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Silicon carbide (fibre dust) (including whiskers)

MAK Value Documentation, addendum – Translation of the German version from 2020

A. Hartwig[1,*] MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

silicon carbide; fibres; lung; carcinogenicity; whisker; genotoxicity; toxicity; pulmonary function; mechanism of action

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and re-evaluated the data for silicon carbide fibres [409-21-2] considering all toxicological end points. Silicon carbide fibres induce mesotheliomas and lung tumours in rats and hamsters. These studies provide evidence for the carcinogenic potential of silicon carbide fibres. As the epidemiological studies have methodological shortcomings such as an inadequate characterisation of exposure and consideration of confounders, a cancer risk for humans associated with exposure to silicon carbide fibres cannot be derived. Therefore, silicon carbide fibres remain classified in Carcinogen Category 2. Silicon carbide fibres are not regarded as germ cell mutagens. Silicon carbide fibres are not taken up via the skin in toxicologically relevant amounts. There are no studies of sensitization.

Citation Note:
Hartwig A, MAK Commission. Silicon carbide (fibre dust) (including whiskers). MAK Value Documentation, addendum – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2024 Mar;9(1):Doc012. https://doi.org/10.34865/mb40921e9_1ad

Manuscript completed:
23 Mar 2019

Publication date:
28 Mar 2024

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MAK value	–
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity (1993)	**Category 2**
Prenatal toxicity	–
Germ cell mutagenicity	–

Synonyms	carborundeum carborundum
Chemical name	silicon carbide
CAS number	409-21-2
Molecular formula	SiC
Melting point	> 2300 °C (IFA 2019) 3070 °C: decomposition and sublimation
Density	3.21 g/cm^3 (IFA 2019)
Hardness (according to Mohs)	9.6
Crystal class/structure	hexagonal, rhombic

Since the publication of the last documentation for fibrous dust in 1993 (Greim 1997) a large number of studies for silicon carbide fibres have become available that have made a re-evaluation necessary.

1 General Characteristics

1.1 Source

Silicon carbide occurs naturally as the very rare mineral moissanite. It forms under high pressure and high temperatures, for example within the Earth's mantle and as a result of the impact of meteorites. Moissanite is thus found in meteorite craters, a number of volcanoes and in diamond mines (see documentation "Siliciumcarbid (faserfrei)", available in German only (Henschler 1987)).

1.2 Production and uses

The silicon carbide used for technical purposes is produced synthetically. The raw materials are: sand, petroleum coke and carbosilanes containing chlorine (chemical vapour deposition (CVD) see below) (IFA 2019).

1.2.1 Production/processing

1.2.1.1 Acheson process

A mixture of sand and petroleum coke is introduced into a round basin containing a central graphite electrode. The mixture is placed under high voltage, forming silicon carbide and carbon monoxide through the application of electrical

current ($SiO_2 + 3\ C \longrightarrow SiC + 2\ CO$). The product of this reaction is α-silicon carbide, which is made up of (spherical) particles and contains small amounts of silicon carbide fibres (Henschler 1987).

- The silicon carbide fibres generated from the Acheson process are unwanted, but unavoidable by-products (Bye et al. 1985), which are present in the air in all work areas involved in production (Skogstad et al. 2006).
- These work areas include:
  i. areas for mixing the raw materials. One source of silicon carbide fibres are materials that did not completely react during earlier Acheson processes and were admixed again
  ii. the furnace area
  iii. the product crushing and sorting area
- Silicon carbide fibres are heterogeneous and polycrystalline (unlike the monocrystalline silicon carbide whiskers; see below).
- At least 7 morphological subpopulations (categories specified) were described; these were collected at 3 Norwegian plants by personal air sampling at the sites specified below and were differentiated from each other by scanning electron microscopy (SEM) (Skogstad et al. 2006). In addition, complex structures, for example branched fibres with up to 9 branches, occurred in all categories listed below (Gunnæs et al. 2005; Skogstad et al. 2006).

Also, the frequency (%) of the morphologically characterized fibre categories was determined. The frequencies are mean values of the air samples that were obtained from the 3 Norwegian plants:

- Category 1 (14%): straight or bent forms; the fibres resembled a stack of discs, mostly perpendicular to the fibre axis; some fibres were only partially covered by discs, revealing a central core
- Category 2 (11%): straight fibres with variable diameters; some of the fibres were wide in diameter, others very narrow with a diameter (0.07 µm) just within the visibility limit for SEM technology
- Category 3 (6.6%): straight, in most cases smooth fibres with spikes or bumps on their surface
- Category 4 (52%): straight, smooth and in most cases tapered fibres with a club-like structure at one end. The Category 4 fibres reached the visibility limit of SEM technology. More than half of the examined fibres were classified in this category.
- Category 5 (7.7%): the forms resembled the fibres in Categories 3 and 4, but the surface was more irregular
- Category 6 (0.96%): these fibres had a hexagonal cross section, without stacks of discs (see Category 1), but with transverse folds
- Category 7 (0.4%): these forms occurred rarely and had an angular cross-sectional shape with distinct steps along the longitudinal axis
- Category 8 (0.04%): fibres that could not be classified in Categories 1–7
- Fragments corresponding to the WHO fibre definition (diameter (D) < 3 µm; length (L) > 5 µm; L/D > 3:1); formed when the raw material was milled to achieve the particle size required for the respective application (1.7%)
- Fibres with a branched morphology consisting of a varying number of branches and different angles of branching were observed in all categories (Gunnæs et al. 2005), but predominantly in Categories 1 and 3 (9.4%) (Skogstad et al. 2006)

1.2.1.2 Chemical vapour deposition (CVD)

In this process, gaseous carbosilanes that contain chlorine are deposited on hot surfaces at high temperatures, where they are cracked into silicon carbide and HCl to produce β-silicon carbide (IARC 2017).

1.2.1.3 PTV-modified Lely method, particle tracking velocimetry (PTV)

Monocrystalline silicon carbide is generated by CVD epitaxy (growth of a new crystal species on the surface of an existing crystal species) or by the sublimation of polycrystalline silicon carbide in a temperature gradient (IARC 2017).

1.2.2 Areas of use

Silicon carbide has a wide range of applications because of its semiconducting properties, hardness, thermal and chemical stability and relatively low manufacturing costs. Granular or powdered silicon carbide products are used as grinding and polishing abrasives (also in the optical industry). Open porous silicon carbide ceramics are used for abrasive wheels and grinding stones. On account of their high thermal stability, silicon carbide stones are used as a lining for blast furnaces and waste incinerators and as cooling bricks in foundry technology and in ferrous and non-ferrous metallurgical furnaces. Silicon carbide moulds are used in the porcelain industry, for example as plate stackers during the firing process. Dense silicon carbide ceramics are used as fibre composites, for example as components of plain bearings. Porous and gas-permeable silicon carbide materials are used in soot traps for engines.

1.3 Exposure at the workplace

Most of the available data were obtained from workplaces with exposure to both fibrous and particulate silicon carbide.

