cancer Stomach cancer	SMR, 1.04 (1205; 0.98-1.10) 0.94 (293; 0.83-1.05) 0.95 (86; 0.76-1.17) 0.94 (27; 0.62-1.37)	
		Lung cancer by years underground		
		Mine A (trend NS)		
		< 11	0.68 (4)	
		11-15	1.18 (7)	
		16-20	1.43 (10)	
		21-25	1.00 (7)	
		> 26	2.04 (5)	
		Mine B (trend NS)		
		< 11	0.78 (14)	
		11-15	0.73 (6)	
		16-20	0.63 (5)	
		21-25	1.22 (4)	
		> 26	1.35 (1)	
Cocco <i>et al.</i> (1994b) Italy	310 belt pickers (F) employed at least one year between 1932 and 1971 at crushers in lead and zinc mines and 173 unexposed (F) to silica; mortality follow-up 1951-88	All causes All cancers Lung cancer Stomach cancer	SMR, 0.78 (163; 0.67-0.91) 0.70 (32; 0.48-0.99) 2.32 (6; 0.85-5.05) 0.32 (2; 0.4-1.15)	

Table 19 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Case-control studies				
Mastrangelo <i>et al.</i> (1988) Italy	309 hospital cases, 309 matched controls (M) between 1973 and 1980	Silicotics exposed to silica dust Non-silicotics exposed to silica dust	OR, 1.9 (50; 1.1-3.2) 0.9 (86; 0.7-1.6)	Adjusted for smoking. Possible detection bias from hospital enrolment
Hessel <i>et al.</i> (1990)	231 lung cancer deaths and 318 other deaths matched by age at death	Lung cancer and silicosis by cumulative dust exposure	Mantel-Haenszel OR, 1.1 (121; 0.77-1.58)	
Fu <i>et al.</i> (1994) China	79 incidence cases and 188 matched controls (M) between 1973 and 1989 from tin miners' medical records	Lung cancer Years of underground exposure to dust 0 years < 10 years 10-19 years ≥ 20 years	OR, 2.13 (1.27-3.60) 1.0 (21) 1.69 (24; [1.08-2.50]) 2.18 (22; [1.31-3.17]) 3.21 (12; 1.7-5.6)	Trend $p = 0.002$ Adjusted for radon
Samet <i>et al.</i> (1994) United States	65 cases and 216 controls (M) from New Mexico uranium miners	Maximal profusion of any type of opacity of at least 1/0 on earliest radiograph Maximal profusion of any type of opacity of at least 1/0 on second radiograph	OR, 1.33 (0.31-5.72) 1.16 (0.35-3.84)	

Table 19 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
de Klerk <i>et al.</i> (1995) Australia	98 cases and 744 controls; Australian gold miners in 1961; follow-up 1969-91	Lung cancer by duration of underground employment None 0-4 years 5-9 years 10-19 years 20-29 years 30-39 years ≥ 40 years	OR 1.0 0.9 (0.4-2.1) 0.9 (0.4-2.3) 1.1 (0.6-2.3) 0.9 (0.4-1.7) 1.1 (0.6-2.3) 2.3 (0.8-6.5)	

Abbreviations: SMR, standardized mortality ratio; WM, white male; RR, relative risk; WL, working level; M, male; F, female; OR, odds ratio; NS, not significant

certificates were obtained from the Vermont State Health Department; the referent population used was United States white males. Of the cohort, 1643 men were known to have died. Death certificates were missing for 116 men. Overall mortality was decreased (1643 observed; SMR, 0.91; 95% CI, 0.87–0.95). The SMR for all malignancies was not increased (321 observed; SMR, 0.94; 95% CI, 0.84–1.05). However, SMRs were increased for lung cancer (118 observed; SMR, 1.16; 95% CI, 0.96–1.39), tuberculosis (124 observed; SMR, 5.86; 95% CI, 4.88–6.99), all respiratory disease (131 observed; SMR, 1.21; 95% CI, 1.01–1.44) and silicosis (41 observed; SMR, 6.36; 95% CI, 4.56–8.62). The mortality from lung cancer was increased in workers who worked in the sheds. In shed workers, the SMRs were: overall mortality (1284 observed, SMR, 0.93; [95% CI, 0.88–0.98]), all cancers (260 observed; SMR, 1.01; [95% CI, 0.89–1.14]), lung cancer (98 observed; SMR, 1.27 [95% CI, 1.03–1.55]), all respiratory disease (106 observed; SMR, 1.28; [95% CI, 1.05–1.55]), tuberculosis (110 observed; SMR, 6.63; [95% CI, 5.45–7.99]) and silicosis (38 observed; SMR, 7.73; [95% CI, 5.47–10.61]). The SMR for lung cancer was increased in workers who had started working before 1940 and had a 'time since hire' period of ≥ 40 years and tenure of ≥ 30 years (47 observed; SMR, 1.81; [95% CI, 1.33–2.41]) and also in workers who had started working after 1940 and who had > 25 years since time of hire and tenure of ≥ 10 years or more (17 observed; SMR, [1.73; 95% CI, 1.01–2.77]). In workers who had worked in quarries, the SMR for lung cancer was not increased (20 observed; SMR, 0.82; [95% CI, 0.50–1.27]). [The Working Group noted that a limitation of this study is that no dust exposure data were included in the exposure–response analyses, as had been done by Davis *et al.* (1983).]

Guénel *et al.* (1989b) identified a cohort of 2175 Danish stone workers from union lists, lists of self-employed workers, census data, and other sources. Criteria for inclusion were to be alive on 1 January 1943 or born later, and less than 65 years of age when identified from the above sources. Of the cohort, 95% of the workers were traced; 2071 cancer cases were identified through the Danish Cancer Registry from 1 January 1943 to 31 December 1984. The SIRs were calculated using the Danish national age- and time-specific incidence rates for men. Individual smoking data were not available, but regional differences in smoking habits were adjusted for using the regional differences in lung cancer. Adjustment for region was made by multiplying the expected number of cancers by the relative risk for the region. The analysis was performed separately for skilled workers ($n = 1081$), unskilled workers ($n = 990$), and by three regions — Bornholm, Copenhagen and elsewhere in Denmark. For the skilled workers, the unadjusted SIR for lung cancer was 1.38 (44 observed; 95% CI, 1.0–1.89) and when adjusted for regional differences in smoking was 2.00 (44 observed; 95% CI, 1.49–2.69). The SIR for workers in Copenhagen was 4.65 (18 observed; 95% CI, 2.74–7.29) and after adjustment for smoking, the SIR was 3.06 (18 observed; 95% CI, 1.81–4.82). The SIR for workers elsewhere in Denmark (18 observed; SIR, 1.61; 95% CI, 0.95–2.54) also increased after adjustment for smoking (18 observed; SIR, 1.92; 95% CI, 1.67–3.03). Stone-cutters known to have worked with sandstone had the highest increase in risk for lung cancer and also the highest occurrence of silicosis (56%). The SIR for all cancers was not increased for the unskilled workers (155 observed; SIR, 1.45; 95% CI, 1.23–1.70). Also in unskilled workers, the SIR for lung cancer before adjustment for smoking was 0.72

(27 observed; 95% CI, 0.46–1.08) and this increased after adjustment for smoking (SIR, 1.81; 95% CI, 1.16–2.70).

Mehnert *et al.* (1990) followed a cohort of 2483 male workers employed for at least one year in one of nine slate quarries in Germany during 1953–85. The follow-up period was from 1970 through 1985. Vital status was obtained for 2475 workers. Death certificates were available from 1970 to 1985. Expected deaths were calculated from age- and sex-specific national mortality rates. Smoking was not considered. The SMR for all causes of death was 1.01 (387 observed; 95% CI, 0.91–1.12). The SMR for all cancers was not increased (77 observed; SMR, 1.00; 95% CI, 0.79–1.26). The SMR for lung cancer was slightly increased (27 observed; SMR, 1.09; 95% CI, 0.72–1.59). Other neoplasms with increased SMRs were buccal cavity and pharynx (3 observed; SMR, 2.05; 95% CI, 0.42–6.00), rectum (12 observed; SMR, 2.63; 95% CI, 1.36–4.60) and lymphomas and myelomas (8 observed; SMR, 3.16; 95% CI, 1.36–6.23). SMRs were increased for pulmonary tuberculosis (5 observed; SMR, 3.76; 95% CI, 1.22–8.77) and non-malignant respiratory diseases (74 observed; SMR, 2.26; 95% CI, 1.77–2.84). There was a trend in SMR for lung cancer with time since first exposure (≥ 30 years: SMR, 1.52), with duration of employment (≥ 20 years: SMR, 1.57), with ranking of exposure (low: SMR, 1.07; high: SMR, 1.40) and with the presence of compensated silicosis (in non-silicotics: 18 observed; SMR, 0.91; 95% CI, 0.54–1.44; in silicotics: 9 observed; SMR, 1.83; 95% CI, 0.84–3.48). In silicotics, the trend increased with duration of employment (1–9 years SMR, 1.0; 10–19 years SMR, 1.81; ≥ 20 years SMR, 2.40). In non-silicotics, there was also trend with duration of employment (SMRs 0.67; 95% CI, 0.08–2.41 for 1–9 years; 0.74; 95% CI, 0.15–2.16 for 10–19 years and 1.32; 95% CI, 0.66–2.36 for 20 or more years). [The Working Group noted the absence of quantification of the silica exposure; the exposure–response is qualitative.]

Koskela *et al.* (1994) followed up 1026 Finnish granite workers who had started working between 1940 and 1971 in quarries and processing yards and had been employed for at least three months. The follow-up was through 1989 and the mean duration of exposure was 12 years. The geometric mean of total dust concentration ranged from 1.7 to 39.8 mg/m³ and that of quartz dust from 1.0 to 1.5 mg/m³. [No detailed information on respirable dusts was given.] The highest concentrations were in drilling. Job titles and duration of employment was known. Only 33 subjects had had other jobs with a potential exposure to carcinogens. Workers came from three regions with three corresponding different types of granite (red, grey and black granite). The mineral composition of the grey granite was 38% feldspar, 31% quartz and 20% plagioclase; the red granite was composed of 41% feldspar, 36% quartz and 16% plagioclase. Smoking data were obtained by questionnaire. Expected deaths were derived from national mortality data for men in the median year of deaths in the cohort (1975). Overall cancer mortality was increased (363 observed; [SMR, 1.09; 95% CI, 0.98–2.1]), mainly due to increased mortality of workers employed on grey granite (160 observed; [SMR, 1.30; 95% CI, 1.10–1.51]). Mortality from lung cancer was significantly elevated in the grey granite area (17 observed; [SMR, 1.75; 95% CI, 1.02–2.81]). Mortality from respiratory diseases was elevated in the red granite area (31 observed; [SMR, 2.31; 95% CI, 1.57–3.28]) and in the grey granite area (16 observed; [SMR, 1.90; 95% CI, 1.10–

3.09]). Workers from both types with 10 or more years of exposure and a ≥ 20 -year latency period had increased risk of lung cancer (22 observed; [SMR, 1.48; 95% CI, 0.93–2.24]). In the grey granite area, the risk for lung cancer was increased already at year of age in the mid-40s and, in the red granite area, after 60 years of age, when compared to the regional populations. [The Working Group noted that expected deaths may have been underestimated, and that standard statistical methods had not been applied.]

Costello *et al.* (1995) studied 3246 United States men who had been employed one or more years during 1940–80 at 20 crushed stone operations. These facilities included quarries and a processing plant for crushing, sorting and cleaning stone. A stratified sample of 20 operations was randomly selected by rock type (granite, limestone or traprock) and by geographical location from all active industries in 1978. The average content of crystalline silica in the personal respirable dust samples was 37% respirable dust (0.06 mg/m^3) for granite, 11% (0.04 mg/m^3) for limestone and 15% (0.04 mg/m^3) for traprock. Vital status was determined in all men and death certificates were obtained for 615 of the 661 subjects who died. Expected deaths were calculated from United States white and non-white male rates separately. The SMRs were calculated for white and non-white males. The SMR was not increased for all causes (661 observed; SMR, 0.96; 95% CI, 0.89–1.04) or for all cancers (125 observed; SMR, 0.96; 95% CI, 0.80–1.15). The SMR for cancer of the peritoneum was increased for the white workers (5 observed; SMR, 9.74; 95% CI, 3.16–22.69). There were three deaths where mesothelioma was mentioned on the death certificates. [The Working Group noted that no information was given on whether this diagnosis was confirmed by histological examination.] The SMR for lung cancer was 1.19 for whites (40 observed; 95% CI, 0.85–1.62) and 1.85 for non-whites (11 observed; 95% CI, 0.92–3.31). The SMR for the cardiovascular diseases was decreased for whites. The SMR for pneumoconiosis and other selected non-malignant respiratory diseases was increased (20 observed; SMR, 1.98; 95% CI, 1.21–3.05) in the whole cohort. Analysed by rock type, the SMR for lung cancer was significantly increased for granite operations in men with ≥ 20 years since first employment and ≥ 10 years of tenure (7 observed; SMR, 3.54; 95% CI, 1.42–7.29). The SMRs were elevated for both whites (3.57; 95% CI, 0.97–9.14) and for non-whites (3.45; 95% CI, 0.71–10.07). In men with ≥ 20 years since first employment, the SMR for lung cancer was elevated for limestone (23 observed; SMR, 1.50; 95% CI, 0.95–2.25) but not for traprock (3 observed; SMR, 0.63; 95% CI, 0.13–1.84).

2.3 Ceramics, pottery, refractory brick and diatomaceous earth industries

In the following industries, silica products are heated. In refractory brick and diatomaceous earth plants, the raw materials (amorphous or crystalline silicas) are processed at temperatures around 1000°C with varying degrees of conversion to cristobalite. In ceramic and pottery manufacturing plants, exposures are mainly to quartz, but where high temperatures are used in ovens, potential exposures to cristobalite may occur.

Table 20. Quarries and granite production: cohort studies of silica

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Costello & Graham (1988) United States	5414 workers (M) in granite sheds and quarries employed between 1950 and 1982	All causes	SMR, 0.91 (1643; 0.87-0.95)	No incorporation of exposure data, which limits conclusions about exposure-response
		All cancer sites	0.94 (321; 0.84-1.05)	
		Lung cancer	1.16 (118; 0.96-1.39)	
		Workers who started before 1940 and had latency \geq 40 years and tenure \geq 30 years	1.81 (47; [1.33-2.41])	
		Workers who started after 1940 and had latency > 25 years and tenure \geq 10 years	[1.73 (17; 1.01-2.77)]	
Guénel <i>et al.</i> (1989b) Denmark	2071 stone workers; cancer incidence follow-up 1943-84	Stomach cancer	0.75 (16; 0.43-1.22)	
		Lung cancer	SIR	Adjustment for regional differences in smoking
		Skilled workers	2.00 (44; 1.49-2.69)	
		Copenhagen	3.06 (18; 1.81-4.82)	
		Other parts of Denmark	1.92 (18; 1.67-3.03)	
		Copenhagen sandstone	8.08 (7; 3.23-16.6)	
		Unskilled workers	1.81 (24; 1.16-2.70)	

Table 20 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths/cases; 95% confidence interval)	Comments
Mehner <i>et al.</i> (1990) Germany	2475 slate facility workers (M) employed between 1953 and 1985; mortality follow-up 1970-85	All causes	SMR, 1.01 (387; 0.91-1.12)	Unadjusted for smoking exposure; classification is uncertain.
		All cancers	1.00 (77; 0.79-1.26)	
		Lung cancer	1.09 (27; 0.72-1.59)	
		By time since first exposure		
		10-19 years	0.50 (2; 0.01-1.8)	
		20-29 years	1.06 (12; 0.55-1.86)	
		≥ 30 years	1.52 (13; 0.81-2.60)	
		By duration of employment		
		1-9 years	0.61 (2; 0.07-2.21)	
		10-19 years	1.05 (6; 0.39-2.28)	
		≥ 20 years	1.57 (17; 0.91-2.51)	
		Stomach cancer	1.16 (13; 0.62-1.99)	
		By time since first exposure		
		0-9 years	2.58 (1; 0.07-14.36)	
		10-19 years	1.63 (3; 0.34-4.75)	
		20-29 years	1.36 (7; 0.55-2.80)	
		≥ 30 years	0.53 (2; 0.06-1.90)	
Silicotics		All causes	1.27 (103; 1.03-1.53)	Trend by duration of employment on small numbers
		All cancers	0.99 (15; 0.56-1.64)	
		Lung cancer	1.83 (9; 0.84-3.48)	
		Stomach cancer	0.82 (2; 0.10-2.95)	
Non-silicotics		All causes	0.94 (284; 0.84-1.06)	
		All cancers	1.01 (62; 0.77-1.29)	
		Lung cancer	0.91 (18; 0.54-1.44)	
		Stomach cancer	1.26 (11; 0.63-2.25)	

Table 20 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Koskela <i>et al.</i> (1994) Finland	1026 granite workers (M), hired between 1940 and 1971; follow-up through 1989	All cancers	SMR, [1.09] (363 [0.98-2.1])	
		Grey granite Lung cancer	[1.30] (160; [1.10-1.51]) [1.40] (36; [1.0-1.9])	
Costello <i>et al.</i> (1995) United States	3246 stone workers (M) in crushing, sorting and cleaning employed between 1940 and 1980; follow-up 1940-80	Grey granite ≥ 10 years exposure and ≥ 20 years latency (grey + red granite)	[1.75] (17; [1.02-2.81]) [1.48] (22; [0.93-2.24])	
		Digestive system cancers	[1.32] (19; [NS])	
		All causes	SMR, 0.96 (661; 0.89-1.04)	Expected deaths calculated from United States white and non-white male rates
		All cancers	0.96 (125; 0.80-1.15)	
		Peritoneum cancer, whites	9.74 (5; 3.16-22.69)	
		Lung cancer		
		Whites	1.19 (40; 0.85-1.62)	
		Non-whites	1.85 (11; 0.92-3.31)	
		All workers, granite (≥ 20 years latency and ≥ 10 years tenure)	3.54 (7; 1.42-7.29)	
		All workers (≥ 20 years latency)		
	Limestone	1.50 (23; 0.95-2.25)		
	Traprock	0.63 (3; 0.13-1.84)		

Abbreviations: M, male; SMR, standardized mortality ratio; SIR, standardized incidence ratio; NS, not significant

2.3.1 *Record-linkage studies*

In the record-linkage study in Norway, Sweden, Finland and Denmark described Section 2.1.1, Lyngne *et al.* (1990) reported results on lung cancer incidence and mortality among glass, porcelain, ceramic and tile workers from Norway (rate ratio, 1.79; 95% CI, 1.00–2.95; 15 cases), Sweden (rate ratio, 1.05; 95% CI, 0.95–1.16; 94 cases), Finland (rate ratio, 1.27; 95% CI, 0.80–1.92; 22 cases) and Denmark (rate ratio, 1.03; 95% CI, 0.90–1.18; 55 cases). In the extended analysis of Finnish records, also described in Section 2.2.1, the adjusted SIR for lung cancer among potters was 1.04 (95% CI, 0.50–1.91; 10 cases) (Pukkala, 1995). In an analysis linking 1981 census records and 1981–1989 mortality records in Turin, Italy, Costa *et al.* (1995) reported four deaths from lung cancer among brick, pottery and glass workers (RR, 1.03). In a parallel analysis of 1981–1982 mortality of the Italian population, 33 deaths from lung cancer were reported (RR, 1.14; $p > 0.05$).

2.3.2 *Cohort studies* (see Table 21)

Ceramics

Thomas (1982) examined the mortality of members of the United States Potters and Allied Workers Union for 1955–77. In men, there were elevated PMRs for tuberculosis (62 observed; PMR, 3.39; [95% CI, 1.36–1.74]), non-malignant respiratory disease (frequently noted as silicosis; 268 observed; PMR, 1.54; [95% CI, 1.36–1.74]) and lung cancer (178 observed; PMR, 1.21; [95% CI, 1.04–1.40]). The lung cancer excess appeared to be localized among workers in the sanitary-ware divisions (62 observed; PMR, 1.80; [95% CI, 1.38–2.31]). Silica exposure was said to be similar in sanitary-ware divisions and in other parts of the plants but to be characterized by the use of talc to dust moulds. [The Working Group noted the possibility that the talc was contaminated with asbestos.]

A cohort mortality study reported by Thomas and Stewart (1987) and Thomas (1990) was based on 2055 white men employed for one year or more in three plants manufacturing ceramic sanitary ware between 1939–1966 and followed up until 1 January 1981. Exposures were predominately to quartz but in some processes also to fibrous (tremolitic) talc until 1976 and non-fibrous (non-asbestiform) talc. Against United States rates for white males, the number of deaths from all causes was significantly fewer than expected (578 deaths; SMR, 0.90; [95% CI, 0.83–0.98]). There was an excess of lung cancer deaths (52 observed; SMR, 1.43; [95% CI, 1.07–1.88]) but a deficit of deaths from digestive cancer (19 observed; SMR, 0.52; [95% CI, 0.31–0.81]). Mortality from non-malignant respiratory disease was also increased (64 observed; SMR, 1.73; [95% CI, 1.33–2.21]). The lung cancer mortality risk increased with number of years of exposure to non-fibrous talc but was unrelated to years of exposure to silica. Information was not available on smoking. [The Working Group noted that the degree of overlap between these studies was not clear.]

A cohort of 1784 male Dutch ceramic workers was constructed based on a nationwide cross-sectional silicosis survey between 1972 and 1982. Follow-up took place between

time of medical examination and 31 December 1991 (Meijers *et al.*, 1996). Only those persons with a total working history of more than two years in the ceramics industry were selected for analysis. No usable quantitative exposure measurements were available, but each worker was classified as having low, medium or high silica exposure according to job description. Cause-, age- and calendar time-specific death rates of the total male Dutch population were applied to calculate expected numbers of deaths and SMRs. Overall lung cancer mortality risk was lower than expected (30 observed; SMR, 0.88 [95% CI, 0.59–1.26]). For silica exposure, there was no exposure–response relationship with respect to cumulative dust exposure (low: 9 observed; SMR, 0.82; [95% CI, 0.37–1.55]; medium: 10 observed; SMR, 0.75; [95% CI, 0.36–1.38]; high: 11 observed; SMR, 1.15; [95% CI, 0.57–2.05]). Stomach cancer was not evaluated in this study.

Pottery

In a large cohort mortality study from southern central China, described in detail in Section 2.1.2 (Chen *et al.*, 1992), 13 719 pottery workers were included with average annual dust exposure of 11.4 mg/m^3 (9.4–23.8 mg/m^3). The SMRs among these pottery workers were 1.44 ($p < 0.05$) for respiratory disease and 0.58 ($p < 0.05$) for lung cancer. In a nested analysis of 316 male lung cancer cases and 1352 controls (62 cases and 238 controls in pottery workers) (McLaughlin *et al.*, 1992), also described in Section 2.1.2, the odds ratios for lung cancer for pottery were 2.0, 1.7 and 1.5 for low, medium and high total dust exposure as compared to no exposure. The trend for cumulative respirable silica exposure was not significant. There was no association with silicosis. Smokers of more than 20 cigarettes a day were at greatly increased risk (OR, 7.4).

In the British pottery industry, a study of mortality in a cohort of 4093 men was made by Winter *et al.* (1990). The subjects had been included in a survey of respiratory disease in the pottery industry conducted in 1970–71. Difficulties were encountered in ensuring the full tracing of the cohort and the investigators decided to limit their study to men and women under 60 years of age in 1970–71 ($n = 3669$). Among these subjects, 390 deaths were observed by the end of 1985 against 363.4 expected from national rates (SMR, 1.07) and 394.7 against local rates (SMR, 0.99). The SMRs for the 60 deaths observed from lung cancer were 1.40 (95% CI, 1.07–1.80) for national rates and 1.32 (95% CI, 1.00–1.69) for local rates. Adjustments for recorded smoking habits made very little difference to these SMRs, but possible exposure to other hazardous dusts was not considered. There was some indication of a relation between risk and estimated cumulative exposure to respirable quartz. Mean respirable quartz concentrations obtained in the workplace in each pottery were used to form four cumulative exposure groups, which assumed that current exposure levels applied to the entire occupational history in the pottery. The smoking adjusted lung cancer SMRs for the four cumulative exposure groups were 1.08 [95% CI, 0.35–2.54] for 0–0.14 (mg/m^3) \times years, 0.99 [95% CI, 0.43–1.95] for 0.15–0.49 (mg/m^3) \times years, 1.62 (95% CI, 1.05–2.39) for 0.50–1.49 (mg/m^3) \times years and 1.51 [95% CI, 0.93–2.31] for 1.50 (mg/m^3) \times years or more. [The Working Group noted the investigators' concern about possible bias in the follow-up and by the fact that mortality results were linked to men under 60 years of age in 1970–71.]

A further investigation in the British pottery industry was based on a cohort of 7020 male pottery workers in Staffordshire, born 1916–45, a few of whom were possibly included in the cohort of Winter *et al.* (1990). This study had three phases: in the first, proportional mortality was analysed in the 1016 men who had died by 30 June 1992 (McDonald *et al.*, 1995); in the second, SMRs were examined in a cohort reduced to 5115 after exclusion of men who had worked in foundries, asbestos or other dusts (Cherry *et al.*, 1995); and, finally, risks were assessed in detail taking account of radiographic changes, exposure estimates and smoking habit (Burgess *et al.*, 1997; Cherry *et al.*, 1997; McDonald *et al.*, 1997). In the first phase of the study, after exclusion of recorded asbestos exposure, the PMR for lung cancer was found to be 1.22 (112 deaths [95% CI, 1.01–1.47]) against national rates but 1.04 (112 deaths; [95% CI, 0.86–1.25]) against local rates. The PMR for lung cancer in those with pneumoconiosis on their death certificate (30) was 1.75 (7 deaths [95% CI, 0.7–3.6]). A nested case-control study of 75 lung cancer cases and 75 controls matched on date of birth and date of first exposure suggested that the risk of lung cancer was associated with smoking history and past asbestos exposure. A further analysis based on 47 case-control pairs, in which both cases and referents were smokers showed evidence that risk was related to the duration of silica exposure (≥ 10 years) in pottery work (odds ratio, 2.8; 90% CI, 1.1–7.5) (McDonald *et al.*, 1995). In the second phase of the study, SMRs against national mortality rates for the period 1985 through June 1992 were as follows: lung cancer, 1.91 (68 deaths [95% CI, 1.48–2.42]); and non-malignant respiratory disease, 2.87 [95% CI, 2.17–3.72]). Against local rates, the corresponding SMRs were 1.28 [95% CI, 0.99–1.62] and 2.04 [95% CI, 1.55–2.65] (Cherry *et al.*, 1995). In the third phase, the three following related analyses were reported (Burgess *et al.*, 1997; Cherry *et al.*, 1997; McDonald *et al.*, 1997): a radiographic validation of the exposure matrix; findings from a nested case-control study of mortality in relation to exposure, smoking and radiological changes using conditional logistic regression; and detailed findings from a sub-cohort of 1083 men used in the radiographic validation. The case-control analysis was based on 52 cases employed for 10 or more years (and 3–4 times as many controls). These three sets of analyses, taken together, showed (i) that a relationship existed between cumulative exposure and small radiographic opacities, and that this relationship was dominated by the intensity of exposure, and (ii) that in both the full cohort and sub-cohort, lung cancer risk was dominated by smoking but in neither was it related to cumulative exposure. However, lung cancer risk was increased in workers whose average intensity of exposure was $200 \mu\text{g}/\text{m}^3$ or greater (odds ratio, 1.88; 90% CI, 1.06–3.34) and in workers whose maximum exposure was $400 \mu\text{g}/\text{m}^3$ or greater (odds ratio, 2.16; 90% CI, 1.11–4.18). The latter risk was limited to workers in firing and post-firing occupations. Eight per cent levels of cristobalite were recorded in dust samples from this industry but these were not specific to firing and post-firing operations. [The Working Group noted that this study was the only epidemiological examination of peak exposure effects in lung cancer risk. Whereas the findings do not support a relation with cumulative exposure, the possibility remains that high-intensity exposures ($\geq 400 \mu\text{g}/\text{m}^3$) may increase risk.]

Refractory brick

A series of reports on refractory brick workers in Genoa (Puntoni *et al.*, 1985, 1988) was updated by Merlo *et al.* (1991). In this latter study, a cohort of 1022 factory brick male workers for six months or more between 1 January 1954 and 31 December 1977 was followed through 1986. Geometric mean concentration of respirable dust ranged from 200–560 $\mu\text{g}/\text{m}^3$; crystalline silica was 30–65%. Observed deaths were compared with mortality for the Italian male population and smoking habits recorded for 285 workers actively employed in 1984 were noted. The overall mortality based on 243 deaths was somewhat above expectation (SMR, 1.10; 95% CI, 0.97–1.25). An excess was more definite for lung cancer (28 observed; SMR, 1.51; 95% CI, 1.00–2.18), urinary bladder cancer (7 observed; SMR, 2.78; 95% CI, 1.12–5.71) and non-malignant respiratory diseases (40 observed, SMR, 2.41; 95% CI, 1.72–3.28). The excess mortality from lung cancer and other respiratory diseases was almost entirely due to the experience of men first employed before 1957. Mortality was stratified by both length of employment and by years since first employment. SMRs for workers with > 19 years since first employment and for the category ≤ 19 years since first employment and > 19 years tenure were: lung cancer, SMR, 1.75 (8 deaths; 95% CI, 0.75–3.46) and SMR, 2.01 (13 deaths; 95% CI, 1.07–3.44); respiratory disease, SMR, 1.58 (7 deaths; 95% CI, 0.64–3.25) and SMR, 3.89 (28 deaths; 95% CI, 2.59–5.63) and bladder cancer, SMR, 5.75 (4 deaths; 95% CI, 1.57–14.74) and SMR, 0.99 (1 death; 95% CI, 0.25–5.49), respectively. A comparison of the smoking habits of the 285 men employed in 1984 and those of the Italian male population showed no significant difference. [The Working Group noted that information was not available on levels of exposure to crystalline silica or on the degree of conversion from quartz to cristobalite.]

A separate analysis was conducted on male silicotics and non-silicotics among 231 workers from the same refractory brick plant employed on 1 January 1960 and followed for mortality through 1979 (Puntoni *et al.*, 1988). Included were 136 silicotics, identified from compensation files. SMRs were calculated using age-specific Genova mortality rates during the follow-up period as the reference. The SMR for all causes was 1.63 (57 deaths; 95% CI, 1.23–2.11) in silicotics and 0.64 (16 deaths; 95% CI, 0.36–1.03) in non-silicotics. Significant non-cancer excesses in the silicotics were reported for cardiovascular (SMR, 1.73) and non-malignant respiratory (SMR, 5.00) diseases. The SMRs for all cancer was 1.42 (16 deaths; 95% CI, 0.81–2.30) in silicotics and 0.88 (7 deaths; 95% CI, 0.35–1.81) in non-silicotics. With six deaths, the SMR for lung cancer was 1.67 (95% CI, 0.61–3.64) in silicotics (two non-smokers) and, with five deaths, 2.08 (95% CI, 0.67–4.84) in non-silicotics (one non-smoker). Laryngeal cancer was in excess in silicotics (3 deaths; SMR, 6.82; 95% CI, 1.40–19.9), while no laryngeal cancer deaths occurred in non-silicotics.

A further cohort mortality study from China was made in 11 refractory brick plants (Dong *et al.*, 1995). Entry to the study was restricted to 6266 men first employed before 1962, almost all between 1950 and 1959. By 1985, 871 (13.9%) had died and 263 (4.2%) were lost to follow-up. Almost all cohort members had been subject to periodic health examination and chest X-ray; the latter classifying in the Chinese system silicosis as

follows: category I, 20%; category II, 7%; and category III, 3%. Smoking habits were also recorded. Standardized rate ratios (SRRs) were calculated by age and cause of death in comparison with a population of 11 470 male workers from 10 rolling steel mills. The overall SRR was 1.44 (871 deaths; 95% CI, 1.35–1.54); among non-silicotics, the SRR for all causes of death was 1.04 (390 deaths; [95% CI, 0.94–1.15]) and among silicotics (categories I, II, III) the SRR was 2.10 (481 deaths; [95% CI, 1.92–2.30]). The corresponding SRRs for cardiorespiratory disease were 1.25 (255 deaths; [95% CI, 1.10–1.41]), 0.96 (111 deaths; [95% CI, 0.79–1.16]) and 1.65 (144 deaths; [95% CI, 1.40–1.94]), and for lung cancer 1.49 (65 deaths; [95% CI, 1.15–1.90]), 1.11 (30 deaths; [95% CI, 0.75–1.58]) and 2.10 (35 deaths; [95% CI, 1.46–2.92]). In men with 20 or more years of exposure, the SRR for lung cancer increased significantly with duration of exposure. In men without silicosis, the SRR for lung cancer was 1.20 (21 deaths; [95% CI, 0.74–1.83]) in smokers and 0.85 (7 deaths; [95% CI, 0.34–1.75]) in non-smokers. The corresponding SRRs for men with silicosis were 2.34 (21 deaths; [95% CI, 1.45–3.58]) and 2.13 (12 deaths; [95% CI, 1.10–3.72]), respectively.

