SILICON CARBIDE

1. Exposure Data

1.1 Chemical and physical properties

1.1.1 Nomenclature

(a) Silicon carbide fibres

Chem. Abst. Serv. Reg. No.: 308076-74-6

Chemical name: Synthetic fibres, silicon carbide

Synonyms: Ceramic fibres, silicon carbide; silicon carbide ceramic; silicon carbide ceramic synthetic fibres; silicon carbide fibres; silicon carbide synthetic fibres

Trade names: Dow X; Enhanced Nicalon; Hi-Nicalon; Nicalon NP 1616; SCS 6; SM; Sigma; Sylramic; Textron SCS 6; Tokamax; Tokawhisker S200; Tyranno ZX (Chemical Book, 2014).

(b) Non-fibrous silicon carbide

Chem. Abst. Serv. Reg. No.: 409-21-2

EINECS: 206-991-8

Chemical name: Silicon carbide

IUPAC systematic name: Silicon carbide

Chemical formula: SiC (ACGIH, 2003)

Molecular formula:

$Si^{+} \equiv C^{-}$

Relative molecular mass: 40.097

Synonyms: Carbon silicide; carborundum, a commercial name for silicon carbide abrasives, is sometimes used as a common name for silicon carbide dust; silicon monocarbide

Trade names: Annanox, Betarundum, Carbofrax, Carbogran, Carbolon, Crystar, Crystolon, Densic, DU-A, Ekasic, Green densic, Halsik, Hexoloy, Hitaceram, Ibiden, Lonza, Norton, Polisher, Shinano Rundum, Sika, Silundum, Sixcy, Supersic, Tokawhisker, Ultrafine (carbide) (CAMEO Chemicals, 2014) [this list is not intended to be exhaustive].

1.1.2 General description

Silicon carbide appears in two different crystalline forms: hexagonal α-silicon carbide is the main product, while cubic β-silicon carbide is formed at lower temperatures (Føreland et al., 2008). Silicon carbide occurs in several forms: as "non-fibrous," as "polycrystalline fibres," or as one of more than 150 different single-crystal modifications (or polytypes) of "whiskers" (Health Council of the Netherlands, 2012). A "whisker" is a type of single-crystal fibre, whereas a "fibre" may be single- or polycrystalline, or non-crystalline (ASTM, 2011).

Non-fibrous silicon carbide or the particulate material – also called silicon carbide dust, silicon carbide particles, or granular silicon carbide – has an average particle size of 1–20 μm. Exposure to silicon carbide dust can occur during the

manufacture or use of synthetic abrasive materials (Health Council of the Netherlands, 2012).

Silicon carbide fibres – also known as silicon carbide continuous fibres or silicon carbide ceramic fibres, which are mostly polycrystalline materials (ASTM, 2011) – are unwanted by-products of silicon carbide particle production and are considered to be pollutants (Bye et al., 1985; Dufresne et al., 1987a, b; Bégin et al., 1989; Scansetti et al., 1992; Dufresne et al., 1993, 1995; Dion et al., 2005; Gunnæs et al., 2005; Skogstad et al., 2006; Føreland et al., 2008; Bye et al., 2009; Føreland et al., 2013). The length and diameter of these fibres are variable, but fulfil the definition of WHO fibres (particles > 5 µm with a width of < 3 µm and an aspect ratio of > 3) (Rödelsperger & Brückel, 2006).

Fibrous silicon carbide may exist as whiskers or continuous fibres (Bye et al., 1985). Silicon carbide whiskers often have a diameter < 5 µm and a length > 20 µm and are thus respirable fibres similar to amphibole asbestos. Silicon carbide whiskers are single-crystal structures that are cylindrical in shape (ACGIH, 2003).

Silicon carbide fibres are unwanted by-products from the Acheson process and are morphologically heterogeneous, whereas silicon carbide whiskers are intentionally produced and have homogeneous morphology. Skogstad et al. (2006) reported the close resemblance of the morphology and size distribution of silicon carbide whiskers to those of the Norwegian airborne industrial by-product fibres used by Stanton & Layard (1978), Stanton et al. (1981) and Johnson et al. (1992) to carry out in-vivo and in-vitro tests.

1.1.3 Chemical and physical properties

From ASTM (1998), ACGIH (2003), Health Council of the Netherlands (2012), Chemical Book (2014)

Density (specific gravity): 3.22 g/mL at 25 °C

Crystalline form: Hexagonal or cubic

Refractive index: 2.650

Oxidation: Occurs above 700 °C

Sublimes and then decomposes: 2700 °C

Solubility: Insoluble in water, alcohol, and acid; soluble in molten alkalis (sodium hydroxide or potassium hydroxide) and molten iron

Reactivity: Chemical reactions do not take place at ordinary temperatures

Appearance: Variable, exceedingly hard, green to bluish-black, iridescent, sharp crystals

Odour: None

Conversion factor: 1 mg/m^3 = 0.5990 ppm at 20 °C.

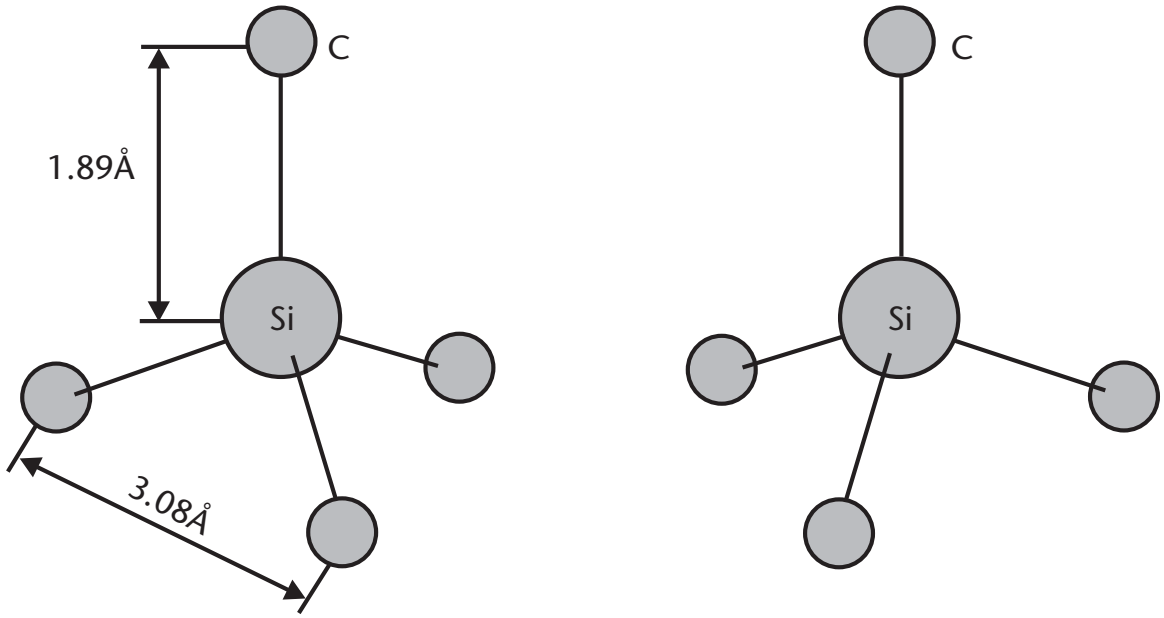
(a) Chemical properties

Silicon carbide is a crystalline material, the colour of which is determined by the level of impurities. Pure silicon carbide is colourless and transparent. The green to black colour of the industrial product results from impurities, mostly iron. The green specimen is a somewhat purer, slightly harder, but more friable form (Wright, 2006).

Although silicon carbide has a very simple chemical formula, it can exist as numerous different structures (polytypes) (Shaffer, 1969). These structures are composed of a single basic unit, a tetrahedral (SiC_4 or CSi_4) layer, with different stacking arrangements for silicon and carbon atoms (Kordina & Saddow, 2006; Oliveros et al., 2013). The distance between the carbon and silicon atom is 0.189 nm, and the distance between the carbon atoms is 0.308 nm (Fig. 1.1; Kordina & Saddow, 2006).

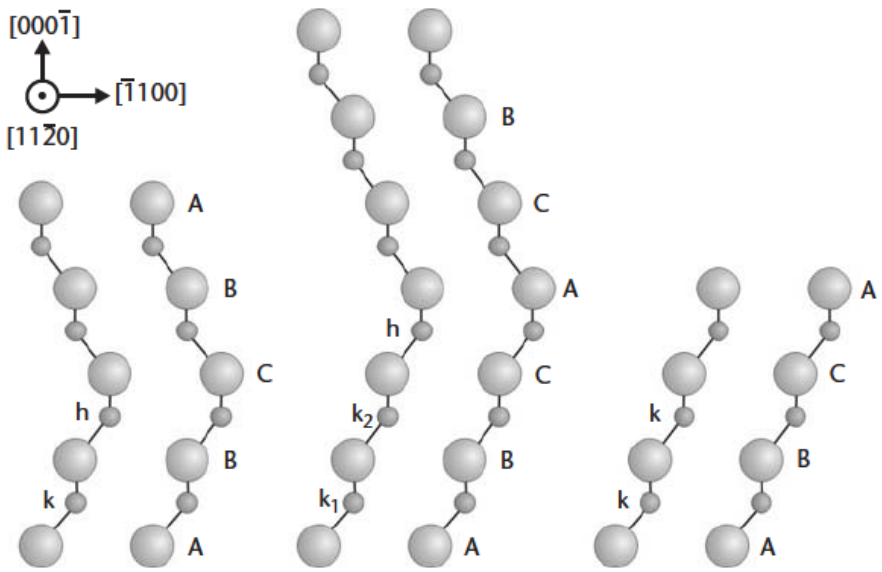
The polytypes are represented by a number showing how many tetrahedra are stacked along a specific direction in the unit cell and by a letter for the crystal symmetry: cubic (C) and hexagonal (H) (Fig. 1.2). The polytypes of silicon carbide are defined by the stacking order of the double layers of silicon and carbon atoms. The polytypes 3C-, 4H-, and 6H-silicon carbide are

Fig. 1.1 Silicon carbide tetrahedron formed by covalently bonded carbon and silicon



The characteristic tetrahedron building block of all silicon carbide crystals. Four carbon atoms are covalently bonded with a silicon atom in the centre. Two types exist. One is rotated 180 ° around the c-axis with respect to the other, as shown.
From Kordina & Saddow (2006). Reproduced with permission from Saddow SE and Agarwal A, Advances in Silicon Carbide Processing and Applications, Norwood, MA: Artech House, Inc., 2003. © 2003 by Artech House, Inc.

Fig. 1.2 Atomic stacking for silicon carbide polytypes



The three most common polytypes in silicon carbide viewed in the [1120] plane. From left to right: 4H-silicon carbide, 6H-silicon carbide, and 3C-silicon carbide; k and h denote crystal symmetry points that are cubic and hexagonal, respectively.
From Kordina & Saddow (2006). Reproduced with permission from Saddow, Stephen E, and Agarwal, Anant, Advances in Silicon Carbide Processing and Applications, Norwood, MA: Artech House, Inc., 2003. © 2003 by Artech House, Inc.

the most frequent. The simplest cubic structure is referred to as β-silicon carbide, whereas the hexagonal structure is referred to as α-silicon carbide (Gunnæs et al., 2005). All polytypes have equal proportions of silicon and carbon atoms but, because the stacking sequences between the planes differ, their electronic and optical properties differ (Kordina & Saddow, 2006; Wright, 2006).

Silicon carbide is very stable, but can nevertheless react violently when heated with a mixture of potassium dichromate and lead chromate. Chemical reactions between silicon carbide and oxygen as well as a variety of compounds (e.g. sodium silicate, calcium, and magnesium oxides) are possible at relatively high temperatures. Indeed, silicon carbide undergoes active or passive oxidation depending on the ambient oxygen potential. Passive oxidation occurs under conditions of high partial pressure of oxygen, producing a protective layer of silicon dioxide on the surface:

$2SiC\ (s) + 3O_2\ (g) \rightarrow 2SiO_2\ (s) + 2CO\ (g)$

[where s = solid and g = gaseous]

Accordingly, silicon carbide crystals take the form of a rainbow-like cluster caused by the layer of silicon dioxide produced by passive oxidation, which is determined primarily by the nature and concentration of impurities.

Active oxidation takes place under conditions of low partial pressure (30 Pa) of oxygen at 1400 °C and gaseous oxidation products are formed:

$SiC\ (s) + O_2\ (g) \rightarrow SiO\ (g) + CO\ (g)$

$SiC\ (s) + 2SiO_2\ (s) \rightarrow 3SiO\ (g) + CO\ (g)$

[where s = solid and g = gaseous]

Fresh surfaces of silicon carbide are thus exposed to the oxidizing atmosphere (Wright, 2006), and can be covered largely by silicon dioxide film or islets, heterogeneously distributed at the surface (Dufresne et al., 1987b; Boudard et al., 2014).

(b) Physical properties

The physical parameters of fibres (density, length, and diameter) as well as their aerodynamic behaviour are important factors that affect their respirability, deposition, and clearance in the respiratory tract (Cheng et al., 1995).

(i) By-product fibres from the Acheson process and cleavage fragments

The generation of fibres as a by-product has been demonstrated during the industrial production of silicon carbide in a Norwegian plant (Bye et al., 1985). Characterization of the airborne fibres from the furnace department in the silicon carbide industry showed that more than 93% of fibres consisted of silicon carbide fibres which were divided into eight categories based on their morphology. In addition, less than 2% of the fibres constituted silicon carbide fragments probably resulting from the cleavage of non-fibrous silicon carbide crystals and corresponding to WHO fibres; these fragments were mostly found during sorting operations. In the processing department, 25% of fibres consisted of silicon carbide fibres and 57% of cleavage fragments. The geometric mean (GM) length of all fibres > 5 μm was 9.5 μm (range, 5–900 μm) and the GM diameter of all fibres was 0.39 μm (range, 0.07–2.90 μm); 33% of the fibres had a diameter between 0.07 and 0.25 μm, and 15% corresponded to Stanton fibres (length, 8 μm; diameter ≤ 0.25 μm) (Skogstad et al., 2006). The occurrence of silicon carbide fibres was also confirmed in a Canadian silicon-carbide production factory (Dufresne et al., 1987b; Dion et al., 2005).

Silicon carbide cleavage fragments are elongated particles produced by the splintering of larger crystals during the grinding and classifying of silicon carbide. They can be distinguished from fibrous particles, such as asbestos, glass fibres, and whiskers, by their irregular shape. Typically they fulfil the WHO criteria for respirable fibres. Even granular or powdered silicon carbide may

Table 1.1 Typical parameters of three characterized types of silicon carbide whisker

Type	Fibre (total/µg)	Percentage of fibres with length > 5 µm	Percentage of fibres with diameter < 0.3 µm and length > 8.0 µm
SiC-W 1	7.6×10^6	31.0	3.8
SiC-W 2	1.61×10^5	93.7	6.9
SiC-W 3	1.05×10^7	30.8	10.8

SiC-W, silicon carbide whisker
Adapted from Johnson et al. (1992), by permission of John Wiley & Sons

contain traces of cleavage fragments that fulfil the definition of WHO fibres (Rödelsperger & Brückel, 2006).

(ii) Synthetic silicon carbide whiskers

Exposure to silicon carbide whiskers may occur during the manufacture of the whiskers or during the production, machining, and finishing of composite materials (Beaumont, 1991).

Silicon carbide whiskers have diameters of a few micrometres (average, 0.5 µm) and lengths of up to 5 cm (average, 10 µm) and occur mostly as hair- or ribbon-like crystals (Wright, 2006). Because whiskers are single crystals, they fracture across and not along the long dimension. They meet the dimensional criteria for a fibre (length:diameter (aspect) ratio, > 3) (Beaumont, 1991) but can exceed an aspect ratio of 10:1 (Rödelsperger & Brückel, 2006). Several types of silicon carbide whisker exist, some of which have been well characterized, and their typical parameters are presented in Table 1.1.

During the manufacture of discontinuously reinforced composites, silicon carbide whiskers are combined with metal or ceramic powders and formed into the desired shape. The metal composites can be extruded, forged, rolled, bent, and machined in a fashion similar to the base alloy. The ceramic composites can be machined on lathes, drill presses, and milling machines and finished by abrasive grinding in a manner similar to that of common metals. Some whiskers are released during the machining of ceramic and metal matrix composites (Beaumont, 1991).

(iii) Polycrystalline silicon carbide fibres

Polycrystalline silicon carbide fibres (diameter, generally < 2 µm; length, generally ≤ 30 µm) can also be manufactured for commercial purposes by various methods (i.e. polymer pyrolysis, chemical vapour deposition, or sintering) (Wright, 2006).

1.2 Sampling and analytical methods

The sampling and analytical methods for silicon carbide fibres are very similar to those for asbestos and man-made mineral fibres. Bulk samples are prepared and ground in an agate mortar to produce fine particles, and further processed using a mesh or gravimetric sedimentation in water. This suspension is then filtered and mounted for observation using appropriate analytical devices. Air samples are obtained using a vacuum pump equipped with a membrane filter to obtain a representative air volume, and the filters are then processed for the analytical methods. Biological specimens, such as lung tissues, lymph nodes, sputum, and bronchoalveolar lavage fluid (BALF), are digested using sodium hypochlorite or hydrogen peroxide or a combination thereof, and the mineral components are recovered on a filter for analysis. Tissue

samples can be ashed using a low-temperature plasma asher, and the ashed solutions are then filtered for further analysis.

All the processed samples on the filters can be analysed using a phase-contrast optical microscope (PCOM) to count the fibres according to WHO (1997) or National Institute for Occupational Safety and Health (NIOSH) method 7400 (NIOSH, 1994a). The sample-loaded filters can also be mounted on a stub and analysed using scanning electron microscopy with an energy dispersive X-ray analyser (SEM-EDX) (Funahashi et al., 1984; Bye et al., 1985) or mounted on a transmission electron microscopy (TEM) grid and analysed using TEM-EDX according to NIOSH method 7402 (NIOSH, 1994b). TEM allows analysis of the crystal structures and identification of the mineral fibres using electron diffraction and comparing them with reference minerals (Bye et al., 1985). Powdered bulk samples can be analysed using X-ray diffraction to observe the different crystalline compounds, based on NIOSH method 9000 (NIOSH, 1994c). To obtain the weight percentage of silicon carbide or other amphiboles, standards for silicon carbide should be prepared. Selected methods for the analysis of silicon carbide fibres in various matrices are presented in Table 1.2.

1.3 Production and use

1.3.1 History

Silicon carbide was first created synthetically by Edward Acheson in 1891 by heating quartz sand and carbon in a large electric furnace. Acheson called the new compound "carborundum", which became a trademark for a silicon carbide abrasive (Encyclopaedia Britannica, 2014). Subsequently, in 1905, silicon carbide was observed in its natural form by the chemist Henri Moissan, in a meteor crater located in Canyon Diablo, Arizona, USA. Moissanite, named in honour of its discoverer, is a transparent mineral that is as brilliant and almost as hard as diamond. Only synthetically produced silicon carbide is used for commercial applications because natural moissanite is very scarce (Wright, 2006).

The available information on history and production levels mostly concerns the Acheson production industry, involving mainly powdered and granular silicon carbide particulates. Thus data on the history and production levels of silicon carbide fibres and whiskers are limited.

1.3.2 Production levels

The world production capacity of silicon carbide was 1 010 000 tonnes in 2013. Of these, the Norwegian plants produced 8%, Japan produced 6%, Brazil produced approximately 4%, the USA and Canada produced 4%, and China was the world's leading producer of abrasive silicon carbide, accounting for 45% of the production capacity (Table 1.3).

Production and salient statistics for abrasive silicon carbide in the USA and Canada for 2013 are shown in Table 1.4. Silicon carbide was produced by two companies at two plants in the USA, and bonded and coated abrasive products accounted for most abrasive uses of silicon carbide (USGS, 2014). [These data were not available for other countries.]

During 2009–12, the USA imported 72% of the silicon carbide demand mainly from China (58%), South Africa (17%), the Netherlands (7%), Romania (7%), and others (11%) for crude products, and China (44%), Brazil (24%), the Russian Federation (8%), Norway (7%), and others (17%) for grains. About 5% of silicon carbide is recycled (USGS, 2014).

Table 1.2 Selected methods of analysis of silicon carbide fibres in various matrices

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Bulk samples				
	Direct transfer to SEM-stub	SEM-EDX	NR	Governa et al. (1997)
	Suspension filtration; mounting on SEM stub	SEM-EDX	NR	Johnson et al. (1992), Governa et al. (1997), Yamato et al. (1998)
	Suspension filtration; mounting on TEM grid	TEM-EDX	NR	Johnson et al. (1992)
	Deposition of fibrous dusts onto filter	PCOM	0.01 fibres/mL	HSE (1995, 1988), Miller et al. (1999)
	Deposition of fibrous dusts onto filter	SEM	NR	WHO (1985), Miller et al. (1999), Rödelsperger & Brückel (2006)
	Powder (for density)	Helium pycnometer	NR	Cheng et al. (1995)
	Powder (for surface area)	BET	NR	Governa et al. (1997)
Air samples				
	Direct reading instrument	Dust monitor	NR	Akiyama et al. (2003, 2007)
	Polycarbonate filter (25 mm, 0.4 µm pore)	SEM-EDX	NR	Bye et al. (1985), Skogstad et al. (2006)
	MCE filter (25 mm, 0.3 µm pore)	TEM-EDX-SAED	NR	Bye et al. (1985)
	MCE filter (25 mm, 0.8–1.2 µm pore)	PCOM	13 fibres/mm^2	Scansetti et al. (1992), WHO (1997); Dion et al. (2005), Føreland et al. (2013)
	Sampling with nylon cyclone (or HD cyclone, or aluminum cyclone); ashing with plasma asher; redeposition on silver membrane	XRD	0.005 mg per sample	Dufresne et al. (1987a), NIOSH (2003), Dion et al. (2005), Bye et al. (2009)
		XRD	12 µg	Føreland et al. (2013)
				Scansetti et al. (1992), NIOSH (1998)
	MCE filter (37 mm, 5 µm pore) with cyclone	Gravimetry	0.06 mg	Bye et al. (2009), Føreland et al. (2013)
	Aerosol generation by small scale particle disperser	Cascade impactor (MMAD)	NR	Cheng et al. (1995)
	Heubach, MRI dustiness tester	Cascade impactor (dustiness)	NR	Plinke et al. (1992)
Biological samples				
Human lung and bronchoalveolar lavage fluid	Digestion with sodium hypochlorite, hydrogen peroxide or low temperature ashing	TEM-EDX	NR	Hayashi & Kajita (1988), Dufresne et al. (1995)
		SEM-EDX	NR	Funahashi et al. (1984), De Vuyst et al. (1986)
Animal lung	Digestion and filtration	XRD	NR	Akiyama et al. (2003, 2007)
		SEM	NR	Davis et al. (1996)
		TEM-EDX	NR	Dufresne et al. (1992)

BET, Brunauer–Emmett–Teller; EDX, energy dispersive X-ray analyser; HD, Higgins–Dewell; MCE, mixed cellulose esters; MMAD, mass median aerodynamic diameter; MRI, Midwest Research Institute; NR, not reported; PCOM, phase-contrast optical microscopy; SAED, selected area electron diffraction; SEM, scanning electron microscopy; TEM, transmission electron microscopy; XRD, X-ray diffraction

Table 1.3 World production capacity for silicon carbide in 2013

Country	Production capacity (tonnes)
China	455 000
Norway	80 000
Japan	60 000
Mexico	45 000
Brazil	43 000
USA and Canada	42 600
Germany	36 000
Venezuela	30 000
France	16 000
Argentina	5 000
India	5 000
Other countries	190 000
World total (rounded)	1 010 000

Compiled by the Working Group with data from USGS (2014)

Table 1.4 Production volume and salient statistics for abrasive silicon carbide in the USA and Canada, 2013

Salient statistic	Amount (tonnes)
Production, USA and Canada (crude)	35 000
Imports for consumption (USA)	108 000
Exports (USA)	17 700
Consumption, apparent (USA)	125 000

Compiled by the Working Group with data from USGS (2014)

1.3.3 Production methods

Silicon carbide is intentionally manufactured by several processes depending on the levels of purity, crystal structure, particle size, and shape required.

(a) Acheson process

The Acheson process is most frequently used for the production of silicon carbide by the carbothermal reaction of a mixture of petroleum coke (carbon) and high purity crystalline silica (quartz) in an open electrical resistance furnace (Gunnæs et al., 2005). A silicon carbide plant can be divided into four different departments: material storage, preparation areas, the furnace department where the crude silicon carbide is produced, and the processing department where the silicon carbide grits are manufactured, as presented in Fig. 1.3 (Føreland et al., 2008).