Occupational exposure to dusts containing silicon carbide fibres is most likely to occur in the manufacturing and application industries and affects all workers who come into direct contact with the material, for example production workers, mechanics, packers and the plant cleaning staff. The exposure levels may vary widely within an individual plant (depending on the workplace) and between plants.

Fibre concentrations of 0.07 to 2.40 fibres/ml were determined in a plant in Italy (Scansetti et al. 1992).

The fibre dust levels determined in samples from 3 Norwegian plants were between 0.034 and 3.7 fibres/ml (Føreland et al. 2008).

Another study identified 8 different types of fibres in the Norwegian silicon carbide industry. The fibres with the dimensions $L > 8$ µm and $D \leq 0.25$ µm, which are associated with the highest tumour risk, made up 15% of the fibres collected in this industry (Skogstad et al. 2006).

A Canadian study reported fibre dust levels of 0.51 to 0.63 fibres/ml; these values were thus lower than those determined in the Italian or Norwegian plants (Dion et al. 2005).

2 Toxic Effects and Mode of Action

See the 2018 supplement “Fibrous dusts, inorganic” (Hartwig and MAK Commission 2019).

3 Mechanism of Action

Various types of silicon carbide were identified in an analysis of the exhaled air at workplaces involved in the Acheson process: the main fraction consisted of silicon carbide microparticles; silicon carbide fibres, quartz, carbon, etc. were also found. Lung biopsies of workers revealed large amounts of silicon carbide particles in the alveoli. They induced interstitial fibrosis and increased the incidence of pneumoconiosis (Dufresne et al. 1992; Funahashi et al. 1984).

The following effects were observed when silicon carbide fibres were administered in vivo: inflammation of the lungs, an increase in the number of alveolar macrophages, increased proliferation of epithelial and interstitial cells in the lungs (Cullen et al. 1997), the formation of granulomas (Vaughan et al. 1993), broncho-alveolar hyperplasia and marked fibrotic changes (Akiyama et al. 2007) and carcinogenicity (whiskers only; Adachi et al. 2001; Rödelsperger and Brückel 2006).

The following effects were induced by silicon carbide fibres in vitro: the release of large amounts of reactive oxygen species (ROS), cytotoxicity resulting from the disruption of cell membranes (Svensson et al. 1997; Vaughan et al. 1991), effects that are often associated with malignant transformation, such as reduced cell-doubling time, an increase in DNA

synthesis and a loss of growth control (Vaughan et al. 1991) and genotoxicity (Svensson et al. 1997; Wang et al. 1999; see Section 6.6.1). In addition, silicon carbide fibres stimulated the synthesis of pro-inflammatory cytokines, particularly multifunctional TNF-α (Cullen et al. 1997).

All studies showed that the biological activity of the silicon carbide fibres was more pronounced than that of the isotropic silicon carbide particles (Svensson et al. 1997).

To characterize the chemical and biological properties of silicon carbide material, Boudard et al. (2014) extensively studied individual chemical and cell-biological effects. They tested 5 different fibre particle fractions of silicon carbide originating from workplaces involved in the Acheson process. The cell model used macrophages of the RAW 264.7 cell line. The release of $HO^{\bullet}$ and $COO^{\bullet-}$ radicals was the only finding investigated in a cell-free system. The chemical and biological effects that were observed were compared with the physico-chemical properties of the particles. They were of different size ("coarse" or "fine") with a surface layer of iron ions that varied in density.

Three mechanistically important parameters were identified as being mainly responsible for the biological effects in vitro: particle size, iron ions on the particle surface and the surface oxidation. In addition to these structural elements, the morphology of the particles and their chemical composition were of relevance.

- Particle size is the main factor influencing the formation of H_2O_2; in macrophages, small particles induced more severe oxidative stress than larger ones. However, larger particles released more $HO^{\bullet}$ and $COO^{\bullet-}$ radicals than small particles. The authors suggested that this may be due to the higher levels of catalytic iron in the larger particles.
- Impurities of metallic iron on the particle surface stimulated the formation and activation of the pro-inflammatory cytokines TNF-α-R1 or TNF-α-R2 and of the nuclear transcription factor NF-κB via various other intermediate steps.
- Thermal treatment (650–1400 °C) changed the oxidation state. An increase in pre-treatment temperature was associated with a decrease in macrophage TNF-α production, whereas the production of $HO^{\bullet}$ and $COO^{\bullet-}$ radicals increased in correlation with the formation of a surface layer of crystalline silicon dioxide. Cytotoxicity increased with the pre-treatment temperature.

As was described above, not only material chemistry, but also shape and particle size are decisive for the effects caused by the silicon carbide particles because the latter 2 parameters regulate phagocytosis by macrophages and the penetration into the pulmonary epithelial cells and the interstitium. This is particularly true for silicon carbide fibres.

It can be assumed that alveolar macrophages are not able to absorb silicon carbide fibres because of their bulky structures. As a result, the fibres cannot be removed and they remain at the site of deposition for a long time, causing biological damage. In a study of Miller et al. (1999 b), rats were given silicon carbide fibres by intraperitoneal injection; 8% were of the branched type. The authors observed that mesotheliomas developed sooner and became larger than those caused by the fibres used for comparison, such as amosite.

3.1 Silicon carbide whiskers

A fundamental difference between silicon carbide whiskers and silicon carbide fibres is that whiskers are individual crystals (monocrystalline) and uniformly linear. By contrast, silicon carbide fibres are polycrystalline, heterogeneous and, in some cases, branched; the branches may differ widely in terms of their number, the branching angle and their length (Gunnæs et al. 2005). Silicon carbide whiskers are not unwanted by-products of the Acheson process, but are produced intentionally by the carbothermal reduction of quartz, for example in an argon/hydrogen atmosphere (Li et al. 2016). Exposure of workers may occur during the synthesis, mechanical treatment and the manufacture of composites. Silicon carbide whiskers have a large number of fibres, a large surface area and a high length/diameter ratio (average length: ≈ 10 µm; average diameter: ≈ 0.5 µm) in relation to their mass (IARC 2017). These parameters apply also to the more extensively studied asbestos and may therefore be included in the discussion of the mechanism of action of silicon carbide whiskers in analogy to asbestos fibres.

Further similarities to asbestos are:

- high biopersistence; long-term retention in the rat lungs depending on the size (Akiyama et al. 2007; Miller et al. 1999 b; Searl et al. 1999)
- oxidative stress; detected in vitro (Svensson et al. 1997)
- genotoxic effects, disturbance in cell division; detected both in vitro by determining the multinucleate giant cells containing large numbers of micronuclei and silicon carbide whiskers (Brooks et al. 1992) and in vivo (Gross et al. 1970)
- damage to lung cells; damage to V79 cells of Chinese hamsters, recorded as reduced cloning efficiency except for the low reference value of crocidolite (Svensson et al. 1997)
- pneumonia
- fibrotic changes; silicon carbide whiskers were detected in the lungs of workers who developed pneumoconiosis and were employed in the abrasive industry (Funahashi et al. 1984; Hayashi and Kajita 1988; Massé et al. 1988)
- induction of mesotheliomas in rats after intrapleural injection

Various types of silicon carbide whiskers were described (named SiCW1, SiCW2 and SiCW3 (Johnson et al. 1992)); they differed with regard to the percentage of fibres with a length > 5 µm (SiCW1: 31%, SiCW2: 93.7%, SiCW3: 30.8%) and induced pleural mesotheliomas of varying severity in rats (see Section 6.2.2; Johnson and Hahn 1996). The authors concluded from their results that the differences in the carcinogenicity induced by the 3 SiCW samples cannot be explained by differences in their fibre morphology alone; other properties such as surface chemistry are of relevance.