Diatomaceous earth

Checkoway *et al.* (1993) conducted a cohort mortality study of 2570 diatomaceous earth industry workers from two plants in Southern California, United States. In this industry, the raw material is calcined at temperatures ranging from 800 °C to 1000 °C with conversion of the amorphous silica mainly to cristobalite. The main study cohort was defined as white men workers employed for at least 12 months' cumulative service. Follow-up was performed for the years 1942–87. The analysis focused on exposures to crystalline silica. Semi-quantitative exposure to airborne dust was estimated for each cohort member and so far as possible workers thought to have been exposed to asbestos were excluded. Vital status was ascertained for 91% of the cohort and certified cause of death obtained for 94% of the 628 deaths. Only 129 workers from the cohort (5%) were classified as only having had amorphous silica exposure, from opencast mining of the ore. Compared with white United States males, the SMR for all causes was 1.12 (95% CI, 1.03–1.21), the excess largely explained by increased risks for lung cancer (59 deaths; SMR, 1.43; 95% CI, 1.09–1.84) and non-malignant respiratory disease (77 deaths; SMR, 2.27; 95% CI, 1.79–2.83). Results obtained by use of local county mortality rates were not shown but the SMR for lung cancer was reported as 1.59. Internal exposure–response analyses were performed for lung cancer and non-malignant respiratory disease mortality with respect to cumulative exposure to crystalline silica. Evidence supportive of dose–response was produced for lung cancer; the rate ratio in the highest exposure category reached 2.74 (19 observed; 95% CI, 1.38–5.46), assuming a 15-year latency. A similar gradient was found for non-malignant respiratory disease (excluding pneumonia and infectious respiratory diseases). Limited data available on cigarette smoking did not suggest that this factor could account for these trends.

In view of the possibility that exposure to asbestos might have been more extensive than originally thought, further analyses were later undertaken to study this question in detail (Checkoway *et al.*, 1996). This examination was restricted to a subset of 2266

workers from the larger of the two diatomite plants in the original cohort of 2570 white men; for these workers, it was possible to add individual assessments of asbestos exposure to those of crystalline silica. Workers hired before 1930 were excluded because of uncertainties of the asbestos exposure data. There were 52 deaths from lung cancer in this subset giving an overall SMR of 1.41 (95% CI, 1.05–1.85). Of the 52 deaths, 22 were in men in the lowest category of silica exposure (SMR, 1.16; 95% CI, 0.73–1.75); 15 of the 22 deaths occurred in men not exposed to asbestos (SMR, 1.13; 95% CI, 0.63–1.86); a total of 31 deaths were seen in men exposed to silica (all categories) but not asbestos (SMR, 1.34; 95% CI, 0.91–1.91). An exposure–response gradient for lung cancer was detected with respect to the crystalline silica index, lagged by 15 years. The rate ratio reached 1.83 (10 observed; 95% CI, 0.79–4.25) in the highest exposure category. Following adjustment for asbestos exposure, the exposure–response gradient for crystalline silica was virtually identical (rate ratio, 1.79; 95% CI, 0.77–4.18).

2.3.3 Case–control studies (see also **Table 21**)

A case–control study of lung cancer and silicosis was carried out in the small town of Civitacastellana, central Italy, which has a long tradition of pottery manufacture employing a large proportion of residents (Forastiere *et al.*, 1986; Lagorio *et al.*, 1990). Silicosis among 72 cases of lung cancer and among 319 controls, all deceased, was ascertained from information on compensated cases of silicosis and from municipal records during the study period 1968–1984. Questionnaires recording past employment and smoking habits were administered blindly to the next-of-kin of the deceased subjects. Controlling for age, period of death and smoking, workers in the ceramics industry with silicosis were found to have a higher lung cancer risk (odds ratio, 3.9; 95% CI, 1.8–8.3). The odds ratio for ceramic workers without silicosis was 1.4 (95% CI, 0.7–2.8). Stratification by smoking showed an odds ratio of 3.9 (95% CI, 1.9–7.9) for smokers of more than 20 cigarettes per day versus non-smokers.

A case–control study of lung cancer and silica exposure in the Dutch fine ceramic industry was reported by Meijers *et al.* (1990). All new cases verified histologically and diagnosed from 1972 to 1988 were selected from the local university hospital and, for each case, a control with any other diagnosis, matched for age and sex, was taken from the same register. Detailed information about past employment in the ceramics industry was obtained from company records for the 414 (381 men and 33 women) case–control pairs thus identified. Because no quantitative data on the past exposure of workers were available, the investigators constructed a cumulative exposure index, which consisted of the product, of the number of years in each job and the ordinal ranking of the estimated silica exposure in each job. Odds ratios calculated across the cumulative exposure index were (exposure index followed by odds ratio and 95% CI): < 1, 1 (referent category); 1–9, 2.11 (0.95–4.68); 10–39, 1.88 (0.74–4.79); 40–79, 2.64 (0.74–9.40); ≥ 80, 9.88 (1.09–89.3).

Table 21. Ceramics, pottery, refractory brick and diatomaceous earth industries: cohort, case-control and proportionate mortality studies of silica

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Cohort studies				
<i>Ceramics</i>				
Thomas (1982) United States	Ceramics industry workers (M) from union files; 3870 (2924 M, 946 F) deaths, 1955-77	Men All cancers Lung cancer Ceramic sanitary ware Stomach cancer	PMR 1.00 (533; [0.9-1.1]) 1.21 (178; [1.04-1.40]) 1.80 (62; [1.38-2.31]) 1.06 (39; [0.72-1.38])	
Thomas & Stewart (1987); Thomas (1990) United States	2055 ceramics industry workers (WM), employed 1939-66; mortality follow-up through 1980	All causes All cancers Digestive cancer Lung cancer Years with non-fibrous talc < 5 5-14 ≥ 15 Years with silica < 15 15-29 ≥ 30	SMR, 0.90 (578; [0.83-0.98]) 1.02 (124; [0.84-1.20]) 0.52 (19; [0.31-0.81]) 1.43 (52; [1.07-1.88]) 0.95 (2; [0.4-5.0]) 2.76 (11; [1.6-7.2]) 3.64 (8; [1.0-2.5])	Slight overlap with Thomas (1982)
Meijers <i>et al.</i> (1996) The Netherlands	1794 M ceramics industry workers between 1972 and 1982 with a minimum of two years of employment; mortality follow-up through 1991	All cancers Lung cancer By silica exposure Low Medium High	SMR, 0.94 (74; [0.74-1.18]) 0.88 (30; [0.59-1.26]) 0.82 (9; [0.37-1.55]) 0.75 (10; [0.36-1.38]) 1.15 (11; [0.57-2.05])	Exposure is qualitative

Table 21 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Pottery</i>				
Chen <i>et al.</i> (1992) China	13 719 pottery workers; mortality follow-up through 1989	Pottery workers All causes All cancers Lung cancer Stomach cancer	SMR 0.93 (1509; [0.88-0.98]) 0.67 ($p < 0.05$) 0.58 ($p < 0.05$) 0.66 ($p < 0.05$)	
McLaughlin <i>et al.</i> (1992) China	62 cases and 238 matched controls from pottery workers	Cumulative respirable silica, ($\mu\text{g}/\text{m}^3$) \times years None Low (0.1-8.69) Medium (8.70-26.2) High (≥ 26.3)	OR 1.0 (11) 1.8 (17; [1.04-2.87]) 1.5 (27; [0.99-2.18]) 2.1 (7; [0.80-4.12])	Odds ratios adjusted for age and cigarette smoking trend, $p > 0.05$
Winter <i>et al.</i> (1990) United Kingdom	3669 male workers, less than 60 years old, in the pottery industry; mortality follow-up, 1970-85	All causes Against national rates Against local rates Lung cancer Against national rates Against local rates By cumulative exposure to respirable quartz (adjusted for smoking) (mg/m^3) 0-0.14 ($(\text{mg}/\text{m}^3) \times \text{years}$) 0.15-0.49 ($(\text{mg}/\text{m}^3) \times \text{years}$) 0.50-1.49 ($(\text{mg}/\text{m}^3) \times \text{years}$) ≥ 1.50 ($(\text{mg}/\text{m}^3) \times \text{years}$) Stomach cancer Against national rates Against local rates	SMR 1.07 (390; [1.0-1.2]) 0.99 (390; [0.89-1.09]) 1.40 (60; 1.07-1.80) 1.32 (60; 1.00-1.69) 1.08 (5; [0.35-2.54]) 0.99 (8; [0.43-1.95]) 1.62 (25; 1.05-2.39) 1.51 (21; [0.93-2.31]) 1.60 (15; [0.89-2.63]) 1.26 (15; [0.70-2.08])	Majority of samples $< 0.1 \text{ mg}/\text{m}^3$ 1970-71 respirable quartz Adjusted for smoking but not other hazardous dust

Table 21 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Pottery (contd)</i>				
McDonald <i>et al.</i> (1995) United Kingdom	1016 pottery workers born in 1916-45 and dead by June 1992	Lung cancer	PMR, 1.04 (112; [0.86-1.25])	Compared with local rates
Cherry <i>et al.</i> (1995) United Kingdom	5115 pottery workers, excluding exposure to asbestos, foundry and other dusts, mortality follow-up, 1985-92	Lung cancer	SMR, 1.28 (68; [0.99-1.62])	Compared with local rates
Burgess <i>et al.</i> (1997); Cherry <i>et al.</i> (1997); McDonald <i>et al.</i> (1997) United Kingdom	Case-control study within Cherry <i>et al.</i> (1995), taking into account duration and intensity of exposure, smoking and radiological changes	Lung cancer Average exposure ≥ 200 µg/m ³ ≥ 400 µg/m ³	OR unrelated to cumulative exposure 1.88 (1.06-3.34) 2.16 (1.11-4.18)	Risk at ≥ 400 µg/m ³ confined to firing and post-firing operations. Unadjusted 90% CI
<i>Refractory brick</i>				
Merlo <i>et al.</i> (1991) Italy	1022 refractory brick workers (M) employed 1954-77; mortality follow-up through 1986	All causes All cancers Lung cancer First employed ≤ 1957 Years since first exposure (≤ 19 years of employment) ≤ 19 > 19 Stomach and oesophageal cancers	SMR, 1.10 (243; 0.97-1.25) 1.26 (79; 0.99-1.56) 1.51 (28; 1.00-2.18) 1.77 (17; 1.03-2.84) 1.05 (7; 0.42-2.16) 1.75 (8; 0.75-3.46) 1.18 (12; 0.61-2.06)	Cohort includes the men in Puntoni <i>et al.</i> (1985, 1988). Smoking habits comparable with national population

Table 21 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Refractory brick</i>				
(contd)				
Puntoni <i>et al.</i> (1988) Italy	136 male silicotics, 95 non silicotics employed on 1 January 1960 from a refractory brick plant; mortality follow-up through 1979)	All causes All cancers Lung cancer Silicotics Non-silicotics	SMR, 1.22 (73; 0.95-1.53) 1.21 (23; 0.76-1.81) 1.83 (11; 0.91-3.27) 1.67 (6; 0.61-3.64) 2.08 (5; 0.67-4.84)	
Dong <i>et al.</i> (1995) China	6266 silicotic and non-silicotic refractory brick workers (M) and 11 470 non-silicotic steel workers (M) as controls; mortality follow-up through 1985	All causes Silicotics Non-silicotics All cancers Silicotics Non-silicotics Lung cancer Silicotics Non-silicotics Smokers Silicotics Non-silicotics Nonsmokers Silicotics Non-silicotics	SRR 2.10 (481; [1.92-2.30]) 1.04 (390; [0.94-1.15]) 1.05 (73; [0.8-1.3]) 1.23 (148; [1.0-1.5]) 2.10 (35; [1.46-2.92]) 1.11 (30; [0.75-1.58]) 2.34 (21; [1.45-3.58]) 1.20 (21; [0.74-1.83]) 2.13 (12; [1.10-3.72]) 0.85 (7; [0.34-1.75])	

Table 21 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Diatomaceous earth workers</i>				
Checkoway <i>et al.</i> (1993) United States	2570 workers (WM) at two diatomaceous earth plants, California; mortality follow-up 1942-87	All causes All cancers Lung cancer	SMR, 1.12 (628; 1.03-1.21) 1.09 (132; 0.91-1.29) 1.43 (59; 1.09-1.84)	Significant (p , 0.02-0.05) trends against duration of employment and cumulative exposure to crystalline silica
		By cumulative exposure (15 years latency)	1.0 (23)	Adjusted for age, calendar year, duration of follow-up and ethnicity
		< 50 (intensity \times years)	1.19 (8; 0.52-2.73)	
		50-99	1.37 (9; 0.61-3.06)	
		100-199	2.74 (19; 1.38-5.46)	
		≥ 200		
Checkoway <i>et al.</i> (1996) United States	2266 workers in one diatomaceous earth plant in California (from Checkoway <i>et al.</i> , 1993); mortality follow-up 1942-87	Lung cancer By cumulative exposure	SMR, 1.41 (52; 1.05-1.85)	Adjusted for asbestos, age, calendar year, duration of follow-up and ethnicity
		< 50 (intensity \times years)	1.0	
		50-99	1.37 (9; 0.61-3.08)	
		100-199	1.80 (11; 0.82-3.92)	
		≥ 200	1.79 (10; 0.77-4.18)	
<i>Case-control studies</i>				
Forastiere <i>et al.</i> (1986) Italy	72 deceased cases, 319 deceased controls (M) from town records	Ceramics industry, lung cancer Silicotics Non-silicotics	OR 3.9 (15; 1.8-8.3) 1.4 (18; 0.7-2.8)	Adjusted for smoking

Table 21 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Case-control studies (contd)				
Meijers <i>et al.</i> (1990) The Netherlands	381 lung cancer case-control pairs (M) from the same hospital matching by gender, year of birth and year of diagnosis	Lung cancer Work with ceramics Estimated cumulative dust exposure (artificial index)	OR, 1.11 (79; 0.77-1.61)	Exposure is a composite of the product of rank and time.
		< 1	OR, 1.0 (17)	
		1-9	2.11 (32; 0.95-4.68)	
		10-39	1.88 (16; 0.74-4.79)	
		40-79	2.64 (8; 0.74-9.40)	
		≥ 80	9.88 (6; 1.09-89.3)	

Abbreviations: M, male; F, female; PMR, proportionate mortality ratio; WM, white male; SMR, standardized mortality ratio; OR, odds ratio; SRR, standardized rate ratio

2.4 Foundry workers

Exposures in foundries are complex: in addition to silica, foundry workers are exposed to polycyclic aromatic compounds, aromatic amines, metals and other known or suspected carcinogens (IARC, 1984). In most available epidemiological studies of foundry workers, exposure to silica was not analysed separately. Only studies specifically associating silica dust and cancer risk in foundry workers were reviewed by the Working Group.

A summary of the data is provided in **Table 22**.

Cohort studies

Sherson *et al.* (1991) studied 6144 male Danish foundry workers who were invited to participate in silicosis surveillance program during 1967–69 and 1972–74. Follow-up was through 1985. The survey covered all Danish iron, steel and metal foundries. Vital status was established via the Central Population Register and subjects were linked with the national cancer registry (introduced in 1943); 647 tumours were diagnosed. Expected rates were based on age-, sex- and calendar year-specific Danish population rates. A significantly increased SIR was observed for all cancers (647 observed; SIR, 1.09; 95% CI, 1.01–1.18) and for lung cancer (166 observed; SIR, 1.30; 95% CI, 1.12–1.51). A systematic trend in SIRs with duration of foundry work was observed for lung cancer; those with duration of 30 years or more had an increased SIR for lung cancer of 1.85 (48 deaths; 95% CI, 1.39–2.45) and for bladder cancer after 20 years (SIR, 1.72; 1.05–2.66). There were 144 silicotics; the SIR for lung cancer in silicotics was 1.71 (11 cases; 95% CI, 0.85–3.06) as opposed to 1.3 (150 cases; 95% CI, 1.07–1.47) in non-silicotics.

Andjelkovich *et al.* (1990, 1992, 1994) conducted a mortality study among 5337 white men, 2810 non-white men and 627 women who had been employed in a grey iron foundry in Michigan, United States, for at least six months from 1950 to 1979. Mortality was followed from 1950 through 1984. Vital status was determined in 97.6% of the cohort and death certificates were obtained for 97.9% of known deaths. Age-, sex-, race- and calendar year-specific mortality rates for the United States and local counties were used to calculate SMRs. Air pollutants at this foundry included crystalline silica, phenol, formaldehyde, acrolein, aldehydes, furfuryl alcohol, isocyanates, amines and polycyclic aromatic hydrocarbons. For white men, SMRs were 0.95 for all causes of death (836 observed; 95% CI, 0.89–1.02), 0.98 for all cancers (177 observed; 95% CI, 0.84–1.14) and 1.23 for lung cancer (72 observed; 95% CI, 0.96–1.54). For non-white males, SMRs were 1.01 for all causes of death (859 observed; 95% CI, 0.94–1.08), 1.16 for all cancers (184 observed; 95% CI, 0.99–1.34) and 1.32 for lung cancer (67 observed; 95% CI, 1.02–1.67). Odds ratios for lung cancer and increasing exposure level to silica dust estimated in a nested case-control study with follow-up until 1989 estimated by quantities of silica exposure index were 1.0, 1.27 (95% CI, 0.74–2.18), 1.14 (95% CI, 0.65–2.01) and 0.90 (95% CI, 0.50–1.64).

Xu *et al.* (1996a) identified all deaths during 1980–89 from workers employed in the iron-steel industry in Anshan, China. A nested case-control study was conducted on

Table 22. Foundry workers: cohort and case-control studies of silica

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Cohort study</i>				
Sherson <i>et al.</i> (1991) Denmark	6144 foundry workers (M); cancer incidence follow-up through 1985	All cancers Lung cancer By duration of employment < 10 years 10-19 years 20-29 years ≥ 30 years Silicotics Non-silicotics Metal foundries Stomach cancer	SIR, 1.09 (647; 1.01-1.18) 1.30 (166; 1.12-1.51) 0.99 (41; 0.73-1.34) 1.19 (34; 0.85-1.67) 1.28 (38; 0.93-1.76) 1.85 (48; 1.39-2.45) 1.71 (11; 0.85-3.06) 1.25 (150; 1.07-1.47) 2.13 (15; 1.19-3.52) 1.15 (34; 0.82-1.61)	
Andjelkovich <i>et al.</i> (1990) United States	8774 workers employed between 1950 and 1979 (5337 WM, 2810 NWM, 627 F) in grey iron foundry; mortality follow- up through 1984	All causes White males Non-white males All cancers White males Non-white males Lung cancer White males Non-white males Stomach cancer White males Non-white males	SMR 0.95 (836; 0.89-1.02) 1.01 (859; 0.94-1.08) 0.98 (177; 0.84-1.14) 1.16 (184; 0.99-1.34) 1.23 (72; 0.96-1.54) 1.32 (67; 1.02-1.67) 1.67 (14; 0.91-2.81) 1.11 (13; 0.59-1.90)	

Table 22 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
<i>Case-control studies</i>				
Andjelkovich <i>et al.</i> (1994)	Case-control studies follow-up until 1989 220 lung cancer cases, 2200 controls (51% W, 49% NW)	Lung cancer Silica quartile Quartile 1 versus 1 Quartile 2 versus 1 Quartile 3 versus 1 Quartile 4 versus 1	OR 1.0 1.27 (0.74-2.18) 1.14 (0.65-2.01) 0.90 (0.50-1.64)	
Xu <i>et al.</i> (1996a) China	903 cases; 959 controls, iron-steel industry with 10 years of employment minimum	Lung cancer Long-term exposed By cumulative silica dust (mg/m ³) × years < 3.7 3.7-10.39 10.4-27.71 ≥ 27.72 Stomach cancer	OR 1.4 (418; 1.1-1.8) 1.7 (82; 1.2-2.4) 1.5 (74; 1.0-2.1) 1.5 (92; 1.0-2.1) 1.8 (108; 1.2-2.5) 1.4 (200; 1.0-1.9)	Trend seen with silica dust exposure for lung cancer ($p = 0.007$), but not stomach cancer ($p = 0.427$)

Abbreviations: M, male; SIR, standardized incidence ratio; WM, white male; NW, non-white; NWM, non-white male; F, female; SMR, standardized mortality ratio; OR, odds ratio

lung cancer cases diagnosed during 1987–93 and stomach cancer cases diagnosed during 1989–93 (total, 903 cases (610 incident cases of lung cancer, 293 incident cases of stomach cancer) and 959 controls). Life-time occupational history and smoking data were obtained by questionnaire and supplemented from company files. Cumulative dust and cumulative silica dust as well as benzo[*a*]pyrene were estimated from occupational hygiene data. Risk of lung cancer was increased among long-term exposed workers (418 cases; OR, 1.4; 95% CI, 1.1–1.8). There was a trend in OR for lung cancer with cumulative silica dust exposure: 1.0, 1.7 (95% CI, 1.2–2.4), 1.5 (95% CI, 1.0–2.1), 1.5 (95% CI, 1.0–2.1), 1.8 (95% CI, 1.2–2.5); $p = 0.007$. Cumulative exposure to polycyclic aromatic hydrocarbons showed a similar trend with lung cancer risk. Risk of stomach cancer was also increased in long-term workers (200 cases; OR, 1.4; 95% CI, 1.0–1.9). [The Working Group noted that it was not clear whether the gradients for either lung cancer or stomach cancer with silica were adjusted for potential confounding by exposures to polycyclic aromatic hydrocarbons.]

2.5 Silicotics (see Table 23)

Studies that identified cases of silicosis using registries of diagnosed or compensated silicotics are considered in this section.

Cancer studies on silicotics may suffer from biases peculiar to the circumstance that this compensable disease is often employed as a surrogate for silica exposure. Apart from this consideration and those of concomitant exposures to and other carcinogens, there are further potential sources of bias. There is and has been variation in the diagnosis and subsequent compensability of silicosis between countries and time periods. For example, mixed-dust pneumoconiosis are classified as silicosis in some systems. In addition, social selection into claiming for compensation may confound silicosis–lung cancer associations. It has been suspected that voluntary examinations may induce detection bias — for example, with ill-health from smoking-related diseases, including incipient lung cancer, would be over-represented. In addition, hospital-based populations may favour the admission of subjects with both silicosis and lung cancer over subjects with silicosis but not lung cancer. Competing causes of death, influenced by exposure to silica dust, such as silicosis itself, or silicotuberculosis, will bias risk estimates for lung cancer if included in the reference deaths in PMR studies or in the controls in case–control studies. The existence and extent of these biases has seldom been evaluated in studies of silicosis and lung cancer. However, correction for them has been attempted, particularly in more recent studies.

Cohort studies (see also Table 23)

Westerholm (1980) reported on the mortality from 1949 through to 1969 of 3610 silicotics diagnosed in 1931–69 and identified from the Swedish Pneumoconiosis Register. For those whose silicosis arose from employment in mining, quarrying and tunnelling and was diagnosed between 1931 and 1948, the SMR for lung cancer was 5.90 [95% CI, 2.8–10.8]; for those whose silicosis was diagnosed from 1949 to 1969, the SMR was 3.80 [95% CI, 2.3–5.8]. Among workers in the iron and steel industry whose

silicosis occurred between 1949 and 1969, the SMR for lung cancer was 220 [95% CI, 1.0–4.0].

Rubino *et al.* (1985) reported on the proportionate mortality of 746 compensated male silicotics who died in 1970–83 in the Piedmont region of Italy. They were identified at the office of National Institute for Compensation of Occupational Diseases in Turin. The PMR for all cancers was 0.8 (158 deaths [95% CI, 0.7–0.9]); that for lung cancer was 1.36 (81 deaths; 95% CI, 1.11–1.62). There were 176 deaths from silicosis and 31 from silicotuberculosis. The PMR for lung cancer was higher in foundry workers (1.59) than in miners (1.06). In foundry workers, the lung cancer PMR rose to 1.73 after 11–20 years of exposure. [The Working Group noted potential biases in the PMR approach.]

A proportionate mortality study of 2399 certified and compensated silicotics, identified at the National Accident Insurance Fund and other sources in Switzerland since 1932 and who died during 1960–78, was reported by Schüler and Rüttner (1986). The subjects represented workers the following occupations: mining (underground); quarrying and stone-cutting; foundries; the ceramics industry; and other industries. Sixty subjects with no silicosis at autopsy and one case with mesothelioma were excluded. Mortality odds ratios were calculated using period-specific distributions of causes of death for the Swiss population, comparing lung cancer with non-pulmonary cancers. A total of 180 lung cancers were observed as causes of death, 157 as the underlying cause; the mortality odds ratio for lung cancer was 2.23 [95% CI, 1.9–2.6]. The mortality odds ratio for lung cancer was particularly elevated in foundry workers with > 30 work-years (3.94; $p < 0.001$).

A total of 284 male silicotics from mining, quarrying, and tunnelling, 428 male silicotics from steel and iron foundries and 334 and 476 male non-silicotics matched to the silicotics by age and calendar year at first exposure to silica dust were identified from the Swedish National Pneumoconiosis Register and the Swedish Silica Register (Westerholm *et al.*, 1986). All subjects were followed up for mortality and cancer incidence during 1961–80. SMRs and SIRs were calculated using general population rates as reference. This study was designed to estimate the cancer risk connected with silicosis, adjusted for silica exposure. Overall mortality in silicotics and non-silicotics did not differ significantly [numbers not given]. From the analysis, it appears that silicotics from mining, quarrying, and tunnelling had an excess lung cancer mortality (7 deaths; SMR, 5.38 [95% CI, 2.2–11.1]) and incidence (9 cases; SIR, 5.29 [95% CI, 2.4–10.0]) relative to the total population. Silicotic foundry workers had a somewhat weaker excess in lung cancer risk, which was more pronounced for mortality (10 deaths; SMR, 3.85 [95% CI, 1.8–7.1]) than for incidence (6 cases; SIR, 1.82 [95% CI, 0.7–4.0]). In exposed non-silicotics, the SMRs could not be recovered. [The Working Group noted the insufficient documentation of the results.]

Mortality in miners receiving compensation for silicosis since 1940 in Ontario, Canada, was followed from 1940 until 1975 (Finkelstein *et al.*, 1982), until 1978 (Finkelstein *et al.*, 1986) and until 1985 (Finkelstein *et al.*, 1987). The cohort consisted of 1190 miners and 289 surface industry workers with silicosis. Mean age at compensation for silicosis was 57 years and mean age at death was 68 years. The 1985 update

found an SMR for all causes of 1.80 (905 deaths) in silicotic miners and 2.25 (206 deaths) in surface workers with silicosis. Deaths from all malignancies were pronounced in silicotic miners (151 deaths; SMR, 1.51 [95% CI, 1.3–1.8]) and surface workers (31 deaths; SMR, 1.59 [95% CI, 1.1–2.3]), due to excesses of lung cancer (in miners: 62 deaths; SMR, 2.30 [95% CI, 1.8–3.0] and in surface workers: 16 deaths; SMR, 3.02 [95% CI, 1.7–4.9]). Among surface workers, granite and quarry workers had the highest rates from all causes (SMR, 2.28; 70 deaths; [95% CI, 1.8–2.9]), all malignancies (1.64; 10 deaths; [95% CI, 0.8–2.9]) and lung cancer (3.60; 5 deaths; [95% CI, 1.2–8.4]).

Zambon *et al.* (1985, 1986, 1987) reported on the mortality of workers compensated for silicosis in the Veneto region, Italy. The most recent update (Zambon *et al.*, 1987) used data on 1313 male silicotics, 96% of the silicotics diagnosed in 1959–63, and identified at the National Institute for Compensation of Occupational Diseases. Most had been employed in mining, tunnelling and quarrying. They were followed up for mortality during 1959–84. SMRs were calculated using both national and regional age- and period-adjusted male rates as references. A total of 878 deaths occurred against a national expectation of 409 (SMR, 2.15; 95% CI, 2.01–2.30). The SMR for all cancers was 1.36 (146 deaths; 95% CI, 1.15–1.60) and that for lung cancer was 2.39 (70 deaths; 95% CI, 1.86–3.02). No other cancer excesses were reported. Using either national or regional reference rates, an increasing trend in the SMR for lung cancer was observed with time since exposure. The highest category of duration of exposure (≥ 20 years) was associated with the highest SMR (3.15 against national rates; 2.17 against regional rates). Silicotics from all major industries (mining tunnelling, quarrying) exhibited elevated lung cancer rates, the highest SMR (3.14) being observed for quarrying. Non-cancer excesses were reported for infectious diseases (SMR, 19.0) due to silicotuberculosis; and diseases of the respiratory system (SMR, 8.07), mostly due to silicosis.

A total of 2212 deceased male Austrian cases of silicosis, diagnosed at medical check-ups in 1950–60 for workers with long-term occupational dust exposure, were identified during 1955–79 (Neuberger *et al.*, 1986, 1988). A proportionate mortality study reported crude mortality odds ratios for lung cancer for the 2212 silicotics versus 1 038 844 population non-silicotics during the same period. The odds ratios ranged from 1.3 to 1.4 during different periods in 1955–79 and was 1.41 overall (182 deaths; 95% CI, 1.21–1.64).

A total of 595 deaths (98% of all deaths) during 1969–84 in 952 male silicotics in the Latium region, Italy, compensated in 1946–84, were identified at the National Institute for Compensation of Occupational Diseases (Forastiere *et al.*, 1989). Mortality odds ratios were calculated using 79 245 deaths from the Latium population, excluding causes of death that could be positively related to silicosis. The mortality odds ratio for all cancers was 1.0 (151 deaths; 95% CI, 0.83–1.1). Excesses were reported for lung cancer (64 deaths; mortality odds ratio, 1.5; 95% CI, 1.1–1.9). Elevated mortality odds ratios for lung cancer were observed in silicotics from mining (mortality odds ratio, 2.5; 10 cases; 95% CI, 1.2–4.6) and pottery (mortality odds ratio, 2.1; 17 cases; 95% CI, 1.2–3.3) but not for those from quarrying, stone-cutting, construction, tunnelling, metal works or bricklaying.

Infante-Rivard *et al.* (1989) reported on the mortality through 1986 of 1072 men who had received compensation for silicosis in Québec, Canada, between 1938 and 1985. The subjects were identified at the registry of the Québec Occupational Health and Safety Commission. Québec male rates were used in the calculation of SMRs. Mean duration between starting work and receiving compensation was 30 years and mean follow-up was nine years. The SMR for all causes was a highly elevated 2.16, based on 565 deaths. Non-cancer excesses were reported for infectious diseases (SMR, 29.7), tuberculosis (SMR, 64.5) and non-malignant respiratory diseases (SMR, 9.75). SMRs were 1.92 (135 deaths; 95% CI, 1.76–2.10) for all neoplasms, and 3.47 (83 deaths; 95% CI, 3.11–3.90) for lung cancer. The SMRs for lung cancer for industries varied between 2.04 (granite) and 4.99 (potteries) and 6.94 (miscellaneous). No clear gradients were seen for date of hire, date of entry or time since entry. The SMR for 0–1 year since entry was elevated (12 deaths; SMR, 7.14; 95% CI, 3.69–12.48). The excess did not reach that level after one year since entry but stayed elevated at a somewhat lower level. Five years after compensation, the SMR was still 3.23 (50; 2.40–4.19). There were more ever-smokers in the cohort than in Québec men in general, but the difference was estimated to explain just a fraction of the observed lung cancer excess. [The Working Group noted a high lung cancer risk shortly after compensation. The excess, however, persisted subsequently.]

Chiyotani (1984) and Chitoyani *et al.* (1990) reported on male silicotics hospitalized in 11 Rosai hospitals in Japan. 3335 pneumoconiotics, including 1941 silicotics, all identified at the Rosai hospital records, were followed up for mortality during 1979–83, excluding the first year of follow-up for each patient to minimize detection bias. SMRs were calculated using age-specific mortality rates in Japan in 1982. In silicotics, the SMR for all causes was 2.93 (352 deaths; 95% CI, 2.75–3.11) and that for all cancers was 2.31 (86 deaths; 95% CI, 1.98–2.64). Significant cancer excesses were reported for two sites: lung (44 deaths; SMR, 6.03; 95% CI, 5.29–6.77) and pancreas (6 deaths; SMR, 3.00; 95% CI, 1.59–4.41). A case-control study of lung cancer within this cohort of pneumoconiosis patients in Japan (Chiyotani *et al.*, 1990) identified 72 pairs of lung cancers and controls, matched on survivorship until death of the case, age and smoking (non-smoker versus ex- or current smoker). Silicosis was associated with an odds ratio of 5.67 and, among the epidermoid lung cancer subgroup, 12.0. [The Working Group noted that the statistical analysis of the case-control study was not specified, and the confidence intervals could not be recovered.]