Sawdust is occasionally added to the mixture to reduce its density, to facilitate the escape of evolved gaseous carbon monoxide, and to improve the porosity of the furnace mix (Smith et al., 1984; Føreland et al., 2008). Silica reacts with carbon to produce silicon carbide and carbon monoxide according to the following overall reaction:

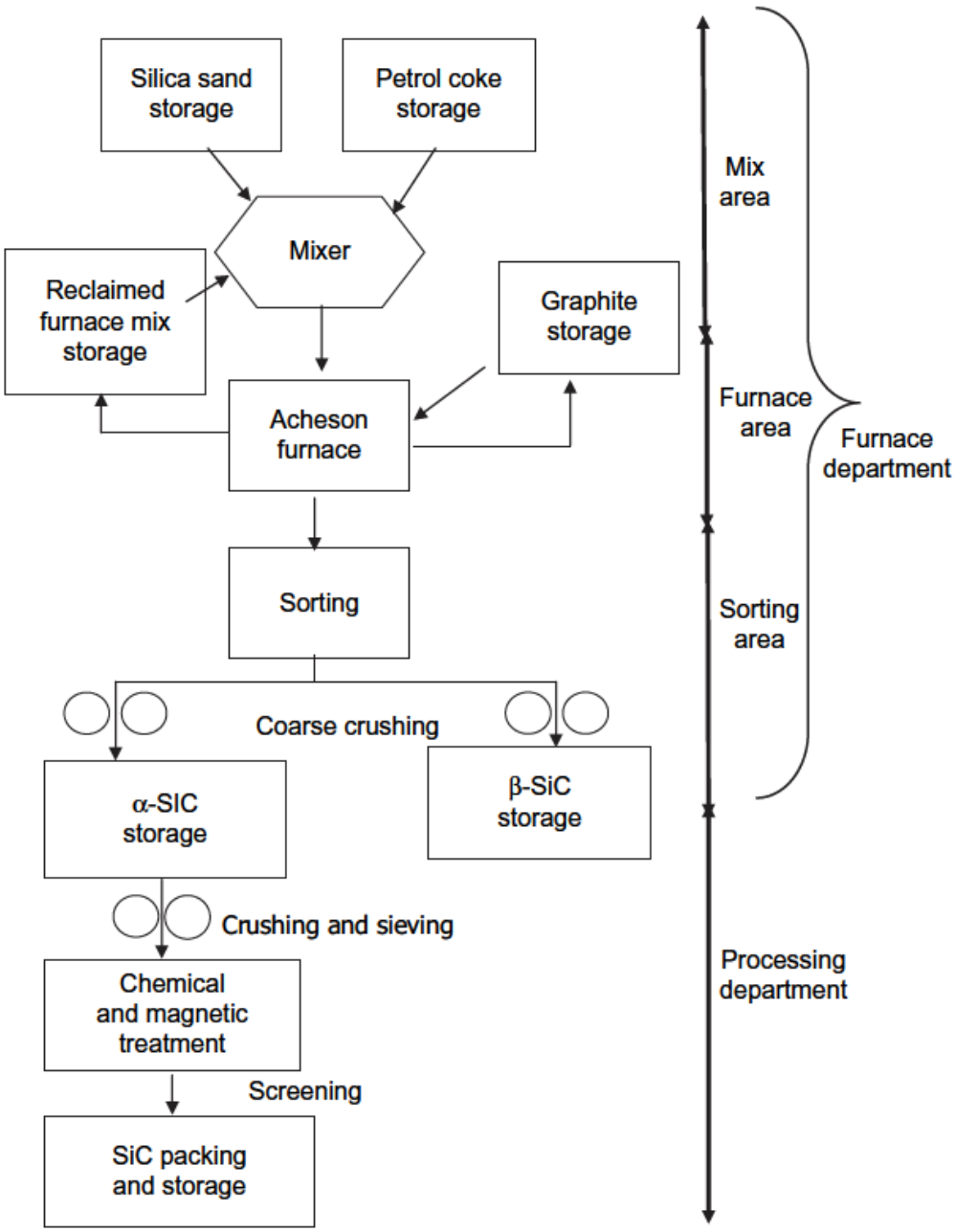
$SiO_2 + 3C \rightarrow SiC + 2CO$ (Føreland et al., 2008)

The Acheson furnace is heated by a direct current passing through powdered graphite within the charge mixture (Fig. 1.4). The furnace is fired for 40–48 hours, during which temperatures in the core vary from > 1700 to 2700 °C, and is < 140 °C at the outer edge. Silicon carbide develops as a cylindrical ingot around the core, with radial layers growing from graphite in the inside (which can be recycled to the next furnace) to hexagonal α-silicon carbide (the highest grade material with a coarse crystalline structure, 98% silicon carbide), cubic β-silicon carbide (metallurgical grade, 90% silicon carbide), firesand (80% silicon carbide, recycled to the next furnace), the crust (a condensation layer of silicon dioxide and other oxide impurities), and finally partly and unreacted material (sand and coke) on the outside (Saint-Gobain, 2014).

After the heating cycle, the furnace is disassembled and the side walls are removed to allow cooling (up to 2 weeks). A cross-sectional view of the resistor furnace after cooling is given in Fig. 1.5 (Indian Institute of Science, 2014).

The outer layer of non-reacted mixture is removed from the crude and returned to the mix area, exposing the core of green or black silicon carbide crystals. The crude silicon carbide is transported to the sorting area where β-silicon carbide is removed from α-silicon carbide. The final α-silicon carbide product is an aggregate of

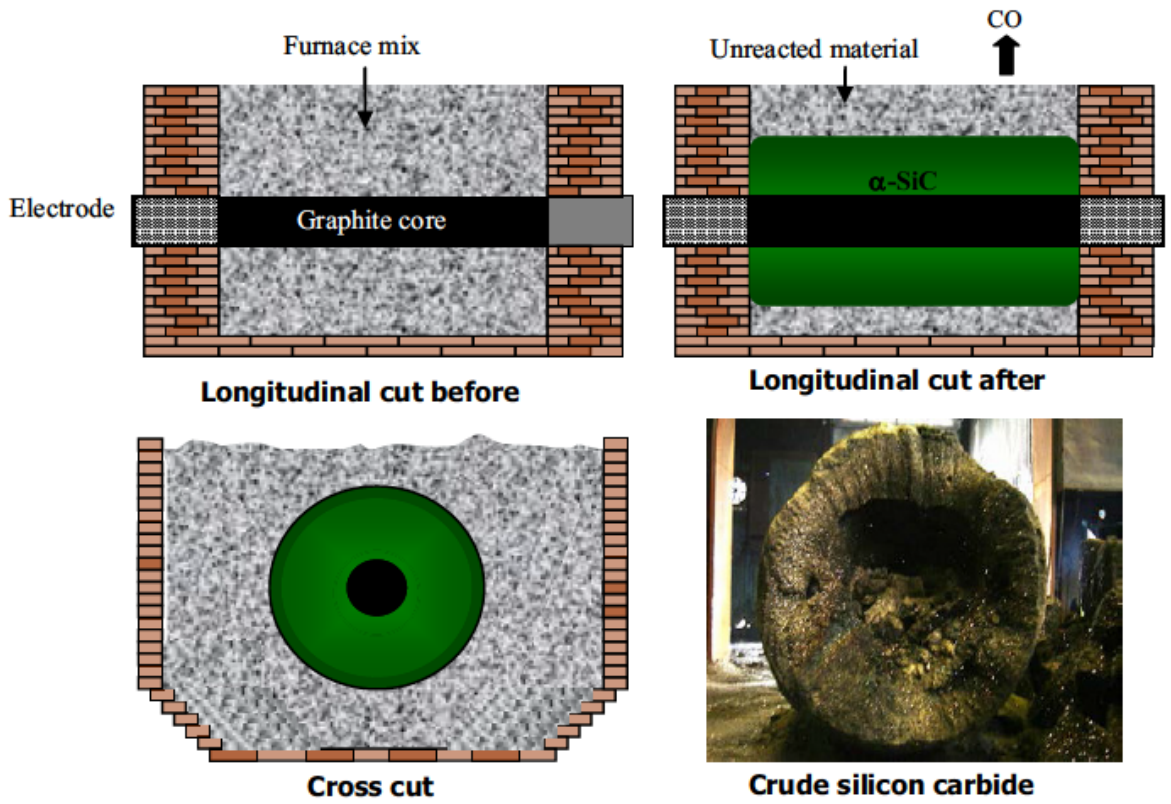
Fig. 1.3 Flow diagram depicting production of silicon carbide by the Acheson process



SiC, silicon carbide

Reproduced from Føreland et al. (2008). Føreland S, Bye E, Bakke B, Eduard W, Exposure to fibres, crystalline silica, silicon carbide and sulfur dioxide in the Norwegian silicon carbide industry, *Annals of Occupational Hygiene*, 2008, volume 52, issue 5, pages 317–336, by permission of Oxford University Press

Fig. 1.4 The Acheson furnace and the crude silicon carbide product



SiC, silicon carbide; CO, carbon monoxide
Reproduced from Føreland (2012), with permission of the author

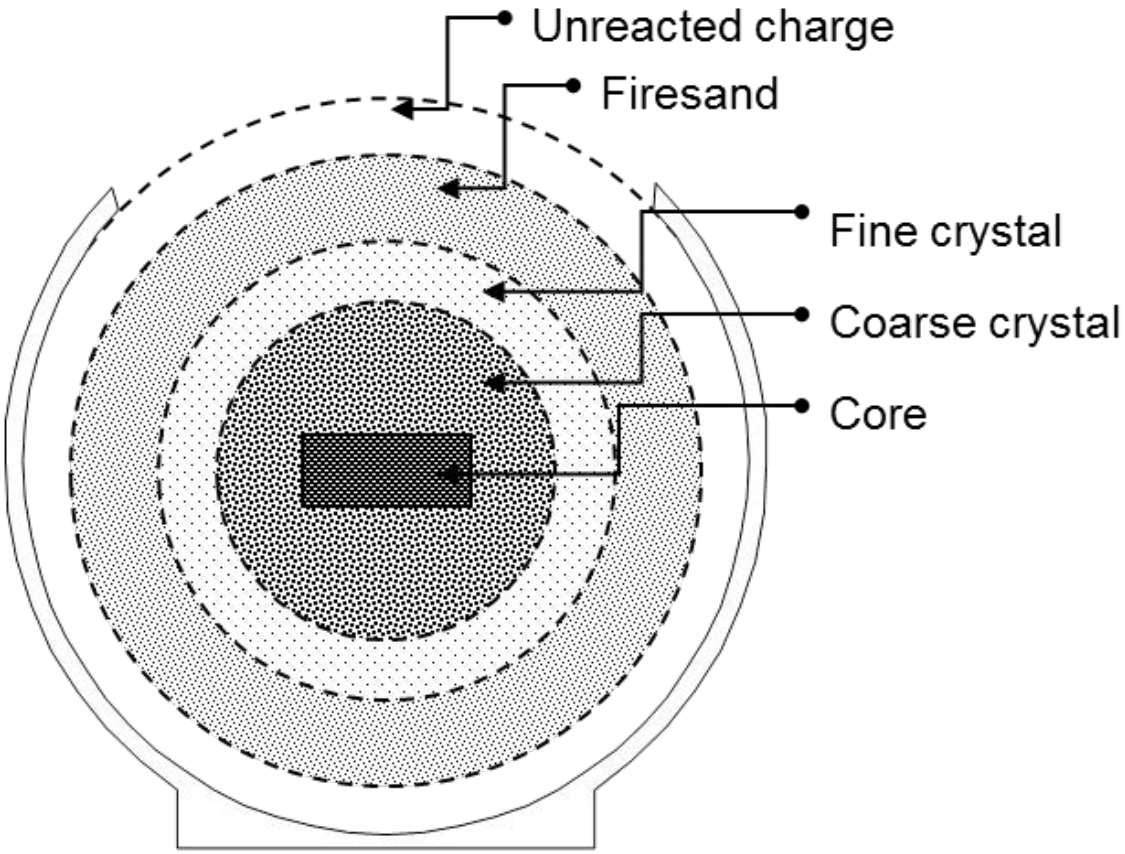
iridescent crystals, due to a thin layer of silica from superficial oxidation of the carbide, which is transported to the processing department for crushing, grounding, magnetic and chemical treatments to remove impurities, and screening into the size required for the end-use (Wright, 2006; Føreland et al., 2008). Two different types of silicon carbide crystal may be obtained: green silicon carbide is the purest material with > 99% silicon carbide, while the black material contains ~98% silicon carbide (Bye et al., 2009).

Formation of silicon carbide fibres

Silicon carbide fibres are formed during the Acheson process in the intermediate region, where the partly reacted material is found (Bye et al., 1985). The fibres are believed to be formed when a blow of gas escapes the baking lump of silicon dioxide–petroleum coke in the electric furnace (Bégin et al., 1989). Different morphologies of fibrous silicon carbide in this layer have been observed by SEM and TEM (Gunnæs et al., 2005; Skogstad et al., 2006). The high concentration of fibres during the handling of the raw material is consistent with the fibres encountered in recycled material. Silicon carbide fibres have not been observed in the final abrasive products, but have been observed in products for refractory and metallurgical purposes (firesand) (Føreland et al., 2008; Bye et al., 2009; Bruch et al., 2014).

In addition to silicon carbide fibres (including whiskers), the production of silicon carbide generates many airborne contaminants including

Fig. 1.5 Cross-sectional view of the Acheson furnace after cooling



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quartz, cristobalite, graphite, and non-fibrous silicon carbide dust (Bye et al., 2009). Sulfur dioxide (from the oxidation of sulfur contained in the petroleum coke) and polycyclic aromatic hydrocarbons are also found in the environment of the Acheson furnace (Bye et al., 1985; Dufresne et al., 1987a; Føreland et al., 2008).

(b) Synthesis of silicon carbide powder and whiskers from rice hulls

The conversion of silicon dioxide particles in plant material (as rice hulls) to silicon carbide is carried out by heating in the excess carbon from the organic material. Rice hulls contain 16–26% by weight of silica. The silica is amorphous and is transformed into β-silicon carbide by pyrolysis. High quality silicon carbide powder and whiskers are produced from rice hulls without catalysts using an inexpensive method. The rice hulls are preheated at 750–850 °C in the absence of air for 3 hours. The temperature is gradually increased to 1300 and 1400 °C over 12 hours in an argon atmosphere. Different structures are found: needles with a diameter of 0.25 μm; fibres of about 0.16 μm in diameter; spherical particles of 1 μm in diameter; and structures with the original morphology. Excess carbon is eliminated by burning in an air atmosphere at 850 °C for 6 hours and residual silicon oxide is

removed by washing with a solution of fluoric acid (Rodriguez-Lugo et al., 2002).

(c) Synthesis of silicon carbide whiskers from waste serpentine

Serpentine rock can be used as a raw material for the production of a high-reactivity amorphous silica powder, which can then be used for the synthesis of silicon carbide. Amorphous silica is obtained by the extraction of waste serpentine at 80 °C in 5M sulfuric acid for 48 hours. The amorphous silica powder is then reacted with carbon black at 1550 °C for 5 hours to obtain β-silicon carbide whiskers for use as a raw material in industry (Cheng & Hsu, 2006).

(d) Other production methods

Silicon carbide is also produced, for special applications, by other advanced processes (Wright, 2006).

(i) Physical vapour transport (or modified Lely process)

Large single crystals of silicon carbide are produced from a form of physical vapour transport growth in which silicon and carbon are transported at high temperatures through a reactor to a growing seed crystal. The silicon carbide crystals can then be sliced into wafers up to 100 mm in diameter (Wright, 2006).

(ii) Chemical vapour deposition

Wear-resistant layers of silicon carbide as well as silicon carbide fibres or whiskers for reinforcing metals or other ceramics can be formed by chemical vapour deposition, a process in which volatile compounds containing carbon and silicon are reacted at high temperatures in the presence of hydrogen. The silicon carbide whiskers produced by chemical vapour deposition with silicon oxide and carbon monoxide as the primary reactants are similar to those produced by pyrolysis or the thermal decomposition of rice hulls (Sharma et al., 1984).

(iii) Vapour–liquid–solid process

Silicon carbide whiskers of high purity are produced by this process, in which the crystal growth occurs by precipitation from the supersaturated liquid at the solid–liquid surface. The vapour contains a carbon-bearing gas (methane) and silicon monoxide (Milewski et al., 1985).

1.3.4 Use

Silicon carbide has been produced on a large scale since 1893 for use as an abrasive. This was followed by electronic applications, in light-emitting diodes and detectors in early radios (Wright, 2006).

Most of the silicon carbide produced worldwide today is in the form of grains or powder for use as an abrasive. Additional silicon carbide applications are: refractories, electrical devices, electronics (semiconductor), diesel particles filters, ceramics, industrial furnaces, structural materials, and metallurgy (Wright, 2006). Silicon carbide is also used by the aerospace, automotive, and power generation industries as a reinforcing material in advanced ceramic composites (ACGIH, 2003; USGS, 2014). Although no application has been found for the unwanted fibres from the Acheson process, metallurgical grade silicon carbide that contains silicon carbide fibres may be sold to the industry.

Silicon carbide whiskers have a wide range of industrial uses related to its high tensile strength, weight advantage over metals, and stability at high temperatures. They are used for ceramic seals, sandblast nozzles, and structural materials for applications at high temperatures, as durable asbestos substitutes (Health Council of the Netherlands, 2012).

1.4 Natural occurrence

Only minute quantities of silicon carbide exist in nature.

1.5 Exposure

1.5.1 Exposure of the general population

No data have been reported on the levels of silicon carbide fibres in non-occupational environmental matrices such as air, water, and soil.

1.5.2 Occupational exposure

Silicon carbide in fibrous and non-fibrous forms has been detected in occupational environments. Various forms of silicon carbide can comply with the WHO definition of a fibre (i.e. a particle longer than 5 µm with a diameter of less than 3 µm and an aspect ratio of more than 3), including intentionally manufactured monocrystalline silicon carbide whiskers, intentionally manufactured polycrystalline silicon carbide fibres, unwanted silicon carbide fibres resulting as by-products of the manufacture of silicon carbide (partially reacted materials), and cleavage fragments of crude silicon carbide (Lockey, 1996; Rödelsperger & Brückel, 2006; Wright, 2006).

Inhalation is the primary route of exposure to fibrous silicon carbide in occupational settings, but data on the number of workers occupationally exposed to silicon carbide fibres are lacking. However, the United States National Occupational Exposure Survey (1981–83) estimated that about 250 900 workers were exposed to silicon carbide. The industries with the largest number of exposed workers included machinery (except for electrical), and electric and electronic equipment. The United States National Occupational Exposure Survey also estimated that about 17 500 and 8700 workers were exposed to silicon carbide powder and silicon carbide dust, respectively (NIOSH, 2014).

(a) Manufactured silicon carbide fibres

The term "silicon carbide whiskers" specifically refers to monocrystalline forms produced at high cost for targeted high technology use, such as in the aerospace industry (Wright, 2006). To characterize silicon carbide whiskers, Cheng et al. (1995) aerosolized them and took samples from a filter. The count median length of the aerosol samples was 3.43 µm and the count median diameter was 0.198 µm. Thus, only a fraction of the aerosol could be defined as WHO fibres. According to the aerodynamic size, 65% (cascade impactor) to 76% (aerosol centrifuge) of the silicon carbide aerosol particles were respirable.

Exposures to both these respirable manufactured silicon carbide whiskers and silicon carbide fibres may occur during their production and the manufacturing/machining/finishing/use of composite materials (Johnson et al., 1992; Lockey, 1996; Cook, 2006; Wright, 2006; Malard & Binet, 2012). However, limited information on the quantification of such exposures has been reported in the literature.

Beaumont (1991) monitored total fibre occurrence during the machining of silicon carbide whisker-reinforced metals and ceramics. Calculated 8-hour time-weighted average (TWA) exposures ranged from 0.031 fibres/mL to 0.76 fibres/mL, depending on the processes used. Control improvements to optimize the local exhaust ventilation and/or cleaning coolant provided a substantial reduction in the exposure to fibres (see Table 1.5).

Possible airborne fibre release from silicon carbide cutting tips used on some machine tools was investigated by on-site monitoring and during simulated work activities in a laboratory (Revell & Bard, 2005). All airborne fibre concentrations for each sample were below the limit of quantification during on-site monitoring. SEM analysis of a fractured surface silicon carbide ceramic tip showed a large number of fibres, typically about 2 µm in length and 0.5 µm in diameter. Using fractured tips could lead to exposures to fibres because protruding fibres could feasibly be broken off easily. However, laboratory tests to simulate a cutting action using silicon carbide

Table 1.5 Calculated 8-hour time-weighted average exposures to fibres during machining of silicon carbide whisker-reinforced composite materials before and after control improvements

Description	Concentration (fibres/mL)	
	Before	After
Machining of metal matrix composites	0.031	NA[a]
Lathe machining of green ceramic composites	0.26	0.034
Lathe machining of pre-sintered ceramic composites	0.76	0.038
Cutting pre-sintered ceramic composites with tool post grinder	NC[b]	0.031
Surface grinding of fired ceramic	0.21	0.0062
Inside/outside grinding of fired ceramic	0.075	0.016

[a] NA, not applicable because no changes were made in the metal machining area
[b] NC, this value could not be calculated from the data collected
Adapted from: Reduction in airborne silicon carbide whiskers by process improvements, Beaumont (1991), *Journal of Occupational and Environmental Hygiene*, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com)

whisker ceramic tips indicated that very few fibres were released; concentrations were below the limit of quantification of 0.04 fibres/mL.

Several other forms of silicon carbide are used in industries. Nixdorf (2008) indicated that new non-respirable silicon carbide (diameter, 5–10 μm) can be used as a substitute for other respirable silicon carbide particles. Malard & Binet (2012) reported the use of the silicon carbide Nicalon® (diameter, typically 14 μm) in reinforced composite materials. However, these silicon carbide forms do not comply with the WHO definition of a fibre. The possibility of releases of submicron airborne particles could be investigated during machining operations on these reinforced materials.

(b) By-products of silicon carbide production

(i) Studies of exposed workers

Silicon carbide fibres also appear and were mainly investigated as unwanted by-products generated during the production of silicon carbide crystals through the Acheson furnace process (Lockey, 1996). Results from field studies are summarized in Table 1.6.

Quantification of these undesired airborne silicon carbide fibres was first reported in three Norwegian silicon carbide production plants by Bye et al. (1985). Short-term (15–50 minutes) personal or stationary samples were collected at various workplaces and fibres were counted using PCOM. The concentrations of silicon carbide fibres reported in the three plants were 0.1–4.9 fibres/mL during the mixing of raw material, 0–3.6 fibres/mL during furnace operations, 0.2–2.7 fibres/mL during the separation of raw products, and 0–0.2 fibres/mL during the preparation of final products. The analysis of an airborne dust sample (100 fibres evaluated) by SEM showed fibres with diameters and lengths ranging from 0.5 μm to 2.5 μm and from 1 μm to 50 μm, respectively. The presence of long (length, up to 20 μm) and thin (diameter, 0.2–0.5 μm) airborne fibres in the silicon carbide industries was later confirmed (but not quantified) by Dufresne et al. (1987b) using SEM.

Scansetti et al. (1992) measured fibre concentrations by PCOM or SEM in samples obtained by static sampling in an Italian plant operating 24 Acheson furnaces. GMs of respirable fibre concentrations determined by PCOM for the different working operations are given in Table 1.6. GMs of respirable fibre concentrations were also determined by SEM and the ratios of SEM to PCOM ranged from 1.15 to 2.02 indicating the presence of thin fibres below the PCOM limit of detection. High variability in

Table 1.6 Reported personal and/or static measurements of fibres (fibres/mL) in silicon-carbide production plants

Reference	Country, year of study	Plant	Furnace department			Processing department	Maintenance department
			Mixing of raw material (No.)	Furnace operations (No.)	Separation of material /sorting (No.)	Preparation of final product/refinery (No.)	
Bye et al. (1985)	Norway, 1985	A B C	0.3 (1) 0.1–1.9 (7) 1.8–4.9 (4)	0–3.6 (16) 0.1–1.9 (4) 0.1–0.7 (7)	0.2–0.7 (6) 0.2–2.7 (6) 0.2 (3)	0–0.1 (2) 0.1–0.2 (3) 0–0.1 (3)	
Romundstad et al. (2001)[a]	Norway, 1982–88	A B C	0.9 (6) 1.1 (15)	0.3 (29) 0.5 (29) 0.4 (14) and 0.9 (12)	0.8 (24) 1.1 (19) 1.8 (13)	0.04 (3)	
Scansetti et al. (1992)[b]	Italy, 1990	–	0.07 (9)	0.11 (6) (loading) 0.14 (4) (heating) 0.63 (6) (side-opening) 0.14 (4) (cooling)	0.58 (6) (cylinder breaking) 2.40 (6) (unreacted material removing)	0.71 (11) (selection) 0.41 (12) (crushing)	
Dion et al. (2005)[c]	Canada, 2000	–	–	0.03–0.11 (3) (assistant operator) 0.16–0.39 (3) (furnace attendant) 0.23–0.67 (3) (subproduct attendant)	0.25–0.89 (12) (carboselector)	0.42–0.77 (3) (crusher) 0.06–0.15 (4) (millwright)	
Føreland et al. (2008)[b]	Norway, 2002–03	A B C	0.097 (14) – 0.046 (10)	0.082–2.7 (54) 0.025–0.062 (44) 0.039–0.36 (72)	0.13 (19) 0.19 (21) 0.43 (21)	0.011–0.030 (94) 0.007–0.037 (102) 0.011–0.021 (100)	0.034–0.086 (69) 0.017–0.041 (69) 0.017–0.049 (37)

[a] Estimates based directly on measurements
[b] Geometric mean values
[c] Values are 8-hour time-weighted averages
Compiled by the Working Group

the workplace environment was reported in the majority of the working operations studied.

