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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

150. Silicon carbide

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The literature search was kindly done by assistance of Line Arneberg at the National Institute of Occupational Health, Norway. The evaluation of the literature and the drafting of this document on Silicon carbide were made by Dr Merete D. Bugge, MD Vidar Skaug and Dr Erik Bye at the National Institute of Occupational Health, Norway.

The draft versions were discussed within NEG and the final version was adopted by the present NEG experts on 21 November 2016. Editorial work and technical editing were performed by the NEG secretariat. The following experts participated in the elaboration of the document:

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All criteria documents produced by the Nordic Expert Group may be downloaded from www.nordicexpertgroup.org.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

ATP	adenosine triphosphate
BAL	bronchoalveolar lavage
BET	Brunauer, Emmet and Teller
BrdU	bromodeoxyuridine
CCF	continuous ceramic filament
CHO	Chinese hamster ovary
CI	confidence interval
ESK	Elektroschmelzwerk Kempten
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
GM	geometric mean
GSD	geometric standard deviation
Ig	immunoglobulin
IL	interleukin
ILO	International Labour Organization
JEM	job exposure matrix
LDH	lactate dehydrogenase
MMAD	mass median aerodynamic diameter
MRV	minute respiratory volume
NEG	The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NFκB	nuclear factor kappa B
OEL	occupational exposure limit
PAH	polycyclic aromatic hydrocarbon
PMN	polymorphonuclear leukocyte
PSLT	poorly soluble, low toxicity
RCF	refractory ceramic fibres
SD	standard deviation
SEM	scanning electron microscopy
SiC	silicon carbide
SIR	standardised incidence ratio
SMR	standardised mortality ratio
SPIN	Substances in Preparations in Nordic Countries
SSA	specific surface area
US	United States
TEM	transmission electron microscopy
TLV	threshold limit value
TNF-α	tumour necrosis factor alpha
TWA	time-weighted average
WHO	World Health Organization

1. Introduction

Silicon carbide (SiC) occurs as an extremely rare mineral in nature, but has been industrially produced at a large scale since the end of the 19th century. Traditionally, the most important use of SiC has been as an abrasive. However, the material has in later years found widespread applications, e.g. as strengthening and wear resistant components in composite materials and metal alloys, and as a semiconductor in electronics.

The present document, which intends to form the scientific basis for an occupational exposure limit (OEL), reviews the literature concerning health effects from SiC exposure. The main concern has been the risk of lung diseases among workers in the SiC production industry. Several research groups in different countries have addressed this issue during the last 30–40 years (80, 126, 134, 143, 150) and much of the recent research has been carried out in Norway (31, 67).

There is little information as to the exposure and health aspects in downstream users, although the risk for end users of SiC products has been addressed in some toxicological studies.

2. Substance identification

SiC exists in many crystalline forms, all classified under the same CAS number. In this document the following terminology of differentiation will be used: angular SiC (non-fibrous SiC particles), SiC whiskers (single crystal SiC fibres) and SiC fibres (polycrystalline SiC fibres). SiC nanomaterials and amorphous SiC (non-crystalline) will also be briefly reviewed. Substance identification data are presented in Table 1.

Table 1. Substance identification data for silicon carbide (93).

Name:	Silicon carbide
Chemical formula:	SiC
CAS No.:	409-21-2
EC No.:	206-991-8
Synonyms:	Silicon monocarbide, carbon silicide
Trade names (not exhaustive):	Carborundum, SIKA, Carborex, Carbofrax (composites), Crystolon (sharpening stone), Nicalon (SiC ceramic fibres), Carbolon (metallurgical)

3. Physical and chemical properties

3.1 Crystal structure

The crystal structure of SiC is quite complex. There are three main crystal systems, cubic (ß-SiC), rhombohedral and hexagonal (α-SiC). The latter system presents various morphological structures. Layers of Si-C can be stacked in a wide

variety of ways, giving rise to more than 215 morphologically different SiC forms. The technologically most interesting crystal forms are 4H- and 6H-hexagonal, being α-SiC, and the cubic form 3C β-SiC (93).

3.2 Morphological features

SiC may exist in non-fibrous (angular particles) and fibrous forms (polycrystalline fibres and single crystal whiskers). The World Health Organization (WHO) definition of fibres is length > 5 µm, width < 3 µm and length:width ratio (aspect ratio) > 3:1 (175). SiC may also appear as cleavage fragments, platelets, nano-materials of various forms, and in amorphous form. Images of various SiC fibres and a cleavage fragment are shown in Figure 1. In this document, the expression "diameter" is normally used to characterise the thickness of fibrous forms of SiC, and "width" to characterise the thickness of angular forms.

3.2.1 Angular (non-fibrous) SiC particles

Angular SiC particles, commonly made by the Acheson method (Section 4.2.1), are the main product of the SiC production industry. They are angular and irregular and break easily, giving sharp edges. Angular SiC is produced in a large range of sizes depending on the needs of the end user (Section 4.3.1, Table 5).

3.2.2 Polycrystalline SiC fibres

SiC fibres occur as pollution in the furnace hall atmosphere during the Acheson production of angular SiC (35). The SiC fibres display a very complex morphology, with a high degree of stacking faults and twinning areas, resulting in angles and branching (73, 155). The size of these fibres varies considerably and they have been classified into eight categories, with median diameters for the six most frequent categories in the range 0.25–1.50 µm, median lengths in the range 7.65–11.60 µm and median aspect ratios (length/diameter) in the range 5.67–32.90. More than one half of the fibres were rectilinear but often tapered along the axis and had a smooth surface and a circular cross section (155).

3.2.3 SiC whiskers (single crystal SiC fibres)

SiC whiskers are synthesised for commercial purposes by specially refined production methods for growing the material along one crystal direction (77, 92) (Section 4.2.4). They can be produced in different diameters up to 6 µm, and lengths up to 100 mm have been described (108, 136).

3.2.4 SiC cleavage fragments

During the crushing process of SiC in the Acheson production, some angular SiC particles (called cleavage fragments) with dimensions within the WHO definition of fibres (see above) (175) may be released to the working atmosphere (155).

3.2.5 SiC platelets

SiC can also be synthesised as platelets. Platelets are single crystal, platelike SiC particles. The maximum dimension of the platelets varies from 5 to 500 µm, with a thickness in the range 0.5–5 µm (151).

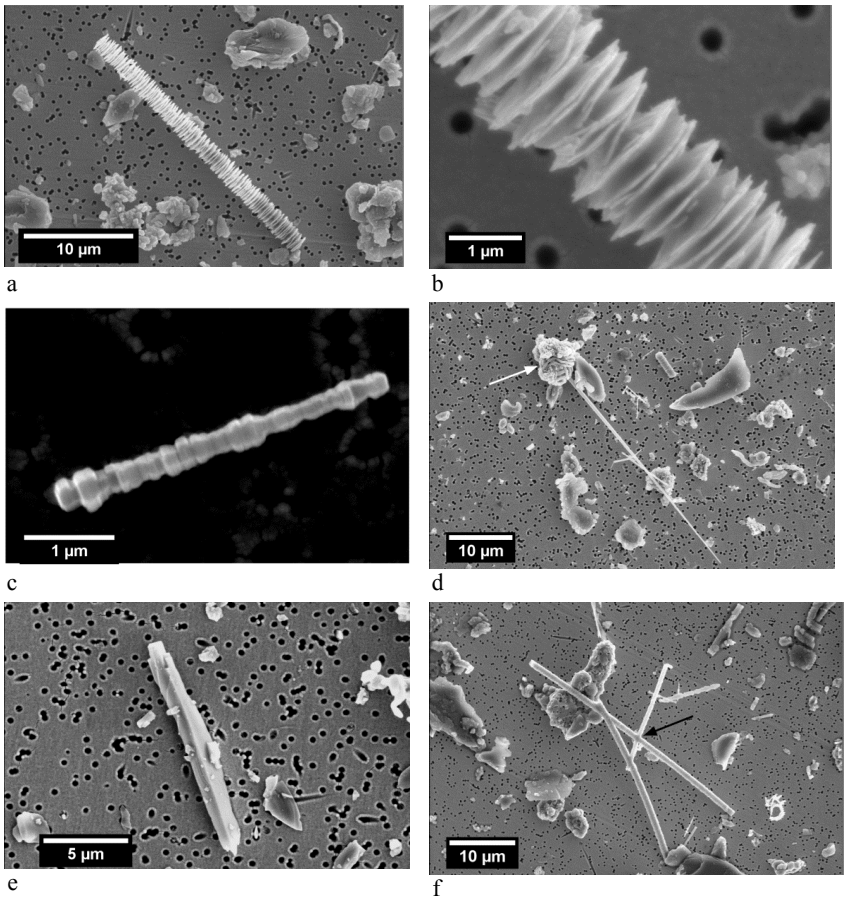

Figure 1. Scanning electron microscopy (SEM) images of various SiC fibres and of a SiC cleavage fragment collected in an Acheson furnace hall:
a) SiC fibre formed like a staple of discs;
b) enlarged portion of a SiC fibre showing the disc pattern;
c) SiC fibre with typically variable diameter along the fibre axis;
d) rectilinear, smooth and tapered SiC fibre (the most frequent type) with a club-like, ornamented structure at one fibre end (arrow);
e) SiC cleavage fragment probably originated from breakage of angular SiC crystals;
f) branched SiC fibre structure consisting of four branches (arrow indicates branching point).
Source: Asbjørn Skogstad, National Institute of Occupational Health, Norway (155).

3.2.6 SiC nanomaterials

Nanomaterials are defined as materials with at least one dimension in the nano-scale, i.e. ≤ 100 nm. SiC nanoparticles, nanowires, nanotubes and nanofilms have been produced for some years, and there is an increasing interest in the known and future possible applications of these materials (39, 124, 148). In addition, other SiC nanostructures such as superlattices, nanoporous structures (110) and SiC tetrapods (106) are described in the literature.

3.2.7 Amorphous SiC (non-crystalline)

SiC may be produced as amorphous films. Like other SiC materials, amorphous SiC is chemically, thermally and mechanically very stable (130).

3.3 Properties

Most of the elements in the periodic system can react to form carbides. SiC belongs to the diamond-like carbides. This classification is due to the crystal structure similarity with diamond, which can be looked upon as C–C (carbon carbide) (92).

The SiC material is thermally and chemically very stable. It has a low coefficient of expansion and high thermal conductivity. However, at high temperatures (above 700 ºC) chemical reactions may take place between SiC and a variety of compounds. It seems that SiC, having a more tightly bound lattice, is less damaged by radiation than silicon (93).

The most characteristic properties of SiC are hardness and brittleness. SiC is one of the hardest materials known, after diamond, boron nitride and boron carbide (42, 60, 61). The hardness constitutes a special type of production problem, as there is an excessive wear on the industrial equipment during the crushing of SiC.

Pure SiC is colourless. Inclusion of impurities (aluminium, iron, nitrogen) gives a colour, varying from nearly clear through pale yellow via green to black (93). The SiC surface reacts with oxygen, forming a thin layer of SiO_2 on the material surface (55, 131). Magnetisation of SiC may be achieved by doping with metals or metalloids (boron, iron) (16, 91).

Angular SiC, the product from Acheson plants, is marketed in different qualities with differing purity grades. The impurities consist mainly of carbon, elemental silicon and silicon dioxide (SiO_2), but very small amounts of other impurities exist. Some physical and chemical properties are presented in Table 2.

SiC whiskers are chemically identical to, and are characterised by the same physical and chemical properties as angular SiC. In addition, SiC whiskers are characterised by high tensile strength and low density (Table 3) (40).

Polycrystalline SiC fibres occur as pollution in the working atmosphere (35) and their physical and chemical properties have not been characterised.

SiC cleavage fragments, being angular SiC grains with certain dimensions, have the same properties as angular SiC (26).

SiC platelets (non-fibrous single crystal particles) are described as having similar properties as SiC whiskers (single crystal fibres) (151).

SiC nanomaterials have high thermal conductivity, high stability, high purity, good wear resistance and a small thermal expansion coefficient. These materials are also resistant to oxidation at high temperatures (9). SiC nanomaterials may possess unique properties that differ from SiC materials at the macroscale. In recent years much attention has been paid to the photoluminescence properties which strongly depend on the size of the SiC particles (139).

Table 2. Chemical and physical properties of angular SiC (93).

Density (g/cm^3):	3.22
Solubility:	Soluble in fused alkali and molten iron, insoluble in water.
Reactivity:	No chemical reactivity at ordinary temperatures. [a]
Colour:	Dependent on purity, nearly clear through pale yellow via green to black.
Purity (% SiC):	
Green SiC	98.8–99.5
Black SiC	90.0–99.2
Metallurgical	70.0–90.0
Decomposition (°C):	
α-SiC	2 825
β-SiC	2 985
Refractive index:	
α-SiC	2.71 (4H), 2.69 (6H)
β-SiC	2.48
Knoop hardness: [b]	
Black SiC	2 839
Green SiC	2 875
Mohs hardness: [c]	
SiC	9.5

[a] The crude material of SiC reacts with oxygen during the production.

[b] Calculated by measuring the indentation produced by a diamond tip that is pressed onto the surface of a sample (60). Only diamond, boron nitride and boron carbide are harder than SiC on this scale (42).

[c] Determined for a mineral by observing whether its surface is scratched by a substance of known or defined hardness. The hardness scale is composed of 10 minerals that have been given arbitrary hardness values of 1–10, where diamond (value 10) is the hardest, corundum (aluminium oxide, Al_2O_3) the second hardest (value 9) and talc the softest (value 1) (61).

Table 3. Typical properties of SiC whiskers (19).

Chemistry:	Stoichiometric SiC
Crystallographic structure:	α- or β-phase SiC
Elastic modulus (GPa): [a]	400–500
Tensile strength (GPa): [b]	> 5
Diameter (μm):	0.5–1.5
Aspect ratio:	10–25
Specific gravity (water = 1):	3.26
Metallic impurities (mg/kg):	< 1 000

[a] A quantitative measure of a substance's resistance to being deformed elastically when a force is applied to it.

[b] The maximum stress that a material can withstand while being stretched or pulled before failing or breaking.

4. Occurrence, production and use

4.1 Occurrence

SiC as a natural mineral is very rare, but was observed in 1893 as part of a meteorite in Canon Diablo in Arizona by Henry Moissan, hence the natural mineral is called Moissanite. Synthetically produced Moissanite was introduced to the jewellery market in 1998. It is an excellent jewel with some optical properties exceeding those of diamond. Moissanite is harder than sapphire and ruby and only slightly softer than diamond (125, 145).

SiC is primarily industrially manufactured and has a wide variety of uses (Sections 4.2–4.3).

4.2 Industrial production

The world-wide production capacity of abrasive SiC in 2014 was 1 010 kilotonnes. Of these, China, as the world's leading manufacturer, had 45% of the capacity. Norway, with 8% of the world production capacity was the second largest producer (167). There is no production of angular SiC in Denmark, Finland or Sweden.

4.2.1 Angular SiC

Angular SiC can be produced by several methods, whereof the Acheson method (156) is the most widely used. This method was developed by Edward G. Acheson around 1890, and is basically the same nowadays although some improvements have been introduced. A mixture of finely ground quartz sand and petroleum coke is placed in open furnaces with removable concrete side walls and electrodes at each end. A graphite core in the middle of the mix functions as an electric leader. The burning process lasts about 40–170 hours (depending on furnace size) during which the temperature of the mix can reach about 2 500 ˚C close to the core. Via a gas phase reaction at a temperature > 1 700 ˚C, the silicon in the quartz (SiO_2) and the carbon in the coke combine and form SiC and carbon monoxide (CO), according to the overall equation: $SiO_2 + 3\ C \rightarrow SiC + 2\ CO$.

Some producers add salt (NaCl) into the mix of raw materials with the intention to remove metallic impurities by converting them to volatile chlorides. This may represent a working atmosphere pollution requiring special precautions. The effectiveness of the technique is disputed. Sometimes saw dust is added to the mix of raw materials to ensure better permeability in order to release the CO gas from the furnace (102).

At the end of the burning process and after cooling for several days, the excess reaction mixture is carried off and a roll of SiC remains. The zone closest to the core consists of SiC of the highest quality, as the largest and purest α-SiC crystals can form in this region. Moving outwards, the crystal growth rate decreases, with the formation of smaller crystals. The outer zone of the SiC roll consists of very fine crystals of β-SiC (102).

In the furnace halls, 4–6 furnaces form a group linked to a single electric source, with one furnace always in operation while the others are in different stages of recharging, cooling or being broken down (102).

An alternative production facility for SiC is the ESK (Elektroschmelzwerk Kempten) process, using a resistance-heat furnace, but with vertical graphite columns. Coke-sand mix is loaded in a mound about 6 metres in height, and all is covered by plastic in order to collect the CO gas. The gas causes the plastic sheet to inflate, keeping it away from the heat. The excess gas is collected, purified and used. The ESK furnaces are considerably larger than the Acheson furnaces (102).

The unreacted and partially crystallised material is removed before further processing, and is either reused as raw material in new furnace cycles (69) or sold to the metallurgical industry for use in steel alloys (Section 4.3.2).

The refinery process of the commercial product includes several crushing and sieving procedures, chemical treatment and fractioning into different grain sizes and qualities, according to desired end use. A detailed description of the production process has been published by Føreland *et al.* (69).

Angular SiC has also been produced from rice husks (the shell of the rice grain). The process involves three major steps: coking in free air, reaction at high temperature in a reducing atmosphere of hydrogen gas, and separation of formed SiC from excess carbon by wet methods (119). Qadri *et al.* described the production of powdered β-SiC through microwave processing of rice husks (140).

High-purity single crystal SiC can be grown using the Lely method (97).

Fine agglomerate-free spherical β-SiC powder has been synthesised from a dispersion of colloidal silica, saccharose and boric acid by means of an ultrasonic spray pyrolysis method (38). High-quality SiC mirrors can be produced by reaction bonding in a vacuum furnace at 1 500–1 600 ºC (179).

4.2.2 SiC fibres

Polycrystalline fibres are formed unintentionally during the Acheson furnace process (35).

4.2.3 SiC cleavage fragments

Cleavage fragments are formed during the crushing of the commercial angular SiC product, and will constitute a part of the end product (147, 155).

4.2.4 SiC whiskers

SiC whiskers may be produced by a large variety of methods. Some of these are described by Hodgson (77): a) by reaction of gaseous silicon monoxide (SiO) and CO at very high temperatures, b) through deposition of silicon from silane/hydrogen vapour onto a carbon filament which remains as a core, c) from rice husks carbonised at 550 ºC, combined with ashed rice husks and reacted at 1 400–1 500 ºC, d) from organosilicon condensates by drawing a glass fibre from a pre-form at very high temperatures, as for optical fibres, and coating the hot fibre with the condensation of gaseous reactants (SiO and CO) – this method is more cost effective than using a tungsten wire core, and e) as insulation produced as a

SiC whisker – SiC composite made by reacting carbon fibre – carbon composites at high temperature with gaseous SiO.

4.2.5 SiC platelets

SiC platelets may be produced by various methods, such as anisotropic etching of SiC whiskers (37). In a plasma thermal system they are produced as β-SiC (polyhedral morphology with regular and irregular shapes) and α-SiC (mainly as truncated triangles and hexagons with regular or irregular shapes) (178). At temperatures of 1 900–2 100 ºC, under an inert atmosphere, the addition of aluminium to the raw mix enhances the growth in the [0001] direction and decelerates the growth perpendicular to the [0001] direction. Boron enhances the growth constantly perpendicular to the [0001] direction (151).

4.2.6 SiC nanomaterials

Different methods for synthesis of SiC nanoparticles have been described. Laser pyrolysis is based on the interaction between a powerful laser beam and a mixture of gaseous or liquid precursors (silane and acetylene) via increase of the reaction temperature and molecular dissociation. The decomposition is followed by nucleation and growth of hot, spherical, nanoparticles. Nanoparticle size is controlled by the time of residence in the reaction zone, and chemical composition and degree of crystallisation is controlled through the C/Si atomic ratio of the gaseous precursors, reactant flow rates and laser power (139).

The sol-gel process is a wet-chemical technique starting from a colloidal solution (sol) which contains the precursors of an integrated network (gel). After the formation of the gel using metal alkoxides and drying of the gel, a thermal treatment is carried out (1 500 ºC during 4 hours) in argon atmosphere leading to carbothermal reduction of SiO_2 (174). The nanoparticles synthesised through this route correspond to spherical nanoparticles of β-SiC (139).

Decomposition of tetramethylsilane in a microwave plasma reactor makes it possible to synthesise SiC nanoparticles with sizes between 4 and 6 nm (103).

Synthesis of SiC nanowires and SiC nanotubes are performed using multi-walled carbon nanotubes as templates with which SiO reacts directly (16, 83). The properties of the nanotubes may be altered through e.g. manipulation of diameter and chirality, bonding of Si and C atoms, and doping with other materials (16). SiC nanotubes were grown from silicon nanowires (99).

4.3 Use

SiC material finds its use in a large variety of material technology and applications and its most important uses are described in this section.

Table 4 shows the annual use of SiC in the Nordic countries as registered in the SPIN (Substances in Preparations in Nordic Countries) database. Norway is as previously mentioned the only producer of angular SiC in the Nordic countries, but Sweden appears to have the by far largest use of SiC, with the majority used in construction (e.g. fireproof/refractory cement) and grinding (abrasives) materials

Table 4. Registered annual total use of SiC in the Nordic countries in tonnes (158).

Country/year	2004	2006	2008	2010	2012	2014
Denmark	2	62	20	1	142	16
Finland	1	2	0	0	111	< 1
Norway	84	56	76	127	56	38
Sweden	5 568	6 319	4 017	2 797	10 782	12 545

(158). However, the figures in Table 4 suggest different ways of reporting use of SiC in the Nordic countries.

4.3.1 Angular SiC

Generally and roughly, abrasives with particle widths larger than 45 µm have been the main products historically. In recent years, the technological development and more advanced use of SiC have resulted in a large variety of products of quite small grain sizes. Some uses are described in Table 5.

4.3.1.1 Abrasive and cutting materials

Angular SiC is traditionally used as an abrasive, for grinding, sharpening, sand-blasting and polishing. These applications are based on the material hardness, temperature resistance and almost no chemical reactivity. SiC is harder yet more brittle than abrasives such as aluminium oxide. Thus it is generally used for grinding hard, low tensile-strength materials such as chilled iron, marble and granite, and materials that need sharp cutting action (93).

Whole sawblades and cut-off wheels made of pure SiC are used in cutting processes. A special application for angular SiC is in the photovoltaic and semi-conductor industry, where small particles of SiC are dispersed in a polyethylene slurry. By means of capillary forces the slurry is attached to a wire and used to cut slices of highly pure silicon wafers. This process is called wiresawing (69).

4.3.1.2 High temperature (electrical) devices

The low coefficient of thermal expansion and high thermal conductivity of SiC bestow it with excellent thermal shock resistance. These properties in combination with a high corrosion resistance make SiC well fitted for use in heat-transfer and furnace components. This includes, among others, boiler furnace walls, mufflers and kiln furniture (93).

Table 5. Mean particle size in some uses of angular SiC [a].

Use	Particle size (mean, µm)
Abrasive	2–1 800
Refractory	< 3 000
Metallurgy	< 50 000
Solar energy	< 10
Various uses of nanomaterials	< 0.1

[a] Product information from Saint-Gobain Ceramic Materials AS, Norway.

Heating elements made of SiC are used in electrical furnaces up to 1 600 °C. It finds it use in equipment for drying processes, as light source for mineral determinations and ignition source for oil- and gas-fired burners (93).

4.3.1.3 Ceramics

The extreme hardness of SiC makes it useful when wear resistance is important, such as in brake linings, electrical contacts and non-slip applications. It is also used as a face material in a large range of seal and nozzle products (93).

The high hardness, compressive strength and elastic modulus of SiC provide superior ballistic capability to defeat high velocity projectile threats, e.g. in bullet-proof vests (93).

4.3.1.4 Metallurgy

SiC dissociates in molten iron, and the silicon reacts with oxides present in the melt, a reaction of use in the metallurgy of iron and steel (93). SiC is used as a carbon and silicon source in steel (see Section 4.3.2).

4.3.1.5 Diesel particulate filter materials

During the last 20 years, micro-sized angular SiC has been used as a filter material for diesel exhaust, removing carbonaceous particles from the outlet (69).

4.3.1.6 Electronic devices

The ability to operate under high voltages, temperature and power densities has made SiC a promising candidate for power electronic technology. However, both the manufacturing challenges and the relative cost compared to silicon wafers have limited the rate of commercialisation (93).

4.3.2 SiC fibres

SiC fibres occur mainly as a pollutant during the industrial production of the standard abrasive and refractory material (Acheson process) and is especially frequent in the partly reacted layer of the furnace (Section 4.2.1). Some plants reuse the partly reacted layer in the new furnace cycles and consequently re-crystallises the material. Other plants sell this material directly to the metallurgical industry where it is used as a source for carbon and silicon. The finest fraction which is normally collected in bag filters (dust extract from Acheson operations) is often briquetted in special plants before delivery to the metallurgical industry. This fine fraction could potentially have the highest fraction of fibres from the Acheson operation (personal communication, Lars Petter Maltby, Saint-Gobain Ceramic Materials AS, Norway).