Virtually all male silicotics alive in Hong Kong as of 30 June 1980 were identified at the registry of a compensation scheme (Ng *et al.*, 1990). Excluding 68 workers with occupational exposures to asbestos or polycyclic aromatic hydrocarbons, 1419 silicotics were followed for mortality during 1980–86. They represented miners, tunnel workers, quarry workers and workers involved in excavating and crushing in the granite industry. SMRs were calculated using sex- and age-specific annual rates as the reference. The SMR for all causes was 3.02 (356 deaths; 95% CI, 2.71–3.35). Excess non-cancer mortality rates were observed for pulmonary tuberculosis (SMR, 3.83), pulmonary heart disease (2.58), pneumonia (2.95), chronic bronchitis, emphysema, and asthma (7.45), chronic airway obstruction not elsewhere classified (7.70) and pneumoconiosis (6.10).

The SMR for all malignancies was 1.27 (53 deaths; 95% CI, 0.94–1.67) and that for lung cancer was 2.03 (28 deaths; 95% CI, 1.35–2.93). The SMR for lung cancer was 3.41 (5 deaths; 95% CI, 1.10–7.97) in underground workers and 1.87 (23 deaths; 95% CI, 1.18–2.81) in surface workers. Risk increased with increasing latency, years of exposure, severity of silicosis and presence of tuberculosis. The numbers of non-tuberculous surface workers by opacity category were too small for trend analysis.

A cohort of 280 male silicotics, who had been employed in the ceramics industry and were alive in 1951, were identified at the Swedish Pneumoconiosis [Silicosis] Registry (Tornling *et al.*, 1990) and were followed up for morbidity during 1958–83 and for mortality during 1951–85. The members of the cohort were generally first employed in the ceramics industry before the age of 25 years, and silicosis was seldom detected until 30 years later. SMRs were calculated using national rates as the reference. The SMR for all causes was 1.38 (218 deaths; 95% CI, 1.20–1.57). Excess non-cancer mortality was observed for respiratory tuberculosis (SMR, 19.3; 95% CI, 11.4–30.5) and non-malignant respiratory diseases (SMR, 7.46; 95% CI, 5.77–9.47). The SMR for all cancers was 0.94 (41 deaths; 95% CI, 0.67–1.26). The only significant cancer excess was for lung cancer more than 10 years after detection of silicosis (9 deaths; SMR, 2.36; 95% CI, 1.07–4.48).

A total of 714 male silicotics, diagnosed since 1940, were identified at the State of North Carolina (United States) Pneumoconiosis Surveillance Program for Dusty Trade Workers; this programme involved periodic voluntary examinations. Mortality was followed up through 1983 (Amandus *et al.*, 1991, 1995). 'Dusty trade workers' represented workers from mining, foundries, quarrying, stone crushing, manufacturing of asbestos and silica products and construction. The completeness of follow-up was 94%. SMRs were calculated using United States age-, period- and race-specific rates as the reference. Non-silicotic metal workers and ex-gold miners with coal workers' pneumoconiosis represented additional reference cohorts, providing for adjustment for cigarette smoking and, with coal workers' pneumoconiosis referents, for competing causes of death. All-cause mortality in silicotics was elevated for both whites (486 deaths; SMR, 2.1 [95% CI, 2.0–2.3]) and non-whites (64 deaths; SMR, 2.4 [95% CI, 1.9–3.1]). Non-cancer mortality was in excess in whites for tuberculosis, pneumonia, bronchitis, emphysema, asthma, pneumoconiosis and infectious kidney diseases and, in non-whites, for tuberculosis, ischaemic heart disease and pneumoconiosis. The SMRs for all cancers were 1.5 (67 deaths [95% CI, 1.2–1.9]) in whites and 1.2 (6 deaths [95% CI, 0.4–2.5]) in non-whites. The SMR for lung cancer was 2.6 (95% CI, 1.8–3.6) in whites, based on 33 deaths. One lung cancer death occurred in non-whites. In white patients with no other known occupational carcinogens (no employment in asbestos manufacturing, insulation, olivine mining, talc mining, or foundry work), the SMR for lung cancer was 2.3 (26 deaths; 95% CI, 1.5–3.4). To minimize detection bias from persons whose silicosis was detected after leaving employment on the basis of self-initiated examinations, lung cancer mortality was examined in a subgroup diagnosed with silicosis while still employed in the North Carolina dusty trades. The SMR was 2.5 (95% CI, 1.7–3.7). Among them, lung cancer risk remained increased also in those who had no exposure to other known occupational carcinogens (SMR, 2.4; 95% CI, 1.5–3.6). Age- and smoking-adjusted relative risk for lung cancer in white silicotics with no other known exposures to

occupational carcinogens, using metal miners as the reference, was 3.9 (95% CI, 2.4–6.4).

Two reports (Carta *et al.*, 1988; Cocco *et al.*, 1990) on lung cancer risk in silicotics in Sardinia, Italy, found an association between silicosis and lung cancer mortality, which remained after adjustment for smoking (Cocco *et al.*, 1990). The most recent update (Carta *et al.*, 1991) was based on 724 male silicotics, diagnosed in 1964–70 and identified at the Institute of Occupational Medicine in Cagliari, Sardinia, representing all cases among those claiming compensation for silicosis in Sardinia during the enrolment period. All radiograms were independently re-evaluated. The subjects had been employed in lead and zinc mines, coal mines and granite quarries. Mean age at admission was 56 years and mean duration of silica dust exposure was 24 years. A cumulative lifetime occupational silica exposure index was calculated for each subject. Interviews at admission provided smoking data. Mortality was followed up through 1987. SMRs were calculated using age- and period-specific regional death rates as the reference. The SMR for all causes was 1.40 (438 deaths; 95% CI, 1.28–1.54). Excess non-cancer mortality rates were reported for tuberculosis (SMR, 11.9) and diseases of the respiratory system (SMR, 6.90). The SMR for all cancers was 0.92 (63 deaths; 95% CI, 0.72–1.17) and that for lung cancer was 1.29 (22 deaths; 95% CI, 0.85–1.96). The only elevated cancer excess was reported for buccal and pharyngeal cancers with four deaths (SMR, 4.0; 95% CI, 1.61–9.89). Lung cancer risk did increase with latency but did not reach significance. It was not associated with severity of radiological category, type of employment or degree of probability and intensity of exposure to silica dust.

A National Silicosis Register identified all 184 confirmed cases of Chinese male silicotics during 1970–84 in Singapore. The confirmation was based on occupational exposure, clinical findings, and chest radiography findings. The data necessary for a 10-year mortality follow-up (Chia *et al.*, 1991) were available for 159 (86%) of the cohort. Mean age at diagnosis of silicosis was 63 years and mean duration of exposure to silica dust was 24 years. All subjects had been employed in granite excavation and crushing on the surface. There were no significant exposures to asbestos or polycyclic aromatic hydrocarbons in the job histories. Nine lung cancers were identified at the National Cancer Registry during an unspecified follow-up period. Age- and period-specific lung cancer rates in Chinese males in Singapore were used to calculate the SIR. The SIR for lung cancer was 2.01 (95% CI, 0.92–3.81). The SIR in smokers was 2.16 (8 deaths; 95% CI, 0.93–4.25). Lung cancer risk appeared to increase with increasing duration of exposure (for ≥ 40 years; SIR, 2.54; 5 cases; 95% CI, 0.64–4.60) and opacity profusion (radiographic classification) (for category 3, SIR, 5.11; 2 cases; 0.62–18.5) although the trends were not significant. The trends were not significant (for duration of exposure, p for trend = 0.28; for opacity profusion, 0.097).

Diagnoses of the North Carolina cohort of silicotics (Amandus *et al.*, 1991) were re-evaluated to correct for misclassification (Amandus *et al.*, 1992). Technically acceptable radiographs were available for 306 out of 760 white men and were independently reclassified for pneumoconiosis by three 'B' readers. The SMR for lung cancer was 2.5 (8 deaths; 95% CI, 1.1–4.9) for 143 subjects reclassified as simple silicosis, in contrast

with no excess (SMR, 1.0; 2 deaths; 95% CI, 0.1–3.5) for 96 subjects whose radiographs were reclassified as ILO category 0 (normal). There were no lung cancer deaths among 67 subjects whose radiographs were reclassified as progressive massive fibrosis. The SMRs for lung cancer for subjects who had not been employed in a job with exposures to other known carcinogens were 2.4 (7 deaths; 95% CI, 1.0–5.0) for those reclassified as having simple silicosis, and 1.2 (2 deaths; 95% CI, 0.2–4.4) for those reclassified as category 0. The corresponding SMRs were 3.4 (5 deaths; 95% CI, 1.1–7.9) for silicotic smokers and 1.3 (1 death; 95% CI, 0.03–7.1) for smokers reclassified as category 0.

Excess lung cancer incidence and mortality were reported in male silicotics in Finland who were identified by an extensive search of sources, including the national register for diagnosed (both compensated and not compensated) occupational diseases (Gudbergsson *et al.*, 1984; Kurppa *et al.*, 1986). The majority of cases represented workers from mining, the stone industry and steel and iron foundries. An update (Partanen *et al.*, 1994) reported on cancer incidence during 1953–91 in 811 of the 1127 silicotics, diagnosed in 1936–77. Reasons for exclusion were death or emigration before 1953 ($n = 220$), missing date of diagnosis of silicosis ($n = 65$) and incomplete personal identification ($n = 21$). The 811 silicotics had a median of 51 years of age at diagnosis and a median of 22 years of exposure to silica dust. Cancers were identified at the Finnish Cancer Registry. SIRs were calculated using national age- and period-specific rates. The SIR for all cancers was 1.67 (190 cases; 95% CI, 1.44–1.91). Lung cancer was in excess (101 cases; SIR, 2.89; 95% CI, 2.35–3.48), in contrast with other smoking-related cancers combined (cancers of the urinary bladder, mouth, pharynx, larynx, pancreas and kidney; 21 deaths; SIR, 1.08; 95% CI, 0.67–1.65). Lung cancer risk increased with increasing length of follow-up, while only one lung cancer occurred against 2.4 expected during the two first years of follow-up. Lung cancer excess was most pronounced for squamous-cell carcinomas (34 cases; SIR, 3.25; 95% CI, 2.25–4.54) and lowest for adenocarcinomas (5 cases; SIR, 1.96; 95% CI, 0.64–4.58). Lung cancer was in excess in all of the seven major industries represented by the patients, with SIRs ranging from 1.75 (95% CI, 1.09–2.64) in casting and founding to 10.4 (95% CI, 1.25–37.4) in construction. The SIR for granite quarrying, cutting, shaping and dressing it was 2.93 (13 cases; 95% CI, 1.56–5.01).

The Ontario (Canada) Silicosis Surveillance Database identified 328 uranium and non-uranium miners with silicosis (Finkelstein, 1995a), the subjects being probably included in the data of Finkelstein *et al.* (1982, 1986, 1987). They were matched on birth year to 970 miners with normal radiographs and followed up for cancer incidence during 1974–92 through the Ontario Cancer Registry. SIRs were calculated using Ontario population rates for cancer incidence. The SIR for all neoplasms was 1.35 (35 cases; 95% CI, 0.95–1.89) in silicotics and 0.90 (70 cases; 95% CI, 0.71–1.14) in non-silicotics. For lung cancer, SIRs were 2.55 (15 cases; 95% CI, 1.43–8.28) for silicotics and 0.90 (16 cases; 95% CI, 0.51–1.47) for non-silicotics. A nested case-control study in this cohort of Ontario (Canada) uranium and non-uranium miners involved 31 lung cancer cases matched on birth year with three controls each. The odds ratio for lung cancer associated for silicosis status, adjusted for radiation exposure, was 6.88 (95% CI, 1.89–25.00).

Goldsmith *et al.* (1995) reported on the mortality of 590 claimants for compensation for silicosis (99% men) from the California Workers' Compensation (United States) records during January 1945–December 1975. Claims with tuberculosis, emphysema, pneumonia or cancer were excluded from the analysis. The subjects had been employed by the construction, mining, quarrying, metallurgy, founding, utilities and transportation industries. Subjects were traced through motor vehicle records and queries to other States for those who had moved from California. Median birth year was 1906; median age at filing the claim was 57 years; median age at death was 68 years. United States age-, year- and race-specific mortality rates were used to calculate SMRs for the period 1946–91. The SMR for all causes was 1.30 (421 deaths; 95% CI, 1.18–1.43). Significant non-cancer SMRs were reported for tuberculosis (56.4), emphysema (3.41) and nonmalignant respiratory diseases including silicosis (6.81). The SMR for all cancer was 1.22 (81 deaths; 95% CI, 0.96–1.52). Excesses were observed for cancers of the large intestine (SMR, 2.08; 14 deaths; 95% CI, 1.14–3.50) and the lung (SMR, 1.90; 39 deaths; 95% CI, 1.35–2.60). There were no significant risks for smoking-related cancers (pancreas, urinary bladder and kidney; data not reported). Lung cancer was elevated in claimants from the construction industry (17 deaths; SMR, 4.04 [95% CI, 2.3–6.4]) and mining and quarrying (19 deaths; SMR, 1.65 [95% CI, 1.0–2.6]). Claimants from other industries had few or no deaths from lung cancer. Those dying from lung cancer did not show a monotonic trend with interval from claim to death. Confounding by smoking was estimated to have explained nearly 100% of the excess cancer risk but only up to 30% of the excess lung cancer rates. [The Working Group noted that the association of silica exposure with lung cancer may have been confounded by exposure of silicotics in this study to asbestos (construction industry), radon (miners) and other occupational respiratory carcinogens, none of which were incorporated into the analysis.]

Merlo *et al.* (1990) reported a 6.85-fold excess mortality from respiratory tract cancers in male silicotics in Genoa, Italy. In an update (Merlo *et al.*, 1995), a cohort of 450 silicotics for whom employment and exposure data were available were followed up for an average of 12 years through 1987. The cohort consisted of in-patients diagnosed as silicotics (based on X-ray and lung-function categories) at the Department of Occupational Health, San Martino Hospital, Genoa, between 1961 and 1980. The mean age at entry to follow-up was 55 years and the mean duration between first employment and silicosis was 12 years. SMRs were calculated using age- and calendar-year-specific Italian male rates as the reference. The SMR for all causes was 1.89 (290 deaths; 95% CI, 1.69–2.12). Excesses in non-cancer mortality were observed for respiratory tract diseases (122 observed; SMR, 8.89; 95% CI, 7.38–10.6), digestive tract diseases (23 deaths; SMR, 2.10; 95% CI, 1.33–3.16) and silicotuberculosis (34 deaths; SMR, 27.0; 95% CI, 18.8–38.0). The SMR for all cancers was 1.61 (56 deaths; 95% CI, 1.26–2.15), the excess being due to lung cancer (35 deaths; SMR, 3.50; 95% CI, 2.44–4.87). Lung cancer SMRs increased with the duration of occupational exposure up to 5.02 (14 deaths; 95% CI, 2.74–8.42) for 30 years or more of exposure. Lung cancer risk was particularly high for silicotics with 15–29 years of employment and a latent period of 15–29 years (5 deaths; SMR, 8.12; 95% CI, 2.64–18.9), and with 30 or more years of employment and 30 or more years of latency (14 deaths; SMR, 5.06; 95% CI, 2.77–8.49). SMRs for lung

cancer were higher for foundry and coke oven workers than for refractory, ceramic and excavation workers. Smoking was estimated by the authors to explain, at most, 50% of the lung cancer excess in silicotics.

Wang *et al.* (1996) conducted a mortality study of 4372 male silicotics alive before 1 January 1980 from 47 mines or metallurgical plants in China. The main industries represented were iron ore mining, ore sintering, refractory brick manufacturing, iron and steel smelting, and steel casting. During the follow-up (1980–1989), the SMR for all causes of death was 1.22 (974 deaths; 95% CI, 1.15–1.30). For all cancers, it was 1.18 (235 deaths; 1.04–1.35) and for lung cancer, 2.37 (104 deaths; 1.96–2.86). Lung cancer SMRs were almost uniformly elevated across industries: 2.47 in mines; 2.11 in refractory brick manufacture; 3.65 in ore sintering; 2.91 in smelting; and 1.57 in casting. Lung cancer SMRs according to categories of simple silicosis were 2.24 (38 deaths; [1.6–3.0]) for category I; 2.64 (34 deaths; [1.8–3.6]) for category II and 1.61 (4 deaths; [0.4–4.1]) for category III. There was no clear exposure–response gradient according to years of exposure to silica dust, the SMRs for < 10, 10–19 and \geq years of exposure being almost identical. The SMR for lung cancer was 2.57 (72 deaths; [95% CI, 2.0–3.3]) in smokers, but it was also elevated in non-smokers (32 deaths; SMR 2.09; [95% CI, 1.4–3.0]). Smoking status was obtained by questionnaire. There was no excess of stomach cancers (SMR, 0.88).

2.6 Community-based studies

The Working Group reviewed industry-based cohort and nested case–control studies of populations exposed to silica. Not included for consideration were community-based studies in which exposure to silica was inferred from self-reported occupation and jobs. The rationale for excluding the community-based studies was that the Working Group considered that they would not add to the information on silica and cancer risks available from specific industry-based studies.

2.7 Amorphous silica

2.7.1 Case reports and descriptive studies

A report by Das *et al.* (1976) of five cases of mesothelioma in a rural community of India among sugar cane workers not known to have been exposed to asbestos suggested a possible association with amorphous biogenic silica fibres (Newman, 1986).

2.7.2 Epidemiological studies

Three population-based case–control studies in the United States addressed associations with amorphous silica resulting from airborne biogenic amorphous silica fibre exposures in the sugar cane industry.

Rothschild and Mulvey (1982) reported an increased lung cancer risk associated with sugar cane farming (odds ratio, 2.3; 45 cases; 95% CI, 1.8–3.0) among 284 persons who had died of lung cancer from 1971–77 and 284 controls who were deaths from any cause other than lung cancer in Southern Louisiana. An association was only evident from

Table 23. Silicotics: Cohort, case-control and proportionate mortality studies of silica

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Westerholm (1980) Sweden	3610 silicotics (M, F) (national register) mortality follow-up 1931-69	Lung cancer Mining/quarrying/tunnelling Silicosis 1931-48 Silicosis 1949-69 Steel/iron Silicosis 1949-69 Non-lung cancers pooled	SMR 5.9 (10; [2.8-10.8]) 3.8 (20; [2.3-5.8]) 2.2 (10; 1.0-4.0) SMRs ranging 0.5-0.9 across period and industry combinations	
Rubino <i>et al.</i> (1985) Italy	746 deaths in silicotics (M) deceased 1970-83 from compensation register	All silicotics All cancers Lung cancer Laryngeal cancer Lung cancer, foundry workers by duration of exposure 1-10 years 11-20 years ≥ 20 years	PMR 0.80 (158; [0.7-0.9]) 1.36 (81; [1.11-1.62]) 0.76 (6; [0.3-1.7]) 1.21 (6; [0.4-2.6]) 1.73 (21; [1.17-2.29]) 1.59 (29; [1.13-2.05])	Negative bias from competing causes of death
Schüller & Rüttner (1986) Switzerland	2399 deaths in silicotics (M) who died between 1960 and 1978 from insurance fund and other sources	Lung cancer All silicotics Miners Deceased 1960-78 Foundry workers < 25 work-years > 30 work-years Others + ceramics Ceramics Stomach cancer	OR 2.23 (180; [1.9-2.6]) 2.29 ($p < 0.001$) 3.27 ($p < 0.001$) 3.55 ($p < 0.01$) 3.94 ($p < 0.001$) 2.46 ($p < 0.05$) 2.05 ($p = 0.25$) PMR, 0.56 (46)	

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Westerholm <i>et al.</i> (1986) Sweden	712 silicotics, 810 non-silicotics (M); mortality and cancer incidence follow-up 1961-80	Lung cancer Mining/quarrying/tunnelling Foundries	SMR, 5.38 (7; [2.2-11.1]) SIR, 5.29 (9; [2.4-10.0]) SMR, 3.85 (10; [1.8-7.1]) SIR, 1.82 (6; [0.7-4.0])	Sketchy data analysis. Possibly incomplete identification of incident lung cancers in foundry workers
Finkelstein <i>et al.</i> (1987) Canada	Silicotics (M): 1190 miners, 289 surface workers receiving workman's compensation since 1940; mortality follow-up through 1985	Miners with silicosis All cancers Lung cancer Stomach cancer Surface workers Lung cancer Silica brick workers Ceramics workers Granite/quarry workers Stomach cancer Silica brick workers Ceramics workers Granite/quarry workers	SMR 1.51 (151; [1.3-1.8]) 2.30 (62; [1.8-3.0]) 1.88 (19; [1.13-2.94]) 3.02 (16; [1.7-4.9]) 1.83 (2; [0.2-6.6]) 2.93 (6; [1.0-6.2]) 3.60 (5; [1.2-8.4]) 3.66 (7; [1.47-7.55]) 5.71 (2; [0.69-20.64]) 1.61 (1; [0.04-8.99]) 2.90 (2; [0.35-10.47])	

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Zambon <i>et al.</i> (1987) Italy	1313 silicotics (M) from compensation registry, diagnosed 1959-63; mortality follow-up through 1984	All causes All cancers Lung cancer Lung by duration of exposure < 10 years 10-19 years ≥ 20 years Lung ≥ 20 years since first exposure Mining Tunnelling Quarrying Mixed Other Digestive tract cancers Lung cancer	SMR, 2.15 (878; 2.01-2.30) 1.36 (146; 1.15-1.60) 2.39 (70; 1.86-3.02) 1.73 (27; [1.1-2.5]) 1.64 (25; [1.1-2.4]) 2.17 (17; [1.3-3.5]) 1.35 (13; 0.72-2.31) 1.87 (28; 1.24-2.71) 3.14 (6; 1.15-6.84) 1.43 (16; 0.82-2.33) 2.22 (6; 0.81-4.82) 0.66 (18; 0.39-1.04) OR, 1.41 (182; 1.21-1.64)	Expected values from national population Expected values from regional population
Neuberger <i>et al.</i> (1986; 1988) Austria	2212 deaths in silicotics (M), diagnosed 1950-60; deceased 1955-79			
Forastiere <i>et al.</i> (1989) Italy	595 deaths in silicotics (M) compensated 1946-84; deceased 1969-84	All cancers Lung cancer Mining Quarrying/stone-cutting Construction/tunnelling Metal Bricklaying Pottery Stomach cancer	OR, 1.0 (151; 0.83-1.1) 1.5 (64; 1.1-1.9) 2.5 (10; 1.2-4.6) 1.1 (6; 0.42-2.5) 1.4 (23; 0.86-2.0) 1.6 (3; 0.32-4.6) 0.89 (4; 0.24-2.3) 2.1 (17; 1.2-3.3) 0.85 (15; 0.48-1.4)	

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Infante-Rivard <i>et al.</i> (1989) Canada	1072 silicotics (M) compensated 1938-85; mortality follow-up through 1986	All causes	SMR, 2.16 (565; 2.08-2.26)	
		All cancers	1.92 (135; 1.76-2.10)	
		Lung cancer	3.47 (83; 3.11-3.90)	
		By industry		
		Mines	3.78 (29; 2.53-5.43)	
		Foundries	3.04 (33; 2.55-3.69)	
		Granite	2.04 (6; 0.75-4.44)	
		Pottery	4.99 (5; 1.62-11.66)	
		By duration of employment		
		≤ 30 years	4.61 (39; 3.93-5.50)	
> 30 years	3.62 (39; 3.08-4.32)			
Chiyotani <i>et al.</i> (1990) Japan	1941 silicotics (M) from hospital records; mortality follow-up 1979-83 (excluding first year of follow-up for each patient)	All causes	SMR, 2.93 (352; 2.75-3.11)	Possible detection bias for lung cancer because of hospital enrolment. Industry sources not clear
		All cancers	2.31 (86; 1.98-2.64)	
		Lung cancer	6.03 (44; 5.29-6.77)	
		Stomach cancer	1.23 (14; 0.64-1.82)	
		All causes	SMR, 3.02 (356; 2.71-3.35)	
		All cancers	1.27 (53; 1.94-1.67)	
Ng <i>et al.</i> (1990) Hong Kong	1419 silicotics (M) excluding those exposed to asbestos and PAHs; mortality follow-up 1980-86	Lung cancer	2.03 (28; 1.35-2.93)	
		Underground	3.41 (5; 1.10-7.97)	
		Surface	1.87 (23; 1.18-2.81)	
		By length of exposure		
		15-29 years	1.62 (10; 1.08-3.01)	
		≥ 30 years	3.06 (16; 1.7-5.01)	
		All causes	SMR, 1.38 (218; 1.20-1.57)	
		All cancers	0.94 (41; 0.67-1.26)	
		Lung cancer	1.88 (9; 0.85-3.56)	
		> 10 years after diagnosis of silicosis	2.36 (9; 1.07-4.48)	
Tomling <i>et al.</i> (1990) Sweden	280 silicotics (M) alive in 1951 from ceramic industry, identified at national registry; mortality follow-up 1951-85	All causes		
		Lung cancer		

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Amandus <i>et al.</i> (1991) United States	714 silicotics (M) from state surveillance programme for dusty trade workers, North Carolina, diagnosed since 1940; mortality follow-up through 1983	All causes	SMR	
		Whites	2.1 (486; [2.0-2.3])	
		Non-whites	2.4 (64; [1.9-3.1])	
		All cancers		
		Whites	1.5 (67; [1.2-1.9])	
		Non-whites	1.2 (6; [0.4-2.5])	
		Lung cancer		
		Whites	2.6 (33; 1.8-3.6)	
		Silica exposure only	2.3 (26; 1.5-3.4)	
		Silica and other exposures	4.5 (7; 1.8-9.2)	
		Time after silicosis		
		< 5 years	3.4 (8; 1.5-6.7)	
		5-9 years	2.2 (6; 0.8-4.9)	
10-19 years	2.3 (11; 1.2-4.1)			
≥ 20 years	2.7 (8; 1.1-5.1)			
Smoking-adjusted/metal miners	3.9 (2.4-6.4)			
Stomach cancer				
Whites	0.6 (2; NS)			
Carta <i>et al.</i> (1991) Italy	724 silicotics (M) (comprehensive series of Sardinian silicotics) diagnosed 1964-70; mortality follow-up through 1987	All causes	SMR, 1.40 (438; 1.28-1.54)	
		All cancers	0.92 (63; 0.72-1.17)	
		Lung cancer	1.29 (22; 0.85-1.96)	
		By latency		
		> 5 years	1.29 (19; 0.8-2.0)	
		> 10 years	1.49 (16; 0.9-2.4)	
		> 15 years	1.53 (9; 0.8-2.9)	
		By estimated cumulative silica exposure (gh/m ³)	OR	
		Low	1.0 (5)	
		Intermediate	1.95 (10; 0.4-1.01)	
High	1.86 (7; 0.4-8.6)			

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Carta <i>et al.</i> (1991) Italy (contd)		By radiological category (adjusted for cigarette consumption)		ILO scale of pneumoconiosis
		1/0-1/2	1.0 (6)	
		2/1-2/3	0.94 (8; 0.8-1.1)	
		3/2 or more	0.65 (8; 0.3-1.4)	
		By FEV ₁ /VC (% predicted)		
		≥ 90	1.0 (5)	
		89-80	2.86 (7; 1.5-5.4)	
		< 80	7.23 (10; 2.2-24.1)	
		Stomach cancer	0.97 (8; 0.48-1.93)	
		Lung cancer	SIR	
Chia <i>et al.</i> (1991) Singapore	159 Chinese incident silicotics (M) diagnosed 1970-84, identified at silicosis registry	All subjects	2.01 (9; 0.92-3.81)	
		By latency		
		20-40 years	2.26 (6; 0.83-4.92)	
		≥ 40 years	2.23 (3; 0.46-6.50)	
		By exposure duration		
		20-40 years	1.76 (4; 0.62-5.81)	
		≥ 40 years	2.54 (5; 0.64-4.60)	
		By radiological category		
		I	1.40 (4; 0.38-3.58)	ILO scale of pneumoconiosis
		II	2.79 (3; 0.58-8.16)	
III	5.11 (2; 0.62-18.5)			
Smokers	2.16 (8; 0.93-4.25)			

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Amandus <i>et al.</i> (1992) United States	A subgroup of 306 (WM) from Amandus <i>et al.</i> (1991); 143 men reclassified as silicotic and 96 with normal radiogram	Lung cancer All subjects Silicotics Normal radiograms Silica exposure only Silicotics Normal radiograms Smokers Silicotics Normal radiograms	SMR 2.5 (8; 1.1-4.9) 1.0 (2; 0.1-3.5) 2.4 (7; 1.0-5.0) 1.2 (2; 0.2-4.4) 3.4 (5; 1.1-7.9) 1.3 (1; 0.03-7.1)	
Partanen <i>et al.</i> (1994) Finland	811 silicotics (M) diagnosed 1936-77 from various sources including nationwide registry; cancer incidence follow-up 1953-91 through cancer registry	All cancers Lung cancer By length of follow-up < 2 years 2-9 years ≥ 10 years By industry Mining/quarrying (excluding granite) Stone quarrying, cutting Glass/ceramic Stomach cancer	SIR, 1.67 (190; 1.44-1.91) 2.89 (101; 2.35-3.48) 0.41 (1; 0.01-2.27) 2.73 (32; 1.87-3.85) 3.27 (168; 2.54-4.14) 3.65 (38; 2.59-5.02) 2.93 (13; 1.56-5.01) 3.33 (10; 1.60-6.13) 1.06 (15; 0.59-1.74)	
Finkelstein (1995a) Canada	328 Ontario miners (M) with silicosis and 970 matched miners without silicosis from the surveillance system; cancer incidence follow-up 1974-92	All cancers Silicotics Non-silicotics Lung cancer Silicotics Non-silicotics	SIR 1.35 (35; 0.95-1.89) 0.90 (70; 0.71-1.14) 2.55 (15; 1.43-8.28) 0.90 (16; 0.51-1.47)	
Finkelstein (1995b) Canada	37 lung cancer cases and 159 controls (M) from miners	Four or five radiographic abnormalities	6.88 (1.89-25.00)	Adjusted for cumulative radon exposure

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Goldsmith <i>et al.</i> (1995) United States	590 claimants (M, F) for compensation for silicosis. California, 1945-75; mortality follow-up 1946-91	All causes	SMR, 1.30 (421; 1.18-1.43)	
		All cancers	1.22 (81; 0.96-1.52)	
		Lung cancer	1.90 (39; 1.35-2.60)	
		Construction	4.04 (17; [2.3-6.4])	
		Mining/quarrying	1.65 (19; [1.0-2.6])	
Merlo <i>et al.</i> (1995) Italy	450 silicotics (M) from hospital registry 1961-80; mortality follow-up through 1987	All causes	SMR, 1.89 (290; 1.69-2.12)	
		All cancers	1.61 (56; 1.26-2.15)	
		Lung cancer	3.50 (35; 2.44-4.87)	
		By years since first employment		
		15-29 years	5.60 (7; 2.63-11.54)	
≥ 30 years	3.24 (28; 2.15-4.68)			
Wang <i>et al.</i> (1996) China	4372 silicotics (M) in metallurgical industry; follow-up 1980-89	All causes	SMR, 1.22 (974; 1.15-1.30)	
		All cancers	1.18 (235; 1.04-1.35)	
		Lung cancer	2.37 (104; 1.96-2.86)	
		Mines	2.47 (55; [1.9-3.3])	
		Refractory brick	2.11 (29; [1.9-3.3])	
		Ore sintering	3.65 (6; [1.4-8.2])	
		Smelting	2.91 (9; [1.3-5.5])	
		Casting	1.57 (5; [0.5-3.8])	
		Silicosis		
		Category I	2.24 (38; [1.6-3.0])	
		Category II	2.64 (34; [1.8-3.6])	
		Category III	1.61 (4; [0.4-4.1])	

Table 23 (contd)

Reference/country	Study base/follow-up	Outcome/subgroup	Relative risk (No. of deaths or cases; 95% confidence interval)	Comments
Wang <i>et al.</i> (1996)		Years of exposure to silica dust		
China		< 10	2.46 (18; [1.5-4.0])	
(contd)		10-19	2.37 (50; [1.8-3.2])	
		≥ 20	2.32 (36; [1.6-3.2])	
		Smokers	2.57 (72; [2.0-3.3])	
		Non-smokers	2.09 (32; [1.4-3.0])	
		Stomach	0.88 (40; 0.66-1.16)	

Abbreviations: M, male; F, female; SMR, standardized mortality ratio; PMR, proportionate mortality ratio; OR, odds ratio; SIR, standardized incidence ratio; PAHs, polycyclic aromatic hydrocarbons; NS, not significant; FEV₁, forced expiratory volume in one second; VC, vital capacity; WM, white males

comparisons of cases and controls in sugar cane farming who were smokers; the odds ratio among smokers was 2.6 (95% CI, 1.8–4.0) which contrasted with an odds ratio of 0.9 (95% CI, 0.2–3.9) among non-smokers. No measurements of fibre concentrations were available [nor did the authors suggest a possible association with silica or biogenic silica fibres.]