To study cancer incidence among 2620 men employed in all three Norwegian silicon carbide plants, Romundstad et al. (2001, 2002) estimated exposures to silicon carbide fibres for different occupations from 1912 to 1996 for plant A, from 1965 to 1996 for plant B, and from 1963 to 1996 for plant C. Estimated exposures, presented in Table 1.6, were based on industrial hygiene measurements carried out between 1982 and 1988 and on descriptions of changes in the process technology and work practices over time. Arithmetic means of silicon carbide fibre concentrations calculated by job over the whole sampling period are presented in Table 1.7. The highest levels were reached during mixing raw materials, oven work, and sorting. Estimated exposures indicated a continual decrease in workplace levels of silicon carbide fibres from the 1910s to the 1990s in plant A.

Gunnæs et al. (2005) investigated the chemical composition, structure, surface properties, and morphology of clustered silicon carbide fibres in one of the three industrial silicon carbide plants in Norway. Fibres were collected both by personal sampling in the furnace hall and by collecting material containing fibres from the zone between the silicon carbide crust and the outer firesand layer. A large variety of silicon carbide fibres was found both in the air samples and in the samples taken from the furnace. The authors described a complex morphology of needles with branches based on a face-centred cubic structure and covered by a thin amorphous layer of carbon.

Additional investigations in the three Norwegian plants by Skogstad et al. (2006) provided a detailed description of the morphological variation of the fibres by classifying their types by shape, chemical composition, and dimensions and exploring possible determinants of the occurrence of these various types. A total of 32 short-term (0.5–2 hours) personal samples were analysed by SEM The authors classified the silicon carbide fibres into categories (K1–K8 and CF) according to their morphologies, including a category for fibres that could not easily be assigned to one of the seven previous groups (K8) and one for those that satisfied the fibre counting criteria (CF). The category K4 comprises around 50% of all fibres identified. These thin fibres were "rectilinear but often tapered along the fibre axis." In addition, approximately 15% and 10% of the fibres counted were classified as K1 ("straight fibres [that] looked like a staple of discs perpendicular to the fibre axis") and K2 ("straight fibres with variable diameter along the fibre axis") categories, respectively. Fewer than 10% of the fibres counted were not silicon carbide fibres, but were carbon fibres, silicon oxide fibres, silicon fibres, vanadium-rich fibres, and man-made vitreous fibres. The proportions of the various silicon carbide categories were shown to differ between plants, jobs, and production parameters. For all categories, the arithmetic means of the diameter, length, and aspect ratio of counted fibres were 0.51 μm, 12 μm, and 36, respectively.

Dion et al. (2005) examined nearly 100 measurements of silicon carbide fibre concentrations in one Canadian factory producing silicon carbide abrasive material (grains or particles). Fibres were counted from personal samples following the WHO method (using PCOM) and the 8-hour TWA concentrations were calculated for six groups of workers: assistant operators of station 01, Acheson furnace attendants (loading mix into the furnace), subproduct attendants, crusher and backhoe operators, carboselectors, and millwrights. The 8-hour TWA concentrations ranged from 0.03 fibres/mL (for assistant operators at station 01) to 0.89 fibres/mL (for carboselectors breaking up and sorting silicon carbide lumps). Crushers, who also screen all grades of the silicon carbide produced into several sizes, had the second highest exposure (8-hour TWA of between 0.42 and 0.77 fibres/mL).

Table 1.7 Comparison of estimated retrospective exposure assessment to silicon carbide fibres for selected job groups and study periods from the studies of Romundstad et al. (2001) and Føreland et al. (2012)

Job group	Study period	Fibre concentrations (fibres/mL), arithmetic mean	
		Romundstad et al. (2001)	Føreland et al. (2012)
Plant A			
Mix	1912–36	4.4	0.37
	1936–52	2.2	0.29
	1953–79	1.6	0.23
	1980–96	0.9[a]	0.15
Charger	1915–38	3.3	0.89
	1939–52	2.8	0.67
	1953–59	2.1	0.55
	1960–79	1.2	0.49
	1980–96	0.3[a]	0.36
Crane	1938–52	2.8	0.33
	1953–58	1.3	0.22
	1959–96	0.3	0.15
Sorter	1913–33	3.2	1.0
	1934–52	2.4	0.76
	1953–96	0.8[a]	0.26
Refinery	1914–43	0.06	0.06
	1947–96	0.04[a]	0.05
Fines	1931–43	0	0.02
	1947–96	0	0.02
Packer	1914–43	0.06	0.25
	1947–96	0.04	0.20
Plant B			
Mix	1965–81	2.8	0.13
	1982–96	1.1[a]	0.1
Crane	1965–81	0.2	0.12
	1982–96	0.2	0.09
Sorter	1965–81	1.1	0.65
	1982–96	1.1[a]	0.46
Refinery	1965–96	0.06	0.05
Fines	1965–96	0	0.03
Plant C			
Mix	1963–96[b] or 1964–96[c]	0.6	0.07
Charger	1963–96[b] or 1964–96[c]	0.4[a]	0.47
Payloader	1963–96[b] or 1964–96[c]	0.9[a]	0.39
Crane	1963–79[b] or 1964–96[c]	0.4	0.10
Sorter	1963–96[b] or 1964–96[c]	1.8[a]	0.67
Refinery	1963–96	0.05	0.03
Fines	1963–96	0	0.02

[a] Measured data
[b] Romundstad et al. (2001)
[c] Føreland et al. (2012)
Adapted from Føreland et al. (2012)

In the three Norwegian plants producing silicon carbide, Føreland et al. (2008) assessed personal exposure to silicon carbide fibres for 13 different job groups classified in three departments (furnace, processing, and maintenance). Approximately 720 new short-term (0.5–3.5 hours) personal measurements were taken during the period 2002–03 and counted according to the WHO counting criteria (WHO, 1997). GMs of fibre levels were in the range 0.007–2.7 fibres/mL for all jobs and plants. The highest exposures were monitored in the furnace department. The Norwegian exposure limit for fibres (0.1 fibres/mL) was exceeded by 53%, 17%, and 0.2% of the samples from the furnace, maintenance, and processing departments, respectively. The authors reported that 78% of the workers in the furnace department used respirators.

To construct a retrospective job–exposure matrix (JEM) for the Norwegian silicon carbide industry, Føreland et al. (2012) combined historical exposure data from company records, the Norwegian Labour Inspectorate records, and studies performed by the National Institute of Occupational Health (NIOH). Mixed-effect models were used to estimate the exposure to silicon carbide fibres for each plant which is expected to give more accurate assessments. Arithmetic means of exposures were estimated for several job groups depending on the plant: mix, charger, payloader, crane, sorter, refinery, fines, and packer (see Table 1.7). The new estimated exposure data were compared with the original JEM developed by Romundstad et al. (2001). The fibre exposure estimates using the novel method (Føreland et al., 2012) were 3.2 times lower on average than those in the previous JEM, and this method was used by Bugge et al. (2011, 2012) to update previous Norwegian epidemiological investigations.

To identify the determinants of exposure to dust and dust constituents in the Norwegian silicon carbide industry, Føreland et al. (2013) assessed exposures to silicon carbide fibres in the three Norwegian plants, and data formerly presented in Føreland et al. (2008) for each plant were grouped for the three plants. As previously reported, work in the furnace department was associated with the highest exposure and that in the processing department with the lowest exposure to fibres. Job group was an important predictor of exposure to silicon carbide fibres and accounted for up to 82% of the between-worker variance. For maintenance workers, increased exposure to fibres was also associated with work in the furnace department.

(ii) Studies with biological samples from exposed workers

Some case studies have evaluated biological samples from workers and the studies of Dufresne et al. (1993, 1995) are particularly relevant regarding exposures to silicon carbide fibres in the Canadian silicon carbide industry. Dufresne et al. (1993) reported a concentration of 39 300 fibres/mg of dry lung tissue for fibres longer than 5 µm (mean diameter, 0.49 µm; mean length, 11 µm) and a concentration of 105 243 fibres/mg of dry lung tissue for fibres shorter than 5 µm (mean diameter, 0.22 µm; mean length, 2.86 µm) in the lung parenchyma of a retired silicon-carbide plant worker (see Table 1.8). The worker was diagnosed with pneumoconiosis and lung cancer and had been exposed for 42 years near an Acheson furnace. The authors noted that the concentration of total pulmonary fibres in this study greatly exceeded (approximately by a factor of 10) the fibre concentrations reported in the lungs of subjects exposed to asbestos in mining activities (Case & Sebastien, 1987). In a subsequent study, Dufresne et al. (1995) examined post-mortem lung material from 15 deceased men who had worked for between 15 and 42 years in the silicon carbide industry. The GM concentrations of fibres shorter than 5 µm were 48 529 fibres/mg of dry lung tissue in workers without lung fibrosis and lung cancer, and up to 147 911 fibres/mg in workers with lung fibrosis but no lung cancer. GM concentrations of fibres longer than 5 µm

Table 1.8 Biological levels of fibres in the lung parenchyma of workers in the silicon carbide industry in Canada

Reference	Subjects	Geometric mean (± geometric standard deviation)		
		Silicon carbide fibres (length, < 5μm) per mg of dry lung	Silicon carbide fibres (length, ≥ 5μm) per mg of dry lung	Ferruginous bodies per g of dry lung
Dufresne et al. (1993)	1 male worker with silicon carbide pneumoconiosis and lung cancer, exposed for 42 yrs, retired for 2 yrs, and smoked 1.5 packs of cigarettes per day for > 40 yrs	105 243	39 300	800 000
Dufresne et al. (1995)	5 male workers with no lung fibrosis or lung cancer exposed for 23.4 ± 6.9 yrs, no longer exposed for the past 7.9 ± 7.1 yrs, and smoked 50.6 ± 30 cigarette pack–yrs	48 529 (± 3.5)	7 586 (± 3.9)	39 903 (± 4.0)
	6 male workers with lung fibrosis but no lung cancer, exposed for 28.8 ± 5.5 yrs, no longer exposed for the past 7.0 ± 1.6 yrs, and smoked 59.8 ± 32.2 cigarette pack–yrs	147 911 (± 2.5)	53 951 (± 3.5)	305 492 (± 3.8)
	4 male workers with lung fibrosis and lung cancer, exposed for 32.3 ± 9.0 yrs, no longer exposed for the past 5.0 ± 3.5 yrs, and smoked 39.2 ± 25.8 cigarette pack–yrs	100 925 (± 1.8)	27 353 (± 1.8)	583 445 (± 2.4)

yr, year
Compiled by the Working Group

were up to 53 951 fibres/mg of dry lung tissue in workers with lung fibrosis but no lung cancer (see Table 1.8). No statistical differences were observed in the dimensions of silicon carbide fibres between each group. Fibres < 5 μm long were approximately 2 μm in length and 0.2 μm in diameter with an aspect ratio of approximately 10. Fibres ≥ 5 μm long were approximately 8 μm in length and 0.3 μm in diameter with an aspect ratio of approximately 25. Ferruginous bodies were also counted in this study. Other types of particle and fibre were also reported, including mica, clays, amosite, and cleavage fragments of tremolite.

(iii) Co-exposures

As shown in the Norwegian silicon carbide industry, workers are also co-exposed to total dust (GM range, < 0.29–21 μg/m^3), respirable dust (GM range, < 0.12–1.3 μg/m^3), respirable quartz (GM range, < 0.44–20 μg/m^3), and respirable cristobalite (GM range, < 0.33– 35 μg/m^3). Some other low-level contaminants, such as sulfur dioxide and polycyclic aromatic hydrocarbons, have also been reported (Føreland et al., 2008). The highest levels of fibres were reached for workers in the furnace department where high exposure to respirable dust also occurs (Føreland et al., 2012).

1.6 Regulations and guidelines

TWA values, short-term exposure limits, and other regulations or guidelines worldwide are summarized in Table 1.9.

Table 1.9 Regulations and guidelines for silicon carbide worldwide

Type of silicon carbide	Country or region	Concentration	Interpretation	Carcinogenicity
Non-fibrous silicon carbide		*(mg/m³)*		
	USA			
	OSHA (PEL)			
	Total dust	15	TWA	
	Respirable fraction	5	TWA	
	ACGIH (TLV)			
	Inhalable fraction[a]	10	TWA	
	Respirable fraction[a]	3	TWA	
	NIOSH (REL)			
	Total dust	10	10-h TWA	
	Respirable fraction	5	10-h TWA	
	United Kingdom			
	Total inhalable	10	TWA	
	Respirable fraction	4	TWA	
Fibrous silicon carbide		*(fibres/cm³)*		
	USA			
	ACGIH (TLV)[b]	0.1	TWA	A2
	Europe			
	SCOEL (OEL)[c]	1	TWA	
	Sweden			
	LLV	0.2		C

[a] Particulate matter containing no asbestos and < 1% crystalline silica
[b] Including whiskers: respirable fibres (length, > 5 µm; aspect ratio, ≥ 3:1) as determined by the membrane filter method at 400–450 × magnification (4 mm objective), using phase-contrast illumination
[c] Refractory ceramic fibres, including fibres of silicon carbide
A2, suspected human carcinogen; ACGIH, American Conference of Governmental Industrial Hygienists; C, carcinogenic; LLV, level limited value; NIOSH, National Institute for Occupational Safety and Health; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; SCOEL, Scientific Committee on Occupational Exposure Limits; TLV, threshold limit value; TWA, 8-hour time-weighted average (unless otherwise specified)
From HSE (2011), NIOSH (2011), Swedish Work Environment Authority (2011), SCOEL (2012), OSHA (2015)

2. Cancer in Humans

2.1 Introduction

Only a few studies that refer directly to exposure to silicon carbide fibres have been published (see Table 2.1) and concerned workers were engaged in the production of silicon carbide, using the Acheson production process, where exposure to silicon carbide fibres was combined with exposure to a range of other dusts and gases, including non-fibrous silicon carbide. The Acheson process remains the dominant method of producing silicon carbide; the process and related exposure conditions are described in Section 1. No studies were found of workers engaged in the production of silicon carbide whiskers. Other studies of workers exposed to silicon carbide include cohort studies of downstream users of the product, especially of workers in the abrasives industry. These studies were reviewed but were regarded as uninformative with respect to silicon carbide fibres because the Working Group had no evidence that workers producing or using abrasive materials were exposed to the fibres.

2.2 Silicon-carbide production industry

The first study to be published on a cohort from the silicon-carbide production industry was conducted in Canada by Infante-Rivard et al. (1994). A cohort of silicon-carbide production workers was subsequently studied in Norway by Romundstad et al. (2001) with updates and exposure–response analyses of lung cancer carried out by Bugge et al. (2010, 2012). Due to the similarities between silicon carbide fibres and asbestos, and also due to the observed induction of mesothelioma by silicon carbide whiskers in experimental animals, whether an increased incidence of mesothelioma was observed in the cohort studies was of special interest. Only the two Norwegian studies reported the incidence of pleural cancer or results for cancer sites other than lung and stomach.

In the Canadian study by Infante-Rivard et al. (1994), 585 silicon carbide industry workers employed for more than 2 years during 1950–80 were identified and their vital status, job history, and smoking histories were ascertained until 1989. A JEM on total dust was developed. No information on exposure to silicon carbide fibres specifically was available. Mortality from total and site-specific cancer was compared with that of the general population of the Province of Québec, and also related to cumulative exposure to total dust. The standardized mortality ratio (SMR) for lung cancer was 1.69 (95% confidence interval [CI], 1.09–2.52). Mortality from lung cancer showed a moderate increase with increasing cumulative exposure to total dust (see Table 2.1). Increased mortality from stomach cancer (SMR, 2.18; 95% CI, 0.88–4.51) was also observed. Data for other cancer sites were not presented. [One strength of this study was the collection of information concerning job history and smoking, either from the worker personally or from relatives. Weaknesses were mainly that the cohort was small and that only total dust estimates were available. In addition, the method used to account for a minimum latency period (ignoring both years at risk and deaths during the first 15 years of employment) may have reduced the power of the study.]

A cohort of 2620 male workers employed for more than 6 months in 1913–96 in the Norwegian silicon carbide industry was established by Romundstad et al. (2001) and followed up from 1953 to 1996. Data on cancer incidence were obtained from the Norwegian Cancer Registry and comparisons were made with the general Norwegian population. A JEM on total dust, crystalline silica, silicon carbide fibres, and inorganic dust other than quartz and cristobalite, and potentially including silicon carbide particles and cleavage fragments, was constructed. Exposure assessments were mainly based on total dust measurements. An estimation of exposures other than those to total dust was based on a few measurements of these factors, and an estimation of the relative content of these factors in total dust was also made. [Uncertainties regarding exposure assessment due to the strong correlation between the different exposure factors and the small number of measurements precluded any firm conclusions based on the available data.]

Bugge et al. (2010) performed an update of the Norwegian cohort study (Romundstad et al., 2001), with the addition of employment information until 2003 and a further 9 years of cancer incidence follow-up (until 2005). A full report of cancer incidence in the silicon carbide industry was given in the study, but no exposure–effect analyses were performed. In a second study of the Norwegian cohort by Bugge et al. (2012), which included data on cancer incidence until 2008, a detailed JEM was constructed, based on new exposure measurements and mathematical modelling of historical exposure levels of total and respirable dust, non-fibrous and fibrous silicon carbide, quartz, and cristobalite (Føreland et al., 2012). In this last study (Bugge et al., 2012), the relative influence of different exposure factors

Table 2.1 Cohort studies of workers in the silicon-carbide production industry

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Covariates; comments
Infante-Rivard et al. (1994), Québec (Province), Canada, 1950–89	585	Job-exposure matrix in 1984, total dust	Lung			SMR	
				Overall	24	1.69 (1.09–2.52)	Compared with age- and calendar-specific death rates among Québec (Province) men
				Total dust (mg–yr/m^3)		IRR	
				< 105	5	1.00	SIRs from internal analysis; no latency
				105–275	9	1.48 (0.47–4.58)	
				> 275	10	1.67 (0.57–4.83)	
				< 105	5	1.00	SIRs from internal analysis; 15-yr latency
				105–275	9	1.25 (0.40–3.90)	
				> 275	10	1.36 (0.47–3.95)	
						SMR	
			Stomach	Overall	7	2.18 (0.88–4.51)	Compared with age- and calendar-specific death rates among Québec (Province) men
Bugge et al. (2010), Norway, 1953–2005	2612	Personnel records, duration of employment	Lung	Overall	103	2.0 (1.6–2.4)	Compared with age- and period-specific cancer incidence rates among Norwegian men
	1687		Lung	Overall	60	1.7 (1.3–2.2)	Long-term workers (≥ 3 yr of employment)
			Stomach	Overall	25	1.3 (0.9–1.9)	
			Lip	Overall	7	2.4 (1.2–5.1)	
			Oral cavity and pharynx (ICD-7: 141, 143–8)	Overall	10	2.1 (1.1–3.9)	
			Larynx	Overall	3	0.9 (0.3–2.8)	
			Pleura	Overall	1	0.8 (0.1–6.0)	
			Prostate	Overall	77	1.2 (1.0–1.5)	
			Leukaemia (ICD-7: 204)	Overall	6	2.8 (1.2–6.1)	

Table 2.1 (continued)

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Covariates; comments
Bugge et al. (2012), Norway, 1953–2008	1687		Lung	Overall	62	1.6 (1.3–2.1)	Long-term workers (≥ 3 yr of employment)
		Department	Lung	Low exposure	3	1.0	Adjusted for age and smoking
				Furnace	20	3.8 (1.1–13)	
				Processing	9	1.6 (0.4–5.9)	
				Maintenance	9	1.5 (0.4–5.7)	
				Mixed	21	2.2 (0.7–7.5)	
	1166	Job-exposure matrix (Føreland et al., 2012)	Lung	Silicon carbide fibres (fibre–yrs/mL)		IRR	Ever-smoking, long-term workers; adjusted for age
				0–0.50	11	1.0	No lag
				0.50–2.0	14	1.0 (0.5–2.2)	
				2.0–93	33	1.7 (0.8–3.3)	
				0–0.50	21	1.0	20-yr exposure lag
				0.50–2.0	14	1.4 (0.7–2.9)	
				2.0–93	23	2.3 (1.2–4.4)	

CI, confidence interval; ICD, International Classification of Diseases; IRR, incidence rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year

(including silicon carbide fibres) was estimated, but only for lung cancer incidence.

In Bugge et al. (2012), the standardized incidence ratio (SIR) for lung cancer in long-term workers (≥ 3 years of employment) was 1.6 (95% CI, 1.3–2.1). The results from the two earlier studies from this cohort showed similar SIRs of 1.9 (95% CI, 1.5–2.3; Romundstad et al., 2001) and 2.0 (95% CI, 1.6–2.4; Bugge et al., 2010) for lung cancer in the entire cohort. The highest incidence of lung cancer was observed among workers in the furnace department (SIR, 2.3; 95% CI, 1.5–3.5) and among workers with employment in more than one department (including furnace work) (SIR, 1.9; 95% CI, 1.3–2.9). Among workers in the processing and maintenance departments the SIR was 1.4 for both groups (95% CI, 0.7–2.7 and 0.7–2.6, respectively). Similar patterns of relative risks were observed in analyses using workers with low exposure as the referent group (Table 2.1). The SIR for lung cancer increased with increasing cumulative exposure to silicon carbide fibres, but also with indicators of other exposures, including cristobalite. Due to a high correlation between the different exposure factors, especially in the furnace halls, Poisson regression models were built to estimate the relative effect of the different exposure factors. The incidence of lung cancer was most strongly associated with exposure to cristobalite (incidence rate ratio, 1.9; 95% CI, 1.2–2.9 per log mg–years/m^3 unadjusted; and 1.6; 95% CI, 0.8–3.3 per log mg–years/m^3 adjusted for silicon carbide fibres and non-fibrous silicon carbide). The unadjusted incidence rate ratio with silicon carbide fibres was 1.9 (95% CI, 1.2–2.9 per log fibre–years/mL), but when adjusted for cristobalite and non-fibrous silicon carbide showed a weaker non-significant association (incidence rate ratio, 1.3; 95% CI, 0.7–2.6 per log fibre–years/mL).

Data for all other cancer sites were reported by Bugge et al. (2010). Only one case of cancer of the pleura (ICD-9 163) was reported among long-term workers, resulting in an SIR of 0.8 (95% CI, 0.1–6.0), but two cases were observed among the short-term workers (SIR, 3.7; 95% CI, 0.9–14.7). [The Working Group noted that the report did not provide information on the time elapsed between exposures in the silicon carbide industry and the diagnosis of mesothelioma.] The SIR for stomach cancer was 1.3 (95% CI, 0.9–1.9), while that for larynx cancer was 0.9 (95% CI, 0.3–2.8). An increased incidence of cancer of the oral cavity and pharynx (SIR, 2.1; 95% CI, 1.1–3.9; 10 cases), lip cancer (SIR, 2.4; 95% CI, 1.2–5.1; 7 cases), prostate cancer (SIR, 1.2; 95% CI, 1.0–1.5; 77 cases), and leukaemia (SIR, 2.8; 95% CI, 1.2–6.1; 6 cases) was also observed among the long-term workers. SIRs did not differ significantly from unity for other cancer sites in this group (Bugge et al., 2010). [Although elevated SIRs were observed for several cancers other than the lung, the confidence intervals were wide, the cancer sites are not known to be specific for exposure to fibres, and numerous comparisons were made. In light of these considerations, the Working Group concluded that a causal interpretation was not possible.]

[The strengths of this study were the access to a detailed JEM, based on a large number of new parallel measurements of total dust, respirable dust, respirable quartz, cristobalite, and non-fibrous silicon carbide, and fibrous silicon carbide. Mathematical modelling of historical exposure to several agents present in the industry allowed analyses of the exposures that were most strongly associated with cancer incidence. However, uncertainties still existed because historical total dust exposures before the late 1960s were estimated based only on knowledge about changes in the work organization and working hours. Correlations between estimated exposures to several agents, including silicon carbide particles and crystalline silica, challenged the interpretation of associations with silicon carbide fibres.]