3.2 Summary

A number of publications carried out a comparison between silicon carbide fibres/whiskers and asbestos, which suggests itself for several reasons. The carcinogenicity induced by asbestos is promoted by the following effects: various types of DNA damage and chromosomal damage and their incomplete repair, oxidative stress, and inflammation accompanied by the activation of a large number of signal chains and numerous genes that mediate these inflammatory functions. Some of these molecular effects and tissue lesions that are associated with the formation of lung carcinomas and mesotheliomas in experimental animals are induced also by silicon carbide fibres/whiskers. These include the activation of NF-κB, the central regulator of pro-inflammatory genes and oxidative stress, genetic effects such as the induction of micronuclei and binuclear cells.

4 Toxicokinetics and Metabolism

A study was carried out to investigate the biological mechanisms of “carborundum pneumoconiosis”, a disease developed by workers who operated Acheson furnaces. The main finding of the study was that samples of test fibres that were thought to be homogeneous were actually heterogeneous in shape and dimension. Two different silicon carbide materials consisting of angular granular and fibrous products from the Acheson process were given to groups of 8 sheep by intratracheal injection. For this purpose, samples were taken of the fibre-like material found on the outside of the cylindrical lump following the removal of its outer layers. In order to disaggregate this material, which was still adherent to the surface, the sample was ground while being cooled with liquid nitrogen. The second fibrous sample of silicon carbide, which was collected from the crystalline centre of the lump, was also ground, then sieved, ground once again, and finally separated from the coarser residue using a 10-µm fine sieve. The shape and chemical composition of the silicon carbide samples were determined by electron microscopy (SEM and TEM) and X-ray diffraction. The granular sample contained the expected morphological types of particles. The particle size distribution was determined by a Coulter Counter and yielded a mean diameter of 0.92 µm. However, the fibrous sample included more than 5 different morphological types: isolated fibrils, aggregated fibrils, rectilinear needles, branched fibres, corrugated fibres, zig-zag fibres and 27% angular (granular) particles with sizes corresponding to a Poisson distribution. No attempt was made

to establish a particle size distribution because of the complexity of the fibre shapes. The authors simply reported that the large fibres were about 30 µm in length and 0.5 µm in diameter. The groups of 8 sheep received single injections of 100 mg of the granular or fibrous silicon carbide samples in 100 ml saline by bronchoscopy-guided catheterization. The site of administration was the tracheal lobe. Broncho-alveolar lavage (4 washes of 50 ml phosphate-buffered saline) was carried out after 2, 4, 6 and 8 months; only the last wash was used to analyse the silicon carbide particles. The animals were sacrificed after 8 months and 9 tissue samples (of about 50 mg wet weight) were taken from the tracheal lobe and evaluated for the retention of silicon carbide/mg tissue dry weight. The samples were analysed by TEM and energy dispersive X-ray spectrometry. It was found that 219 ng/mg lung dry weight of the administered 100 mg sample of granular silicon carbide was retained. Of the fibre sample containing 68 mg fibrous and 27 mg granular silicon carbide, after 8 months only about 4.6 ng/mg lung dry weight of the fibrous material was detected, as opposed to 58 ng of the granular material. The analysis of the mass retained at the time points of 2, 4, 6 and 8 months yielded unexpected results: granular particles were found to have a half-life of 5.8 months, while that of fibrous material was only 1.7 months. At the time of necropsy, which was 8 months after exposure, 80% of the fibres retained in the lung tissue were longer than 5 µm. This is evidence of the more rapid clearance of morphologically small silicon carbide fibres. However, there was no change in the size distribution of the granular silicon carbide particles that were analysed concurrently. This study shows that 8 months after exposure, more silicon carbide fibres than granular silicon carbide were retained, with a more rapid clearance of shorter fibres (Dufresne et al. 1992).

The clearance of silicon carbide whiskers was investigated in rat lungs after 4-week inhalation exposure. The whiskers had a mean length of 2.2 µm and a mean diameter of 0.4 µm. The biological half-life was 4 months (Akiyama et al. 2003). A follow-up study that was carried out with these whiskers 4 years later yielded a biological half-life of 16 months with a mean fibre diameter of 0.5 µm and a mean fibre length of 2.8 µm (Akiyama et al. 2007).

The biopersistence of the fibres can be determined in vivo and in vitro. In the rat lung, crocidolite fibres were found to be similar to silicon carbide fibres because they were more biopersistent than refractory ceramic fibres (RCF), stone wool and slag wool (Searl et al. 1999).

The absorption rate, the dose–time relationship of clearance and the presence of non-fibrous fractions have marked effects on the biopersistence of silicon carbide fibres.

5 Effects in Humans

5.1 Single exposures

There are no data available.

5.2 Repeated exposure

In a prospective longitudinal study carried out in Norway, 3924 workers (a total of 16 570 examinations) employed in the smelting industry were examined once a year over a period of 5 years. At each examination, clinical symptoms, smoking habits and a description of the workplace were recorded in questionnaires and spirometry was performed. The first examination included additional questions about previously diagnosed bronchial asthma and a family history of allergy and asthma. A significant decrease in the forced expiratory volume in one second (FEV_1) of 5.6 ml/year per squared body height was recorded in the group of silicon carbide workers compared with the non-exposed control group. In workers 180 cm in height, the decline in FEV_1 increased each year by 18.1 ml. In workers in ferrosilicon or silicon production, the rate of decline was 7.5 ml per year compared with that in the non-exposed control group. As expected, the decline in FEV_1 was greater in smokers than in former smokers or non-smokers; however, the decline in FEV_1 was not statistically significant in the workers employed in silicon carbide production. Surprisingly, the decline in FEV_1 was less pronounced

in the group of silicon carbide workers, particularly when the group of smokers was compared with the workers who had contact with ferrosilicon or silicon (Søyseth et al. 2007).