4.3.3 SiC whiskers

SiC whiskers have found application in metal-matrix composites, e.g. with copper, magnesium and aluminium. The addition of SiC whiskers to aluminium increases the elastic modulus to levels near that of steel, while maintaining an overall density about one-third of that of steel. Aluminium oxide (Al_2O_3) reinforced with

25–30% (w/w) SiC whiskers is the material of choice for inserts used in high-speed cutting of high-nickel-content alloys (aerospace materials) (19).

SiC whiskers have the specific resistivity of a semi-conductor, and is used in electronic components (82). They are also used as strengthening material in composite coatings for hip replacement prosthesis (8).

4.3.4 SiC platelets

SiC platelets may be used as building blocks in the fabrication of sensors, cellular probes, and electronic, optoelectronic, electromechanical and other devices (37).

4.3.5 SiC nanomaterials

The use of SiC nanoparticles as a strengthening material in metal, plastic and rubber composites has been a field of extensive research (3, 96, 168). SiC nanowires are highly elastic, a valuable property in some nanocomposites. SiC nanotubes are useful for catalytic support in oxidation reactions and chemical conversions.

The electronic and optical properties of SiC nanostructures may be important in the field of ultrasensitive gas sensors (177).

Refractory carbide nanostructured ceramics such as SiC constitute interesting materials for high temperature applications, such as structural materials for the future generation of nuclear reactors (101). The application of SiC nanoparticles as a strengthening material in different metal alloys is also a growing field (110).

The biomedical application of SiC nanoparticles is a large research field (112). Due to their photoluminescence properties, SiC nanoparticles are also envisaged as biological labels for cell imaging (64, 154).

4.3.6 Amorphous SiC

Amorphous SiC film is mainly used as a thin coating of microelectronic components (130). SiC film is also used as photovoltaic solar cell material for devices which require very little power, such as pocket calculators. Improvements in amorphous SiC construction techniques have made them more attractive also for large-area solar cell use. Amorphous SiC may also be used as a substrate for formation of silicon nanocrystals (11, 95).

5. Measurements and analysis of workplace exposure

Due to the mixed and complex exposures to dusts and gases in the SiC industry (Chapter 6), it has been a challenge to get an overview of the exposure pattern. Methods for sampling and analyses of dusts and gases have gradually been developed and thereby more detailed information about the exposures have become available.

In the first years of exposure measurements in the Norwegian SiC industry (1940s–1970s), a Watson thermal precipitator was used to collect short-term samples of dust particles that were counted using microscope. From the end of

the 1960s and onward dust has been sampled mainly as full-shift personal samples using total dust open face (150) or closed face (69) aerosol filter cassettes (giving different results as the open face cassette will allow larger particles to deposit on the filter) and/or respirable dust cyclones (69, 150, 156). The samples are analysed gravimetrically (weighing of the collected dust). Speciation of the crystalline components (SiO_2, i.e. quartz and cristobalite, and SiC) in the dust is carried out by X-ray powder diffraction (36) according to standard procedures (7, 165). Fibres have been collected with open-face conducting aerosol filter cassettes (69). Counting of fibres has been performed with phase contrast optical microscopy (69, 150) or by using scanning or transmission electron microscopy (SEM or TEM) (55). According to the WHO counting criteria, airborne fibres in the work environment should be determined by counting procedures using phase contrast optical microscope (175) for comparison with the OEL. A drawback with optical microscopy is that it does not distinguish between different SiC fibres, whiskers and cleavage fragments, and other fibres. SEM or TEM may therefore be used for a more detailed characterisation and specification of the fibres (155). SEM and TEM also make it possible to count thinner fibres than does optical microscopy (69).

The exposure measurement techniques in the SiC industry have varied over time. Both stationary and personal sampling methods have been used, giving different results. In addition, sampling strategies may have varied. Accordingly, comparisons of exposure levels between studies should be performed with great caution.

6. Occupational exposure data

Almost all available information about exposure to SiC is from measurements in the Acheson production industry, where exposures to both angular and SiC fibres have been surveilled. Only a few measurements have been made in user industries and among downstream users. No exposure measurements in the SiC whiskers production industry, or of cleavage fragments, amorphous SiC, SiC platelets and nanomaterials were located.

Workers in the SiC production industry are exposed to a large variety of airborne particulates and gases; the diversity being greatest in the furnace hall. The raw materials consist of quartz sand and petroleum coke, in addition to unreacted and partly reacted material from previous furnace cycles. Graphite is used as electric conductor, and some graphite is also formed around the core during the heating process where SiC is decomposed to graphite. During the heating process some of the quartz is converted to cristobalite, giving a higher concentration of cristobalite than quartz in some of the working processes (69). SiC fibres are formed during the heating process (35), and these are most frequently found in the borderline zone between partly crystallised and fully crystallised SiC (73). Polycyclic aromatic hydrocarbons (PAHs) are to a certain

degree liberated from the petrol coke during heating, and sulphur dioxide (SO_2) is also formed, depending on the sulphur content of the coke. CO is an important by-product of the furnace heating process, and represents a life threatening danger which is controlled to a certain degree by igniting the gas at the furnace surface. Nowadays, a continuous personal monitoring of the CO levels in the furnace hall is performed. The end product of the heating process is angular SiC, which represents 20–40% of the respirable dust in the furnace hall.

Angular SiC is the by far most important exposure in the processing department, representing 60–80% of the respirable dust. In addition, some remnants from the furnace hall, mainly crystalline silica, are found in the processing department, but these are cleared out during the refining of the product, giving a more and more clean SiC exposure towards the end of the process (69).

Maintenance personnel, electricians and mechanics work all over the plant and are sometimes exposed to very high levels. As the exposure duration is shorter, their average exposure is lower than that of workers affiliated to the respective departments (69).

6.1 Production industry

Several studies present measurements of pollutants in the working atmosphere at indoor Acheson furnace plants, comprising total dust, respirable dust, angular SiC, SiC fibres and crystalline silica (quartz and cristobalite). In addition, some measurements of PAHs, CO and SO_2 have been performed – these are not referred to in this document.

Tables 6–9 present the exposure data on SiC from the investigations of Smith *et al.* (156), Dufresne *et al.* (52), Føreland *et al.* (69) and Scansetti *et al.* (150), respectively. Even though the production methods are very similar, the organising of the work differs somewhat between the plants, making direct linkage between job titles at the different plants problematic. In order to ease the comparison of these tables, job titles are organised by work areas (preparation, furnace, processing and maintenance).

A systematic description of the exposure related to various job types or tasks in an industrial work place is given by a job exposure matrix (JEM). Smith *et al.* were the first to publish a JEM for the SiC industry (Table 6). A total of 182 full-shift personal samples of respirable dust from the Canadian industry were collected and stratified by job category and work area. Some measurements of SO_2 and CO exposure were also performed. Half the respirable samples were obtained with filters for X-ray diffraction analysis of α-quartz and the other half for hydrocarbon analysis. Semiquantitative analyses were performed to determine the approximate amounts of cristobalite and SiC. SiC was presumed to form most of the inorganic portion of the particulate, i.e. the difference between the amount of total dust and the amount of crystalline silica. The respirable dust levels were in the range 0.11–1.46 mg/m^3 and the levels of inorganic matter were 0.065–0.57 mg/m^3. Only small amounts of cristobalite were observed (156).

Table 6. Concentrations of respirable dust, quartz and inorganic matter by work area and job task (personal sampling). Adapted from Smith *et al*. (156) [a].

Work area	Job task	Geometric mean			No. of samples
		Resp. dust mg/m^3	Quartz mg/m^3	Inorganic matter [b] mg/m^3	
Preparation	Coke	0.48	0.028	0.32	4
	Sawdust	0.21	na	na	2
	Mixer	1.01	0.050	0.42	5
Furnace	Craneman	0.42	0.010	0.065	20
	Loader	0.59	0.10	0.17	4
	Electrode cleaner	0.44	0.020	0.20	5
	Assist. operator	0.17	0.015	0.07	8
	Payloader	1.46	0.040	0.57	13
	Old mix operator	0.85	0.060	0.30	7
	Carboselector	0.72	0.055	0.26	24
Maintenance	Maintenance	0.11–0.28	< 0.010	0.19	8

[a] Year of sampling: 1980.
[b] SiC was presumed to form most of the inorganic portion of the particulate.
na: not analysed.

Dufresne *et al.* (52) and Føreland *et al.* (69) are the only ones that report a specific determination of angular SiC. Dufresne *et al.* collected dust samples in Canadian SiC plants by personal sampling, primarily for characterisation of crystalline components (Table 7). Exposure to quartz, cristobalite and crystalline SiC was determined by X-ray diffraction. The 8-hour time-weighted average (TWA) exposure to angular SiC was in the range 0.029–0.592 mg/m^3, depending on job group (52).

Føreland *et al.* collected approximately 720 fibre samples, 720 respirable dust samples and 1 400 total dust samples by personal sampling from randomly chosen workers from different departments and job groups in the three Norwegian SiC plants (Table 8). Sampling duration was full-shift (6–8 hours), except for fibre sampling, which was limited to 0.5–3.5 hours to avoid particle overload of the filters. The respirable dust samples were analysed for the content of quartz, cristobalite and angular SiC using X-ray diffraction. Fibres were counted with a light microscope according to the WHO counting criteria (length > 5 µm, diameter < 3 µm and aspect ratio > 3:1) (69, 175). The exposure to respirable angular SiC was in the range 0.011–0.89 mg/m^3, and exposure to SiC fibres was 0.01–2.8 fibres/ml (69).

Table 7. Concentrations of respirable dust, quartz, cristobalite and angular SiC by work area and job task (personal sampling). Adapted from Dufresne *et al.* (52) [a].

Work area	Job task	Geometric mean				
		Resp. dust mg/m^3	Quartz mg/m^3	Cristobalite mg/m^3	Angular SiC mg/m^3	No. of samples
Plant 1						
Preparation	Old mix operator	0.72	0.007	0.014	0.099	4
Furnace	Loader	0.32	nd	nd	0.029	4
	Unloader	0.63	0.086	0.006	0.088	2
	Labourer	0.49	0.012	0.005	0.054	13
	Carboselector	0.95	0.009	0.020	0.422	22
Processing	Crusher operator	0.43	nd	0.004	0.082	4
Plant 2						
Preparation	First level	0.87	0.02	0.006	0.084	8
	Mixer/balance	0.93	0.112	0.009	0.070	4
	Fourth level	3.13	0.085	0.036	0.188	7
	Vehicle driver	1.08	0.023	0.028	0.095	15
Furnace	Loader	1.24	0.031	0.012	0.186	3
	Crane operator	0.76	nd	0.004	0.042	4
	Labourer	0.85	0.014	0.006	0.062	8
	Utilities men	0.65	0.007	0.008	0.042	7
	Assist. operator	0.73	0.012	0.012	0.105	6
	Millwright	0.68	0.02	0.003	0.105	4
	Carboselector	0.76	0.012	0.015	0.592	8
Processing	Crusher operator	0.63	0.006	0.012	0.202	3

[a] Year of sampling not given.
nd: not detected.

Table 8. Concentrations of total dust, respirable dust, quartz, cristobalite, SiC fibres and angular SiC by work area and job task (personal sampling). Adapted from Føreland *et al.* (69) [a].

Work area	Job task	Geometric mean						
		Total dust mg/m^3	Resp. dust mg/m^3	Quartz mg/m^3	Cristo-balite mg/m^3	SiC fibres fibres/ml	Angular SiC mg/m^3	No. of fibre samples [b]
Plant A								
Preparation	Mix	1.5	0.45	0.014	na	0.11	0.014	14
Furnace	Payloader	2.7	0.54	0.004	0.0049	0.12	0.17	10
	Crane	0.85	0.17	na	0.0016	0.18	0.014	21
	Control room	1.3	0.28	0.003	0.0039	0.87	0.044	21
	Cleaning	22	1.3	0.023	0.029	2.8	0.54	2
	Sorter	1.1	0.22	na	na	0.21	0.10	19
Processing	Crusher	7.4	1.1	0.0028	na	0.029	0.89	29
	Other	1.4	0.23	na	na	0.050	0.11	29
	Fines	9.2	0.81	na	na	0.015	0.12	36
Maintenance	Mechanics	1.5	0.31	0.0018	0.0014	0.057	0.098	48
	Electrician	1.3	0.24	0.0023	na	0.15	0.068	21
Plant B								
Furnace	Payloader	1.2	0.24	na	na	0.037	0.046	5
	Crane	1.5	0.26	0.0036	0.0042	0.056	0.019	19
	Control room	1.3	0.28	0.0026	0.0035	0.11	0.034	20
	Sorter	5.0	0.79	0.0024	0.027	0.32	0.48	21
Processing	Crusher	4.0	0.82	0.0017	0.0099	0.058	0.54	15
	Other	2.5	0.43	0.0018	0.0031	0.019	0.26	27
	Fines	3.7	0.49	0.0015	na	0.010	0.29	60
Maintenance	Mechanics	3.1	0.59	0.017	0.0028	0.050	0.14	47
	Electrician	2.0	0.28	0.017	0.0017	0.096	0.12	22
Plant C								
Preparation	Mix	3.9		0.015	0.036	0.072	0.66	10
Furnace	Charger	4.6		0.01	0.031	0.43	0.75	10
	Charger/mix	9.3		0.021	0.046	0.39	0.18	11
	Payloader	2.0		0.0035	0.026	0.58	0.046	18
	Crane	0.72		0.0034	0.012	0.082	0.016	14
	Control room	1.3		0.0021	0.0056	0.12	0.011	19
	Sorter	5.3		0.0066	0.019	0.50	0.35	21
Processing	Crusher	4.7		0.0026	0.0041	0.032	0.69	19
	Other	2.7		0.0023	na	0.019	0.38	32
	Fines	3.3		na	na	0.014	0.29	49
Maintenance	Mechanics	1.8		na	0.0017	0.092	0.075	27
	Electrician	1.8		na	na	0.025	0.086	10

[a] Year of sampling: 2002–2003.

[b] The numbers are representative, with a slight variation (± 3 samples), for the sampling of the other exposure components, for all job types in the three plants, except for fines at plant A, where the number of fibre samples was almost twice the number of total and respirable dust samples.

na: not analysed.

Table 9. Fibre concentrations by work area and job task (stationary sampling). Adapted from Scansetti *et al.* (150) [a].

Work area	Job task	Fibre concentration (geometric mean)			No. of samples
		Total fibres/ml by OM	Resp. fibres/ml by OM	Resp. fibres/ml by SEM	
Preparation	Mix preparation	0.11	0.07	0.11	9
Furnace	Furnace loading	0.17	0.11	0.19	6
	Furnace heating	0.16	0.14	0.23	4
	Side opening	0.85	0.63	1.07	6
	Furnace cooling	0.18	0.14	0.19	4
	Cylinder breaking	0.71	0.58	0.69	6
	Removal unreacted	2.63	2.40	2.75	6
	Selection	1.32	0.71	1.15	11
Processing	Crushing	0.81	0.41	0.83	12

[a] Year of sampling not given.
OM: optical microscopy, SEM: scanning electron microscopy.

Scansetti *et al.* performed static dust sampling in several departments of an Italian SiC plant with measurements of total and respirable dust and counting of fibres using phase contrast microscopy at ×450 magnification (Table 9). Elongated particles (> 5 µm and aspect ratio ≥ 3:1) were counted as total fibres. Fibres with diameter > 5 µm were classified as coarse fibres, whereas thinner fibres were classified as respirable. SEM analysis was carried out on a part of the same filter. For both types of fibres only the peak of Si was evident at energy dispersive X-ray analysis (EDXA). The SEM analysis revealed that exposure to respirable fibres varied from 0.11 to 2.75 fibres/ml, depending on job group (150). According to Skogstad *et al.,* the main proportion (> 90%) of fibres in the working atmosphere in Acheson plants are SiC fibres (155).

The exposure data from the following epidemiological studies in SiC production plants have not been tabulated in the present criteria document because they contain relatively few samples and contribute with little extra information: Dion *et al.* published a table showing mean levels of exposure to respirable dust and fibres in a Canadian SiC production plant. Respirable dust levels (range 0.35–1.16 mg/m^3) were reported for only five job groups, of which three in the furnace hall. Fibre exposure levels were reported for six job groups in the furnace hall, and ranged from 0.07 to 0.63 fibres/ml (49). In a study in the Italian SiC production industry by Marcer *et al.*, 120 respirable dust samples were collected. No average respirable dust exposure measurements exceeded the current permissible limits (Italy, 1992), but some high levels were measured in the screening, mixing and selection areas [geometric mean (GM) ≤ 1.0 mg/m^3, range 0.10–7.82 mg/m^3]. Crystalline silica (quartz and cristobalite, respectively) concentrations were always low (< 0.04 mg/m^3). No specific analyses of angular SiC or SiC fibres were performed (107).

6.2 User industry

Only one study with exposure measurements of SiC whiskers in the user industry was identified. In this study, stationary sampling was used and exposure to fibres during machining of SiC whiskers-reinforced ceramics was counted by SEM, before and after improvements of the local exhaust ventilation (Table 10). The exposure for different job tasks decreased from 0.031–0.76 fibres/ml before exhaust control improvements to 0.0062–0.038 fibres/ml after improvements (14).

6.3 Historical development of occupational exposure to SiC

Several research groups have constructed historical JEMs consisting of calculations of exposure levels connected with different time periods. The calculations may be based on current and/or previous measurements and direct calculations using arithmetic or geometric means or exposure modelling using more advanced statistical methods. The variation in methods used for development of the different JEMs makes it difficult to compare the reported exposure levels (67).

A historical JEM with total dust levels developed by Infante-Rivard *et al.* (80) on the basis of measurements performed by Dufresne *et al.* (52) was used in the first published mortality study from the SiC industry. Mean exposure levels before 1966 were in the range 0.5–159 mg/m^3 in different job groups, and decreased to 0.1–80 mg/m^3 after 1966 (80).

Based on previous exposure measurements and knowledge about historical technical changes in the production, Romundstad *et al.* (143) constructed a JEM for the three Norwegian SiC plants with information on mean exposure to total and respirable dust, crystalline silica, SiC dust and SiC fibres. This JEM was used in two epidemiological studies (143, 144). To improve the quality of the exposure-response associations, Føreland *et al.* increased the number of measurements available for construction of the JEM, by performing new measurements and by collecting more historical measurements from the plants (Table 11).

Table 10. Calculated 8-hour TWA exposure to fibres (counted by SEM) during machining of SiC whisker-reinforced composite materials before and after improvements of the local exhaust system (stationary sampling). Adapted from Beaumont (14) [a, b].

Job task	Concentration, fibres/ml (arithmetic mean)	
	Before improvement	After improvement
Machining of metal matrix composites	0.031	na
Lathe machining, green ceramic composites	0.26	0.034
Lathe machining, presintered ceramic composites	0.76	0.038
Cutting presintered ceramic composites	nc	0.031
Surface grinding of fired ceramic	0.21	0.0062
ID/OD [c] grinding of fired ceramic	0.075	0.016

[a] Year of sampling not given.
[b] The numbers of samples were 2–10, mostly 2–5.
[c] Grinder used both inside (ID) and outside (OD) of the ceramic part.
na: not applicable (no changes made in this area), nc: not calculated, SEM: scanning electron microscopy, TWA: time-weighted average.

Table 11. Extracts from a JEM describing historical exposure to total dust, SiC fibres and angular SiC for selected job tasks. Adapted from Føreland *et al.* (68).

Work area	Job task	Time period	Total dust mg/m^3	SiC fibres fibres/ml	Angular SiC mg/m^3
Plant A					
Preparation	Mix	1912–1936	25	0.37	0.08
		1936–1952	13	0.29	0.05
		1953–1979	6.9	0.23	0.03
		1980–1996	2.5	0.15	0.02
Furnace	Charger	1915–1938	52	0.89	0.69
		1939–1952	24	0.67	0.35
		1953–1959	13	0.55	0.21
		1960–1979	9.6	0.49	0.15
		1980–1996	4.5	0.36	0.08
	Crane	1938–1952	10	0.33	0.03
		1953–1958	3.5	0.22	0.01
		1959–1996	1.8	0.15	0.01
	Sorter	1913–1933	36	1.0	1.9
		1934–1952	17	0.76	1.0
		1953–1996	7.9	0.26	0.41
Processing	Refinery	1914–1943	19	0.06	12
		1947–1996	9.1	0.05	0.88
	Fines	1931–1943	12	0.02	0.21
		1947–1996	7.1	0.02	0.14
	Packer	1914–1943	15	0.25	0.51
		1947–1996	6.8	0.20	0.36
Plant B					
Preparation	Mix	1965–1981	19	0.13	0.17
		1982–1996	8.8	0.10	0.09
Furnace	Crane	1965–1981	10	0.12	0.05
		1982–1996	3.9	0.09	0.03
	Sorter	1965–1981	43	0.65	1.6
		1982–1996	16	0.46	0.79
Processing	Refinery	1965–1996	10	0.05	0.71
	Fines	1965–1996	11	0.03	0.71
Plant C					
Preparation	Mix	1964–1996	5.4	0.07	0.05
Furnace	Charger	1964–1996	10	0.47	0.16
	Payloader	1964–1996	4.3	0.39	0.06
	Crane	1964–1996	4.5	0.10	0.02
	Sorter	1964–1996	13	0.67	0.76
Processing	Refinery	1964–1996	6.2	0.03	0.71
	Fines	1964–1996	8.3	0.02	0.72

JEM: job exposure matrix.

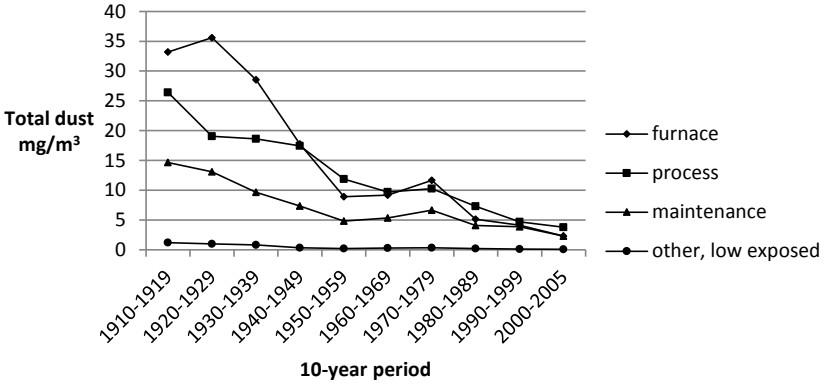

Figure 2. Estimated mean total dust exposure per 10-year period in a cohort of 1 687 Norwegian long-term SiC industry workers, by department (32). The exposure estimates before 1960 are based on backward extrapolation as described in Føreland *et al*. (68).

Multiple linear regression models were used to estimate historical exposure to total dust whereas mixed-effect models were used to estimate the relative content of respirable dust, respirable quartz, cristobalite and angular SiC, and SiC fibres in total dust (68). The dust exposure in the Norwegian SiC industry can be estimated using information from the historical JEM from Føreland *et al.* (68) together with each individual's employment history. Figure 2 shows the workers' mean total dust exposure over 10-year time periods in different departments (32).

Corresponding data for angular SiC and SiC fibre exposure are shown in Figures 3 and 4, respectively.

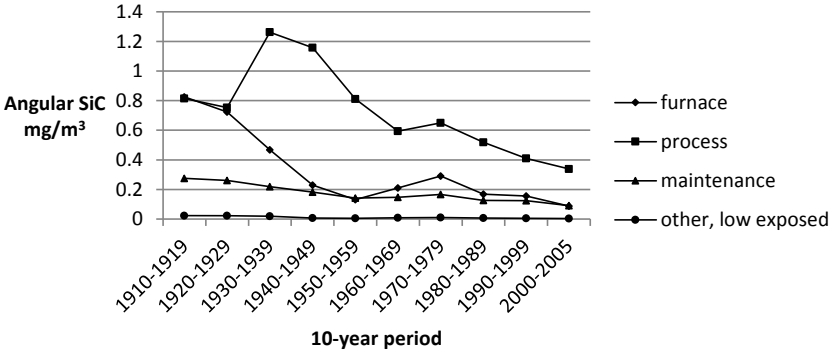

Figure 3. Estimated mean exposure to angular SiC per 10-year period in a cohort of 1 687 Norwegian long-term SiC industry workers, by department. The figure is constructed by applying exposure data from Føreland *et al*. 2012 to the individuals in the Norwegian SiC cohort (32, 68).

