Health Council of the Netherlands

Silicon carbide

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Silicon carbide*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-7475/BvdV/fs/246-S17
Bijlagen : 1
Datum : 7 december 2012

Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan siliciumcarbide.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

De commissie heeft in haar advies een aparte classificatie aanbevolen voor vezelvormig siliciumcarbide (1A) en granulair siliciumcarbide (categorie 3). De commissie maakt zich zorgen over de vraag of het commerciële granulaire s iliciumcarbide voldoende vrij is van vezelvormig siliciumcarbide. Daarom adviseert de commissie, in aanvulling op de voorgestelde classificaties, om het kankerrisico te kwantificeren en om veilige blootstellingwaarden vast te stellen.

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
E-mail: b.v.d.voet@gr.nl
Telefoon (070) 340 74 47

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Gezondheidsraad
Health Council of the Netherlands

Ik heb het advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
E-mail: b.v.d.voet@gr.nl
Telefoon (070) 340 74 47

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Silicon carbide

Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances
of the Dutch Expert Committee on Occupational Safety (DECOS),
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2012/29, The Hague, December 7, 2012

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with health technology assessment.

INAHTA

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Silicon carbide. Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2012; publication no. 2012/29.

ISBN: 978-90-5549-922-9

Contents

Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige blootstelling aan Stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt deze commissie siliciumcarbide onder de loep. Siliciumcarbide is een stof die onder andere wordt gebruikt als synthetisch slijpmiddel en in brandsteen-, metaalgieterij-, keramiek- en vulmiddelindustrieën.

Op basis van de beschikbare gegevens concludeert de commissie dat siliciumcarbide in vezelvorm (vezels, 'whiskers') kanker kan veroorzaken volgens een niet-stochastisch genotoxisch werkingsmechanisme en geclassificeerd moet worden als 'kankerverwekkend voor de mens' (in categorie 1A). De gegevens over de granulaire vorm van siliciumcarbide zijn onvoldoende om de carcinogene eigenschappen hiervan te kunnen klassificeren (categorie 3).*

De commissie maakt zich zorgen over de vraag of het commerciële granulaire siliciumcarbide voldoende vrij is van vezelvormig siliciumcarbide.

* Volgens het classificatiesysteem van de Gezondheidsraad (zie bijlage E).

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In this report, the Committee evaluated silicon carbide. Silicon carbide is, among others, used as an artificial abrasive, and also in the refractory, foundry, ceramic and filler industries.

Based on the available information, the Committee concludes that fibrous silicon carbide (fibers, whiskers) may cause cancer according to a non-stochastic mechanism and should be classified as 'carcinogenic to humans' (in category 1A). The data on the non-fibrous form of silicon carbide are considered insufficient to classify the carcinogenic properties of this substance (category 3).*

The Committee is concerned about the question whether the commercial non-fibrous silicon carbide is sufficiently free of fibrous silicon carbide.

* According to the classification system of the Health Council (see Annex E).

Chapter 1

Scope

1.1 Background

In the Netherlands, a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances and to propose a classification (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex E).

This report contains the evaluation of the carcinogenicity of silicon carbide.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the Minister can be found in Annex C.

In July 2011, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is generally based on scientific data, which are publicly available. The starting points of the committees' reports are, where possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of silicium carbide, an IARC-monograph was not available.

The relevant data were obtained from the online databases Toxline, Medline and Chemical Abstracts, using carcinogenic, cancer, carcinogenicity or mutagenic, mutagenicity, chromosome and CAS no. 409-21-2 as key words. The last updated online search was performed in August 2012.

Chapter 2

General information

2.1 Identity and physicochemical properties

The data have been retrieved from the European Substance Information System (ESIS)*, an IUCLID chemical data sheet, which can be accessed via the same website, and the Hazardous Substances Data Bank (HSDB)**.

Chemical name	:	Silicon carbide
CAS registry number	:	409-21-2
EINECS number	:	206-991-8
Synonyms	:	Silicon monocarbide, carborundum, carbofrax m, carbon silicide
Appearance	:	Exceedingly hard, green to bluish-black, iridescent, sharp crystals
Use	:	Abrasive for cutting and grinding metals, grinding wheels, refractory in non-ferrous metallurgy, ceramic industry and boiler furnaces, composite tubes for steam reforming operations. Fibrous form is used in filament-wound structures and heat-resistant, high-strength composites.
Chemical formula	:	SiC
Molecular weight	:	40.07
Boiling point	:	> 2300 ˚C at 1013 hPa
Melting point	:	-
Vapour pressure	:	-
Vapour density (air = 1)	:	-
Solubility	:	Silicon carbide is not soluble in water or other common solvents

* ESIS can be accessed via the ECB-site: http://esis.jrc.ec.europa.eu/ (accessed September 9, 2012).
** HSDB; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (accessed September 9, 2012).

Conversion factor	:	1 mg/m^3 = 0,5990 × ppm at 20^o C
EU Classification (100% solution)	:	Not classified

In addition, silicon carbide (SiC) appears in several crystal modifications based on how the different silicon and carbon layers are stacked.[1,2] The following definitions will be used in this report:

- "Non-fibrous" silicon carbide is an amorphous and/or particulate material. This term is often used alongside with other terms, such as silicon carbide dust (an average particle size 1-20 μm), silicon carbide particles, or granular silicon carbide (particle size not specified in the available literature). Exposure to silicon carbide dust can occur at enterprises manufacturing or using synthetic abrasive materials. Despite being called non-fibrous, long fibrous particles with length > 100 μm have been shown also to occur in this type of material.
- Silicon carbide fibres, sometimes also addressed as siliconcarbide continuous fibres, or silicon carbide ceramic fibres, which is often a polycrystalline material, and mostly generated during silicon carbide crystal production. Exposure to silicon carbide fibres may also occur when silicon carbide particles are produced. The size and diameter of these fibres varies in quite broad ranges, but can fulfill the definition of WHO fibres (see below).
- Silicon carbide whiskers, which are single crystal structures possessing a fine fibrous morphology similar to that of amphibole asbestos. They are approximately cylindrical in shape with an aspect ratio equal to or greater than 3 and a diameter less than 5 μm. Silicon carbide whiskers were developed as a durable asbestos substitute and are used for ceramic seals, sandblast nozzles, and structural materials for use at high temperatures. Workers may be exposed to silicon carbide whiskers during manufacture of the whiskers, during production of the composite material, or as a result of machining and finishing a component made of the composite material. The silicon carbide whiskers can also occur as a byproduct of silicon carbide production for the abrasive industry.
  Several types of silicon carbide whiskers exist; the following well-characterized types are described in this report: SiCW 1, SiCW 2 and SiCW 3. The typical parameters of these whiskers are presented below:

Type	Fibre total/µg	Percentage of fibres >5.0 µm length	Percentage of fibres <0.3 µm diameter, >8.0 µm length
SiCW 1	7.6 x $l0^6$	31.0	3.8
SiCW 2	1.61 x 10^5	93.7	6.9
SiCW 3	1.05 x 10^7	30.8	10.8

Furthermore, the term “WHO fibres” is used in this report. WHO fibres refer to particles longer than 5 µm with a width of less than 3 µm and an aspect ratio of more than 3.[1]

2.2 IARC classification

Silicon carbide has not been evaluated by IARC.