A study from Romania investigated bronchial hyperreactivity in 191 workers involved in silicon carbide production. The production site was antiquated without a clear separation of the different work areas. There was a high level of dust pollution and the workers were exposed to silicon carbide dust at levels that far exceeded the maximum permitted dust concentration. The gravimetrically determined total dust levels were between 262.8 and 630 mg/m^3. The respirable fraction (R dust) was 3.4%, while the level of non-reactive free SiO_2 was about 0.2%. The workers, who were on average 37.2 years old, had been exposed for periods between 4 and 14 years. Symptoms such as wheezing, dyspnoea and breathlessness after exercise were observed in 26.1% (n = 50) of the workers. Histamine provocation tests were carried out in 24 workers with the described symptoms, yielding positive results in 79.2% (n = 19). The majority of the 19 positive results were obtained in female patients (70.5%); there was no significant difference between smokers and non-smokers. The smokers were older on average than the non-smokers. The workers reported that the respiratory symptoms increased towards the end of the working week and subsided during holidays. On the basis of their findings, the authors concluded that the occurrence of bronchial hyperreactivity was associated with exposure to silicon carbide and estimated a prevalence of 20.9% in workers exposed to silicon carbide (Petran et al. 2000).

The authors of a longitudinal mortality study in Norway examined the mortality from non-malignant diseases among 2562 workers (52 618 person-years) who had worked at 3 silicon carbide plants between 1962 and 1996. While the incidence of mortality from cardio-vascular diseases was not increased, chronic obstructive pulmonary diseases such as asthma, emphysema and chronic bronchitis combined with an increased exposure to dust led to a considerable increase in mortality (standardized mortality ratio (SMR): 2.2; 95% confidence interval (CI): 1.6–2.95) compared with the general male population. In addition, mortality from pneumoconiosis was increased (SMR = 7.9; 95% CI 2.9–1.7) based on 6 deaths. Five workers died from silicosis after more than 25 years of employment and 1 worker died from asbestosis after only a short period of exposure of less than 1 year. Differences between smokers and non-smokers were not observed. There was a dose-dependent relationship between cumulative exposure to total dust and mortality from chronic obstructive pulmonary diseases. Increased mortality was found in the subgroup with more than 3 years of exposure, particularly at cumulative dust exposures of 15 to 69 mg/m^3 × years and above (SMR = 2.1; 95% CI: 1.6–2.95). Mortality was increased in the subgroup that was exposed to more than 70 mg/m^3 × years (SMR = 2.6; 95% CI: 1.44–4.4) (Romundstad et al. 2002).

A study from Italy examined 267 workers of a silicon carbide plant. Exposure to respirable dust was determined by taking 120 personal samples in 7 work areas. At the time of sampling, the dust concentrations varied among the work areas with geometric means between 0.44 and 1.00 mg/m^3. The workers were exposed to silicon carbide and silicon dioxide, sulfur dioxide, carbon monoxide and polycyclic aromatic hydrocarbons (PAHs). The cumulative dust exposure was 9.7 mg/m^3 × years, and the cumulative exposure to silicon carbide was 0.6 mg/m^3 × years. The overall average age of the 40.1% smokers, 21% former smokers and 38.8% non-smokers was 45.9 years. A group of 141 workers was compared with a group of 126 former workers of this plant. Individual subgroups of the employees were divided into job categories after determining the level of exposure to respirable dusts, quartz and cristobalite. FEV_1, forced vital capacity (FCV) and X-rays of the thorax were examined and information on health and smoking habits was obtained by questionnaire. Pulmonary opacities were found in 7 former workers and 3 current workers with scores of ≥ 1/0 and in 3 former workers and 1 current worker with scores of ≥ 1/1. The workers with scores of ≥ 1/1 were exposed for 19 years with a cumulative exposure to dust of 25.3 mg/m^3 × years. The pulmonary opacity score increased in a statistically significant manner with the cumulative exposure to dust. A statistically significant association with exposure to sulfur dioxide was not found. The differences in FEV_1 and FVC levels found between smokers and non-smokers were statistically significant. In smokers, the average FVC was 94% and the FEV_1 was 96.4% of the predicted values. The values determined in non-smokers were much better with a FVC of 97.1% and a FEV_1 of 104.2% of the predicted values. Likewise, significant differences were found in smokers for the pulmonary function parameters and exposure periods. Among smokers exposed for more than 15 years, the FVC dropped to 86.1% of the predicted value and the FEV_1 to 86.9% of the predicted value (Marcer et al. 1992).

The pulmonary function parameters declined sharply per year of employment in workers in the silicon carbide industry. The study evaluated 156 workers who were exposed to a mixture of dusts containing silicon carbide, PAHs and small

quantities of quartz, cristobalite and graphite. The workers were employed at the plant for an average of 16 years. The cumulative dust exposure was 9.5 mg/m^3 × years, and the average dust concentration was 0.63 mg/m^3. The predicted and actual pulmonary function parameters were evaluated by means of linear regression. The annual declines in the FEV_1 of 8.2 ml and in the FVC of 9.4 ml were statistically significant in the total group of 156 workers. Much higher rates of decline were determined in the non-smokers with 17.8 ml/year for FEV_1 and 17.0 ml/year for FVC. A lower rate was found in the group of smokers at 9.1 ml/year (FEV_1) and 14.4 ml/year (FVC). The cumulative dust exposure was evaluated for 138 workers with complete exposure data. The results were similar. Statistically significant decreases in the FEV_1 of 40.7 ml per mg/m^3 × years and in the FVC of 32.9 ml per mg/m^3 × years were found in the non-smokers of this group. In the smokers of this group, the losses of FEV_1 of 7.1 ml per mg/m^3 × years and the FCV of 11.7 ml per mg/m^3 × years were not statistically significant. There was no statistically significant association between cumulative SO_2 exposure and a loss of pulmonary function. In the total group, the FEV_1 decreased by 0.2 ml per ml/m^3 × years and the FVC decreased by 3.2 ml per ml/m^3 × years, whereas in the group of non-smokers, the FEV_1 was lower by 52.7 ml per ml/m^3 × years and the FVC was lower by 43.1 ml per ml/m^3 × years. These values were not statistically significant because of the small number of cases and the wide variation (Osterman et al. 1989).

A study examined histological material from 3 workers exposed to silicon carbide while working in the industry for 30 to 40 years. The first patient had silicotic nodules, mainly in the lower sections of the lungs, and the second patient a squamous cell carcinoma; after lobectomy he no longer had any symptoms. The third patient died from a metastasized undifferentiated lung carcinoma. Besides the 2 carcinomas, the following findings were obtained by light microscopy: an abundance of intra-alveolar macrophages associated with the accumulation of inhaled particles including carbon, silicon, polymorphic crystals, silicon carbide and ferruginous bodies; nodular fibrosis, generally profuse, containing silica and ferruginous bodies, and large amounts of carbon pigments; interstitial fibrosis less pronounced than the nodular form (Massé et al. 1988).

Pairs of thoracic radiographs obtained from 128 Canadian workers in a silicon carbide plant in Quebec were examined and evaluated according to the ILO classification. There are no data available for the levels or duration of exposure. The workers were on average 35.4 years old at the initial examination (1977) and 41.6 years old at the follow-up examination (1984). No significant deterioration was observed in the X-ray findings during the period of observation. The authors concluded that, over a period of 6 to 7 years, the radiological findings did not suggest a deterioration of the lung changes under the prevailing working conditions (Durand et al. 1991).