In a study in four Florida counties, Brooks *et al.* (1992) compared residential and occupational histories of 98 male lung cancer cases and 44 male mesothelioma cases with 136 community controls matched on sex, age and race over a 18-month period beginning in 1989. There was no consistent association of lung cancer with residence near sugar cane growing areas. The odds ratios for residence near sugar cane areas were 0.6 (95% CI, 0.2–1.6) for within one mile and 1.9 (95% CI, 0.8–5.0) for within one to 4.9 miles, compared to the reference category of more than five miles. No cases or controls in the mesothelioma analysis had ever lived within 12 miles of a sugar cane growing area. Twenty-three lung cancer cases and 17 controls reported employment history in the sugar cane industry for one year or longer (odds ratio, 1.8; 95% CI, 0.5–7.5). However, the mean years of employment for these cases and controls were nearly identical (20.2 for cases, 21.3 for controls). One mesothelioma case and no matched control worked in the sugar cane industry. The case was a processing machinery supervisor in sugar mills in the United States and Cuba, and who had a history of asbestos exposure in those jobs.

Sinks *et al.* (1994) evaluated employment in the sugar cane industry as a risk factor for mesothelioma from 1960–87 in Hawaii. The study compared employment histories of 93 mesothelioma cases with 281 age- and gender-matched controls who had other types of cancers. Cases were identified from a population-based cancer registry. An odds ratio of 1.1 (95% CI, 0.4–2.9) was found for employment as a sugar cane worker, based on seven exposed cases and 19 exposed controls. The odds ratio increased slightly (1.3; 95% CI, 0.3–5.2) when cancers potentially related to asbestos (trachea, bronchus, larynx, stomach) were eliminated from the control group.

From a cohort of workers from the diatomite industry, only 129 (5%) were classified as only having had amorphous silica exposure, from opencast mining of the ore (Checkoway *et al.*, 1993). Separate mortality analyses were not carried out for this group.

3. Studies of Cancer in Experimental Animals

In this section, the description of silica samples and preparations conforms to the specific details presented by the author(s) of the various studies. [The Working Group noted that important properties such as the exact mineral and chemical compositions and particle size distribution of the samples are not reported systematically in all studies.]

Crystalline silica

3.1 Inhalation exposure

3.1.1 Mouse

A group of 60 female BALB/cBYJ mice, six weeks old, was exposed by inhalation in chambers to quartz (Min-U-Sil, a crystalline silica containing more than 96% quartz) for 8 h per day on five days per week. Subgroups of six to 16 mice each were exposed for total periods of 150, 300 or 570 days, and mice were necropsied either immediately after the end of the exposure period or following a holding period of 30 or 150 days. The average exposure concentrations of particles (diameter < 2.1 μm [diameter not further specified]) were approximately 1475, 1800 and 1950 $\mu\text{g}/\text{m}^3$ for the subgroups exposed for 150, 300 and 570 days, respectively. A similar group of 59 controls consisting of subgroups of seven to 13 mice each was not exposed to silica but was sacrificed by the same schedule. Pulmonary adenomas (type II, Clara-cell and mixed type II and Clara-cell tumours) were found in both silica-exposed mice (overall incidence, 9/60) and in controls (overall incidence, 7/59); these incidences were not significantly different. The overall incidences of severe pulmonary lymphoid cuffing and heavy alveolar macrophage accumulation were 37/60 and 39/60, respectively, in silica-treated mice and 5/59 and 3/59, respectively, in controls; the difference in incidences between the silica-treated and control animals was statistically significant ($p < 0.05$) (Wilson *et al.*, 1986). [The Working Group noted the small numbers of animals in the subgroups and the variable exposure and observation periods.]

3.1.2 Rat

Groups of 72 male and 72 female Fischer 344 rats, 3 months old, were exposed by inhalation in chambers to 0 or 51.6 mg/m^3 quartz (Min-U-Sil 5; mass median aerodynamic diameter, 1.7–2.5 μm ; geometric standard deviation, 1.9–2.1) for 6 h per day on five days per week for 24 months. After four, eight, 12 and 16 months of the experiment, 10 males and 10 females per group were removed from the chambers; five were sacrificed and five were retained with no further exposure. All survivors were killed at 24 months. Mean survival was 688 ± 13 days for controls and 539 ± 13 days for rats exposed to quartz until death, the difference being statistically significant ($p < 0.05$). The incidence of epidermoid carcinomas of the lungs in treated rats still alive at 494 days, when the first pulmonary tumour appeared, was 10/53 (19%) females and 1/47 (2%) males. Three of five female rats that received no further exposure to quartz after four months also developed epidermoid carcinomas; metastasis to the mediastinal lymph nodes was reported in one of these female rats. None of the 42 male or 47 female controls developed a lung tumour. Additional lesions in quartz-treated rats included areas of pulmonary adenomatosis and nodular fibrosis, cuboidal metaplasia of the alveolar epithelium, as well as alveolar proteinosis and peribronchiolar lymphoreticular hyperplasia (Dagle *et al.*, 1986). [The Working Group noted that, due to inadequate reporting, it cannot be determined from which exposure subgroups animals surviving at 494 days were derived; no statistical analysis of lung carcinoma incidences was reported.]

One group of 62 female Fischer 344 rats [age unspecified] was exposed by nose-only inhalation to 12 ± 5 mg/m³ quartz (Min-U-Sil; mass median aerodynamic diameter: 2.24 ± 0.2 μ m, and a geometric standard deviation of 1.75 ± 0.3 ; respirable fraction $70 \pm 3\%$ according to the criteria of the American Conference of Governmental and Industrial Hygienists; all particles < 5.0 μ m) for 6 h per day on four days per week for 83 weeks; the animals were observed for the duration of their life span. Controls were sham-exposed to filtered air (62 females) or were unexposed (15 females). Mean survival times were 683 ± 108 days for quartz-exposed rats and 761 ± 138 days for sham-exposed controls. [The survival time of the unexposed controls was not specified.] Of the quartz-exposed rats, 18/60 had lung tumours (three squamous-cell carcinomas, 11 adenocarcinomas and six adenomas), all of which were observed after 17 months or more of exposure. No lung tumour was observed in 54 sham-exposed controls; 1/15 unexposed controls had an adenoma of the lung. Most of the quartz-exposed rats still alive after 400 days developed pronounced pulmonary fibrosis, lung granulomas and silicotic nodules, often accompanied by emphysema and alveolar proteinosis (Holland *et al.*, 1983, 1986). A morphological description of the tumours is given by Johnson *et al.* (1987). The peripheral adenomatous lung tumours were found to be composed predominantly of alveolar type II pneumocytes.

Groups of 50 male and 50 female viral antibody-free SPF (specific pathogen-free) Fischer 344 rats, eight weeks old, were exposed by inhalation in chambers to 0 or 1 mg/m³ silica (silicon dioxide, type DQ 12; 87% crystallinity as quartz; mass median aerodynamic diameter about 1.3 μ m, with a geometric standard deviation of 1.8; respirable fraction 74% according to the criteria of the American Conference of Governmental and Industrial Hygienists) for 6 h per day, five days per week for 24 months; the rats were then kept without further exposure for another six weeks. Mean survival in the treated and control groups was comparable; at the termination of the study at 25.5 months, 40% of the control and 35% of the silica-treated animals survived (not statistically different by the Kaplan–Meier method using a life-test programme). The incidences of primary lung tumours in rats exposed to silica were 7/50 males (one adenoma, three adenocarcinomas, two benign cystic keratinizing squamous-cell tumours, one adenosquamous carcinoma and one squamous-cell carcinoma; one animal had an adenoma and an adenocarcinoma) and 12/50 females (two adenomas, eight adenocarcinomas and two benign cystic keratinizing squamous-cell tumours); only 3/100 controls [sex unspecified] had primary lung tumours (two adenomas and one adenocarcinoma). The combined incidence of benign and malignant lung tumours in silica-treated rats (19%) was significantly elevated compared to the incidence of 3% in the control group (using simple tests for homogeneity of contingency tables using χ^2 -statistics or Fisher's exact methods) [no *p* values were given]. The first tumour in silica-exposed rats was observed after 21 months of exposure. In a 21-month parallel serial sacrifice study, one further lung tumour (an adenoma) was found among 13 silica-exposed rats versus no lung tumours in a total of 11 controls. Nodular bronchoalveolar hyperplasia, interpreted as borderline to adenoma, was found in 13/100 silica-exposed rats (distributed about equally between the sexes) and was not reported to occur in controls. Other non-neoplastic pulmonary lesions occurring in high incidences in silica-exposed rats included

the following: multifocal lipoproteinosis with and adjacent to fibrotic areas, foamy macrophages containing lipoid substances; intra-alveolar and interstitial inflammatory cell infiltrates mainly consisting of polymorphonuclear leukocytes; moderate degrees of multifocal (predominantly subpleural and peribronchiolar) fibrosis; and alveolar- and bronchiolar-type bronchoalveolar hyperplasia. The severity of these pulmonary lesions, in particular the fibrosis, increased with increasing exposure time (Muhle *et al.*, 1989, 1991, 1995).

Two groups of 70 male and 70 female (Cpb:WU, Wistar random) rats, six weeks old, were exposed by inhalation in chambers to 0 (controls) or 58.5 ± 0.7 mg/m³ quartz (Sikron [Sykron] F300 obtained from Guertz Werke, Frechen, Germany, crystalline, hydrophilic, pH 7, 99% SiO₂; BET-surface area, < 1.5 m²/g; geometric diameter (mean), 8 µm with a global range of 0.1–25 µm; no agglomeration; edges coarse, irregular and sharp) for 6 h per day on five days per week for 13 weeks. At the end of the exposure period and at 26, 39, 52 and 65 weeks after the start of exposure, 20, 10, 10, 10 and 20 rats per sex per group were killed, respectively. Only one respiratory tract tumour was observed, namely a small squamous-cell carcinoma in the lung parenchyma of a quartz-treated female killed at 65 weeks. In addition, a focus of squamous metaplasia in the periphery of the lung was found in one quartz-treated male killed at 65 weeks. Major non-neoplastic pulmonary changes in quartz-treated animals were the accumulation of alveolar macrophages, granulomatous inflammation, interstitial fibrosis, bronchiolo-alveolar hyperplasia and fibrotic granulomas. Associated lymph nodes contained many macrophages with or without cellular necrosis and slight fibrosis (Reuzel *et al.*, 1991). [The Working Group noted the short duration of the study, the lack of information on survival and that only a small proportion of the quartz particles was respirable to rats.]

Three groups of 90 female Wistar rats, six to eight weeks old, were exposed by nose-only inhalation to 0, 6.1 ± 0.36 or 30.6 ± 1.59 mg/m³ quartz (DQ 12; mass median aerodynamic diameter, 1.8 µm with a geometric standard deviation of 2.0) for 6 h per day, on five days per week for 29 days. In each group, interim sacrifices of two to six rats each were made directly after quartz exposure and six, 12 and 24 months later; the terminal sacrifice was made 34 months after exposure. The mean survival times were 741 ± 179 and 739 ± 191 days for the control and low-dose groups, respectively. The mean survival in the high-dose group, reported as a survival curve only, seemed to be slightly lower than that in the two other groups, particularly in the final few months of the study (Kaplan–Meier curves). Twenty-four months after treatment, the numbers of rats with lung tumours were 8/37 and 13/43 in the low- and high-dose groups, respectively. The total incidences of lung tumours were 37/82 (45.1%) and 43/82 (52.4%) for the low- and high-dose groups, respectively. No lung tumour was observed in controls. In many animals, more than one lung tumour of the same type or different types were found; 62 tumours (eight bronchiolo-alveolar adenomas, 17 bronchiolo-alveolar carcinomas, 37 squamous-cell carcinomas, one anaplastic carcinoma) were found in the low-dose group and 69 (13 bronchiolo-alveolar adenomas, 26 bronchiolo-alveolar carcinomas, 30 squamous-cell carcinomas) in the high-dose group. Metastases were observed most frequently in the tracheobronchial lymph nodes and occasionally in the kidneys and the heart. Treatment- and dose-related non-neoplastic pulmonary lesions

included increased numbers of alveolar macrophages, thickening of the alveolar walls, perivascular accumulation of inflammatory cells, degeneration of alveolar macrophages, alveolar proteinosis, granulomas, emphysema, interstitial fibrosis and proliferation of alveolar and bronchiolar epithelium. Only in single cases were bronchiolo-alveolar carcinomas accompanied by marked fibrosis, indicating, at most, a weak influence of marked fibrosis on lung-tumour development in female rats (Spiethoff *et al.*, 1992).

3.2 Intranasal administration

Mouse: Two groups of 40 female (C57×BALB/c) F₁ mice, two months old, received a single intranasal inoculation of 4 mg *d*- or 4 mg *l*-quartz (synthetic *d*- and *l*-quartz obtained from Tokyo Communication Equipment Co., Japan; impurities given as median atomic parts per million relative to silica: H/400, Li/20, C/12, Na/3, Al/3, S/1, F/1, Cl/1, Ca/0.5, K/0.3, Br/0.1, Zn/0.1, Fe/0.1, Co/0.06) in 0.1 mL saline. A group of 60 female mice was treated with saline only [volume and route of administration unspecified]. Survivors (56/60, 36/40 and 37/40 mice treated with saline, *d*-quartz and *l*-quartz, respectively) were killed 18 months after treatment. Incidences of lymphomas/leukaemias were 0/60, 2/40 and 6/40 for saline-, *d*-quartz- and *l*-quartz-treated mice, respectively (statistical analysis indicated a significant difference between *l*- and *d*- forms; $p < 0.01$). In addition, 3/40 *l*-quartz-treated mice had a benign-looking liver adenomas, whereas no liver tumours were observed in *d*-quartz-treated mice or in controls. Liver granulomas with lymphocytes and fibroblasts were found in 10/40 mice treated with *d*-quartz and in 14/40 mice treated with *l*-quartz, the difference being statistically insignificant at the 0.01 level (double-tailed exact probability test). No liver granulomas were found in controls. Peribronchiolar lymphoid infiltration occurred in 21/40 *d*-quartz-treated, 29/40 *l*-quartz-treated and in 3/60 control mice (Ebbesen, 1991). [The Working Group noted the lack of information on retention of the material following single intranasal inoculation.]

3.3 Intratracheal administration

3.3.1 *Mouse*

In a screening study based on the induction of lung adenomas in strain A mice, a group of 30 male strain A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg (9.75 mg/kg bw) silica (Min-U-Sil 216 quartz purchased from Whittaker, Clark and Daniels, Inc., NJ, United States; 1–5 μm) [size not further specified] in 0.02 mL vehicle [vehicle unspecified] for 15 weeks. A group of 20 mice was treated similarly but with the vehicle only. A positive control group of 30 mice received a single intraperitoneal injection of 0.1 mL urethane (64.1 mg/kg bw) in sterile saline. Survivors (all animals but one of the vehicle control group) were killed 20 weeks after study initiation. The incidences of lung adenomas were 9/29 (31%), 4/20 (20%) and 18/30 (60%) in the vehicle control, silica-treated and positive control groups, respectively. The average numbers of lung adenomas per mouse were 0.31 ± 0.09 , 0.20 ± 0.09 and 0.97 ± 0.19 for vehicle controls, silica-treated mice and positive controls, respectively. The differences in tumour incidence and multiplicity were statistically significant

between positive and vehicle controls (Fisher's exact test; $p < 0.05$ for tumour incidence, $p < 0.01$ for tumour multiplicity). Differences in tumour incidence and multiplicity between silica-treated and vehicle controls were not statistically different (McNeill *et al.*, 1990).

Two groups of 26 male mice from each of three strains (A/JCr, BALB/cAnNCr and (athymic nude) NCr-NU) received one single intratracheal instillation of either 10 mg/animal quartz (Min-U-Sil < 5; 99% pure with 0.1% iron [presence of iron in Min-U-Sil is not uncommon]; surface area 3.15 m²/g; particle size distribution mostly between 0.5 and 2.0 µm) or 10 mg/animal tridymite (area surface 5.24 m²/g) [particle size and particle size distribution unspecified] in 0.1 mL saline. Survivors for more than six months were studied at unscheduled death up to 24 months. The incidences of lung tumours in animals treated with Min-U-Sil and tridymite were 2/15 (one adenoma and one adenocarcinoma) and 4/16 (four adenomas, one of the adenomas not in a silicotic area) in A/JCr mice, 2/26 (one adenoma and one adenocarcinoma, the adenocarcinoma not in a silicotic area) and 2/22 (two adenomas) in BALB/cAnNCr mice and 1/4 (one adenoma) and 0/5 in NCr-NU mice, respectively. In view of the incidence of spontaneous lung adenomas in strain A mice and the low incidence of the lung tumours in tridymite-treated mice, the authors regarded the observed tumours as unrelated to treatment. Non-neoplastic pulmonary changes were analogous in the three strains of mice for both types of silica, and mainly consisted of silicotic granulomas with large necrotic centres, alveolar proteinosis, transient hyperplasia of bronchial and bronchiolar epithelium and only sporadic and transient hyperplasia of the alveolar epithelium (Saffiotti, 1990; 1992; Saffiotti *et al.*, 1996). [The Working Group noted both the lack of information on survival and the absence of a control group.]

3.3.2 Rat

A group of 40 Sprague-Dawley rats [sex and age unspecified] received weekly intratracheal instillations of 7 mg quartz (Min-U-Sil; mean particle size 1.71 ± 1.86 µm; all particles < 5 µm) in 0.2 mL saline for 10 weeks. A group of 40 rats received saline only and another group of 20 animals was untreated. All animals were observed for the duration of their life span. Lung tumours were reported in 6/36 quartz-treated rats (one adenoma and five carcinomas) [type of carcinomas unspecified] and in 0/40 saline-treated and 0/18 untreated controls. Focal and diffuse pulmonary fibrosis was only observed in quartz-treated animals (Holland *et al.*, 1983). [The Working Group noted the absence of information on survival.]

Groups of 85 male Fischer 344 rats, obtained when weighing 180 ± 15 g and treated two weeks later, received a single intratracheal instillation of 20 mg quartz into the left lung either as Min-U-Sil (particle size, 0.1% ≥ 5 µm; surface area, 4.3 m²/g) or as novaculite (from Malvern Minerals Co., Hot Springs, AR, United States; particle size, 2.2% ≥ 5 µm; surface area, 1.6 m²/g) in a suspension of filtered, deionized water [volume unspecified]. Controls received the suspension vehicle alone. Interim sacrifices of 10 rats each were made at six, 12 and 18 months; terminal sacrifice was made at 22 months. In the Min-U-Sil-treated group, the incidences of lung tumours were 1/10 at 12 months,

5/10 at 18 months, 5/17 in rats that died between 12 and 22 months, and 19/30 at 22 months; total incidence was 30/67 (45%). All tumours were adenocarcinomas, some of which had squamous and/or undifferentiated areas. The incidences of lung tumours in the novaculite-treated group were as follows: 1/10 at 12 months, 2/10 at 18 months, 2/17 in rats that died between 12 and 22 months, and 16/35 at 22 months; total incidence was 21/72 (29%). One tumour was an epidermoid carcinoma; all others were adenocarcinomas; 87% of the tumours were in the left lung. In the control group, 1/44 had a lung tumour (an adenocarcinoma) at 22 months; total incidence was 1/75. The total lung tumour incidences in Min-U-Sil- or novaculite-treated rats were significantly different from that in controls (Fisher's exact test; $p < 0.001$). The Min-U-Sil-treated group had larger lung tumours and more extensive granulomatous and fibrotic lung lesions than the novaculite-treated group (Groth *et al.*, 1986).

Groups of male and female F344/NCr rats [initial numbers unspecified], four to five weeks old, received one single intratracheal instillation of 12 or 20 mg/animal quartz Min-U-Sil 5 (99% pure with 0.1% iron; surface area 3.15 m²/g; particle size distribution mostly between 0.5 and 2.0 µm) in 0.3 and 0.5 mL saline, respectively [one source mentions 0.3 mL saline for the 20 mg dose], 12 mg hydrofluoric acid-etched Min-U-Sil 5 (prepared as described by Saffiotti, 1962) (99% pure with no iron; surface area 2.98 m²/g; particle size distribution mostly between 0.5 and 2.0 µm) in 0.3 mL saline, or 20 mg ferric oxide (haematite, Fe₂O₃; non-fibrogenic dust) in 0.3 mL saline [or 0.5 mL saline; see above]. A group of untreated controls was also observed. The number of animals in each group [not further specified], the number of animals observed at interim kills or after unscheduled death and the incidences, total numbers, multiplicity and types of lung tumours found are summarized in **Table 24**. Type, degree and incidences of non-neoplastic pulmonary changes were very similar in each of the quartz-treated groups, and included the following: macrophage reaction; interstitial fibrosis; hyperplasia of peribronchial lymphoid tissue; silicotic granulomas increasing in size and becoming more fibrotic with time; and hypertrophy, hyperplasia and adenomatoid proliferation of alveolar epithelium. The mediastinal lymph nodes showed reactive hyperplasia (Saffiotti, 1990; 1992; Saffiotti *et al.*, 1996).

Six groups of female Wistar rats, 15 weeks old, received one single intratracheal instillation or 15 weekly intratracheal instillations of one of three quartz preparations (DQ 12, Min-U-Sil, quartz ± 600 [sources unspecified]) in 0.4 mL 0.9% sodium chloride solution (see **Table 25**). An additional control group of rats received 15 weekly instillations of the sodium chloride solution only. To retard silicosis development, two of the experimental groups of rats each received seven subcutaneous injections of 2 mL 2% polyvinylpyridine-*N*-oxide (PVNO) in saline; the first injection was given one day before the first intratracheal instillations of quartz, and the remaining six injections were given at four-month intervals. The animals died spontaneously or were killed when moribund or at 131 weeks. Animals treated with quartz DQ 12 developed severe silicosis and had a relatively short survival (median survival time about 15 months as visible from mortality curves). Owing to the protective effect of PVNO against silicosis, the groups treated with DQ 12 or Min-U-sil and PVNO developed more pulmonary squamous-cell carcinomas (Pott *et al.*, 1994).

Table 24. Incidence, numbers and types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz^a

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

^aFrom Saffiotti (1990, 1922); Saffiotti *et al.* (1996)

^bSuspended in 0.3 or 0.5 mL saline

^cHydrogen fluoride

Table 25. Incidence of lung tumours in female Wistar rats after intratracheal instillation of quartz^a

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

^aFrom Pott *et al.* (1994)

^bIf an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows: ^eadenoma; ^fadenocarcinoma; ^gbenign CKSCT

^cCKSCT, cystic keratinizing squamous cell tumour

^dOther types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

^ePVNO, polyvinylpyridine-N-oxide

3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex and age unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil; mean particle size $1.71 \pm 1.86 \mu\text{m}$; all particles $< 5 \mu\text{m}$) in 0.2 mL saline once a week for 10 weeks. A group of 68 animals received saline only and another group of 72 animals was untreated. All animals were observed for the duration of their life span. No lung tumour was observed among 31 low-dose animals, 41 high-dose animals, 58 saline controls or 36 untreated controls. Both the incidence and severity of pulmonary fibrosis were minimal. Pneumonitis-pneumonia complex occurred in 13/31 and 21/41 of animals receiving the low and high dose, respectively, late in the exposure period (Holland *et al.*, 1983). [The Working Group noted absence of information on survival.]

Groups of 25–27 male outbred (LAK:LVG) Syrian golden hamsters, 11 weeks old, received weekly intratracheal instillations of 0.03, 0.33, 3.3 or 6.0 mg quartz (Min-U-Sil; particle diameter: median, $0.84 \pm 0.07 \mu\text{m}$; average, $1.06 \pm 0.07 \mu\text{m}$; mass median, $3.14 \pm 0.24 \mu\text{m}$; mass aerodynamic, $5.13 \pm 0.40 \mu\text{m}$) in saline [volume unspecified] for 15 weeks. Groups of 27 saline-treated and 25 untreated hamsters served as controls. Animals were killed when moribund or when survival within the group reached 20%; any remaining groups were killed at 24.5 months of age. The average survival times were 498 ± 44 , 506 ± 41 , 383 ± 31 ($p < 0.005$ compared with saline-treated controls) and 348 ± 26 days ($p < 0.005$ compared with saline-treated controls) for the groups treated with 0.03, 0.33, 3.3 and 6.0 mg quartz, respectively, and 534 ± 35 and 595 ± 14 days for the saline-treated hamsters and untreated controls, respectively. No pulmonary tumour was observed in any of the groups. In animals treated with quartz, dose-related alveolar septal fibrosis of slight to moderate degree, granulomatous inflammation and alveolar proteinosis were observed in the lungs, but no animal developed nodular fibrosis or foci of dense fibrous tissue in the lung (Renne *et al.*, 1985).

Three groups of 50 male outbred Syrian golden hamsters, seven to nine weeks old, received weekly intratracheal instillations of 1.1 mg quartz as Sil-Co-Sil (Ottawa Silica Sand; Sil-Co-Sil 395–325 grain fineness number; surface area 0.0021 m^2), 0.7 mg Min-U-Sil ($5 \mu\text{m}$; surface area 0.0021 m^2) or 3.0 mg ferric oxide (particulate negative control) in 0.2 mL saline for 15 weeks. A group of 50 vehicle controls received instillations of 0.2 mL saline alone. Survivors were killed 92 weeks after first treatment. Survival was significantly lower in the Sil-Co-Sil-treated group than in the Min-U-Sil-treated group and in the saline control group ($p < 0.05$) [survival not further specified; method of statistical analysis unspecified]. One adenosquamous carcinoma of the bronchi and lung was observed in the Min-U-Sil-treated group at week 68 (effective number of animals, 35). No respiratory tract tumour was found in the 50 hamsters treated with Sil-Co-Sil or in the 48 saline-treated controls. In the ferric oxide-treated group, one benign tumour of the larynx (papilloma or adenoma) was observed at week 62 (effective number of animals, 34). Bronchiolo-alveolar hyperplasia was occasionally seen in the particulate-treated animals. No pulmonary fibrosis was observed; however, pulmonary granulo-

matous inflammation was significantly increased in Sil-Co-Sil- and Min-U-Sil-treated hamsters compared to saline controls ($p < 0.001$) (Niemeier *et al.*, 1986).

3.4 Intrapulmonary deposition

Rabbit: A group of seven rabbits [strain, sex and age unspecified], weighing 1550–2350 g, received by operation a single intrapulmonary deposit of quartz (particle size, about 2 μm) [origin, type and dose unspecified] suspended in 0.5 mL saline. Two animals died post-operatively. Of the five remaining rabbits that survived five to six years, four developed malignant lung tumours: three adenocarcinomas involving both lungs and one sarcoma involving the pleura. The adenocarcinomas had metastasized to the pleura and the mediastinum (probably to the mediastinal lymph nodes), and in two cases also to the liver. No silicotic lesions were found, but fibrous capsules were formed around the quartz deposits. Atypical hyperplasia and metaplasia of the alveolar epithelium were observed (Kahlau, 1961). [The Working Group noted the small number of animals and the lack of controls.]

3.5 Intrapleural and intrathoracic administration

3.5.1 Mouse

In a study reported as an abstract, three groups of 37–43 male Marsh mice, three months of age, received a single intrathoracic injection [method of administration not further specified] of 10 mg/animal tridymite (prepared in the laboratory from silicic acid with a 0.002% heavy metal–iron content; particle size, 20% $< 3.3 \mu\text{m}$ and 40% in the range 6.6–15 μm) in saline, 5 mg/animal chrysotile (acid washed, containing 0.4% iron and 0.05% copper) in saline or saline alone. After 19 months, the effective numbers of mice were 32–34 per group. Among the animals given tridymite one developed a lung adenocarcinoma and two intrapleural lymphoid tumours; there was one lung adenocarcinoma and no lymphoid tumour in saline controls; there were four lung adenocarcinomas and four lymphoid tumours in the chrysotile group. Lesions reported as ‘lymph node reactive hyperplasia simulating malignancy’ were found in 19/32 tridymite-, 1/32 chrysotile- and 1/34 saline-treated mice; the differences between the tridymite-treated mice and the chrysotile- and saline-treated were highly statistically significant ($p < 0.02$; Yates correction) (Bryson *et al.*, 1974).

3.5.2 Rat

Two groups of 48 male and 48 female SPF Wistar rats and two groups of 48 male and female standard Wistar rats, six weeks old, received a single intrapleural injection of 20 mg/animal quartz (alkaline-washed silica supplied by Dr G. Nagelschmitt, Safety in Mines Research Establishment who prepared it from Snowit, a silica sand produced commercially in Belgium; particle size $< 5 \mu\text{m}$) suspended in 0.4 mL saline or 0.4 mL saline alone, and were observed for their life span. The 50% survival of quartz-treated rats was about 850 days and that of quartz-treated standard rats about 700 days [distribution of survival times of males and females together given as bar diagrams]. Mean

survival times of saline-treated controls (males and females) were 883 and 725 days for SPF and standard rats, respectively. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats (23 histiocytic lymphomas, five Letterer-Siwe or Hand-Schüller-Christian's disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas and six spindle-cell sarcomas) and in 31/94 standard rats (30 histiocytic lymphomas, one spindle-cell sarcoma) compared to 8/96 SPF controls (three lymphoblastic lymphosarcomas, five reticulum-cell sarcomas) and 7/85 standard controls (one lymphoblastic lymphosarcoma and six reticulum-cell sarcomas) [$p < 0.001$]. The earliest quartz-induced tumour occurred 296 days after injection in SPF rats and 58 days after injection in standard rats, but the next tumour in standard rats did not occur until more than 300 days after injection. Most tumours occurred between 300 and 1000 days after injection [time to appearance of reticuloendothelial thoracic tumours in controls unspecified]. These tumours were predominantly observed in the upper mediastinum, the pericardium, the diaphragm and the lungs, and their distribution corresponded to that of silicotic nodules. In addition to the reticuloendothelial tumours in about one third of the quartz-treated animals, another third (21 standard and 30 SPF-rats) showed 'hyperplastic reaction' (granulomatous lesions) only, mainly in the thoracic cavity. A variety of other tumours did not appear to be associated with treatment. Standard rats often had accompanying infections that were absent in the SPF rats (Wagner & Berry, 1969; Wagner, 1970; Wagner & Wagner, 1972).

In a larger study, a total of 23 malignant reticuloendothelial tumours (21 malignant lymphomas of the histiocytic type (MLHT) with often widespread dissemination, two lymphosarcomas/thymomas/spindle-cell sarcomas) was observed in a group of 80 male and 80 female Caesarean-derived SPF inbred Wistar rats [distribution of the tumours over the sexes unspecified], on average 39 days old, that received a single intrapleural injection of 20 mg/animal quartz (alkaline-washed quartz (see above); particle size, $< 5 \mu\text{m}$) suspended in 0.4 mL saline. Two males and two females were sacrificed every five weeks; at 120 weeks, the remaining rats were killed. No MLHT and one thymoma/lymphosarcoma occurred in a group of 15 saline-treated controls. In addition to tumours, (widespread) silicotic nodules occurred in most of the quartz-treated rats examined (Wagner, 1976).

A group of 16 male and 16 female Caesarean-derived SPF inbred Wistar rats, on average 39 days of age, received a single intrapleural injection of 20 mg/animal quartz (Min-U-Sil, a naturally occurring, commercial, fine quartz said to be 99% pure) in 0.4 mL saline. The animals were killed when moribund (mean survival, 678 days). Eight of 32 rats developed MLHT and 3/32 developed thymomas/lymphosarcomas [sex unspecified]. In 15 controls treated with saline only (mean survival, 720 days), no MLHT but one thymoma/lymphosarcoma was found. In addition to tumours, 'hyperplastic reaction' was reported to occur in 16/32 quartz-treated rats and in none of the rats treated with saline (Wagner, 1976).