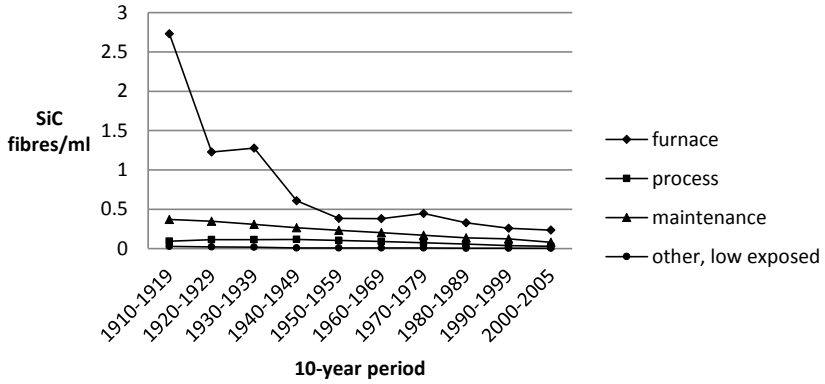

Figure 4. Estimated mean exposure to SiC fibres per 10-year period in a cohort of 1 687 Norwegian long-term SiC industry workers, by department. The figure is constructed by applying exposure data from Føreland *et al*. 2012 to the individuals in the Norwegian SiC cohort (32, 68).

7. Toxicokinetics

The only relevant uptake route of SiC in occupational settings is via the respiratory tract. There are no data on other human exposure routes, but dermal uptake of SiC is unlikely because of the insolubility in water. Transport and deposition in the airstream depend mainly on the aerodynamic diameter of the particles, which varies among and between angular SiC and fibrous forms of SiC. From case reports, it has been shown that all types of SiC are observed in lung parenchyma from SiC exposed workers, confirming the existence of respirable fractions of SiC (53, 54, 66). No information about uptake to the systemic circulation and translocation to other tissues were located. No information on the toxicokinetics of cleavage fragments, amorphous SiC, SiC platelets or nanosized SiC was found.

7.1 Angular SiC

The size distribution of angular SiC results in deposition all along the airways, including in the alveolar region of the lung. Deposition in the respiratory region was shown microscopically in a lung lobectomy specimen from an employee in an abrasive manufacturing plant (74). An open lung biopsy from a worker presenting chest X-ray abnormalities after exposure to SiC in a refractory brick factory also revealed deposits of 1–20 µm particles in the tissue. Most of the particles were granular (angular) but some had fibrous form (66). For further details, see Section 11.3.2.

No reports have been found on biotransformation or biodegradability of angular SiC in lung tissue. Due to the low solubility, such particles may be poorly biodegradable.

When Wistar rats (20/group) were exposed to 20 mg/m^3 angular SiC or quartz by inhalation for 10 days (5 hours/day for 2 weeks), examination of the lungs 3, 11, 21 and 90 days post-exposure revealed that initially (3 days post-exposure) the concentration of angular SiC was higher than that of quartz, indicating a higher uptake or reduced clearance compared to quartz. Subsequently the clearance of SiC was more efficient; at 90 days post-exposure, 23% of the original SiC was recovered from the lungs, whereas 60% of the quartz was still retained. There is no clear explanation for this difference in clearance, but the authors discussed the smaller size of quartz particles compared to angular SiC, facilitating the translocation and deposition of quartz in the interstitium and lymphatics, and subsequently inhibiting the elimination of quartz to a greater extent than SiC. The higher toxicity of quartz particles may additionally inhibit their elimination due to inflammation and fibrosis in the lung tissue (27).

Keeling *et al.* reported that the uptake of angular SiC particles in the epithelium of rat tracheal explants was not enhanced by pre-exposure of the epithelium to cigarette smoke (90) (Section 10.2.2.3).

Elimination of angular SiC was studied by Dufresne *et al*. in the sheep model of pneumoconiosis. Animals were injected in the tracheal lobe with 100 mg angular SiC or 100 mg fibrous SiC prepared from bulk material taken in the Acheson furnaces of a SiC plant. Lung samples collected 8 months after injection and analysed by TEM generally showed much higher retention of angular SiC than of fibrous SiC, although with a high variability between animals. In agreement with this finding, measurements in bronchoalveolar lavage (BAL) fluid at 2, 4, 6 and 8 months post-dosing showed a lower clearance of angular SiC (approximate half-time 5.8 months assuming a monoexponential decrease) compared to fibrous SiC (1.7 months). The BAL analyses further indicated that there was no change in the size distribution of angular SiC (56).

7.2 SiC fibres and SiC whiskers

SiC fibres found in the lungs of SiC (Carborundum) workers display a variety of morphologies and dimensions, such as isolated fibrils, agglomerated fibrils, rectilinear fibres and corrugated fibres, all presenting different aerodynamic diameters (53, 56). As for any mineral fibre, the diameter of SiC whiskers is the most critical factor for the depth of penetration in the airways, as inspired fibres presenting diameters > 4.5 μm (163) generally do not pass beyond the larynx. Elongated SiC particles with lengths up to 100 μm have been located in the lung tissue of a SiC exposed worker (66).

Characterisation and aerodynamic behaviours of SiC whiskers (Industrial grade bulk, Lot No 8291, Grade SC-9, Advanced Composite Materials Corp., South Carolina) were studied by Cheng *et al*. The SiC whiskers were aerosolised and

aerodynamic size distributions assessed by impactor sampling. The mean SiC whisker diameter was 0.2 µm and the mean length was 3.4 µm, with a mean aspect ratio of 17.3. The fibre mass fractions in the aerosol were: inspirable (inhalable) fraction 98%, thoracic fraction 88% and respirable fraction 65% (40).

SiC whiskers are solid, durable, nearly insoluble and non-biodegradable in tissues (5, 128). Davis *et al.* demonstrated insignificant release of elemental silicon from SiC whiskers, in a series of fibre dissolution studies using different solutions and a variety of pH concentrations (46). The durability of SiC whiskers in rat lungs has also been shown by Searl *et al*., since virtually no dissolution occurred in the lung tissues 12 months after intratracheal instillation (153).

The uptake of fibrous SiC in the epithelium of rat tracheal explants was significantly increased by pre-exposure of the epithelium to cigarette smoke (Section 10.2.2.3) (90).

After intratracheal instillation of rats (1 mg in phosphate-buffered saline per animal) with commercial samples of SiC whiskers (diameter 0.32 µm), amosite asbestos and glass microfibres, Davis *et al*. observed that short SiC whiskers were more readily eliminated than long ones (length > 20 µm) after a 1-year observation period (46). In a parallel 12-month inhalation study (approximately 1 000 fibres/ml > 5 µm), the clearance of fibres > 20 µm was lower for SiC whiskers (45%) than for asbestos (65%) 12 months post-exposure (46).

In the experiment by Dufresne *et al.* using single intratracheal instillation of SiC fibres or angular SiC in sheep, the clearance of fibres was much higher than that of angular SiC (see Section 7.1 for more details). The proportion of long fibres (> 20 µm) was below 20% in the injected material, but increased gradually from 41% at month 2 to 84% at month 8 in BAL fluid, indicating a faster clearance of the shorter fibres (56).

Nine-week old Wistar rats were inhalation exposed to 0 or 10.4 ± 0.5 mg/m^3 (214 ± 31 fibres/ml) of SiC whiskers 6 hours/day, 5 days/week for 4 weeks. The mass median aerodynamic diameter (MMAD) was 2.5 µm and the fibre diameter and length were 0.4 and 2.2 µm (GMs), respectively. More than 90% of the fibres were less than 10 µm in length. The animals were serially sacrificed from day 3 to 12 months post-exposure. The lung burden of SiC whiskers was 0.60 ± 0.09 mg at day 3, declining to 0.07 ± 0.03 mg at 12 months. The biological half-time of the deposited SiC whiskers in the lungs was calculated to be 4 months, which was similar to the values for glass fibres, potassium titanate whiskers and aluminium silicate-ceramic fibres under similar experimental conditions (4).

In another experiment by the same research team, experimental conditions were similar but the inhalation exposure was 12 months at 2.6 ± 0.4 mg/m^3 (98 ± 19 fibres/ml) daily (5). The lung burden of SiC whiskers was 5.3 ± 1.4 mg at day 6 post-exposure. The deposited SiC whiskers in the lung decreased exponentially during the observation period. The calculated biological half-time from the 1-compartment model was 16 months, as opposed to 4 months in the previous 4-week study (4). This difference was thought to be due to a slow clearance after 6 months, subsequent to an accumulated volume of particles in alveolar

macrophages that impedes normal macrophage clearance (volumetric particle overload). Longer SiC whiskers (> 20 μm) tended to be retained in the lungs as the clearance time increased, notably after 6 months, whereas the diameters remained unchanged, indicating a faster clearance of the shorter fibres (5) (Section 10.5.2.1).

7.3 Nanosized SiC particles

Funahashi *et al.* examined lung tissue from two refractory brick workers, using microscopy and the X-ray diffraction pattern of deposited particles (Section 7.1). The tissue from the alveolar region appeared to contain a large number of particles less than 0.1 μm in diameter in addition to larger particles (66).

Instillation studies in female Wistar rats using 0.5 and 5 mg nanosized SiC (hydrodynamic diameter 31 nm, range 23–52 nm) per animal showed exponential elimination up to 60 days (105).

No other data on uptake, distribution or elimination of synthesised SiC nanoparticles were found.

8. Biological monitoring

No methods for biological monitoring of exposure or early effects of SiC were found.

9. Mechanisms of toxicity

Generation of reactive oxygen species (ROS) and subsequent inflammation are important toxicological mechanisms for most of the observed effects from exposure to SiC and may apply also for its carcinogenic effect, besides more specific mechanisms of carcinogenesis. Although the various non-fibrous and fibrous types of SiC have similar chemical properties, their different morphologies and sizes may induce different biological effects.

Although not specific for SiC, concern has been raised about animal long-term inhalation studies with high doses, which may impair clearance and enhance toxicity. In a review, Morrow discussed this as particle overloading of the macrophages, impeding mobility and lung clearance. The overloading is calculated to initiate at 60 μm^3 per alveolar macrophage in the Fischer 344 rat, whereas at 600 μm^3, clearance virtually ceases and agglomerated particle-laden macrophages remain in the alveolar region. During chronic exposure, these conditions usually progress to development of alveolitis and granulomatous lung disease such as fibrosis. Accumulation of sufficient number of persistently retained particles may also lead to tumourigenesis (116). This applies to durable particles with low toxicity [so called poorly soluble, low toxicity (PSLT) dusts], but has also been described for other particles (41). Thus, it may be applicable also for angular and

fibrous SiC. It has been shown for fibres such as potassium octatitanate whiskers that, even if short enough to be engulfed by the alveolar macrophages, a pulmonary deposition of 2 mg or more may exceed the clearance capacity of the macrophages in the Wistar rat (129). Mechanisms of reduced clearance during alveolar macrophage overload imply reduced cellular mobility, increased interstitial dust uptake and prolonged inflammatory response, and possibly excessive elaboration of chemotactic and chemokinetic factors by the alveolar macrophages (117).

9.1 Angular SiC

Observations on mechanisms of angular SiC induced toxicity are very few. In fact nearly all experimental studies on animals exposed to angular SiC do not indicate noteworthy adverse pulmonary effects (15, 25, 27, 28, 62). However, one study showed major pulmonary tissue response (granulomas and fibrotic lesions), but no mechanisms were proposed (135) (Section 10.2.1.1).

Angular SiC (Carborundum, FFF) was shown to induce cytochrome oxidase *in vivo* after intratracheal instillation. The authors suggested that the response was related to phagocytic activity in the lungs since no fibrosis was observed (62) (Section 10.2.1.1).

In vitro studies of angular SiC indicating no cytotoxic effects have nevertheless shown release of transient oxidative stress mediators and proinflammatory cytokines such as tumour necrosis factor alpha (TNF-α) (18, 25, 26) (Section 10.2.1.2).

Ballew *et al.* estimated the lung dust dose for 170 SiC production workers on the basis of a dust overload model. The authors found that the dose estimates from the overload model made a better fit with the radiological findings of opacities among the workers than a traditional cumulative exposure model (10).

9.2 SiC fibres and SiC whiskers

Fibrous structured SiC are fibrogenic and carcinogenic, as supported by mechanistic studies. The fibre pathogenesis of SiC has not been examined to the same extent as that of asbestos, but mechanistic similarities have been observed in the tissues affected. There are data to support that mineral fibre induced inflammation is an important pathogenetic factor for the development of respiratory diseases such as pneumoconiosis and cancer (51).

9.2.1 Biopersistence

The fact that fibrous forms of SiC are very poorly soluble and once deposited in the lungs tend to be retained for long periods in the lung tissue (notably the elongated ones) is important for understanding their pathogenicity. SiC whiskers are solid, durable, nearly insoluble and non-biodegradable in tissues (5, 46, 128, 153). The durability of fibres may in part explain their high biopersistence and pathogenicity due to persistent mineral interaction with lung tissues.

Alveolar macrophages involved in clearance of fibres from the non-ciliated portion of the airways can easily engulf fibre lengths < 5 μm. Fibres with a length exceeding 15–20 μm may not be completely phagocytised by the alveolar macrophages, which in turn may lose mobility and phagocytic capacity ("frustrated phagocytosis"). This will result in less efficient clearance of fibres and prolonged secretion of inflammatory mediators to the surrounding cells. Thin fibres with lengths exceeding the diameter of the macrophages may thus be more toxic than shorter ones (50).

A sequestration model favoured by Vincent *et al.* (176) is one in which the longest particles remain in the lung without being cleared.

Tran *et al.* found that overloading of the lung by fibres less than 15 μm long and more compact particles leads to sequestration of material at locations in the lung from which it cannot be cleared. Further, for long fibres (> 25 μm), the author assessed that the clearance of such fibres occur by dissolution and fragmentation into shorter fibres (164).

9.2.2 Inflammation and fibrosis

Fibrous SiC caused a dose-dependent translocation of the transcription nuclear factor kappa B (NFκB) to the nucleus in A549 lung epithelial cells where transcription of proinflammatory genes such as cytokines, growth factors and enzymes involved in inflammation occur. Various antioxidants reduced the translocation of NFκB (22). These findings may also have a bearing on tumourigenesis (Section 9.2.3).

Analysis of BAL fluid collected from rats after inhalation exposure of SiC whiskers identified markers of acute pulmonary inflammation such as increased polymorphonuclear leukocytes (PMNs), alveolar macrophages and increase in lactate dehydrogenase (LDH). In the lung tissue of these animals, alveolitis with acute inflammatory cells and subsequent lung fibrosis was confirmed. These findings, further described in Section 10.5.2.1, were similar to those observed after inhalation exposure to amosite asbestos (46).

Begin *et al.* (1989) identified increased levels of fibroblast growth factors in the BAL supernatant from sheep intratracheally exposed to SiC fibres prepared from material collected from Acheson production furnaces (15) (Section 10.2.2.1).

TNF-α, an important signalling substance in the inflammatory pathway, has been shown to be produced by alveolar macrophages *in vitro* following exposure to some SiC whiskers (43, 65) (Section 10.2.2.3).

9.2.3 Tumourigenesis

Most of the commercially produced SiC whiskers used for toxicity testing are long and thin, with a high aspect ratio. According to the Stanton hypothesis, durable fibres with lengths > 8 μm and diameters < 0.25 μm are the most carcinogenic in experimental animals, irrespective of type and composition (159).

A study of mouse BALB/3T3 embryonic cells exposed to two types of long SiC whiskers or crocidolite asbestos (described further in Section 10.2.2.3) revealed

high cytotoxicity for all dusts, increased cell proliferative activity, shortened cell generation time, increased rate of DNA synthesis, increased total DNA cell content and induction of cell transformation, indicating neoplastic potential. Similarities between SiC whiskers and asbestos were observed (170).

Davis *et al.* found SiC whiskers longer than 20 µm to be the most potent carcinogen when compared with other dusts and fibres in a series of animal experiments. In this study, 10% of the fibres were longer than 20 µm, and the length distribution of SiC was similar to that of amosite asbestos. The authors considered the low solubility of SiC whiskers and high lung fibre retentions to be important factors for the greater potential of SiC whiskers to induce mesotheliomas compared to amosite (46).

As shown above (Section 9.2.2), carcinogenic fibrous SiC caused a dose-dependent translocation of transcription factor NFκB to the nucleus in A549 lung epithelial cells where transcription of proinflammatory genes occur. The same result was observed for the carcinogenic long amosite asbestos fibres and refractory ceramic fibres (RCF1), but not for some non-carcinogenic fibres (22) (Section 10.2.2.3).

9.2.4 Formation of free radical oxygen species (ROS)

A significantly increased hydroxyl radical generation was shown *in vitro* for long amosite asbestos fibres and RCF1, but not for SiC whiskers (Advanced Composite Materials Cooperation, dimensions not specified), indicating that hydroxyl radical formation may be important for many carcinogenic mineral fibres but not for these SiC whiskers (23).

In a study on interaction between fibres and alveolar macrophages, Brown *et al.* demonstrated an enhanced oxidative burst when a normal constituent of the lower lung fluid, immunoglobulin G (IgG), was added to SiC whiskers and alveolar macrophages *in vitro*. This was also shown for asbestos, RCF1 and glass fibres, whereas such coatings on RCF4 and special purpose glass microfibres did not alter the activity. However, coating with surfactant inhibited the ability of all these fibres to stimulate an oxidative burst (24).

Indirect increased oxidative activity may occur by depletion of antioxidant constituents of the alveolar fluid. Exposure of lung cell lining fluid and a cell free solution to SiC whiskers and other carcinogenic fibres induced depletion of glutathione and ascorbate in a fibre number dependent manner, but to a lesser degree than some non-carcinogenic man-made fibres. Antioxidant depletion of the cell lining fluid seems therefore not to be involved in tumour induction by SiC (21).

Fibrous forms of SiC residing inside alveolar macrophages in lungs of a SiC production worker were shown to appear as “ferrugineous bodies” (54). Such bodies have also been detected by SEM in low-temperature ashed lung residues from an abrasive worker (74). Also asbestos fibres may form ferrugineous bodies which in general consist of a fibrous core coated by protein and hemosiderin which is shown to result from oxidation of ferritin added to the protein coating

formed in the phagolysosome of the alveolar macrophages. The ferrugineous bodies may thus be a result of oxidative activity of ferritin coated fibres of many origins other than asbestos (70). Ferrugineous bodies have also been found in the alveoli of guinea pigs after pulmonary exposure to SiC whiskers (45). In the sheep model of pneumoconiosis, ferrugineous bodies were recovered from the lung tissue after intratracheal instillation (56), whereas no such bodies were observed in rats following inhalation (98) or intratracheal instillation (172).

9.2.5 Other mechanisms

Cell proliferation in the terminal bronchiolar/alveolar ducts was shown in rats after 1 hour of exposure to SiC whiskers [SiC1: geometric mean ± geometric standard deviation (GM ± GSD): length 8.73 ± 2.25 µm, diameter 0.47 ± 1.49 µm] and amosite asbestos, but not with glass microfibre (code 100/475) and a negative control. The proliferation [detected as bromodeoxyuridine (BrdU) immunohistochemical staining of nuclei of the epithelial cell lining] was most marked in the highest levels of the lung (apex), decreasing towards the lower levels (base) (43).

Nitric oxide (NO) has been demonstrated on the surface of SiC whiskers as well as on asbestos fibres (100) suggesting that this signalling molecule acts also as a pathogenetic factor for toxicity. Nitric oxide inhibits the enzymes involved in adenosine triphosphate (ATP) production by mitochondrial respiration. Insufficient ATP production due to nitric oxide from SiC whiskers may cause impaired movement and polymerisation of the cytoskeleton, suggesting that the impaired cytoskeleton function may be attributed to altered energy metabolism (169).

9.2.6 Combined exposure

No studies on mechanisms for toxic effects of exposure to SiC in combination with other pollutants in the SiC production industry were located.

10. Effects in animals and in vitro studies

Although it is the main commercial product, very few animal and *in vitro* studies have been performed on angular SiC. Among the fibrous SiCs, commercial SiC whiskers are the ones most studied, whereas SiC fibres as an industrial pollutant are less studied. Cleavage fragments do not seem to have the toxicological properties of fibrous SiC despite fulfilling the WHO fibre criteria. Rödelsperger *et al.* suggested that the carcinogenic properties of fibres are mainly restricted to a subgroup of WHO fibres longer than about 10 µm and thinner than about 1 µm (26, 147).

Selected animal studies are presented in Tables 12–17.

10.1 Irritation and sensitisation

No studies on irritation or sensitisation were found.

10.2 Effects of single exposure and in vitro studies

10.2.1 Angular SiC

10.2.1.1 Intratracheal instillation studies

Bruch *et al.* instilled a single dose of angular SiC (50 mg in 0.5 ml physiological saline, F1200 Grün, ESK, Germany) by the intratracheal route to SPS Wistar rats. Saline was used as negative control and quartz (DQ12, 2 mg) as a positive control. At 3, 8 and 12 months post-exposure mediastinal lymph nodes and lung parenchyma of SiC-exposed animals showed no abnormal histopathological findings. A significant increase in the wet weight of lymph nodes from 3 to 12 months post-exposure was recorded in the parallel quartz exposed group (28).

In another study, Bruch *et al.* compared the biological effects of two angular SiC samples (SiC-A, F1200, mean diameter 2.26 µm and SiC-B, NF2, mean diameter 1.14 µm, both from Wacker Chemie, Germany). Details on control animals were not given. SiC dust (20 mg/animal, medium not stated) was instilled intratracheally in rat lungs (number of rats not given) and the animals were killed after 2, 14, 21 or 90 days. Proteins, cells and lung surfactant lipids in BAL fluid were determined. The granulocytic response was high in both groups at 5 days after exposure, reflecting immediate alveolar stress following the dust instillation. Thereafter the SiC-A exposed group showed decreasing granulocytic response with time, whereas the SiC-B group showed a drop in response at day 14 followed by a new elevation which persisted until day 90. A similar response was observed for lung surfactant lipids, with an initial increase in both groups followed by reduction in the SiC-A group, and a drop at day 14 followed by persistent increase in the SiC-B group (25).

Using the sheep model, Begin *et al.* observed no major histopathological alterations in the lung tissue 8 months after intratracheal instillation of 100 mg per animal of raw angular SiC (99.5% < 5 µm) or 100 mg/animal of angular SiC after ashing (to remove possible graphite contamination). Neither were any major histopathological findings observed in the lungs of animals exposed to latex beads, graphite or saline, whereas exposure to quartz (Minusil-5) was associated with diffuse alveolitis and early stage nodular silicotic lesions. The authors concluded that angular SiC is inert (15). The study also included SiC fibres (Section 10.2.2.1).

In contrast, another study showed pulmonary inflammation and fibrosis among in total 30 male guinea pigs after intratracheal exposure to angular SiC (50 mg per animal, standardised and commercialised by Duke Scientific Corporation, catalogue no 349). Saline was used in controls. Only minor macroscopic changes in the lungs, in addition to black colouring from dust, were observed. Histopathological examination of the lungs at 40 days post-exposure showed ruptures of alveolar walls and dilation of alveolar spaces, with inflammation. Examinations at 70 and 100 days showed increasing inflammatory and fibrotic changes. At 100 days, many airspaces were obliterated by massive localised fibrous tissue, extending into adjacent peripheral lung tissue. No histopathological changes were observed in the control group. Hydroxyproline in lung tissue, a marker for

collagen synthesis, was increased 3-fold compared to controls on day 100 (135). The particular SiC used in this study was not characterised with respect to impurities other than absence of crystalline silica. The microbiological status of the animals was not stated. No other dusts were included in the study and no observations or suggestions on possible mechanisms for these effects were discussed. These findings are in contrast to other intratracheal instillation studies in rats (50 mg SiC) (28) and sheep (100 mg SiC) (15).

To assess the effect of angular SiC as a "non-fibrogenic" dust and of quartz as a fibrogenic dust on the cytochrome oxidase activity of lung tissue *in vivo*, 50 mg quartz dust (most particles < 5 μm) or 50 mg abrasive SiC (Carborundum, FFF, size distribution approximating that of the quartz dust) was instilled by the intra-tracheal route to male albino rats. The quartz group had lower levels of DNA content and cytochrome oxidase activity than both the carborundum group and the control group (not stated whether saline or untreated) throughout the follow-up period of 90 days. The cytochrome oxidase activity of quartz exposed lung tissue decreased gradually after an initial increase over the first 4 days. The decreases in DNA content and cytochrome oxidase activity are indicative of a reduction in the number of cells and their respiration activity. In the quartz group, this may be due to replacement of cells by fibrous tissue. The cytochrome oxidase activity and DNA content of lung tissues exposed to carborundum were higher than in the control tissues. However, on the basis that no fibrosis was reported, the authors could not exclude that the initial effects were related to transient cellular destruction and phagocytic activity, and concluded that the effects induced by SiC are not predictive for lung fibrosis (62).

10.2.1.2 In vitro studies

Bruch *et al.* examined the toxicity of angular SiC (F1200 Grün, ESK, Germany), three different clays, quartz (DQ12) and corundum (Al_2O_3) in two biological assays: 1) the H_2O_2 release test, in which alveolar macrophages collected from guinea pigs were exposed to the dusts (20 and 60 μg per 300 000 cells, i.e. 0.67 and 2 $\mu g/10^4$ cells) for 16 hours followed by determination of inhibition of stimulation of H_2O_2 release as a marker for cellular toxicity. No inhibition was observed following exposures (60 μg) to corundum and SiC, whereas 60 and 20 μg quartz inhibited completely and 40%, respectively; 2) the release of TNF-α from cultures of activated bone marrow macrophages (L929) of CBF1 mice was used to assess growth inhibition. The various dusts were studied at dose ranges from 10 $\mu g/10^4$ cells to 100 $\mu g/10^4$ cells. Growth inhibition was shown for quartz at concentrations down to 10 $\mu g/10^4$ cells, whereas SiC did not induce growth inhibition at concentrations up to 50 $\mu g/10^4$ cells. In conclusion, angular SiC produced no effect on H_2O_2 release from guinea pig alveolar macrophages and no obvious inhibition of TNF-α on activated bone marrow macrophages from mice (28).