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

3.1.1 Cohort studies

Infante-Rivard et al.[3] published a retrospective cohort study among 585 Québec silicon carbide production workers who had worked at any time between 1950 and 1980 at the three Québec silicon production plants. The vital status of these workers was ascertained up to December 31, 1989. Data collected during a hygiene survey in two of the three plants were also used to assess the relation between exposure and mortality. The workers were classified according to 29 job titles grouped under the main production process areas. Exposure data were collected on respirable quartz, cristobalite (both substances being a form of SiO_2 which is considered to be one of the major contaminants in silicon carbide production industry, forming islets at the surface of silicon carbide crystals), and polycyclic aromatic hydrocarbons, but as this information was not available for all jobs, it was decided to use only total dust concentrations. Estimates were based on 121 dust samples. Total dust cumulative exposure was defined as a sum of the products of exposure concentration and duration for each job held, and was expressed as mg/m^3-years. A baseline category of less than 105 mg/m^3-years corresponding to the 50^{th} percentile of the distribution was defined, and the division between the two more highly exposed groups corresponded to 75^{th} percentile.

Standardized mortality ratios (SMR) and 95% CI were estimated using the age- and calendar-specific death rates for Québec males between 1931 and 1985. The upper age limit for calculation of person-years and observed deaths was 85 years. Mean age at hire in the cohort was 29.9 (standard deviation (SD) = 14.2). Mean duration of follow-up was 22.9 years (SD = 9.3). A total of 13,394 person-years were accumulated. SMRs for all malignant diseases were not increased, whereas they were increased for stomach cancer (7 observed versus 3.19 expected; SMR = 2.18; 95% CI 0.88-4.51; not significant), and lung cancer (24 observed versus 14.14 expected; SMR = 1.69; 95% CI 1.09-2.52; significant $p < 0.05$). Among the 24 workers with lung cancer, 21 were smokers at the time of the interview, and 3 were ex-smokers. For all workers, smoking status was unknown for 3 subjects; 374 were reported smokers, 118 were ex-smokers and 80 were non-smokers. Controlling for smoking, the risk of lung cancers increased with the level of exposure (rate ratio (RR) = 1.48 for category 2 [cumulative exposure level 105-275 mg/m^3]) in comparison with baseline, and 1.67 for category 3 (cumulative exposure level above 275 mg/m^3). After a 15-year latency period, although somewhat lower, rate ratios also increased with exposure.

Although the results of this study seem to support the hypothesis of an increased risk for lung cancer among production workers in the silicon carbide industry, the fact that only total dust exposure was assessed limits the interpretation of the results. Furthermore, confounding by smoking is of concern; however, the authors found only very small difference: 86% of ever-smokers in the cohort versus 82% in a similar age cohort of men in the comparison population. Assuming that smokers were 20 times more likely to die from lung cancer than non-smokers, the lung cancer SMR due to smoking was calculated to be 1.05, giving a smoking-adjusted SMR of 1.61 (95% CI 1.04-2.41).

In the Québec plants the concentrations of quartz and cristobalite measured were much below the ones considered to entail health risks; quartz concentrations ranged from 0 to 113 μg/m^3 and cristobalite concentrations from 0 to 36 μg/m^3. The authors also could not measure asbestos fibres neither in this industry nor in the lungs of deceased workers. Polycyclic aromatic hydrocarbons could only be detected at the head of one of the furnaces, but their concentration away from the head of the furnace and in the ambient air rapidly decreased.

Romundstad et al. (2001)[4] studied cancer incidence among 2,620 men employed for more than 6 months in three Norwegian silicon carbide smelters. The company records included 2,720 men; 40 had died before the start of the follow-up and 60 (3%) were not traceable. Follow-up of cancer incidence was performed from January 1, 1953, and continued until December 31, 1996, or

until the date of death or emigration, giving 59,251 person-years of follow-up. Smoking habits were determined for 80% of the cohort, 26% of whom were never smokers, 63% of whom were current smokers, and 11% of whom were former smokers. For this time period, The Cancer Registry of Norway offers complete coverage of the population for all site and types of cancer except basal cell carcinoma of the skin.

Estimation of exposure was based mainly on industrial hygiene measurements and on descriptions of changes in the process technology and work practices over time. To categorize the dust, silicon carbide fibre and crystalline silica (quartz and cristobalite) measurements were performed between 1982 and 1988.

The cohort's incidence of lung cancer was increased (74 observed cases versus 39.9 expected; Standardized incidence ratio (SIR) = 1.9; 95% CI 1.5-2.3), and the numbers of stomach cancer (39 observed cases versus 26.5 expected; SIR = 1.5; 95% CI 1.1-2.0) and cancers of the upper respiratory tract (16 observed cases versus 9.6 expected; 95% CI 1.0-2.7) were also higher than expected. The overall incidence of lung cancer was elevated at all three plants, with SIR of 1.7 (8 cases), 1.9 (60 cases) and 2.0 (6 cases). The SIR of lung cancer was associated with cumulative exposure to different types of dust, showing an increasing incidence with increasing cumulative exposure. Total dust, silicon carbide fibre, silicon carbide particle, and crystalline silica exposure measures all showed the same pattern. The standardized incidence ratio (SIR) for the upper silicon carbide fibre exposure category (indicated by $\geq$ 5 fibres/mL×year) was 2.9 (95% CI 1.8-4.5), and, when exposure was lagged by 20 years 3.5 (95% CI 2.1-5.6). In the upper exposure category there was a further increment in risk with increasing cumulative exposure, with SIR = 7.1 (95% CI 1.6-16.7) for cumulative exposures of more than 25 fibres/mL×year. The associations between cumulative exposure to SiC fibres and the SIRs of lung cancer were almost similar between workers who were first employed before or in 1960 and those employed later.

The SIR for stomach cancer increased only slightly with increasing cumulating exposure to total dust, but it was more pronounced with increasing exposure to silicon carbide particles (SIR = 2.3; 95% CI 1.2-4.0 for silicon carbide particles $\geq$ 40 fibres/mL×year). For lag times of 20 years or more the association diminished gradually (SIR = 1.3; 95% CI 0.4-3.3 for silicon carbide particles $\geq$ 40 fibres/mL×year). The incidence of stomach cancer was highest among workers employed in a refinery department, where the silicon carbide products were crushed, cleaned, and packed. For workers employed in a refinery department for more than 1 year, the SIR was 2.6 (95% CI 1.5-4.1). However, no further increment in risk was observed with increasing duration of employment

in these departments. In addition, no association was observed between exposure to various particulates and the incidence of upper respiratory tract cancer.

This study revealed a dose-response relation between lung cancer incidence and cumulative exposure to various types of particulates. Smoking could probably be excluded as an important confounder in the present study. Asbestos was also not a likely explanation for the observed effect of lung cancer, as it has been used on only a small scale, with the highest level of exposure among maintenance workers, and the SIR of lung cancer for more than 5 years of maintenance work was 1.7 (95% CI 0.8-3.3) compared with 3.1 (99.5% CI 1.9-4.9) for more than 5 years of work in the sorting or oven department. Polyaromatic hydrocarbons (PAH) were present in the oven departments of these plants, but in low concentrations and mainly as volatiles and therefore of less or no carcinogenic potency. Measurements of samples at the Norwegian plants suggested exposure levels of less than 10 $\mu g/m^3$ for particulate PAH (n = 10) and less than 0.1 $\mu g/m^3$ for benzo[α]pyrene (n = 3). Crystalline silica exposure would be a more likely causal agent, but the general exposure level also seemed to be low when compared to the substantial lung cancer risk observed in the present study.