A group of 16 male and 16 female Caesarean-derived SPF inbred Wistar rats, on average 39 days of age, received a single intrapleural injection of 20 mg/animal cristo-

balite (prepared by heating Loch Aline sand for 1 h at 1620 °C; containing 0.6×10^6 particles/ μg ; particle size distribution: 58.7% 0–1 μm , 28.9% 1–2 μm , 10.4% 2–4.6 μm ; Wagner *et al.*, 1980) in 0.4 mL saline. The animals were killed when moribund; mean survival time was 714 days. Eighteen of 32 rats developed malignant lymphoma (13 MLHT and five thymomas/lymphosarcomas) [sex unspecified]. In 15 controls treated with saline only (mean survival, 720 days), no MLHT but one thymoma/lymphosarcoma was found. In addition to tumours, 'hyperplastic reaction' was reported to occur in 13/32 cristobalite-treated rats and in none of the rats treated with saline (Wagner, 1976).

Groups of 16 male and 16 female Wistar-derived Alderley-Park rats, five to six weeks of age, received a single intrapleural injection of 20 mg of one of four quartz preparations (**Table 26**) in 0.4 ml saline. The incidence of MLHT observed in each treated group (except that receiving DQ 12) over the life span was statistically significantly higher than that in saline controls (Wagner *et al.*, 1980).

Groups of 16 male and 16 female Wistar-derived Alderley-Park rats, 12 male and 12 female PVG rats and 20 male and 20 female Agus rats, five to six weeks of age, received a single intrapleural injection of 20 mg quartz (Min-U-Sil) in 0.4 mL saline. Groups of 16 male and 16 female Wistar rats, 12 male and 12 female Agus rats and eight male and four female PVG rats were injected with saline alone. All rats were observed for the duration of their life span. Mean survival times for quartz-treated animals were 545 days for Wistar rats, 666 days for PVG rats and 647 days for Agus rats [mean survival times of controls unspecified]. MLHT was seen in 11/32 (34%) Wistar-derived, 2/24 (8.3%) PVG and 2/40 (5%) Agus rats [sex unspecified]. Tumour morphology was similar in all strains, except that the Wistar rats showed histological evidence of tumour spread below the diaphragm. No MLHT was found in any saline-injected control rat (Wagner *et al.*, 1980).

A group of 16 male and 16 female Wistar-derived Alderley-Park rats, five to six weeks of age, received a single intrapleural injection of 20 mg/animal cristobalite (see above; containing 0.6×10^6 particles/ μg ; particle size distribution: 58.7% 0–1 μm , 28.9% 1–2 μm , 10.4% 2–4.6 μm) in 0.4 mL saline. Mean survival was 597 days. Of 32 rats observed for life span, four developed MLHT [sex unspecified]; no such tumour was found in 16 male and 16 female saline controls (mean survival, 717 days) (Wagner *et al.*, 1980).

A group of 16 male and 16 female Wistar-derived Alderley-Park rats, five to six weeks of age, received a single intrapleural injection of 20 mg/animal tridymite (prepared by Safety-in-Mines Research Laboratories, Sheffield, United Kingdom, by dissolving impurities from silica cement that had had long service at approximately 1380 °C in a gas-retort house; the sample contained 0.35×10^6 particles/ μg ; particle size distribution: 34.9% 0–1 μm , 44.9% 1–2 μm , 21.2% 2–4.6 μm) in 0.4 ml saline. Mean survival was 525 days. Of 32 rats observed for life span, 16 developed MLHT [sex unspecified]. No such tumour was found in 16 male and 16 female saline controls (mean survival, 717 days) (Wagner *et al.*, 1980).

Two groups of 36 male SPF non-inbred Sprague-Dawley rats, two months old, received a single intrapleural injection of 20 mg/animal quartz (DQ 12) in 1 mL saline or

Table 26. Incidences of malignant lymphoma of the histiocytic type (MLHT) in rats after an intrapleural injection of 20 mg/animal quartz^a

Sample	No. of particles $\times 10^7/\mu\text{g}$	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%) ^b
		0-1 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%)
D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz)	0.30	48.4	33.2	18.4	633	8/32 (25%)
Snowit (commercially prepared washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%)
DQ 12 (standard pure quartz prepared by Robach (1973))	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	-	-	-	-	717	0

^a From Wagner *et al.* (1980)

^b Sex unspecified

^c [Significantly different from controls by Fisher's exact test, $p < 0.05$]

1 mL saline only. A group of 27 male rats served as untreated controls. All rats were allowed to live until they died or were moribund. Mean survival times were 769 ± 155 , 809 ± 110 and 780 ± 132 days for untreated, saline- or quartz-treated groups, respectively; differences between groups were not statistically significant (Student's *t*-test). Six malignant histiocytic lymphomas (17%; observed between 899 and 911 days after treatment) and two malignant Schwannomas (6%; observed between 885 and 911 days after treatment) were found in the quartz-treated group. One chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline and untreated groups, respectively. 'Granulomatous reactions' were observed in 5/34 quartz-treated rats but in none of the controls (Jaurand *et al.*, 1987).

3.6 Intraperitoneal administration

Rat: Two groups of 16 male and 16 female Caesarean-derived SPF inbred Wistar rats, aged six to eight and eight to 12 months, respectively, received a single intraperitoneal injection of 20 mg quartz (Min-U-Sil; 99% pure) in 0.4 mL saline. Twelve rats [sex unspecified] associated with the eight- to 12-month-old group received saline only. Animals were killed when moribund. Mean survival of quartz-treated animals (both age groups together) was 462 days and that of controls was 332 days. A total of 9/64 quartz-treated rats developed malignant lymphomas, two of which were MLHT and seven of which were thymoma/lymphosarcoma. None of the saline controls developed MLHT, but one developed a thymoma/lymphosarcoma. In addition to tumours, 'hyperplastic reaction' was reported to occur in 32/64 quartz-treated animals and in none of the controls (Wagner, 1976).

3.7 Subcutaneous administration

Mouse: Two groups of 40 female (C57×BALB/c) F₁ mice, two months old, received a single subcutaneous injection of 4 mg/animal *d*- or 4 mg/animal *l*-quartz (synthetic *d*- and *l*-quartz (see section 3.2); impurities given as median atomic parts per million relative to silica: H/400, Li/20, C/12, Na/3, Al/3, S/1, F/1, Cl/1, Ca/0.5, K/0.3, Br/0.1, Zn/0.1, Fe/0.1, Co/0.06) in 0.1 mL saline. A group of 60 female mice were treated with saline only [volume and route of administration unspecified]. Survivors (56/60, 35/40 and 38/40 saline-, *d*-quartz- and *l*-quartz-treated mice, respectively) were killed 18 months after treatment. Incidences of lymphomas/leukaemias were 0/60, 1/40 and 12/40 for saline-, *d*-quartz- and *l*-quartz-treated mice, respectively; the difference between *d*- and *l*-quartz-treated mice was statistically significant ($p < 0.001$; double-tailed exact probability test). In addition, 1/40 *d*-quartz-treated mice and 3/40 *l*-quartz-treated mice had a benign-looking liver adenoma, whereas no liver tumour was observed in controls. Liver granulomas with lymphocytes and fibroblasts were observed in 5/40 mice treated with *d*-quartz and in 17/40 mice treated with *l*-quartz, whereas no liver granulomas occurred in controls [the difference between the *d*- and *l*-quartz not being statistically significant at $p = 0.01$]. Subcutaneous fibrotic nodules at the injection site were seen in 17/40 *d*-quartz-treated mice and in 27/40 *l*-quartz-treated mice, but in none of the

controls (Ebbesen, 1991). [The Working Group noted the absence of local tumours at the injection site, whereas systemic tumours were reported.]

3.8 Intravenous administration

Mouse: A group of about 25 male and about 25 female strain A mice, two to three months of age, received a single intravenous injection in the tail vein of 1 mg/animal quartz [source unspecified] (average particle size, 1.6 μm) in 0.1 mL saline. A group of 75 (male and female) mice served as controls. Eleven quartz-treated mice were killed at three months, 10 at 4.5 months and 20 at six months; the number of controls killed at these time points were 25, 25 and 22, respectively. The incidences of pulmonary adenomas were 3/11, 1/10 and 8/20 in quartz-treated mice killed at three, 4.5 and six months, respectively, and those in controls were 5/25, 6/25 and 9/22, respectively. The multiplicity of the pulmonary adenomas was 1.0 in both quartz-treated and untreated mice killed at three or 4.5 months, and 1.2 in quartz-treated and 1.3 in untreated mice killed at six months (Shimkin & Leiter, 1940).

3.9 Administration with known carcinogens

3.9.1 Inhalation exposure

Rat: Two sets of three groups of 90 female Wistar rats, six to eight weeks of age, were exposed by nose-only inhalation to 0, 6.1 ± 0.36 or 30.6 ± 1.59 mg/m^3 quartz (DQ 12; mass median aerodynamic diameter, 1.8 μm with a geometric standard deviation of 2.0) for 6 h per day on five days per week for 29 days. Immediately after the last exposure, five rats of both the low- and high-quartz exposure group and two sham-exposed control animals were sacrificed. One week after the end of the exposure period, all 90 rats of one of the two sham-exposed control groups, and of one of the two low- and high-quartz exposure groups received a single intravenous injection of 600 μL enriched Thorotrast (2960 Bq ^{228}Th per mL) in saline. In each of the six groups, interim sacrifices of three or six animals each were made six, 12 and 24 months after the end of the exposure period. Survival was reduced and deaths occurred earlier (Kaplan–Meier curves) in the rats exposed to low- and high-quartz levels combined with Thorotrast as compared with their quartz-exposed but Thorotrast-free counterparts; the differences were highly statistically significant ($p < 0.001$; log-rank test). A similar difference was found between sham-exposed controls and rats treated with Thorotrast only. The reduction in survival was caused by a higher incidence of (fatal) lung cancer at earlier times, by the occurrence of Thorotrast-induced (fatal) liver and spleen tumours and by Thorotrast-treated non-specific life-shortening effects. Incidences, numbers and types of lung tumours, and total incidences of liver and spleen tumours in the six groups are presented in **Table 27**. Comparison of the cumulative rates of animals with fatal and incidental lung tumours (Kaplan–Meier curves) in the groups exposed to quartz and treated with Thorotrast with those in the corresponding Thorotrast-free groups revealed for the Thorotrast treatment a marked, positive trend of high statistical significance ($p < 0.001$). This trend suggests a pronounced interactive effect of Thorotrast and quartz

Table 27. Numbers of animals with lung, liver and spleen tumours, numbers and types of lung tumours, and total incidences of liver and spleen tumours in female Wistar rats after inhalation exposure to quartz and Thorotrast^c

Treatments	Number of rats ^a	Lung tumours		Incidence			Type			Incidence of liver and spleen tumours
		Observed	Expected	Obs./Exp.	Total number					
					Bronchiolo-alveolar adenoma	Bronchiolo-alveolar carcinoma	Squamous-cell carcinoma			
Controls	85	—	—	—	—	—	—	—	—	5
Low quartz	82	37	50.14	0.738	62	8	17	37	—	4
High quartz	82	43	66.93	0.642	69	13	26	30	—	4
Thorotrast	87	3	—	—	6	—	5	1	—	42
Low quartz + Thorotrast	87	39	24.86	1.508	68	10	28	30	—	47
High quartz + Thorotrast	87	57	33.10	1.724	98	16	47	35	—	28

^a From Spiethoff *et al.* (1992)

^b Number of rats after the first and second interim sacrifice

^c Apart from the tumours listed in this table a few thoracic tumours were detected, namely one anaplastic carcinoma in the low-quartz group, and one malignant histiocytoma and one pleural mesothelioma in the high-quartz plus Thorotrast group.

on pulmonary carcinogenesis in female rats. Non-neoplastic pulmonary changes in quartz-exposed rats with or without Thorotrast treatment included the following: degeneration of alveolar macrophages; alveolar proteinosis; granulomas; interstitial inflammation and early fibrosis; emphysema; and hyperplasia of alveolar and bronchiolar epithelium. These non-neoplastic changes were more pronounced in the high- than in the low-quartz-exposure group, but were not aggravated in animals also given Thorotrast. Marked pulmonary fibrosis occurred only in a few quartz-exposed or quartz-exposed plus Thorotrast-treated animals, and only occasionally were bronchiolo-alveolar carcinomas accompanied by extensive scar tissue, indicating at most a weak influence of fibrosis on lung tumour development. Results obtained in animals treated with quartz only are reported Section 3.1 (Spiethoff *et al.*, 1992).

3.9.2 *Intratracheal administration*

(a) *Rat*

Four groups of white rats, weighing approximately 100 g, were given the following treatments by intratracheal instillation: Group 1 (28 males and 30 females) received a single instillation of 50 mg/animal quartz (particle size, 82% < 2 µm) and 5 mg/animal benzo[*a*]pyrene suspended in saline [volume unspecified]; Group 2 (37 males and 33 females) received a single instillation of 50 mg/animal quartz followed four months later by a single instillation of 5 mg/animal benzo[*a*]pyrene; Group 3 (10 males and 18 females) received a single instillation of 5 mg/animal benzo[*a*]pyrene; and Group 4 (39 males and 30 females) received no treatment. The animals were observed until death and were necropsied. Lung tumours were observed in 3/11 males and 11/20 females in Group 1 that survived seven months or more (three papillomas in females; all other tumours were squamous-cell carcinomas); in 4/11 males and 0/7 females in Group 2 that survived 11.5 months or more (two papillomas and two squamous-cell carcinomas); in 0/8 males and 0/11 females in Group 3 that survived nine months or more; and in 0/16 males and 0/29 females in Group 4 that survived 16 months or more. The incidence of tumours at other sites was not related to treatment (Pylev, 1980). [The Working Group noted the absence of control groups receiving quartz without benzo[*a*]pyrene.]

(b) *Hamster*

Groups of 50 male outbred Syrian golden hamsters, seven to nine weeks of age, received the following weekly intratracheal administrations in 0.2 mL saline for 15 weeks: 3 mg/animal benzo[*a*]pyrene; 3 mg ferric oxide; 3 mg ferric oxide with 3 mg benzo[*a*]pyrene; 1.1 mg/animal Sil-Co-Sil from Ottawa Silica Sand; 1.1 mg of the Sil-Co-Sil with 3 mg benzo[*a*]pyrene; 0.7 mg Min-U-Sil; 0.7 mg Min-U-Sil with 3 mg benzo[*a*]pyrene; 7 mg/animal Min-U-Sil plus 0.3 mg/animal ferric oxide; 7 mg Min-U-Sil plus 0.3 mg ferric oxide plus 3 mg benzo[*a*]pyrene. Control animals received administrations of 0.2 mL saline alone. Survivors were killed 92 weeks after the first treatment. In addition to the tumour data presented in Table 28, bronchiolo-alveolar hyperplasia was commonly seen in the particulate plus benzo[*a*]pyrene groups and only occasionally in the particulate control groups. No pulmonary fibrosis was observed;

however, pulmonary granulomatous inflammation was significantly increased compared to saline controls in the groups receiving Sil-Co-Sil, Min-U-Sil or Min-U-Sil plus ferric oxide alone or in combination with benzo[*a*]pyrene. Results obtained in animals treated with quartz only are discussed in Section 3.3 (Niemeier *et al.*, 1986). [The Working Group noted the inadequate reporting of survival times.]

Table 28. Incidences of respiratory tract tumours in hamsters after intratracheal administration of quartz with or without benzo[*a*]pyrene^c

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

BP, benzo[*a*]pyrene

^aFrom Niemeier *et al.* (1986)

^bTypes of tumours: polyps, adenomas, carcinomas, squamous-cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas

^cStatistically significantly higher ($p < 0.00001$; two-tailed Fisher's exact test) compared with the corresponding particulate group not treated with benzo[*a*]pyrene

^dStatistically significantly higher ($p < 0.01$; two-tailed Fisher's exact test) compared with the saline plus benzo[*a*]pyrene group

3.9.3 Intrapleural administration

Rat: Eighty male SPF Sprague-Dawley rats, three months of age, were exposed by inhalation to ²²²Ra at 100% equilibrium with radon daughters for 10 h per day on four days per week for 10 weeks (dose rate of 3000 WL/day; total dose of 6000 working-level months). Sixty rats received no further treatment. Two weeks after exposure to radon, two groups of 10 rats each received a single intrapleural injection of 2 mg/animal of either DQ 12 quartz (particle size, 90% < 0.5 μm) or BRGM quartz (French quartz from Fontainblau prepared by the Bureau de Recherches Géologiques Minières, Orléans la Source, France; particle size, 90% < 4 μm) in 0.5 mL saline. The animals were observed for life span, and all were necropsied. Of the group exposed only to radon by inhalation, 17/60 developed bronchopulmonary carcinoma (28%) and 0/60 pleural or combined

pulmonary-pleural tumours. In the group receiving radon plus DQ 12 quartz, 4/10 developed bronchopulmonary carcinomas and 2/10 combined pulmonary-pleural tumours. In the group receiving radon plus BRGM quartz, 1/10 developed a bronchopulmonary carcinoma and 3/10 pulmonary-pleural tumours (Bignon *et al.*, 1983). [The Working Group noted that groups receiving quartz alone or vehicle alone were not included and that the groups receiving combined treatment were comprised of small numbers of animals.]

Diatomaceous earth

3.1 Oral administration

Rat: A group of 30 weanling Sprague-Dawley rats [sex unspecified] received each day 20 mg/animal diatomaceous earth (John Manville, Co., Denver, United States) [particle size unspecified] mixed with cottage cheese at a concentration of 5 mg/g cheese in addition to commercial rat chow and filtered tap-water *ad libitum*. The animals were observed for life span (mean survival, 840 days after the start of treatment). Five malignant tumours (one salivary-gland carcinoma, one skin carcinoma, two sarcomas of the uterus, one peritoneal mesothelioma) and 13 benign tumours (nine mammary fibroadenomas, one adrenal phaeochromocytoma and three pancreatic adenomas) were observed in treated animals. A group of 27 controls fed commercial rat chow (mean survival, 690 days) had three carcinomas (one each in the lung, forestomach and ovary) and five mammary fibroadenomas. The difference in cancer incidence between treated and control rats was not statistically significant ($0.25 < p < 0.5$, χ^2 -test) (Hilding *et al.*, 1981). [The Working Group noted the absence of a control group fed cottage cheese not containing diatomaceous earth.]

3.2 Subcutaneous administration

Mouse: A group of 36 female Marsh mice, three months old, received a subcutaneous injection of 20 mg/animal diatomaceous earth (uncalcined, commercial diatomite deposit in Lompoc, CA, United States, marketed as Celite; water content, 5.1%; particle size, 3-9 μm , with some crystalline material of larger size) suspended as a 10% slurry in isotonic saline [volume unspecified]. A group of 36 female litter-mate controls received an injection of 0.2 mL saline only. The numbers of mice still alive at 19 months were 19/36 in the treated group and 20/36 in the control group. The treated group showed an extensive reactive granulomatous and fibroplastic reaction at the site of injection but no malignant tumours (Bryson & Bischoff, 1967). [The Working Group noted the presence of crystalline material in the diatomaceous earth.]

3.3 Intraperitoneal administration

Mouse: A group of 29 female Marsh mice, three months old, received an intraperitoneal injection of 20 mg/animal diatomaceous earth (as used in the above study) suspended as a 10% slurry in isotonic saline. A group of 32 female litter-mate controls

received an injection of the same volume of saline only [volume unspecified]. The numbers of mice still alive at 19 months were 11/29 in the treated group and 19/32 in the control group. Lymphosarcomas at the injection area in the abdominal cavity were reported in 6/17 treated animals and 1/20 controls ($p = 0.02$) [method of statistical analysis unspecified] (Bryson & Bischoff, 1967). [The Working Group noted the presence of crystalline silica in the diatomaceous earth.]

Biogenic silica fibres

3.1 Intrapleural administration

Rat: Two groups of 40 young adult male SPF Sprague-Dawley rats [age not further specified] received a single intrapleural injection of 20 mg/animal biogenic silica fibres (isolated from the surface of seeds of *Phalaris canariensis*; 2×10^5 fibres per rat) or 20 mg/animal crocidolite (UICC; 10^9 fibres per rat) in 0.5 mL saline. A third group of 40 rats served as controls [vehicle-treated or untreated not specified]. One rat from each group was killed at three, six and 10 months; survivors were killed at 31 months. Nine crocidolite-treated rats developed mesotheliomas (epithelial and spindle-cell; $p < 0.01$ Fisher's exact test), whereas no epithelioma was found in rats treated with silica fibres or in controls. The total numbers of other tumours were 11 (four lung adenomas, three lymphatic vascular tumours, one thyroid tumour and three multinucleated giant-cell tumours) in crocidolite-treated rats ($p < 0.0001$; Fisher's exact test), six (two squamous carcinomas in the lung, two lymphatic vascular tumours, two leukaemias) in silica fibre-treated rats ($p < 0.1$; Fisher's exact test) and one (leukaemia) in controls. Giant-cell foci with asbestos bodies in the pleura and nearby lung tissue were found in crocidolite-treated rats [number unspecified, but at most seven] but not in silica-treated rats or in controls (Bhatt *et al.*, 1991). [The Working Group noted the lack of information on survival.]

3.2 Administration with known carcinogens

Rat: Three groups of 40 young adult male SPF Sprague-Dawley rats [age not further specified] received a single intrapleural injection of 20 mg/animal biogenic silica fibres (isolated from the surface of seeds of *Phalaris canariensis*; 2×10^5 fibres per rat), 20 mg/animal crocidolite (UICC; 10^9 fibres per rat) or 20 mg/animal silica fibres plus 20 mg/animal crocidolite in 0.5 mL saline. Two further groups of 40 rats received a single intraperitoneal injection of 0.5 mL of a 20 mg/mL suspension of 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one (11-methyl-17-ketone) in corn oil or the same intraperitoneal injection followed by a single intrapleural injection of 20 mg/animal biogenic silica fibres eight days later. A sixth group of 40 rats served as controls [vehicle-treated or untreated not specified]. One rat of each group was killed at three, six and 10 months; survivors were killed at 31 months. In the group treated with 11-methyl-17-ketone and biogenic silica fibres, the incidence of mesotheliomas was slightly increased when compared to animals receiving biogenic silica alone (see **Table 29**)

Table 29. Number and type of tumours induced in Sprague-Dawley rats after a single intrapleural injection of 20 mg/animal biogenic silica fibres alone or in combination with a single intrapleural injection of 20 mg/animal crocidolite or a single intraperitoneal injection of 10 mg/animal 15,16-dihydro-11-methylcyclopenta[α]phenanthren-17-one in saline^a

Treatment	Total no. of tumours	Mesothelioma	Lung adenoma	Lung squamous carcinoma	Lymphatic vascular tumour	Leukaemia	Multi-nucleated giant-cell tumour	Other tumours
Crocidolite	20 ^b	9 ^c	4 ^d	0	3	0	3	1 thyroid
Crocidolite + silica fibres	19 ^b	11 ^c	2	0	0	1	5	-
Silica fibres	6 ^b	0	0	2	2	2	0	-
Silica fibres + 11-methyl-17-ketone ^e	30 ^b	4 ^c	7 ^d	1	1	9 ^f	2	1 mammary gland 1 mouth 1 ear 1 urinary bladder 1 head 1 back 1 mouth 1 thymus 1 ear
11-methyl-17-ketone	25 ^{b,g}	0	8 ^d	0	0	11 ^f	1	1 mammary gland
Control	1	0	0	0	0	1	0	1 mammary gland

^aFrom Bhatt *et al.* (1991); initial number of rats, 40 per group. Groups were compared to the control group by Fisher's exact probability test: $p < 0.01$, $p < 0.01$, $p < 0.001$, $p < 0.0001$.

^b11-methyl-17-ketone = 15,16-dihydro-11-methylcyclopenta[α]phenanthren-17-one.

^c[The Working Group noted a discrepancy between this figure and the sum (24) of the different tumours in this treatment group.]

(Bhatt *et al.*, 1991). [The Working Group noted the lack of information on survival and of the persistence of fibres in body fluid.]

Synthetic amorphous silica

3.1 Oral administration

3.1.1 Mouse

Four groups of 40 male and 40 female B6C3F₁ mice, five weeks old, were fed diets containing 0 (controls), 1.25, 2.5 or 5% food-grade micronized silica (Syloid 244; SiO₂ · xH₂O; a fine white silica powder). The total intake of silica was 38.45, 79.78 and 160.23 g/mouse for males, and 37.02, 72.46 and 157.59 g/mouse for females in the low-, mid- and high-dose group, respectively. After six and 12 months, 10 animals per sex per group were killed; the remaining animals were killed at 21 months. Survival was high in all groups (data presented as cumulative survival rate curves). Mean survival was greatest in the 5%-dose group for both sexes, but there were no statistically significant differences in survival rate between groups (Mantel–Hanszel χ^2 -test). Tumour response in the silica-fed mice was not statistically significantly different from that in controls (Fisher's exact test; Cochran–Armitage test for trend) (Takizawa *et al.*, 1988) [The Working Group noted the development of tumours in the haematopoietic organs, particularly malignant lymphoma/leukaemia in females of the 2.5%-dose group, but considered the increased incidence to be random since no dose–response relationship was observed.]

3.1.2 Rat

Four groups of 40 male and 40 female Fischer rats, five weeks old, were fed diets containing 0 (controls), 1.25, 2.5 or 5% food-grade micronized silica (Syloid 244; SiO₂ · xH₂O; a fine white powder). The total silica intake was 143.46, 179.55 and 581.18 g/rat for males, and 107.25, 205.02 and 435.33 g/rat for females in the low-, mid- and high-dose group, respectively. After six and 12 months, 10 animals per sex per group were killed; the remaining animals were sacrificed at 24 months. Survival was high in all groups (data presented as cumulative survival rate curves) and highest in the 5%-dose group, but there were no statistically significant differences in mean survival rate between groups (Mantel–Hanszel χ^2 -test). Tumour response in silica-fed rats was not increased significantly in comparison to that in controls (Fisher's exact test; Cochran–Armitage test for trend) (Takizawa *et al.*, 1988).

3.2 Inhalation exposure

3.2.1 Mouse

Groups of 75 mice of a mixed strain, divided approximately equally by sex, about three months old, were either untreated or exposed by inhalation in a chamber (capacity of 600 L) to about 0.5 g per day precipitated silica [source unspecified] (particle size: 'many appeared to be about 5 μ m or less in diameter') or to ferric oxide dust once an

hour for 6 h on five days per week for one year. The animals were observed for life span. Survival at 600 days was 12/74 and 19/75 for the silica-treated and ferric oxide-treated mice, respectively, and 17/75 in the control group for silica and 13/73 in the control group for ferric oxide. The incidences of pulmonary tumours (adenomas and adenocarcinomas) in mice surviving 10 months or longer were 13/61 (21.3%) for silica-exposed animals and 5/63 (7.9%) for the controls, and 17/52 (32.7%) for ferric oxide-exposed animals and 5/52 (9.6%) for the controls. Nodular fibrotic overgrowth or hyperplasia of the tracheobronchial lymph nodes was found in 18/61 (29.5%) silica-treated mice, in 26/52 (50%) ferric oxide-treated mice and in 9/63 (14.3%) and 7/52 (13.4%) of the respective controls that survived 10 months or more (Campbell, 1940). [The Working Group noted the inadequate description of the test material and the exposure conditions.]

3.2.2 Rat

Two groups of 35 male SPF-bred Han:Wistar rats, about 10 weeks old, were exposed by inhalation in chambers (capacity 2 m³) to 10.91 mg/m³ quartz-glass (amorphous glass dust VP 203-006 with an infrared spectrum corresponding to that of silicic acid; 50%-value for the particle size distribution in the inhalation chamber was 0.42 µm) or 11.12 mg/m³ crystalline quartz (DQ 12; 99% of the particles < 4 µm; 50%-value for the particle size distribution in the inhalation chamber was 0.40 µm) for 7 h per day on five days per week for a maximal period of 12 months (in total, 251 exposure days during 56 weeks). A similar group of unexposed male rats served as controls. After four and eight months, five rats from each group and, after 12 months, 15 rats of each of the exposed groups and 10 controls were killed. The remaining survivors were kept for a 12-month post-exposure period. Six rats of the quartz-glass group, three rats of the crystalline-quartz group and three controls died or were killed because they were seriously injured during fighting with their cage mates, resulting in 4/35, 7/35 and 7/35 survivors in the respective groups at the end of the study [survival not further specified]. Only one primary respiratory tract tumour was found, namely a squamous-cell carcinoma of the lung in a crystalline-quartz-treated animal. The major non-neoplastic pulmonary change in quartz-glass-exposed rats was slight, focal cellular reaction with minimal fibrosis; lungs of crystalline-quartz-exposed rats showed severe macrophage reaction, fibrosis, emphysema and focal adenoid transformation of type II pneumocytes. Mediastinal lymph nodes in both exposed groups were strongly enlarged and showed severe fibrosis with bundles of hyalinized collagen fibres (Rosenbruch *et al.*, 1990). [The Working Group noted the small number of animals surviving to two years.]

3.3 Intratracheal administration

Hamster: Two groups of 24 male and 24 female randomly bred Syrian golden hamsters, six to seven weeks of age, received weekly intratracheal instillations of 3 mg/animal silica (fine particles) [the nature of the sample was not further described, except that it was obtained from Sigma Chemical Co., St Louis, MO, United States; the company's catalogues first described the item as amorphous silica and subsequently as

a mixture of amorphous and crystalline particles, particle size unspecified] or 1.5 mg/animal manganese dioxide (fine particles) [particle size not further specified] in 0.2 mL saline for 20 weeks and were maintained for the duration of their life span. A control group of 24 males and 24 females received saline alone, and a group of 50 males and 50 females served as untreated controls. Survival rates in the treated groups were comparable; all animals were dead by 80 weeks. Untreated controls had a better survival (at week 80, 13/100 were still alive). No respiratory-tract tumours and no pulmonary granulomas were observed. However, both silica and manganese dioxide produced a minimal (silica) to slight (manganese dioxide) fibrotic response in the lungs (Stenbäck & Rowland, 1979). [The Working Group noted the limited survival and the uncertainty of the nature of the test material.]

3.4 Intrapleural administration

Rat: Groups of 30 female SPF Osborne-Mendel rats, 11–16 weeks of age, received an intrapleural implantation, through thoracotomy, of a coarse fibrous glass pledget. On one side of the pledget was spread 1.5 mL of 10% gelatin containing 40 mg of either Cab-O-Sil (prepared by flame hydrolysis of silicon tetrachloride; agglutinated clumps of minute spheres with a size of 0.05–0.15 μm ; 99.9% pure) or silica soot (prepared by flame hydrolysis of silicon tetrachloride; size, 0.005–0.015 μm ; 99.9% pure). A group of 90 controls received the gelatin-covered pledget alone. Rats were observed for two years, and terminal sacrifice was performed during the 25th month. In the Cab-O-Sil-treated group, 1/18 rats surviving one year or more developed a mesothelioma; no respiratory-tract tumour was observed in the 24 silica soot-treated rats or in the 58 controls that survived one year or more (Stanton & Wrench, 1972).

3.5 Administration with known carcinogens

3.5.1 Intratracheal administration

Hamster: Groups of 24 male and 24 female randomly bred Syrian golden hamsters, six to seven weeks of age, received weekly intratracheal instillations of 3 mg/animal silica (fine particles) [the nature of the silica sample was not further described, except that it was obtained from Sigma Chemical Co., St Louis, MO, United States; the company's catalogues first described the item as amorphous silica and subsequently as a mixture of amorphous and crystalline particles, particle size unspecified] or 1.5 mg/animal manganese dioxide (fine particles) [particle size not further specified], 3.0 mg/animal benzo[*a*]pyrene (ground for 24 h in a mullite mortar; particle size, 100% < 20 μm , 98% < 10 μm , 79% < 5 μm , 5% < 1 μm), a mixture of 3.0 mg/animal silica and 3.0 mg/animal benzo[*a*]pyrene (prepared by ball-milling the suspensions together for seven days) [particle size of the mixed dust unspecified] in 0.2 mL saline for 20 weeks. A control group of 24 males and 24 females received saline alone, and a group of 50 males and 50 females served as untreated controls. Survival at 50 weeks was 18/48 saline controls, 13/48 silica-treated, 9/48 manganese dioxide-treated, 15/46 benzo[*a*]pyrene-treated, 19/48 silica plus benzo[*a*]pyrene-treated and 16/46 manganese dioxide plus

benzo[*a*]pyrene-treated animals and 75/100 untreated controls. The incidences of respiratory-tract tumours were 0/48 saline controls, 0/48 silica-treated, 0/48 manganese dioxide-treated, 5/48 benzo[*a*]pyrene-treated (one papilloma and one squamous-cell carcinoma of the larynx, four papillomas of the trachea), 21/48 silica plus benzo[*a*]pyrene-treated (eight papillomas of the trachea, one squamous-cell carcinoma of the larynx, two of the trachea and three of the bronchus/lung, three adenocarcinomas and six adenomas of the bronchus/lung) [$p < 0.001$ as compared to benzo[*a*]pyrene alone] and 5/46 manganese dioxide plus benzo[*a*]pyrene-treated (one papilloma of the larynx and three of the trachea, one squamous-cell carcinoma of the respiratory tract) animals and 0/100 untreated controls. Bronchiolar and alveolar adenomatoid lesions were frequently encountered in animals treated with silica plus benzo[*a*]pyrene; these lesions occurred much more frequently in animals treated with manganese dioxide plus benzo[*a*]pyrene and were not seen at all in any of the other groups (Stenbäck & Rowland, 1979). The authors later reported similar effects with silica and with other dusts, such as ferric oxide, titanium dioxide and talc, mixed with benzo[*a*]pyrene (Stenbäck *et al.*, 1986). [The Working Group noted that the silica tested might have been a mixture of amorphous and crystalline silica.]