2.3 Silicon-carbide user industry

Five studies on the incidence of or mortality from cancer with data from industries that use silicon carbide were found, two of which were carried out in the abrasives producing industries. Wegman & Eisen (1981) conducted a proportionate mortality study of abrasives manufacturers in Massachusetts, USA, and Edling et al. (1987) studied cancer incidence among Swedish workers manufacturing abrasives. The other three studies were performed in industries using abrasives for polishing. Sparks & Wegman (1980) studied proportionate mortality among jewellery polishers in Massachusetts, USA, Järvholm et al. (1982) studied cancer incidence among steel polishers in Sweden, and Jakobsson et al. (1997) studied cancer incidence among workers in a Swedish stainless steel factory.

[These studies contained very little information on levels of exposure to dust in general and no information on exposure to silicon carbide fibres specifically. Because the Working Group had no evidence that workers producing or using abrasive silicon carbide products have significant exposure to silicon carbide fibres, these studies were not considered to be relevant for the evaluation.]

3. Cancer in Experimental Animals

Studies of fibrous silicon carbide in experimental animals were available only for silicon carbide whiskers and only in rats.

3.1 Inhalation

See Table 3.1

Two groups of 40 AF/Han specific pathogen-free rats [sex and age unspecified] were exposed by inhalation for 7 hours per day on 5 days a week for approximately 12 months to silicon carbide whiskers (Advanced Composite Materials Corporation (ACMC), Greer, SC, USA; mean diameter, 0.45 μm; 984 whiskers/mL, > 5 μm in length in airborne dust clouds). After exposure, the rats were allowed to live their full life-span, although the study was terminated when the number of survivors in each group decreased to 6. Moribund animals and those surviving to the end of the study were killed and the lungs were examined microscopically for tumours. In the silicon carbide whisker-exposed rats, pulmonary carcinomas were present in 5 out of 42 (12%) [not significant] animals, pulmonary adenomas in 5 out of 42 (12%) [not significant] animals, and pleural mesotheliomas in 10 out of 42 (24%) [$P = 0.0003$] animals (Davis et al., 1996). A concurrent control group was not included in the study; however, the authors stated that in a group of control rats of the same strain and maintained in the same laboratory from a previous study with a similar study design, the incidence of pulmonary adenoma was 1 out of 47 (2%), that of pulmonary carcinoma was 1 out of 47 (2%), and that of mesothelioma was 0 out of 47 (Davis et al., 1991). [The Working Group noted the absence of a concurrent control group. Statistical analysis was not performed by the authors, but statistics were calculated by the Working Group based on the incidence of tumours reported for the control group of the previous study.]

Two groups of 42 male Wistar rats (age, 4 weeks) were exposed by inhalation for 6 hours per day on 5 days a week for 12 months to silicon carbide whiskers (GM length, 2.8 μm; GM diameter, 0.5 μm; mass median aerodynamic diameter [MMAD], 2.4 μm; daily average fibre count, 98 ± 19 whiskers/mL) or clean air (control) and were killed 6 days, or 3, 6, or 12 months after exposure. No lung tumours were reported. However, 12 months after exposure, fibrotic changes were present in the lungs and bronchiolo-alveolar hyperplasia was observed in two exposed animals (Akiyama et al., 2007). [The Working Group noted that this study was designed to evaluate the biopersistence of silicon

Table 3.1 Studies of carcinogenicity with silicon carbide whiskers in rats

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%)	Significance	Comments
AF/Han (SPF) (NR) Lifetime Davis et al. (1996)	7 h/day, 5 days/wk, by inhalation, for about 12 mo, then held for life SiC-W (ACMC): mean diameter, 0.45 µm; length, > 5 µm; 984 whiskers/mL 2 × 40/group	Pulmonary carcinoma: control, 1/47 (2%); SiC-W, 5/42 (12%) Pulmonary adenoma: control, 1/47 (2%), SiC-W, 5/42 (12%) Pleural mesothelioma: control, 0/47; SiC-W, 10/42 (24%)	[NS] [NS] [$P = 0.0003$]	Statistics, Fisher exact test; age at start, NR; no concurrent control group; a group of control animals of the same strain and maintained in the same laboratory from a previous study with a similar design (Davis et al., 1991) was used by the Working Group for statistical analysis instead of a concurrent control group
Wistar (M) 24 mo Akiyama et al. (2007)	6 h/day, 5 days/wk, by inhalation, for 12 mo, then held for up to an additional 12 mo 0 (clean air, control) or 98 ± 19 whiskers/mL (GM diameter, 0.5 µm; GM length, 2.8 µm; MMAD, 2.4 µm) 42/group	Lung tumours: 0/33, 0/31 Bronchiolo-alveolar hyperplasia at 24 mo: 0/13, 2/11	NS NS	Rats (exposed and control) killed at 6 days ($n = 10$ and 10), 3 mo ($n = 5$ and 5), 6 mo ($n = 5$ and 5) or 12 mo ($n = 11$ and 13) after the 12 mo exposure period; although the study was 2 yr in duration, the exposure duration may have been too short to evaluate carcinogenicity
F344/NTacBR (F) 18 mo Vaughan et al. (1993)	Single administration, by intratracheal instillation, then held for 18 mo SiC-W-1 (GM diameter, 0.8 µm; GM length, 18.1 µm)/SiC-W-2 (GM diameter, 1.5 µm; GM length, 19.0 µm) suspended in PBS and instilled at doses of 1.0 or 5.0 mg/100 mL MRV; controls received PBS 25/dose per group	No treatment-related mesotheliomas or other malignant tumours reported	NS	The duration of the study was probably too short to evaluate carcinogenicity; the Working Group noted the limited reporting of the study and the low dose used
Osborne-Mendel (F) 2 yr Stanton et al. (1981)	Single dose of 40 mg SiC-W or one of 71 mineral fibres and particles dispersed in hardened gelatin and implanted onto the left pleural surface (intrapleural implantation) after thoracotomy, then held for 2 yr 30–50/group	Pleural sarcoma [sarcomatoid mesothelioma]: Untreated controls, 1/248 (0.4%); sham controls, 8/267 (3.0%); negative controls, 16/562 (2.8%); combined controls, 25/1077 (2.3%); SiC-W-treated, 17/26 (65%)	[$P = 0.0001$]	Statistics, Fisher exact test; fibre dimensions NR; statistics calculated by the Working Group, based on a combination of controls (untreated), sham controls (thoracotomy, no implant), and negative controls (thoracotomy with non-fibrous implant) that were controls (from numerous experiments) of the same species, sex, and age, from the same laboratory

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%)	Significance	Comments
F344/N (F) Up to 28 mo Johnson & Hahn (1996)	Single dose by intrapleural injection (in 4 mL saline) of 0 (50 rats) or 20 mg of SiC-W-1 (length, 4.5 µm; diameter, 0.42 µm), SiC-W-2 (length, 20.1 µm; diameter, 0.75 µm), or SiC-W-3 (length, 6.6 µm; diameter, 0.32 µm) 30/group unless otherwise specified	Pleural mesothelioma: control, 0/50; SiC-W-1, 27/30; SiC-W-2, 26/30; SiC-W-3, 7/30	[$P = 0.0001$], [$P = 0.0001$], [$P = 0.0006$]	Statistics, Fisher exact test; survival of rats treated with SiC-W-1 or SiC-W-2 lower than that of controls
Wistar (F) At least up to 130 wk Pott et al. (1991)	Single dose 0 (72 rats), 0.05, 0.25, 1.25, 6.25, or 25 (48 rats) mg of SiC-W (diameter, 0.31 µm; length, 3.1 µm) by intraperitoneal injection in 2 mL of saline, then held at least up to 130 wk 36/group unless otherwise specified	Mesothelioma or sarcoma in the abdominal cavity: control: 2/50 (4%); 0.05 mg, 2/16 (12.5%); 0.25 mg, 5/23 (21.7%), 1.25 mg, 13/21 (61.9%); 6.25 mg, 23/30 (76.7%); 25 mg, 36/37 (97.3%)	[NS], [$P = 0.0285$], [$P = 0.0001$], [$P = 0.0001$], [$P = 0.0001$]	Statistics, Fisher exact test; age at start NR; weight, 160 g; statistical analyses not reported by the authors; the study was compromised by an infectious disease of the lung in experimental months 12 and 13 that significantly reduced the mean life span; the Working Group judged that this did not influence the induction of abdominal cavity tumours
F344/ NTacfBR (F) 18 mo Vaughan et al. (1993)	Single dose of 0 or 20 mg of SiC-W-2 (GM diameter, 1.5 µm; GM length, 19.0 µm) by intraperitoneal injection in 1 mL PBS, then held for 18 mo 20/group	No malignant mesothelioma in SiC-W-2-treated or control groups and no treatment-related tumours reported at other sites	NS	SiC-W-2 from American Matrix, Knoxville, KY, USA
AF/Han (NR) Lifetime Davis et al. (1996)	Single dose of 10^9 fibres/2 mL of SiC-W (ACMC; mean diameter, 0.45 µm) or glass microfibres (C100/475; mean diameter, 0.32 µm) by intraperitoneal injection in PBS, then held for life Fibres all > 5 µm long 24/group	Mesothelioma: SiC-W, 22/24 (92%); glass microfibre, 8/24 (33%)	NA	Age at start NR; mesotheliomas appeared most rapidly in SiC-W-treated rats; time at which 50% survival was achieved, 257 days for SiC-W and 679 days for glass microfibres; no vehicle control group included in this study, so statistical analysis could not be performed; the Working Group noted the limited reporting of the study
F344/Nslc (F) Up to 2 yr Adachi et al. (2001)	Intraperitoneal injection 5 or 10 mg (mean ± SD: 414 × 10^3 whiskers/µg; length, 6.40 ± 2.45 µm; diameter, 0.30 ± 1.58 µm) of SiC-W or 10 mg of UICC chrysotile B (positive control) fibres suspended in saline (1 mg/mL) by intraperitoneal injection; animals were held up to 2 yr 330 rats divided into 24 groups [estimate, 13–14/group]	Peritoneal mesothelioma (epithelial or sarcomatous): 10 mg SiC-W, 100% (within 1 yr); 5 mg SiC-W, 70% (within 1 yr); UICC chrysotile B, 85% (within 2 yr)	NA	Highest volume of an administration to rat in a week was 5 mL; no vehicle controls in the study, therefore statistical analyses could not be performed; the Working Group noted the limited reporting of the study; length and diameter reported by Kohyama et al. (1997)

ACMC, Advanced Composite Materials Corporation; d, day; F, female; GM, geometric mean; M, male; MMAD, mass median aerodynamic diameter; MRV, minute respiratory volume; mo, month; NA, not applicable; NR, not reported; NS, not significant; PBS, phosphate-buffered saline; SD, standard deviation; SiC-W, silicon carbide whisker; wk, week; yr, year

carbide whiskers and not as a carcinogenicity study.]

3.2 Intratracheal instillation

Groups of female Fischer 344/NTacfBR rats (age, 9 weeks) received a single intratracheal instillation of one of two samples of silicon carbide whiskers: SiC-W-1 (GM diameter, 0.8 μm; GM length, 18.1 μm; Tateho, Inc., Japan) and SiC-W-2 (GM diameter, 1.5 μm; GM length, 19.0 μm; American Matrix, Knoxville, KY, USA). The minute respiratory volume (MRV) was estimated for each animal, and the test materials were suspended in phosphate buffered saline (PBS) and diluted to 1.0 mg/100 mL MRV (low dose) and 5.0 mg/100 mL MRV (high dose). Each of the two samples was administered to a minimum of 50 rats, half of which received the low dose and half received the high dose. A group of control animals of similar size received the PBS vehicle. The animals were killed 18 months after treatment, and the lungs, liver, spleen, kidneys, heart, and incidental tumours were collected for histopathological evaluation. Exposure to SiC-W-1 and SiC-W-2 induced the development of pulmonary granulomas, and exposure to SiC-W-1 also produced bronchiolar mucosal hyperplasia. However, no mesotheliomas or other malignant tumours that could be attributed to treatment were observed (Vaughan et al., 1993). [The Working Group noted the limited reporting of the study, the low dose used, and the duration of the study that was probably too short for an evaluation of carcinogenicity.]

3.3 Intrapleural implantation

In a study to evaluate the relationship between fibre dimension and carcinogenicity, groups of 30–50 female Osborne-Mendel rats (age, 12–20 weeks) were implanted with a hardened gelatin pellet containing 40 mg of one of 72 uniformly distributed mineral fibres, including silicon carbide whiskers [fibre dimensions unspecified], into the left pleura after thoracotomy and were followed for 2 years, at which time the survivors were killed and necropsied. Three groups of controls from numerous experiments from the same laboratory were also available: untreated rats, sham controls that underwent thoracotomy but no fibre implant, and rats that received implants of non-fibrous materials. Fibrosarcomas of the left mammary gland and subcutaneous fibrosarcomas were considered to be spontaneous tumours or to be induced by the suture material. At 2 years, pleural sarcomas [sarcomatoid mesotheliomas] were present in 25 out of 1077 (2.3%) animals of the three control groups (combined). The incidence of pleural sarcomas in silicon carbide whisker-treated rats was 17 out of 26 (65%) [$P = 0.0001$] (Stanton et al., 1981). [Statistical analysis was not reported by the authors, but statistics were calculated by the Working Group, based on the combination of controls from numerous experiments from the same laboratory.]

Another study was conducted to determine the potential of three samples of silicon carbide whiskers to induce mesothelioma after intrapleural injection. Groups of female Fischer 344/N rats (age, 6–8 weeks) were given a single intrapleural injection of either 4 mL saline (vehicle controls; 50 rats), 20 mg of SiC-W-1 (length, 4.5 μm; diameter, 0.42 μm; 30 rats) in 4 mL saline, SiC-W-2 (length, 20.1 μm; diameter, 0.75 μm; 30 rats) in 4 mL saline, or SiC-W-3 (length, 6.6 μm; diameter, 0.32 μm; 30 rats) in 4 mL saline. The rats were killed when moribund or after 28 months. Animals were necropsied and the incidence of pleural mesotheliomas was determined after microscopical examination. The survival of rats treated with SiC-W-1 or SiC-W-2 was significantly shorter than that of saline controls ($P < 0.05$). The incidence of pleural mesothelioma in rats treated with SiC-W-1 or SiC-W-2 was 27 out of 30 [$P = 0.0001$] and 26

out of 30 [P = 0.0001], respectively. SiC-W-3 caused pleural mesotheliomas in 7 out of 30 rats [P = 0.0006]. No pleural mesotheliomas were identified in the 50 saline controls (Johnson & Hahn, 1996).

3.4 Intraperitoneal injection

Groups of female Wistar rats [age not reported] (weight, 160 g) were given a single intraperitoneal injection of 0.05 (36 rats), 0.25 (36 rats), 1.25 (36 rats), 6.25 (36 rats) or 25 (48 rats) mg of silicon carbide whiskers (length, 3.1 µm; diameter, 0.31 µm) in 2 mL saline. A control group of 72 rats received weekly intraperitoneal injections of 2 mL of saline for 5 weeks. Animals surviving until termination of the experiment were observed for up to 130 weeks. The number of rats with mesothelioma or sarcoma in the abdominal cavity relative to the number of rats examined that survived at least 56 weeks or died earlier with tumours was: control, 2 out of 50 (4%); 0.05 mg, 2 out of 16 (12.5%) [not significant]; 0.25 mg, 5 out of 23 (21.7%) [P = 0.0285]; 1.25 mg, 13 out of 21 (61.9%) [P = 0.0001]; 6.25 mg, 23 out of 30 (76.7%) [P = 0.0001]; and 25 mg, 36 out of 37 (97.3%) [P = 0.0001] (Pott et al., 1991). [The study was compromised by an infectious disease of the lung that occurred during experimental months 12 and 13 and significantly reduced the mean lifespan. The Working Group judged that this did not influence the induction of abdominal cavity tumours. Statistical analyses were not reported by the authors.]

Groups of 20 female Fischer F344/NTacfBR rats (age, 9 weeks) received a single intraperitoneal injection of 0 or 20 mg of silicon carbide whiskers (SiC-W-2; GM diameter, 1.5 µm; GM length, 19.0 µm; American Matrix) in 1 mL of PBS and were killed 18 months later, at which time the lungs, liver, spleen, kidneys, heart, and incidental tumours were collected for histopathological evaluation. Peritoneal fibrosis occurred in 90% of the silicon carbide whisker-treated animals; however, no malignant mesotheliomas were found. No treatment-related tumours were reported at other sites (Vaughan et al., 1993).

A study was conducted to assess the ability of SiC-W to produce mesotheliomas. Groups of 24 AF/Han rats [sex and age unspecified] received a single intraperitoneal injection of 10^9 fibres (length, > 5 µm) of silicon carbide whiskers (ACMC) or glass microfibres (C100/475) suspended in 2 mL PBS. The incidence of mesotheliomas was 22 out of 24 (92%) for silicon carbide whiskers and 8 out of 24 (33%) for glass microfibres. Mesotheliomas appeared more rapidly in silicon carbide whisker-treated rats. The time at which 50% survival was achieved was 257 days for silicon carbide whiskers and 679 days for glass microfibres (Davis et al., 1996). [A vehicle control group was not included in this study and statistical analysis was not performed. The Working Group also noted the limited reporting of the study.]

Groups of 13–14 female Fischer 344/Nslc rats (age, 5 weeks) received intraperitoneal injections of 5 or 10 mg of silicon carbide whiskers (length, (mean ± standard deviation [SD]), 6.40 ± 2.45 µm; diameter (mean ± SD), 0.30 ± 1.58 µm (reported by Kohyama et al., 1997); 414 × 10^3 whiskers/µg) suspended in saline (1 mg/mL). A third group of rats was injected with 10 mg of UICC chrysotile B as a positive control. The greatest volume administered to rats in a week was 5 mL. The animals were observed for up to 2 years. Dead and moribund animals were necropsied and fixed tissues were examined microscopically for peritoneal mesothelioma. All rats given 10 mg of silicon carbide whiskers and 70% of rats injected with 5 mg of silicon carbide whiskers developed peritoneal mesotheliomas within 1 year. Microscopically, the tumour cells exhibited a variety of characteristics including epithelial or sarcomatous structures. UICC chrysotile B produced peritoneal mesotheliomas in 85% of treated rats by the end of the study (2 years)

(Adachi et al., 2001). [The Working Group noted the limited reporting of the study. The authors stated that 330 rats were divided into 24 groups, but the exact number of rats per treatment group was not reported and was assumed to be 13–14 per group. No vehicle controls were available and statistical analyses could therefore not be performed.]

4. Mechanistic and Other Relevant Data

4.1 Deposition, phagocytosis, retention, translocation, and clearance

The characteristics of the silicon carbide forms employed in experimental studies are reported in Table 4.1.

4.1.1 Humans

Several studies have been published concerning the occupational exposure of humans to silicon carbide (see Table 4.2). In the human setting, very little is known regarding the specific deposition, phagocytosis, and translocation of silicon carbide fibres in the lungs, with the exception of studies of silicon carbide in human monocytes in vitro (Nordsletten et al., 1996). However, it is clear that silicon carbide fibres are highly respirable (Funahashi et al., 1984; Dufresne et al., 1993, 1995).

4.1.2 Experimental animals

See Table 4.3

(a) Deposition

The deposition fraction of silicon carbide whiskers (TWS-100; 98% silicon carbide; CAS No. 409-21-2) was estimated in the lungs of male Wistar rats exposed by whole-body inhalation for 6 hours per day on 5 days per week for 4 weeks to 10.4 (± 0.5) mg/m^3 (214 ± 31 fibres/mL). The GM fibre length was 2.2 µm (GSD, 1.9), indicating that > 90% of fibres were less than 10 µm in length, the GM fibre diameter was 0.4 µm (GSD, 1.6), and the MMAD was 2.5 µm (GSD, 2.7). A total of 77 rats (42 exposed, 35 unexposed controls) were studied, and groups of 5 or 12 rats were killed 3 days, 2 weeks, and 1, 2, 3, 6, and 12 months after exposure. The average lung burdens of silicon carbide measured at each time-point after exposure were: 0.60, 0.52, 0.44, 0.36, 0.34, 0.19, and 0.07 mg, respectively. The deposition fraction of silicon carbide whiskers in the lungs was estimated by calculating the ratio of the measured mass of silicon carbide in the lungs divided by the mass of silicon carbide whiskers inhaled during the exposure. The mass of inhaled silicon carbide was calculated by multiplying the average exposure concentration by the total exposure time by the respiratory volume. The estimated average total mass inhaled was reported as 12.5 mg, and the apparent deposition fraction (as a percentage) was reported as 4.8%. [These reported values can be calculated as follows: total mass inhaled – 12.5 mg = 10.4 mg/m^3 × (6 h/day × 5 days/week × 4 weeks × 60 min/h) × 0.167 L/min × (1 m^3/1000 L); deposition fraction – 4.8% = (0.6 mg (silicon carbide lung burden on day 3 after exposure)/12.5 mg) × 100.] The minute ventilation of 0.167 L/min used in the calculations herein was estimated to obtain the reported total inhaled mass of silicon carbide (i.e. 12.5 mg) (Akiyama et al., 2003). This was lower by a factor of 4 than the value of 0.037 L/min for mice reported by the Environmental Protection Agency (EPA, 1988, 2006), but was very similar to the value of 0.165 L/min (165 cm^3/min) for mice reported by Shvedova et al. (2008).

In a 1-year whole-body inhalation study (with exposure conditions similar to those in Akiyama et al. (2003)), the mass of silicon carbide whiskers deposited in each rat lung 6 days after exposure (measured by X-ray diffraction) was 5.3 ± 1.4 mg. The lung deposition fraction (as a percentage)

Table 4.1 Main characteristics of the forms of silicon carbide employed in experimental studies

Silicon carbide form	Particle/fibre type	Purity
Abrasive dust from the Acheson process[a]	Mixture of particles, fibres and fibre fragments	High level of impurities
Whiskers	Needle-like single crystals	Pure
Nanoparticles	Isometric nanoparticles	Pure

[a] In one study (Dufresne et al., 1992), the angular fragments and fibres isolated from the Acheson process were studied separately

was estimated to be 12.9% (calculated as in Akiyama et al. (2003)), which was higher than the estimated 4.8% deposition estimated after 4 weeks of inhalation exposure (Akiyama et al., 2007). [In the calculation of deposition fractions in Akiyama et al. (2003, 2007), the use of the measured lung dose at the end of the 4-week or 12-month exposure period would not have accounted for the portion of deposited silicon carbide whiskers that were cleared from the lungs during the exposure period. Thus, the deposition fraction would be underestimated by the amount that was cleared during the exposure period (and therefore not measured in the lungs at the end of the exposure).]

See Sections 4.1.2 (d) and 4.1.2 (e) for more information on the retention and clearance of silicon carbide in the 4-week and 1-year inhalation studies (Akiyama et al., 2003, 2007), each with follow-up examinations at up to 12 months after exposure.

(b) Phagocytosis

Inhaled fibres can be deposited in the pulmonary (alveolar) region of the lungs, depending on their aerodynamic or diffusion diameter, their shape, and orientation in the air stream (Asgharian & Yu, 1989a, b). Alveolar macrophages can phagocytize shorter fibres (e.g. < 5 μm) and clear them from the lungs via the mucociliary escalator. However, fibres that are physically longer than macrophages cannot be fully engulfed or effectively cleared (Lippmann, 1993; Oberdörster, 1994). Rat macrophages are approximately 10–13 μm long (human alveolar macrophages are approximately 14–21 μm long) (Stone et al., 1992; Oberdörster, 2000). Fibres that are not cleared by macrophages could undergo dissolution and breakage over time (depending on their solubility in biological fluids) or enter the lymphatic system if shorter (e.g. < 5 μm in length) (Oberdörster et al., 1988; Murphy et al., 2011). Fibres may also be actively transported to the lymphatic system by alveolar macrophages, as was shown for particles in dogs, in which macrophages carried red fluorescent microspheres (diameter, 1.3 μm; 5×10^{10} particles instilled per lung) to the regional tracheobronchial lymph nodes (Harmsen et al., 1985).

Studies of silicon carbide have reported that most structures are < 10 μm in length and insoluble (Dufresne et al., 1992; Searl et al., 1999; Akiyama et al., 2003). Thus, macrophage-mediated clearance of these structures would be expected at lung doses that do not cause overloading (e.g. 0.6 mg in rats) (Akiyama et al., 2003). However, a proportion of silicon carbide fibres may be longer; Akiyama et al. (2003) reported that approximately 10% of silicon carbide whiskers were > 10 μm in length and Miller et al. (1999) estimated that approximately 30% of silicon carbide whiskers were > 10 μm in length. Longer insoluble fibres that are inhaled and deposited in the alveolar region would be unlikely to be cleared by macrophages or to dissolve, and would therefore have long retention half-times in the lungs.