5.3 Local effects on skin and mucous membranes

There are no data available.

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

There are no data available.

5.6 Genotoxicity

There are no data available.

5.7 Carcinogenicity

A retrospective cohort study examined 585 silicon carbide production workers in Quebec (Canada). The mortality of the workers from 3 plants who had been employed there for at least 2 years between 1950 and 1980 was analysed until 1989 (13 394 person-years). High total dust concentrations were determined at various workplaces. In the period until 1966, the median was about 17.9 mg/m^3 (0.5–159.0 mg/m^3). From 1966 onwards, the concentrations in many work areas decreased to 6.5 mg/m^3 (0.1–80 mg/m^3). The quartz concentrations at the Quebec plants were between 0 and 0.1 mg/m^3 and the cristobalite concentrations were between 0 and 36 µg/m^3. The mortality from lung cancer was significantly increased in the cohort (SMR = 1.69; 95% CI: 1.09–2.52). Increases that were not significant were found for total cancer mortality (SMR = 1.25; 95% CI: 0.94–1.65) and mortality from stomach cancer (SMR = 2.18; 95% CI: 0.88–4.51). After adjustment for smoking, the relative risk for lung cancer was increased for the group with the highest exposure to total dust (> 275 mg/m^3 cumulative) compared with that for the group with the lowest exposure (< 105 mg/m^3 cumulative), but the increase was not significant (relative risk = 1.67; 95% CI: 0.57–4.83) (Infante-Rivard et al. 1994). The authors did not provide any details about the concentrations or the amounts of silicon carbide fibres. It was not possible to calculate fibre concentrations for individual workplaces. In addition, total dust exposure was determined for only 2 of the 3 plants and not for all workplaces; the analyses were supplemented by estimates. A further limitation of this study is that the authors had no access to the employee databases of the plants; the data were obtained from unions and may therefore have been incomplete. Information about job histories and smoking habits was obtained from the relatives of workers who had died by the time of the interview; this adds a degree of uncertainty. Even if the findings of this study suggest an increased lung cancer risk for workers in silicon carbide production, a causal relationship between exposure to silicon carbide fibres and lung cancer cannot be derived.

A study from Norway examined a cohort of 2620 men who were employed in 3 silicon carbide production plants for at least 6 months from 1913 onwards. The follow-up evaluation focussed on the period from 1953 to 1996 (59 251 person-years). From 1950 onwards, dust samples were taken in different work areas and analysed. From 1950 to 1974, the estimates of total dust exposure were based on measurements carried out by thermal precipitator. Gravimetric determinations began to be used only from 1974 onwards. Silicon dioxide and silicon carbide fibres were also determined. In the cohort, the authors found increased incidences of lung cancer (standardized incidence ratio (SIR) = 1.9; 95% CI: 1.5–2.3), stomach cancer (SIR = 1.5; 95% CI: 1.1–2.0) and all cases of cancer (SIR = 1.2; 95% CI: 1.1–1.3). The incidences of cancer of the upper respiratory tract (SIR = 1.7; 95% CI: 1.0–2.7) and basal cell cancer (SIR = 1.5; 95% CI: 0.9–2.5) were increased, but not with statistical significance. The incidences of lung cancer were increased in association with exposure to total dust even if smoking was taken into account. When the lung cancer incidences were analysed in relation to exposure to silicon carbide fibres, the increases in SIRs were statistically significant for all exposure categories with incidences above zero. The SIR was 2.9 (95% CI: 1.9–4.2) in the category ≥ 5 fibres/ml × years (Romundstad et al. 2001). One strength of the study design is the use of a job exposure matrix that makes it possible to describe the type of exposure to silicon carbide fibres. Another strength is the use of the Cancer Registry of Norway, which includes data for all types of cancer except basal cell carcinomas. However, critical analysis is required because of the absence of accurate data for smoking (no data for the year the smoking status was ascertained, the duration and amount of tobacco consumption) and the strong correlation between the different exposures, for example between the exposures to silicon carbide fibres and silicon carbide particles. Therefore, the causal relationship between specific exposures (for example to silicon carbide fibres) and the end points of the study (for example lung cancer) cannot be evaluated reliably. The authors themselves addressed the uncertainties relating to the evaluation of exposure.

Another study that used the same cohort from Norway investigated 2612 male workers employed in silicon carbide production for more than 6 months between 1913 and 2003. The follow-up evaluation focussed on the period from 1953 to 2005 (63 197 person-years). The exposure period was used to divide the cohort into short-term workers (< 3 years) and long-term workers. Among the short-term workers, increases were statistically significant both for the overall incidence of cancer (SIR = 1.4; 95% CI: 1.2–1.6) and the incidences of tracheal, bronchial and lung cancers (SIR = 2.6; 95% CI: 1.9–3.5), oral cavity and pharyngeal cancer (SIR = 2.5; 95% CI: 1.1–5.6), basal cell cancer (SIR = 2.1; 95% CI: 1.1–3.7), thyroid cancer (SIR = 5.8; 95% CI: 2.2–15.4), Hodgkin's lymphomas (SIR = 5.2; 95% CI: 2.0–13.9) and cancers at other sites (SIR = 2.1; 95% CI: 1.2–4.0). Among the long-term workers, increases were likewise statistically significant for the overall

incidence of cancer (SIR = 1.2; 95% CI: 1.1–1.3) and the incidences of tracheal, bronchial and lung cancers (SIR = 1.7; 95% CI: 1.3–2.2), oral cavity and pharyngeal cancer (SIR = 2.1; 95% CI: 1.1–3.9), lip cancer (SIR = 2.4; 95% CI: 1.2–5.1) and leukaemia (SIR = 2.8; 95% CI: 1.2–6.1) (Bugge et al. 2010). The authors did not correlate the cancer incidences specifically with the exposure to silicon carbide fibres. Particularly in the case of the short-term workers, potential risks arising from other jobs (for example exposure to asbestos) have to be taken into account.

Another study that used this Norwegian cohort investigated the mortality of 1687 male, long-term workers employed in the silicon carbide industry with a focus on non-malignant respiratory diseases. These authors likewise reported an increase in cancer mortality; however, the increase was not statistically significant (SMR = 1.2; 95% CI: 1.0–1.4) (Bugge et al. 2011). Again, exposure to silicon carbide fibres was not evaluated separately. In the publications of the latter 2 studies of the Norwegian cohort, the findings substantiate an increased risk of cancer among workers in silicon carbide production; however, no conclusions can be drawn about the source of the risk, particularly the risk arising from silicon carbide fibres.

Summary: Overall, the data currently available from epidemiological studies do not confirm the carcinogenicity of silicon carbide fibres; however, a suspicion in this regard cannot be refuted either.

In an analysis published by the International Agency for Research on Cancer, silicon carbide fibres were classified as possibly carcinogenic to humans (Group 2B). The evaluation was based on the results of 2 cohort studies from Canada and Norway. Both studies investigated workers involved in silicon carbide production. In the Norwegian study, a clear association between production using the Acheson process and the occurrence of lung carcinomas was found for workers who were employed for at least 3 years; this would justify classification of the fibres in Group 1. However, as the carcinomas could not be clearly attributed to silicon carbide, the fibres have been classified in Group 2B (Grosse et al. 2014).