A study of Bruch *et al.* using the vector model (141) compared the effects of five samples of angular SiC (commercial products) containing different amounts

of cleavage fragments (17×10^6/g to 493×10^6/g) with crystalline silica [quartz (DQ12) and cristobalite], SiC whiskers (Section 10.2.2.3), UICC crocidolite asbestos and electrocorundum (Al_2O_3, control). The materials were assessed for cytotoxicity, glucuronidase release and ROS release using alveolar macrophages from guinea pigs, whereas TNF-α release was measured on rat alveolar macrophages. Doses of 15, 30, 60 and 120 µg dust per 10^6 alveolar macrophages were used. Cytotoxicity, glucuronidase release and TNF-α release were similar to the control sample (electrocorundum) for all five angular SiC samples. A dose-dependent secretion of ROS was induced by all five angular SiC samples, higher than that induced by quartz and electrocorundum, and at the same level as that induced by cristobalite, crocidolite and SiC whiskers. All reference samples except electrocorundum showed higher responses than the angular SiC samples as follows; cytotoxicity (quartz, cristobalite, crocidolite, and, to a lesser degree, SiC whiskers); glucuronidase release (all four); TNF-α release (quartz and crocidolite, and to a lesser degree, cristobalite and SiC whiskers) (26).

Six different angular SiC produced by the Acheson process, collected at the plant, were non-toxic in the LDH assay *in vitro* towards RAW 264.7 macrophages. However, a proinflammatory response assessed as an increase in TNF-α was shown for one type of SiC containing crystalline silica (5% quartz, 9% cristobalite) and a high content of iron impurities. This dust is not commercial, but may be disseminated to the workplace environment. The other SiC samples also induced TNF-α to some extent, still significantly different from non-exposed cells (18).

Two samples of angular SiC (SiC-A, F1200, mean diameter 2.26 µm, and SiC-B, NF2, mean diameter 1.14 µm) were compared with quartz and corundum (Al_2O_3) as positive and negative controls, respectively, in a test using a set of toxicity parameters [LDH, fluorescein diacetate (FDA) hydrolysis] and H_2O_2 release from male guinea pig alveolar macrophages. Dusts were tested in doses ranging from 20 to 180 mg/10^6 cells (200–1 800 µg/10^4 cells). Cell viability measured by FDA showed no significant differences between SiC samples; quartz reduced cell viability even in low doses. Quartz and SiC-B but not SiC-A exerted a significant and dose-dependent reduction in H_2O_2 release. The toxicity of SiC-B could partly, but not solely, be explained by grain size; with the finest dust fractions showing the more pronounced toxicity. However, SiC-A had no effect in any dose grain size combination (25).

Allen *et al.* tested the effect of α-SiC (0.9 µm) and β-SiC (0.5 µm) particles, used in medical implants, on LDH released from murine macrophages, human osteoblasts and human synovial fibroblasts. Concentrations up to 0.1 mg/ml were well tolerated by all cell lines, whereas both α- and β-SiC particles induced high levels of LDH release at 1.0 mg/ml. Cytotoxicity was also studied by light microscopy, with widespread cell death evident at SiC particle concentrations of 1.0 mg/ml (6).

SiC dust from the processing area of a SiC plant (no crystalline silica present) was tested in several *in vitro* assays. The haemolytic effect on human erythrocytes of unmilled SiC particles (diameter 150–300 µm) was greater than that of milled

SiC particles (diameter predominantly < 10 µm, a few particles 50–100 µm) and also greater than that of the positive controls, quartz and asbestos, whereas the haemolytic effect of milled SiC particles was less than that of quartz and asbestos. Milled and unmilled SiC particles showed the same chemoattracting activity towards human PMNs, which was lower than that of quartz and asbestos, however higher than control levels (71).

The possible use of SiC as a ceramic coating material of titanium-based total hip replacement implants was examined in a cytotoxicity test using JCRB0603 cells (V79, Chinese hamster lung fibroblasts). SiC particles (5 µm, not further identified) inhibited colony outgrowth by one-third (67% ± 10% vs. control), while SiC-coated pins did not cause any inhibition and acted similarly to uncoated titanium pins (149).

Human mononuclear cells from buffy coats of healthy volunteers were cultured for 48 hours with and without the additives hydroxyapatite (size 1–50 µm), SiC (5 µm) or diamond particles, or collagen in solution (25 µg/ml). After 48 hours, cell viability measured by the trypan blue exclusion test was > 95% irrespective of additive. Monocytes exposed to hydroxyapatite, SiC or diamond contained intracellular particles. Interleukin (IL)-1β production was significantly increased in monocytes exposed to hydroxyapatite or SiC (30-fold and 38-fold, respectively), whereas diamond particles did not stimulate IL-1β production (121).

Angular SiC was unequivocally negative in a cytotoxicity test (cloning efficiency in Chinese hamster lung V79-4 cells) (17) that has been shown to correlate well with results from *in vivo* tests for mesothelioma risk (137) (for results on SiC whiskers, see Section 10.2.2.3).

SiC powder (angular SiC) showed low activity in several cytotoxicity tests; inhibition of the cloning efficiency of Chinese hamster lung V79 cells, formation of DNA strand breaks by means of a nick translation assay, formation of hydroxyl radicals, and the ability to stimulate neutrophils to produce oxygen radicals (160) (for results on SiC whiskers, see Section 10.2.2.3).

Table 12. Effects in animals following a single intratracheal instillation of angular SiC.

Absolute dose	Species/strain no. and sex	Width (mean)	Attributes	Observation period	Results	Reference
20 mg	Rats, (no. and sex not given)	2.26 µm 1.14 µm	SiC-A (F1200) SiC-B (NF2) (Wacker-Chemie, Germany)	5, 14, 21 and 90 d	*Total cells in BAL fluid:* SiC-A and SiC-B induced a transient increase on day 5, which decreased continuously to values close to those of control animals on day 90. *Granulocytes in BAL fluid:* SiC-B gave increased levels at day 5, which were somewhat reduced at day 14. The levels increased again at day 21 and were constantly high until day 90; SiC-A gave a weaker response initially with levels continuously decreasing until day 90. *Lung surfactant lipids from epithelial cell stimulation observed at day 90:* SiC B gave a significantly increased response compared to SiC-A. Details on control animals were not given.	(25)
50 mg	SPS Wistar rats, 60 (sex not given)	< 3 µm	F1200 Grün (ESK, Germany)	3, 8 and 12 mo	No histological changes in the lungs.	(28)
50 mg	Albino rats, 18 males	< 5 µm (> 50%)	Abrasive carbo-rundum (FFF) (origin not stated)	90 d	Increased cytochrome oxidase activity in wet lung tissue (in the quartz exposed group cytochrome oxidase activity decreased).	(62)

Table 12. Effects in animals following a single intratracheal instillation of angular SiC.

Absolute dose	Species/strain no. and sex	Width (mean)	Attributes	Observation period	Results	Reference
50 mg	Guinea pigs, 10 males/group	0.7–7 µm	Catalogue no 349 (Duke Scientific Corp.)	40, 70 and 100 d	Day 40: Macroscopically no major changes other than black colouring of the lung tissue. Microscopically ruptured alveolar walls, dilated alveolar spaces, interstitial inflammatory cells and histiocytosis resulting in nodular lesions. Thickened bronchial walls and arterioles. Hydroxyproline significantly increased compared to controls. Day 70: Peribronchial and perivascular fibrosis. Numerous mononuclear inflammatory cells, fibroblast proliferation in the interalveolar walls. Hydroxyproline non-significantly increased compared to controls. Day 100: Massive localised fibrous obliteration of airspaces, extending into adjacent peripheral lung tissue, showing the appearance of diffuse interstitial fibrosis. No lesions similar to silicotic nodules were noted. Hydroxyproline increased, highly significantly, compared to controls.	(135)
100 mg raw or ashed	Sheep, 8 (sex not given)	< 5 µm (99.5%)	Collected from the centre of SiC lumps, raw or ashed (to remove graphite contamination), (Quebec SiC industry)	8 mo	Accumulation of particles mostly within macrophages in alveoli and interstitium without cellular reaction.	(15)

BAL: bronchoalveolar lavage, ESK: Elektroschmelzwerk Kempten.

10.2.2 SiC fibres and SiC whiskers

10.2.2.1 Intratracheal instillation studies

Ogami *et al.* exposed Wistar rats to 2 mg or 10 mg of SiC whiskers by the intratracheal instillation route. The fibre length of the bulk material was approximately 5.1 µm [standard deviation (SD) 2.3] and the mean diameter was 0.3 µm (SD 1.5). During the 6-month period after the intratracheal instillation, an inflammatory response was observed in both exposure groups, characterised by dust laden macrophages and inflammatory cells, some alveolar wall destruction and slight pulmonary fibrosis. The tissue changes reversed to normal after 3 months in the 2-mg instilled group, whereas they persisted up to 6 months in the 10-mg group. The 10-mg group also had a significantly higher collagen deposition than the 2-mg or control group (saline injection) at 1, 3 and 6 months post-instillation. In conclusion, the low dose (2 mg) of this particular type of SiC whiskers induced minor and mostly reversible histological changes (123).

In a subsequent study, using a similar study design, the authors instilled Wistar rats with 2 mg identical SiC whiskers and added control groups exposed to well-characterised potassium octatitanate whiskers, crystalline silica (quartz), UICC crocidolite asbestos and titanium dioxide (TiO_2). In the SiC whiskers and potassium octatitanate whiskers groups, an acute alveolar inflammation was evident at day 3. At 6 months, small foci of low grade fibrosis were observed. In comparison, quartz induced increasing inflammatory responses up to 6 months, and crocidolite showed a significantly higher, but not increasing inflammatory score from 1 to 6 months, as opposed to the SiC whiskers score which levelled off from 1 month to values higher than, but not significantly different from, control TiO_2 values at 6 months (122).

Fisher 344/NTacfBR rats were exposed by the intratracheal route to two different SiC whiskers [mean diameter (µm) and length (µm): SiCW-1: 0.8 and 18.1; SiCW-2: 1.5 and 19.0], SiC platelets (Section 10.2.4.1), crocidolite asbestos (0.4 and 4.2 µm) and boron carbide whiskers, in doses adapted to the minute respiratory volume (MRV) of the rodents, using 1 mg (low dose) or 5 mg (high dose)/100 ml MRV. The SiCW-1 exposed groups exhibited high initial mortality (up to 50% dying within 24 hours) attributable to pulmonary haemorrhage accompanied by congestion, oedema and interstitial pneumonia. Dramatic increases in alveolar macrophage populations within 1 week of exposure to SiCW-1 persisted for at least 28 days, and chronic inflammation was observed in necropsies during the first month of the study. Macrophage response in animals exposed to SiCW-2 was also significantly higher than in controls, but only half of that seen for SiCW-1. After 18 months, a high incidence (> 85% of SiCW-1 animals and 28% of SiCW-2 animals) of multiple pulmonary granulomas was observed, which occasionally occluded the airways. The frequency of granulomas found in crocidolite exposed animals was similar to that found in SiCW-2 animals. Other pathological conditions, such as fibrosis, interstitial pneumonia, atelectasis, hyperplasia and squamous metaplasia, were associated with SiCW-1 and to a

lesser degree with crocidolite. In general, pulmonary lesions associated with SiC whiskers and crocidolite occurred in a ranking of SiCW-1 > SiCW-2 > crocidolite. Boron carbide whiskers and SiC platelets did not cause significant histological changes (172).

In another study by the same research group, SiC whiskers (SiCW-2, see above) in doses of 1–5 mg/100 ml MRV were intratracheally instilled in Sprague Dawley rats. Histological preparations of tracheal samples taken after 24, 48 or 72 hours showed lesions in the trachea similar to those shown in cultured ciliated outgrows (Section 10.2.2.3). Three days after instillation, multiple necrotic foci were observed in relatively non-ciliated regions, with large numbers of SiC whiskers being observed to penetrate beneath the epithelium or to be engulfed by epithelial cells (171).

After intratracheal instillation of SiC whiskers (Carborundum Company, diameter 0.5–3 μm) in rats, dust-filled alveolar macrophages were observed, in addition to much extracellular dust. The walls of the alveoli were thickened. Development of fibroblastic tissue processes from one or several of the evaginating alveoli of respiratory bronchioles and alveolar ducts was also observed. These lesions started to disappear 14 days after injection, and could not be found after 6 months. No collagenisation of the lesions was observed, in contrast to what was found after injection of microquartz, asbestos and talc. Dust-laden macrophages, however, were observed after 6 months, but were less numerous and less confluent. In addition, the walls of the air spaces were thin and delicate. No deaths occurred among the animals in 6 months. For some reason, the instillation dose of SiC whiskers was only 3.5 mg, whereas the doses of all the other fibres used in this study were at least 10.5 mg (72).

In another study, 100 mg raw SiC fibres, collected outside the lumps at SiC plants (see Section 4.3.2) or 100 mg ashed SiC fibres (to reduce surface graphite flakes) in 100 ml saline were each injected into the tracheal lobe of 8 sheep. The two samples produced an almost similar sustained nodular fibrosing alveolitis, and showed fibrogenic activities comparable to crocidolite asbestos fibres of similar size (15) (for results on angular SiC, see Section 10.2.1.1).

In a series of rat intratracheal instillation experiments aiming at the relevance of cellular markers after exposure to many dust types, Morimoto *et al.* showed a variability over time with no clear trends in Clara Cell Secretory Protein (CCSP) and CCSP mRNA for SiC whiskers in particular (113). This was also the case for lung protective surfactant protein A and C (SP-A and SP-C) mRNA, thyroid transcription factor-1 (TTF-1) mRNA (114), and calcitonin gene-related peptide (CGRP) mRNA (115). The role of these markers in the evaluation of lung tissue damage remains to be determined.

10.2.2.2 Intraperitoneal injection studies

After intraperitoneal injection of various fibres, approximately 8.2×10^7 fibres in each group of 3–4 mice, the peritoneal cavities were lavaged at day 4 and the cells

enumerated. SiC whiskers, amosite asbestos and microfibre all stimulated an increase in the number of inflammatory cells (46).

10.2.2.3 In vitro studies

SiC whiskers and a commercial angular SiC (Section 10.2.1.2) were assayed in an *in vitro* test (cloning efficiency of V79-4 Chinese hamster lung cells) and compared to crocidolite asbestos (positive control) (17). An assessment of cytotoxicity by this test has shown to correlate well with results from *in vivo* tests for mesothelioma risk (137). The dose-response curve showed that SiC whiskers had a cytotoxicity comparable to crocidolite (17).

Translocation of NFκB to the nucleus in lung A549 cells increased in a dose-dependent manner after *in vitro* exposure to the carcinogenic fibres SiC whiskers (lengths 61% > 10 μm; 28% > 20 μm), long amosite asbestos (lengths 65% > 10 μm; 35% > 20 μm) and RCF1 (lengths 59% > 10 μm; 18% > 20 μm). The most potent of the carcinogenic fibres were SiC whiskers (based on fibre number concentration). The non-carcinogenic man-made vitreous fibre (MMVF10), RCF4 and glass microfibre (code 100/475) did not activate NFκB (22).

The effects of two types of SiC whiskers (SiC1: Advanced Composite Materials Corporation, Greer, South Carolina; SiC2: Third Millennium Technologies, Malibu, California) on the production of TNF-α by rat alveolar macrophages were studied *in vitro* (8.2×10^6 fibres/10^6 cells, 24 hours culture). SiC1 was particularly active in inducing TNF-α release, also compared to SiC2, but both showed a higher activity than the crocidolite and amosite asbestos samples (43).

The release of TNF-α from four different cell cultures (Thp-1 cells, J774 cells, primary rat alveolar macrophages and human peripheral monocytes) was measured after incubation with e.g. manufactured SiC fibres (length 61% > 10 μm, 28% > 20 μm) and long fibre amosite asbestos (length 65% > 10 μm, 35% > 20 μm). The response differed somewhat between the cell cultures, but for J774 cells, rat alveolar macrophages and human peripheral monocytes, the release of TNF-α was highest after exposure to SiC fibres (65).

Suspensions of SiC whiskers (Tokai 100, Tokai Carbon, Tokyo, Japan, diameter 0.3–0.6 μm, length 5–15 μm) and other fibres in RPMI 1640 medium were added to monolayers of rat alveolar macrophages, and incubated for 90 minutes or 4 hours. The transcription of TNF-α mRNA was significantly increased after 90 minutes incubation with SiC whiskers, whereas the activity of TNF-α was not significantly increased after 90 minutes or 4 hours (the latter in contrast to chrysotile or crocidolite asbestos) (104).

An increase of LDH transudation and a decrease of murine macrophage-like cell viability after 24 hours of incubation were induced by SiC whiskers (with GM ± SD of length and diameter: 6.4 ± 2.45 μm and 0.30 ± 1.58 μm) in a dose-dependent manner (1, 10, 100 and 1 000 μg/ml), and TNF-α in the culture medium showed a plateau at 12 hours in a dose-dependent manner up to 0.1 mg/ml. No marked increase of intracellular IL-1β was observed (81).

SiC whiskers and several other fibres were compared as to their ability to stimulate superoxide production in isolated rat alveolar macrophages. The cells were exposed to naked fibres and to fibres coated with rat IgG, a normal component of lung lining fluid. Naked fibres stimulated a modest release of superoxide anion from alveolar macrophages. When IgG was adsorbed onto the fibres, only a modest superoxide anion release was stimulated by SiC whiskers, in contrast to some of the other fibres, which showed a dramatic increase in superoxide release after IgG coating. The modest superoxide release by IgG-coated SiC whiskers was assumed to be connected with a modest affinity for opsonin (76).

SiC whiskers, in contrast to cristobalite (crystalline silica) but similar to crocidolite asbestos, induced no cytotoxicity in alveolar macrophages (15–120 µg dust/10^6 alveolar macrophages). The release of TNF-α, ROS and glucuronidase by SiC whiskers was comparable to that by cristobalite (26) (for results on angular SiC, see Section 10.2.1.2).

The toxicities of three different SiC whisker samples were compared to those of UICC crocidolite asbestos (mean diameters and lengths (µm): SiC-1: 0.42 and 4.5; SiC-2: 0.75 and 20.1; SiC-3: 0.32 and 6.6; crocidolite: 0.12 and 2.1), a continuous glass filament sample, glass microfibre and erionite (a zeolite mineral) in four cellular assay systems. Cytotoxicity was measured by the viability (trypan blue exclusion) of rat alveolar macrophages after incubation for 20 hours with 0–50 µg/ml (0–250 µg/10^6 cells) of the inorganic materials. All three SiC whisker samples showed a dose-dependent cytotoxicity; on a mass basis two of them were more toxic than crocidolite. All the three SiC whisker samples showed a dose-dependent toxicity towards cultured tracheal epithelial cells, incubated 20 hours with 0, 5, 10, 15, 25 or 50 µg/ml and then cultured for 9 days. On a mass basis, one of the SiC whisker samples was more toxic than crocidolite. The three SiC whisker samples showed a dose-dependent toxicity towards cultured lung epithelial cells, incubated for 20 hours with 0, 5, 15, 25 or 50 µg/ml, and then cultured for 8 days. On a mass basis, two of the SiC whisker samples were equally or more toxic than crocidolite. Towards A549 human lung carcinoma cells, incubated and cultured similar to the lung epithelial cells above, the three SiC whisker samples showed a dose-dependent toxicity. On a mass basis, one of the SiC whisker sample was more toxic than crocidolite. Overall, however, on a fibre number basis, all SiC whiskers were more toxic than crocidolite (86).

Two SiC whisker samples and crocidolite asbestos (mean diameters and lengths (µm): SiCW-1: 0.8 and 18.1; SiCW-2: 1.5 and 19.0; crocidolite: 0.4 and 4.3) were compared with regard to cytotoxicity to BALB/3T3 embryonic mouse cells in culture. Similar cytotoxicity was observed for SiC whiskers and asbestos in two tests: Trypan blue dye exclusion was tested 24 hours after incubation with fibres in doses of 5, 10, 15 or 20 µg/cm^2 of plate surface area. A dose-related dye exclusion was observed, with no clear threshold. Cells exposed for 18 hours to 5 µg/cm^2 SiC whiskers or crocidolite asbestos showed a 20–30% increased leakage of previously accumulated ^{51}Cr compared to controls. Proliferative ability was

measured by number of formed colonies of 50 or more cells after 7 days of incubation with the test materials at varying concentrations. On a mass basis, SiCW-1 was more toxic than asbestos and SiCW-2. The latter showed about the same cytotoxicity as asbestos. However, on a fibre number basis, no difference between the two SiC whisker samples was observed. No comparison with asbestos on a fibre number basis was presented. Cellular transformation was determined by scoring focal colonies after 10–14 days incubation following 24 hours of exposure to the test materials (5 $\mu g/cm^2$). SiCW-1 was more toxic than SiCW-2 on a mass basis, with 65% versus 20% transformation. On a fibre number basis, there was no difference between the two SiC whisker samples. The rate of DNA synthesis in cells exposed to the test materials at concentrations ranging from 0 to 2 $\mu g/cm^2$ was determined by the [3H]thymidine method. Although DNA synthesis rates for both asbestos fibre and SiC whisker exposed cells were generally elevated compared to controls, the results were inconsistent. This could be due to the high mitotic activity in the fibre/whisker treated cells. A 6–8-fold increase in the number of binucleate cells after a 48-hour incubation with the test materials at 5 $\mu g/cm^2$ was observed for both asbestos fibres and SiC whiskers (170). Significant increases in total cellular DNA content, using the Keck method (89), were consistently observed 10–20 generations after treatment, in agreement with other observations where transformed cells and those cells associated with malignancies have elevated levels of DNA. The authors concluded that the amount of damage appeared to be more a function of the number of SiC whiskers present than of their size (170).

Alveolar macrophages from Syrian golden hamsters were exposed to iron oxide (Fe_3O_4) as an indicator for magnetometry, and concurrently exposed to 20, 40 or 60 µg/ml SiC whiskers (mean diameter and length: 0.3 and 6 µm) for 18 hours. A weak dose-related but not statistically significant release of LDH was observed. DNA fragmentation as shown by the DNA ladder detection method was observed in cells exposed to 60 µg/ml SiC whiskers. Ultrastructural alterations indicative of apoptosis were shown in 10% of the exposed cells and in 2% of the controls (dose not clearly stated). Relaxation, a rapid decrease of the remanent magnetic field strength radiating from the phagocytised iron particles, and considered to indicate the cytoskeletal function, was significantly reduced in SiC whiskers-exposed cells compared to controls (169).

The uptake of fibrous SiC was enhanced by pre-exposure to cigarette smoke of the epithelium in rat tracheal explants, as shown also for asbestos, talc and titanium dioxide. Oppositely, there was no increased uptake of angular SiC, fibrous and non-fibrous iron oxide or wollastonite. The explants were exposed to a mixture of fibrous and non-fibrous particles and the individual data were obtained by counting each polymorph separately in the cell cultures (90).

Outgrowth of ciliated cells from dog tracheal explants was used to test the sensitivity of ciliary activity to SiC whiskers. Three different SiC whiskers (mean diameters and lengths (µm): SiCW-1: 0.8 and 18.1; SiCW-2: 1.5 and 19; SiCW-3: 1.6 and 22.6) were added to the cultures in concentrations ranging from 5 to 100

μg/cm^2. The ciliary frequency was measured at 24, 48 and 72 hours, using a photomultiplier detection system and spectral characterisation. SEM was also performed. SiC whiskers, even at the highest doses studied, had no measurable effect upon the ciliary mobility. However, when SiC whiskers were swept by ciliary activity into non-ciliated epithelium, the SiC whiskers penetrated and killed cells, producing necrotic foci which extended below the epithelium into the underlying connective tissue. In some cases the SiC whiskers seemed to have been phagocytosed, often with rupture of cell membranes. Similar lesions were observed in rats delivered SiC whiskers by intratracheal instillation (Section 10.2.2.1) (171).

Milled SiC whiskers (SiCW-3S and SiCW-3L; milled for 3 and 58 hours, respectively) showed less toxicity than intact SiC whiskers [mean diameters and lengths (μm): SiCW-1: 0.8 and 14; SiCW-2: 0.9 and 14; SiCW-3: 0.7 and 12; SiCW-4: 0.7 and 12] regarding inhibition of the cloning efficiency of V79 cells. SiC whiskers showed concentration-dependent inhibition comparable to crocidolite asbestos. Formation of hydroxyl radicals was shown only for crocidolite asbestos and SiCW-4, which had the highest aspect ratio and the highest specific area among the SiC whiskers. Both milled and unmilled SiC whiskers showed a high ability to stimulate neutrophils to produce oxygen radicals (160) (for results on angular SiC, see Section 10.2.1.2).