A study in Syrian golden hamsters showed that silicon carbide whiskers were taken up by primary alveolar macrophages obtained from the BALF. SEM showed that some of the macrophages were penetrated by fibres that were longer than the cells. A dose-dependent effect of the silicon carbide whiskers on the cell

Table 4.2 Studies of occupational exposure to silicon carbide

Setting	Activity	Sampling event parameters	Concentration of silicon carbide	Reference
Two workers in a factory using silicon carbide	Manufacturing refractory bricks	Personal exposure over many years; bilateral reticulonodular densities on chest radiograms; biopsy from one patient revealed fibrosed alveolar septums; X-ray powder diffraction analysis of the lung tissue revealed at least 6 different types of silicon carbides, traces of tungsten carbide, and an insignificant amount of quartz	NR	Funahashi et al. (1984)
Silicon-carbide factory workers with low levels of exposure to sulfur dioxide	145 production workers with an average of 13.9 (range, 3–41) yr of employment in this industry	Respiratory symptoms (phlegm, wheeze, and mild exertional dyspnea) were more closely associated with exposure to sulfur dioxide than exposure to silicon carbide	Cumulative exposure to sulfur dioxide averaged 1.94 (range, 0.02–19.5) ppm–years; low-level exposures to respirable dust also occurred (0.63 ± 0.26 mg/m^3); cumulative exposure to dust was significantly associated with chronic wheeze in the 10–20 mg-yrs/m^3 exposure category (odds ratio, 3.45; $P < 0.05$, chi-squared statistics)	Osterman et al. (1989)
267 silicon carbide factory workers	Production of silicon carbide abrasive (carborundum)	Chest opacities (profusion q1/0 and q2/1) on X-ray film were correlated with cumulative exposure to dust; pulmonary function was affected by cumulative dust exposure, profusion of opacities, and smoking	No exposure concentrations exceeded the permissible limits during the study period. (0.30–1.0 mg/m^3)	Marcer et al. (1992)
Silicon carbide factory worker	Working near a Acheson furnace of a silicon carbide plant for 42 yr	At autopsy, the concentration of silicon carbide fibres longer than 5 µm was 39 300 fibres/mg dry lung; the fibres had a similar morphology to those observed in the working environment	NR	Dufresne et al. (1993)
Silicon carbide factory workers	15 Canadian men who worked in the primary silicon carbide industry	Five men had neither lung fibrosis nor lung cancer (NFNC), 6 had lung fibrosis (LF), and 4 had lung fibrosis and lung cancer (LFLC); the workers had 23–32 yr of exposure, with means of 23.4 (SD, 6.9) yr in the NFNC group, 28.8 (SD, 5.5) yr in the LF, and 32.3 (SD, 9.0) yr in the LFLC group	Excess pulmonary retention of silicon carbide fibres ≥ 5 µm in LF and LFLC cases	Dufresne et al. (1995)
Three Norwegian silicon carbide plants	Identification and quantification of airborne fibrous particles in the plants	Silicon carbide fibres generated during the industrial production of silicon carbide; most fibres found during the mixing of the raw material; 47 different dust samples examined; several α-silicon carbide polytypes were present along the axis in each single fibre particle; no fibrous particles were observed in the final abrasive products	Fibre concentration (10^6 fibres/m^3) during mixing of raw material (0.3 in plant A; 0.1–1.9 in plant B; 1.8–4.9 in plant C)[a]	Bye et al. (1985)

Table 4.2 (continued)

Setting	Activity	Sampling event parameters	Concentration of silicon carbide	Reference
Canadian silicon-carbide production plants	Report on the concentration of silicon carbide fibres, crystalline silica, and respirable dust in the plants	In the Canadian silicon-carbide production plants, two silica polymorphs, quartz, and cristobalite, were present as respirable particulates; respirable silicon carbide fibres were present in Norwegian and Italian occupational settings at a higher concentration than in the Canadian industries	Highest 8-h time-weighted average concentrations of fibres were found among crusher and backhoe attendants and carboselectors (arithmetic means of 0.63 fibres/mL and 0.51 fibres/mL, respectively)	Dion et al. (2005)
Norwegian silicon carbide industry	1687 long-term Norwegian silicon carbide workers employed from 1913 to 2003	Lifetime occupational exposure of workers based on total dust, silicon carbide, and crystalline silica concentrations found in the silicon carbide industry associated with increased mortality from non-malignant respiratory diseases (obstructive lung disease); exposure–response relationships were found for both silicon carbide and crystalline silica (twofold risk)	Total dust: low, 0–28.6 mg–yrs/m^3; medium, 28.7–86.1 mg–yrs/m^3; high, > 86.2 mg–yrs/m^3 Silicon carbide dust: low, 0–0.7 mg–yrs/m^3; medium, 0.8–2.6 mg–yrs/m^3; high, > 2.7 mg–yrs/m^3	Bugge et al. (2011)
Norwegian silicon carbide industry	Silicon carbide workers (see Bugge et al., 2011)	Cumulative exposure to total and respirable dust, respirable quartz, cristobalite, and silicon carbide particles and silicon carbide fibres was assessed	Exposure level and lung cancer risk most significant for total dust and cristobalite; a moderate association with silicon carbide	Bugge et al. (2012)
Employees in Norwegian silicon carbide plants	All employees, age 20–55 yr at inclusion (n = 456), were examined annually for up to 5 yr (1499 examinations)	The annual change in forced expiratory volume (FEV) in one second per squared height (FEV1/height^2) per mg/m^3 increase in dust exposure was –2.3 (95% confidence interval, –3.8 to –0.79) (mL/m^2)/yr	Dust exposure, expressed by a quantitative job–exposure matrix, was found to be associated with an increased yearly decline in FEV1 in employees of Norwegian silicon carbide plants	Johnsen et al. (2013)

[a] Number of samples: plant A, 1; plant B, 7; plant C, 4

NR, not reported; yr, year

Table 4.3 Kinetics of silicon carbide in experimental animals

Type of silicon carbide	Dimensions and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Silicon carbide whiskers (CAS No. 409-21-2), TWS-100 (Tokai Carbon Co.); 98% silicon carbide	GM length, 2.2 µm (GSD, 1.9); GM diameter, 0.4 µm (GSD, 1.6); MMAD, 2.5 µm (GSD, 2.7)	Wistar rat (male; age, 9 wk)	Whole-body inhalation; 10.4 (± 0.5) mg/m^3 (214 ± 31 fibres/mL)	4-wk exposure (6 h/day, 5 days/wk); animals killed 3 days, 2 wk, 1, 2, 3, 6, or 12 mo after exposure	Average lung burdens of silicon carbide whiskers were 0.60, 0.52, 0.44, 0.36, 0.34, 0.19, and 0.07 mg, respectively, at the time-points after exposure; estimated total mass inhaled was 12.5 mg; lung deposition fraction estimated at 4.8%; estimated biological $t_{1/2}$ of 4 mo		Akiyama et al. (2003)
Silicon carbide whiskers, TWS-100 (Tokai Carbon Co.) [same as Akiyama et al. (2003)]	GM length, 2.4 µm (GSD, 2.3); GM diameter, 0.5 µm (GSD, 1.5); MMAD, 2.4 µm (GSD 2.4)	Wistar rat (male; age, 4 wk)	Whole-body inhalation; 2.6 (± 0.4) mg/m^3 (98 ± 19 fibres/mL)	1-yr exposure (6 h/day, 5 days/wk); animals killed 6 days, 3, 6, or 12 mo after exposure	Lung burden of silicon carbide whiskers 6 days after exposure was 5.3 ± 1.4 mg; lung deposition fraction was estimated at 12.9%. At 6 days, 3, 6, and 12 mo after exposure, respectively: mean fibre diameter: 0.32, 0.29, 0.35, and 0.32 µm; mean fibre length: 1.55, 1.40, 1.90, and 2.62 µm; estimated biological $t_{1/2}$ of 16 mo		Akiyama et al. (2007)

Table 4.3 (continued)

Type of silicon carbide	Dimensions and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Silicon carbide whiskers (ACMC)	Fibre distribution injected: 821, 577, 387, 307, 185, and 121 × 10^6 for cumulative length categories of > 0.4, > 5, > 8, > 10, > 15, and > 20 µm, respectively (fibre diameter < 0.95 µm); 1–4 × 10^6 fibres per cumulative length category (fibre diameter > 0.95 µm)	Wistar rat (male; age NR)	Intratracheal instillation (Searl et al., 1999); intraperitoneal injection (Miller et al., 1999) [intratracheal instillation also mentioned in Miller et al. (1999)]; 14.2 mg (821 × 10^6 fibres > 0.4 µm long)	3 days, 1, 6, and 12 mo after exposure	Mean fibre number in the lungs was 80.9 × 10^6 at 3 days and 29.3 × 10^6 at 12 mo after exposure by intratracheal instillation; retention of fibres 1 yr after exposure was 36%; mean fibre diameter for all fibres > 0.4 µm long was 0.48 µm at 3 days and 0.50 µm at 12 mo after exposure; that for fibres > 20 µm long was 0.53 µm at 3 days and 0.55 µm at 12 mo; no significant change in the length of whiskers up to 12 mo after exposure; the ratio of complex whiskers (i.e. > 1 fibrous component) to single whiskers was unchanged over the 12 mo period; the estimated retention of fibres in the cumulative length categories (> 0.4, > 5, > 8, > 10, > 15, and > 20 µm) was 52.6, 53.7, 47.7, 49.2, 54.5, and 59.2%, respectively		Searl et al. (1999), Miller et al. (1999)

Table 4.3 (continued)

Type of silicon carbide	Dimensions and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Silicon carbide (carborundum)	Non-fibrous (angular) or fibrous; largest fibres, ~30 µm in length and 0.5 µm in diameter; mean diameter of non-fibrous particles, 0.92 µm	Sheep [see Bégin et al. (1985, 1989) for more details]	Injection of 100 mg of either fibrous or non-fibrous silicon carbide (in 100 mL saline) into the tracheal lung lobe	BALF was obtained before and 2, 4, 6, and 8 mo after exposure	Mass concentration of carborundum in BALF at 2 mo was ~60 and 200 ng/mL for fibrous and non-fibrous silicon carbide, respectively; estimated clearance $t_{1/2}$ of 1.7 or 5.8 mo, respectively, for the sheep in the fibrous or non-fibrous groups; average retained lung dose in tracheal lobe 8 mo after exposure was 219 ng/mg dry lung in the non-fibrous group, and 4.6 and 58 ng/mg dry lung for fibrous and angular silicon carbide, respectively, in the fibrous group	Samples collected from a workplace furnace; fibrous sample contained several morphological types of fibre as well as angular particles (27% by wt) and graphite (5% by wt); non-fibrous sample was ~90% silicon carbide and 10% aluminium oxide	Dufresne et al. (1992)
Silicon carbide (carborundum)	Information on size NR [carborundum dust separated from powder, suggesting fine-sized (vs ultrafine-sized) fraction was used]	Mouse (strain, sex, and age NR)	Intraperitoneal injection; ~4 mg of carborundum silica (as silicon dioxide) in peanut oil	14 days after exposure	Elevated mass levels of silicon dioxide measured in liver, spleen, and abdominal lymph glands 14 days after injection; those in kidney were slightly elevated relative to those in controls; carborundum (expressed as silicon doxide) not measurably excreted in urine during the 14 days after exposure		Holt (1950)

ACMC, Advanced Composite Materials Corporation; BALF, bronchoalveolar lavage fluid; MMAD, mass median aerodynamic diameter; mo, month; GM, geometric mean; GSD, geometric standard deviation; NR, not reported; $t_{½}$, retention half-life; wk, week; wt, weight; yr, year

cytoskeleton function was observed by magnetometry (a technique involving pretreatment of cells with magnetite). Impaired cytoskeleton function was observed at the lowest dose tested (20 µg/mL) (Watanabe et al., 2000). [Loss of function of the macrophage cytoskeleton (which includes microtubules, microfilaments, and intermediate filaments) could alter mobility of the cells as well as cell polarity, the integrity of the cytoplasm, and transport of organelles, resulting in a reduced ability of alveolar macrophages to phagocytize and clear silicon carbide (and other exogenous materials) from the lungs.]

(c) Translocation

The disposition of various silica compounds, including carborundum (silicon carbide), was evaluated in mice [strain and sex unspecified]; solubility in vivo was determined by measuring the amount excreted in the urine after intraperitoneal injection of the dust samples. [Information on particle size was not provided. The statement that the carborundum dust was separated from carborundum powder using a commercial type elutriator suggests that a fine-sized rather than an ultrafine-sized fraction was used.] Approximately 4 mg of carborundum silica (expressed as silica dioxide) in peanut oil was injected intraperitoneally. Elevated mass levels of silica dioxide were measured in the liver, spleen, and abdominal lymph glands (para-aortic, iliac, and mesenteric) 14 days after the injection of carborundum. The mass levels of silica dioxide in the kidney were also elevated relative to those in control (unexposed) mice, but to a much lesser degree compared with the elevated levels in the liver, spleen, and lymph nodes. Carborundum (as expressed by silica dioxide content) was not measurably soluble or excreted in urine during a 14-day period after exposure in mice (Holt, 1950). [The Working Group noted that the relationship between the administered dose of carborundum and the expression of the carborundum administered or tissue dose as silica dioxide is unclear; in the publication, the footnote to Table 2 states that values are expressed as silica dioxide for easy comparison. The Working Group also noted that, in the publication, the rows within dust material in Tables 1, 2, and 3 are not labelled but might be assumed to be individual mouse data; the units of "Dust injected" in Table 2 are not specified, and what those values represent is therefore not clear.]

(d) Retention

(i) Rats

The biopersistence of silicon carbide whiskers was studied in male Wistar rats after a 1-year whole-body inhalation exposure for 6 hours per day on 5 days per week to an average daily exposure concentration of 2.6 (± 0.4) mg/m^3 (98 ± 19 fibres/mL) (Akiyama et al., 2007). The GM fibre length was 2.4 µm (GSD, 2.3), the GM fibre diameter was 0.5 µm (GSD, 1.5), and the MMAD was 2.4 µm (GSD, 2.4). Groups of rats were killed 6 days and 3, 6, or 12 months after the exposure, and the lungs were processed for measurement of the silicon carbide mass retained as well as the determination of fibre sizes. The average deposited mass of silicon carbide in rat lungs (6 days after exposure) was 5.3 ± 1.4 mg. The deposition fraction (as a percentage) was estimated to be 12.9% [calculated as in Akiyama et al. (2003)]. The mean fibre dimensions of silicon carbide measured in the lungs were: 0.32, 0.29, 0.35, or 0.32 µm in diameter and 1.55, 1.40, 1.90, and 2.62 µm in length, at 6 days, 3, 6, or 12 months, respectively. These results show that the mean diameter of fibres retained in the lungs did not change appreciably during the observation period after exposure. However, the mean length of the fibres retained appeared to increase at the 6- and 12-month time-points after exposure (Akiyama et al., 2007). These findings are consistent with those of other studies that showed reduced clearance and increased retention of the longer fibres

for some types of fibres (e.g. amosite) (Searl et al., 1999; Yamato et al., 2003). However, Searl et al. (1999) found no significant change in the length of silicon carbide whiskers in the lungs of rats 12 months after intratracheal instillation. [The estimated deposition fraction was calculated from the ratio of the measured silicon carbide lung burden at the end of the exposure to the estimated total inhaled mass of silicon carbide. As such, the amount of silicon carbide that was cleared from the lungs during the exposure period (e.g. by macrophage-mediated clearance) was not considered, which would result in an underestimation of the daily deposition fraction. The higher estimated deposition fraction after the 1-year exposure (Akiyama et al., 2007) compared with that estimated after the 4-week exposure (Akiyama et al., 2003) may in part be due to the higher total lung burden and reduced clearance rate of the rats in the 1-year exposure study.]

Searl et al. (1999) measured the biopersistence of nine mineral fibre types, including silicon carbide whiskers, for up to 12 months after intratracheal injection in male specific pathogen-free Wistar rats [as reported in Miller et al. (1999)]. The silicon carbide whiskers (Advanced Composite Materials Corporation (ACMC)) were described as semi-crystalline often with small hooks at one end and/or buds along their length. Approximately 40% of the fibres consisted of two or more "fully developed, bonded" whiskers. The silicon carbide was used in high-temperature composite materials and was supplied as a fine powder of whiskers, which was reportedly entirely within the respirable size range [the particle size distribution of the powder was not reported, but fibres in the rat lungs were reported to be up to 20 µm in length or greater]. After injection of 14.2 mg (821×10^6 fibres > 0.4 µm in length) [reported in Miller et al. (1999)], the lung fibre burdens of silicon carbide (recovered by bleach digestion of lung tissue) were measured 3 days, and 1, 6, and 12 months after injection. The fibres were counted and sized using SEM. The mean (standard error) number of silicon carbide fibres in the lungs was 80.9 (14) $\times 10^6$ at 3 days and 29.3 (6.6) $\times 10^6$ at 12 months after injection. Retention of 36% of silicon carbide fibres was measured in rat lungs 1 year after intratracheal exposure. The mean diameter of the silicon carbide fibres recovered was similar throughout the observation period. The mean diameter for all fibres > 0.4 µm in length was 0.48 µm at 3 days and 0.50 µm at 12 months after exposure, and that for fibres > 20 µm in length was 0.53 µm at 3 days and 0.55 µm at 12 months after exposure. The persistence rates of silicon carbide showed no length specificity.

The retention of length fibres in the lungs at 12 months after exposure by intratracheal instillation was reported as the percentage of fibres in the same cumulative length categories (Miller et al., 1999). Four rats per group were killed 3 days after injection and at three additional time-points, and the retained fibre number in the lungs was determined using the same counting and sizing criteria as for the injected samples. The biopersistence was estimated by fitting an exponential decay model to the fibre count and data on time after exposure. These data were re-expressed as the expected percentage of fibres remaining in the lungs 12 months after exposure. The estimated percentages of retained silicon carbide whiskers in the cumulative length categories (i.e. > 0.4, > 5, > 8, > 10, > 15, and > 20 µm) were 52.6, 53.7, 47.7, 49.2, 54.5, and 59.2%, respectively. Among the nine fibre types examined, silicon carbide whiskers showed the greatest percentage of retained total fibres (53% weighted average) 12 months after exposure. [The Working Group noted the difference in the 36% versus 53% weighted average retention.] The ratio of complex silicon carbide whiskers (i.e. more than one fibrous component) to single silicon carbide whiskers reportedly remained unchanged over the 12 months experiments because their dissolution was expected to be "immeasurably small."

Miller et al. (1999) studied factors such as biopersistence and fibre dimensions as predictors of mesothelioma, which was measured as survival time in rats exposed by intraperitoneal injection to nine different fibre types, including silicon carbide whiskers [the experimental data were reported in Searl et al. (1999)]. The silicon carbide whiskers were prepared as a respirable size sample and counted and sized by optical and electron microscopy. Fibres were counted if their length:diameter aspect ratio was greater than 3:1 and the length was greater than 0.4 µm. The counted fibres were sized by diameter and length (in 0.1 µm increments). The silicon carbide whiskers included structures with complex shapes (e.g. multiple branches), which required a more detailed system of quantification that involved recording the dimensions of each branch (as if a separate fibre) as well as estimating these structures as rectangles (with length measured parallel to the longest branch and width at the thickest branch). Miller et al. (1999) used the estimated rectangular dimensions of silicon carbide in their analysis. The target fibre doses were 10^9 fibres ≥ 5 µm in length, which resulted in different mass doses across fibre types. The injected mass dose of length whiskers was 14.2 mg (suspended in sterile physiological saline). Most of the length fibres had diameters of less than approximately 1 µm. The length distribution of injected fibres was reported as: 821, 577, 387, 307, 185, or 121 × 10^6 fibres in cumulative length categories of > 0.4, > 5, > 8, > 10, > 15, and > 20 µm, respectively. Fibre numbers with diameters greater than approximately 1 µm were: 4, 3, 3, 3, 3, or 1 x 10^6 fibres, respectively, in the same length categories.

Combining the data from all nine fibre types examined in a regression analysis, Miller et al. (1999) estimated the most predictive factors of survival of rats for deaths from all causes or mesothelioma were the number of fibres > 20 µm in length injected and the biopersistence of fibres > 5 µm in rat lungs. The lowest median survival of rats injected with the nine fibre types examined was found for silicon carbide whiskers in this study.

(ii) Sheep

During the production of silicon carbide, also known commercially as carborundum, both fibrous and angular particles can be emitted. Samples of two types of silicon carbide were obtained from the Acheson furnaces of a silicon carbide plant (Dufresne et al., 1992). The silicon carbide was reportedly obtained from the field because no reference material was available. The non-fibrous (angular) silicon carbide sample was collected from the centre of the hot material at the end of the firing process, and the fibrous silicon carbide sample was collected from the outside of the cylindrical lump near the graphite core. The non-fibrous sample was ground, sieved, and micronized (10 µm), while the fibrous sample was disaggregated by grinding at cold temperature (near liquid nitrogen).

The prepared samples were analysed by SEM, TEM, and energy dispersive spectrometer of X-rays. At least five morphological types of particle were identified: isolated fibrils, aggregated fibrils, rectilinear fibres, corrugated fibres, and angular particles. All particles in the non-fibrous sample were reported to be angular in shape (Dufresne et al., 1992). The non-fibrous material consisted of a particular polymorph of carborundum as well as an aluminium oxide corundum (estimated at approximately 90 and 10%, respectively). In contrast, the fibrous sample contained several morphological types of fibre as well as angular particles (27% by weight) and graphite (5% by weight). The size distribution of the particles in the fibrous sample was not measured, although the largest fibres were reported to be approximately 30 µm in length and 0.5 µm in diameter. The size distribution of the non-fibrous particles was measured by a Coulter Counter; 95% of the particles were

less than 2 μm in "equivalent" diameter and the mean diameter was 0.92 μm.

Groups of eight sheep (weighing 25–45 kg) were studied for the pulmonary clearance of silicon carbide up to 8 months after injection of 100 mg of either fibrous or non-fibrous silicon carbide (in 100 mL of saline) into the tracheal lobe. The administered dose ("exposure") of non-fibrous (angular silicon carbide) was estimated to be 90 mg [i.e. by subtraction of the 10% aluminium oxide corundum], and the administered dose of fibrous silicon carbide was estimated to be 95 mg [i.e. by subtraction of the 5% carbon], which comprised 27 mg of angular and 68 mg of fibrous silicon carbide. BALF was obtained before and 2, 4, 6, and 8 months after exposure by slow infusion of four 50-mL aliquots of PBS through the bronchoscope and by gentle aspiration of the effluent. The fourth syringe of BALF was retained for particle analysis. [The rationale for not including the first three syringes of BALF is unclear because that approach would seem to reduce the yield of particles and cells from the BALF, resulting in lower estimates of the carborundum in the BALF.] Sheep were killed 8 months after exposure, the lungs were removed, and nine tissue samples were taken from the tracheal lobe for particle analysis (Dufresne et al., 1992).

The mass concentration of carborundum in the BALF at the first time-point after exposure (2 months) was approximately 60 and 200 ng/mL of fibrous and non-fibrous silicon carbide, respectively. [To what extent this difference was due to a faster clearance of the fibrous silicon carbide, greater deposition efficiency of the non-fibrous silicon carbide, or possibly differential recovery of the BALF cannot be determined from the available data. If BALF had been obtained earlier (e.g. 1–3 days) after the tracheal lobe injection, data could have been obtained on the initial deposition efficiency of each material as noted by the authors in the Discussion section of the article.] However, the data from 2–8 months after exposure show a faster rate of clearance in the fibrous group. From these data, the authors estimated the clearance half-time ($t_{1/2}$) [i.e. the time required to reduce the lung dose by half] to be 1.7 or 5.8 months, respectively, for the sheep in the fibrous or non-fibrous groups. Lower retention of fibrous versus angular silicon carbide was also reported in the lung parenchyma (tracheal lobe tissue), i.e. the retention of silicon carbide in the lung tissue in the fibrous group was approximately 30 times lower than that in the non-fibrous group. The "retention rate" of the angular fraction of the fibrous silicon carbide was nearly the same as that of the non-fibrous (angular) silicon carbide. The average retained lung tissue dose measured in the tracheal lobe at 8 months after exposure was 219 ng/mg of dry lung tissue in the non-fibrous (angular) silicon carbide group, and 4.6 and 58 ng/mg for fibrous and angular silicon carbide, respectively, in the fibrous group (Dufresne et al., 1992). The "retention rate" was calculated as the ratio of the "retention" (ng/mg)/"exposure" (mg) (i.e. the administered dose of silicon carbide).