The elevated risk of stomach cancer was restricted mainly to employment in the refinery department, where the main exposure has been to silicon carbide particles. However, the association between stomach cancer risk and silicon carbide particles was modest and disappeared with lag times of longer than 10 years.

Bugge et al. (2010)[5] analyzed the same cohort as Romundstad et al.[4] after nine more years of follow-up. This follow-up focused on cancer risk among short- and long-term workers, based on the assumption that these two groups had different exposure and lifestyle characteristics. Short-term workers were defined as having < 3 years (and long-term workers as as having ≥ 3 years) of total employment in the industry. Altogether 531 cancer cases among the 2,612 workers in the total cohort were observed, compared to the expected number of 424.9, which gives a SIR of 1.3 (95% CI 1.1-1.4). The most important single cancer site contributing to the observed excess was an increased lung cancer incidence with 103 cases versus the 51.7 expected (SIR 2.0; 95% CI 1.6-2.4).

Among the short-term workers, they observed an overall excess incidence of cancer (SIR 1.4; 95% CI 1.2-1.6, with an excess of lung cancer (SIR 2.6, 95% CI 1.9-3.5) as the most important contributing factor. The long term workers also had an excess incidence of total cancer (SIR 1.2; 95% CI 1.1-1.3) and lung cancer (SIR 1.7; 95% CI 1.2-2.2).

The short term workers also had increased incidence of non-melanoma skin cancer, thyroid cancer, Hodgkin's lymphoma and cancer at 'unspecified sites'. Elevated SIR levels, although not significant, were seen for several other cancers sites, such as lip, esophagus, stomach, liver, pleura, and bladder. In the long-term worker group, there was an increased incidence of lip cancer and leukemia, in addition to a borderline increased incidence of prostate cancer. Non-significant excesses of cancers of the stomach, nose and skin were also observed.

They conclude that dust exposure in the silicon carbide industry may have contributed to the increased risk among long-term workers, whereas the increased risk among short-term workers may be due to a combination of occupational and lifestyle factors.

In another follow-up study Bugge et al. (2012)[6] examined the relative importance of the exposure factors quartz, cristobalite, SiC particles and SiC fibers, with respect to lung cancer risk, by using a comprehensive historic job exposure matrix based on about 8000 measurements (Føreland et al., 2012[7]). The study cohort was based on the above-mentioned cohort in the Norwegian silicon carbide industry (Bugge et al., 2010[8], Romundstad 2001 et al.[4]) and consisted of 1,687 men, employed between 1913 and 2003, and alive after 1 January 1953. Standardized incidence ratios for lung cancer, with follow up during 1953-2008, were calculated stratified by cumulative exposure categories.

The lung cancer incidence was about twofold increased at the highest level of cumulative exposure to each of the exposure factors (standardized incidence ratios 1.9-2.3 for all agents). Internal analyses showed associations between exposure level and lung cancer incidence for all investigated factors, but a significant trend only for total dust and cristobalite. In multivariate analysis, cristobalite showed most consistent associations, followed by silicon carbide fibers.

The results indicated that crystalline silica in the form of cristobalite was the most important occupational exposure factor responsible for lung cancer excess in the Norwegian silicon carbide industry, but silicon carbide fibers seemed to have an additional effect.

Exposure to quartz and silicon carbide particles did not seem to influence the lung cancer incidence.

3.1.2 Additional human studies

The additional cohort studies are summarized in Table 1 relating exposure to silicon carbide (next tot other substances) to the risk of cancer. Moreover two studies on non-malignant mortality are included in the table which are based on

data from the same abovementioned population of silicon carbide workers in Norway. In these latter two studies increased mortality from non-malignant respiratory disease was observed (Romundstad et al. 2002[9]; Bugge et al. 2011[10]).

Table 1 Overview of additional human studies.

Design, number of workers, gender, country; follow up (years)	Control	Exposure assessment	Effects	Effect	Reference
Cohort of 86 males, Sweden exposed for at least 5 years, follow up 10 years	General male population of Sweden	Exposure to polishing pastes (tallow, beeswax, carnauba wax, alundum, silicon carbide, ferric oxide and chalk)	18 death, 7 died of cancer	RR (95% CI)2.5 (0.9-4.8) No definite conclusions, slightly increased risk of stomach cancer	Järvholm et al., 1982[11]
Cohort of 521 males, Sweden for at least 5 years, follow up 25 years	General population of Sweden	Exposure to abrasives (aluminium oxide and silicon carbide), possible exposure to silica and formaldehyde	79 death, 17 died of cancer, 24 cancer cases in total	RR (95% CI): 2.7 (0.7-6.8) No significant increase in total and cancer mortality Increased risk of lymphoma/myeloma	Edling et al,.1987[12]
Cohort of 727 males, Sweden exposed for at least 1 year, follow up 41 years	Reference cohorts of 3,965 other industrial workers and 8,092 fishermen	Exposure to metal dust (stainless steel; 18% nickel, 8% chromium) and dust from the abrasives (including silicon carbide, aluminium oxide, amorphous carbon dioxide, clay, and phenol-formaldehyde resins	112 cancer cases	RR (95% CI): 0.9 (0.7-1.2) Only increased risk of colon cancer	Jacobsson et al., 1997[13]
Mortality among 2,562 men, working in one of three silicon carbide smelters in the Norwegian SiC industry between 1962 and 1996.	General male population of Norway	Exposure to SiC fibers, quartz, crystobalite, SiC particles	Cancer (n=204)	SMR (95% CI): 1.2 (1.0-1.4)	Romundstad et al., 2002[9]
			Asthma, bronchitis, emphysema (n=45)	SMR (95% CI): 2.2(1.6-3.0)	
			Pneumoconiosis (n=6)	SMR (95% CI): 7.9 (2.9-17.1)	
Mortality among 1,687 long-term workers employed in 1913-2003 in the Norwegian SiC industry	General male population of Norway	Exposure to SiC fibers, quartz, crystobalite, SiC particles using a newjy-revised job exposure matrix	Cancer (n=201)	SMR (95% CI): 1.2 (1.0-1.4)	Bugge et al., 2011[10]
			Asthma, bronchitis, emphysema (n=45)	SMR (95% CI): 2.0 (1.5-2.7)	
			Pneumoconiosis (n=7)	SMR (95% CI): 15 (7.0-31)	

3.1.3 Case studies

Massé et al.[14] reported the results of examination of three workers with the history of long-term exposure to silicon carbide after they had been admitted to a hospital. Patient 1 was a 72-year old man with the history of working at a silicon carbide plant for 35 years prior to retirement at age 65. He had no history of exposure to other industrial dust and had been a moderate smoker. He died soon after admission of ventricular arrhythmia. At autopsy both lungs showed multiple 1- to 3-mm firm "silicotic" nodules with a predilection for the upper lobes and a right ventricular hypertrophy. Patient 2 was a 60-year old man who worked for 30 years at a silicon carbide plant and diagnosed with silicosis at 56. At that time he complained of moderate dyspnoea and pulmonary function tests revealed a very slight decrease in vital capacity. One year later, he developed a well-differentiated squamous cell carcinoma of the lung for which he had a pneumonectomy and remained disease-free at follow-up. He died of central nervous system complications following carotid surgery. Patient 3 was a 69-year old man who had worked for 40 years at a silicon carbide plant before retiring at age 66. He died of a metastatic undifferentiated large cell carcinoma of the lung with a minor component of neoplastic multinucleated giant cells.