10.2.3 SiC nanoparticles

10.2.3.1 In vivo studies

No studies were found.

10.2.3.2 In vitro studies

Five different SiC nanoparticles were produced by laser pyrolysis of gaseous precursors (12). Their specific surface areas (SSAs) calculated according to the Brunauer, Emmett and Teller (BET) protocol (29) were 33–125 m^2/g, and particle diameters calculated from the SSAs were in the range 13–58 nm. Si/C ratios were 0.8–1.2, higher values indicating more Si at the particle surface. After 24 hours exposure of cultured A549 human carcinoma cells (CCL-185) to SiC nanoparticles, the nanoparticles were shown to be localised in intracellular compartments as clusters 20–100 nm in size. The accumulation of SiC nanoparticles induced low but significant cell death, assessed by the MTT assay (118). Cell death increased slightly between 4 and 48 hours of exposure, with significant cell death at 50 μg/ml and 32% cell death after 48 hours of exposure to 100 μg/ml of one of the nanoparticles. No correlation could be established between cytotoxicity and SiC nanoparticle diameter or Si/C ratio. Increased intracellular ROS generation was observed at exposure to 100 μg/ml SiC nanoparticles, dependent on the Si/C ratio, with a high ratio causing intracellular ROS formation at an earlier time. The SiC nanoparticles also induced DNA strand breakages (Section 10.4.1). These responses were dependent both on the particulate cluster size and the Si/C ratio (12). Micro-sized SiC were not included in this study for comparison.

In the rat NRK-52E kidney cell line, cell mortality from SiC nanoparticles (BET size 17 nm, SSA 125 m^2/g and Si/C ratio 0.8) was low. At concentrations 50–200 µg/ml there was an insignificant dose-related increase in ROS production, but no DNA damage was shown (13).

Six samples of SiC nanopowders in doses of 15, 30, 60 and 120 µg nanoparticles per ml of medium (DMEM) were tested for toxicity using a macrophage cell line (the RAW 264.7 cell line derived from murine peritoneal macrophages transformed by the AML virus). None of the six samples showed signs of cytotoxicity assessed in terms of cell membrane damage (LDH release), whereas remarkable pro-oxidative reactions (ROS generation) and inflammatory response (TNF-α production) were recorded, the intensity of which appeared to be related to the physico-chemical features of the SiC nanoparticles. The extent of nanoparticle surface area and the nature of crystalline phases (α-SiC vs β-SiC) had an impact on the TNF-α production, surface iron showed an impact on free radical release, and the oxidation state showed an impact on cellular H_2O_2 production (139).

3C-SiC quantum dots displayed dose- and time-dependent selective cytotoxicity on cancer (oral squamous carcinoma) versus immortalised cells *in vitro* (112).

Jiang *et al.* studied the effects of SiC nanowires on Chinese hamster ovary (CHO) cells via cell cycle test, apoptosis analysis, micronuclei test, phosphorylation of mitogen-activated protein kinases and expression of cyclooxygenase-2 (COX-2). SiC nanowires stimulated COX-2 expression upon contact, and induced low rates of cell proliferation. Cell apoptosis and DNA damage were considered the consequence of COX-2 expression (83).

10.2.4 SiC platelets

10.2.4.1 Intratracheal instillation studies

SiC platelets (commercial product) (mean diameter 24.5 µm, thickness 1.2 µm) were intratracheally instilled in Fisher rats in a dose of 1 mg or 5 mg/100 ml MRV. At histopathological examination after 28 days, macrophages in the lung, and infiltration and increased mucus in the trachea were observed, but no nodules or pulmonary tissue changes of significance were seen (172).

Table 13. Effects in animals following a single dose of SiC whiskers (SiCW) or SiC fibres.

Absolute dose	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
Intratracheal instillation						
2 mg	Wistar rats, 25 males	D: 0.3 (1.5) µm L: 5.1 (2.3) µm	SiCW (Tokai Carbon Co., Tokyo, Japan)	3 d, 1 wk, 1, 3 or 6 mo	Initial inflammatory pulmonary response with dust laden macrophages, returning to normal after 3 mo.	(123)
2 mg	Wistar rats, 25 males	D: 0.3 (1.5) µm L: 5.1 (2.3) µm	SiCW (Tokai Carbon Co., Tokyo, Japan)	3 d, 1 wk, 1, 3 or 6 mo	Alveolar inflammation with aggregated fibres at day 3, increasing up to 1 mo, then attenuation to a level higher than but not significantly different from saline and TiO_2 controls at 6 mo. Animals receiving crystalline silica or crocidolite asbestos showed a more extensive and progressive inflammatory reaction.	(122)
3.5 mg	Rats, 22 (sex not given)	D: 0.5–3.0 µm L: 100–750 µm	SiCW (Carborundum Company)	4 d or > 6 mo	Dust-filled alveolar macrophages, much extracellular dust. Alveolar walls thickened by a combination of surface cell enlargement and arborescence of the septal argyrophilic stroma. Lesions disappeared 14 d–6 mo after injection.	(72)
10 mg	Wistar rats, 25 males	D: 0.3 (1.5) µm L: 5.1 (2.3) µm	SiCW (Tokai Carbon Co., Tokyo, Japan)	3 d, 1 wk, 1, 3 or 6 mo	Initial inflammatory pulmonary response with dust laden macrophages, persistent after 6 mo. Collagen deposition after 1, 3 and 6 mo.	(123)
1–5 mg/ 100 ml MRV	Sprague Dawley rats (no. and sex not given)	D: 0.8 µm L: 18.1 µm D: 1.5 µm L: 19.0 µm D: 1.6 µm L: 22.6 µm	SiCW-1 (Tateho, Japan) SiCW-2 (American Matrix, Inc., Knoxville, TN) SiCW-3 (same as SiCW-2)	72 h	The paper does not differentiate between effects of the different SiC whiskers and doses. The effects observed were changes in the tracheal epithelium. Multiple necrotic foci in relatively non-ciliated regions, with large numbers of whiskers penetrating the epithelium. Whiskers were observed to penetrate beneath the epithelium or to be engulfed by epithelial cells.	(171)

Table 13. Effects in animals following a single dose of SiC whiskers (SiCW) or SiC fibres.

Absolute dose	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
1 or 5 mg/ 100 ml MRV	Fisher 344/ NTacfBR rats, 23–25 females/ group	D: 0.8 µm L: 18.1 µm D: 1.5 µm L: 19.0 µm	SiCW-1 (Tateho, Japan) SiCW-2 (American Matrix, Inc., Knoxville, TN)	18 mo	SiCW-1: High initial mortality (50% dying in 24 h) attributable to pulmonary haemorrhage accompanied by congestion, oedema and interstitial pneumonia. Increases in alveolar macrophage populations within 1 wk of exposure, chronic inflammation. Initial weight loss, recovering after 14 d. Multiple pulmonary granulomas in 85% of the animals. Histopathological analyses of lung tissues showed mainly granulomas both at high and low doses. Splenomegaly observed in the high dose SiCW-1 group, as well as in the crocidolite asbestos group. SiCW-2: Macrophage response was significantly higher than in negative controls, but only half of that seen for SiCW-1. Multiple pulmonary granulomas in 28% of the animals. Histopathological analyses showed lung granulomas and macrophages at both high and low doses. In summary, the pulmonary lesions were ranked: SiCW-1 > SiCW-2 > crocidolite.	(172)
100 mg raw or ashed (to remove graphite contamination)	Sheep, 8 (sex not given)	D: 0.27 (0.27) µm L: 6.8 (11.2) µm	SiC fibres collected from the outside part of the lumps (Quebec SiC industry)	8 mo	Nodular fibrosing alveolitis, fibrogenic activities comparable to crocidolite asbestos fibres of the same size.	(15)
Intraperitoneal injection						
8.2×10^7 fibres	C57/B16 mice, 3–4 males	D: 0.45 µm L: > 5 µm	SiCW (origin not stated)	4 d	Increased number of inflammatory cells in peritoneal lavage.	(46)

D: diameter, L: length, MRV: minute respiratory volume, SD: standard deviation, TN: Tennessee.

10.3 Effects of short-term exposure (up to 90 days)

10.3.1 Angular SiC

Wistar rats (92 females) were exposed by inhalation (5 hours/day, 5 days/week for 2 weeks) to 20 mg SiC/m^3. Additionally, groups were exposed to combinations of SiC/quartz, SiC/kaolinite and appropriate controls (quartz, clay, corundum and air) at doses of 20 mg/m^3 for a total of 50 hours. The combination exposure was 20 mg/m^3 quartz or kaolinite for 1 hour/day followed by 20 mg/m^3 SiC for 4 hours per day. At 3, 21 and 90 days post-exposure, total cells, alveolar macrophages and granulocytes in BAL fluid were counted, and lung surfactant factor phospholipids were extracted. A lung function test was performed on 8 animals/group after 90 days. Seven rats per group were killed 3, 11, 21 and 90 days post-exposure. Dust content of the lungs was determined gravimetrically and wet weight of mediastinal lymph nodes was measured. No increased effects compared to negative controls were observed in the SiC exposed group. SiC and quartz combined gave increased effects in all end points studied, similar to the effects of quartz alone (27).

10.3.2 SiC fibres and SiC whiskers

To study SiC whisker induced pulmonary inflammation, Davis *et al.* exposed AF/HAN rats whole-body to SiC whiskers (origin not stated, mean diameter 0.45 µm, lengths 63% > 5–10 µm and 10% > 20 µm), amosite (commercial asbestos with a similar length distribution) and glass microfibre (code 100/475) during 7 hours/day, 5 days/week for 1, 3, 7 or 14 days. The mean exposure concentration was approximately 1 000 fibres/ml (> 5 µm). At day 3, amosite induced more PMNs in the BAL fluid than SiC whiskers (0.67×10^6 vs 0.44×10^6 cells). However, at day 14 the PMN population was halved in the BAL fluid of amosite exposed rats (0.30×10^6), whereas it was doubled in SiC whisker exposed rats (0.84×10^6). During the same period, LDH in BAL fluid doubled in both groups, from day 3 to day 14; the values being 3 times higher at both time-points in BAL fluid from amosite exposed rats. There was no significant difference in cell proliferation in the terminal bronchiole/alveolar ducts by histopathological counting of the number of BrdU (commonly used to detect proliferation) positive cells (46).

In another inhalation study, male Wistar rats were exposed to 10.4 mg/m^3 SiC whiskers (Tokai Carbon Co., Tokyo, Japan) 6 hours/day, 5 days/week for 4 weeks [mean fibre length 5.1 µm (SD 2.3), mean diameter 0.3 µm (SD 1.5) and MMAD 2.5 µm as determined by an Anderson cascade impactor]. Minor histopathological changes, such as sparse thickening of the alveolar wall with increased dust laden alveolar macrophages in the alveoli, were observed in the lung parenchyma with no progress during the 6 months post-exposure observation period. According to the authors, possible explanations for the low toxicity findings in comparison to others were e.g. the short fibre lengths of the SiC whiskers used, the low exposure concentration and short exposure time (123). This study also included an experiment on intratracheal instillation of the same material, leading to more abundant pulmonary fibrosis than after the inhalation exposure (Section 10.2.2.1).

Table 14. Effects in animals following short-term inhalation exposure of angular SiC (up to 90 days).

Exposure regimen	Species/strain, no. and sex	Width (mean)	Attributes	Observation period	Results	Reference
20 mg/m^3, 5 h/d, 5 d/wk for 2 wk	Wistar rat, 92 females	< 3 µm	Mikro-F1200 M678, batch no. D (Wacker GmbH)	3, 21 and 90 d post-exposure	No effect on several markers of inflammation. SiC in combination with quartz gave increased effects, but not higher than quartz alone.	(27)

Table 15. Effects in animals following short-term inhalation exposure of SiC whiskers (SiCW) (up to 90 days).

Exposure regimen	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
1 000 fibres/ml (> 5 µm), 7 h/d for 1, 3, 7 or 14 d	AF/HAN rats, 24 (sex not given)	D: 0.45 µm, L: 5–10 µm: 63% > 20 µm: 10%	SiCW (origin not stated)	At end of exposure	*BAL fluid*: Significantly increased number of PMNs at day 3 and 14, compared to controls, and 3 times more than from a similar amosite asbestos (with similar fibre length distribution) exposure at day 14. No increase of LDH, whereas amosite asbestos exposure gave 3 times higher levels than controls. *BrdU-IHC:* Significant increase in proliferation of bronchiolar cells after 7 h.	(46)
10.4 mg/m^3, 6 h/d, 5 d/wk for 4 wk	Wistar rats, 25 males	D: 0.3 (1.5) µm L: 5.1 (2.3) µm	SiCW (Tokai Carbon Co., Tokyo, Japan)	3 d, 2 wk, 1, 3 and 6 mo	Minor histopathological changes, sparse thickening of alveolar walls with increased dust laden alveolar macrophages.	(123)

BAL: bronchoalveolar lavage, BrdU-IHC bromodeoxyuridine immunohistochemistry, D: diameter, LDH: lactate dehydrogenase, L: length, PMN: polymorphonuclear leukocyte, SD: standard deviation.

10.4 Genotoxicity

10.4.1 In vitro studies

In a comparison of several whiskers and powders regarding formation of DNA strand breaks by means of a nick translation assay, SiC whiskers and crocidolite asbestos showed a high DNA breaking potential, whereas SiC powder (angular SiC) showed low activity. One sample of milled SiC whiskers (SiCW-3S) showed increased DNA strand breaks (160).

Genotoxic effects of SiC whiskers (mean diameter 0.32 µm, mean length 6.5 µm) were evaluated in lung epithelial and CHO cells. The cells were incubated with 0, 2.5, 5, 10, 15, 25 or 50 µg SiC whiskers/ml. SiC whiskers produced a concentration-related lethal cell cytotoxicity measured by the colony formation assay, the concentration resulting in 50% survival being 12 µg/ml of SiC for lung epithelial cells and 40 µg/ml for CHO cells. The whiskers caused a significant increase in multinucleated giant cells indicative of interference with cytokinesis. For lung epithelial cells, this increase was significant only at 20 µg/ml, whereas there was a linear increase in CHO cells. There was no increase in the frequency of micronuclei (20).

SiC whiskers (SiCW-1 and SiCW-2) were shown to induce cellular transformation in BALB/3T3 cells. The amount of damage appeared to be more a function of number of whiskers present than of their size (170).

Exposure of A549 human carcinoma cells to SiC nanoparticles with a Si/C ratio > 1 induced permanent DNA strand breakages after 4, 8 and 24 hours of exposure in the alkaline version of the comet tail assay. Conversely when cells were exposed to SiC nanoparticles with a Si/C ratio ≤ 1, the genotoxic effect was transient, i.e. the length of the comet tails decreased with exposure duration (12).

In the rat NRK-52E kidney cell line, no DNA damage was shown from SiC nanoparticles (BET size 17 nm, SSA 125 m^2/g and Si/C ratio 0.8) at concentrations 50–200 µg/ml (13).

SiC nanowires induced DNA damage in a micronuclei test on CHO cells, which was considered the consequence of COX-2 expression (83).

10.4.2 In vivo studies

No studies were found.

10.5 Effects of long-term exposure and carcinogenicity

Due to the concern about lung overload in animal long-term inhalation studies with high doses (Chapter 9), a cautious interpretation of such studies is warranted, and the interpretation for the effects of human exposure is challenging (117).

10.5.1 Angular SiC

No long-term exposure studies were found.

10.5.1.1 Intraperitoneal injection studies - tumourigenesis

Female and male (n = 48 and 72) Wistar rats were repeatedly intraperitoneally injected with angular SiC (NF2) (5 × 50 mg or 20 × 50 mg) in 2 ml saline, at 2-week intervals. Glass fibres (20 × 25 mg at 2-week intervals or 40 × 25 mg weekly) were administered to 54 males per group. A control group was injected 20 times with 2 ml saline. Animals were sacrificed when in bad health. One year after the first intraperitoneal injection of SiC, the average body weight of the rats injected with 20 × 50 mg was about 5% lower than that of the controls, and 6 months later this difference was 7–8%. The mortality was less than 20% at 90 weeks in all SiC groups, and no serosal tumours were found in the abdominal cavity. No body weight loss was observed in the glass fibre injected rats. Serosal tumours (mesotheliomas) were found in 3 rats injected with 20 × 25 mg and 20 rats injected with 40 × 25 mg glass fibres (138).

In an experiment by the same team, Wistar rats were treated repeatedly intraperitoneally with saline or angular SiC (5 × 50 mg or 20 × 50 mg at 2-week intervals) and followed for 130 weeks. Totally 2 rats had mesotheliomas, 1 among 69 male rats receiving 20 × 2 ml saline and 1 among 47 female rats receiving 250 mg SiC. No mesotheliomas were found among 45 female and 70 male rats receiving 1 000 mg SiC (142). The data suggest that there is no increased mesothelioma risk from angular SiC, since spontaneous mesotheliomas may occur in control animals (162), and since no tumours were found in the high-dose group.

10.5.2 SiC fibres and whiskers

10.5.2.1 Inhalation studies

Davis *et al.* exposed AF/HAN rats whole-body to SiC whiskers 7 hours/day, 5 days/week for 238 days. The mean diameter was 0.45 µm, lengths 63% 5–10 µm and 10% > 20 µm. The mean exposure concentration was approximately 1 000 fibres/ml (> 5 µm), which is very high compared to workers' exposures. For comparison, amosite asbestos (with a similar fibre length distribution and the same fibre number concentration) and glass microfibre were included in the same protocol (no further information was given for control animal conditions). In the SiC whisker group, one week post-exposure, pulmonary fibrosis was evident in bifurcations of peripheral bronchioles, as well as thickenings in the interstitial tissue of adjacent alveoli, lined by hypertrophic type II cells. The alveolar space contained macrophages with engulfed fibres. At 10–12 months later, advanced fibrotic thickening and remodelling of the peripheral tissue were observed. A marked increase in pneumocytes type II was observed and in some areas up to 1 cm in diameter there were lesions classified as bronchoalveolar hyperplasia. The extent and intensity of benign lesions in the amosite exposed lungs were not very different from the ones exposed to SiC whiskers. The extent of fibrosis in the groups exposed to SiC whiskers, amosite and microfibres was 8.7%, 7.6% and 0.2% respectively. The percentages of animals bearing lung carcinomas and adenomas were 12%/12% (SiC whiskers), 17%/21% (amosite) and 0%/11% (microfibre). Corresponding values for mesotheliomas were 24%, 5% and 0%.

In the SiC whisker group the mesotheliomas appeared earlier than in the other groups. In conclusion, the SiC whisker group had the highest cumulative incidence of mesotheliomas, whereas the amosite group presented more pulmonary carcinomas than the SiC whisker group (46).

Wistar rats (42 males) were exposed to SiC whiskers 6 hours/day, 5 days/week for 1 year by inhalation. The MMAD (GSD), the GM (GSD) diameter and length were 2.4 (2.4) µm, 0.5 (1.5) µm and 2.8 (2.3) µm, respectively. The daily average exposure concentrations were 2.6 ± 0.4 mg/m^3 (98 ± 19 fibres/ml) and the rats were sacrificed at 6 days and 3, 6 and 12 months after the exposure. At 6 days post-exposure, small fibre-aggregated foci were observed in alveoli in the entire lung, and some were deposited in the interstitial tissue with some collagen deposition. A slight thickening of the pleura was observed due to fibre disposition. One year later, there was a remarkable wide spread and more profound fibrosis, inflammatory cellular infiltrations and some bronchoalveolar hyperplasia. The histopathological changes were more severe than those in rat lungs exposed to glass fibres, alumina silicate refractory fibres or potassium octatitanate fibres under similar exposure conditions (shown in previous studies by the same team). This may partly be explained by the higher deposition of SiC whiskers (5.3 mg) compared to the other fibres (1.5–2.5 mg) (Section 7.2) (5).

COBS-CD Sprague Dawley BR rats (200/sex) were exposed for 6 hours/day, 5 days/week for 13 weeks to filtered air, 500, 1 500 or 7 500 SiC whiskers/ml air in an exposure chamber. The mean diameter of the SiC whiskers was 0.555 µm and the mean length 4.68 µm. Five rats/sex/group were sacrificed at each of the first 5 days after the end of exposure, the rest were sacrificed after an additional 26 weeks in a fibre-free atmosphere. Lung weights were significantly increased in the high-dose group (group 4). Lung foci (generally tan) were seen in 0/50, 3/50, 12/50 and 23/50 rats (groups 1 through 4) after the 13-week exposure period, and in 0/50, 14/50, 33/50 and 24/50 rats after the 26-week recovery period. Bronchial and occasional mediastinal lymph nodes were enlarged in some rats after the exposure, however, fewer rats had enlarged lymph nodes after the recovery period. Nodules were noted in the lungs of 1 rat in each of exposure groups 2 and 4 and of 2 rats in group 3. After exposure, a dose-related accumulation of fibres was observed in the lung, primarily concentrated at bifurcations of alveolar ducts and respiratory bronchioles. Most of the observed SiC whiskers were within free alveolar macrophages or were intracellular or partially intracellular in the alveolar septae. After the 26-week recovery period, there was an exposure-related increase in the accumulation and retention of whiskers within macrophages and alveolar septae. A single whisker associated with focal mesothelial hyperplasia was noted in the parietal pleura of 2 rats in group 2. A dose-related accumulation of SiC whiskers in lymph nodes was also observed, to a greater extent after the 26-week recovery than after the 13-week exposure period. Exposure-related thickening of bronchiolar walls declined after the recovery. Alveolar wall thickening did not resolve with time. Adenomatous hyperplasia of the alveoli after the exposure was only observed among female rats (12/25) in the highest exposure group. However,

after 26 weeks of recovery, adenomatous hyperplasia was seen in all exposed groups, both male and female. Severity and incidence seemed to be dose-related. Thickening of the visceral mesothelium and pleural fibrosis, often associated with alveolitis, were observed in all exposed groups, but without significant dose relation (98).

10.5.2.2 Intraperitoneal injection studies – tumourigenesis

Intracavitary injections have been used to examine the tumour formation potential of mesothelial – mineral fibre interactions.

The study by Vaughan *et al*. described in Section 10.2.2.1 also included an intraperitoneal injection of 20 mg/ml of SiC whiskers (SiCW-2: mean diameter 1.5 µm, mean length 19.0 µm) or phosphate-buffered saline in 20 Fischer rats. No mesotheliomas were observed after 18 months. The most prominent lesion was a diffuse, intense desmoplastic reaction of serosal surfaces. Peritoneal fibrosis, with abdominal organ adhesions, occurred in 90% of the animals exposed to SiCW-2 (172).

Davis *et al.* injected 1×10^9 fibres (length > 5 µm) of amosite asbestos, SiC whiskers and microfibre (in 2 ml phosphate-buffered saline) into the peritoneum of 24 rats in each group. In this life-long study, the numbers of peritoneal mesotheliomas were 21, 22 and 8, respectively (46). The results were alike the ones from the Miller *et al.* study (below) (111), so this is probably a summary of the work by Miller *et al*.

In the study by Miller *et al*., male specific pathogen free (SPF) Wistar AF/HAN rats in groups of 18–24 animals were injected intraperitoneally with a range of respirable fibres, at a dose of 10^9 fibres > 5 µm of length. When animals showed signs of debilitation they were euthanised at which time mesothelioma was usually macroscopically observed at autopsy. The mass dose of SiC whiskers was 14.2 mg, and 99% of the SiC whiskers had a diameter < 0.95 µm. The persistence in the lung of injected SiC whiskers at 12 months was 47–60%. The median survival of the SiC whisker exposed animals was 250 days, and 22 (92%) of the animals had peritoneal mesothelioma, compared to 509 days median survival and 21 (88%) mesotheliomas in the amosite asbestos group. No untreated control group was included (111).

In a carcinogenicity study, 5-week old female Fischer 344 rats were injected intraperitoneally with SiC whiskers or 8 other standard fibre samples (Japan Fibrous Materials Research Association) and followed for 2 years (94). All animals injected with 10 mg SiC whiskers (mean diameter 0.30 µm, mean length 6.4 µm) developed local peritoneal mesotheliomas within 1 year. The cumulative incidence of mesothelioma after 10 mg UICC Chrysotile B asbestos at the end of the study period was 85%, whereas 70% were observed in the 5-mg SiC whisker group, indicating a higher carcinogenicity potency of SiC whiskers relative to chrysotile asbestos (2).

10.5.2.3 Intrapleural inoculation studies

A standard 40-mg dose of fibrous materials uniformly dispersed in hardened gelatine was applied by open thoracotomy directly to the left pleura of female Osborne-Mendel rats. In each experiment, 30–50 rats were followed for 2 years, at which time the survivors were sacrificed. Three types of controls were considered: untreated rats, rats with thoracotomy but no implants and rats with implants of different non-fibrous materials. SiC whiskers of fine, uniform dimension were compared to, among others, crocidolite, tremolite and amosite asbestos. Seventeen tumours (pleural sarcomas resembling mesenchymal mesotheliomas in humans) were observed in 26 (65.4%) SiC whisker exposed animals, compared to 56%, 67.7% and 76.8% in the animals exposed to amosite, crocidolite and tremolite asbestos, respectively (159).