[The Working Group noted that the "retention rate" column in Table 1 of Dufresne et al. (1992) is not clear. The reported values of 2.43 for angular (non-fibrous group) and 0.07 and 2.15 for angular and fibrous silicon carbide, respectively, in the fibrous group can be calculated directly from the "exposure" (mg of silicon carbide) and "lung retention" (ng of silicon carbide/mg of dry tracheal lobe tissue) columns, as follows: retention/exposure = "retention rate." However, the units were apparently not taken into account, i.e. the calculation should be: (ng/mg)/(mg × 106 ng/mg). Moreover, the total dry mass of the tracheal lobe into which the silicon carbide was injected did not seem to be taken into account, i.e. the correct calculation would be: lung retention (mass silicon carbide/mass tracheal lobe tissue)/exposure (mass silicon carbide/total mass of tracheal lobe). Also, as calculated, the "retention rate" is

a proportion (not a rate) because it is described as the retained mass at the 8-month time-point after exposure. Finally, values greater than 1 do not make sense for a proportion. Thus, the values in "retention rate" are apparently reported incorrectly. Nevertheless, the relative values reported (if they are correct) are approximately 30 times higher for the angular silicon carbide in either the fibrous or non-fibrous group compared with the fibrous silicon carbide value; another error is that, for angular silicon carbide, the exposure is listed as 100 versus 90 in the "retention rate" column, although the resulting value of 2.24 is arithmetically correct if 90 is substituted for 100; in addition, the issues on units and total tracheal lobe mass are still not resolved.]

[Despite the lack of clarity of the values reported for "retention rate" (see Table 1 of Dufresne et al. (1992)), the data on BALF are consistent in showing a faster rate of clearance from 2 to 8 months after exposure and a lower retained proportion of fibrous silicon carbide at 8 months compared with "particulate" (angular) silicon carbide (see Fig. 5 of Dufresne et al. (1992)). The lower estimated retention of fibrous silicon carbide (ng/mg lung tissue) might be explained by the fibrotic lung response – which occurred in sheep exposed to fibrous (with 27% angular) silicon carbide but not in sheep exposed to the non-fibrous (angular) silicon carbide – and the associated increased lung tissue weight, resulting in a low mass of silicon carbide per mass of lung tissue. However, the similar reported lung tissue retention for the angular silicon carbide fraction in either the non-fibrous or fibrous group were considered to provide evidence against a fibrotic lung response explaining the different retention rates (assuming the reported values are correct). The fate of the fibrous or non-fibrous silicon carbide after clearance from the lungs was not reported, due to the lack of data on doses of silicon carbide in other organ tissues (including lymph nodes) or in the urine/faeces.]

In summary, the Dufresne et al. (1992) study reported shorter retention half-times for fibrous silicon carbide in the lungs of sheep than for non-fibrous (angular) silicon carbide at approximately equal administered mass doses.

[The findings of Dufresne et al. (1992) would appear to contradict those from other studies that showed greater lung retention with increasing length of biopersistent amosite fibres (Searl et al., 1999), which would suggest greater retention of the fibrous versus angular silicon carbide. A higher dissolution rate of the fibrous silicon carbide might be a possible explanation, given the smaller diameter of the fibrous silicon carbide (0.5 µm maximum reported diameter) compared with that of angular silicon carbide (mean diameter, 0.92 µm) (Dufresne et al., 1992). However, the dissolution of silicon carbide was found to be very low in either cell-free assays (simulated physiological saline) (Searl et al., 1999) or in mice (Holt, 1950). Experimental data and modelling of other fibre types found that dissolution and breakage of non-biopersistent fibres results in a decrease in longer fibres and an increase in shorter fibres. Although shorter fibres can be cleared more effectively than longer fibres by alveolar macrophages, the fibre breakage resulted in a higher proportion of fibres in the shorter size categories 1 year after exposure (Searl et al., 1999; Tran et al., 2003). However, a breakage of the silicon carbide fibres would not explain the lower mass retention of fibrous silicon carbide because the angular silicon carbide would also be expected to be cleared effectively by alveolar macrophages. In addition, the fibrogenic response in sheep to fibrous silicon carbide is not consistent with its lower retained lung dose compared with angular silicon carbide, which did not cause fibrosis (Dufresne et al., 1992). A possible explanation for the findings in Dufresne et al. (1992) might be that the fibrous silicon carbide had more highly reactive surfaces (as well as a greater total surface area) than the angular silicon carbide, resulting in greater

reactivity with lung tissues, as well as to faster translocation from the lungs to the lymph nodes (where the silicon carbide would pass through the epithelial cells and could damage cells in the process). Some support for this explanation is the finding that toxic crystalline silica causes adverse lung effects at lower mass doses and is translocated to the lung-associated lymph nodes at a faster rate than less toxic particles (Tran et al., 2002). This possibility cannot be evaluated from the data available in Dufresne et al. (1992), however, because no measurements were reported of the surface reactivity of the fibrous versus angular silicon carbide particle surfaces, nor was the translocation of silicon carbide to the lymph nodes measured.]

(e) Clearance

The clearance of silicon carbide whiskers was studied in rats after a 4-week whole-body inhalation exposure (Akiyama et al., 2003) [see experimental details in Section 4.1.2(a)]. The mass lung burden of silicon carbide 3 days, 2 weeks, and 1, 2, 3, 6, and 12 months after exposure was used to estimate the clearance of fibres. A one-compartment exponential decay model was shown to fit the retained lung burden and data on time after exposure adequately (R^2 = 0.90). A biological half-time ($t_{1/2}$) of 4 months was calculated from that model.

In a 1-year whole-body inhalation study of silicon carbide whiskers by the same group (Akiyama et al., 2007), the mass lung burden was measured 6 days, 3, 6, and 12 months after exposure [see Section 4.1.2(d) for the values measured]. A biological half-time ($t_{1/2}$) of 16 months was calculated from these data.

The authors argued that one of the reasons for the longer retention half-time may have been due to the lung dose of silicon carbide exceeding the alveolar macrophage-mediated clearance capacity (i.e. overloading; Morrow et al., 1991). From the measured lung dose of 5.4 mg of silicon carbide whiskers 6 days after the end of the 1-year exposure and a specific gravity of silicon carbide whiskers of 3.2 g/cm^3, Akiyama et al. (2007) calculated that the retained volumetric dose of silicon carbide whiskers in the lungs was approximately 1600 nL, which exceeds the 1000-nL dose associated with overloading of lung clearance in rats reported by Morrow et al. (1991). In comparison, the mass retained lung dose of silicon carbide whiskers after a 4-week inhalation exposure (Akiyama et al., 2003) was approximately 190 nL [calculated from 0.6 mg/(3.2 g/mL × 1000 mg/g × 1 mL/10^6 nL)].

4.2 Physico-chemical properties associated with toxicity

4.2.1 Crystal structure

Silicon carbide may occur in several crystalline forms (polymorphs) after a different stacking of silicon and carbon atoms. In the non-fibrous form, silicon carbide particles may be amorphous. Traditional industrial production via the Acheson process yields polydispersed particulates with particles from several micron- to nano-size, often containing quartz, cristobalite, and carbon particles (Scansetti et al., 1992; Boumahdi, 2009).

The nature of the crystalline phases (α- versus β-silicon carbide) in nano-size (α-silicon carbide, 16 nm; β-silicon carbide, 4 nm; β-silicon carbide with α-silicon carbide < 10% and iron impurities ≈500 ppm, 14 or 26 nm) influenced tumour necrosis factor (TNF)-α production. α-Silicon carbide induced higher TNF-α production than β-silicon carbide. When the presence of α-silicon carbide was detected by X-ray diffraction analysis, a moderate or elevated level of TNF-α was found, while this pro-inflammatory cytokine was not elicited by exposure to pure β-silicon carbide (Pourchez et al., 2012).

Silicon carbide may be prepared in a non-stoichiometric form, i.e. with a variable silicon/carbon ratio, which influenced the in-vitro

cellular responses to micron- and nano-size particles (Boumahdi, 2009; Barillet et al., 2010a). A comparison of the cellular responses induced in human A549 lung adenocarcinoma cells by a panel of silicon carbide nanoparticles (for details, see Section 4.2.2) led to the conclusion that silicon carbide nanoparticles with a high silicon/carbon ratio induced the production of reactive oxygen species (ROS) and inhibited glutathione (GSH) reductase activity earlier than those with a low silicon/carbon ratio. They also induced more persistent genotoxicity. The authors considered that the presence of silicon dioxide residues on the surface of these nanoparticles renders them more toxic (Barillet et al., 2010a).

Conversely, three silicon carbide nanoparticles showing similar crystallite size (4 nm), Brunauer–Emmett–Teller (BET) size (14–15 nm), specific surface area (125–139 m^2/g), and oxidation state of the surface (7–8% of O1s) but increasing carbon/silicon atomic ratios from 0.88 to 1.21 did not differ in their cytotoxicity or pro-inflammatory response (TNF-α values at the same level as the negative control), showing no influence of the carbon/silicon atomic ratio on the in-vitro cellular responses (Pourchez et al., 2012).

4.2.2 Form and size

Silicon carbide may assume a large variety of forms from isometric particles to fibres and whiskers. Most silicon carbide industrial dusts may contain some particles with a fibrous shape. The material is usually comprised of particles of different sizes, some of which may be of greater concern than others. The term whiskers is confined to monocrystals with a fine fibre morphology, resembling amphibole asbestos or erionite. Being single crystals, silicon carbide whiskers have sharp tips and high tensile strength (Svensson et al., 1997).

(a) Silicon carbide particles (Acheson process)

Five silicon carbide industrial powders (silicon carbide C1, C2, F1, F2, and I) were collected after their production in the Acheson process in industrial plants (see Table 4.4 for the characteristics of the particles used in this study). Silicon carbide C1 and C2 are coarser than silicon carbide F1 and F2. They are mostly constituted by the α-silicon carbide phase. Silicon carbide I is a metallurgically impure dust representative of airborne dusts inhaled in the workplace environment. Free radical release but also iron content increased with particle size. Hydrogen peroxide production by RAW 264.7 macrophage cells was induced to a greater extent by exposure to fine silicon carbide F1 and F2 particles than that to coarse silicon carbide C1 or C2 or to silicon carbide I and was proportional to surface area (Boudard et al., 2014).

(b) Silicon carbide whiskers

Five whiskers (four silicon carbide whiskers, SiCW-1, -2, -3, and -4, and one silicon nitride, SiNW) and two powders (one silicon carbide, SiCP, and one silicon nitride, SiNP) were studied (Svensson et al., 1997; see Table 4.5 for the characteristics of the particles/whiskers used in this study). One of the silicon carbide whiskers, SiCW-3, was also ball-milled in water for 3 hours (SiCW-3S, short-milled) and 58 hours (SiCW-3L, long-milled). The cloning efficiency of Chinese hamster V79 cells was inhibited in a concentration-dependent manner by all materials. At least five different concentrations (range, 0.25–80 $\mu g/cm^2$) of each material were tested for 20 hours. The dose–response curves were linear and the concentration resulting in 50% survival (EC_{50}) was calculated. A clear difference in viability was observed after exposure to milled whiskers and powders. The EC_{50} for the whiskers ranged from 0.9 to 4.2 $\mu g/cm^2$, whereas that for crocidolite asbestos (positive control) was 1.4 $\mu g/cm^2$. The milled whiskers

Table 4.4 Physico-chemical characteristics of different microparticles comprised of silicon carbide from the study by Boudard et al. (2014)

Sample	Specific surface area (m^2/g)	Median diameter D_{50} (µm)	Crystallite phases	O1s (% atomic)	Carbon/silicon (atomic ratio)	Iron (ppm)	Aluminium (ppm)
SiC C1	4.0	2.5	SiC-6H (91%), SiC-4H (7%), SiC-15R (< 1%)	17 (presence of a SiO_2 layer)	0.98	2 370	350
SiC F1	11.0	0.5	SiC-6H (91%), SiC-4H (7%), SiC-15R (2%)	22 (presence of a SiO_2 layer)	1	1 570	560
SiC I	3.0	6.0	SiC-6H (53%), SiC-4H (7%), SiC-15R (5%), SiO_2 quartz (9%), SiO_2 cristobalite (5%)	23 (presence of a SiO_2 layer)	1.66	20 000	1 300
SiC C2	3.5	2.5	SiC-6H (90%), SiC-4H (7%), SiC-15R (2%)	17 (presence of a SiO_2 layer)	0.99	2 230	730
SiC F2	8.5	0.8	SiC-6H (90%), SiC-4H (3%), SiC-15R (7%)	23 (presence of a SiO_2 layer)	0.98	1 370	0

SiC, silicon carbide; SiO_2, silicon dioxide

Adapted from *Toxicol In Vitro*, Volume 28, issue 5, Boudard et al. (2014) In vitro cellular responses to silicon carbide particles manufactured through the Acheson process: Impact of physico-chemical features on pro-inflammatory and pro-oxidative effects, Page Nos 856–865, Copyright (2014), with permission from Elsevier

and powders were less potent than the whiskers. Milling SiCW-3 for 3 and 58 hours decreased its toxicity (EC_{50}) from 4.2 µg/cm² to 6.9 µg/cm² and 10.7 µg/cm², respectively. The powders of both silicon nitride and silicon carbide were much less toxic in this test system, although the silicon nitride powder was more toxic than the silicon carbide powder, in line with the toxicity of the whiskers.

Three well-characterized whiskers of different sizes (SiCW 1, SiCW 2, and SiCW 3; characteristics reported in Table 4.6) were tested in vivo (Johnson & Hahn, 1996) and their effects were compared with those of continuous silicon carbide ceramic filaments. Crocidolite asbestos fibres were used as a positive control. A size analysis of the morphology of the three whiskers is illustrated in Table 1.1 (Health Council of the Netherlands, 2012). Silicon carbide whiskers, but not continuous silicon carbide ceramic filaments, induced mesotheliomas after intrapleural injection into rats (see also Section 3.3). A difference in the biological activity of the three samples of whiskers (SiCW 1, SiCW 2 >> SiCW 3) was observed, which could not be explained on the basis of their physical dimensions.

(c) Silicon carbide nanoparticles

Five silicon carbide nanoparticles (characteristics reported in Table 4.7) with varying diameters and silicon/carbon ratios that were synthesized by laser pyrolysis of gaseous precursors were taken up by human A549 lung adenocarcinoma cells, in which their cytotoxicity was low (Barillet et al., 2010a). [The low cytotoxicity of silicon carbide nanoparticles has also been demonstrated in studies of silicon carbide nanocrystals (Fan et al., 2008) or microscaled silicon carbide particles (Bruch et al., 1993a, b), suggesting that the absence of cytotoxicity after contact with a silicon carbide surface is unrelated to particle size.] However, silicon carbide nanoparticles induced major redox alterations. Cell redox status was markedly affected: silicon carbide nanoparticles caused the production of ROS, the depletion of GSH and the inactivation of some antioxidant enzymes (GSH reductase and superoxide dismutase) (Barillet et al., 2010a).

Table 4.5 Characteristics[a] of silicon carbide and silicon nitride particles and whiskers from the study by Svensson et al. (1997)

Composition and sample No.[b]	Manufacturer/ type	Content of discriminated whiskers × 10^{10}/g	Content of long fibres (≥ 20 µm) × 10^{10}/g	Length (µm)	Diameter (µm)	Length/ diameter	Specific area (m^2/g)
SiCW-1	Tokai 100	1.2	0.23	14 ± 10	0.8 ± 0.4	18 ± 11	3.0
SiCW-2	Tokai 400	0.9	0.20	14 ± 9	0.9 ± 0.4	17 ± 10	1.5
SiCW-3	Tateho SCW10	4.3	0.52	12 ± 10	0.7 ± 0.4	19 ± 13	4.2
SiCW-4	Tateho SCW1S	1.1	0.14	12 ± 9	0.7 ± 0.4	21 ± 12	4.9
SiCW-3L[c]	Tateho SCW10	3.9	0.12	9 ± 5	0.6 ± 0.3	16 ± 10	11.7
SiCW-3S[d]	Tateho SCW10	5.2	0.44	11 ± 7	0.7 ± 0.4	16 ± 9	5.2
SiNW	UBE	2.2	0.42	13 ± 8	0.9 ± 0.4	16 ± 8	2.2
SiNP	UBE E10				0.4 ± 0.4		10.9
SiCP	UF 15, Lonza				0.4 ± 0.3		14.9

[a] Further information on measurement and characterization in Nyberg et al. (1995); data comprise mean ± standardard deviation
[b] Length/diameter ≥ 5 µm, diameter ≤ 3 µm. Discrimination limit in image analysis
[c] L, long-milled (for 58 h)
[d] S, short-milled (for 3 h)
SiCW, silicon carbide whiskers; SiNW, silicon nitride whiskers; SiNP, silicon nitride powder; SiCP, silicon carbide powder
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Table 4.6 Characteristics of silicon carbide particles/whiskers and crocidolite from the study by Johnson & Hahn (1996)

Sample	Mean length (in µm) (standard error of the mean)	Mean diameter (in µm) (standard error of the mean)	Fibre (n/mg)	Specific surface area (m^2/g)	Specific gravity
SiCW 1	4.5 (0.23)	0.42 (0.02)	7.6×10^6	3.0	3.4
SiCW 2	20.1 (1.01)	0.75 (0.02)	1.6×10^5	1.4	3.3
SiCW 3	6.6 (0.40)	0.32 (0.01)	1.1×10^7	3.6	3.2
Crocidolite	2.1 (0.31)	0.12 (0.01)	3.6×10^9	7.0	3.2
CCF (PRD-166)[a]	40–100	12	ND	1.5	4.3

[a] Values determined approximately by light microscopy
CCF, continuous silicon carbide ceramic filament; ND, not determined; SiCW, silicon carbide whiskers
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Six ultrafine silicon carbide nanoparticles were prepared using both sol-gel and a laser (the physical characteristics, including size, crystallinity, silicon/carbon ratio, and oxygen or iron contaminants, of which are reported in Table 4.8; Pourchez et al., 2012). None of the nanoparticles tested induced cytotoxicity in RAW 264.7 cells derived from murine peritoneal macrophages. Conversely, other adverse cellular responses elicited (see Section 4.4) were markedly dependent upon crystal phase, silicon/carbon ratio, and level of contaminants. The nature of the surface oxidation layer (silica versus silicon oxycarbide) did not modulate the pro-inflammatory response (TNF-α production) while a linear correlation was observed (R^2 = 0.97) between TNF-α production and the total surface area exposed to silicon carbide nanoparticles. Such

Table 4.7 Characteristics[a] of silicon carbide nanoparticles from the study by Barillet et al. (2010a)

Sample	SSA (m^2/g)	BET size (nm)	TEM size (nm)	Silicon/carbon	ζ (mV)	Hydrodynamic diameter (nm)
SiC-A	125	15	17 ± 3	0.8	–24	168 (100%)
SiC-B	134	14	13 ± 3	1.0	–22	125 (100%)
SiC-C	140	13	12 ± 3	1.2	–31	97 (100%)
SiC-D	52	36	31 ± 8	1.1	–28	190 (100%)
SiC-E	33	58	45 ± 18	1.1	–28	280 (100%)

[a] SSA, specific surface area, measured according to Brunauer–Emmett–Teller (BET); BET size, diameters of silicon carbide nanoparticles calculated from SSA; TEM size, diameters of silicon carbide nanoparticles measured by transmission electron microscopy; ζ, zeta potential measured just before nanoparticle dilution into cell culture medium; hydrodynamic diameter measured by photon correlation spectroscopy after nanoparticle dilution into cell culture medium

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a correlation was obtained for β-silicon carbide nanoparticles with the presence of α-silicon carbide, confirming the impact of both crystalline phase and the specific surface area.

4.2.3 Surface reactivity

Because the bonding energy between silicon and oxygen is higher than that between silicon and carbon, the silicon atoms exposed at the surface of silicon carbide are highly likely to react with oxygen, particularly if loosely bound to the underlying crystal structure. The particles obtained by using the Acheson process had the following surface species (as shown by X-ray photoelectron spectroscopy): silicon dioxide, silicon oxycarbure, carbon residues (C–C), silicon impurities (Si–Si) and oxidized carbon forms (C–O, C=O) (Boumahdi, 2009).

All forms of silicon carbide that are exposed to the atmosphere tend in the long-term to be covered by one or more layers of silica over time. However, this process may occur through different kinetics and is greatly accelerated by heating (Deal & Grove, 1965; Boch, 2001; Boumahdi, 2009). Consequently, heated silicon carbide particles may be covered with a thick external layer of silicon dioxide, while unheated particles may be only partially covered by a few silicon–oxygen patches, e.g. only on some crystal faces or at steps, kinks, and corners, thus exposing the silicon–carbon structure to fluids, cells, and tissues. This is fairly relevant to the fate of the particles in vivo as various studies have shown that cells react quite differently to a silicon–carbon surface than to a silica-like surface. While the silica-like surface always induces a substantial level of cytotoxicity, the silicon–carbon surface appears to be non-cytotoxic in the RAW 264.7 cell line derived from murine peritoneal macrophages (toxicity assessed as cell membrane damage (release of lactate dehydrogenase; Pourchez et al., 2012; Boudard et al., 2014)) or in the human A549 lung adenocarcinoma cells (toxicity assessed by impaired mitochondrial activity as detected using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide assay (Barillet et al., 2010a)). Boudard et al. (2014) compared several cellular responses to unheated and heated silicon carbide dust, taking into account that the oxidation of silicon to silica is favoured on heating and that heated particles were almost completely covered by a thick layer of silica. Although the starting material was non-toxic, heating increased cytotoxicity which was assessed by the release of lactate dehydrogenase.

Conversely, both oxidized silicon carbide C1 and F1 particles treated at 1400 °C induced lower

Table 4.8 Characteristics of silicon carbide nanoparticles from the study by Pourchez et al. (2012)

Sample	ρ (g/cm^3)	SSA (m^2/g)	BET size (nm)	Crystallite size	Crystalline phases	O1s (% atomic)	Iron (ppm)	Carbon/silicon (atomic ratio)
SG	3.2	125	15	14-nm monocrystalline nanograins	β-SiC (SiC-3C), α-SiC < 10% (SiC-6H)	8	0	0.88
LP1	3.2	139	14	4-nm polycrystalline nanograins	β-SiC (SiC-3C)	8	105	1.00
LP2	3.1	125	15	4-nm polycrystalline nanograins	β-SiC (SiC-3C)	7	200	1.21
LP3	3.0	140	14	4-nm polycrystalline nanograins	β-SiC (SiC-3C)	14 (presence of a SiO_2 layer)	605	0.81
LP4	3.1	52	37	16-nm nanograins with stacking faults	β-SiC (SiC-3C), α-SiC < 10% (SiC-6H)	8	592	0.88
LP5	3.1	33	59	26-nm nanograins with stacking faults	β-SiC (SiC-3C), α-SiC < 10% (SiC-6H), Si (< 2%)	22 (presence of a SiO_2 layer)	415	0.88
M	3.0	62	32	16-nm nanograins with stacking faults	α-SiC (SiC-6H)	25 (presence of a SiO_2 layer)	2830	0.70

BET, Brunauer–Emmett–Teller; LP1, typical nanoparticles of β-SiC synthesized by laser pyrolysis; LP2 and LP3, SiC nanoparticles enriched in carbon and silicon, respectively; LP4 and LP5, nanopowders with coarse grains of larger size; M, pure α-SiC nanoparticles; SG, nanopowder synthesized chemically; SiO_2, silicon dioxide; SSA, specific surface area

Adapted from *J Nanopart Res*, In vitro cellular responses to silicon carbide nanoparticles: impact of physico-chemical features on pro-inflammatory and pro-oxidative effects, volume 14, 2012, page 1143, Pourchez et al. (2012), with permission of Springer

levels of TNF-α than their unheated counterparts. Cellular production of hydrogen peroxide was unrelated to surface oxidation (Boudard et al., 2014).

(a) Generation of free radicals and depletion of antioxidants

Conflicting evidence has been shown for the direct generation of free radicals by silicon carbide particles. An earlier study reported that both the supercoiled plasmid assay for DNA scission and high-performance liquid chromatography using salicylate as an hydroxyl radical trap gave negative results with silicon carbide fibre (ACMC) but positive results with amosite asbestos (Brown et al., 1998).

(i) Silicon carbide particles (Acheson process)

The ability of silicon carbide particles to generate HO• and COO•⁻ radicals was assessed under cell-free conditions using electron paramagnetic resonance spectroscopy (Boudard et al., 2014). All particles were able to generate free radicals and were more effective in generating COO•⁻ than HO•. Free radical production increased with particle size and was 3–5-fold higher with coarse silicon carbide C1/C2 particles than with fine silicon carbide F1/F2 particles (maximal COO•⁻ production with silicon carbide C2). The silicon carbide I powder was characterized by the generation of HO• radicals, with a 5-fold greater production compared with silicon carbide F1/F2. This behaviour may be related to the large amount of iron in the coarse particles compared with the fine particles, especially silicon carbide I, which also exhibited a partially crystallized surface layer of silica. The potential to release the particle-derived free radicals HO• and COO•⁻ decreases with surface oxidation but, at very high temperatures (> 1400 °C), the specific surface area markedly decreases and the external silica layer that was originally amorphous crystallizes into cristobalite. The amount of free radical released per unit surface under these circumstances markedly increases in respect to the original material. The decrement in radical yield upon heating up to 850 °C is caused by both development of an amorphous surface layer and the conversion of Fe^{2+} into Fe^{3+} after oxidation [as reported for other toxic particulates (Tomatis et al., 2002)].