Based on light microscopic examination of lung tissues and intrathoracic lymph nodes in all three patients (i.e. nodules containing variable amounts of small needle-shaped birefringent crystalline particles consistent with silica), and scanning electron microscopy and X-ray dispersive spectrometry on a lung sample of patient 3, the authors believe that these tumours and nodular lesions were the result of lung reaction to silicon-containing particles and could, therefore, be considered as silicotic, i.e. inducing pneumoconiosis. The extensive association of anthracotic deposits was thought to be caused by inhalation of unfused finely ground carbon used in the manufacturing process or in the milling, crushing and screening procedures. The ferruginous bodies were believed to be formed in reaction to silicon carbide fibres and were the cause of interstitial fibrosis. They shared features with the uncoated fibrous silicon carbide particles found in the alveoli where a severe macrophagic reaction was observed.

Funahashi and co-workers[15] came to the same conclusion with regard to pneumoconiosis induction by prolonged exposure to silicon carbide. They examined two men, both smokers, who were exposed to silicon carbide for many years in a factory manufacturing refractory bricks and subsequently developed progressive dyspnoea and bilateral reticulonodular densities, using different

instruments and techniques, e.g. pulmonary function tests, chest roentgenograms, energy dispersive X-ray analysis, and High resolution X-ray powder diffraction analysis.

Dufresne et al.[16] evaluated the fibrous inorganic content of post-mortem lung material obtained from 15 men who worked in the primary silicon carbide industry. Lung tissue samples were obtained from pathology departments of six hospitals in Québec. The lungs were examined by transmission electron microscopy, X-ray diffraction, and phase contrast microscopy. Five of the lungs showed evidence of neither lung fibrosis nor lung cancer, six showed evidence of lung fibrosis but not lung cancer, and four showed evidence of both lung fibrosis and lung cancer. Mean duration of exposure was 23.4 (SD = 6.9) years in the first group (lungs that showed evidence of neither lung fibrosis or lung cancer), 28.8 (SD = 5.5) in the second group (evidence of lung fibrosis, but not lung cancer) and 32.3 (SD = 9.0) in the third group (evidence of both lung fibrosis and lung cancer). Smoking consumption was 50.6 pack-years (SD = 30) in the first group, 59.8 (SD = 32.2) in the second group and 39.2 (SD = 25.8) in the third group. Mean years since last exposure were 7.9 (SD = 7.1) in the first group, 7.0 (SD = 1.6) in the second group and 5.0 (SD = 3.5) in the third group.

A substantial number of silicon carbide fibres was observed in the lungs of the subjects in the second and the third groups. The morphology, chemistry and mineralogy of the fibres were similar to those observed in the occupational environment. The geometric mean concentrations of fibres < 5 μm were found to be two and three times higher in the second and third groups in comparison to the first group, though these differences did not approach statistical difference. In the case of silicon carbide ceramic fibres ≥ 5 μm, an excess pulmonary retention was observed in the second and third groups, that approached statistical significance ($p = 0.06$) when compared to controls; for other types of fibres (such as mica, clays, etc.) no statistically significant differences between the first group and the other two groups were observed for both lengths. A substantial number of ferruginous bodies was measured in lung tissues, as was also observed by both Massé et al.[14], and by Funahashi and co-workers[15], and there was a statistically significant difference for lung retention of ferruginous bodies between the first group and the other two groups ($p = 0.02$). Also for silicon angular particles (quartz, cristobalite or silicon carbide) pulmonary retention showed an excess in the second and third group cases that approached statistical significance ($p = 0.06$). These results were taken to indicate that SiC fibres ≥ 5 μm and angular particles containing silicon, and especially ferruginous bodies in lung at higher concentrations relate to lung fibrosis and lung cancer induction. This observation

arises among workers with 23 to 32 years of exposure who had ceased to be exposed for 5 to 9 years.

3.1.4 *Summary of the human data*

Silicon carbide production workers have shown increased risk of lung cancer. In all epidemiological studies concomitant exposure to several other (potentially) carcinogenic substances occurred; therefore lung cancer risk or mortality observed may not be assigned with complete certainty to a single exposure factor. However, the case studies of Masse et al.[14] suggest that the exposure to silicon carbide dust may cause a distinctive pneumoconiosis, and, more importantly, the study of Romundstad et al.[4] showed an increased incidence of lung cancer among workers in three SiC smelter plants. These latter investigators also found an increased incidence of stomach cancer. The exposure to other carcinogenic agents, i.e. asbestos, crystalline silica and polyaromatic hydrocarbons, was not a likely explanation for these observed effects. The incidence of stomach cancer was highest among workers employed in a refinery department, where the SiC products were crushed, cleaned, and packed.

Elevated incidences of lung and stomach cancer were also reported by Infante-Rivard et al.[3] among 585 Québec silicon carbide production workers; however, concomitant exposure to crystalline silica could not be excluded in this case.

The most recent study of Bugge et al. (2012)[6] however, examined the relative importance of the exposures including quartz, cristobalite, silicon carbide particles and silicon carbide fibers, with respect to lung cancer risk. The results indicated that crystalline silica in the form of cristobalite was the most important occupational exposure factor responsible for lung cancer excess in the Norwegian silicon carbide industry, but silicon carbide fibers seemed to have an additional effect. Exposure to quartz and silicon carbide particles did not seem to influence the lung cancer incidence. This is the only human study discriminating between the contribution of fibrous and non-fibrous silicon carbide to the effect.

3.2 Carcinogenicity studies in animals

3.2.1 Exposure by inhalation

Fibrous forms

Davis et al.[17] studied the biological effects of man-made mineral fibres, including silicon carbide whiskers, in long-term inhalation toxicity studies with rats. Two groups of 40 specific-pathogen-free (SPF) rats of AF/HAN strains were whole-body exposed for 7 hours/day, 5 days/week, for almost 41 weeks to each dust. The target airborne fibre concentration was 1,000 fibres/mL (fibre length > 5 μm). The used fibres were glass microfibers, silicon carbide whisker fibres, used commercially for the reinforcement of specialized plastic and metal products and with a mean diameter of 0.45 μm, and an amosite asbestos sample. In addition to the long-term inhalation studies, studies of pulmonary inflammation were performed, as well as intratracheal and intraperitoneal injection studies (the results of the latter studies are reported in the respective sections below). Fibre number concentrations and fibre size distribution for the experimental dust clouds were assessed from membrane filter "snatch" samples collected on 26 sampling days in the case of silicon carbide. In the case of silicon carbide, the following values were obtained: of 984 fibres/mL with the length 5 μm 615 were of length 5-10 μm, 167 of length 10-15 μm, 100 of length 15-20 μm and 102 > 20 μm. Groups of 4 rats from each experimental study were killed after the 12-month inhalation period to examine levels of tissue damage at this stage. The remaining animals were left for their full life span until they showed some kind of debilitation or until the number of survivors in each group had dropped to six. For estimations of advanced alveolar interstitial fibrosis occurring in the oldest animals, all those dying within 2 months of the final killing date were included. In practice this produced 9 animals in the case of silicon carbide.