Female Fischer 344/N rats were intrapleurally inoculated with crocidolite asbestos (20 mg), continuous ceramic filaments (CCF) or one of three individual samples of SiC whiskers (20 mg) suspended in saline or saline only. Mean diameters and lengths (μm) were: SiCW-1: 0.42 and 4.5; SiCW-2: 0.75 and 20.1; SiCW-3: 0.32 and 6.6; crocidolite: 0.12 and 2.1; CCF: 12 and 40–100. The life spans were significantly reduced in rats injected with SiCW-1 or SiCW-2 (mean 453–519 days) or crocidolite (548 days) compared with the rats treated with saline (753 days), CCF (708 days) or SiCW-3 (635 days). The two SiC whisker samples that induced shortened life spans also induced a higher rate of mesothelioma (87–90%) than the crocidolite (57%) and the third SiC whisker sample (23%) (87).

10.6 Reproductive and developmental effects

No studies were found.

10.7 Effects of combined exposure

When albino rats were exposed by intratracheal instillation to crocidolite asbestos (50 mg) with 85% of the fibres < 5 μm in length, or finely powdered quartz without impurities (50 mg) with and without addition of carborundum (angular SiC, 7 mg), all four groups presented time-dependent increases in inflammation and fibrosis at 20, 100 and up to 200 days, but the alterations in the lung tissue were significantly more severe in the two quartz groups compared to the asbestos group. Addition of angular SiC to quartz had an aggravating effect on fibrosis up to 100 days. Thereafter, no differences in the fibrosis grade were observed for this combined exposure, while in the asbestos combined group the fibrosis grade was the same or less than in the pure asbestos exposed group (63). No studies were done to explain these differences in the fibrogenic response obtained with small amounts of angular SiC in combination with quartz and asbestos respectively (63).

Inhalation of 20 mg/m^3 quartz 1 hour/day followed by 20 mg/m^3 angular SiC 4 hours/day gave higher measures on inflammatory markers than 20 mg/m^3 angular SiC alone 5 hours/day, but not higher than 20 mg/m^3 quartz alone 5 hours/day (all exposures 5 days/week for 2 weeks) (27) (Section 10.3.1).

Table 16. Animal carcinogenicity studies of angular SiC.

Exposure regimen	Species/strain, no. and sex	Width	Attributes	Observation period	Results	Reference
Intraperitoneal injection						
5 × 50 mg and 20 × 50 mg, at 2-wk intervals	Wistar rats, 48 females and 72 males	Not given	SiC NF2 (ESK, GmbH, Munich, Germany)	52, 78, 90 and 130 wk after the first injection	Mesothelioma in 1 female rat dosed with 5 × 50 mg after 130 wk observation. 1 mesothelioma also among controls.	(142)
5 × 50 mg and 20 × 50 mg, at 2-wk intervals	Wistar rats, 48 females and 72 males	Not given	SiC NF2 (as above)	52, 78 and 90 wk after the first injection	After 52 wk, the average body weight was 5% lower than controls in the high-dose group, after 78 wk the difference was 7–8%. Mortality was less than 20% at 90 wk in both groups. No serosal tumours.	(138)

ESK: Elektroschmelzwerk Kempten.

Table 17. Long-term exposure and carcinogenicity studies of SiC whiskers (SiCW).

Exposure regimen	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
Inhalation exposure						
98 ± 19 fibres/ml, 6 h/d, 5 d/wk, 1 y	Wistar rats, 42 males	D: 0.5 (1.5) µm L: 2.8 (2.3) µm	SiCW, TWS-100, 98% SiC (Tokai Carbon Co.)	6 d (10 rats), 3, 6 and 12 mo (10–11 rats) post-exposure (histopathology only given for 6 d and 12 mo)	6 d: Small fibre-aggregated foci in alveoli in the entire lung. No cellular inflammation, and some fibre-related interstitial collagen deposition. 12 mo: Widespread collagen fibrosis and macrophage/ monocyte inflammation. Bronchoalveolar hyperplasia in 2 animals.	(5)
500 fibres/ml, 6 h/d, 5 d/wk, 13 wk	COBS-CD Sprague Dawley BR rats, 50/sex	D: 0.577 µm L: 4.68 µm AR: 8.67	SiCW (Advanced Composite Materials Corp., Greer, SC)	0–26 wk post-exposure	0 wk: Bronchiolar wall thickening in 9 animals (8 slight, 1 moderate) and alveolar wall thickening in 40 animals (38 slight, 2 moderate). 26 wk: Bronchiolar wall thickening in 1 animal and alveolar wall thickening in 40 animals (all slight). Nodules (not further specified) in the lungs of 1 rat. A single whisker associated with focal mesothelial hyperplasia in the parietal pleura in 2 rats. Note: A few control rats (filtered air) showed increased numbers of macrophages in the alveolar walls.	(98)
1 000 fibres/ml (> 5 µm), 7 h/d, 5 d/wk, 1 y	AF/HAN rats, 46 (sex not given)	D: 0.45 µm L: 5–10 µm: 63% >20 µm: 10%	SiCW (origin not stated)	0 wk (4 rats) post-exposure and end of full life span (42 rats)	0 wk: Marked macrophage reaction, cells containing numerous fibres. Pathological changes at bifurcations of terminal and respiratory bronchioles, increased interstitial fibroblasts, staining for reticulin and collagen. Rounded epithelial cells. The effects were similar to those of amosite asbestos. End of full life span: Progressively increasing involvement of alveolar walls in bronchoalveolar hyperplasia. Increase in connective tissue staining, conversion of	(46)

Table 17. Long-term exposure and carcinogenicity studies of SiC whiskers (SiCW).

Exposure regimen	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
					lining epithelium to rounded cells of Type II pneumocyte pattern. Restructuring of lung tissue in the oldest animals. The effects were similar to those of amosite asbestos (with a similar fibre length distribution). 10 lung tumours, of which 5 carcinomas. For amosite asbestos the numbers were 16/7. 10 mesotheliomas in the SiC group, 2 in the amosite group.	
1 500 fibres/ml, 6 h/d, 5 d/wk, 13 wk	COBS-CD Sprague Dawley BR rats, 50/sex	D: 0.577 µm L: 4.68 µm, AR: 8.67	SiCW (Advanced Composite Materials Corp., Greer, SC)	0–26 wk post-exposure	0 wk: Bronchiolar wall thickening in 15 animals (14 slight, 1 moderate) and alveolar wall thickening in 46 animals (42 slight, 4 moderate). 26 wk: Bronchiolar wall thickening in 4 animals (3 slight, 1 moderate) and alveolar wall thickening in 48 animals (44 slight, 4 moderate). Nodules (not further specified) in the lungs of 2 rats.	(98)
7 500 fibres/ml, 6 h/d, 5 d/wk, 13 wk	COBS-CD Sprague Dawley BR rats, 50/sex	D: 0.577 µm L: 4.68 µm, AR: 8.67	SiCW (Advanced Composite Materials Corp., Greer, SC)	0–26 wk post-exposure	0 wk: Adenomatous hyperplasia in 12 female rats. Accumulation of fibres in bifurcations. Bronchiolar wall thickening in 38 animals (22 slight, 16 moderate) and alveolar wall thickening in 49 animals (4 slight, 45 moderate). 26 wk: Adenomatous hyperplasia in 37 female and 8 male rats. Increase in the accumulation and retention of whiskers within macrophages and alveolar septae. Bronchiolar wall thickening in 40 animals (28 slight, 12 moderate) and alveolar wall thickening in 49 animals (1 slight, 48 moderate). Nodules (not further specified) in the lungs of 1 rat.	(98)

Table 17. Long-term exposure and carcinogenicity studies of SiC whiskers (SiCW).

Exposure regimen	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
Intratracheal instillation						
1 or 5 mg/100 ml MRV	Fisher 344/ NTacfBR rats, 23–25 females/ group	D: 0.8 µm L: 18.1 µm D: 1.5 µm L: 19.0 µm	SiCW-1 (Tateho Inc., Japan) SiCW-2 (American Matrix, Inc., Knoxville, TN)	18 mo	SiCW-1: Pulmonary granulomas in 88% (low dose) and 91% (high dose) of the animals. SiCW-2: Pulmonary granulomas in 30% of the animals (both low and high dose). No mesotheliomas observed after 18 mo. Lesions associated with SiCW and crocidolite asbestos occurred in a ranking of SiCW-1 > SiCW-2 > crocidolite.	(172)
Intraperitoneal injection						
5 mg	Fisher 344/Jslc rats, ~14 females	D: 0.30 (1.58) µm L: 6.4 (2.45) µm	SiCW (JFM standard sample, Japan)	2 y	70% of rats had developed peritoneal mesothelioma within 1 y.	(2)
10 mg	Fisher 344/Jslc rats, ~14 females	D: 0.30 (1.58) µm L: 6.4 (2.45) µm	As above	2 y	All rats had developed peritoneal mesothelioma within 1 y. Carcinogenicity 2.4 times that of chrysotile asbestos.	(2)
14.2 mg	SPF Wistar AF/HAN rats, 24 males	10^9 fibres > 5 µm in length	SiCW (origin not stated)	Until debilitation	22/24 animals developed peritoneal mesothelioma. Median survival 257 d, as compared to 509 d for amosite asbestos exposed animals.	(111)
1×10^9 fibres	Rats, 24 (sex not given)	D: 0.45 µm L: > 5 µm	SiCW (origin not stated)	Lifelong	22 peritoneal mesotheliomas, median survival time 257 d. For amosite asbestos (similar fibre length distribution), 21 mesotheliomas, median survival time 509 d. [Probably the same study as (111)].	(46)
20 mg/ml (not further specified)	Fisher 344/ NTacfBR rats, 20 females	D: 1.5 µm L: 19.0 µm	SiCW-2 (American Matrix Inc., Knoxville, TN)	18 mo	No mesotheliomas after 18 mo. Diffuse, intense desmo-plastic reaction of serosal surfaces. Peritoneal fibrosis with abdominal organ adhesions in 90% of the animals.	(172)

Table 17. Long-term exposure and carcinogenicity studies of SiC whiskers (SiCW).

Exposure regimen	Species/strain, no. and sex	Mean (SD) diameter and length	Attributes	Observation period	Results	Reference
Intrapleural inoculation						
0 mg (negative controls, saline or CCF)	Fisher 344/N rats, 50 females/ group	CCF D: 12 µm L: 40–100 µm		Until moribund or only 20% of animals alive	Median life span: saline 753 d and CCF 708 d. No animals in either group developed mesothelioma.	(87)
0 mg (positive controls, 20 mg crocidolite asbestos)	Fisher 344/N rats, 30 females	D: 0.12 µm L: 2.1 µm		As above	Median life span: 548 d. 57% developed mesothelioma.	(87)
20 mg	Fisher 344/N rats, 30 females Controls: see above	D: 0.42 (0.02) µm L: 4.5 (0.23) µm	SiCW-1 (Alcan Aluminum Corp., Clarks Summit, PA)	As above	Median life span 453 d. 90% developed pleural mesotheliomas.	(87)
		D: 0.75 (0.02) µm L: 20.1 (1.01) µm	SiCW-2 (Advanced Composite Materials Corp., Greer, SC)		Median life span 519 d. 87% developed pleural mesotheliomas.	
		D: 0.32 (0.01) µm L: 6.6 (0.40) µm	SiCW-3 (American Matrix Inc., Knoxville, TN)		Median life span 635 d. 23% developed pleural mesotheliomas.	
40 mg	Osborne-Mendel rats, 30–50 females/ group	Single sample, uniform dimension	SiCW (General Technologies Corp.)	2 y	17 tumours (pleural sarcomas resembling mesenchymal mesotheliomas in humans) in 26 animals (65.4%), compared to 50/74 (67.6%) in animals exposed to the three most active crocidolite asbestos samples.	(159)

AR: aspect ratio, CCF: continuous ceramic filaments, MRV: minute respiratory volume, PA: Pennsylvania, SC: South Carolina, SD: standard deviation, SPF: specific pathogen free, TN: Tennessee.

11. Observations in man

11.1 Irritation and sensitisation

No studies were found.

11.2 Effects of single and short-term exposure

No studies were found.

11.3 Non-carcinogenic effects of long-term exposure

Airborne exposure in the SiC production industry, especially in the furnace departments, is a mixture of several agents, many of these with a potentially detrimental effect on workers' health. Some attempts have been made to examine the effects of individual exposure factors (32), but due to high correlation between the exposure factors, the results were ambiguous and limited to a suggestion of which exposure factors were the more important.

Cancer incidence and cancer mortality studies are described in Section 11.5.

11.3.1 Production industry

11.3.1.1 Pneumoconiosis

Pneumoconiosis is an inflammatory disease caused by inhalation of mineral dust, characterised by lung fibrosis and restrictive lung function. The diagnosis is usually based on radiographic findings of small opacities in the lung parenchyma. The association between work in the SiC industry and increased risk of pneumoconiosis was confirmed in the 1940s.

In 1941, after a case of pneumoconiosis was identified among workers in the Norwegian SiC industry, all employees went through health examinations, and 49 out of 222 workers presented pneumoconiotic changes on pulmonary X-ray. Bruusgaard reported a higher risk of pneumoconiosis particularly among workers employed in quartz grinding, mixing of the mass and handling of the residues from the furnaces. The investigation indicated that many of the cases could be attributed to a considerable dust exposure during the first years of operation of the plant, before adequate ventilation and exhaust had been installed. However, a considerable number of cases were found among workers that had not been exposed to quartz, but to dust of carborundum (SiC) only. Among 32 such workers, 10 presented with roentgenographic findings indicative of pneumoconiosis, increasing in profusion with employment duration. All were tuberculin positive, but tuberculosis could not be detected in any of the cases. No good exposure estimates were presented, except for some results from particle counting ranging from < 200 to > 2 000 particles/ml. The radiographic findings were, however, non-specific, and could, in addition to pneumoconiosis due to SiC dust, be explained by X-ray dense deposits of SiC dust or fibrotic changes due to other causes (30).

Table 18. ILO profusion (> 0/1) on chest radiograph by cumulative exposure to respirable particulates and smoking category in SiC workers (132).

Respirable particulates ($mg/m^3 \times$ year)	Never-smokers (%)	Ever-smokers (%)	Total (%)
0–3.6	0/14 (0)	6/37 (16)	6/51 (12)
3.7–7.4	1/11 (9)	10/32 (31)	11/43 (26)
7.5–14.9	2/7 (29)	17/38 (45)	19/45 (42)
≥ 15	5/6 (83)	19/26 (73)	24/32 (75)
Total	8/38 (21)	52/133 (39)	60/171 (35)

ILO: International Labour Organization.

Durand *et al.* examined pairs of lung radiographs from 128 SiC plant workers taken 1977 and 1984 to evaluate whether current exposure conditions [as described by Dufresne *et al.* (52)] contributed to an increase of density and profusion of parenchymal opacities and enlarging of pleural plaques. The results showed that density and profusion actually was reduced during the 6–7 years and that no changes had incurred in the pleural plaque images (57).

In 1950, the International Labour Organization (ILO) established a system for standardised classification of X-ray findings in pulmonary and pleural pneumoconiosis. The system has been revised several times, the latest in 2011. By the help of a set of standard radiographs the X-ray reader classifies the small pulmonary opacities into 6 categories based on shape and size (p, q, r, s, t and u), in addition to 12 categories based on profusion (from 0/0 to 3/3). The system also includes standards for classification of large pulmonary opacities and pleural changes (79).

Peters *et al.* studied chest X-rays of 171 SiC workers, related to their estimated life-time exposure to respirable particulates (organic and inorganic fractions) (Table 18). Of these, 60 workers (35%) had opacities defined as an average ILO profusion > 0/1, whereas 24 (14%) had profusion > 1/1. An exposure-response association was observed between cumulative exposure to respirable particles and the percentage of workers having radiographic rounded opacities (132).

Marcer *et al.* examined 267 SiC industry workers (for details on exposure measurements, see Section 6.1). Cumulative exposure to respirable dust was calculated on the basis of time spent in each job and its mean current exposure level (Table 19). In total, 10 subjects (3.7%) showed rounded opacities (ILO profusion ≥ 1/0). The duration of exposure in workers with ILO profusion ≥ 1/1

Table 19. Average cumulative particulate exposure by ILO profusion in SiC workers (107).

Profusion	No. of subjects	GM (SD) ($mg/m^3 \times$ years)
None	240	8.8 (11.1)
0/1	17	13.7 (13.9)
1/0	3	29.8 (30.8)
1/1	3	20.4 (15.5)
> 1/1	4	25.3 (20.1)

GM: geometric mean: ILO: International Labour Organization, SD: standard deviation.

was 19 (SD 7.8) years (range 8–29). The average cumulative exposure to respirable dust increased significantly with profusion level ($p < 0.03$) (107).

Petran *et al.* studied pulmonary X-rays from 191 SiC industry workers and observed a high prevalence of radiological findings. The dust exposure largely exceeded the current OELs (Romania, 1999). Exposure levels were not reported in the English abstract of this paper in Romanian (133), but in a paper from 2000 the same authors reported results from a similar sized cohort with total dust measurements ranging from 263 to 630 mg/m^3 (134). The crystalline silica content of the dust was < 1% (133). The exposure levels reported in the paper from 2000 (134) are far too high to be relevant for OEL setting (for respiratory symptoms, see Section 11.3.1.2).

Increased mortality from pneumoconiosis among Norwegian SiC industry workers, compared to age- and calendar-specific death rates in the general population, was observed by Romundstad *et al.* (144), with 6 observed deaths versus 0.8 expected [standardised mortality ratio (SMR) 7.9, 95% confidence interval (CI) 2.9–17] and by Bugge *et al.* (32) in an update among long-term workers in the same cohort, with 7 observed deaths versus 0.5 expected (SMR 15, 95% CI 7.0–31). No exposure-response analyses were performed in these two studies.

Schneider reported several cases of serious silicosis or silicotuberculosis from the SiC industry, many of these cases occurring among workers in the milling and sieving departments. Some theories were discussed: a) an oxidative material, "siloxykone", formed a surface layer on the SiC "bread". This surface layer contained crystalline silica and was, according to Schneider, removed in the cleaning section, but the separation between the departments was not good enough; b) a small percentage of quartz was present in the processing department. If this silica formed a thin film on the particle surface, the silica surface could become very large. Even after a consideration of these theories, not all cases of silicosis could be explained, and Schneider finally c) questioned the premise of quartz being necessary for the development of silicosis (152).

Massé *et al.* studied lung tissues from three workers with long-term exposure (> 30 years) in the SiC industry. A mixed pneumoconiosis was found, and lesions could be summarised as follows: a) abundance of intraalveolar macrophages associated with a mixture of inhaled particles including carbon, silicon, pleomorphic crystals, SiC and ferrugineous bodies showing a thin black central core; b) nodular fibrosis, generally profuse, containing silica and ferrugineous bodies and associated with large amounts of carbon pigment; c) interstitial fibrosis, less prominent than the nodular form; d) carcinoma in two cases. The authors suggested that this form of pneumoconiosis was sufficiently characteristic to be recognised as a distinct entity (109).

Dufresne *et al.* studied the fibrous inorganic content of post-mortem lung material from 15 men 5–9 years after they had been exposed 23–32 years in different parts of the SiC production. Of these, 5 men had neither lung fibrosis nor lung cancer, 6 had lung fibrosis, and 4 had lung fibrosis and lung cancer.

Concentrations of SiC fibres and other fibrous minerals and angular particles in the lungs were determined by TEM and energy dispersive spectroscopy. Higher concentrations of SiC fibres, ferrugineous bodies and angular particles containing elemental silicon were found in lungs from workers with lung fibrosis (with or without lung cancer) than from workers without these diseases (53).

In conclusion, a high incidence of pneumoconiosis has been observed in many studies of SiC workers. Although crystalline silica (quartz) is a main raw material in the industry, some studies demonstrated pneumoconiosis among workers with no known exposure to crystalline silica, pointing to angular SiC or SiC fibres as possible causative factors. In these studies, however, too little was known about possible confounders to allow a firm conclusion about exposure-response associations.

11.3.1.2 Obstructive pulmonary diseases

Infante-Rivard *et al.* studied cause-specific mortality, related to cumulative exposure to total dust, in a cohort of 585 Canadian SiC workers, using age- and calendar-specific death rates among Quebec males for comparison. In total, 167 deaths were observed (SMR 1.05, 95% CI 0.90–3.22) and the SMR for non-malignant respiratory diseases was 2.03 (1.21–3.22) for 18 observed cases. An exposure-response association was observed in internal analyses using cumulative exposure < 105 mg/m^3 × years as reference. Fifteen years of exposure lagging increased the exposure-response association. For chronic non-malignant respiratory diseases a weaker exposure-response association was observed. The association was somewhat reduced with 15 years lagging. However, the exposure-response associations with non-malignant respiratory diseases were statistically significant, and increasing with exposure lagging (80). The method used for exposure lagging was to ignore all deaths and all person-years at risk in the first 15 years of employment at the SiC plant. This method of lagging and the low number of participants reduced the power of the study considerably.

Romundstad *et al.* studied cause-specific mortality among 2 562 SiC industry workers, compared to the general Norwegian population, with follow-up 1962–1996. The authors found increased mortality from all causes (SMR 1.1, 95% CI 1.1–1.2), cancer (SMR 1.2, 95% CI 1.0–1.4), cerebrovascular disease (SMR 1.3, 95% CI 1.0–1.6), sudden death (SMR 1.5, 95% CI 1.1–2.1) and respiratory diseases (SMR 1.4, 95% CI 1.1–1.7). Among respiratory diseases there was increased mortality from the subgroups obstructive lung diseases (asthma, chronic bronchitis and emphysema) (SMR 2.2, 95% CI 1.6–3.0) and pneumoconiosis (SMR 7.9, 95% CI 2.9–17). Among workers with > 3 years employment, an exposure-response association with cumulative total dust exposure was observed for obstructive lung diseases. No analyses using specific exposure factors were performed (144).

In a subsequent follow-up of the Norwegian cohort, with cause-specific mortality 1951–2007 among 1 687 long-term workers (employed ≥ 3 years), Bugge *et al.* had access to a detailed JEM (68), and the separate effects of several exposure factors

could be studied. Increased total mortality was observed (SMR 1.1, 95% CI 1.0–1.2), in addition to increased mortality from cancer (SMR 1.2, 95% CI 1.0–1.4), respiratory diseases (SMR 1.6, 95% CI 1.3–1.9) and external causes (SMR 1.5, 95% CI 1.1–2.0). Increased mortality was also observed for the respiratory subgroups pneumoconiosis (SMR 15, 95% CI 7.0–31), obstructive lung diseases (SMR 2.0, 95% CI 1.5–2.7) and pneumonia (SMR 1.4, 95% CI 1.0–1.9). Exposure-response associations were studied for obstructive lung diseases, and the SMR was significantly increased at the two higher tertiles of cumulative exposure to total dust, respirable dust, respirable angular SiC and cristobalite (SiO_2), at all tertiles of cumulative fibre exposure, and at the lowest and highest tertiles of cumulative quartz exposure (Figure 5). Internal analyses using the lowest tertile as reference showed a significant trend with increasing exposure to angular SiC, total dust and cristobalite. When the analyses were stratified by employment duration less than and more than 15 years, there was a significant exposure-response trend with angular SiC exposure among workers employed less than 15 years, whereas significant trends were observed for cristobalite and total dust among workers with employment for 15 years or longer. Multivariate analyses with adjustment for the other exposure factors gave the same results. An explanation could be that SiC induces a symptom-giving inflammatory reaction in the airways, causing affected workers to leave the occupation, whereas cristobalite/total dust may induce a slower working detrimental effect, perhaps a fibrotic reaction (32).

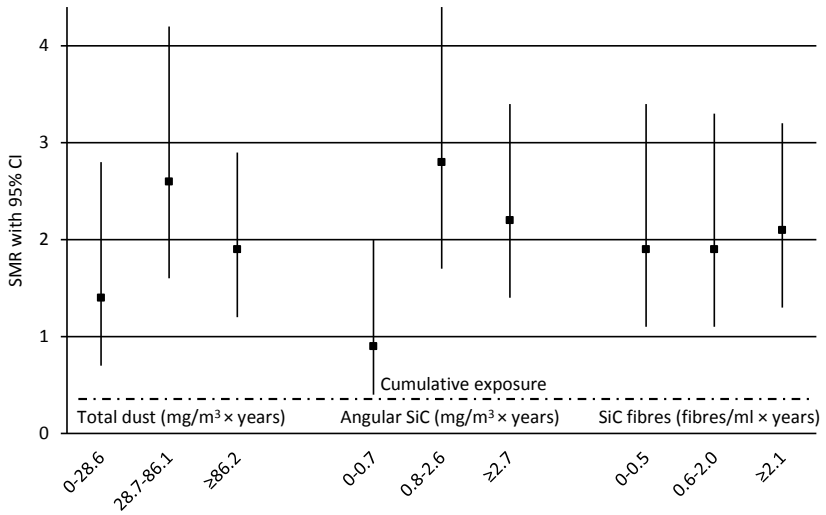

Figure 5. Standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) of obstructive lung diseases as underlying cause of death 1951–2007 stratified by cumulative exposure among 1 687 male Norwegian silicon carbide (SiC) industry workers employed (> 3 years) during 1913–2003. Adapted from Bugge *et al.* (32).