(ii) Silicon carbide whiskers

The generation of hydroxyl radicals by a panel of silicon carbide whiskers was investigated using three independent assays: deoxyguanosine hydroxylation, dimethyl sulfoxide as a scavenger, and deoxyribose assays. Table 4.9 summarizes the release of free radicals from silicon carbide whiskers and Table 4.5 shows the characteristics of the whiskers (Svensson et al., 1997). The HO• radical tests showed that only crocidolite (positive control) and silicon carbide whiskers-4 could potentiate the formation of hydroxyl radicals. The other materials tested did not differ from the control. [Analysis using the nick translation assay detected DNA strand breaks with all fibres except silicon carbide whiskers-2 and silicon nitride whiskers. Taking into account the concentration used, exposure to all of the silicon carbide whiskers induced DNA breaks (of the same magnitude as crocidolite) compared with a low rate for the other material. The highest activity was found for silicon carbide whiskers-3S.]

(iii) Silicon carbide nanoparticles

In the study by Pourchez et al. (2012) (see Table 4.8 for characteristics of the particles), in which free radicals were measured directly using electron paramagnetic resonance spectroscopy under cell-free conditions, no radical release was observed with LP1 and SG. LP2 and LP3 were able to generate COO•⁻, but not HO• radicals. Significant HO• radical release was observed with LP4 (21 nmol/m²) and more importantly with LP5. This sample exhibited the highest activity for COO•⁻ (400 nmol/m²) and HO• generation

Table 4.9 Free radical release from silicon carbide and nitride whiskers/particles[a]

Sample	8-OHdG/10^3dG	Deoxyribose (A_{532})	DMSO/MSA (A_{425})
Control	0.28 ± 0.1	0.05 ± 0.03	0.40 ± 0.17
SiCW-1	0.28 ± 0.09	0.09 ± 0.02	0.34 ± 0.09
SiCW-2	0.35 ± 0.10	0.09 ± 0.04	0.36 ± 0.11
SiCW-3	0.54 ± 0.16	0.15 ± 0.14	0.33 ± 0.14
SiCW-4	2.34 ± 1.80	0.64 ± 0.58	0.68 ± 0.11
SiCW-3L	0.46 ± 0.19	0.17 ± 0.06	0.61 ± 0.02
SiCW-3S	0.71 ± 0.21	0.15 ± 0.09	0.56 ± 0.02
SiNW	0.31 ± 0.17	0.13 ± 0.03	0.19 ± 0.06
SiNP	0.49 ± 0.24	0.05 ± 0.03	0.31 ± 0.09
SiCP	0.32 ± 0.16	0.07 ± 0.02	0.26 ± 0.06
Crocidolite	3.59 ± 1.20	1.73 ± 0.04	Not measured

[a] Data are given as mean of three experiments ± standard deviation. Values represent number of molecules of 8-hydroxydeoxyguanosine per 10^3 deoxyguanosine and absorbence at A_{532} and A_{425}, respectively

dG, deoxyguanosine; DMSO, dimethyl sulfoxide; 8-OHdG, 8-hydroxydeoxyguanosine; MSA, methanesulfonic acid; SiCP, silicon carbide particles; SiCW, silicon carbide whiskers; SiNP, silicon nitride particles; SiNW, silicon nitride whiskers

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per unit surface (47 nmol/m^2). LP5 contained the highest amount of surface iron. The authors concluded that free radical production under acellular conditions is associated with the iron content at the nanoparticles surface; in contrast to other cases (e.g. silica and asbestos) in which even traces of iron ions are able to trigger the Fenton reaction (Fubini et al., 2001; Turci et al., 2011), a threshold effect of surface iron of around 11 µg/m^2 has been observed for silicon carbide nanoparticles.

(b) Bioavailability and biodeposition of metals

Substantial amounts of iron or other metal impurities are present at the surface of particles produced by the Acheson process, which are probably bioavailable although bioavailability per se has not been measured. Metal ion bioavailability has not been reported for whiskers. Iron was present at the surface of the silicon carbide nanoparticles studied by Pourchez et al. (2012), while Barillet et al. (2010a) considered the particles they studied to be free from any metal-based impurities, thus ruling out any effect caused by Fenton-like and Haber-Weiss reactions.

(c) Antioxidant depletion

The ability of several types of fibre, including silicon carbide, to deplete the antioxidants, ascorbic acid and GSH, was investigated in the lining fluid of rat lung epithelial cells. Silicon carbide whiskers (ACMC), as well as other fibres, were able to deplete GSH in lung lining fluid and depletion was dependent on the number of fibres (Brown et al., 2000).

Silicon carbide nanoparticles (Barillet et al., 2010a) caused the depletion of cellular GSH, the major antioxidant cellular defence mechanism. GSH may either be released from cells to the extracellular medium or oxidized intracellularly to oxidized GSH (GSSG) by GSH peroxidase, which is coupled to the reduction of hydrogen peroxide to water. Because high levels of ROS accumulate in cells exposed to silicon carbide nanoparticles, the oxidation of GSH to GSSG by GSH peroxidase was hypothesized. However, the total glutathione content (GSH + GSSG) decreased. Consequently, GSH may be oxidized to GSSG, but GSH and/or GSSG must also be released from cells to the extracellular medium. To support this hypothesis,

Brown et al. (2000) demonstrated that silicon carbide whiskers (ACMC) deplete GSH from lung lining fluid. Moreover, Zhang et al. (1999) suggested that GSH was released from alveolar macrophages exposed to silica as a consequence of GSH depletion in the extracellular fluid, and hypothesized that silicon carbide nanoparticles deplete GSH and/or GSSG from the extracellular fluid and that the cells then release these molecules to re-establish the GSH intra-/extracellular balance. GSH reductase, which is responsible for the reduction of GSSG to GSH, is inactivated (see also Barillet et al., 2010a). The GSH pool is thus not re-established, leading to the accumulation of hydrogen peroxide in the cells. Superoxide dismutase, which is responsible for $O_2^{\bullet-}$ dismutation to hydrogen peroxide, was also partially inactivated in cells exposed to silicon carbide nanoparticles, resulting in the intracellular accumulation of $O_2^{\bullet-}$.

4.2.4 Fibre durability (leaching, phagocytosis, dissolution, and breaking)

Silicon carbide is a very durable material that is poorly dissolved in aqueous media. Biopersistence is linked not only to durability in biological fluids, but also to the form of the material (see Table 4.1).

(a) In vivo

(i) Silicon carbide whiskers

Silicon carbide whiskers (mean diameter, 0.45 µm), as a very durable material, were compared with less durable glass microfibres (code 100/475), relatively soluble man-made vitreous fibres (Davis et al., 1996). Amosite asbestos was used as a positive control. After inhalation for 1 year, fewer very long glass microfibres (length, > 20 µm) remained in rats lungs at the end of the exposure compared with amosite or silicon carbide. After exposure, amosite and glass microfibres were removed from the lungs at rates similar to those of most fibre dimensions whereas the clearance of silicon carbide was much slower. When dust was administered by intratracheal instillation, the differences in length with regard to fibre removal from the lung tissue were less marked.

Silicon carbide whiskers exhibit high biopersistence and are not modified in vivo. Over the long-term, longer whiskers are more biopersistent than shorter whiskers. Akiyama et al. (2003) reported an exponential clearance of deposited silicon carbide whiskers (MMAD, 2.5 µm; GM diameter, 0.4 µm; GM length, 2.2 µm) from rat lungs after 4 weeks of inhalation. The apparent deposition fraction was 4.8% ± 0.7%. During the clearance period, the amount of silicon carbide whiskers deposited in the rat lungs decreased exponentially with increasing duration of clearance. The biological half-time in the one-compartment model was determined to be 4.0 months, similar to that of other biopersistent inorganic fibres.

The biopersistence of deposited silicon carbide whiskers was measured after a longer inhalation exposure in rats (Akiyama et al., 2007). A group of 42 male Wistar rats was exposed by inhalation to daily average concentrations of 2.6 ± 0.4 mg/m^3 (98 ± 19 fibres/mL) of silicon carbide whiskers (MMAD, 2.4 µm (GSD, 2.4); GM diameter, 0.5 µm (GSD, 1.5); GM length, 2.8 µm (GSD, 2.3)) for 6 hours per day on 5 days per week for 1 year; the rats were killed 6 days and 3, 6, and 12 months after the exposure. The amount of silicon carbide whiskers deposited in each rat lung 6 days after the exposure, determined by an X-ray diffraction method, was 5.3 ± 1.4 mg. The biological half-time was 16 months, calculated from the amount of deposited silicon carbide whiskers at 6 days and 3, 6, and 12 months, and was more prolonged than normal physiological clearance. The diameter of the silicon carbide whiskers in the lung at each time-point during the 12 months of clearance after inhalation did not change. However, longer silicon carbide whiskers tended to be retained in

the lung as the clearance time increased, especially after 6 months. Histopathological examination revealed bronchoalveolar hyperplasia in 2 rats 1 year after the exposure and severe fibrotic changes around aggregated silicon carbide whiskers.

(ii) Silicon carbide particles, fibres, and angular particles

Pioneer studies on the fate of siliceous dusts in the body compared the in-vivo solubility of cement, carborundum, quartz, and moulding sand by estimating urinary silica values after intraperitoneal injection of different dusts into mice. An increase in the excretion of silica was found only with exposure to cement (Holt, 1950).

The lung tissue of a worker exposed for 10 years in an abrasive manufacturing plant was analysed by bulk analysis and in situ analytical electron microanalysis. Total dust in the lung was 120 mg/g of the dried lung tissue, 43% of which was silicon carbide (Hayashi & Kajita, 1988).

Materials taken in the field (carborundum from Acheson furnaces at a silicon carbide plant) contained both angular and fibrous silicon carbide particulates emitted by the silicon-carbide production operations. The pulmonary retention of the two morphological types was studied in sheep. Animals were injected in the tracheal lobe with an equal mass (100 mg) of particulates prepared from silicon carbide materials collected in the workplace. Particles were measured by analytical TEM in samples of BALF obtained 2, 4, 6, and 8 months after the injection and also in samples of lung parenchyma obtained at 8 months. Measurements in BALF and lung samples both indicated a much lower retention of fibrous than of angular silicon carbide. The retention rate in lung parenchyma at 8 months was 30 times lower for fibrous silicon carbide. The half-life of the decrease in concentrations was 3.4 times shorter for fibrous silicon carbide (Dufresne et al., 1992).

A study on pulmonary dust retention in a worker who had a lung lobectomy for an epidermoid carcinoma and who had been employed for 42 years in the vicinity of an Acheson furnace in a silicon carbide plant reported silicon carbide fibres in the lung parenchyma. The concentration of silicon carbide fibres longer than 5 µm was 39 300 fibres/mg of dry lung (Dufresne et al., 1993).

Particle-induced X-ray emission is a technique used to measure X-rays induced by proton irradiation that requires minimal sample preparation, can yield a detection limit as low as a few parts per million, and is based on the excitation of the electronic levels of atoms by means of an ion beam, producing X-ray emissions. These X-rays are characteristic and proportional to every element. Doses of 0.5 and 5 mg of silicon carbide nanoparticles were instilled into female Wistar rat lungs and were investigated using this technique for 60 days. The biopersistence of silicon carbide at a dose of 5 mg showed the typical trend reported for larger amounts of nanoparticles during the first few days after exposure to high doses. For lower doses (0.5 mg), only 0.074 mg of silicon carbide remained in the lungs 1 hour after instillation, representing 14.8% of the original dose. After 60 days, the biopersistence of the lower dose (0.5 mg) was 2.84%. The higher dose (5 mg) resulted in the retention of 1.834 mg in the lungs, representing 36.68% of the administered dose, 1 hour after instillation. After 60 days, only 1.17% of the higher dose was retained in the lungs (Lozano et al., 2012).

(b) In vitro

An examination of the in-vitro solubility of silicon carbide whiskers and their chemical composition after extraction from lung tissues showed almost no change in chemical composition (Davis et al., 1996).

4.3 Genetic and related effects

See Table 4.10

4.3.1 Human cells in vitro

Silicon carbide whiskers were reported to increase the level of DNA strand breaks and DNA–DNA interstrand crosslinks in human A549 lung adenocarcinoma cells after exposure at 200 µg/mL for 1 hour (Wang et al., 1999). [The Working Group noted that the report lacked information on the number of independent replicates.]

DNA strand breaks were measured using the alkaline comet assay in human A549 lung adenocarcinoma cells after exposure to 50 µg/mL of five different silicon carbide nanomaterials for 4, 24, or 48 hours (Barillet et al., 2010a). The silicon carbide nanoparticles were synthesized by laser pyrolysis of gaseous silane and acetylene precursors to materials with different sizes and ratios between silicon and carbon. Measurements of size included the specific surface area (33–140 m^2/g), BET size (13–58 nm), TEM size (12–45 nm), and hydrodynamic diameter (97–280 nm, measured by photon correlation spectrometry in cell culture medium). All of five silicon carbide materials were reported to increase the level of DNA strand breaks 4 hours after exposure, whereas genotoxicity was less evident after 24 and 48 hours. No difference in the generation of DNA strand breaks between the silicon carbide samples was observed after 4 hours of exposure, whereas one sample with a large specific surface area (125 m^2/g), median hydrodynamic diameter (168 nm), and low silicon:carbon ratio (0.8) was not genotoxic at 24 or 48 hours. [The data appear to have been obtained from only a single experiment and the statistical analysis was based on 50 comets from this experiment.]

Silicon carbide whiskers were reported to increase the number of chromosomal aberrations (acentric fragments, chromosome breaks, chromosome fragments, chromatid breaks, chromatid exchanges, and structural chromosomal aberrations) in human embryo lung cells after exposure to 2.5 or 5 µg/mL for 24 hours (Wang et al., 1999).

4.3.2 Experimental systems in vitro

Svensson et al. (1997) measured DNA strand breaks using the nick translation assay in Chinese hamster lung fibroblast V79 cells treated with 0.3–15 µg/mL whiskers (four silicon carbides, SiCW-1, -2, -3, and -4, and one silicon nitride, SiNW) and powders (one silicon carbide, SiCP, and one silicon nitride, SiNP) for 20 hours. The length of the silicon carbide whiskers ranged between 12 ± 10 µm and 14 ± 10 µm and the diameters between 0.7 ± 0.4 and 0.9 ± 0.4 µm. Accordingly, their length:diameter ratios were similar. The SiCW-3 whiskers were also ball-milled in water for 3 hours (SiCW-3S, short-milled) or 58 hours (SiCW-3L, long-milled). The mean length of SiCW-3S and SiCW-3L was 11 ± 7 µm and 9 ± 5 µm, respectively. High rates of DNA strand breaks were observed for all of the silicon carbide whiskers (of the same magnitude as crocidolite). The highest effect was found for SiCW-3S and the lowest for SiCP.

The induction of DNA strand breaks was investigated by alkaline comet assay in rat kidney proximal tubule NRK-52E cells 24 hours after exposure to 2–200 µg/mL of a silicon carbide nanopowder. The silicon carbide nanoparticles, synthesized by pyrolysis, were described as having a spherical morphology with a specific surface area of 125 m^2/g and a particle size of 15 nm (BET) or 17 nm (TEM). The results were not statistically significant. The authors also reported that the silicon carbide sample did not generate DNA double-strand breaks although the results were not shown (Barillet et al., 2010b).

Using the M3E3/C3 lung epithelial cell line from Syrian golden hamsters, exposure to silicon carbide fibres for 48–96 hours at doses between

Table 4.10 Studies of genotoxicity in human cells and in experimental systems in vitro after exposure to silicon carbide

Material[a]	Dose and cells	Effect	Comments	Reference
Human cells in vitro				
5 SiC-NP (SiC-A–E) with diameters of 13–68 nm and silicon/carbon ratio of 0.8–1.3	50 µg/mL for 4–48 h in human A549 lung adenocarcinoma cells	Increase in DNA strand breaks with all SiC-NP (assessed by the alkaline version of comet assay; genotoxicity appeared to be transient in cells exposed to SiC-A and SiC-B, and permanent in cells exposed to the other SiC-NP (higher silicon/carbon ratio)	Uncertainty about number of independent replicates and statistical analysis	Barillet et al. (2010a)
SiCW	200 µg/mL for 1 h in human A549 lung adenocarcinoma cells or 2.5 or 5 µg/ml for 24 h in human embryo lung cells	Increase in DNA strand breaks and DNA–DNA interstrand crosslinks in A549 cells; increased frequency of chromosomal aberration in human embryo lung cells	Lack of information on the number of independent replicates	Wang et al. (1999)
Other experimental systems				
SiC nanoparticles synthetized by pyrolysis, with spherical morphology, a specific surface area of 125 m^2/g and particle size of 15 nm (BET) or 17 nm (TEM)	2–200 µg/mL for 24 h in rat kidney proximal tubule NRK-52E cells	No increase in DNA strand breaks (measured by alkaline comet assay)		Barillet et al. (2010b)
SiC fibres	0.1–2 µg /mL for 48–96 h in Syrian golden hamster M3E3/C3 lung epithelial cells	Increase in micronuclei frequency; both kinetophore-positive and -negative micronuclei were detected, evocative of chromosomal aberration and breakage and aneuploidy	Fibre characteristics NR	Peraud & Riebe-Imre (1994)
Five SiC (SiCW-1, -2, -3, and -4 and 1 SiCP); diameter, 0.4–0.8 µm	0.3–15 µg/mL for 20 h in Chinese hamster lung fibroblast V79 cells	Increase in DNA strand breaks (assessed by nick translation assay); high rate of breakage for all SiCW (of the same magnitude as crocidolite); highest effect found for SiCW-3S and the lowest for the SiCP		Svensson et al. (1997)

BET, Brunauer–Emmett–Teller; NR, not reported; SiCP, silicon carbide powder; SiC-NP, silicon carbide nanoparticles; SiCW, silicon carbide whiskers; TEM, transmission electron microscopy

0.1 and 2 µg/mL increased the frequency of micronuclei (Peraud & Riebe-Imre, 1994). [The Working Group noted that no information was available on fibre characteristics in this study.]

4.4 Other mechanisms of carcinogenesis

4.4.1 Humans

See also Section 4.1, Table 4.2

Several studies have been published concerning occupational exposure to silicon carbide in humans. In contrast, information in humans on cellular mechanisms such as apoptosis, with the exception of studies in human monocytes in vitro after exposure to silicon carbide (Nordsletten et al., 1996), is limited. A dose–response has been demonstrated for decreased lung function and increased incidence of obstructive lung disease with particle mass (Bugge et al., 2011, 2012; Johnsen et al., 2013). Table 4.2 provides a summary of studies conducted among workers within the silicon carbide industry and the adverse health outcomes observed, including decreased lung function and increased incidence of obstructive lung disease (Bugge et al., 2010, 2012).

Fibrosis

Two men exposed only to silicon carbide powder for many years in a factory manufacturing refractory bricks developed bilateral reticulonodular densities as detected by chest radiography. An open lung biopsy from one patient showed a large amount of black material in the fibrosed alveolar septa. X-Ray diffraction revealed silicon carbide powder to which they had been exposed, but not quartz; X-ray diffraction analysis of the lung tissue confirmed at least six different types of silicon carbide, traces of tungsten carbide, and an insignificant amount of quartz (Funahashi et al., 1984).

No data on persistent inflammation, activation of intracellular signalling pathways, resistance to apoptosis, or cell proliferation in humans were available to the Working Group.

4.4.2 Experimental animals

(a) Inflammasome activation

Persistent inflammation accompanied by epithelial cell injury and repair by cell proliferation are important in the development of diseases associated with the inhalation of fibres (Bissonnette & Rola-Pleszczynski, 1989; McGavran & Brody, 1989; Rom et al., 1991; Donaldson & Brown, 1993; Barrett, 1994; Davis et al., 1996).

In a short-term inhalation experiment silicon carbide whiskers caused the recruitment of inflammatory cells and increased protein levels in BALF similarly to code 100/475 glass fibres and amosite asbestos fibres. Rats were exposed by whole-body inhalation to the fibre types at a concentration of 1000 WHO fibres/mL for 7 hours per day. The granulocyte response, commonly used as a measure of inflammation, showed a different pattern of time dependence for each fibre type but no clear differences between fibre types was found for BALF protein levels (Cullen et al., 1997). The bronchiolar alveolar deposition of fibres results in increased proliferation in epithelial and interstitial cells in the lung (Chang et al., 1988; Brody & Overby, 1989; Warheit et al., 1992). In the study of Cullen et al. (1997), the proliferative response to code 100/475 glassfibres was no greater than that in unexposed control animals, whereas amosite and silicon carbide whiskers both produced significant increases in cell proliferation.

Nine groups of eight sheep were exposed to saline, latex, graphite, raw silicon carbide particles, ashed silicon carbide particles, quartz, crocidolite, raw silicon carbide fibres, and ashed silicon carbide fibres by instillation once into the tracheal lobe (Bégin et al., 1989). BALF was

obtained at 2-month intervals and animals were necropsied after 8 months. Analyses of cellularity and cytotoxicity in the BALF in association with histopathology to assess fibrosis demonstrated that all particles except for quartz were inert.

(b) Biomarkers of lung injury

Studies on intratracheal instillation have shown that exposure to silicon carbide whiskers produces pulmonary fibrotic changes, suggesting that these whiskers might have fibrogenic potential (Morimoto et al., 2003a, b).

Male Wistar rats were given a single intratracheal instillation of 2 or 10 mg of silicon carbide whiskers suspended in saline and were killed after 3 days, 1 week, 1 month, 3 months, or 6 months of recovery time. Expression of Clara cell secretory protein (CCSP) was detected using reverse transcriptase-polymerase chain reaction (RT-PCR), Western blot, and immunostaining. Exposure to 10 mg of silicon carbide whiskers decreased CCSP mRNA expression at 3 days, 1 week, 1 month, and 6 months after intratracheal instillation. Protein levels of CCSP in rats were decreased at 1 day, 3 days, and 1 month after a single instillation of 2 or 10 mg of silicon carbide whiskers (Morimoto et al., 2003b). CCSP is one of the major secretory products specifically produced by Clara cells and is hypothesized to inhibit inflammation and fibrosis because it is homologous with lipocortin (Mantile et al., 1993). CCSP has also been hypothesized to play a role as a phospholipase A_2 inhibitor in suppressing inflammation and fibrosis (Mango et al., 1998). [The results obtained by Morimoto et al. (2003b) suggest that CCSP is involved not only in the acute phase but also in the chronic phase of the lung injury induced by silicon carbide whiskers.]

Surfactant protein (SP) is a biomarker of lung injury and pulmonary fibrotic activity. SP mainly produced by type II alveolar epithelial cells, acts as a control tower responsible for guiding the secretion and re-uptake of phospholipids, which decrease alveolar surface tension, and prevent alveolar collapse, which are thought to play contributory roles in limiting the progression of fibrosis (Hawgood & Clements, 1990; Batenburg, 1992; McCormack et al., 1995). The expression of SP-A, SP-C, and thyroid transcription factor-1 (TTF-1), a common transcription factor of SP-A and SP-C mRNA in lungs exposed to silicon carbide whiskers, was examined in male Wister rats given a single intratracheal instillation of 2 or 10 mg of silicon carbide whiskers suspended in saline and killed 3 days, 1 week, 1 month, 3 months, and 6 months after the exposure. RNA was subsequently extracted from the lungs and the expression of SP-A, SP-C, and TTF-1 mRNA from the lungs was quantified using RT–PCR. Exposure to 2 mg of silicon carbide whiskers decreased mRNA expression of SP-A and TTF-1 at 6 months, and exposure to 10 mg of silicon carbide whiskers decreased the levels of SP-A and TTF-1 mRNA after 3 days and 6 months. In contrast, no clear alteration in the expression of SP-C was observed (Morimoto et al., 2003a). [These data suggest that SP-A and TTF-1 are associated not only with the acute phase but also the chronic phase of lung injury induced by silicon carbide whiskers.]