For each type of dust a very heavy lung burden was achieved at the end of the 12-month exposure period, with approximately 500×10^6 fibres > 10 μm per rat lung. However, for glass microfiber treatment group the lung burden of fibres below 5 μm in length was more than 5 times higher than with the other dusts. Also, although the number of long fibres (> 15 μm in length) in the dust clouds had been very closely matched, animals treated with microfiber had fewer of these long fibres in their lungs at the end of the 12-month exposure period than animals treated with the other two dusts. This difference was particularly marked

for fibres > 20 μm. Following the end of dusting, clearance for silicon carbide was minimal 12 months after the end of the exposure period, independently of the fibre length, whereas in the case of amosite and glass microfibers the shortest material was largely eliminated, although the removal of fibres > 5 μm in length was slower.

As age increased, animals dying from the silicon carbide treatment group showed progressively more involvement of alveolar walls in bronchoalveolar hyperplasia. Multiple areas of lung tissue up to 1 cm in diameter showed marked thickening of alveolar walls with increase in connective tissue staining and complete conversion of the lining epithelium to rounded cells of Type II pneumocyte pattern. Within these thick-walled alveoli there were usually aggregates of fibre-containing macrophages and desquamated epithelial cells. In the oldest animals pathological changes had sometimes become so marked that there was some restructuring of the lung tissue, with epithelial lined spaces no longer corresponding to the original alveoli. These changes could progress in two directions. Sometimes fibrous thickening of the airspace walls predominated, although spaces were lined with rounded epithelial cells; in others, hyperplasia of the epithelium was more apparent with much smaller epithelial-lined spaces that presented a pattern of adenomatosis. In animals treated with microfiber, these advanced lesions were almost entirely absent. Areas of advanced fibrosis/ bronchoalveolar hyperplasia were estimated in all animals from the treatment groups that survived until 2 months or less before the end of the study. In the 9 silicon carbide-treated animals that lived until 2 months or less before the final killing date the mean areas of advanced fibrosis were 8.7% of the lung parenchyma.

In 42 silicon carbide-treated rats that were allowed to survive beyond the end of the dusting period, 20 tumours of the lung and pleura were recorded (5 carcinomas, 5 adenomas and 10 malignant mesotheliomas). A few animals had more than one type of tumour so that the number of tumour-bearing animals was 16. In comparison, in the group of rats treated with microfibers only 4 out of 38 rats developed single benign pulmonary neoplasms. Furthermore, several of the benign tumours found in silicon carbide-treated animals were quite large lesions several millimetres in diameter and visible at autopsy, while all four found in the microfiber treatment group were < 1 mm in diameter and were only found by microscopic examination following step sectioning of the lung.

In comparison to amosite, silicon carbide produced slightly fewer tumours in the lung parenchyma, but produced a total of 10 mesotheliomas compared with 2 with amosite. Some of these mesotheliomas were obvious at autopsy where they

had caused haemorrhage into the pleural cavity or pericardium, in some cases leading to pericardial rupture.

The group of control rats designated for this group of inhalation studies was run synchronously with the later experiments and still had some survivors at the moment of article publication. In the previous batch of controls of the same rat strain maintained in the same laboratory, the figures for pulmonary tumours were 1 adenoma and 1 carcinoma in 47 rats.

For estimations of advanced alveolar interstitial fibrosis occurring in the oldest 9 animals in the case of silicon carbide, there was a marked macrophage reaction with most of the cells containing numerous fibres, next to other pathological changes. This was mainly located at the bifurcations of the terminal and respiratory bronchioles, where much fibre had become interstitialised. Fibres were present in macrophages, but there was a significant increase in the number of other interstitial cells including fibroblasts, with an increase in staining for both reticulin and collagen. In contrast, animals treated with glass microfibers showed much less reaction to inhaled dust, the amount of this change was probably < 1% of that occurring with the amosite treatment.

Miller et al.[18] used the data of Davis et al.[17] to examine the influence of fibre dimensions, persistence in the lung, and dissolution and cell toxicity in vitro, on the risks of developing lung tumours in rats. The silicon carbide whisker fibres in the Davis study were found to include a significant proportion of fibres with unusual shapes, resembling complexes of joined fibres, shaped, variously, like a “7”, or a “T”, or a “W”. To avoid including the very large number of variables represented by a complete bivariate set of length and diameter variables, airborne fibre concentrations were summarized not only in cumulative length categories but also in two diameter classes according to whether the fibre diameters were greater or smaller than 0.95 μm. The incidence of tumours was treated as a binomial response variable. Its relationship with characteristics of individual fibre types was investigated by standard methods of multiple logistic regression using the statistical software package Genstat. Despite the small number of data points, the results suggested a primary influence of the airborne concentrations of the numbers of fibres thinner than 1 μm and longer than 20 μm, and of the measured dissolution rate of the fibres. The obtained results were thus consistent with the hypothesis that, for inhalation studies, lung carcinogenicity of man-made fibres in rats is a function of fibre length and that the man-made fibres longer than 20 μm, longer than would be easily engulfed by macrophages, had the greatest potency to be carcinogenic. The length influence in man-made fibres appeared to be similar to that of the asbestos minerals. The authors also

concluded that the dissolution measure of the fibres was a somewhat better predictor of carcinogenicity than the direct biopersistence measure.

Non-fibrous forms

No long-term animal studies designed to detect carcinogenicity could be retrieved on inhalatory exposure to non-fibrous silicon carbide particles (see also Table 3).

3.2.2 Intrapleural administration

Fibrous forms

Stanton et al.[19] implanted durable minerals, including silicon carbide whiskers, in the form of particles of respirable size in the pleurae of outbred female Osborne-Mendel rats for periods of more than 1 year. A total of 72 experiments were performed, by applying a standard 40 mg dose of particles (corresponding to ca. 145 mg/kg bw*) uniformly dispersed in hardened gelatine by open thoractomy directly to the left pleural surface of 12- to 20-week-old rats. In each experiment, 30-50 rats were treated and followed for 2 years, at which time the survivors were killed. All rats were necropsied and all organs and tissues were examined microscopically. A positive response was the occurrence of pleural sarcomas that resembled the mesenchymal mesotheliomas of man, developing after 1 year. Three types of controls were considered: untreated rats, rats that received thoratectomies but no pleural implant, and rats with pleural implants of non-fibrous material. There were two types of spontaneous tumours observed in the studies: the fibrosarcomas of left mammary gland and the subcutaneous fibrosarcomas induced by suture material. Vigilance and early surgical removal accounted for most mammary tumours; the use of synthetic, biodegradable, polyglycolic acid sutures largely eliminated suture sarcomas.

Silicon carbide used in the study was a single sample (whiskers), which was of exceptionally fine uniform dimension.

The incidence of clearly apparent pleural neoplasms in untreated, aged outbred Osborne-Mendel female rats was essentially non-existent. However, a few pleomorphic sarcomas that might be confused with pleural tumours occurred in the left thorax of both treated and, to a lesser degree, untreated controls.

---

* The value has been calculated using the default value for average body weight of female rats of 275 gram in chronic studies.[20]

Although these tumours involved the thickness of the chest wall, in most cases the tumours appeared to be derived either from mammary gland fibroadenoma or from suture granuloma in the subcutaneous tissues. But there remained a few tumours for which no definite origin could be determined and which were histologically comparable with pleural sarcomas. In both the experimental groups and the control groups these questionable tumours were counted as pleural sarcomas. The incidence of pleural sarcomas in all 3 control groups combined was 7.7 ± 4.2% (calculated by the life table method). The incidence of pleural sarcoma in a particular experimental group was significantly greater than the incidence in the combined control group only if it exceeded 30%. For silicon carbide, actual tumour incidence was 17/26, with the common log particles of dimensions ≤ 0.25 μm × > 8 μm/mg of 5.15.