Crystalline silica plus ferric oxide

3.1 Intratracheal administration

Hamster: Four groups of 25–27 male outbred (LAK:LVG) Syrian golden hamsters, 11 weeks old, received weekly intratracheal instillations of 0.03, 0.33, 3.3 or 6.0 mg/animal quartz (Min-U-Sil; particle diameter: median, $0.84 \pm 0.07 \mu\text{m}$; average, $1.06 \pm 0.07 \mu\text{m}$; mass median, $3.14 \pm 0.24 \mu\text{m}$; mass aerodynamic, $5.13 \pm 0.40 \mu\text{m}$) in saline [volume unspecified] for 15 weeks. A further four groups of 24–28 hamsters received the same treatment with the same quartz to which an equal dose of ferric oxide (particle diameter: median, $0.27 \mu\text{m}$; average, $0.29 \mu\text{m}$; mass median, $0.60 \mu\text{m}$; mass aerodynamic, $1.37 \mu\text{m}$; 'the ferric oxide sample was highly aggregated; the ultimate particle size appeared to be 0.02 mm ') was added. Groups of 27 saline-treated and 25 untreated hamsters served as controls. Animals were killed when moribund or when survival within the groups reached 20%; termination of the study was at 24.5 months of age. The average survival times were 498 ± 44 , 506 ± 41 , 383 ± 31 ($p < 0.005$ compared with saline-treated controls) and 348 ± 26 days ($p < 0.005$ compared with saline-treated controls) for the 0.03-, 0.33-, 3.3- and 6.0-mg quartz-treated groups, respectively, 558 ± 32 , 578 ± 28 , 379 ± 37 ($p < 0.005$ compared with saline-treated controls) and 335 ± 32 days ($p < 0.005$ compared with saline-treated controls) for the four quartz plus ferric oxide-treated dose groups, respectively, and 534 ± 35 and 595 ± 14 days for the saline and untreated controls, respectively. No pulmonary tumour was observed in any of the groups. In animals treated with quartz or quartz plus ferric oxide, dose-related alveolar septal fibrosis (of slight to moderate degree), granulomatous inflammation and alveolar proteinosis were observed in the lung, but no animal developed nodular fibrosis or foci of dense fibrous tissue in the lung (Renne *et al.*, 1985).

Three groups of 50 male outbred Syrian golden hamsters, seven to nine weeks old, received weekly intratracheal instillations of 0.7 mg/animal Min-U-Sil ($5\ \mu\text{m}$; surface area, $0.0021\ \text{m}^2$), 3.0 mg/animal ferric oxide or 0.7 mg/animal Min-U-Sil plus 3.0 mg/animal ferric oxide in 0.2 mL saline. A fourth group of 50 vehicle controls received instillations of 0.2 mL saline alone. Survivors were killed 92 weeks after first treatment. Survival in the Min-U-Sil plus ferric oxide group was statistically significantly lower than in the Min-U-Sil or the control group ($p < 0.05$). One adenosquamous carcinoma of the bronchi and lungs was observed in the Min-U-Sil group at week 68 (effective number of animals, 35), and one benign tumour (papilloma or adenoma) of the larynx was seen in the ferric oxide group at week 62 (effective number of animals, 34). No respiratory tract tumour was observed in the 49 animals treated with Min-U-Sil plus ferric oxide or in the 48 controls. Slight bronchiolo-alveolar hyperplasia was occasionally found in particulate-treated animals. No pulmonary fibrosis was observed. However, pulmonary granulomatous inflammation was significantly increased in Min-U-Sil- and Min-U-Sil plus ferric oxide-treated animals (Niemeier *et al.*, 1986).

Amorphous silica plus ferric oxide

Inhalation exposure

Mouse: Groups of 75 mice of a mixed strain, divided approximately equally by sex, about three months of age, were exposed daily to about 0.5 g/animal precipitated silica [source unspecified] (particle size: 'many appeared to be about $5\ \mu\text{m}$ or less in diameter'), ferric oxide dust or a 1 : 1 mixture of the two dusts [exposure concentrations unspecified] in an inhalation chamber (600 L) once an hour for 6 h on five days per week for one year and observed for life span. Groups of 75 controls of both sexes were used; survival at 600 days was 17/75 in the control group for silica and 13/73 in the control group for ferric oxide or the mixture. Survival at 600 days was as follows: 12/74 in the silica-treated group; 19/75 in the ferric oxide-treated group; and 18/74 in the silica plus ferric oxide-treated group. The incidences of pulmonary tumours (adenomas and adenocarcinomas) in mice surviving 10 months or more were 5/63 (7.9%) and 5/52 (9.6%) in the control groups, 13/61 (21.3%) for silica alone, 17/52 (32.7%) for ferric oxide alone and 12/62 (19.3%) for silica plus ferric oxide. Nodular fibrotic overgrowth or hyperplasia of the tracheobronchial lymph nodes was found in 18/61 (29.5%) silica-treated mice, in 26/52 (50%) ferric oxide-treated mice, in 22/62 (35.5%) silica plus ferric oxide-treated mice, in 9/63 (14.3%) controls for silica, and in 7/52 (13.4%) controls for ferric oxide and for the mixture (Campbell, 1940). [The Working Group noted the inadequate description of the test material and the exposure conditions.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Deposition, distribution, persistence and biodegradability

4.1.1 Humans

(a) Deposition

The deposition of a respirable particle is a function of its aerodynamic diameter, which is defined as the diameter of a sphere of unit density having the same terminal settling velocity as the particle itself (Jones, 1993). The site of deposition in the respiratory tract is dictated by the aerodynamic diameter. In humans, while large particles with an aerodynamic diameter greater than 10 μm will deposit in the upper respiratory tract, only those below 10 μm will deposit with any efficiency in the tracheobronchial region; for the alveolar region, deposition only begins to become substantial with aerodynamic diameters well below 10 μm (Task Force Group on Lung Dynamics, 1966).

Deposition of particles in the respiratory bronchioles and proximal alveoli results in slow clearance, interaction with macrophages and a greater likelihood of lung injury. This contrasts with deposition on the conducting airways where the majority of the particles are cleared by the mucociliary escalator. Therefore, quartz particles with an aerodynamic diameter below 10 μm are likely to be the most harmful to humans.

(b) Distribution and clearance

There are few data on human lung quartz-dust burdens that allow conclusions to be drawn about deposition or clearance. However, quartz is found in the bronchoalveolar macrophages and sputum of silicotic patients (Sébastien, 1982; Porcher *et al.*, 1993). Also, at autopsy, there is wide variation in the masses and proportions of quartz retained in the lung (Verma *et al.*, 1982; Gibbs & Wagner, 1988). For example, Verma *et al.* (1982) reported 25–264 mg per single lung at autopsy in hard-rock miners with 14–36 years of exposure; these miners had variable amounts of pathological response but there was not a good correlation between lung crystalline quartz content and pathological score. The well-documented effect of smoking on clearance (Morgan, 1984) is a further confounding factor in drawing conclusions about clearance kinetics in humans.

(c) Biopersistence of silica

The physico-chemical changes in quartz that result from residence in the lung could be an important factor in determining the continuing toxicity of quartz to the lung following deposition. As a response to the rejection of the 'mechanical model' of silicosis, which had propounded that any particle with 'sharp or jagged edges' might injure tissue, a solubility theory of silicosis was proposed. The solubility theory was based on the release from silica of silicic acid, which was considered to be a 'protoplasmic poison' (King & McGeorge, 1938; King, 1947). In fact very little dissolution occurs; for example, 9 mg SiO_2 (0.45%) was released from 2 g crystalline silica placed in

ascitic fluid for two weeks (King & McGeorge, 1938). Current theories no longer consider that the dissolution of quartz contributes substantially to its clearance or to changes in its biological activity (Vigliani & Pernis, 1958; Heppleston, 1984). Indeed there is evidence of enrichment of crystalline silica in lungs of individuals exposed to hard rock compared to the dust in the air they breathed (Verma *et al.*, 1982), suggesting that crystalline silica is less-efficiently cleared, either by dissolution or mechanical clearance, than the non-silica mineral components of the dust. In the study of Pairon *et al.* (1994), biopersistence was assessed in occupationally exposed subjects by counting silica particles in bronchoalveolar lavage (BAL) fluid after varying periods of time since their last occupational exposure. Crystalline silica was found to be among the most biopersistent of non-fibrous mineral particles.

4.1.2 *Experimental systems*

(a) *Deposition*

Animals such as the rat demonstrate different alveolar deposition patterns from humans, with negligible deposition of particles of aerodynamic diameter above 6 μm . This variation arises because of differences in the mode (mouth and nose) and pattern (cycle period and tidal volume) of inhalation between the species (Jones, 1993); these factors need to be considered in the interpretation of animal studies.

Quartz particles with an aerodynamic diameter below 6 μm are likely to be most harmful in rats. Brody *et al.* (1982) confirmed, in rats exposed short term to 109 mg/m^3 quartz (high purity Thermal Americal Fused Quartz Co.), that there was a substantial deposition on the alveolar duct/terminal bronchiolar surfaces of silica particles with an average aerodynamic diameter of 1.4 μm (range, 0.3–4.0 μm). In another inhalation study in rats, which used Min-U-Sil silica of aerodynamic diameter 3.7 μm , more than 80% of the particles that deposited peripherally were found on the alveolar ducts, particularly their bifurcations, and on the distal terminal bronchioles (Warheit *et al.*, 1991a).

(b) *Distribution and clearance*

Immediately following deposition of quartz on the surface of the mammalian lung, there is either rapid mucociliary clearance if deposition is in the upper airways, or phagocytosis by alveolar macrophages and slower clearance if deposition is in the lung periphery (Brody *et al.*, 1982; Warheit *et al.*, 1991a). There are differences between species in terms of clearance rates (Oberdörster, 1988; Jones, 1993), with clearance from the lungs of humans, dogs and guinea-pigs being slower than from the lungs of rats and hamsters.

Clearance by mucociliary mechanisms is generally considered to be efficient; clearance from the lung periphery is slow and incomplete, i.e. there is a sequestered dust fraction that is never cleared (Morgan, 1984; Vacek *et al.*, 1991).

A number of possible fates of particles after deposition in the lung periphery have been suggested: (i) phagocytosis by macrophages followed by migration to the mucociliary escalator for clearance; (ii) persistent macrophage accumulations in the airspaces (Stöber *et al.*, 1989); (iii) penetration to the interstitium for phagocytosis by interstitial

macrophages and possible exudation back on to the alveolar surface (Vacek *et al.*, 1991); (iv) penetration to the interstitium; and (v) translocation to the lymph nodes (McMillan *et al.*, 1989; Absher *et al.*, 1992). All of these possibilities, except the first, would result in slower clearance or sequestration.

The kinetics of deposition and clearance of quartz have been successfully studied in the rat model. In rats, three days after a 3-h inhalation exposure to quartz, it was observed (using scanning electron microscopy) that the particles that had deposited on the terminal bronchiolar and alveolar duct surfaces were translocated into epithelial cells and to the interstitium (Brody *et al.*, 1982). McMillan *et al.* (1989) reported impaired clearance of an inhaled, relatively innocuous particle of similar size, titanium dioxide, during concomitant inhalation of Sykron F600 quartz. Furthermore, analysis of the lymph nodes revealed that the decreased lung burden could be largely explained by translocation of the quartz to the lymph nodes. More recently, Vacek *et al.* (1991) monitored the disposition of Min-U-Sil 5 quartz and C&E Mineral Corp. cristobalite in alveolar fluid, free cells, lung tissue and lymph nodes over six months following eight days of exposure of rats for 7 h per day to 11–65 mg/m³ particles with a mass median aerodynamic diameter of around 1.0 µm. Twenty-four hours were allowed to elapse for tracheobronchial clearance and thereafter rats were killed at regular time-points for assessment of the lung burden in the various compartments. The data were then applied to a number of mathematical models and the best fit determined. The model that fitted the data best used no clearance of quartz via the mucociliary escalator, which was explained by the relative toxicity of the cristobalite and Min-U-Sil to macrophages, preventing their movement. Donaldson *et al.* (1990a) demonstrated that alveolar macrophages from rats inhaling Sykron F600 quartz were indeed impaired in their ability to migrate in response to a standard chemotactic signal, C5a. The model of Vacek *et al.* (1991) also showed considerable transfer of quartz to the lymph nodes and to another, notional, compartment. The continued accumulation of quartz in the lymph nodes up to 150 days after cessation of exposure in this model of cristobalite silicosis (Absher *et al.*, 1992) reveals the dynamic nature of the redistribution of cristobalite that occurs following deposition. The same laboratory (Hemenway *et al.*, 1990) also described clearance of C&E Mineral Corp. cristobalite and two types of quartz (Min-U-Sil 5 and Thermal American Fused Quartz Co.; TAFQ), which had similar aerodynamic diameters, following inhalation exposure in rats. There were very large differences in the clearance of the three samples, with cristobalite being cleared markedly more slowly than the two types of quartz. These differences have been a result of the greater severity of lung injury and inflammation caused by inhalation of cristobalite compared to the two quartz types.

Heating of CRS cristobalite increased its accumulation in the lungs and lymph nodes. TAFQ quartz heated to 800 °C for 24 h was found in high amounts in the thymus and lymph nodes of rats exposed by inhalation; an unheated sample was biologically inactive (Hemenway *et al.*, 1994).

A physiologically based kinetic model of quartz deposition and lung response suggested the probable importance of interstitialization of quartz, followed by interstitial inflammation, in the development of silicosis (Tran *et al.*, 1996). Transport of Sykron

F600 quartz to the lymph nodes has been found to coincide with the onset of inflammation (Vincent & Donaldson, 1990) in a rat model of ongoing quartz exposure. Inflammatory leukocytes from DQ 12 quartz-exposed lung have been shown to cause loss of integrity and detachment of epithelial cell monolayers in culture (Donaldson *et al.*, 1988a), which may be a factor that promotes the interstitialization of quartz in the inflamed lung.

More experimental evidence for the importance of interstitialization in the pathogenic effects of silica comes from Adamson (1992) who demonstrated that depletion of the macrophage defences in male Swiss-Webster mice by 6.5 Gy whole body irradiation allowed increased interstitial access of quartz particles (Dowson & Dobson). This led to enhanced phagocytosis by interstitial macrophages, which in turn led to a florid interstitial response with fibroplasia and collagen accumulation. This study emphasized the importance of the macrophage response in dealing with deposited quartz. The same laboratory (Adamson *et al.*, 1994) showed that generation of a controlled inflammatory response in the alveolar space by instillation of *N*-formyl-L-methionyl-leucyl-phenylalanine (FMLP), a leukocyte chemotactic factor, ameliorated the harmful effects of quartz. In this case, mice received an instillation of quartz and a subgroup received an instillation of FMLP two to three weeks later. The quartz plus FMLP-treated rats showed significantly lower lung tissue burden and lymph node burden of quartz, which resulted in less fibrosis. This outcome was interpreted to be a consequence of the attraction of quartz-loaded macrophages from the interstitium into the alveolar space, with concomitant lowering of the interstitial dose of quartz and the dose available for lymphoid transport.

Amorphous silica is cleared more quickly from the lungs of rats than quartz. For instance, rats inhaling Ludox colloidal amorphous silica at 50 or 150 mg/m³ showed clearance half-times of 40 and 50 days, respectively (Lee & Kelly, 1992). This contrasts with half-times of > 125 days for rats inhaling cristobalite (Hemenway *et al.*, 1990), while Driscoll *et al.* (1991) described only 20% clearance of Min-U-Sil quartz 20 days after a five-day inhalation of 50 mg/m³.

4.2 Toxic effects

4.2.1 Humans

Crystalline silica

In humans, exposure to crystalline silica causes the following range of non-neoplastic pulmonary effects:

(a) Inflammation

Bégin (1986) and Rom *et al.* (1987) described increased uptake of ⁶⁷Ga, an index of inflammatory macrophage activation, in the lungs of silicotics. Increases in neutrophils, macrophages and lymphocytes in the BAL fluid of silica-exposed populations was reported by Bégin (1986), while Rom *et al.* (1987) found increases only in lymphocytes in a population of silicotics. In another BAL study, healthy granite workers showed only

a modest, insignificant increase in neutrophils in BAL fluid, although an increase in lymphocytes was significant (Christman *et al.*, 1985). A study of granite workers with silicosis in Québec, Canada, showed a 2.4-fold increase in macrophage numbers and a 4.4-fold increase in lactate dehydrogenase (LDH), suggesting that cell death occurred in the silicotic lung (Bégin *et al.*, 1993) (see Table 30).

(b) *Silicosis*

Silicosis has been detected by X-ray (e.g. Graham, 1992), lung-function testing (e.g. Ng & Chan, 1992) and computed tomography (CT) scan (e.g. Bégin *et al.*, 1988). Parkes (1994) described the following four different types of silicosis:

- (1) Nodular fibrosis — comprising collagenous nodular lesions with a substantial content of quartz. These nodules arise focally in macrophage/reticulin complexes within the interstitium at the level of the respiratory bronchioles and become progressively more collagenized until the full-blown silicotic nodule arises; as they evolve, the nodules become more-or-less hyalinized, necrotic or calcified (Graham, 1992). Progressive massive fibrosis (PMF) arises from the agglomeration of nodules (Silicosis and Silicate Disease Committee, 1988) possibly as a result of high focal quartz content (Leibowitz & Goldstein, 1987).
- (2) Mixed dust fibrosis — less-well-defined stellate fibrotic lesions of radially arranged collagen strands and dust-containing macrophages caused by exposure to free silica plus an inert material (Silicosis and Silicate Disease Committee, 1988).
- (3) Diffuse interstitial pulmonary fibrosis — this type of focal interstitial change is associated with combined exposure to silica plus other silicate minerals, e.g. in foundries and diatomaceous earth processing plants where cristobalite is present (Silicosis and Silicate Disease Committee, 1988).
- (4) Rapidly occurring diffuse interstitial pulmonary fibrosis with alveolar lipoproteinosis (acute or accelerated silicosis) — this condition develops after heavy exposure to silica-containing dust (e.g. during sandblasting) and is progressive in the absence of further exposure (Silicosis and Silicate Disease Committee, 1988); the patient often dies of respiratory failure.

(c) *Lymph node fibrosis*

Silicotic mediastinal adenopathies were found in two workers exposed to cristobalite during the changing of diatomaceous earth-containing filters in breweries (Nemery *et al.*, 1992).

Preferential transport of quartz to the lymph nodes in lungs exposed to mixed dust has been described by Chapman and Ruckley (1985) and hilar and mediastinal lymph nodes frequently show silicotic nodules at autopsy (Silicosis and Silicate Disease Committee, 1988) with calcification in some cases (Sargent & Morgan, 1980). In a necropsy study, fibrosis of the lymph nodes appeared to be a factor that predisposed to parenchymal silicosis (Murray *et al.*, 1991).

Table 30. Bronchoalveolar lavage (BAL) fluid leukocyte populations in crystalline silica-exposed populations

Reference	No. of subjects examined	BAL cell differential (%) \pm SD			Comments
		Macrophage	Lymphocyte	Neutrophil	
Rom <i>et al.</i> (1987)					
Controls	28	83 \pm 2	15 \pm 2	2 \pm 2	Silicotic subjects reported to have radiographic evidence of silicosis; ILO classification \geq 1/0
Silicotics	6	74 \pm 7	22 \pm 7	4 \pm 2	
Rom (1991)					
Controls	28	83 \pm 2	15 \pm 2	2 \pm 2	Same controls as from Rom <i>et al.</i> (1987) Average of 21 years occupational silica exposure in potteries, foundries, quartz mills or working with diatomaceous earth
Silicotics	13	72 \pm 4	25 \pm 5	3 \pm 1	
Schuylar <i>et al.</i> (1980)					
Controls	10	99.0 \pm 0.8"		1.0 \pm 1.6	Controls were smokers All silicotics had greater than 1 cm nodules on radiographs; all silicotics were smokers
Silicotics	6	99.5 \pm 0.8"		0.5 \pm 0.8	
Christman <i>et al.</i> (1985)					
Controls	27	92.1 \pm 1.8	6.5 \pm 1.8	1.1 \pm 0.2	All granite workers had a minimum of 4 years occupational silica exposure; no radiographic evidence of silicosis
Granite workers	9	82.0 \pm 3.9	15.5 \pm 3.5	2.3 \pm 0.5	
Bégin <i>et al.</i> (1986)					
Controls	19	~90	~8	ND	Silicotics were described as having increased ^{67}Ga uptake and/or radiographic evidence of silicosis
Silicotics	17	~85	~14	~1	
Bégin <i>et al.</i> (1993)					
Controls	15	69.1 \pm 2.3	28.1 \pm 2.1	1.7 \pm 0.4	All non-smokers for a minimum of two years prior to study All silicotics were reported to have chest radiographs indicating simple or confluent silicosis; all non-smokers for a minimum of two years prior to study
Silicotics	28	78 \pm 4.1	17.8 \pm 3.6	2.2 \pm 1.2	

" Mononuclear cells; macrophages and lymphocytes were not differentiated
SD, standard deviation; ND, not detected

(d) *Airways disease*

Neukirch *et al.* (1994) described chronic airflow limitation that was independent of radiographic change in pottery workers exposed to silica dust. Cowie and Mabena (1991) reported chronic airflow limitation afflicting all of a population of South African gold miners who were exposed to silica-containing dust, as well as symptoms of bronchitis in men who worked in the dustiest occupations. Ng and Chan (1992) reported obstructive impairment of lung function in active and retired granite workers and that was related to the extent of radiological opacities. Using a sensitive measure of airway function, Chia *et al.* (1992) demonstrated significant small airways obstruction associated with silica dust exposure in the absence of radiological evidence of silicosis among currently employed granite quarry workers. Hnizdo (1990) noted a synergistic effect of smoking and gold-mine dust exposure in leading to death from chronic obstructive lung disease, with 5% of deaths from chronic obstructive lung disease being attributable to dust alone, 34% from smoking and 59% from the combined effects of dust and smoking.

(e) *Emphysema*

An association has been demonstrated between emphysema and exposure to silica-containing dusts or silicosis (Becklake *et al.*, 1987; Hnizdo & Sluis-Cremer, 1991; Cowie *et al.*, 1993; Leigh *et al.*, 1994). In non-smoking South African gold miners with a long duration of exposure, only a minimal degree of emphysema was found at autopsy (Hnizdo *et al.*, 1994). Using CT, 48 out of 70 men who had worked underground for an average of 29 years in the gold mining industry were found to have emphysema (Cowie *et al.*, 1993).

(f) *Epithelial effects*

Increased permeability of the airspace epithelium to inhaled small molecular weight compounds is a feature of smokers (Minty *et al.*, 1981) and is considered to play a role in the development of lung inflammation in smokers. Nery *et al.* (1993) reported that the airspace epithelium of non-smoking silicotics was more permeable than that of normal individuals and that there was an additive effect in smoking silicotics, who showed a markedly increased permeability. Hyperplastic type II cells were found in increased numbers in the BAL of silicotics (Schuyler *et al.*, 1980) even years after cessation of exposure to silica, suggesting ongoing injury and proliferation.

(g) *Tuberculosis*

The highly fatal consumptive disease of the lungs in hard-rock miners, described by G. Agricola in the sixteenth century, is thought to have resulted from exposure to quartz, arsenic and uranium in the presence of tuberculosis (TB). However, despite the dramatic reduction in the prevalence of TB in the twentieth century, a South African study recently reported that the annual incidence of TB was 981/100 000 in men without silicosis and 2707/100 000 in men with silicosis (Cowie, 1994). In a study of 5406 underground haematite miners in China, 25% of the workers had silicosis and 42% of these silicotics had TB (Chen *et al.*, 1989).

(h) *Extra-pulmonary effects of silica*

Silica exposure has been found to have a number of extra-pulmonary effects and indeed the term 'extrapulmonary silicosis' has been coined (Slavin *et al.*, 1985). This term encompasses the spread of lesions to the liver, spleen, kidneys, bone marrow and extrathoracic lymph nodes. Silicosis of the liver has been especially well documented (reviewed in Slavin *et al.*, 1985).

Abnormal renal function has been recorded in silica-exposed individuals with and without silicosis (Hotz *et al.*, 1995). Also, a relationship has been described between length of exposure to silica and to severity of renal dysfunction (Ng *et al.*, 1993). However, in another case-control study, silicosis was associated with renal alterations but there was no relationship between the loss of renal function and the length of exposure or severity of silicosis (Boujemaa *et al.*, 1994). Persistence of renal effects after cessation of silica exposure was reported in the study of Ng *et al.* (1992). A relationship between rapidly progressive glomerulonephritis and silica exposure was shown in a hospital-based case-control study by Gregorini *et al.* (1993), and Michigan men with exposure to silica were found to have an elevated odds ratio for end-stage renal disease (Goldsmith & Goldsmith, 1993). The presence of silica within the renal tubules was reported in one case study of silica-related glomerulonephritis (Osornio *et al.*, 1987). Systemic sclerosis-like (scleroderma-like) disorders have been reported following exposure to silica (Cowie & Dansey, 1990; Haustein *et al.*, 1990; Rustin *et al.*, 1990).

Abrasion-related deterioration in dental health has been recorded in Danish granite workers (Petersen & Henmar, 1988), and evidence of increased incidence of rheumatoid arthritis was found in Finnish granite workers (Klockars *et al.*, 1987). Occasionally, cutaneous exposure to silica causes granulomas that may mimic cutaneous sarcoidosis (Mowry *et al.*, 1991) or granulomatous cheilitis (Harms *et al.*, 1990).

Amorphous silica-mixed dust

Two studies of exposed workers have suggested that amorphous silica causes airflow limitation; these studies found no evidence of pneumoconiotic effects. In 172 potato workers exposed to inorganic dust (7.7–15.4 mg/m³) high in diatomaceous earth and crystalline quartz (10%) (the soil was overlying a marine deposit), airflow limitation was noted in retired workers (> 20 years of exposure) and workers currently exposed (12 years). No radiological or biochemical (serum type III procollagen) evidence of pulmonary fibrosis was present (Jorna *et al.*, 1994). Another study of 759 agricultural workers in California, United States, revealed reduced FVC in 238 grape workers and suggested mixed silica-dust exposure to be the cause (Gamsky *et al.*, 1992). However, other exposures could have caused this effect.

4.2.2 *Experimental systems*

Crystalline silica has been reported to cause a range of effects in experimental animals and cells *in vitro*.

(a) *In-vivo effects of silica*

(i) *Inflammation*

Exposure of rats to crystalline silica results in a marked inflammatory response characterized by a high percentage of neutrophils (see **Table 31**).

Female Fischer 344 rats were exposed by inhalation to air, 0.1, 1.0 or 10 mg/m³ quartz (Min-U-Sil) for 6 h per day on five days per week for four weeks (Henderson *et al.*, 1995). The mass median aerodynamic diameter of the aerosol was 1.3–2.0 µm. Lung responses were characterized by analysis of BAL fluid one, eight and 24 weeks after exposure and by histopathology 24 weeks after exposure. Mean lung burdens, determined one week after the end of exposure, were 43, 190 and 720 µg/mg quartz for the low-, mid- and high-exposure levels. Exposure to 10 mg/m³ resulted in lung injury and inflammation demonstrated by progressive increases in BAL fluid neutrophils and lactate dehydrogenase. Exposure to 1.0 mg/m³ quartz resulted in a transient increase in BAL fluid neutrophils one week after exposure. Histopathology 24 weeks after exposure to 10 mg/m³ demonstrated an active-chronic inflammatory response associated with the bronchial-associated lymphoid tissues, interstitium and intrapleural regions. In this study, exposure to 0.1 mg/m³ quartz had no apparent effects with no changes in BAL fluid or histopathology.

Exposure of rats to quartz (Sykron F600; Min-U-Sil 5) by inhalation produced a time-dependent and dose-dependent accumulation of macrophages and neutrophils in the BAL fluid (Donaldson *et al.*, 1988b; Warheit *et al.*, 1991a; Velan *et al.*, 1993). The inflammation persisted after the end of exposure and progressed in the rats that had received high exposures (Donaldson *et al.*, 1988b, 1990b) suggesting a mechanism for the well documented progressive nature of silicosis. In contrast, a similar airborne mass concentration of Ludox colloidal amorphous silica caused only very modest neutrophilic inflammation that resolved over a three-month recovery period (Warheit *et al.*, 1991b; Lee & Kelly, 1993). Following long-term, moderate inhalation exposure of rats, guinea-pigs and adult male cynomolgus monkeys to amorphous silica (origin not stated), Groth *et al.* (1981) reported that, histologically, only the monkeys showed evidence of inflammatory macrophage accumulations and early silicotic lesions, suggesting species differences in deposition, clearance or response to this material. [The Working Group noted that no information was provided on species differences in lung dust burdens.]

Instillation of quartz in rats (Dowson & Dobson; DQ 12; Moores *et al.*, 1981; Brown *et al.*, 1991), guinea-pigs (Min-U-Sil; Lugano *et al.*, 1982) and Syrian hamsters (Min-U-Sil; Beck *et al.*, 1982) caused neutrophilic inflammation that persisted over time. Quartz (Dowson & Dobson)-induced inflammation is reflected in increases in BAL lysosomal enzyme levels in mice (Adamson & Bowden, 1984). Increased phospholipids were also recovered, which may arise from type II cell proliferation in rats in response to epithelial injury caused by Min-U-Sil (Heppleston *et al.*, 1974) or natural sand (Eklund *et al.*, 1991). In general, these responses were more persistent and of greater magnitude than those seen with low-toxicity dusts particles such as latex, titanium dioxide or iron.

In comparative tests, the inflammation and acute lung injury caused by freshly fractured (milled) quartz was much greater in intensity than that caused by aged quartz

Table 31. Bronchoalveolar lavage (BAL) cell populations in rats exposed to crystalline silica

Reference	Treatment	Exposure method	Cell differential (%)			Comments
			Macrophages	Lymphocytes	Neutrophils	
Hemenway <i>et al.</i> (1986)	Air (control)	inh.	98	1	1	Results are for 120 days after exposure.
	Quartz 36 mg/m ³ 6 h/day × 8 days	inh.	93	2	5	
	Cristobalite 73 mg/m ³ 6 h/day × 8 days	inh.	50	3	45	
Donaldson <i>et al.</i> (1988b, 1990b)	Quartz (Sykron F600) 10 mg/m ³ 7 h/day, 5 days/week × 15 weeks	inh.	51.3	NR	48.7	Control rats (air exposed only) were reported to contain predominantly macrophages in BAL fluid.
	Quartz (Sykron F600) 50 mg/m ³ 7h/day, 5 days/week × 15 weeks	inh.	46.9	NR	53.1	
Muhle <i>et al.</i> (1991)	Air (control)	inh.	97.2	1.7	1.1	Results are for 24 months of exposure. The mean lung SiO ₂ burden was 0.9 mg.
	Quartz (DQ 12) 1 mg/m ³ , 6 h/day, 5 days/week × 15 months × 21 months	inh.	21.3	13.0	65.8	
	Quartz (DQ 12) 1 mg/m ³ , 6 h/day, 5 days/week × 15 months × 24 months	inh.	31.3 38.9	17.6 13.3	51.1 47.8	
Driscoll <i>et al.</i> (1991)	Air (control)	inh.	97.0	2.0	1.0	Mean lung SiO ₂ burden at the end of exposure was 1.9 mg; results are for 63 days after the 5-day exposure.
	Quartz (Min-U-Sil), 50 mg/m ³ , 6 h/day × 5 days	inh.	62.0	6.8	31.0	
Warheit <i>et al.</i> (1991a)	Air (control)	inh.	99	NR	1	Results are for 2 months after exposure
	Quartz 100 mg/m ³ 6h/day, 3 days	inh.	50	NR	50	

Table 31 (contd)

Reference	Treatment	Exposure method	Cell differential (%)			Comments
			Macrophages	Lymphocytes	Neutrophils	
Henderson <i>et al.</i> (1995)	Air (control)	inh.	99	not reported	1	Results are for 24 weeks after the 4-week exposure. The mean lung SiO ₂ burdens 1 week after the 4-week exposure was 720, 190 and 43 µg/mg for 10, 1 and 0.1 mg/m ³ exposures, respectively.
	Quartz	inh.	99.5	not reported	0.5	
	0.1 mg/m ³ , 6 h/day, 5 days/week × 4 weeks	inh.	97	not reported	2.5	
	1 mg/m ³ , 6 h/day, 5 days/week × 4 weeks	inh.	59	not reported	41	
	10 mg/m ³ , 6 h/day, 5 days/week × 4 weeks	i.t.	98	not reported	2	
	Saline (vehicle control)	i.t.	38	not reported	62	
Warheit <i>et al.</i> (1995)	750 µg Quartz	inh.	NR	NR	~ 1	Results are for 24 weeks after i.t. exposure.
	Air (control)	inh.	NR	NR	~ 43	
	Quartz (Min-U-Sil) 100 mg/m ³ , 6 h/day × 3 days	inh.	NR	NR	~ 34	
	Cristobalite 10 mg/m ³ , 6 h/day × 3 days	inh.	NR	NR	~ 50	
	Cristobalite 100 mg/m ³ , 6 h/day × 3 days	inh.	98.5 ± 1.9	< 2	0	
	Saline (vehicle control)	i.t.	55.0 ± 2.6	< 2	45.0 ± 6.7	
Donaldson <i>et al.</i> (1988a)	Quartz (DQ 12) 1 mg	i.t.	97	1	2	Response was examined 5 days after exposure.
	Saline (vehicle control)	i.t.				
Lindenschmidt <i>et al.</i> (1990)	Quartz (Min-U-Sil)	i.t.	25	5	69	Results are for 63 days after exposure.
	1 mg/kg	i.t.	21	13	65	
	10 mg/kg	i.t.	29	17	63	
	100 mg/kg	i.t.				