6 Animal Experiments and in vitro Studies

6.1 Acute toxicity

There are no data available.

6.2 Subacute, subchronic and chronic toxicity

In general, the test materials used in the available studies were not characterized adequately. No information was provided about the different shapes of the fibres, their heterogeneity or their chemical composition. However, the shapes or dimensions of the fibres and their physico-chemical properties determine their biological activity. Furthermore, the studies did not include information about the site of sampling and type of production, crystallinity, mechanical treatment, for example by ball mill, the shape and branching of the fibres, carbon deposits, or plant-specific additives (Gunnæs et al. 2005).

6.2.1 Inhalation

In a study, 25 male Wistar rats were exposed for 1 month by inhalation to silicon carbide whiskers at an average concentration of 10.4 mg/m^3. The fibres were 5.1 µm in length (geometric mean) and 0.3 µm in diameter (geometric mean). Slight inflammatory changes, a thickening of the alveolar walls and fibre-laden macrophages were observed during exposure and during the 6-month recovery period (Ogami et al. 2001).

6.2.2 Intratracheal administration

The publications of Dufresne et al. (1987), Gunnæs et al. (2005) and Skogstad et al. (2006) demonstrated not only the structural heterogeneity of silicon carbide fibres but also the difference in their biological activity, which results alone from the different clearance rates of their components (see Sections 3 and 4).

The fibrogenic effects of raw and ashed silicon carbide particles with a diameter of < 5 µm (median) and raw and ashed silicon carbide fibres with a diameter of 0.27 ± 0.27 µm (median) and a length of 6.8 ± 11.2 µm (median) were investigated in groups of 8 sheep and compared with the effects of quartz and crocidolite. The animals were given a single dose of 100 mg silicon carbide by intratracheal injection. Bronchial lavage was carried out every 2 months and the lavage fluid was investigated. After 8 months, the animals were sacrificed and the lungs were examined for the intensity of lung tissue proliferation. The lungs and the lavage fluid of the animals exposed to particulate silicon carbide did not differ from those of the control animals. The effects observed in the sheep that received silicon carbide fibres, for example bronchiolar fibrosing alveolitis, were the same as those observed in the animals exposed to crocidolite fibres. The intensity of lung tissue proliferation was scored from 0 to 3 (0 for normal histopathological findings and 3 for pneumonia). The scores determined in the sheep of the different treatment groups were: silicon carbide particles (raw and ashed) 0, quartz 2.9, crocidolite 1.9 ± 0.25, raw silicon carbide fibres 1.2 ± 0.21 and ashed silicon carbon fibres 1.6 ± 0.2 (Bégin et al. 1989). In this test system, silicon carbide particles did not induce the proliferation of lung tissue, whereas silicon carbide fibres and crocidolite induced this effect in sheep at about the same intensity.

Another study carried out in 9-week-old female Fischer rats investigated the effects of particulate silicon carbide with an average diameter of 24.5 ± 14.0 µm and 2 different materials made up of silicon carbide whiskers (SiCW1 and SiCW2) with an average fibre diameter of 0.8 µm (SiCW1) and 1.5 µm (SiCW2) and an average fibre length of 18.1 µm (SiCW1) and 19.0 µm (SiCW2). The animals were given intratracheal doses of 1 mg/100 ml respiratory minute volume and 5 mg/100 ml respiratory minute volume. After an observation period of 18 months, the animals were sacrificed and evaluated histopathologically. High incidences of multiple granulomas were observed in the group exposed to SiCW1: in 88% of the 25 animals in the low dose group and in 91% of the 23 animals in the high dose group. Granulomas were observed with a frequency of 28% of the 25 animals that received the high crocidolite dose and 30% of the 23 animals given the SiCW2 sample. In the high dose groups, the incidences of fibrosis were 31% (SiCW1) and 36% (crocidolite). While no differences were found between the animals exposed to particulate silicon carbide and those of the control group, the effects observed in the rats exposed to silicon carbide fibres (multiple granulomas and fibrosis) were even more severe than those observed in the animals exposed to crocidolite asbestos. In the histological preparations, the most severe changes were found in the animals sacrificed 18 months after the last exposure to SiCW1: marked development of granulomas in 85% of the animals both “at the low and high dose levels” (no quantitative doses reported; see above). The lesions found in the animals treated with crocidolite were similar, but their incidences were far lower. The granulomas induced by SiW1 varied in number and size and in some cases extended far into the bronchial passages, blocking them. Fibres with ferruginous bodies inside the cells were not observed; this finding would have been expected for rats, but not for hamsters. Furthermore, the following histopathological changes were found. Tracheal mucosa: thickened epithelium and epithelial metaplasia; peribronchial granulomas with numerous macrophages and multinucleate giant cells loaded with fibres. In the submucosa: accumulation of intact fibres that had penetrated the epithelial layer and had persisted there for a period of 1.5 years after exposure. The main conclusion of this study with regard to the tested end points was that SiCW1 is more toxic than crocidolite in relation to the mass applied (Vaughan et al. 1993). The silicon carbide particles did not have diameters within the respirable range. The OECD Test Guidelines do not recommend using particles in this diameter range for testing.

Groups of 25 male Wistar rats were given single intratracheal injections of 2 or 10 mg silicon carbide whiskers with an average length of 5.1 µm and an average diameter of 0.3 µm. In each group, 5 rats were sacrificed after 3 days, 1 week, 1 month, and 3 and 6 months. The histopathological examination revealed focal alveolitis mainly after 3 days and foci in the lungs after 6 months (Ogami et al. 2001).

In another study, 25 male Wistar rats were given single intratracheal injections of 2 mg silicon carbide whiskers with a length of 5.1 µm and a diameter of 0.3 µm. Crocidolite (length: 1.3 µm; diameter: 0.2 µm) and quartz (diameter: 1.6 µm)

were used in the same doses as positive control substances. In each group, 5 rats were sacrificed after 3 days, 1 week, 1 month, and 3 and 6 months. Morphometric analysis was carried out based on digital images of lung sections. One week after exposure, moderate alveolitis was observed, followed later by foci of fibres. The authors concluded that silicon carbide fibres were less toxic than crocidolite or quartz (Ogami et al. 2007).