In general, the results indicated that particles in the relatively thin- and long-dimensional categories were associated with higher tumour probabilities. The best correlation was obtained with the fibres that measure ≤ 0.25 μm × > 8 μm.

Johnson and Hahn[21] investigated whether silicon carbide whiskers are carcinogenic in the intrapleural inoculation assay, by injecting 3 groups of 30 female F344/N rats, 6 to 8 weeks old, intrapleurally with 20 mg (corresponding to ca. 73 mg/kg bw*) of 3 different silicon carbide whiskers samples (SiCW 1, SiCW 2 and SiCW 3), suspended in 0.4 ml saline. The mean fibre length in three samples was determined by scanning electron microscopy and amounted to 4.5 (±0.23), 20.1 (±1.01) and 6.6 (±0.40) μm and the diameter < 1 μm. The number of fibres in three samples was 7.6×10^6, 1.6×10^5 and 1.1×10^7 fibres per 1 mg samples, respectively, resulting in the doses of 5.6×10^8 fibres/kg bw, 1.2×10^7 fibres/kg bw and 8×10^8 fibres/kg bw. The rats were killed by intraperitoneal injection of sodium pentobarbitone when moribund or when 20% of the longest surviving group of rats remained alive. All rats were necropsied and examined for gross lesions. The first rat died from respiratory distress at 166 days after inoculation with SiCW 2, and the first tumour was found 273 days after inoculation with SiCW 2. Rats inoculated with SiCW 1 or 2 had the shortest life spans, which were significantly shorter than those of the control animals treated with saline. The life spans of the rats treated with SiCW 3 were not significantly different from those of control rats.

Out of 30 animals treated with SiCW 1 and SiCW 2, 27 (90% CI) and 26 (87% CI) developed pleural mesotheliomas, with the median survival time (days after injection) of 453 (±21) and 519 (±20) days, respectively. In contrast, 7 rats

* This value has been calculated using the default value for average body weight of female rats of 275 gram in chronic studies.[20]

(27% CI) of the rats treated with SiCW 3 developed pleural mesotheliomas, in comparison to 57% of those treated with the positive control (crocidolite). No tumours were identified in the animals treated with saline. The tumours identified, with one exception, were sarcomatous in appearance and, in all but one case, involved the visceral pleura. Fibres were found in sections from all treatment groups.

Vasil'eva et al.[22] (article published in Russian) studied the carcinogenicity of silicon carbide by injecting three times groups of 93 male and female rats into the pleural cavity with 20 mg of silicon carbide in 1 mL of physiological solution. The interval between injections was one month. Ninety-six rats of the second group were injected three times with the same doses of chrysotile B (positive control) and 52 rats with physiological salt solution (negative control). The animals were observed until their natural death and tumours, as well as organs, were subjected to morphological evaluation. Pleural mesothelioma's were induced in 47.7% of the silicon carbide treated group and in 34.1% of chrysotule B treated group, while in the control group no mesothelioma's were seen. [The Committee was unable to evaluate the details of this study.]

Non-fibrous forms

No relevant animal studies were retrieved on pleural administration of non-fibrous silicon carbide particles (see also Table 3).

3.2.3 Intraperitoneal injection

Fibrous forms

Adachi et al.[23] evaluated the carcinogenic risk of man-made fibres, including silicon carbide whiskers, based on mesothelioma incidence in female F344 rats after intraperitoneal administration. Female F344/Jslc rats were administered intraperitoneally a suspended solution (1 mg/ml) of fibres in saline. Five millilitres was the highest volume administered to a rat in a week. At first, all types of fibres were examined at a dose of 10 mg/rat (corresponding to ca. 36 mg/kg bw*). Based on the tumour incidence at 10 mg/rat, doses for the second experiment were either increased to 20 mg/rat (corresponding to ca. 73 mg/kg bw*), or reduced to 5 mg/rat (corresponding to ca. 18 mg/kg bw*). Rats were

* This value has been calculated using the default value for average body weight of male and female rats of 375 gram in chronic studies.[20]

observed for two years after the administration. The number of fibres were counted by scanning electron microscopy, resulting in $414 \cdot 10^3$ fibres/µg. This corresponded to the doses of 4.14×10^9 fibres/kg bw for the dose of 10 mg/rat; 8.3×10^9 fibres/kg bw for the dose of 20 mg/rat and 2.1×10^9 fibres/kg bw for the dose of 5 mg/rat.

All rats administered 10 mg of silicon carbide whisker developed peritoneal mesothelioma within a year. In the group of rats administered 5 mg of silicon carbide whisker, incidence of mesothelioma was 70% at one year after the administration. The authors estimated the carcinogenic potency of silicon carbide whiskers as 2.4 times that of IUCC chrysolite B. The fastest development of peritoneal mesothelioma was identified in the rat administered 5 mg of silicon carbide whisker at 133 days of the experiment. At autopsy, hemorrhagic ascites fully filled the abdominal cavity and numerous nodules, ranging from 1 to 3 mm, were spread at the abdominal wall and epithelium of the organs. These lesions were found in most (95%) rats which eveloped peritoneal mesothelioma at the terminal stage.

Tumour cells spread the whole gamut of abdominal cavity, however, no metastases to other organ were found. Adhesive growth of the tumour between liver and diaphragm was common in the rats with mesothelioma and coagulation of deposited fibres at the same site was also common in the autopsied rats at the end of the experiment. Microscopically, tumour cells showed a variety of characteristics including epithelial or sarcomatous structures and some of the extensive cases had osseous formation in the tumour.

Miller et al.[24] tested a range of man-made mineral fibres, including silicon carbide whiskers, for evidence of carcinogenicity by injection into the peritoneal cavity of 24 male SPF Wistar rats and monitored them for the rest of their lives for the development of mesothelioma. The target dose was designed as the estimated mass required to contain 10^9 fibres > 5 µm in length and amounted to 14.2 mg silicon carbide (corresponding to ca. 30 mg/kg bw* and 2.1×10^{10} fibres/kg bw). The fibres were < 0.95 µm in diameter.

Out of 24 rats administered silicon carbide whiskers, 22 (92% CI) developed mesothelioma, with median mesothelioma survival of 257 days (SD = 52). Similarly to the study of Adachi et al.[23], the samples of silicon carbide whiskers was found to produce mesotheliomas earlier and at a faster rate than any other fibre type which was tested, at least in the first 300 days after injection. However, mesothelioma production appeared to slow down relative to the other fibres, after

* This value has been calculated based on the default value for average body weight of male rats of 475 gram in chronic studies.[20]

a particularly rapid start. A plausible explanation suggested by authors include the hypothesis that silicon carbide with its unusually complex fibrous shape may undergo some modification in vivo that reduces its carcinogenic potential over time, or possible variations between animals in the actual dose injected or reaching the target organs.