Table 31 (contd)

Reference	Treatment	Exposure method	Cell differential (%)			Comments
			Macrophages	Lymphocytes	Neutrophils	
Driscoll <i>et al.</i> (1997)	Saline (vehicle control)	i.t.	95.9 ± 0.9	3.6 ± 0.6	1.6 ± 0.7	Results are for 15 months after exposure.
	Quartz (Min-U-Sil), 10 mg/kg	i.t.	36.3 ± 5.1	6.7 ± 0.4	57.0 ± 1.9	
	Quartz (Min-U-Sil), 100 mg/kg	i.t.	28.2 ± 2.5	7.5 ± 1.1	64.5 ± 2.8	

i.t., intratracheal instillation; inh, inhalation; NR, not reported; BAL, bronchoalveolar lavage; i.t., intratracheal instillation

(Iota standard quartz sand), even though the aerodynamic diameters were very similar in the two samples (Shoemaker *et al.*, 1995; Vallyathan *et al.*, 1995). [The Working Group noted that the milled samples contained 222 $\mu\text{g/g}$ iron, compared with 7 $\mu\text{g/g}$ in the unmilled sample.] Inflammatory leukocytes from DQ 12 quartz-instilled lung caused detachment of epithelial cells in culture and degraded extracellular matrix (Donaldson *et al.*, 1988b) by a largely protease-mediated mechanism which appeared to be mediated by the neutrophils and not the macrophages (Donaldson *et al.*, 1992). In a sheep model, following multiple quartz [origin not stated] instillations, BAL cells showed increased release of superoxide (Cantin *et al.*, 1988) but there was no such increase in BAL cells of rats following a single instillation of quartz (DQ 12; Donaldson *et al.*, 1988c).

Groups of male and female Wistar rats (Cpb:WU, Wistar random) were exposed by inhalation in chambers to three types of amorphous silica (Aerosil 200, Aerosil R 974, Sipernat 22S), for 6 h per day on five days per week for 13 weeks. Groups of rats were killed at the end of the exposure period and at weeks 13, 26, 39 and 52. Non-neoplastic pulmonary changes seen in rats killed at the end of the exposure period comprised slight to severe accumulation of alveolar macrophages, intra-alveolar granular material, cellular debris and polymorphonuclear leukocytes in the alveolar spaces, and increased septal cellularity, seen as an increase in the number of type II pneumocytes and macrophages within the alveolar walls. In general, the most severe changes were found in rats exposed to Aerosil 200, and the mildest changes were seen in rats exposed to Sipernat 22S. Alveolar bronchiolization occurred mainly in males exposed to 5.9 or 31 mg Aerosil 200/m³ or to Aerosil R 974. During the post-exposure periods, no recovery from lung lesions was observed in a comparison group of quartz (Sikron [Sykron] F300)-exposed rats, whereas in rats exposed to the amorphous silicas, the changes disappeared partly or completely. In rats exposed to 31 mg Aerosil 200/m³ or to quartz, accumulations of alveolar macrophages were still found 52 weeks after the end of exposure. In rats exposed to Sipernat 22S or Aerosil R 974, lesions were found until week 39 after exposure. Accumulation of intra-alveolar granular material, cellular debris and polymorphonuclear leukocytes were occasionally found in the group exposed to 31 mg Aerosil 200/m³ and in all quartz-exposed rats during the post-exposure period. Rats exposed to Sipernat 22S recovered completely from the slight increases in septal cellularity that were observed at the end of the exposure period. A lesser degree of recovery was observed in rats exposed to Aerosil 200 or Aerosil R 974, and no recovery occurred in rats exposed to quartz. Alveolar bronchiolization persisted mainly in quartz-exposed animals and in some rats exposed to Aerosil 200. Focal interstitial fibrosis was first observed 13 weeks after exposure in all exposed group. During the subsequent post-exposure period, this condition disappeared completely in rats exposed to Aerosil R 974 or quartz at the end of the exposure period. This lesion disappeared completely in rats of the Aerosil 200 group within 13 weeks after the end of exposure, but in rats exposed to Aerosil R974, recovery took more than 39 weeks. Slight fibrosis was observed in the granulomas in animals of the quartz group (Reuzel *et al.*, 1991).

The substantially lower inflammatory effects of synthetic, precipitated, amorphous silica relative to crystalline silica has been demonstrated in several other inhalation studies (Hemenway *et al.*, 1986 (precipitated Zeofree 80); Lee & Kelly, 1992 (Ludox

colloidal); Warheit *et al.*, 1995 (Zeofree 80 and Ludox)). For example, a four-week exposure of rats to airborne mass concentrations of 150 mg/m³ colloidal silica showed a return to virtually normal lung morphology after a three-month recovery period (Lee & Kelly, 1993).

(ii) Cytokines

Intratracheal instillation of Min-U-Sil 5 quartz (5–100 mg/kg bw) into Fischer 344 rats induced a dose-dependent release of the cytokines tumour necrosis factor- α (TNF α) and interleukin-1 (IL-1) by alveolar macrophages (Driscoll *et al.*, 1990a). The increase in macrophage TNF α correlated with the severity of the inflammatory response.

Intratracheal instillation of Min-U-Sil quartz (5 or 10 mg/kg bw) into Fischer 334 rats or subchronic inhalation of cristobalite (1 mg/m³, 6 h per day, 5 days per week for 13 weeks) increased expression of the neutrophil chemotactic cytokines macrophage inflammatory protein 2 (MIP-2) and cytokin-induced neutrophil chemoattractant (CINC) (Driscoll *et al.*, 1993; Driscoll, 1994). Passive immunization of Fischer 344 rats with antibody to MIP-2 markedly reduced the neutrophil recruitment in rat lungs induced by Min-U-Sil quartz (1 mg intratracheally), indicating a key role for MIP-2 in quartz-elicited inflammation (Driscoll *et al.*, 1997). Other in-vitro studies on crystalline silica and cytokines are summarized in **Table 27** in the monograph on coal dust.

Yuen *et al.* (1996) instilled Min-U-Sil quartz into the lungs of rats and demonstrated gene expression for the cytokines, MIP-2 and KC, two known chemotactic factors for neutrophils.

(iii) Fibrosis

Instillation and inhalation of quartz causes a fibrogenic response in rats (Martin *et al.*, 1983 (Min-U-Sil); Reiser *et al.*, 1983 (Dowson & Dobson)), guinea-pigs (Lugano *et al.*, 1982 (acid-washed Min-U-Sil)) and mice (Adamson & Bowden, 1984 (Dowson & Dobson); Callis *et al.*, 1985 (Min-U-Sil)). Strain-specific differences in the fibrotic response of DBA/2 and C3H/He mice to instilled quartz were evident in the study of Callis *et al.* (1985), suggesting that there is a role for the immune system in the response. The dependence of experimental silicosis in mice on the cytokine TNF α was demonstrated by Piguet *et al.* (1990), who was able to inhibit fibrosis (to control levels) in silica-instilled mice by giving them concomitant antibody against TNF α . Alveolar macrophages from rats instilled with Min-U-Sil quartz showed sustained release of fibronectin (Driscoll *et al.*, 1990b) whilst inhalation was associated with a late (63 days after the end of a five-day exposure) peak of fibronectin release (Driscoll *et al.*, 1991). Fibronectin could be a factor in attracting fibroblasts and promoting mesenchymal cell growth, leading to fibrosis in quartz-exposed lung.

While mast cells are not generally recognized as having a major role in the fibrogenicity of silica, the inflammatory and fibrogenic response to silica (Wako Co.) was substantially reduced in a mast cell-deficient strain of mice (Suzuki *et al.*, 1993). The fibrogenic response to instilled DQ 12 quartz in mice was significantly attenuated on simultaneous treatment with anti-CD11a or anti-CD11b, demonstrating the importance of these adhesion molecules in the silica response (Piguet *et al.*, 1993).

The role of concomitant immuno-stimulation in the fibrogenic response to silica (hydrofluoric acid-etched tridymite) was investigated in the study of Chiappino and Vigliani (1982). In this study, rats were instilled with tridymite and then kept in SPF conditions or in a normal animal house conditions where they were 'exposed to the endemic bacterial flora'. The animals kept under normal conditions developed silicosis more rapidly and severely than those kept under SPF conditions. This suggests that the normal bronchopulmonary infections that are endemic to animal houses were a co-stimulus for the silicotic fibrosis.

(iv) *Lymph node fibrosis*

Klempman and Miller (1977) described fibrotic responses in the thoracic lymph nodes of rats following inhalation exposure to quartz (Dowson & Dobson), whilst Rosenbruch (1992) reported that amorphous silica (quartz glass VP203-006) was as potent as quartz (DQ 12) in causing lymph node fibrosis following intratracheal instillation.

(v) *Emphysema*

Rats administered Min-U-Sil quartz intratracheally showed evidence of airflow limitation, emphysema and small airways disease (Wright *et al.*, 1988). These responses may be a consequence of extracellular matrix destruction by the increased connective tissue protease activity shown by the BAL cells from quartz (DQ 12)-exposed rats (Brown *et al.*, 1991).

(vi) *Epithelial injury and proliferation*

Following intratracheal instillation of quartz (Dowson & Dobson) in mice, Adamson and Bowden (1984) reported a wave of type II cell proliferation to regenerate damaged type I cells. This was accompanied by a sustained interstitial proliferative response that mirrored increasing hydroxyproline levels in the lungs, suggesting that there was mesenchymal cell proliferation and fibrosis. Warheit *et al.* (1991) reported that 48 h after a three-day exposure of rats to 100 mg/m³ Min-U-Sil or carbonyl-iron, there was increased proliferation in the lung parenchyma of the Min-U-Sil-exposed rats only. Exposure of rats to amorphous colloidal silica (Ludox) at 150 mg/m³ for four weeks caused increased proliferation of pulmonary epithelial cells (labelling index increased from ca. 0.6% in controls to 1.8%), which returned to normal levels of cell division after three months in clean air (Warheit *et al.*, 1991b). There was an approximately twofold increase in the number of type II epithelial cells in quartz (Min-U-Sil)-exposed lung and a change in their morphology (Miller & Hook, 1988). Phenotypically, the type II epithelial cells of Min-U-Sil quartz-exposed lung were hypertrophic and had increased numbers of lamellar bodies, which may have contributed to the phospholipidosis characteristic of quartz-exposed lungs in rats and humans (Miller & Hook, 1990). Type II cells isolated from Min-U-Sil-exposed lung synthesized DNA *in vitro*, but did not divide (Panos *et al.*, 1990). A suggestion that the accumulation of phospholipid in quartz-exposed lung could be protective came from a study by Antonini and Reasor (1994) who demonstrated that pharmacological induction of phospholipidosis ameliorated the acute toxicity of instilled Min-U-Sil quartz in rats.

(vii) *Oxidative stress in quartz-exposed lungs*

Evidence that the inflammation caused by Min-U-Sil quartz results in oxidative stress has been shown by the measurement of hydroxyl radicals after instillation of quartz or titanium dioxide; there was significantly more (approximately 2–3-fold) hydroxyl radical activity per gram of lung (wet) after quartz than after titanium dioxide or saline (Schapira *et al.*, 1994). Presumably as a response to this type of oxygen stress, induction of anti-oxidant enzyme gene expression (manganese superoxide dismutase (MnSOD), catalase and glutathione peroxidase) and *c-fos* and *c-jun* expression was increased in lungs of rats inhaling cristobalite (C&E Minerals Corp.) (Janssen *et al.*, 1992, 1994). The MnSOD expression was correlated with neutrophil numbers in BAL.

Both reactive oxygen species and reactive nitrogen species (NO and peroxynitrite) are generated in Min-U-Sil quartz inflammation (Blackford *et al.*, 1994; Van Dyke *et al.*, 1994). In the study by Van Dyke *et al.* (1994), BAL cells from quartz-instilled rats showed chemiluminescence (chemically assisted light emission *in vitro* resulting from the respiratory burst) that could be inhibited by both MnSOD and *N*-nitro-L-arginine methyl ester hydrochloride (L-NAME), a competitive inhibitor of NO synthase. Since MnSOD and NO react to form the highly toxic oxidant peroxynitrite, NO may therefore be involved in causing lung damage in silica-exposed lung.

A role for iron in silica-mediated oxidative stress is suggested by the accumulation of iron in the lung and on the surface of Min-U-Sil quartz with residence in the lung following a single 50-mg dose given by instillation (Ghio *et al.*, 1994). The accumulation of iron in the lung was accompanied by depletion of anti-oxidant defences, such as non-protein sulphhydryls, ascorbate and urate and increases in MnSOD and progressive fibrosis. In rats given an iron-deficient diet, the fibrosis was ameliorated. [The Working Group noted that an extremely high bolus dose was used in this study.]

Min-U-Sil quartz causes oxidative damage to α -1-protease inhibitor (Zay *et al.*, 1995) and, in a manner analogous to the commonly postulated mechanism for emphysema in smokers, this could lead to localized elastase- and other protease-mediated injury in silica-inflamed lung.

(viii) *Modification of quartz toxicity*

Quartz can differ in its toxicity to the lung depending on the minerals with which it is combined. This has been shown by Le Bouffant *et al.* (1982) who demonstrated that coal mine dusts with 5 and 15% quartz were markedly less fibrogenic than an artificial mixture of coal mine dust with negligible quartz but supplemented with NI quartz to the same proportion. The ability of trace contaminants to modify quartz toxicity was further shown by the fact that simple treatment of DQ 12 quartz with aluminium lactate dramatically attenuated its ability to cause pulmonary inflammation in rats following instillation (Brown *et al.*, 1989). The fact that freshly fractured quartz (Generic Respirable Dust Technology Center standard reference sample) is more haemolytic and, to a lesser extent, cytotoxic than 'aged' quartz to macrophages (Vallyathan *et al.*, 1988) further shows that there can be differences in the specific reactivity of the quartz surface. [The Working Group noted that this sample was ground with an agate mortar and pestle.] Min-U-Sil quartz coated with synthetic lung surfactant also had less toxicity than native

quartz (Antonini & Reasor, 1994) and the differences in cytotoxicity of a range of quartz samples was found to be related to the 'uncontaminated' quartz surface (Kreigseis *et al.*, 1987). Additionally, Vallyathan *et al.* (1991) have reported amelioration of the haemolytic and macrophage stimulatory activity of quartz (Generic Respirable Dust Technology Center standard reference sample) with an organosilane coating.

(ix) *Role of the immune system*

The presence of increased numbers of lymphocytes in the BAL of silicotics (see above) suggests that immunological phenomena occur in silica-exposed lungs. In addition, immunoglobulin (IG) and complement have been found in silicotic nodules (Vigliani & Pernis, 1958; Pernis & Vigliani, 1982). Silica and other mineral dusts have been proposed to produce an adjuvant-like effect via macrophage stimulation (Pernis & Vigliani, 1982) and increased release of cytokines such as IL-1 (Oghiso & Kubota, 1987; Min-U-Sil). However, in mice and rats inhaling Min-U-Sil quartz, there is a generalized immunosuppression in the spleen and lymph nodes (Miller & Zarkower, 1974; Bice *et al.*, 1987). Following instillation of DQ 12 quartz in rats, however, the immunosuppressive functions of normal BAL cells were reversed to immunostimulation, which appeared to be related to the inflammatory neutrophil component and to release of increased amounts of IL-1 (Kusaka *et al.*, 1990a,b).

Increased systemic immune complexes and antinuclear antibody have been described in silica-exposed individuals (Rustin *et al.*, 1990), suggesting the development of autoimmunity of a systemic adjuvant effect of silica might play a role in systemic sclerosis in silica-exposed individuals (Haustein *et al.*, 1990).

(b) *In-vitro cellular effects of silica*

(i) *Macrophages*

Toxicity

Quartz is toxic to macrophages *in vitro*. This toxicity was initially suggested to involve lysosomal rupture (Harrington *et al.*, 1975), although this has now been disproved. Instead, the influx of calcium ions has been shown to be a key toxic event in silica-treated macrophages (Kane *et al.*, 1980). The interaction between quartz and macrophage membranes may result in a direct membranolytic action in the non-physiological absence of protein (Harrington *et al.*, 1975). However, in the lung the quartz is likely to be coated with lung lining fluid and this ameliorates the cytotoxicity of the quartz (Schimmelpfeng & Seidel, 1991; DQ 12); nevertheless, proteins do not afford protection against the toxicity of DQ 12 quartz at later time-points (Tilkes & Beck, 1983). Quartz may express its cytotoxic action via free radical injury to the macrophage membrane (Gabor *et al.*, 1975 [quartz sample not specified]; Razzaboni & Bolsaitis, 1990 (Min-U-Sil); Vallyathan, 1994 (Min-U-Sil)) which increases the calcium-ion permeability of the membrane (Kane *et al.*, 1980; Pneumoconiosis Research Centre, Johannesburg silica). Using polyunsaturated linoleic acid as a model membrane and quartz from the Generic Respirable Dust Technology Center, a correlation was demonstrated between the extent of peroxidation and ROS derived from fracture-induced silicon-based radicals at the quartz surface (Dalal *et al.*, 1990; Shi *et al.*, 1994).

Activation

Activation of the respiratory burst during phagocytosis of quartz particles would have, as its sequel, release of ROS such as superoxide anion, hydrogen peroxide and peroxy-nitrite; these could contribute to lung injury and inflammation. Increased production of these mediators on treatment with quartz [origin not stated] has been described by Gusev *et al.* (1993) but was not found in either control or inflammatory rat leukocytes treated with DQ 12 quartz or other phagocytic stimuli (Donaldson *et al.*, 1988c). The ability of the opsonin IgG to enhance the oxidative burst caused by acid-washed quartz [origin not stated] was demonstrated by Perkins *et al.* (1991).

Quartz-stimulated activation of monocyte/macrophages *in vitro* to release cytokines that promote the growth of mesenchymal cells has been demonstrated in several studies (IL-1, Schmidt *et al.*, 1984 [quartz origin not stated]; TNF α , Savici *et al.*, 1994 (Min-U-Sil); TNF α , Claudio *et al.*, 1995 (Instituto Naçionale de Silicosis, Barcelona quartz)). Segade *et al.* (1995) demonstrated the induction of nine gene sequences in a macrophage cell-line treated with silica (Instituto Naçionale de Silicosis, Barcelona quartz).

Quartz treatment of alveolar macrophages also caused stimulation of arachidonic acid metabolism with the production of eicosanoids such as prostaglandin, thromboxane and leukotriene B4 (Englen *et al.*, 1989 (Sigma Chemical Co.); Driscoll *et al.*, 1990c (Min-U-Sil); Demers & Kuhn, 1994).

Rabbit alveolar macrophages treated with DQ 12 quartz released increased amounts of elastase, which could contribute to lung remodelling in quartz-exposed lung (Gulyas *et al.*, 1988). Mobilization of intracellular calcium appears to underly the triggering of macrophages by DQ 12 quartz (Tuomala *et al.*, 1993), although mobilization of calcium may also be related to the cytotoxic effects of quartz (Kane *et al.*, 1980 (Pneumoconiosis Research Centre, Johannesburg quartz); Chen *et al.*, 1991 (Min-U-Sil)).

Both damage and activation of macrophages are likely to arise in silica-exposed lung and dead and damaged cells will lead to inflammatory activation of other macrophages.

(ii) *Granulocytes*

In analogy to the situation with macrophages, the phagocytosis of quartz by granulocytes recruited to quartz-inflamed lung could lead to further accumulation of harmful ROS. Hedenborg and Klockars (1989) reported the release of ROS by human granulocytes on treatment with quartz (fractionated Fyle quartz) but not with diamond dust. Furthermore, the release of ROS could be decreased by the presence of the antioxidant *N*-acetylcysteine.

(iii) *Epithelial cells*

Using freshly-derived rat epithelial cells, Lesur *et al.* (1992) demonstrated proliferation and thymidine uptake at low concentrations of Min-U-Sil 5 quartz. These responses were replaced by cytotoxic effects at higher concentrations. However, macrophages exposed to Min-U-Sil 5 quartz *in vitro* also released factor(s) that stimulated growth of type II epithelial cells (Melloni *et al.*, 1993), suggesting that quartz may cause both direct growth-promoting effects on epithelial cells and effects via macrophages.

Quartz [origin not stated] treatment of rat type II cells *in vitro* caused stimulation of prostaglandin release (Klien & Adamson, 1989).

In-vitro exposure of primary cultures of rat alveolar type II cells or a rat alveolar epithelial cell line to Min-U-Sil quartz ($6\text{--}60\ \mu\text{g}/\text{cm}^2$) activated expression of the MIP-2 gene and production of MIP-2 protein. MIP-2 has been shown to contribute to quartz-elicited neutrophil recruitment in rats. In-vitro exposure of rat alveolar type II epithelial cells to crocidolite (20 and $60\ \mu\text{g}/\text{cm}^2$) also increased MIP-2 expression; however, treatment with MMVF-10 (man-made vitreous fibre-10) glass fibre or titanium dioxide particles did not (Driscoll, 1996). These results indicate that lung epithelial cells can be directly activated by quartz.

(iv) *Erythrocytes*

Erythrocytes have been used as a rapid screen for the ability of particles to interact with and cause damage to membranes because release of haemoglobin is a ready index of membrane damage in these cells; there is no suggestion that damage to erythrocytes has any role in pathogenesis of pneumoconiosis. Hefner and Gehring (1975) suggested that there was a relationship between the ability of a range of particles, including Min-U-Sil quartz, to cause haemolysis and their ability to cause fibrosis *in vivo*. Hemenway *et al.* (1993) however cast doubt on this relationship in studies with C&E Mineral Corp. cristobalite, which is very haemolytic and inflammogenic/fibrogenic to the lung. Whereas heating the cristobalite reduced its haemolytic potency to about 50%, this treatment had no effect on its ability to cause lung injury. The haemolytic potential of silica (Harley & Margolis, 1961) is related to the presence of silanols which bind some membrane components (Nash *et al.*, 1966; Nolan *et al.*, 1981; Kozin *et al.*, 1982; Razzaboni & Bolsaitis, 1990). Haemolysis is reduced if the silica surface is coated with polyvinylpyridine-*N*-oxide (Stalder & Stöber, 1965; Nash *et al.*, 1966), following hydrofluoric acid etching (Langer & Nolan, 1985) or upon heating (Hemenway *et al.*, 1993). The haemolytic activity of silicas calcined at different temperatures and rehydrated in air is related to surface hydration (Pandurangi *et al.*, 1990). Alternatively, quartz particles cause haemolysis by a mechanism that involves hydrogen peroxide and possibly copper ions (Razzaboni & Bolsaitis, 1990).

Contaminants may modify chemical and surface properties. Metal ions either compensate the dissociated silanol negative charge or substitute for silicon in the tetrahedra. Metal ions fixed at the ionized silanol groups diminish haemolysis (Nolan *et al.*, 1981). The solubility of silica is reduced when aluminium contaminates the surface of quartz (Beckwith & Reeve, 1969). The modulation of quartz fibrogenicity by aluminium was discovered long ago and aluminotherapy was established in several countries; this has recently been reviewed (Brown & Donaldson, 1996). The effect of aluminium has now been thoroughly investigated in a sheep model (Bégin *et al.*, 1987). The presence of aluminium at the silica surface decreases uptake by alveolar macrophages and inhibits the inflammatory and fibrotic response *in vivo*. The mechanism has not yet been elucidated but the suppressive effect is due to the direct interaction of aluminium with silica.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

Studies retained in this section included the following: assays to assess results of the interaction of crystalline silica with isolated DNA; cellular genotoxicity assays, evaluating gene mutation, sister chromatid exchange, chromosomal aberrations, micronuclei and aneuploidy/polyploidy; and cell transformation assays.

4.4.1 Humans

Significant increases in the levels of sister chromatid exchange and chromosomal aberrations in peripheral blood lymphocytes were reported in a group of 50 male workers (mean age, 30.9 years) from a stone crushing unit, who were compared to 25 white-collar controls (mean age, 30.4 years; sex not specified); the crude sandstone contained 50–60% SiO₂. These increases were maintained when comparison was restricted to different classes of alcohol consumption or different classes of tobacco smoking. A dose–response relationship was reported between increasing classes of duration of exposure and the level of sister chromatid exchange or chromosomal aberrations (Sobti & Bhardwaj, 1991). [The Working Group noted that the relevance of the controls included is questionable, since exposed subjects seem to be blue-collar and controls white-collar workers. No information is provided on the level of exposure to quartz. The number of subjects in some classes of duration of exposure was rather small. No statistical test is presented for correlation between duration of exposure and the levels of sister chromatid exchange or chromosomal aberrations.]

No data were available to the Working Group on the genetic and related effects of amorphous silica in humans.

4.4.2 Experimental systems (see also **Table 32** and Appendices 1, 2 and 3)

Crystalline silica

(a) Free radicals and isolated DNA

Damage of λ HindIII-digested DNA was reported after treatment with at a high dose (30 mg/mL) of Min-U-Sil 5 quartz for three weeks. Damage was also observed in herring sperm DNA after 12 h and at a lower quartz dose (10 mg/mL). This DNA damage was related to the generation of hydroxyl radicals. DNA damage was seen more rapidly with a native quartz sample than with hydrofluoric acid-etched quartz (Daniel *et al.*, 1993). The ability of crystalline silica to cause direct DNA damage was investigated with five quartz samples, one cristobalite sample and one tridymite sample using various DNA damage assays (Daniel *et al.*, 1995). DNA damage was affected by the presence of oxygen and was accelerated by SOD and hydrogen peroxide. Desferrioxamine B (an iron chelator) blocked damage by hydrogen peroxide but accelerated damage by silica alone or silica and SOD. DNA damage was blocked by catalase and by free-radical-scavenging agents (dimethyl sulfoxide and sodium benzoate). Chemical etching of crystalline silica

Table 32. Genetic and related effects of silica

Test system	Result ^a		Dose ^b (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Crystalline silica: quartz				
* , DNA strand breaks, λ HindIII-digested DNA	+	NT	30 000'	Daniel <i>et al.</i> (1993)
* , DNA strand breaks, herring sperm genomic DNA	+	NT	10 000'	Daniel <i>et al.</i> (1993)
* , DNA strand breaks, λ HindIII-digested DNA	+	NT	9 500'	Daniel <i>et al.</i> (1995)
* , DNA strand breaks, PM2 supercoiled DNA	+	NT	9 500'	Daniel <i>et al.</i> (1995)
GIA, Gene mutation, <i>hprt</i> locus, rat RLE-6TN alveolar epithelial cells <i>in vitro</i>	-	NT	NG	Driscoll <i>et al.</i> (1997)
SIC, Sister chromatid exchange, Chinese hamster V79-4 cells <i>in vitro</i>	-	NT	15 ^d	Price-Jones <i>et al.</i> (1980)
SHL, Sister chromatid exchange, human lymphocytes <i>in vitro</i>	-	NT	100'	Pairon <i>et al.</i> (1990)
SIH, Sister chromatid exchange, human lymphocytes and monocytes <i>in vitro</i>	-	NT	100'	Pairon <i>et al.</i> (1990)
MIA, Micronucleus test, Syrian hamster embryo cells <i>in vitro</i>	-	NT	18.75'	Oshimura <i>et al.</i> (1984)
MIA, Micronucleus test, Syrian hamster embryo cells <i>in vitro</i>	+	NT	70 ^d	Hesterberg <i>et al.</i> (1986)
MIA, Micronucleus test, Chinese hamster lung fibroblasts (V79) <i>in vitro</i>	+	NT	200'	Nagalakshmi <i>et al.</i> (1995)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts (V79) <i>in vitro</i>	-	NT	1 600'	Nagalakshmi <i>et al.</i> (1995)
CIS, Chromosomal aberrations, Syrian hamster embryo cells <i>in vitro</i>	-	NT	18.75'	Oshimura <i>et al.</i> (1984)
AIA, Aneuploidy, Chinese hamster lung cells (V79-4) <i>in vitro</i>	-	NT	15 ^d	Price-Jones <i>et al.</i> (1980)
AIA, Aneuploidy, Syrian hamster embryo cells <i>in vitro</i>	-	NT	18.75'	Oshimura <i>et al.</i> (1984)
AIA, Tetraploidy, Syrian hamster embryo cells <i>in vitro</i>	-	NT	70 ^d	Hesterberg <i>et al.</i> (1986)
TBM, Cell transformation, BALB/3T3/31-1-1 mouse cells <i>in vitro</i>	+	NT	30 ^{d,*,**}	Saffiotti & Ahmed (1995)
TBM, Cell transformation, BALB/3T3/31-1-1 mouse cells <i>in vitro</i>	+	NT	60 ^d	Saffiotti & Ahmed (1995)
TCS, Cell transformation, Syrian hamster embryo cells <i>in vitro</i>	+	NT	18 ^d	Hesterberg & Barrett (1984)

Table 32 (contd)

Test system	Result ^a		Dose ^b (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
TCS, Cell transformation, Syrian hamster embryo cells <i>in vitro</i>	+	NT	70'	Hesterberg & Barrett (1984)
TCL, Cell transformation, foetal rat lung epithelial cells <i>in vitro</i>	(+)	NT	NG ^c	Williams <i>et al.</i> (1996)
MIH, Micronucleus test, human embryonic lung (Hel 299) cells <i>in vitro</i>	+	NT	800'	Nagalakshmi <i>et al.</i> (1995)
CIH, Chromosomal aberrations, human embryonic lung (Hel 299) cells <i>in vitro</i>	-	NT	1 600'	Nagalakshmi <i>et al.</i> (1995)
DVA, 8-hydroxy 2' deoxyguanosine DNA extract from lung tissue, male Wistar rats	+		50 × 1 it ^d	Yamano <i>et al.</i> (1995)
DVA, 8-hydroxy 2' deoxyguanosine DNA extract from peripheral blood leukocytes, male Wistar rats	-		50 × 1 it ^d	Yamano <i>et al.</i> (1995)
GVA, Gene mutation, <i>hprt</i> locus, rat alveolar epithelial cells <i>in vivo</i>	+		100 × 1 it	Driscoll <i>et al.</i> (1995)
GVA, Gene mutation, <i>hprt</i> locus, rat alveolar epithelial cells <i>in vivo</i>	+		5 × 2 it	Driscoll <i>et al.</i> (1997)
MVM, Micronucleus test, albino mice <i>in vivo</i>	-		500 ip	Vanchugova <i>et al.</i> (1985)
SLH, Sister chromatid exchange, human lymphocytes <i>in vivo</i>	+		NG	Sobti & Bhardwaj (1991)
CLH, Chromosomal aberrations, human lymphocytes <i>in vivo</i>	+		NG	Sobti & Bhardwaj (1991)
BID, Calf thymus DNA binding <i>in vitro</i>	+	NT	200 ^e	Mao <i>et al.</i> (1994)
ICR, Metabolic cooperation using 8-azaguanine resistant cells, Chinese hamster lung cells (V79-4) <i>in vitro</i>	-	NT	50	Chamberlain (1983)
Crystalline silica: tridymite				
*, DNA strand breaks, λ HindIII-digested DNA	+	NT	5 700	Daniel <i>et al.</i> (1995)
*, DNA strand breaks, PM2 supercoiled DNA	+	NT	5 700	Daniel <i>et al.</i> (1995)
SHL, Sister chromatid exchange, human lymphocytes <i>in vitro</i>	-	NT	100	Pairon <i>et al.</i> (1990)
SIH, Sister chromatid exchange, human lymphocytes and monocytes <i>in vitro</i>	+	NT	100	Pairon <i>et al.</i> (1990)

Table 32 (contd)

Test system	Result ^a	Dose ^b (LED/HID)		Reference
		Without exogenous metabolic system	With exogenous metabolic system	
Cristobalite				
* DNA strand breaks, λ HindIII-digested DNA	+	NT	7 600	Daniel <i>et al.</i> (1995)
* DNA strand breaks, PM2 supercoiled DNA	+	NT	7 600	Daniel <i>et al.</i> (1995)

*Not included on the profile

^a+, positive; (+), weakly positive; -, negative; NT, not tested; ?, inconclusive

^bLED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μ g/ml; in-vivo tests, mg/kg bw/day; NG, not given

¹Min-U-Sil 5

²Min-U-Sil unspecified

³ α -Quartz

⁴Min-U-Sil 5 and Min-U-Sil 10

⁵Min-U-Sil 5, hydrofluoric acid-etched

⁶A Chinese standard quartz sample

⁷DQ 12, a standard German quartz sample

⁸F600 quartz

⁹Min-U-Sil 5 or Chinese standard quartz

by hydrofluoric acid resulted in a markedly diminished ability to damage DNA, implicating trace iron impurities. A study of DNA strand breakage of PM2 supercoiled DNA and λ HindIII digested DNA by five quartz samples (Min-U-Sil 5; hydrofluoric acid-etched Min-U-Sil; DQ 12; F600 quartz; Chinese standard quartz (CSQZ)), cristobalite and tridymite samples showed the following gradient of toxicity when using a similar surface area of particles: F600 > Min-U-Sil > DQ 12 > cristobalite > tridymite and hydrofluoric acid-etched Min-U-Sil > CSQZ. Relative ranking of the potency of these crystalline silica samples depends on the endpoint. Addition of hydrogen peroxide modified the order of activity of the samples, cristobalite exhibiting the highest toxicity (Daniel *et al.*, 1995). Interaction of λ DNA and calf thymus DNA with Min-U-Sil quartz and CSQZ, measured by infrared spectroscopy, indicated structural changes in the DNA backbone and reorientation of the phosphate groups. The close proximity of the silica surface to the DNA molecule brought about by this binding might contribute to DNA strand breakage produced by the free radicals released by silica (Mao *et al.*, 1994). [The Working Group considered that the relevance of these assays in the assessment of quartz-related genetic effects remains questionable, as the experimental conditions are not applicable to intracellular silica exposure. Moreover very high doses of silica were used in the DNA breakage assays.]