The expression of calcitonin gene-related peptide (CGRP) was quantified using RT–PCR and the enzyme immunometric assay in the lungs of male Wistar rats given a single intratracheal instillation of 2 mg of crystalline silica, crocidolite, silicon carbide whiskers, or potassium octatitanate whiskers suspended in saline and killed after recovery periods of 3 days, 1 week, 1 month, 3 months, and 6 months. CGRP protein levels in the lungs of rats exposed to silicon carbide whiskers and potassium octatitanate whiskers were higher after 3 days of recovery than those in rats exposed to silica and crocidolite (Morimoto et al., 2007). CGRP, which is found in the central and peripheral nerves, pancreatic Langerhans cells, adrenal cortex, and hypophysis, is a 37-amino acid neuropeptide (Dakhama et al., 2004). In the lung, it is secreted

from the neuroendocrine cells and nerve endings (Russwurm et al., 2001). The reported functions of CGRP include strong vasodilation, inhibition of inflammatory mediator activity, modulation of macrophage function, and maintenance of airway responsiveness (Dakhama et al., 2002, 2004). CGRP has also been reported to stimulate the proliferation of epithelial and endothelial cells in various organs (White et al., 1993; Kawase et al., 1999). In the lung, CGRP facilitates the proliferation of alveolar and airway epithelial cells; the proliferation of alveolar epithelial cells stimulated by CGRP is mediated by the mitogen-activated protein kinase signalling pathway (Kawanami et al., 2009). In animal models of airway and alveolar epithelial injury, pulmonary neuroepithelial cells and neuroepithelial bodies producing CGRP have been reported to undergo hyperplasia these cells produce CGRP in a paracrine fashion and proliferate in this lung microenvironment (Elizegi et al., 2001).

(c) Persistent inflammation

See Table 4.11

Persistent inflammation in the lung has been reported in experimental animals exposed to asbestos or silica, and is an important mechanism that leads to the production of irreversible chronic lesions, including fibrosis and tumours.

(i) Inhalation

Inhalation exposure of female Wistar rats to silicon carbide powder (mean diameter, < 3 μm) for two periods of 5 days did not induce inflammation (Bruch et al., 1993a).

(ii) Intratracheal instillation

Two studies of silicon carbide administered by intratracheal instillation of fibres in sheep and of whiskers in rats showed fibrosing alveolitis in sheep lungs (Bégin et al., 1989), and transient alveolitis in rat lungs (Ogami et al., 2007).

(d) Cell proliferation

Bronchiolar and alveolar epithelial cells in vivo

Studies of acute and chronic inhalation of silicon carbide whiskers and intratracheal instillation of silicon carbide powder and whiskers all showed that the proliferation of bronchiolar and alveolar epithelial cells was induced by exposure to silicon carbide whiskers but not to silicon carbide powder. In the 1-year study of Akiyama et al. (2007), histopathological examination revealed hyperplasia of bronchoalveolar epithelial cells in 2 out of 11 Wistar rats exposed to silicon carbide whiskers. In a 13-week study (Lapin et al., 1991), adenomatous hyperplasia of the lung was observed in male and female Sprague-Dawley rats exposed to silicon carbide whiskers.

In two studies of acute exposure to silicon carbide whiskers (Davis et al., 1996; Cullen et al., 1997), analysis of the expression of 5-bromo-2-deoxyuridine revealed the induction of hyperplasia of the bronchiolar and alveolar epithelial cells in rat lungs after 1 and 7 days, respectively.

In sheep that were instilled intratracheally with non-fibrous silicon carbide and two types of silicon carbide fibres, a fibroblast proliferation assay using BALF recovered from the lungs revealed that both fibres, but not particles, induced the proliferation of sheep lung fibroblasts (Bégin et al., 1989).

(e) Granuloma formation and fibrosis

See Table 4.11

(i) Inhalation

Exposure of rats to silicon carbide whiskers for 1 year induced severe fibrotic changes in the lung in two studies (Davis et al., 1996; Akiyama et al., 2007).

Inhalation exposure of Sprague-Dawley rats to silicon carbide whiskers for 13 weeks induced minimal or slight pleural fibrosis (Lapin et al., 1991). [Although this study also

Table 4.11 Studies on persistent inflammation, granuloma formation, and fibrosis in experimental animals

Route of administration	Type of silicon carbide	Species, strain, (sex)	Dosing regimen	Duration of exposure/ recovery	Bulk sample	Inflammation	Fibrosis or granulomatosis	Reference
Inhalation	Whiskers	Rat, Wistar (M)	2.6 ± 0.6 mg/m³, (98 ± 19 fibres/mL)/ day	Exposure, 1 yr; recovery, 1 yr	Tokai Carbon Co.; purity, 98%		Hyperplasia, severe fibrosis	Akiyama et al. (2007)
	Whiskers	Rat, Sprague-Dawley (M, F)	0.09, 3.93, 10.7, 60.5 mg/m³ (0, 630, 1746, 7276 fibres/mL) /day	Exposure, 13 wk; recovery, 26 wk	Whiskers, 80–90%; mean diameter, 0.555 ± 0.197 µm; mean length, 10 ± 11.2 µm	Adenomatous hyperplasia (minimum/slight)	Pleural fibrosis (minimum/ slight)	Lapin et al. (1991)
	Whiskers	Rat, AF/HAN (NR)	1000 fibres/mL, 7 h/day, 5 days/wk for 1 yr	Exposure, 1 yr; recovery, lifespan (1 yr)	Mean diameter, 0.45 µm including fibres > 20 µm		Fibrosis (Wagner scale 4)	Davis et al. (1996)
	Powder	Rat, Wistar (F)	20 mg/m³, 5 h/day, 5 days/wk followed by a rest period of 2 days and a re-exposure period of 5 days	Exposure, 2 × 5 days; recovery, 90 days	Mean diameter, < 3 µm	No inflammation		Bruch et al. (1993a)
Intratracheal instillation	Powder	Rat, Wistar (F)	50 mg	Single dose; recovery, 3 and 8 mo	Mean diameter, < 3 µm	No inflammation		Bruch et al. (1993b)
	Whiskers	Rat, F344 (F)	1 or 5 mg/rat	Recovery, 18 mo	Sample 1: GM diameter, 0.8 µm (SD, 0.3); GM length, 18.1 µm (SD, 14.3) Sample 2: GM diameter, 1.5 µm (SD, 0.6); GM length, 15.3 µm (SD, 11.2)		Multiple nodular granulomas	Vaughan et al. (1993)
	Whiskers	Rat, Wistar (M)	2 mg/rat	Recovery, 6 mo	GM diameter, 0.3 µm (SD, 1.5); GM length, 5.1 µm (SD, 2.3)	Inflammation (transient)		Ogami et al. (2007)
	Non-fibrous and fibres	Sheep (NR)	100 mg/sheep	Recovery, 8 mo	99.5% < 5 µm	Nodular fibrosing alveolitis: fibres only		Bégin et al. (1989)
	Silicon carbide	Rat, Wistar (M)	50 mg/rat	Recovery, 12 months	Average size < 3 µm		No fibrosis	Bruch et al. (1993b)

F, female; GM, geometric mean; M, male; mo, month; NR, not reported; SD, standard deviation; wk, week; yr, year

revealed persistent alveolar wall thickening, it is unclear whether this finding was associated with pulmonary fibrosis.]

(ii) Intratracheal instillation

A single dose of 50 mg of silicon carbide powder did not induce fibrosis in the lung [even though the dose was excessive] (Bruch et al., 1993b).

Two studies of silicon carbide whiskers provided evidence of various degrees of granuloma formation or fibrosis (Vaughan et al., 1993; Morimoto et al., 2003a).

No data on immunosuppression, apoptosis, activation of intracellular signalling pathways, or resistance to apoptosis were available to the Working Group.

4.4.3 Experimental systems in vitro

(a) Release of cytokines, chemokines, and growth factors

Macrophages exposed to toxic and carcinogenic dusts and fibres in vitro release pro-inflammatory mediators, and the release of TNF-α is commonly used as a biomarker for acute pro-inflammatory effects. Primary rat alveolar macrophages were exposed to two samples of silicon carbide whiskers (ACMC) in comparison with amosite or crocidolite asbestos fibres and a variety of man-made mineral fibres at equal fibre numbers (length, > 5 μm) for 24 hours. Both samples of silicon carbide whiskers were as potent as or more potent than asbestos fibres in eliciting TNF-α release (Cullen et al., 1997).

Nuclear translocation of the transcription factor nuclear factor (NF)-κB is associated with pro-inflammatory gene activation (Mossman et al., 1997). In the human A549 lung adenocarcinoma cell line, exposure to silicon carbide whiskers (ACMC) for 8 hours induced the activation of NF-κB in 38% of cells compared with 55% of cells exposed to long-fibre amosite asbestos at equal fibre numbers (Brown et al., 1999). Translocation of NF-κB was significantly decreased by antioxidants (curcumin, pyrrolidine dithiocarbamate, or nacystelin).

(b) Apoptosis and necrosis

In explants of dog tracheal epithelium, a dose of 10 μg/cm^2 of one of three samples of silicon carbide whiskers (Tateho, Japan, or American Matrix, Inc., Tennessee, USA) induced necrosis of non-ciliated cells after 3 days (Vaughan et al., 1991b). At doses of between 5 and 20 μg/cm^2, two of these samples also induced acute toxicity in BALB/3T3 mouse embryonic cells, as assessed by trypan blue exclusion, ^{51}Cr release, and colony-forming efficiency, that was comparable with that of crocidolite asbestos fibres (Los Alamos National Laboratory, New Mexico, USA) (Vaughan et al., 1991a).

Three samples of silicon carbide whiskers (Alcan Aluminum Corp., Pennsylvania; ACMC; American Matrix Inc.) were compared with crocidolite asbestos fibres (UICC), erionite fibres (Rome, Oregon, USA), and JM Code 100 glass-fibres (Johns Manville Corp., Colorado, USA). At doses between 5 and 50 μg/mL, all fibrous samples induced toxicity in primary rat alveolar macrophages, as assessed by trypan blue exclusion, and decreased colony-forming efficiency in primary rat tracheal epithelial cells, lung epithelial cells, and the human lung adenocarcinoma A549 cell line (Johnson et al., 1992). The authors noted that these toxicity end-points based on mass doses may not correlate with toxicity ranked on the basis of equal fibre numbers.

Svensson et al. (1997) assessed the effects of silicon carbide whiskers (Tokai Carbon Co., Ltd, Japan; Tateho Chemical Co., Ltd), silicon carbide powder (UF15, Lonza) and crocidolite asbestos fibres (UICC) on colony-formation efficiency in the V79 Chinese hamster lung fibroblast cell line exposed to 0.25–80 μg/cm^2 for 20 hours. The silicon carbide whiskers and crocidolite asbestos fibres showed highest potency; milled silicon

carbide whiskers and silicon carbide powder were less potent.

In primary cultures of hamster alveolar macrophages, silicon carbide whiskers (Japan Fibrous Materials Research Association) induced apoptosis after exposure to 20–60 μg/mL for 18 hours assessed by the detection of a DNA ladder and nuclear morphology using TEM (Watanabe et al., 2000). Using the same sample of silicon carbide whiskers in comparison with chrysotile asbestos fibres (Japan Association for the Working Environment Measurement) at doses of 20–60 μg/mL, Shibata et al. (2007) detected plasma membrane injury assessed by lactate dehydrogenase release in primary cultures of rat alveolar macrophages and the murine peritoneal macrophage RAW 264.7 cell line.

(c) Impaired DNA repair

No data on impaired DNA repair were available to the Working Group.

DNA breakage was detected in M3E3/C3 lung epithelial cells exposed to silicon carbide, as measured by the detection of micronuclei (Peraud & Riebe-Imre, 1994). Both kinetochore positive and kinetochore negative micronuclei were detected as evidence for chromosome breakage and aneuploidy.

(d) Depletion of antioxidants

No direct data on the depletion of antioxidants in cells were available to the Working Group.

In an acellular test system, the effects of five whiskers (four silicon carbides, SiCW-1, -2,-3, and -4, and one silicon nitride, SiNW) and two powders (one silicon carbide, SiCP, and one silicon nitride, SiNP) were determined. SiCW-3 was also ball-milled in water for 3 hours (SiCW-3S, short-milled) or 58 hours (SiCW-3L, long-milled). The lengths of the silicon carbide whiskers ranged between 12 ± 10 and 14 ± 10 μm and the diameters between 0.7 ± 0.4 and 0.9 ± 0.4 μm and their length/diameter ratios were therefore similar. The mean length of SiCW-3S and SiCW-3L was 11 ± 7 μm and 9 ± 5 μm, respectively. The assay detected the reaction product, 8-hydroxydeoxyguanosine, formed in the presence of hydrogen peroxide and deoxyguanosine. The 8-hydroxydeoxyguanosine/deoxyguanosine ratio was taken as an index of hydroxyl radical formation. Only SiCW-4 and crocidolite, used as positive control, could potentiate the formation of hydroxyl radicals. In the presence of the scavenger dimethyl sulfoxide, the hydroxyl radical production of these samples was lowered (Svensson et al., 1997). In an acellular system, silicon carbide whiskers (ACMC) had the ability to deplete both GSH and ascorbate from pure solutions of GSH or ascorbate, and GSH from Wistar rat lung lining fluid (Brown et al., 2000).

The formation of oxygen radicals by human neutrophils treated with samples of silicon carbide whiskers and silicon nitride whiskers was assessed by chemiluminescence and the formation of hydrogen peroxide was determined (Svensson et al., 1997). Several samples – SiCW-1, SiCW-3, SiCW-4, SiCW-3S, and SiCW-3L – induced chemiluminescence and a relatively good correlation was found between the magnitude of chemiluminescence and the neutrophil-mediated formation of hydrogen peroxide. [These results showed that some samples could trigger the intracellular production of ROS and suggest that silicon carbide whiskers may disturb the cellular oxidant/antioxidant balance.]

Another study demonstrated the production of ROS by silicon carbide-exposed cells. In addition, the authors suggested that the generation of ROS was dependent on NF-κB activation. In this study, human A549 lung adenocarcinoma cells were exposed to silicon carbide (60.86% > 10 μm in length; ACMC). The effects on hydrogen peroxide formation of silicon carbide, long amosite asbestos fibres, and refractory ceramic fibres were compared. All fibres produced positive nuclear staining of NF-κB in A549 cells, as well as generation of hydrogen peroxide. Several

Table 4.12 Summary of the results of mechanistic studies for the three categories of silicon carbide

Category of silicon carbide	End-point			Reference
	Biopersistence	Inflammation/ fibrosis in lung	Genotoxicity	
Abrasive dust from the Acheson process	Weak	Weak	No data	Dufresne et al. (1992)
Silicon carbide whiskers	Strong	Strong	Moderate[a]	Akiyama et al. (2003, 2007)
Silicon carbide nanoparticles	No data	No data	Inadequate data	Barillet et al. (2010a)

[a] Chromosomal aberrations in human cells

antioxidant inhibitors and a specific inhibitor of NF-κB activation inhibited the effect of the fibres (Brown et al., 1999). [These results showed the involvement of oxidants in silicon carbide-dependent activation of the transcription factor NF-κB and also suggest that silicon carbide fibres could perturb the cellular oxidant/antioxidant balance.]

No data on inflammasome activation, immunosuppression, alteration of DNA methylation, or the activation of oncogenes and tumour-suppressor genes in other experimental systems were available to the Working Group.

4.5 Susceptible populations

No data were available to the Working Group.

4.6 Mechanistic considerations

The summary of the relevant data available are reported separately in Table 4.12 for the three categories of silicon carbide and for the three most relevant end-points: biopersistence, inflammation and fibrosis, and genotoxicity.

5. Summary of Data Reported

5.1 Exposure data

Silicon carbide occurs in several forms: non-fibrous or granular particulate material (dust, crude, and grains), fibres, and whiskers. A fibre is typically polycrystalline, whereas the name whisker is applied only to monocrystalline (or single-crystal) fibres. Whiskers are intentionally produced and have a homogeneous morphology whereas silicon carbide fibres are morphologically heterogeneous. Silicon carbide whiskers are cylindrical in shape, similar in size to asbestos amphiboles, and may meet the definition of WHO fibres.

Silicon carbide is very stable, but chemical reactions between silicon carbide and oxygen occur at relatively high temperatures. Fresh surfaces of silicon carbide exposed to an oxidizing atmosphere could thus be covered by a film of silicon dioxide.

Silicon carbide can be manufactured by several processes, resulting in different levels of purity, crystal structure, particle size, and shape; the most frequently used method is the Acheson process for the production of silicon carbide particles, in which silicon carbide fibres are unwanted by-products. Different morphologies of silicon carbide fibres formed during the Acheson process have been observed by electron microscopy. Their length and diameter

are variable, but can fulfil the WHO definition of fibres, and may include fibres that are indistinguishable from whiskers. Silicon carbide fragments (probably derived from the cleavage of non-fibrous silicon carbide crystals), also corresponding to the WHO definition of fibres, were found in the processing department and in sorting operations.

Other methods for the production of silicon carbide particulates, fibres, or whiskers exist but have not been well documented with respect to the generation of fibrous silicon carbide in the air.

Silicon carbide production began in the early twentieth century mostly for use as abrasives. Carborundum is a commercial name for silicon carbide abrasives and is occasionally used as a common name for silicon carbide dust. In 2013, the global production capacity was estimated to more than 1 000 000 metric tonnes, of which China was the leading producer. The available information on production levels mostly concerns the Acheson process. Additional applications of silicon carbide include: refractories, electrical devices, electronics, diesel particle filters, ceramics, industrial furnaces, structural materials, metallurgy, and in the aerospace, automotive, and power generation industries as reinforcing materials in advanced ceramic composites. Unwanted fibres from the Acheson process are usually recycled in further reactions in the Acheson furnace; they may also occasionally be sold as part of metallurgical-grade silicon carbide. Silicon carbide whiskers are used as a durable industrial substitute for asbestos.

Insufficient data have been reported to reach a conclusion on the exposure of workers to whiskers and silicon carbide dust used as abrasive products. However, high levels of silicon carbide fibres have been measured in the Acheson process during the mixing of materials, furnace operations, and the separation of products with average concentrations of > 0.1 fibres/cm^3. The majority of the silicon carbide fibres were thin with an average diameter < 1 μm and an aspect ratio > 35. Lower levels of fibres have been measured in the processing department, but cleavage fragments were present at higher concentrations. Exposures to respirable silicon carbide fibres were confirmed by the analysis of human lung tissues. Most of the fibres in lung samples were < 5 μm in length. In silicon carbide industries, workers are also co-exposed to quartz and cristobalite.

5.2 Human carcinogenicity data

The carcinogenic risk associated with exposure to silicon carbide fibres has been investigated in two cohort studies of occupational exposure among workers using the Acheson process in silicon-carbide manufacturing plants. This process is characterized by multiple exposures, among them fibrous and non-fibrous silicon carbide, quartz, and cristobalite. The first cohort study included workers in the Canadian silicon-carbide manufacturing industry. An excess of mortality from lung cancer was observed in comparison with the general population. Mortality from mesothelioma was not reported for this cohort. In the second cohort, the incidence of lung cancer was investigated among workers in the Norwegian silicon-carbide manufacturing industry. In a series of studies, the most informative analysis was limited to long-term workers with at least 3 years of employment, and was based on a detailed job–exposure matrix taking into account total and respirable dust, non-fibrous and fibrous silicon carbide, quartz, and cristobalite. Overall, the incidence of lung cancer was increased, with the highest risk for workers in the furnace department who were believed to have the highest exposures to fibrous silicon carbide and crystalline silica dust. In multivariate modelling, an exposure–response effect was observed for silicon carbide fibres. The effect was weakened and no longer statistically significant after adjustment for concurrent exposure to cristobalite. The Working Group noted

that the strong correlation between exposures to silicon carbide fibres and cristobalite made the disentanglement of their respective effects difficult. Silicon carbide particles were not associated with cancer of the lung independently of silicon carbide fibres or cristobalite. No excess in the incidence of mesothelioma was observed in the Norwegian cohort. No data were available on cancer in populations exposed to manufactured silicon carbide whiskers.

5.3 Animal carcinogenicity data

Studies of fibrous silicon carbide in experimental animals were available only for silicon carbide whiskers.

Silicon carbide whiskers significantly increased the incidence of mesothelioma in three studies in female rats treated by intrapleural injection, intrapleural implantation, or intraperitoneal injection, and the increase was dose-related in rats treated by intraperitoneal injection. In a study in female rats treated by intratracheal instillation with two types of silicon carbide whiskers, judged by the Working Group to be limited because of its short duration, no treatment-related neoplasms were observed. One study of inhalation in male rats and one study of intraperitoneal injection in female rats gave negative results.

Mesotheliomas were reported in one study of intraperitoneal injection in female rats and in one study each of inhalation and intraperitoneal injection in rats (sex unspecified); however, these studies did not include concurrent controls. Because the background incidence of mesotheliomas is very low in rats, some consideration was given to these three studies that gave positive results, despite their lack of concurrent controls.

5.4 Mechanistic and other relevant data

5.4.1 Silicon carbide produced by the Acheson process

Airborne silicon carbide from the Acheson process, containing silicon carbide dust and fibres, can be deposited and retained in the human lung. After intratracheal instillation, silicon carbide dust and fibres were retained in the lungs of sheep. Mechanistic studies on silicon carbide materials in humans are lacking. The few available studies in experimental animals do not provide any insight into the mechanisms of carcinogenicity.

5.4.2 Silicon carbide whiskers

Studies on silicon carbide whiskers demonstrated biopersistence in the rat lung. The Working Group noted the lack of studies on the translocation of silicon carbide materials to the pleural cavity in experimental animals. Pulmonary exposure to silicon carbide whiskers in experimental animals has been associated with lung cell injury, inflammation, and fibrotic responses. Oxidative stress has been reported in studies in vitro. Genotoxicity measurements were limited to in-vitro studies. One study of genotoxicity demonstrated chromosomal aberrations in human embryonic lung cells exposed to silicon carbide whiskers. The few available studies reported data which are fully consistent with the mechanisms of carcinogenicity proposed for asbestos and erionite (see *IARC Monographs* Volume 100C).

5.4.3 Silicon carbide nanoparticles

Mechanistic studies of silicon carbide nanoparticles are sparse. The production of reactive oxygen species and the depletion of antioxidants have been reported in a few in-vitro studies, which have not been independently replicated

across different cell cultures or in in-vivo models and thus do not provide conclusive evidence that oxidative stress is a mechanism of the toxicity of silicon carbide nanoparticles. The results from experimental models do not provide adequate information to support a conclusion regarding the potential mechanisms of carcinogenicity of silicon carbide nanoparticles.

6. Evaluation

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures associated with the Acheson process. Occupational exposures associated with the Acheson process cause cancer of the lung.

There is *limited evidence* in humans for the carcinogenicity of fibrous silicon carbide. Positive associations have been observed between exposure to fibrous silicon carbide and cancer of the lung.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of silicon carbide whiskers.

6.3 Overall evaluation

Occupational exposures associated with the Acheson process are *carcinogenic to humans (Group 1).*

Fibrous silicon carbide is *possibly carcinogenic to humans (Group 2B).*

Silicon carbide whiskers are *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

Rationale for a separate evaluation of whiskers and fibres – majority view

The rationale for a separate evaluation of whiskers and fibres is based on differences in the nature of the agents.

The cohort of workers at plants using the Acheson process was occupationally exposed to non-fibrous and fibrous silicon carbide, potentially including some fibres that could be defined as whiskers, whereas exposure in most of the studies in experimental animals and in experimental systems was to silicon carbide whiskers.

Silicon carbide whiskers are monocrystalline and homogeneous in form, while fibrous silicon carbide is mostly polycrystalline and heterogeneous in form. The physico-chemical characteristics of these fibres were considered to be distinct, and therefore the fibres and whiskers warrant separate evaluations.

Rationale for a combined overall evaluation of whiskers and fibres – minority view

The argument for a combined overall evaluation of silicon carbide whiskers and fibres was that a proportion of the fibres in the epidemiological study in Norway had dimensions that were consistent with silicon carbide whiskers, and were morphologically indistinguishable from silicon carbide whiskers under electron microscopy. Thus, the excess of cancer of the lung observed was relevant for evaluating the carcinogenicity of silicon whiskers as well as other fibrous silicon carbide. Had the minority view been adopted, it would have supported an overall evaluation of *probably carcinogenic to humans (Group 2A).*

Rationale for classification in Group 2A – majority view

A narrow majority of the Working Group voted for the classification of silicon carbide whiskers as *probably carcinogenic to humans (Group 2A)* rather than as *possibly carcinogenic to humans (Group 2B)*.

The majority view was primarily based on their expert opinion that the major physical properties of silicon carbide whiskers resembled those of asbestos and erionite fibres, which are classified as *carcinogenic to humans (Group 1)*. This information was used to upgrade the overall evaluation of carcinogenicity to humans to Group 2A.

Rationale for classification in Group 2B – minority view

A minority of the Working Group voted for the classification of silicon carbide whiskers as *possibly carcinogenic to humans (Group 2B)* because:

- the evidence for the carcinogenicity of silicon carbide whiskers in experimental animals was based on direct bolus delivery into the pleura or peritoneum at high mass doses;
- only one study of inhalation was available and was considered by the minority as inadequate for the evaluation due to lack of concurrent unexposed controls; and
- the available mechanistic data did not provide strong support for an upgrade of the overall evaluation.

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