To assess the ability of amosite, silicon carbide, and microfiber to produce mesotheliomas, Davis et al. 1996[17] injected intraperitoneally a dose of 1 x 10^9 fibers (length > 5 pm) into groups of 24 rats. The appropriate mass of fiber was suspended in saline so that the required dose was administered as a single intraperitoneal injection of 2 ml. Following the intraperitoneal injection, the numbers of mesotheliomas developing in groups of 24 rats were 21 for amosite, 22 for silicon carbide, and 8 for microfiber. The silicon carbide produced mesotheliomas particularly rapidly, and even with amosite almost half of the mesothelioma deaths had occurred before any of the microfiber group died from mesothelioma. The median survival time (at which 50% survival was achieved) was 257 days for silicon carbide and 509 days for amosite. For the microfiber, it was 679 days, although the smaller number of mesothelioma deaths causes a much less precise estimate for this fiber.

A steep dose-response relationship for tumours was reported by Pott et al.[25] after application of 0.05 to 25 mg (corresponding to ca. 0.13 mg/kg bw and 91 mg/kg bw*) of SiC whiskers in a chronic intraperitoneal injection study in rats. The percentage of tumours steadily increased from 12.5% up to 97% as a function of the quantity of these whiskers. The whiskers contained 107,000,000 fibres > 5 μm in length and < 2 μm in width and an aspect ratio > 5/1 per 1 mg of the sample. This corresponded to doses of 1.4×10^6 and 7.1×10^8 fibres/kg bw for 0.05 mg and 25 mg doses, respectively. Unfortunately, the experiment was disturbed by an infection occurring in the months 12 and 13. About 34% of the rats died, mainly in the groups with low exposure. Therefore the percentage of mesotheliomas and sarcomas observed in the abdominal cavity was not a function of all the rats that were present at the start, but only of those that either survived 56 weeks or died earlier and were diagnosed as tumour-bearing.

Non-fibrous forms

Roller et al.[26] examined groups of male or female rats for 30 months for tumours in the abdominal cavity after repeated intraperitoneal injections with dust

* This value has been calculated based on the default value for average body weight of female rats of 275 gram in chronic studies.[20]

suspensions of mineral and vitreous fibres. Two groups of 48 female and 72 male rats were injected either 5 or 20 times with 50 mg of granular silicon carbide (corresponding to total doses of approximately 667 mg/kg bw and 2,666 mg/kg bw*). Two mesotheliomas were found in a total of 395 evaluated rats treated with saline or granular silicon carbide. Other tumours are listed in Table 2.

Table 2 Tumours except mesothelioma in the abdominal cavity of rats.

Treatment (total dose)	Sex	Rats evaluated	Uterus	Ovary	Testicle	Liver	Pancreas	Kidney	Suprarenal gland	Mesentery	Lymph nodes	Scrotum	Intestine	Bile-duct	Abdominal cavity
NaCl 40 mL	female	93	12	-	-	1	-	-	-	1	1	-	-	-	1
	male	69	-	-	2	-	-	-	1	-	1	1	-	-	-
SiC	Female	47	6	2	-	-	-	-	-	1	-	-	-	-	-
(granular)	male	71	-	-	-	1	-	-	2	1	-	-	-	-	-
250 mg															
SiC	female	45	7	1	-	-	-	-	-	1	-	-	-	-	-
(granular)	male	70	-	-	1	-	-	-	-	-	-	-	-	-	-
1,000 mg															

In contrast to their above-mentioned study on whiskers Pott and co-workers observed no increase in tumours in a carcinogenicity study with nonfibrous silicon carbide[27], which was injected in Wistar rats (WU/Kiβlegg-Iva: WIWU, 8-10 weeks) intraperitoneally under CO_2 anaesthesia as dust suspensions in 2 ml buffered 0.9% sodium chloride solution. Silicon carbide was injected repeatedly at intervals of two weeks into 48 female and 72 male rats at two dose levels (5 times 50 mg and 20 times 50 mg, corresponding to total doses of ca. 667 mg/kg bw and 2,666 mg/kg bw*).

One year after the first intraperitoneal injection of silicon carbide, the average body weight of the rats injected with 20×50 mg was about 5% lower in both sexes than in the control group injected 20 times with 2 ml saline. Six months later this difference was between 7 and 8% in both sexes. The mortality was less than 20% after 90 weeks in all silicon carbide groups. No serosal tumours were found in the abdominal cavity of 35 histopathologically examined rats. Observations 90 weeks after the start of the experiment did not indicate any

* This value has been calculated using the default value for average body weight of male and female rats of 375 gram in chronic studies.[20]

obviously acute or chronic toxic effect in male and female rats due to 1000 g nonfibrous silicon carbide dust administered intraperitoneally.

Rödelsperger and Brückel[1] analyzed the results reported by Pott et al.[27] to determine whether the granular silicon carbide may still contain fibrous cleavage fragments which fulfil the definition of WHO fibres. Samples of the original granular and fibrous silicon carbide were suspended in water and filtered. One half of each filter was analyzed by scanning electron microscopy (SEM, magnification ×2,500) and transmission electron microscopy (TEM, magnification ×10,000). The concentration of WHO fibres was determined to be 58,000 fibres/mg for the granular sample compared to 48,000,000 (SEM) and 42,000,000 (TEM) fibres/mg for the whiskers. The aspect ratio exceeded 10/1 for only 3.3% of the fragments in the granular sample, but in each analysis for 96% of the whiskers. In addition, 0% of the fragments in the granular sample compared to 44% and 30% of the whiskers were more than 10 µm long. In total, 15 and 58×10^6 WHO fibres were injected with 250 mg and 1000 mg of the granular silicon carbide, respectively, even though only 0.8% and 0% tumours were recorded. However, 20.1% and 43.3% tumours would have been expected if the carcinogenic potency were the same for the fragments and for the whiskers.

The authors concluded that the carcinogenic potency appeared to be a function of the shapes of the WHO fibres and was much lower for silicon carbide cleavage fragments than for whiskers. They concluded that carcinogenicity was mainly restricted to a subgroup of WHO fibres longer than about 10 µm and thinner than about 1 µm.

3.2.4 *Additional animal studies*

Besides the studies reported above, a number of additional studies were available, which did not demonstrate occurrence of neoplastic lesions upon exposure to silicon carbide (see Table 3). Exposure periods in these studies were generally too short for such lesions to develop.

Akiyama et al.[28] exposed 42 male Wistar rats to silicon carbide whiskers for 6 h/day, 5 days/wk for 1 yr by inhalation. The control rats were exposed to clean air in identical, adjacent chambers under similar conditions of flow, temperature, and humidity.The mass median aerodynamic diameter, the geometric mean fibre diameter and the geometric mean fibre length were 2.4 µm (± 2.2), 0.5 µm (± 1.5) and 2.8 µm (± 2.3), respectively. The daily average exposure concentrations were 2.6 ± 0.4 mg/m^3 (98 ± 19 fibres/mL) The rats were sacrificed at 6 days and 3,6, and 12 months after the exposure.

Table 3 Additional animal studies with silicon carbide.