Groups of 9-week-old F344/NTacfBR rats were given a single intratracheal instillation of SiCW1 with a length of 18.1 µm and a diameter of 0.8 µm. Crocidolite was used as the positive control substance and for comparison. One, 7 and 28 days after instillation, the tracheae of the animals were cut open under anaesthesia, and the accessible airways were washed 4 times with 5 ml phosphate-buffered saline. Subsequently, the numbers of macrophages, monocytes and lymphocytes were determined in the lavage fluids. After 24 hours, the monocyte and lymphocyte counts were significantly increased, whereas the incidences of macrophages were not increased. After 1 week, the number of macrophages was 6 times as high as the control value, the monocyte counts were increased 5-fold and the lymphocyte counts were increased 45-fold. The authors concluded that the marked changes were caused either by non-specific interactions of the immune system with fibre-activated macrophages or by an infection induced by tissue damage. The increased cell counts of monocytes and lymphocytes subsided within 4 weeks, but the number of macrophages remained high. According to the authors, the persistent proliferation of macrophages was evidence of a prolonged inflammation in the respiratory tract. Similar changes were observed with the second fibre sample, SiCW2 (length: 19 µm; diameter: 1.5 µm) (Vaughan et al. 1993).

6.3 Local effects on skin and mucous membranes

There are no data available.

6.4 Allergenic effects

There are no data available.

6.5 Reproductive and developmental toxicity

There are no data available.

6.6 Genotoxicity

6.6.1 In vitro

Chinese hamster V79 lung fibroblasts were treated with 4 samples of silicon carbide whiskers (SiCW1, SiCW2, SiCW3 and SiCW4; no data whether monocrystalline or polycrystalline); the fibres were between 12 µm and 14 µm long with diameters between 0.6 µm and 0.8 µm. Crocidolite was used as the positive control substance. Tests were carried out to determine cloning efficiency and to analyse DNA strand breaks (method: nick translation in permeabilized cells after the addition of DNA polymerase I; however, this is not a validated test), the release of hydroxyl radicals (method: hydroxylation of deoxyguanosine; trapping reaction with DMSO) and the activation of neutrophilic leukocytes (method: chemiluminescence determination of reactive oxygen intermediates). All 4 SiCW samples inhibited the cloning efficiency; this effect was dependent on the concentration and in the same order of magnitude as that of crocidolite. According to the authors, the cytotoxic effects may have been caused by the damage to the cell membrane. The frequency of DNA strand breaks induced by SiCW1, SiCW3 and SiCW4 was about the same as that induced by crocidolite. When 8-hydroxyguanosine levels were determined as an indicator of the release of hydroxyl radicals, only SiCW4 was found to induce effects similar to those induced by crocidolite. However, only a small fraction of SiCW4 consisted of long fibres that were coated with graphitic carbon. In the test for the activation of neutrophilic leukocytes, far more neutrophilic leukocytes were activated after exposure to silicon carbide samples than after exposure to crocidolite. This

was associated with a marked increase in the formation of superoxide anions, H_2O_2, singlet oxygen, nitrogen oxides, peroxynitrite and hypochloric acid. The authors concluded that the leukocytes that infiltrated the lungs after exposure to fibres would damage the pulmonary epithelial cells and might induce inflammation-mediated carcinogenesis. The authors emphasized that different fibre properties caused different biological effects (Svensson et al. 1997).

In a comet assay in vitro, silicon carbide whiskers caused DNA defects (breaks and cross-links) in the human A549 pulmonary epithelial cell line at a concentration of 200 µg/ml (40 µg/cm^2). In addition, structural chromosomal anomalies were observed in human embryo lung cells after treatment with silicon carbide whiskers (Wang et al. 1999).

In a micronucleus test, silicon carbide fibre concentrations of 0.1 µg/ml, 1.0 µg/ml and 2 µg/ml (no other details) were investigated in the M3E3/C3 epithelial cell line. The number of micronuclei increased in a concentration-related manner while the mitotic rate decreased. However, the number of micronuclei containing kinetochores did not increase. This suggests that the silicon carbide fibres were clastogenic, but not aneugenic (Peraud and Riebe-Imre 1994).

6.6.2 In vivo

There are no data available.

6.7 Carcinogenicity

6.7.1 Short-term tests

After the treatment of BALB/3T3 cells with silicon carbide whiskers 0.8 µm and 1.5 µm in diameter, the frequencies of transformed cell colonies were increased with statistical significance at a concentration of 5 µg/cm^2. However, the study was inadequately documented and does not comply with current quality criteria because only one concentration was tested, no positive control group was included and a blind evaluation was evidently not performed (Vaughan et al. 1991).

6.7.2 Long-term tests

The documentation for fibrous dust that was published in 1993 (Greim 1997) described animal studies carried out with intraperitoneal or intrapleural administration. These studies revealed dose-dependent increases in the tumour incidences in rats. The studies that were published after 1990 are described in detail below.

In an inhalation study, 42 SPF rats of the AF/HAN strain were exposed to a silicon carbide fibre concentration of 11.4 mg/m^3, which is equivalent to 984 fibres/ml (length: 5 to > 20 µm) for 7 hours a day on 5 days a week for 238 working days (this corresponds to about 1 year). The animals were observed for their entire lifetime until only about 15% survived; the study was then terminated. No other details about mortality were provided. The lungs were examined histopathologically for neoplasms. Lung tumours were observed in 10 of 42 rats (24%); 5 of these tumours were described as adenocarcinomas. Mesotheliomas were also observed, again in 10 of 42 rats (24%). Another group of rats was exposed to an amosite concentration of 5.5 mg/m^3 (981 WHO fibres per ml). In this group, 16 of 42 animals developed lung tumours, 7 of which were adenocarcinomas. In addition, 2 mesotheliomas were detected in this group. In a group of 38 rats that was investigated in parallel and was exposed to 100/475 glass microfibre in a concentration of 5.8 mg/m^3, 4 benign tumours were found. In the rats that survived longest, extensive lung fibrosis was observed in 9 animals exposed to amosite and 9 animals exposed to silicon carbide fibres. In 11 rats exposed to glass microfibre, there were occasional findings of minimal fibrosis. This is a common finding in control animals with exposure to clean air. The study does not include information about body weight gains or other clinical signs that would allow an evaluation of the general state of the animals (Davis et al. 1996; Miller et al. 1999 a).

Groups of 24 rats were given intraperitoneal injections of 4×10^9 fibres > 5 µm in length (silicon carbide whiskers, man-made vitreous fibres MMVF-100/475, amosite asbestos, MMVF-10, MMVF-21, MMVF-22, refractory ceramic fibres RCF-1, RCF-2 and RCF-4). Mesotheliomas were observed in 88% of the rats exposed to amosite asbestos and RCF-1 fibres,

in 92% of the rats exposed to silicon carbide whiskers and in 72% of the animals treated with RCF-2 fibres. Mesotheliomas did not develop in the group of animals that received RCF-4 fibres by injection (Davis et al. 1996; Miller et al. 1999 b).

Groups of 30 female F344/N rats were given intrapleural injections of suspensions of 20 mg of SiCW1, SiCW2 and SiCW3 silicon carbide whiskers in 0.4 ml saline. The fibres had an average length of 4.5, 6.6 and 20.1 µm, respectively, and an average diameter of 0.42, 0.32 and 0.75 µm, respectively. A group of animals was exposed to crocidolite asbestos (length: 2.1 µm; diameter: 0.12 µm) for comparison. After treatment with SiCW1 and SiCW2, the lifespan of the animals was significantly reduced and 90% and 87% of the animals (based on 30 animals), respectively, developed mesotheliomas. The lifespan of the animals treated with SiCW3 was not significantly shorter, and only 23% developed mesotheliomas. Mesotheliomas were observed in 57% of the animals treated with crocidolite. The difference in biological activity between the SiCW samples could not be explained on the basis of their physical dimensions (Johnson and Hahn 1996).