(b) *Cellular systems*

No significant effect of silica (type of silica and sample not specified; dose not indicated) was reported in the *Bacillus subtilis* rec-assay (Kada *et al.*, 1980; Kanematsu *et al.*, 1980).

Min-U-Sil quartz did not induce sister chromatid exchange, aneuploidy nor polyploidy in Chinese hamster V79-4 cells (Price-Jones *et al.*, 1980). [The Working Group noted that the dose was rather low when compared with positive studies.] Tridymite (87.9% of particles with diameter less than 1 μ m) was reported to significantly increase the number of sister chromatid exchanges in co-cultures of human lymphocytes and monocytes, while results were less reproducible for Min-U-Sil quartz (56% of particles with diameter less than 1 μ m) (Pairon *et al.*, 1990). In contrast, no modification of the number of sister chromatid exchanges was observed after treatment of purified human lymphocytes with the same dose of particles. [The Working Group noted that this observation suggests that the induction of sister chromatid exchange in lymphocytes was mediated through an interaction between monocytes and lymphocytes, the former having phagocytized particles as assessed by electron microscopy.]

A significant increase in bi-nucleated cells and micronuclei was observed in Syrian hamster embryo cells treated with Min-U-Sil quartz but there was no significant increase in tetraploid cells (Hesterberg *et al.*, 1986). Quartz particles were taken up and accumulated in the perinuclear region of the cells. By contrast, another sample of quartz [granulometry not indicated] did not induce micronuclei, bi-nuclei nor a modification of the number of chromosomal aberrations, aneuploid cells or tetraploid cells (Oshimura *et al.*, 1984). [The Working Group noted that only a single, low dose of silica was used.] While Min-U-Sil 5 and Min-U-Sil 10 quartz samples were shown to induce a significant dose-related increase in micronuclei in Chinese hamster lung V79 cells and human

embryonic lung Hel 299 cells, no chromosomal aberrations were observed in either cell type using the same and higher doses of silica (Nagalakshmi *et al.*, 1995).

A significant and dose-dependent increase in the frequency of morphologically transformed Syrian hamster embryo cells was reported following treatment with Min-U-Sil quartz ($2 \mu\text{g}/\text{cm}^2$) and another quartz sample ($10 \mu\text{g}/\text{cm}^2$) (Hesterberg & Barrett, 1984). [No precise data were provided on the granulometry of these quartz samples.] A significant increase in the frequency of foci of transformed mouse embryo BALB/c-3T3 cells was also reported after treatment with Min-U-Sil 5 quartz at doses of 90 and $180 \mu\text{g}/\text{cm}^2$ (Gu & Ong, 1996). [No control particle was used in this experiment.] Min-U-Sil 5 quartz had a slight effect (two transformed colonies) in a transformation assay of foetal rat lung epithelial cells, but only at the highest dose tested at which there was almost no survival of cells and colony forming efficiency was reduced to 70% (Williams *et al.*, 1996). [The Working Group noted that no statistical analysis was present in this paper and no dose-response relationship was shown.]

A dose-response relationship was observed in a mouse embryo BALB/c-3T3 cell transformation assay with five samples of quartz (Min-U-Sil 5, hydrofluoric acid-etched Min-U-Sil 5, CSQZ, DQ 12, F600 Quartz). Low doses were used and maximal frequency of transformation occurred at $25 \mu\text{g}/\text{cm}^2$, after which there was a plateau. No transformation was observed with haematite or two titanium dioxide samples. An inhibition of transforming potency was observed when cells were exposed to a combination of Min-U-Sil and haematite particles. Cytogenetic analysis revealed additional marker chromosomes in some quartz-transformed murine BALB/c-3T3 cell lines. Analysis of RNA expression for *p53* and nine oncogenes in a small number of cell lines suggested an increased mRNA expression of four oncogenes (*myc*, *H-ras*, *K-ras*, *abl*) and of *p53* gene in some quartz-transformed cell lines (Saffiotti & Ahmed, 1995).

A significant increase in *hprt* mutant frequency was reported in rat alveolar type II cells isolated from female Fischer 344 rats instilled intratracheally with Min-U-Sil quartz and sacrificed seven months later (Driscoll *et al.*, 1995). A further study in this laboratory demonstrated increased *hprt* mutant frequency in rat alveolar type II cells following intratracheal instillation of Min-U-Sil quartz with a lesser, but also a significant response to carbon black and titanium dioxide. The in-vivo mutagenic effects of these materials were associated with significant neutrophilic inflammation. Inflammatory cells isolated from the lungs of Min-U-Sil- and, to a lesser extent, carbon black-treated rats were mutagenic to a rat alveolar epithelial cell line (RLE-6TN). This effect was inhibited by catalase, an observation that suggested the role of cell-derived oxidants in this phenomenon. Direct exposure of the rat epithelial cell lines to Min-U-Sil, carbon black or titanium dioxide did not induce *hprt* locus mutations (Driscoll *et al.*, 1997).

DQ 12 quartz did not induce micronuclei in polychromatic erythrocytes in the bone marrow of Albino mice 6-96 h following intraperitoneal injection (Vanchugova *et al.*, 1985).

A significant increase in 8-hydroxy 2' deoxyguanosine (8-OHdG) was observed in the DNA extracts from lung tissue of male Wistar rats one to five days after a single intratracheal instillation of 50 mg/kg bw quartz Min-U-Sil 5. In contrast, there was no signi-

ficant modification in the level of 8-OHdG in DNA extracts from lung tissue at later times (week 1 to week 32) nor in the level of 8-OHdG in the DNA from peripheral blood leukocytes of rats at any time after intratracheal instillation (Yamano *et al.*, 1995). [The Working Group noted that results with peripheral blood leukocytes should be interpreted taking into account that these cells are not a target for neoplastic transformation.]

A strong immunoreactivity of the p21 ras protein was reported in foci of hyperplastic alveolar type II cells in Fischer 344 rats after intratracheal instillation of 12 mg Min-U-Sil 5 quartz. In contrast, no reactivity was shown in adenomas or carcinomas in this study. A nuclear immunostaining to p53 protein was also reported in two of eight silica-associated lung carcinomas examined (Williams *et al.*, 1995). [The Working Group noted that only qualitative results are reported with no description of quantitative abnormalities observed at different times after intratracheal injection. No statistical analysis was presented.]

Min-U-Sil quartz did not inhibit intercellular communication as measured by metabolic cooperation in *hprt* Chinese hamster V79 cells (Chamberlain, 1983).

Amorphous silica

Unique or multiple (four times) epidermal application of biogenic silica fibres (mean length, 150 μm) [size distribution not described; dose unknown] in female skin promotion-responsive mice (SENCAR) resulted in an induction of ornithine decarboxylase activity in epidermal cells (Bhatt *et al.*, 1992). Induction was maximum at 4–6 h and inhibitor studies revealed some similarities with 12-*O*-tetradecanoylphorbol-13-acetate. [The Working Group noted that no statistical analysis was available. The relevance of this paper in the field of the effects of amorphous silica may be questioned as only extremely long silica fibres were evaluated.]

4.5 Mechanistic considerations related to carcinogenicity

Several in-vitro studies evaluated the direct genotoxic activity of crystalline silica particles, primarily quartz, in a number of assay systems. These studies are summarized in **Table 33**. A preponderance of the cellular genotoxicity assays are negative or doubtful, however, some positive results have been reported primarily for micronucleus induction. Overall, these in-vitro data provide only weak evidence for a direct genotoxic action of crystalline silica, which contrasts with the genotoxicity of asbestos fibres in some of these same assays. Additional studies characterized the action of crystalline silica particles on isolated DNA in acellular systems. While these studies indicate that crystalline silica can directly damage DNA, the non-physiological nature of the assay systems combined with the extremely high doses of crystalline silica used make their in vivo relevance questionable. At this time, there is no convincing evidence for a direct physico-chemical mechanism for crystalline silica-induced genotoxicity to target cells *in vivo*.

There is increasing evidence that marked and persistent inflammation and specifically inflammatory cell-derived oxidants provide a mechanism by which crystalline silica

Table 33. Summary of genotoxic effects of quartz in mammalian cells (positive studies/studies available)

	<i>In vitro</i>	<i>In vivo</i>
Sister chromatid exchange	?/3	?/1
Chromosomal aberrations	0/3	?/1
Micronuclei	3/4	0/1
Aneuploidy	0/3	—
<i>hprt</i> Mutation	0/1	2/2 ^a

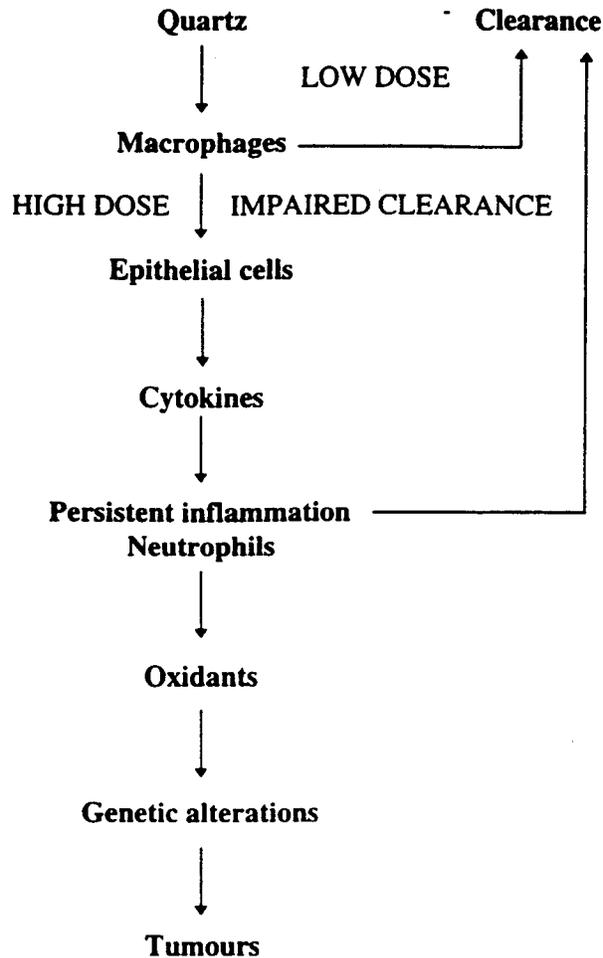
?, One questionably positive study available

^aMutagenic response associated with inflammation

exposure can result in genotoxic effects in the lung parenchyma. This hypothetical mechanism is summarized in **Figure 1**. The combination of marked persistent inflammation and epithelial hyperplasia resulting from crystalline silica exposure increases the likelihood that the genetic alterations associated with neoplastic transformation will occur. Supporting this mechanism is evidence from a number of studies including studies on crystalline silica and other poorly soluble particles shown to produce lung cancer in rats. First, there are in-vivo and in-vitro data demonstrating that crystalline silica can activate the production of both inflammatory and growth stimulatory factors as well as ROS and reactive nitrogen species by immune and/or non-immune cells. Additionally, it is well established that crystalline silica under certain exposure conditions produces an inflammatory and hyperplastic response in the lung. Numerous in-vitro studies using a variety of assays have demonstrated a role for inflammatory cells in genotoxic responses. These studies have shown that activated neutrophils and/or monocytes can be genotoxic due to the release of ROS (for example, see: Weitzman & Stossel, 1981, 1982; Hsie *et al.*, 1986; Jackson *et al.*, 1989). Regarding crystalline silica, Pairon *et al.* (1990) have demonstrated that the genotoxic effects on cultured lymphocytes were dependent on the presence of monocytes in the co-cultures. Additional support for an inflammation-dependent mechanism for crystalline silica-induced genotoxicity comes from both in-vivo and in-vitro studies on alveolar epithelial cells. In-vivo studies have demonstrated an association between mutation at the *hprt* locus in rat alveolar epithelial cells and pulmonary inflammation in rats exposed to quartz and other poorly soluble particles (Driscoll *et al.*, 1995; Borm & Driscoll, 1996; Driscoll *et al.*, 1997). In-vitro studies have shown that inflammatory cells taken from the lungs of rats exposed to high doses of quartz are mutagenic to alveolar epithelial cells in culture (Driscoll *et al.*, 1997). The in-vitro mutagenic action of the inflammatory cells was dependent on the release of ROS and was greater for quartz-elicited neutrophils than macrophages. The quartz particles themselves were not mutagenic in these same assays. Thus, there is evidence that inflammatory cells including those elicited in rat lungs by particle exposure can have genotoxic effects through the release of ROS. To the extent that genotoxicity contributes to the neoplastic process, these observations have implications for mechanisms of

tumorigenicity after exposure to inflammatory doses of crystalline silica. Other as yet unidentified epigenetic mechanisms may also be operative.

Figure 1. A hypothetical inflammation-based mechanism for carcinogenicity of quartz in rats



This hypothesis is supported by *in-vitro* studies as well as *in-vivo* studies in rats. Other pathways, such as a role for quartz surface-generated oxidants or a direct genotoxic effect, are not ruled out; however, at present there is no convincing evidence for these alternative pathways.

An inflammatory mechanism for the induction of lung tumours after crystalline silica exposure could have implications for (i) species differences in response and (ii) extrapolation from high- to low-exposure levels in animals. Regarding species differences, the findings on the mutagenic activity of quartz-elicited inflammatory cells are based on studies using rats. In these studies, both quartz-elicited rat neutrophils and macrophages were mutagenic to epithelial cells *in vitro*, although the neutrophils were significantly more mutagenic than macrophages. In this respect, existing data suggest that rats exposed to quartz concentrations associated with an increased incidence of lung tumours develop a neutrophilic inflammatory response remarkably greater than that determined in crystalline silica-exposed humans, including silicotics (~ 5% in human silicotics versus

30–50% in rats exposed to crystalline silica at levels producing tumours; see **Table 33**). This marked difference in quartz-induced inflammation may explain the apparent sensitivity of the rat to lung tumour development after exposure to quartz as well as several other poorly soluble particles. A high degree of sensitivity of the rat to lung cancer after quartz exposure is further indicated by studies demonstrating that other laboratory animal species (i.e. hamster and mouse) do not develop lung cancer after exposure to a variety of poorly soluble particles (e.g. quartz, diesel soot, talc, titanium dioxide) — a species difference that cannot be attributed to differences in lung particle dose. A comparison of the lung response to intratracheally instilled quartz in rats, hamsters and mice indicated that rats develop a more pronounced and persistent inflammatory and epithelial proliferative response than the other species (Saffiotti & Stinson, 1988).

A secondary mechanism of lung tumour induction could also have implications for extrapolation of high- to low-exposure situations. Inherent in this mechanism is the concept that there are exposures to crystalline silica that produce minimal or no inflammation and can be dealt with adequately by host defences (e.g. clearance mechanisms, anti-oxidant defences, etc.); a concept supported by experimental evidence in animals (Henderson *et al.*, 1995; Borm & Driscoll, 1996; Driscoll *et al.*, 1997). When defence mechanisms are overwhelmed, a threshold may be exceeded, genetic alterations could occur and the slope of the dose–response curve for induction of tumours may rise.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Silica (silicon dioxide) occurs in crystalline and amorphous forms. Of the several crystalline polymorphs of silica found in nature, quartz is by far the most common, being abundant in most rock types, notably granites, sandstones, quartzites and in sands and soils. Cristobalite and tridymite are found in volcanic rocks. Because of the wide usage of quartz-containing materials, workers may be exposed to quartz in a large variety of industries and occupations. Respirable quartz levels exceeding 0.1 mg/m^3 are most frequently found in metal, non-metal and coal mines and mills; in granite quarrying and processing, crushed stone and related industries; in foundries; in the ceramics industry; in construction and in sandblasting operations. Cristobalite is formed from quartz or any other form of silica at high temperatures ($> 1400 \text{ }^\circ\text{C}$) and from some amorphous silicas (e.g. diatomaceous earth) at somewhat lower temperatures ($800 \text{ }^\circ\text{C}$). Cristobalite exposure is notably associated with the use and calcination of diatomaceous earth as well as refractory material installation and repair operations. Few data exist on non-occupational exposures to crystalline silica. It has been estimated that respirable crystalline silica levels in the low $\mu\text{g/m}^3$ range are common in ambient air. Exposure may also occur during the use of a variety of consumer or hobby products.

Amorphous silica is found in nature as biogenic silica and as silica glass of volcanic origin. One form of biogenic silica, diatomaceous earth, originates from the skeletons of

diatoms deposited on sea floors and contains small amounts of cristobalite and quartz. After calcination (which significantly increases the cristobalite content), diatomaceous earth is used as a filtration agent, carrier for pesticides, filler in paints and paper and as a refractory or abrasive product in a variety of industries. Occupational exposure to both amorphous and crystalline silica may occur during the production and use of diatomaceous earth. Fibres of amorphous silica are produced by a variety of plants, such as sugar cane and rice, and may be inhaled when released into the air during farming operations.

Large quantities of synthetic amorphous silica are produced as pyrogenic (fumed) silicas and wet process silicas (precipitated silicas and silica gels) which are used, notably, for reinforcing elastomers, for thickening resins, paints and toothpaste, and as free-flow additives. Exposure to synthetic amorphous silica may occur during its production and use. Synthetic amorphous silica may also be ingested as a minor constituent (< 2%) of a variety of food products where it serves as an anti-caking agent, and as an excipient in some pharmaceutical preparations. Silica fume is a form of amorphous silica (with small amounts of crystalline silica) unintentionally released into the air from certain metallurgical processes.

The mechanical, thermal and chemical history of a silica particle determines its surface properties and presence and abundance of various surface functionalities. Surface reactivity varies among silica samples from different sources. Heating converts hydrophilic surfaces into hydrophobic ones. In particular, freshly fractured surfaces are more reactive than aged ones.

5.2 Human carcinogenicity data

The evaluations for both crystalline and amorphous silica pertain to inhalation resulting from workplace exposures. Lung cancer was the primary focus. The Working Group's evaluation of the epidemiological evidence for potential causal relations between silica and cancer risk was focused principally on findings from studies that were least likely to have been distorted by confounding and selection biases. Among these studies, those that addressed exposure-response associations were especially influential in the Working Group's deliberations.

Crystalline silica

Possible differences in carcinogenic potential among polymorphs of crystalline silica were considered. Some studies were of populations exposed principally to quartz. In only one study (that of United States diatomaceous earth workers) was the exposure predominantly cristobalite. Studies of mixed environments (i.e. ceramics, pottery, refractory brick) could not delineate exposures specifically to quartz or cristobalite. Although there were some indications that cancer risks varied by type of industry and process in a manner suggestive of polymorph-specific hazards, the Working Group could only reach a single evaluation for quartz and cristobalite. Nonetheless, the Working Group did note a reasonable degree of consistency across studies of workers exposed to one or both polymorphs.

Ore mining

Seventeen cohort and five case-control studies were reported on ore miners potentially exposed to silica dust. The majority of these studies reported an elevated mortality for lung cancer among silica-exposed workers. However, in only a few ore mining studies were confounders such as other known occupational respiratory carcinogens taken into account. In such studies consistent evidence for a silica-lung cancer relationship was not found. Noteworthy instances where a relationship between lung cancer and crystalline silica was not detected include two independent studies of gold miners in South Dakota, United States, a study of miners in one lead and one zinc mine in Sardinia, Italy, and a study of tungsten miners in China. The results of most of the other studies could not be interpreted as an independent effect of silica — workers were concomitantly exposed to either radon, arsenic, or both, and in some cases other known or suspected occupational respiratory carcinogens were present in the work environment (e.g. diesel exhaust, polycyclic aromatic hydrocarbons, cadmium). In a few studies, no information was provided on exposure to radon or arsenic, in spite of the likelihood of these exposures.

Quarries and granite works

Six cohort studies were available for review. These studies provide important information on cancer risks because the workplace environments were generally free of reported exposures to potentially confounding agents (e.g., radon). All studies revealed lung cancer excesses. Direct quantification of silica dust exposure concentrations in relation to lung cancer risk was not conducted in any of these studies, mainly due to sparse occupational hygiene measurement data. However, some studies provided indications of exposure-response associations when surrogate dose data, such as duration of employment and category of exposure, were used. For example, findings for lung cancer include a nearly twofold mortality elevation among long-term granite shed workers in Vermont, United States, an eightfold elevation among sandstone workers in Copenhagen, Denmark, and a relative risk of roughly 3.5 among crushed granite stone workers in the United States with long duration of exposure and time since exposure onset. One study of German slate quarry workers indicated a more prominent relationship between employment duration and lung cancer among workers with silicosis than among workers without silicosis. The Working Group regarded radiographic evidence of silicosis as a marker of high exposure to silica.

Ceramics, pottery, refractory brick and diatomaceous earth industries

In refractory brick and diatomaceous earth plants, the raw materials (amorphous or crystalline silica) are processed at temperatures around 1000 °C with varying degrees of conversion to cristobalite. The results of two cohort studies of refractory brick workers from China and Italy and of one cohort study of diatomaceous earth workers from the USA provided consistent evidence of increased lung cancer with overall relative risks of about 1.5. In the study of refractory brick workers from China, a modest increasing trend of lung cancer was found with radiographic profusion category. A nearly twofold

elevated lung cancer risk was found among long-term workers in the Italian study. In the study of United States diatomaceous earth workers, increasing exposure-response gradients were detected for both non-malignant respiratory disease and lung cancer mortality.

In ceramic and pottery manufacturing plants, exposures are mainly to quartz, but where high temperatures are used in ovens, potential exposures to cristobalite may occur. In a cohort study of British pottery workers, lung cancer mortality was slightly elevated; a nested case-control analysis of lung cancer did not show an association with duration of exposure, but indicated a relationship between lung cancer mortality and average and peak exposures in firing and post-firing operations, with relative risks of approximately 2.0. In an Italian case-control study, apart from a fourfold increase in lung cancer in registered silicotics, there was a small increase in lung cancer for subjects without silicosis. In a case-control study from the Netherlands, there was little relationship overall between work in ceramics and lung cancer risk, but there was some suggestion that lung cancer risk was related to cumulative exposure.

Foundry workers

There were only three large cohort studies of foundry workers where silica dust or silicosis were considered as risk factors for cancer. One study from Denmark found a slightly elevated risk of lung cancer in silicotics compared with non-silicotics. Two studies, one from the United States and one from China, yielded conflicting results for lung cancer. The Chinese study suggested positive associations of silica with both lung cancer and stomach cancer, although there remained a potential for confounding by exposures to polycyclic aromatic hydrocarbons. The United States study did not demonstrate an association of lung cancer with cumulative silica exposure.

Silicotics

The vast majority of studies on registered silicotics reported excess lung cancer risks, with relative risks ranging from 1.5 to 6.0. Excesses were seen across countries, industries and time periods. A number of studies reported exposure-response gradients, using varying indicators of exposure. Some studies, in particular one from North Carolina (USA) and one from Finland, provide reasonable evidence for an unconfounded association between silicosis and lung cancer risk.

Summary of findings for crystalline silica (quartz and cristobalite)

For the evaluation of crystalline silica, the following studies provided the least confounded examinations of an association between silica exposure and cancer risk: (1) South Dakota, United States, gold miners; (2) Danish stone industry workers; (3) Vermont, United States, granite shed and quarry workers; (4) United States crushed stone industry workers; (5) United States diatomaceous earth industry workers; (6) Chinese refractory brick workers; (7) Italian refractory brick workers; (8) United Kingdom pottery workers; (9) Chinese pottery workers; (10) cohorts of registered silicotics from North Carolina, United States and Finland. Not all of these studies demonstrated excess

cancer risks. However, in view of the relatively large number of epidemiological studies that have been undertaken and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results would be expected. In some studies, increasing risk gradients have been observed in relation to dose surrogates — cumulative exposure, duration of exposure or the presence of radiographically defined silicosis — and, in one instance, to peak intensity exposure. For these reasons, the Working Group therefore concluded that overall the epidemiological findings support increased lung cancer risks from inhaled crystalline silica (quartz and cristobalite) resulting from occupational exposure. The observed associations could not be explained by confounding or other biases.

Amorphous silica

Very little epidemiological evidence was available to the Working Group. No association was detected for mesothelioma with biogenic amorphous silica fibres in the three community-based case-control studies. Separate analyses were not performed for cancer risks among a subset of diatomaceous earth industry workers exposed predominantly to amorphous silica.

5.3 Animal carcinogenicity data

Various forms and preparations of crystalline silica were tested for carcinogenicity by different routes of exposure.

Different specimens of quartz with particle sizes in the respirable range were tested in four experiments in rats by inhalation and in four experiments in rats by intratracheal instillation. In these eight experiments, there were significant increases in the incidence of adenocarcinomas and squamous-cell carcinomas of the lung; marked, dense pulmonary fibrosis was an important part of the biological response.

Pulmonary granulomatous inflammation and slight to moderate fibrosis of the alveolar septa but no pulmonary tumours were observed in hamsters in three experiments using repeated intratracheal instillation of quartz dusts.

No increase in the incidence of lung tumours was seen with one sample of quartz in the strain A mouse lung adenoma assay and with another quartz sample in a limited inhalation study in mice. Silicotic granulomas and lymphoid cuffing around airways but no fibrosis were seen in the lungs of quartz-treated mice.

In several studies in rats using single intrapleural or intraperitoneal injection of suspensions of several types of quartz, thoracic and abdominal malignant lymphomas, primarily of the histiocytic type (MLHT) were found. In rats, intrapleural injection of cristobalite and tridymite with particles in the respirable range resulted in malignant lymphomas, primarily MLHT.

A pronounced positive interactive effect of one sample of quartz and Thorotrast (an α -radiation emitting material) on pulmonary carcinogenesis was observed in one inhalation study in rats. Enhancement of benzo[*a*]pyrene-induced respiratory tract carci-

nogenesis by two different samples of quartz was seen in one intratracheal instillation study in hamsters.

In two studies in hamsters given mixtures of quartz and ferric oxide (1 : 1) by intratracheal instillation, no pulmonary tumours were observed.

Diatomaceous earth was tested by oral administration in rats and by subcutaneous and intraperitoneal injection in mice. No increase in the incidence of tumours was found after oral and subcutaneous administration; after intraperitoneal injection, a slightly increased incidence of intra-abdominal lymphosarcomas was reported.

In one test by intrapleural injection of biogenic silica fibres to rats, the silica fibres were not found to influence the tumour response to crocidolite but a small number of pleural mesotheliomas was reported in animals injected with 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one followed by administration of the biogenic silica fibres.

A food-grade micronized synthetic amorphous silica was tested by oral administration to mice and rats. No increased incidence of tumours was seen. In one study in rats using intrapleural implantation of two different preparations of synthetic amorphous silica, no increased incidence of tumours was observed.

5.4 Other relevant data

Crystalline silica

Crystalline silica deposited in the lungs causes epithelial and macrophage injury and activation. Crystalline silica translocates to the interstitium and the regional lymph nodes. Crystalline silica results in inflammatory cell recruitment in a dose-dependent manner. Neutrophil recruitment is florid in rats exposed to high concentrations of quartz; marked, persistent inflammation occurs accompanied by proliferative responses of the epithelium and interstitial cells. In humans, a large fraction of crystalline silica persists in the lungs, culminating in the development of chronic silicosis, emphysema, obstructive airways disease and lymph node fibrosis in some studies. In-vitro studies have shown that crystalline silica can stimulate release of cytokines and growth factors from macrophages and epithelial cells; evidence exists that these events occur *in vivo* and contribute to disease. Crystalline silica stimulates release of reactive oxygen and nitrogen intermediates from a variety of cell types *in vitro*. Oxidative stress is detectable in the lungs of rats following exposure to quartz.

Much less is known about the acute lung responses to inhaled crystalline silica in humans. Subjects with silicosis show an inflammatory response characterized by increased macrophages and lymphocytes but minimal increases in neutrophil numbers.

Only one human study was available on subjects exposed to dust containing crystalline silica, with no indication of the level of exposure; it showed an increase in the levels of sister chromatid exchange and chromosomal aberrations in peripheral blood lymphocytes.

Most cellular genotoxicity assays with crystalline silica have been performed with quartz samples. Some studies gave positive results, but most were negative. Some quartz

samples induced micronuclei in Syrian hamster embryo cells, Chinese hamster lung V79 cells and human embryonic lung Hel 299 cells, but not chromosomal aberrations in the same cell types. Two quartz samples induced morphological transformation in Syrian hamster embryo cells *in vitro* and 5 quartz samples induced transformation in BALB/c-3T3 cells. While quartz did not induce micronuclei in mice *in vivo*, epithelial cells from the lungs of rats intratracheally exposed to quartz showed *hprt* gene mutations. Inflammatory cells from the quartz-exposed rat lungs caused mutations in epithelial cells *in vitro*. Direct treatment of epithelial cells *in vitro* with quartz did not cause *hprt* mutation.

Tridymite was tested in only one study, where it induced sister chromatid exchange in co-cultures of human lymphocytes and monocytes.

Increasing in-vitro and in-vivo evidence suggests that the rat lung tumour response to crystalline silica exposure is a result of marked and persistent inflammation and epithelial proliferation. Other pathways such as a role for crystalline silica surface-generated oxidants or a direct genotoxic effect are not ruled out; however, at present, there is no convincing evidence for these alternative pathways.

Amorphous silica

Amorphous silicas have been studied less than crystalline silicas. They are generally less toxic than crystalline silica and are cleared more rapidly from the lung.

Biogenic silica fibres induced ornithine decarboxylase activity of epidermal cells in mice following topical application. No data were available to the Working Group on the genotoxicity of other amorphous silica particles.

5.5 Evaluation¹

There is *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources

There is *inadequate evidence* in humans for the carcinogenicity of amorphous silica.

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

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

There is *inadequate evidence* in experimental animals for the carcinogenicity of uncalcined diatomaceous earth.

There is *inadequate evidence* in experimental animals for the carcinogenicity of synthetic amorphous silica.

Overall evaluation

In making the overall evaluation, the Working Group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be

¹ For definition of italicized terms, see Preamble, pp. 24-27

dependent on inherent characteristics of the crystalline silica or on external factors, affecting its biological activity or distribution of its polymorphs.

Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources *is carcinogenic to humans (Group 1)*.

Amorphous silica *is not classifiable as to its carcinogenicity to humans (Group 3)*.

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