Peters *et al*. studied pulmonary function in relation to respirable dust exposure among 171 SiC industry workers. A significantly reduced pulmonary function measured as percentage of predicted was observed both for forced expiratory volume in the first second (FEV_1) and for forced vital capacity (FVC) related to cumulative exposure to both respirable dust and sulphur dioxide (SO_2) among ever-smokers. This effect was not observed among never-smokers (132).

Pulmonary function related to cumulative and average respirable dust exposure was studied among 156 workers in the Canadian SiC production industry. The authors observed an overall significant increased loss of 8.2 ml of FEV_1 and 9.4 ml of FVC per year of employment in the SiC industry, when adjusted for smoking, age and height. This extra loss was highest in never-smokers (FEV_1 17.8 ml/year employed and FVC 17.0 ml/year employed). A significant decrement in FEV_1 was also observed among never-smokers (not significant among current smokers) related to cumulative respirable dust exposure. No significant effects of average current exposure were observed. Mean cumulative respirable dust exposure was 9.5 (range 0.6–39.7) $mg/m^3 \times$ years, with average respirable dust exposure 0.63 (range 0.18–1.42) mg/m^3 and average employment duration 9.5 (range 2–41) years (126).

The same authors also studied respiratory symptoms related to respirable dust and SO_2 exposure among 145 SiC industry workers. Pulmonary symptoms were significantly associated with average and cumulative exposure to SO_2, but not with respirable dust exposure (127).

In a study of 267 SiC industry workers, Marcer *et al.* examined the effects of cumulative exposure to respirable dust (presumably mainly angular SiC) and SO_2 on pulmonary function. Average years worked were 15.2 (SD 8.9) and average cumulative respirable dust exposure was 9.7 (SD 12.1) $mg/m^3 \times$ years. Among smokers, reduced lung function (FEV_1 and FVC compared to predicted values quoted by the European Community of Coal and Steel) related to cumulative respirable dust exposure was observed with a significant trend. No significant effect of cumulative exposure to SO_2 was observed (107).

Spirometry was performed on 3 924 employees in Norwegian smelters (including the SiC industry) and the workers were allocated to one of three job categories; line operator (full-time employed in production); non-exposed (did not work in production); and the remainders, classified as non-line operators. Compared to the non-exposed workers, FEV_1 was reduced by 87 ml (95% CI 33–141 ml) and 65 ml (95% CI 12–118 ml) among line operators and non-line operators, respectively. Of the line operators, 8.3% had airflow limitation defined as FEV_1/FVC below the 5th percentile of the predicted value (lower limit of normal, LLN) (85). The paper did not differentiate between SiC workers and workers in other smelter industries.

In a longitudinal (5-year) follow-up among the same workers, Søyseth *et al.* found that line operators in the SiC industry had a steeper annual decline in lung function ($FEV_1/height^2$) compared with non-exposed (mean difference 5.6 ml/m^2

per year, 95% CI 0.7–10.4) (161). No exposure measurements were available at this point of time.

In a subsequent study, the researchers had access to a JEM from the Norwegian SiC industry and found that an increased annual fall in FEV_1 was associated with increasing levels of total dust. In an employee of mean height (1.79 m) and with average total dust exposure (1.4 mg/m^3) the estimated contribution to the annual decline in FEV_1 associated with dust exposure was 10.4 ml, whereas the contribution from smoking compared with non-smoking was 6.1 ml (84).

Using a questionnaire, Petran *et al.* examined the prevalence of respiratory symptoms (wheezing, dyspnoea, breathlessness after exercise) among SiC industry workers. Out of 191 workers, 50 reported such symptoms and 24 of these were tested for bronchial hyperreactivity with 19 being positive. The pollution level was extremely high, ranging between 263 and 630 mg/m^3, with a respirable fraction of 3.4% (134).

11.3.2 User industry

In a mortality and cancer incidence study among 521 workers in a Swedish abrasives manufacturing plant, Edling *et al.* observed no significant increases in total mortality or mortality from non-malignant respiratory diseases, compared to the general population. The cohort was followed 1958–1983. The workers were exposed to aluminium oxide, SiC and formaldehyde at total dust levels in the range 0.1–1.0 mg/m^3 (58).

Wegman *et al.* studied causes of death 1954–1973 among 968 deceased workers from a Massachusetts abrasives manufacturer by proportional mortality analysis using data from the population of the United States (US). Elevated odds ratios were observed for respiratory disease deaths among those most exposed to the synthetic abrasive dust. The excesses were greatest in those exposed 20 years or more. Two deaths from silicosis were observed where the workers had been employed in the crushing of SiC for 28 and 29 years. The level of free silica in the SiC was presumed to never have exceeded 1% (173).

The discussion whether pneumoconiosis may be caused by exposure to SiC alone, or whether it requires exposure to crystalline silica (see Section 11.3.1.1), has to a certain degree been continued related to the abrasives industry. Some reports of cases and pathological analyses of lung tissue have been published from this industry, and are shortly summarised below, in order to fill in some of the missing evidence.

Rüttner *et al.* analysed dust content from pneumoconiotic lungs of 16 metal grinders exposed to hard metals for 5–44 years and found only small or trace amounts of hard metals. Quartz and silicates were, however, found in all lung specimen, and carborundum (angular SiC) and corundum (Al_2O_3) in most. The authors suggested that in view of the mixed exposure the pneumoconiotic condition among hard metal grinders should be called “mixed dust pneumoconiosis in hard metal grinders” rather than “hard metal lung” (146).

Hayashi and Kajita examined lung tissue from a worker who had been dust exposed in an abrasives manufacturing plant for 10 years. No protective mask had been used. The dust content was 120 mg/g dried lung tissue. X-ray diffraction analyses revealed that the lung dust consisted of SiC, aluminium oxide (Al_2O_3), quartz and cristobalite (SiO_2), feldspar and talc. SiC accounted for 43% of the lung dust, and even though the effect of aluminium oxide or crystalline silica (cristobalite and quartz) could not be ignored, the authors concluded that SiC was the predominant intrapulmonary dust inhaled and retained in the lung tissue and acted fibrogenically in this case (74). It could, however, be argued that a small amount of a dust with high fibrogenic potency could be a more important causative factor than a preponderant dust with less inherent fibrogenic potential. Thus, this study represents no proof against crystalline silica as the fibrogenic material in this industry.

Funahashi *et al.* examined 2 men who had worked for many years in a factory manufacturing refractory bricks. Both had developed bilateral reticulonodular densities, as shown on chest radiographs, and complained of dyspnoea. Open lung biopsy from one of them showed a large amount of black material in the fibrosed alveolar septae. Studies of the dust in the working environment showed that the men had not been exposed to quartz dust. Meanwhile, studies of the lung material revealed six different SiCs, traces of tungsten carbide and insignificant amounts of quartz. Fibres of SiC and typical ferrugineous bodies were observed in the lung tissue. The patient had no known exposure to asbestos (66).

11.3.3 Conclusion

Employment in SiC production is associated with reduced lung function, increased lung fibrosis and increased mortality from obstructive lung diseases. The information about exposure levels is sparse, and exposure to a mixture of components makes exposure-response analyses difficult. However, associations have been shown between total dust exposure and reduced lung function (84), and between death from obstructive lung diseases and exposure to angular SiC and cristobalite (crystalline silica) (32). Studies from the abrasives industry have shown increased respiratory diseases, including pneumoconiosis (146). Lung tissue examinations have revealed a large variety of dusts, among these both angular and fibrous SiC, and crystalline silica (66, 146). Overall, the epidemiological studies are of limited value as a scientific basis for setting OELs.

11.4 Genotoxic effects

No studies were found.

11.5 Carcinogenic effects

11.5.1 Production industry

Four papers were found concerning cancer related to exposures in the SiC production industry. Cancer mortality compared to cause specific death rates

among Quebec males was studied in a Canadian SiC industry worker cohort (80). Three cancer incidence studies were related to the same Norwegian cohort of SiC industry workers, all of these using death rates in the general Norwegian population for comparison [Romundstad *et al.* 2001 (143), Bugge *et al.* 2010 (34) and Bugge *et al.* 2012 (33)].

11.5.1.1 Overall cancer

The Canadian study included 585 SiC industry workers employed 1950–1980, with follow-up through 1989. The overall cancer mortality was not significantly increased (SMR 1.25, 95% CI 0.94–1.65) (80).

Romundstad *et al.* studied 2 620 men, employed 1913–1996, with follow-up 1953–1996. The overall cancer incidence was significantly increased [standardised incidence ratio (SIR) 1.2, 95% CI 1.1–1.3] (143). In an update of the Norwegian cohort, Bugge *et al.* studied 2 612 workers employed 1913–2003, with follow-up 1953–2005. The overall cancer incidence was increased (SIR 1.3, 95% CI 1.1–1.4). The cohort was stratified into 925 short-term workers (< 3 years total employment) and 1 687 long-term workers. The overall cancer incidence (SIR) among short-term workers was 1.4 (95% CI 1.2–1.6) and among long-term workers 1.2 (95% CI 1.1–1.3). The negative trend that short-term workers were unhealthier than long-term workers has been observed in cancer and mortality studies in other industries, and has been explained by a combination of lifestyle and occupational risk factors (34). No analyses on exposure-response associations were reported for overall cancer.

11.5.1.2 Lung cancer

In the Canadian study, Infante-Rivard *et al.* observed significantly increased lung cancer mortality in SiC industry workers (SMR 1.7, 95% CI 1.2–3.2, 24 cases). A weak, non-significant exposure-response association with total dust exposure was observed. When exposure was lagged 15 years, the relative risks were reduced, but an exposure-response association was still observed (80). Lagging of exposure was performed through ignoring years at risk and deaths in the first 15 years of employment. This method of lagging reduced the power of the study considerably.

In the Norwegian study by Romundstad *et al.*, the lung cancer SIR was 1.9 (95% CI 1.5–2.3). Exposure-response analyses were stratified by quartiles of cumulative exposure to total dust, SiC fibres and particles, and crystalline silica. The SIR increased with increasing levels of all the studied exposure factors, and even higher SIRs were observed with 20 years exposure lag. In this study, 20 years exposure lag meant that exposure during the last 20 years prior to each year of observation was disregarded. The exposure-response association with SiC fibres was studied in Poisson regression analyses controlled for crystalline silica exposure, and with 20 years lag, and a significant exposure-response trend was observed (143).

In the update, Bugge *et al.* (2010) observed a lung cancer SIR of 2.6 (95% CI 1.9–3.5) among short-term workers and 1.7 (95% CI 1.3–2.2) among long-term

workers (34). In a follow-up until 2008, with the addition of an updated, detailed JEM (68), Bugge *et al.* (2012) observed a SIR of lung cancer among long-term workers of 1.6 (95% CI 1.3–2.1). The highest SIR was observed among furnace workers (SIR 2.3, 95% CI 1.5–3.5). Increasing SIRs were observed with increasing cumulative exposure to total dust, respirable dust, respirable quartz, cristobalite, angular SiC and SiC fibres, and higher SIRs were observed with 20 years exposure lag (Figure 6). Internal analyses using Poisson regression gave significant tests of trend with total dust, respirable dust and cristobalite, and when applying 20 years exposure lag significant trends were observed also with SiC fibres and angular SiC. Because of the high correlation between exposure factors, analysis using multivariate Poisson regression was performed. In this analysis, cristobalite (SiO_2) seemed to be the strongest causative factor. However, an effect of SiC fibres still remained after controlling for cristobalite and the other exposure factors. On the other hand, the associations with quartz and angular SiC were nullified when cristobalite and SiC fibres were added to the regression model (33). Lung cancer incidence was stratified by period of first employment, and a weak reduction in incidence was observed through the years. However, the SIR was significantly increased also for workers first employed in the period 1960–1979 (SIR 1.7, 95% CI 1.1–2.5), whereas the incidence among workers employed after 1980 could not yet be interpreted due to the long latency period of lung cancer (34).

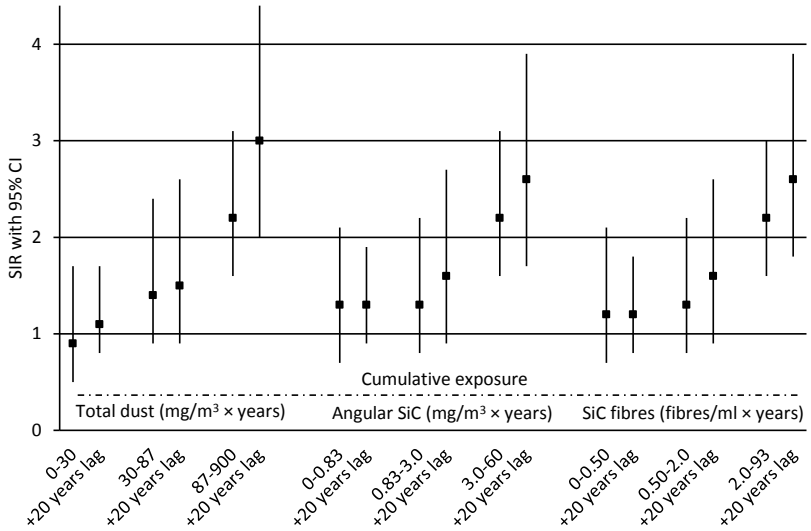

Figure 6. Standardised incidence ratios (SIRs) with 95% confidence intervals (CIs) of lung cancer stratified by cumulative exposure with and without 20 years lag of exposure among 1 687 male Norwegian silicon carbide (SiC) industry workers employed (> 3 years) during 1913–2003 and followed up during 1953–2008. Adapted from Bugge *et al*. (33). Note: The association with angular SiC was nullified after multivariate regression with cristobalite and/or SiC fibres included in the model (more details are provided in the text).

11.5.1.3 Other cancer sites

Stomach cancer mortality was non-significantly increased in the study by Infante-Rivard *et al.* with 7 cases, SMR 2.18 (95% CI 0.88–4.51) (80). In Romundstad *et al.*, the SIR of stomach cancer was 1.5 (95% CI 1.1–2.0). Most of these cases were associated with work in the processing department, where the main exposure was to angular SiC. Analyses stratified by cumulative exposure to angular SiC showed increased SIRs by increasing exposure (143). However, this exposure-response association was nullified when exposure was lagged with 10 and 20 years. In the Norwegian cancer incidence update by Bugge *et al.,* the SIR for stomach cancer was 1.4 (95% CI 0.8–2.4) among short-term workers and 1.3 (95% CI 0.9–1.9) among long-term workers (34). No extra stomach cancer cases were added to the cohort between 1996 (143) and 2005 (34).

Lip cancer was non-significantly increased in Romundstad *et al.* (SIR 2.0, 95% CI 0.9–3.9) (143). Bugge *et al.* reported a non-significantly increased lip cancer SIR among short-term workers (SIR 2.1, 95% CI 0.7–6.7, 3 cases), and a significantly increased incidence among long-term workers (SIR 2.4, 95% CI 1.2–5.1, 7 cases) (34). No exposure-response analysis was reported for lip cancer.

In addition, SIRs for cancers at the following sites were significantly increased in Bugge *et al.* Among short-term workers, SIRs (95% CIs) were: 2.5 (1.1–5.6) for oral cavity and pharynx, 2.1 (1.1–3.7) for non-melanoma skin cancer, 5.8 (2.2–15.4) for thyroid gland, 5.2 (2.0–13.9) for Hodgkin lymphoma and 2.1 (1.2–4.0) for cancer at unspecified sites. Among long-term workers, numbers were: 2.1 (1.1–3.9) for oral cavity and pharynx, 1.2 (1.0–1.5) for prostate and 2.8 (1.2–6.1) for leukaemia (34). No exposure-response analyses were reported for any of these sites.

11.5.2 User industry

Edling *et al.* observed no significant increases in cancer mortality among Swedish abrasives manufacturing workers compared to the Swedish general population (58) (see also Section 11.3.2).

Wegman *et al.* observed increased mortality from Hodgkin's disease, oesophageal and rectal cancers among Massachusetts' abrasives manufacturer workers compared to the US general population. However, the numbers were small (173) (see also Section 11.3.2).

Sparks *et al.* reported causes of death among 931 male jewellers, and found a 5 times increase in stomach cancer among polishers. This is in contrast to other jewellers, where the stomach cancer mortality was the same as in the comparison population (US white males). Polishers may be exposed to SiC, in addition to metal dust, chromium oxide, silica and diatomaceous earth (157).

Järvholm *et al.* studied the mortality pattern among 86 steel polishers and found an increased mortality from stomach cancer compared to the general Swedish population (4 deaths observed vs 0.44 expected). The polishing pastes contained tallow, beeswax, carnauba wax, alundum, carborundum (SiC), ferric oxide and chalk (88).

11.5.3 Conclusion

Workers in the SiC production industry have an increased risk of lung cancer, with an exposure-response association with cumulative exposure to total dust, angular SiC, SiC fibres and cristobalite (crystalline silica). In one study, multivariate Poisson regression models showed that the strongest associations were with cristobalite, but SiC fibres represented an additional risk factor independent of cristobalite. In contrast, the association with angular SiC was nullified in the multivariate models (33). Increased incidences of other cancers than lung cancer are also observed, but data are lacking with respect to exposure specific analyses. No increased risk of mesothelioma was observed (34).

Mortality studies in the abrasives industry showed no increase in lung cancer. Two studies showed an increased mortality from stomach cancer among polishers exposed, among others, to SiC. No exposure-related analyses were, however, performed (88, 157).

11.6 Reproductive and developmental effects

No studies were found.

12. Dose-effect and dose-response relationships

Dose-effect and dose-response relationships of angular and fibrous SiC observed in animal studies are compiled in Tables 12–17 (Chapter 10). No data on dose-effect relationships with SiC cleavage fragments, amorphous SiC, SiC platelets or SiC nanomaterials were located.

12.1 Animal studies

12.1.1 Single/short-term exposures

12.1.1.1 Angular SiC

Rats were exposed by inhalation to 20 mg/m^3 angular SiC for 2 weeks. Cells in BAL fluid, lung surfactant factor phospholipids, dust content in lungs, wet weight of mediastinal lymph nodes and lung function at intervals up to 90 days post-exposure were studied. No effects compared to negative controls were shown (27).

Five intratracheal instillation studies in animals have been described. In three of them, exposure of rats or sheep to 20–100 mg SiC, with observation periods of 3–12 months, did not reveal notable histopathological changes (15, 28, 62). One study compared two samples of angular SiC intratracheally instilled in rats at a single dose of 20 mg, with follow-up after 5, 14, 21 and 90 days. Analyses of cells and lung surfactant lipids in BAL fluid showed an inflammatory response up to 90 days for one of the samples, but not the other (25). In the 5th study, instillation of 50 mg SiC, with observation from 40 to 100 days, revealed severe inflammation and fibrosis in the lungs of guinea pigs (135). The results in this latter study

contrast with the other instillation studies, and no explanation for this notable lung pathology was proposed by the authors.

12.1.1.2 SiC fibres and SiC whiskers

Rats exposed to 1 000 fibres/ml (> 5 μm) SiC whiskers or amosite asbestos by inhalation for up to 14 days showed significant increases in the number of PMNs in BAL fluid at days 3 and 14, and an increase in proliferation of bronchiolar epithelial cells after 7 hours compared to controls. At 14 days, PMNs were elicited 3 times more efficiently by SiC whiskers than by amosite asbestos (46). Rats exposed by inhalation for 4 weeks to 10.4 mg/m^3 SiC whiskers showed minor inflammatory changes at the end of exposure, and no progression up to 6 months (123).

In the same study, rats were also exposed to 2 mg or 10 mg SiC whiskers by the intratracheal instillation route. After the instillation, an inflammatory response was observed in the lungs of both exposure groups. The tissue changes reversed to normal after 3 months in the 2-mg instilled group, whereas the initial changes persisted up to 6 months in the 10-mg group (123).

After intratracheal instillation of 3.5 mg SiC whiskers in rats, dust-filled macrophages and alveolar wall thickening were observed initially, but these lesions diminished from day 14 and was not found at 6 months (72).

After intratracheal instillation of rats with different SiC whiskers in doses of 1–5 mg/100 ml MRV, histopathological lesions were observed in the trachea, and fibres penetrating the epithelium (171). Another study with the same design described differing effects from two different SiC whiskers (SiCW), and somewhat more histopathological lesions with higher doses. In summary, the pulmonary lesions were ranked SiCW-1 > SiCW-2 > crocidolite asbestos (172).

Sheep exposed by intratracheal instillation to 100 mg raw or ashed fibres from the SiC production developed sustained nodular fibrosing alveolitis, comparable to the effect of asbestos fibres of similar size (15).

12.1.2 Long-term exposure (non-cancer effects)

12.1.2.1 Angular SiC

No studies were found.

12.1.2.2 SiC fibres and SiC whiskers

Nine-week old rats were inhalation exposed to 98 fibres/ml SiC whiskers during 6 hours/day, 5 days/week for 12 months. At 6 days after the end of exposure, minor findings of lung inflammation and fibrosis were observed. Twelve months later, corresponding findings were identified to a much higher degree (5).

Rats were exposed to SiC whiskers by inhalation for 13 weeks at doses of 500, 1 500 or 7 500 fibres/ml. Dose-response relationships for inflammatory and fibrotic changes in the lung tissue were observed at 26 weeks post-exposure (98).

Rats exposed to 1 000 fibres/ml (> 5 μm) SiC whiskers by inhalation for one year and examined at end of exposure or after full life span showed a time-dependent increase in pulmonary inflammation and fibrosis. The effects were

similar to the effects from amosite asbestos (with similar fibre number concentration and fibre length distribution) (46).

12.1.3 Carcinogenicity

12.1.3.1 Angular SiC

After exposure of rats (48 females and 72 males) by the intraperitoneal route with 5 × 50 mg angular SiC at 2-week intervals, one mesothelioma was observed in one female rat after 130 weeks. One mesothelioma was also observed among rats exposed to saline (142).

12.1.3.2 SiC fibres and SiC whiskers

After exposure of 14 rats to 5 mg SiC whiskers by the intraperitoneal route, 70% of the rats developed peritoneal mesotheliomas within one year, whereas in a 10-mg exposure group, all rats developed mesotheliomas within one year. SiC whiskers had higher carcinogenic potency than chrysotile asbestos (on a mass basis) (2).

After exposure of 24 SPF rats to 1×10^9 (14.2 mg) SiC whiskers by the intraperitoneal route, and life-time follow-up, mesotheliomas were observed in 22 animals (92%). Median survival was 257 days. For amosite asbestos with similar fibre number concentration and fibre length distribution (mass dose: 6.1 mg), 21 mesotheliomas were observed in 24 animals (88%), and median survival was 509 days (46, 111).

By the intrapleural inoculation technique there were no individual studies using more than one dose. Four SiC whiskers with different diameters and lengths were injected at doses of 20 or 40 mg. In all groups, observed for lifetime, 23–90% of the rats developed pleural mesotheliomas, and median life span was 453–635 days (87, 159). In a crocidolite asbestos exposed group, 57% of the animals developed mesothelioma, and median life span was 548 days (87).

In a study of Davis *et al.*, 42 rats were exposed to 1 000 SiC whiskers/ml (> 5 μm) by the inhalation route for one year, and followed up for the full life span. A total of 10 lung tumours (of which 5 were carcinomas) and 10 mesotheliomas were observed. No other doses were administered. For animals exposed to a similar fibre number concentration of amosite asbestos with similar length distribution the corresponding numbers were 16/7/2 (46).

12.1.4 Summary

Angular SiC: But for one animal study, showing severe inflammation and fibrosis in the lungs (135), there is no evidence that exposure to angular SiC induces more than cellular inflammatory reactions (15, 25, 27, 28, 62). One study, however, showed a variation in inflammatory potency between different angular SiCs (25).

Fibrous SiC: For comparison, amosite and crocidolite asbestos were included in animal studies on effects of SiC whiskers. It was shown in most of these that the inflammatory, fibrogenic and carcinogenic effects of SiC whiskers are of

comparable magnitude to those of amphibole [1] asbestos (2, 15, 46, 87, 111, 159, 172).

12.2 Human studies

SiC production workers are exposed to a mixture of dusts and gases, many of these potentially detrimental to worker's health. The observed health effects in these workers are lung cancer, obstructive lung diseases and lung fibrosis/ pneumoconiosis. Some attempts have been made to examine the effects of specific exposure factors (32, 33, 143), but due to a high degree of coexistence between the various exposure factors, the results were ambiguous and give only limited information on the relationship between the different exposures and effects in humans.

12.2.1 Lung fibrosis/pneumoconiosis

The study of Dufresne *et al.* points in direction of an association between SiC fibre exposure and development of lung fibrosis. The researchers studied the fibrous inorganic content of post-mortem lung material from 15 men who had worked 23–32 years in different parts of the SiC production. Of these men, 5 had neither lung fibrosis nor lung cancer, 6 had lung fibrosis, and 4 had lung fibrosis and lung cancer. Concentrations of SiC fibres and other fibrous minerals and angular particles in the lungs were determined by TEM and energy dispersive spectroscopy. Higher concentrations of SiC fibres, ferrugineous bodies and angular particles containing elemental silicon (Si) were found in the lungs from workers with lung fibrosis (with or without lung cancer) than from workers without these diseases (53).