The tumour risk was quantified on the basis of a long-term study in female Wistar rats with administration by intraperitoneal injection. For this purpose, 330 rats were divided into 24 groups that were treated with 5 to 20 mg of different fibres including silicon carbide whiskers by intraperitoneal injection. Data for the number of fibres or their geometry were not reported. The observation period was 2 years. Mesotheliomas were observed in the group of about 14 rats (no details) given 10 mg of silicon carbide whiskers. In another group of about 14 rats given chrysotile asbestos, 85% of the animals developed mesotheliomas. In the other groups, 10% to 77% developed mesotheliomas. On the basis of the results of this study, the tumour risk after exposure to silicon carbide whiskers was calculated to be 2.4 times as high as that after exposure to chrysotile asbestos (Adachi et al. 2001).

Female Wistar rats received intraperitoneal injections of 0.05, 0.25, 1.25, 6.25 or 25 mg silicon carbide whiskers in saline and were then observed for 130 weeks. Dose-dependent increases in the incidences of mesotheliomas or sarcomas were found in the abdominal cavities of the rats; the incidences ranged from 4% in the control group to 97.3% in the animals that were given 25 mg. Although some animals developed a lung infection during the study, the authors concluded that this had no influence on the development of the tumours in the abdominal cavity (Pott et al. 1991).

6.8 Other effects

The cytotoxicity of 3 different silicon carbide whiskers (length: 4.5–20.1 µm; diameter: 0.32–0.75 µm) was examined by trypan blue cell viability assay in alveolar macrophages of rats and human tracheal and pulmonary epithelial cell lines. In all cell lines, silicon carbide whisker concentrations of 0 to 50 µg/ml induced more severe cytotoxic effects than crocidolite (Johnson et al. 1992).

An in vitro study in alveolar macrophages of rats investigated the ability of different types of fibres to generate superoxide anions. The cells were exposed to different types of fibres (amosite asbestos, MMVF-21, MMVF-100/475, silicon carbide and RCF-1) with lengths of 5 to 100 µm and diameters of < 3 µm; the fibres were both uncoated and coated with rat immunoglobulin G (IgG), a component of lung fluid. The RCF-1 and MMVF-21 fibres led to a marked release of superoxide, which correlated with the high affinity of the fibres for IgG. The silicon carbide whiskers and MMVF-100/475 fibres showed a poor affinity for IgG and stimulated only a modest release of superoxide. However, amosite asbestos induced a high release of superoxide in spite of a poor affinity for IgG (Hill et al. 1996).

The release of ROS caused by silicon carbide whiskers (length: 1.5–16 µm; diameter: 0.25–3 µm) was examined in the alveolar macrophages of guinea pigs. Various concentrations of 15 µg to 120 µg fibres per 10^6 alveolar macrophages were tested. A concentration-dependent increase in reactive oxygen species was detected during the incubation of the cells with the fibres (Bruch et al. 2014).

Furthermore, another research group observed increased apoptosis in MC3T3 cells of mice after treatment of the cells with β-silicon carbide nanowires. The effects of fibres with a length of 100 ± 42 nm were investigated and compared with those of fibres with a length of 100 ± 23 µm. Increased, concentration-dependent apoptosis was observed only after treatment with fibres with a length of 100 nm (Xie et al. 2014).

The cytotoxicity of silicon carbide whiskers was determined in murine alveolar macrophages. The effects of silicon carbide whiskers, potassium octatitanate and chrysotile asbestos were compared. The toxic effects were determined by means of cell magnetometry and LDH assay. Dose-dependent positive effects were observed for all fibres (Shibata et al. 2007).

A study investigated the nuclear translocation of NF-κB by means of immunohistochemical staining with an antibody to p50 (NF-κB subunit) as an activator of pro-inflammatory genes in human A549 lung epithelial cells. The positive control substance hydrogen peroxide caused the dose-dependent activation of NFκB. The RCF-1 and silicon carbide fibres and amosite asbestos led to positive test results. The silicon carbide fibres were either > 10 µm (60.9%) or > 20 µm (27.6%) in length (Brown et al. 1999).

Another study carried out by the authors in A549 human lung epithelial cells in vitro investigated the activation and translocation of NF-κB into the nucleus by silicon carbide fibres (from Advanced Composite Materials Corporation; no other details). The authors hypothesized that this can be used as a marker for the expression of genes responsible for inflammation. The silicon fibres varied in length: 61% were longer than 10 µm and 28% were longer than 28 µm. The test concentration was 8.24×10^6 fibres per ml. After 8-hour incubation, a higher level of translocation and activation of NF-κB from the cytoplasm into the nucleus was induced by the silicon carbide fibres than by long amosite fibres. Curcumin inhibited this translocation, but had hardly any effect in the parallel study with amosite. However, in earlier studies, the authors had found that the levels of physiological antioxidants (for example glutathione) in the lung lining fluid were only modestly decreased after silicon carbide administration. Therefore, they assumed that the translocation was induced by the mobilization of intracellular Ca^{++} ions rather than by oxidative stress (contrary to expectations). Curcumin disturbed the flow of calcium ions and thus blocked the expression of pro-inflammatory genes. Overall, the mechanism regulating the activation of translocation remains unclear. However, the authors concluded that the release of ROS was not the mechanism, or not the primary mechanism, responsible for the translocation (Brown et al. 2000).

7 Manifesto (classification)

Silicon carbide fibres are artificially produced inorganic fibres of high biopersistence that can be used for a broad range of applications. The lungs are the target organ of the effects of silicon carbide fibres.

Carcinogenicity. After exposure by inhalation and by intratracheal, intraperitoneal or intrapleural application, silicon carbide fibres increased the tumour incidence in rats and hamsters. The studies demonstrate clearly that silicon carbide fibres are strong carcinogens in experimental animals. This is consistent with the severe inflammatory effects and high biopersistence that are responsible for the strong carcinogenicity of critical fibres. New epidemiological studies suggested that exposure to silicon carbide increases the lung tumour incidence in humans. These studies have methodological shortcomings as regards the characterization of exposure (mixed exposure) and the adequate consideration of confounders. Therefore, silicon carbide fibres remain classified in Carcinogen Category 2.

Absorption through the skin. Silicon carbide fibres have not been shown to be absorbed through the skin. A designation with "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) is not required.

Sensitization. There are no data available for sensitizing effects on the skin or respiratory tract. Silicon carbide fibres have therefore not been designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

Germ cell mutagenicity. The genotoxicity data that are currently available do not indicate that silicon carbide fibres cause germ cell mutagenicity. Therefore, silicon carbide fibres have not been classified in any of the categories for germ cell mutagens.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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