12.2.2 Lung cancer

Bugge *et al.* studied the associations between several exposure factors in the SiC production industry and the risk of lung cancer. Whereas cristobalite (crystalline silica) exposure had the largest impact on lung cancer development, an association with SiC fibres still existed after adjustment for cristobalite. Exposure to angular SiC was not associated with lung cancer, when adjusted for other exposures (33). Although quantitative exposure estimates were used and a lot of dust sampling was performed in order to get detailed information about exposures, the estimates for the earlier years of production relied on advanced mathematical modelling and assumptions of the effect of production changes. Hence, the human studies provide no good basis for dose-effect estimations.

12.2.3 Obstructive lung diseases

Obstructive lung diseases in the SiC industry have been studied on several occasions, and an increased risk is observed with increasing exposure to total dust.

[1] Amphibole asbestos fibres are rod- or needle-shaped and include amosite, crocidolite, tremolite, anthophyllite and actinolite (UK Health Protection Agency, https://www.gov.uk/government).

Johnsen *et al.* calculated that in an employee of mean height (1.79 m) and with an average total dust exposure of 1.4 mg/m^3 in Norwegian SiC plants the estimated isolated contribution from dust exposure to the annual decline in FEV_1 was 10.4 ml, whereas the isolated contribution from smoking was 6.1 ml (84). In a study of mortality from obstructive lung diseases, multivariate analyses showed an effect of angular SiC within the first 15 years of exposure, whereas cristobalite (crystalline silica) seemed to be a more important exposure factor among those with longer employment than 15 years (32).

13. Previous evaluations by national and international bodies

American Conference of Governmental Industrial Hygienists (ACGIH) 2003
ACGIH concluded that *non-fibrous* forms of SiC have a very low toxicity in humans and experimental animals. The threshold limit value – time-weighted average (TLV-TWA) for non-fibrous forms was, therefore, set at 10 mg/m^3 for inhalable particles and 3 mg/m^3 for respirable particles.

As regards SiC *fibres*, ACGIH stated that the human clinical and epidemiologic data, combined with animal experimental data, indicate that SiC fibres can cause lung fibrosis, cancer and possibly mesothelioma. It was further stated that animal data indicate that the toxicity of SiC fibres is similar to crocidolite asbestos on a fibre-to-fibre basis. Thus, the health risks from exposures to SiC fibres should be considered of the same magnitude as those caused by crocidolite asbestos and exposure to airborne SiC fibres should therefore be limited to the level set for crocidolite asbestos, namely, a TLV-TWA of 0.1 fibre/cm^3. The carcinogen designation of A2, Suspected Human Carcinogen, was recommended for fibrous forms.

There were no data upon which to base skin or sensitiser (SEN) notations or recommend a TLV-STEL (short-term exposure limit) (1).

German Research Foundation (DFG) 1997, fibrous SiC
The MAK Commission referred to data showing that two samples of SiC whiskers produced marked and dose-dependent increases in the tumour incidence in rats after administration by the intratracheal, intraperitoneal or intrapleural routes. The carcinogenic potency of SiC fibres appeared to be high since increased tumour incidences were produced even by small numbers of critical fibres. It was further stated that one of these samples showed cell transforming activity *in vitro* in mesothelial cells from the rat diaphragm and pulmonary epithelial cells from the hamster.

It was concluded that the studies with intratracheal, intraperitoneal or intra-pleural administration revealed clear evidence of a marked carcinogenic activity of SiC fibres in experimental animals and that these results were in accordance with the cell transforming activity demonstrated *in vitro*.

SiC fibrous dust was therefore to be handled like those fibrous dusts classified as “Substances that are considered to be carcinogenic for man because sufficient

data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can contribute to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of *in vitro* tests and short-term animal studies" (category IIIA2, i.e. present category 2) (47).

German Research Foundation (DFG) 2013, fibre-free SiC

The MAK Commission regarded fibre-free SiC to be a granular biopersistent dust. Based on the available data, in particular the *in vitro* data, it was not considered clear whether SiC dust has substance-specific effects beyond the general particle effects. Several studies among employees in the SiC industry indicate a fibrotic effect of SiC particles.

The present epidemiological studies on workers in the SiC production were regarded unsuitable for assessing the carcinogenic effects of fibre-free SiC because exposure was to a mixture of fibres and particles.

In a rat carcinogenicity study by intraperitoneal application, particulate SiC induced no mesotheliomas. Data to assess the carcinogenic effects were considered limited.

Overall, it was concluded that human experience and animal studies that are appropriate for deriving a MAK value were not present and an assignment to a maximum limitation category omitted.

It was further stated that SiC is water insoluble and dermal absorption therefore unlikely. Thus, fibre-free SiC was not marked with "H".

No data were available for evaluation of sensitisation or teratogenicity (48).

Health Council of the Netherlands: Evaluation of the carcinogenicity and genotoxicity 2012

The Committee concluded that fibrous SiC (fibres, whiskers) may cause cancer according to a non-stochastic mechanism and should be classified as "carcinogenic to humans" (category 1A). The data on the angular form of SiC were considered insufficient to classify the carcinogenic properties of this substance (category 3). The Committee was concerned about the question whether the commercial angular SiC is sufficiently free of fibrous SiC (75).

International Agency for Research on Cancer (IARC) 2017, SiC whiskers and fibres

Occupational exposures associated with the Acheson process were classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that they cause lung cancer. Since the correlation between exposures to SiC fibres and cristobalite made it difficult to disentangle their independent effects, the Working Group concluded that fibrous SiC is possibly carcinogenic to humans (Group 2B) based on limited evidence in humans that it causes lung cancer. No data on cancer in humans exposed to SiC whiskers were available. In experimental animals, there was sufficient evidence for the carcinogenicity of SiC whiskers.

Although not unanimous, the Working Group classified SiC whiskers as probably carcinogenic to humans (Group 2A). It was stated that SiC whiskers are monocrystalline and homogeneous in form, while fibrous SiC is mostly polycrystalline and heterogeneous in form. The physico-chemical characteristics of these fibres were considered to be distinct. The majority of the Working Group therefore considered that the differences in the nature of SiC fibres and SiC whiskers warranted separate evaluations (78).

14. Evaluation of human health risks

14.1 Assessment of health risks

In this document, the health risks from SiC are assessed separately according to the two main morphological types:

1) angular SiC (crystalline, non-fibrous particles)
2) fibrous SiC (polycrystalline fibres and single crystalline whiskers) [2].

Available human studies are from the production industry where exposures to angular SiC and unintentionally formed polycrystalline SiC fibres occur simultaneously and in mixture with other contaminants (such as crystalline silica) in the working atmosphere. These combined exposures complicate the assessments of exposures and outcomes. There are no human studies on manufactured SiC whiskers.

No reports on dermal uptake were identified**,** however, significant dermal uptake of SiC is considered unlikely.

14.1.1 Angular SiC

One intratracheal study using guinea pigs showed pulmonary inflammation and fibrosis, increasing with the observation time up to 100 days (135) and another intratracheal study in rats showed some cellular inflammatory reactions (25). On the other hand, one 2-week inhalation study in rats (27), supported by three intratracheal instillation studies in rodents and sheep (15, 28, 62), implied that the lungs exposed to angular SiC were practically without inflammatory or other histopathological changes.

In the production industry, increased mortality from obstructive lung diseases was associated with exposure to angular SiC (32) and reduced lung function (FEV_1) with exposure to total dust (84). There is uncertainty whether the observed effects were actually caused by angular SiC or by other exposures in the working environment. Consequently, these studies cannot be used as a scientific basis for OEL setting.

Overall, angular SiC should be considered a poorly soluble, low toxicity (PSLT) dust. This term has been used for biopersistent, low toxic particles, which may

[2] Polycrystalline SiC fibres are formed unintentionally (pollutant) during the Acheson production of angular SiC, whereas single crystalline whiskers are manufactured for specific purposes.

confer inflammation, fibrosis and cancer, primarily due to long standing interaction with cells and tissues after high exposure of the lungs in experimental animals (41, 44). As reviewed by US NIOSH, TiO_2 and other PSLT particles of fine and ultrafine sizes show a consistent dose-response relationship for adverse pulmonary responses in rats, including persistent pulmonary inflammation and lung tumours, when dose is expressed as particle surface area (166).

14.1.2 Fibrous SiC

Almost all animal studies have been performed on SiC whiskers.

14.1.2.1 SiC whiskers

SiC whiskers have been shown to cause inflammation, fibrosis, lung cancer and mesothelioma. Single intratracheal instillations of 2 or 3.5 mg SiC whiskers in rats observed for up to 6 months gave transient inflammatory effects (72, 122, 123), whereas animals receiving 2 mg of quartz or crocidolite asbestos showed a more extensive and progressive inflammatory reaction (122). At a single intratracheal dose of 10 mg of SiC whiskers, inflammatory responses, and collagen deposits (fibrosis) remained after 6 months but did not progress during the latter half of this observation period (123).

Inhalation exposure of rats to 98 SiC whiskers/ml for one year caused inflammatory and severe fibrotic changes (5). Inhalation exposure of rats to 1 000 SiC whiskers/ml (mean diameter 0.45 µm and lengths 63% 5–10 µm and 10% > 20 µm) for one year resulted in fibrotic changes similar to those produced by an equivalent fibre number concentration of amosite asbestos although SiC exposure produced a higher incidence of mesotheliomas and the number of lung tumours was higher in the amosite exposed group (46). Rats exposed to 500, 1 500 or 7 500 fibres/ml of SiC whiskers by inhalation for 13 weeks exhibited dose-related inflammatory and fibrotic changes in the lung tissue 26 weeks post-exposure (98).

In two intraperitoneal injection studies in rats, SiC whiskers were compared with asbestos. One study showed a carcinogenicity 2.4 times that of chrysotile asbestos on a mass basis, with all SiC whiskers exposed rats developing mesothelioma within one year (mean diameter and length 0.30 µm and 6.4 µm; 10 mg) (2). In the other study (10^9 fibres > 5 µm long; 14.2 mg of SiC and 6.1 mg of asbestos) the number of mesotheliomas was similar in the two groups, but the median survival time in the SiC whisker group was half that of amosite asbestos exposed animals (46, 111).

Intrapleural inoculation studies in rats revealed a similar or greater potency of SiC whiskers to induce mesothelioma than amphibole asbestos after administration of equivalent doses by mass (87, 159).

The results above are in accordance with the fibre paradigm stating that long thin durable fibres may be fibrogenic and tumourigenic (159).

There are no human data on exposures and effects in the production and user industry of SiC whiskers.

14.1.2.2 Polycrystalline SiC fibres

Epidemiological data from the SiC production industry suggest an association between exposure to pollutant (unintentionally formed) SiC fibres and pneumoconiosis, lung cancer and obstructive lung diseases, after evaluating the role of other pathogenic co-exposures such as crystalline silica (quartz and cristobalite) (32, 33). No increased risk of mesothelioma compared to the general population has been shown (34). The power to detect mesotheliomas was however low, due to small numbers of exposed and cases. Overall the human data support an association between exposure to SiC fibres and increased risk for lung disease, but there are no data on dose-response relationships to be used as a scientific basis for the OEL setting.

14.1.2.3 Conclusion fibrous SiC

Although in several aspects different, many morphological features are shared between manufactured single crystalline SiC whiskers and polycrystalline SiC fibres formed unintentionally during the Acheson furnace process. Based on analogies, and given sparse experimental evidence from SiC fibres, NEG proposes to use the experimental findings from SiC whiskers as a basis for the evaluation of SiC fibres.

Although there are differences in chemical composition, crystallinity and the ability to break transversely, important characteristics such as dimensions and biopersistence in tissues are similar between SiC whiskers and amphibole asbestos fibres. They also share common toxicological properties such as the ability to induce pulmonary inflammation, fibrosis, lung cancer and mesothelioma in experimental animals. By analogy and supported by results from animal studies, the potency of SiC whiskers to cause adverse health effects should be considered comparable to that of amphibole asbestos on a fibre-to-fibre basis.

Clearly, it is a simplification to equate these fibre types, which is nevertheless proposed due to limited experimental and epidemiological evidence. Different asbestos fibres have inherently different toxicological potencies and effects but are still equated by most regulatory authorities; animal studies have shown that also different SiC whiskers have different toxicological properties, and that morphological features (size and shape) explain only partly the differences. NEG considers the similarities among these fibre structures to be more important than the differences in a preventive context.

In summary, the potency of SiC whiskers and polycrystalline SiC fibres to cause health effects from occupational exposures are considered comparable to that of amphibole asbestos on a fibre number concentration basis.

14.2 Groups at extra risk

The known health effects from manufactured SiC whiskers in animal studies are pulmonary inflammation, pulmonary fibrosis, lung carcinoma and mesothelioma development. Tobacco smoking is known to induce pulmonary inflammation, fibrosis and lung cancer, and it is plausible that the combined effect of tobacco

smoke and SiC whisker exposure will increase these risks. Pre-exposure to cigarette smoke increased the epithelial uptake of fibrous SiC, but not that of angular SiC, in tracheal explants from rats (90). However, no animal data were found on the combined effect of fibrous SiC and tobacco smoke on obstructive lung diseases, fibrosis or lung cancer.

Concerning human data, smokers in the SiC production industry had a steeper fall in FEV_1 than non-smokers (84). In addition, the increase in lung cancer incidence among SiC production workers was observed nearly exclusively among smokers (34).

The statistical interaction between asbestos and tobacco smoking was reviewed in two recent meta-analysis. In one of the reviews, the results pointed to synergism between exposure to asbestos and cigarette smoking (120), whereas the results from the other review were less clear (59). The potentially synergistic health effects of asbestos fibre exposure and tobacco smoke may, by analogy, apply also for fibrous SiC.

14.3 Scientific basis for an occupational exposure limit

From a health effect perspective it is expedient to operate with two major forms of SiC: the non-fibrous (angular) form and the fibrous form (polycrystalline SiC fibres and single crystalline SiC whiskers).

For angular SiC, the physico-chemical properties supported by experimental data indicate that it should be considered a poorly soluble, low toxicity (PSLT) dust. Inflammatory responses and fibrosis, analogous with effects shown by other PSLT dusts, have been shown in some experimental studies at high doses. The pulmonary effects may be related to surface area rather than to mass.

As regards fibrous SiC, many morphological features are shared between SiC polycrystalline fibres and SiC whiskers. NEG therefore proposes to use the experimental findings from SiC whiskers as a basis for the evaluation of SiC fibres. Further, SiC whiskers and amphibole asbestos display many similarities in physico-chemical characteristics and in biological effects (inflammation, fibrosis, lung cancer and mesothelioma) induced in experimental animals. By analogy, and supported by results from animal studies, polycrystalline SiC fibres and SiC whiskers should be considered to be equally potent as amphibole asbestos fibres on a fibre number concentration basis.

In conclusion, for OEL setting, NEG considers

1) angular SiC to be a PSLT dust [3],
2) fibrous SiC to be equally potent as amphibole asbestos.

[3] For recommended exposure limits for PSLT dusts, see Appendix 1.

15. Research needs

Exposure to particles and fibres with inflammatory properties has been associated with increased risk of cardiovascular diseases. Possible cardiovascular effects of SiC should be surveyed in epidemiological studies, preferably supplemented by animal studies.

Further mechanistic studies would be helpful to explain the effects of SiC. In particular, the toxicological effects of different size fractions of SiC, among these nanosized particles, should be studied further *in vivo* and *in vitro*.

Characterisation of exposures is needed e.g. among downstream users, in the production of SiC whiskers, and regarding nanosized SiC.

16. Summary

Bugge M, Skaug V, Bye E. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 150. Silicon carbide. Arbete och Hälsa 2018;52(1):1–96.

Silicon carbide (SiC) is a rare naturally occurring mineral, but manufactured industrially at a large scale. SiC may exist in non-fibrous (angular) and fibrous forms (polycrystalline fibres and single crystal whiskers). It may also appear as cleavage fragments, platelets and in amorphous form, and in a large range of particles sizes.

Angular SiC is produced mainly for use as abrasives and cutting devices, but also as a refractory product, in ceramic applications, in heating elements, electronic devices, and in composites and metallurgy. Polycrystalline SiC fibres are formed unintentionally during the production of angular SiC. SiC whiskers are manufactured for specific use such as strengthening of composite materials and in electronic components. SiC nanoparticles are increasingly being produced.

Nearly all epidemiological studies on SiC have been performed in the SiC production industry where workers have been exposed to a mixture of angular SiC, SiC fibres, quartz, cristobalite and other dusts and gases. Adverse health outcomes in the respiratory system are lung fibrosis, obstructive lung diseases and lung cancer. Due to the mixed and complex exposures, the human data cannot be used for assessing exposure-response relationships for angular SiC and polycrystalline SiC fibres. There are no human data on the health effects of SiC whiskers.

Angular SiC: Some animal and *in vitro* studies indicate a slight inflammatory activity, but most studies conclude that the toxicity is low. There are no experimental data to identify dose-response relationships. The physico-chemical properties indicate that angular SiC should be considered to confer similar toxicity as other poorly soluble, low toxicity (PSLT) dusts. Data from other PSLT dusts indicate that the effects may be related to particle surface area rather than to mass.

Fibrous SiC: SiC whiskers induce inflammation and fibrosis in the lungs of rats and mice after intratracheal instillation and inhalation. In life-long studies with SiC whiskers, rats develop local mesotheliomas after inhalation and intrapleural and intraperitoneal injection, in accordance with the fibre paradigm stating that long thin durable fibres may be fibrogenic and tumourigenic. The inflammatory, fibrogenic and carcinogenic effects observed in experimental animals exposed to SiC whiskers are comparable to those of amphibole asbestos fibres. For the setting of occupational exposure limits (OELs), considering the similarities in morphology, biopersistence and effects in experimental animals, SiC whiskers and polycrystalline SiC fibres should be considered to be equally potent in humans as amphibole asbestos fibres.

Keywords: carborundum, inflammation, lung cancer, lung fibrosis, obstructive lung diseases, occupational exposure limit, review, risk assessment, SiC, silicon carbide, toxicity.

17. Summary in Norwegian

Bugge M, Skaug V, Bye E. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 150. Silicon carbide. Arbete och Hälsa 2018;52(1):1–96.

Silisiumkarbid (SiC) forekommer sjelden i naturen, men produseres industrielt i stor skala. SiC kan eksistere i ikke-fibrøse (angulære) og fibrøse former (polykrystallinske fibrer og enkeltkrystallinske whiskers). SiC kan også foreligge som kløvfragmenter, små flak, i amorf form, og i et stort spekter av partikkelstørrelser.

Angulær SiC produseres hovedsakelig for bruk som slipe- og skjæremiddel, men også som et ildfast produkt, i keramiske anvendelser, i varmeelementer, elektronisk utstyr, og i kompositter og metallurgi. Polykrystallinske SiC-fibrer dannes utilsiktet under produksjon av angulær SiC. SiC whiskers produseres for andre formål, som for eksempel styrking av kompositttmaterialer og i elektroniske komponenter. SiC nanopartikler blir stadig mer brukt.

Nesten alle epidemiologiske studier av SiC er utført i SiC-produksjonsindustrien, hvor arbeiderne har vært eksponert for en blanding av angulær SiC, fibrøs SiC, kvarts, kristobalitt og andre typer støv og gasser. Alvorlige helseutfall i luftveiene er lungefibrose, obstruktive lungesykdommer og lungekreft. På grunn av blandingseksponeringer kan humane data ikke benyttes til å vurdere eksponeringsresponsrelasjoner for angulær SiC og polykrystallinske SiC-fibrer. Det finnes ingen humane data om helseeffekter av SiC whiskers.

Angulær SiC: Noen dyrestudier og *in vitro*-studier indikerer en lett inflammatorisk aktivitet, men de fleste studier konkluderer med at toksisiteten er lav. Det finnes ingen eksperimentelle data for å identifisere dose-respons-forhold. De fysisk-kjemiske egenskapene indikerer at angulær SiC bør antas å gi tilsvarende toksisitet som andre dårlig løselige, lav-toksiske (PSLT) støvtyper. Data fra andre PSLT-støvtyper indikerer at effekten kan være relatert til partikkeloverflateareal mer enn til vekt.

Fibrøs SiC: SiC whiskers induserer inflammasjon og fibrose i lunger hos rotter og mus etter intratrakeal instillasjon og i inhalasjonsstudier. I livslange studier med SiC whiskers utvikler rotter lokale mesoteliomer etter inhalasjon og intrapleural og intraperitoneal injeksjon, i overensstemmelse med fiberparadigmet som fastslår at lange, tynne, varige fibrer kan være fibrogene og tumorigene. De inflammatoriske, fibrogene og karsinogene effekter observert i forsøksdyr eksponert for SiC whiskers er sammenlignbare med effektene av amfibol-asbestfibrer. Ved fastsettelse av grenseverdi, hensyntatt likheter i morfologi, biopersistens og effekter i forsøksdyr, bør SiC whiskers og polykrystallinske SiC-fibrer vurderes som like potente i mennesker som amfibolasbestfibrer.

Nøkkelord: inflammasjon, karborundum, litteraturgjennomgang, lungefibrose, lungekreft, obstruktive lungesykdommer, risikovurdering, SiC, silisiumkarbid, grenseverdier, toksisitet, yrkeseksponering.

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19. Data bases used in search of literature

In the search for literature the following data bases were used:

Chemical abstracts
HSELINE
Medline
NIOSHTIC
Toxline

Last search was performed in October 2016.

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Appendix 1. Occupational exposure limits

Country	8-hour TWA	Substance	Note	Ref.
Non-fibrous SiC	*mg/m³*			
Belgium	10	SiC	–	1
Canada (Ontario)	10 (inh.) 3 (resp.)	SiC (non-fibrous)	–	2
Denmark	10 (total) 5 (resp.)	Inorganic dust	–	3
European Union	–	–	–	4
Finland	10 (inh.)	Inorganic dust	–	5
Germany (DFG)	– [a]	SiC (without fibres)	–	6
Norway	0.5 (resp.)	Dust in the SiC industry [b]	–	7
Sweden	10 (inh.) 5 (resp.)	Inorganic dust	–	8
United Kingdom	10 (total inh.) 4 (resp.)	SiC (not whiskers)	–	9
US (ACGIH)	10 (inh.) 3 (resp.)	SiC (non-fibrous)	–	10
US (NIOSH)	10 (total) [c] 5 (resp.) [c]	SiC (non-fibrous)	–	11
US (OSHA)	15 (total) 5 (resp.)	SiC (non-fibrous)	–	12
Fibrous SiC	*fibres/ml*			
Belgium	0.1 (resp.)	SiC fibres (incl. whiskers)	–	1
Canada (Ontario)	0.1 (resp.)	SiC (fibrous; incl. whiskers)	–	2
Denmark	–	–	–	3
European Union	–	–	–	4
Finland	0.1	SiC fibres	–	5
Germany (DFG)	–	SiC (fibrous dust)	C	6
Norway	0.1	SiC fibres	C	7
Sweden	0.2 (resp.)	SiC fibres	M	8
United Kingdom	1 (5 mg/m³)	Refractory ceramic fibres (incl. SiC)	C	9
US (ACGIH)	0.1 (resp.)	SiC (fibrous; incl. whiskers)	C [d]	10
US (NIOSH)	–	–	–	11
US (OSHA)	–	–	–	12
PSLT dust	*mg/m³*			
Germany (DFG)	0.3 (resp.)	Biopersistent granular dust (with the exception of ultrafine particles) at a material density of 1 g/m³. [e]		13
US (NIOSH)	2.4 (resp.) [c, f] 0.3 (resp.) [c, f]	Fine TiO_2 Ultrafine (incl. engineered nanoscale) TiO_2.		14

[a] Insufficient information for the establishment of MAK values.
[b] Respirable dust in the silicon carbide industry (in furnace hall or related departments).
[c] 10-hour TWA.
[d] Suspected human carcinogen.
[e] Equivalent e.g. to 1.3 mg/m³ for TiO_2 (0.3×4.23 g/cm³) .
[f] Recommendation. Represent levels that over a working lifetime are estimated to reduce risks of lung cancer to below 1 in 1 000.

ACGIH: American Conference of Governmental Industrial Hygienists, C: carcinogen, DFG: Deutsche Forschungsgemeinschaft, inh.: inhalable fraction, MAK: Maximale Arbeitsplatz-konzentration, M: medical control, NIOSH: National Institute for Occupational Safety and Health, OSHA: Occupational Safety and Health Administration, PSLT: poorly soluble, low toxicity, resp.: respirable fraction, SiC: silicon carbide, TWA: time-weighted average, US: United States.

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Appendix 2. Previous NEG criteria documents

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D
Diesel exhaust	1993:34, 1993:35*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*

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Substance/Agent	Arbete och Hälsa issue
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

*: In English, remaining documents are in a Scandinavian language.
D: Collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: Collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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