Species/Strain/ No. per Sex per Group	Route of exposure, exposure duration Concentration tested	Fibrous/non-fibrous form	Observed effects	Reference
Rats (gender not specified)/ Sprague-Dawley/ n = 50	Inhalation 6 hours/day, 5 days/week for 13 weeks 0.09, 3.93, 10.7 and 60.5 mg/m^3 (0, 630, 1,746 and 7,276 SiC whiskers/ mL)	Fibrous form (=whiskers)	Increased lung weight; Inflammatory lesions; bronchiolar, alveolar, and pleural wall thickening; local pleural fibrosis in lung; reactive lymphoid hyperplasia in bronchial and mediastinal lymph nodes	Lapin et al., 1991[29]
Male rats / Wistar/ n=42	Inhalation 6 hours/day, 5 days/week for one year 2.6 ± 0.4 mg/m^3 (98 ± 19 fibres/mL)	Fibrous form (=whiskers)	Increased lung weight; fibrotic changes in lungs	Akiyama et al., 2007[28]
Female rats/ Wistar n=50/ group and n=42/ group	Inhalation exposure for five hours a day on five consecutive days, followed by a rest period of two days and a re-exposure period of five consecutive days. Total exposure time was 50 hours. Observation period up to 90 days 20 mg/m^3	Non-fibrous form (grain size < 3 µm)	Increased lymph node weights; No significant changes in lung weights. High total cell numbers as well as alveolar macrophages three days after the end of inhalation. SiC produced no specific stimulation of granulocytes. No divergent results from those of controls. SiC is deposited practically inert in the lung.	Bruch et al., 1993[30]
Female rats/ F344/50	Single intratracheal administration, followed by 18 months observation period 1 mg SiC/100 mL minute respiratory volume) and 5 mg SiC/100 mL minute respiratory volume	Fibrous form (=whiskers)	Extensive pulmonary granuloma; fibrosis, interstitial pneumonia, atelectasis, bronchial mucosal hyperplasia, squamous metaplasia	Vaughan et al., 1993[31]
Female rats/ F344/50	Single intratracheal administration, followed by 18 months observation period 1 mg SiC/100 mL minute respiratory volume and 5 mg SiC/100 mL minute respiratory volume	Non-fibrous form (=platelets)	No significant histopathological changes	Vaughan et al., 1993[31]
Female rats/ Wistar	Single intratracheal injection, followed by observation period of 3, 8 and 12 months 50 mg SiC/0.50 mL	Non-fibrous form (diameter < 3 µm)	Slight increase in average lymph node weights with no further alterations from three to 12 months. Completely inert deposition of SiC dust in the lung and the lymph nodes. The dust was compactly located without accompanying cellular responses (no granulocytes). No collagen development was not identified. SiC dust can be considered inert from the experimental results.	Bruch et al., 1993[32]

Sheep n=8/group	Intratracheal, catheterisation of the tracheal lobe, followed by 8 month observation period 100 mg in 100 mL	Fibrous form	Peribronchiolar fibrosing alveolitis. Nodular lesions in the parenchyma composed of multinucleated macrophages, monocytes and a few neutrophils and containing several SiC fibers and "bodies". Cellularity (macrophages,lymphocytes, neutrophils) was increased with an attenuation over time. This pattern was also seen in the response of LDH over time. Fibronectin production at month 8 was significantly increased. Fibroblast growth activity was increased Essentially the whiskers produced a sustained nodular fibrosing alveolitis.	Begin et al., 1989[33]
Sheep n=8/group	Intratracheal catheterisation of the tracheal lobe, followed by 8 month observation period 100 mg in 100 mL	Non-fibrous form	Slight and transient early increase in cellularity (macrophage population, lymphocytes and neutrophils). Essentially granular SiC appeared inert.	Begin et al., 1989[33]
Rats (gender not specified)/F344/ 20	Single intraperitoneal administration, followed by 18 months observation period 20 mg/mL	Fibrous form (=whiskers)	Diffuse, intense desmoplastic reaction of serosal surfaces, peritoneal fibrosis	Vaughan et al., 1993[31]

The amount of silicon carbide whiskers deposited in rat lungs 6 days after the end of the inhalation period of 12 months was 5.3 ± 1.4 mg. This amount declined exponentially. A biological half life of 16 months was calculated using a one-compartment kinetic model.

Histopathological observations were made at 6 days and 12 mo after 1 yr of inhalation. Small fiber-aggregated foci were diffused in the alveolar space in the entire lung field shortly at 6 days after 1 yr of inhalation. Some of the silicon carbide whiskers were deposited in the interstitial tissue and some of them were accompanied by collagenous material. The infiltration of inflammatory cells around the aggregated fibers was not remarkable. There was a slight thickening of a part of the pleura due to fiber deposition.

One year after the end of the 1-yr inhalation exposure, fibrotic changes were remarkable around some fiber-aggregated regions. In these regions, fibrous thickening of the alveolar wall around fiber aggregations and infiltration of inflammatory cells, mainly macrophages and monocytes, were found. They were observed in the lung field as a magnified image of alveolitis at low magnification. Bronchoalveolar hyperplasia formation was observed in two animals in the exposed group. Fibrous aggregations were scattered in the bronchoalveolar hyperplasia. No neoplastic lesions were observed. No follow up more than 1 year was performed after the end of the inhalation period.

3.2.5 *Summary of the animal data*

From the available animal data it can be concluded that the fibrous form of silicon carbide is able to induce tumours upon inhalation, as well as upon intraperitoneal and intrapleural administration.

Upon inhalation Davis et al.[17] reported the development of carcinomas, adenomas and methotheliomas in lungs of rats exposed to silicon carbide fibres. In addition, bronchoalveolar hyperplasia and advanced fibrosis of the lung parenchyma were found in two available studies.[28,29] Dose-response studies were unfortunately not available. Findings of Miller and co-workers[18] suggest that silicon carbide is carcinogenic when present in the fibrous form, and its carcinogenicity is a function of the fibre length, with fibres longer than 20 µm having the greatest effect on carcinogenicity. In a short-term inhalation study (90 days) in rats non-fibrous silicon carbide was considered inert (Bruch et al.[30]), but data from long term studies are lacking.

Intraperitoneal administration of silicon carbide fibres to rats could lead to early development of peritoneal mesotheliomas. A steep dose-response relationship for tumours was reported by Pott and co-workers[25] in a chronic intraperitoneal injection study in rats after application of silicon carbide whiskers. However, no increased tumour incidence was found in rats which had received an injection of non-fibrous silicon carbide.

Stanton et al.[19] reported the increased incidence of pleural carcinomas, resembling mesenchymal mesotheliomas in man, 1 year after intrapleural administration of silicon carbide in rats. The development of pleural mesotheliomas was also reported in other studies upon intrapleural administration. Also development of adenocarcinomas in combination with mesotheliomas, and development of peritoneal mesotheliomas upon intrapleural administration of silicon carbide to rats was reported. The overall frequency of mesotheliomas was found to be comparable to that of rats injected with asbestos, used as a positive control in some studies. No animal data on pleural administration of non-fibrous silicon carbide were retrieved.

Intratracheal administration of fibrous silicon carbide did not result in tumour development. In rats hyperplasia and metaplasia were observed, in sheep a sustained nodular fibrosing alveolitis developed. Non-fibrous silicon carbide did not lead to significant histopathological changes in rats and sheep.

Chapter 4

Mode of action

4.1 Genotoxic mode of action

4.1.1 Gene mutation assays

In vitro

No data on mutagenicity of silicon carbide in prokaryotes and yeast have been recovered from public literature.

In vivo

No in vivo data (from humans and experimental animals) on mutagenicity of silicon carbide have been recovered from public literature.

4.1.2 Cytogenetic assays

In vitro

Peraud and Riebe-Imre[34] studied the toxic and chromosome-damaging properties of several man-made fibres, including silicon carbide, in an in vitro cell system of epithelial lung cells M3E3/C3 of the Syrian golden hamster. The test substances suspended in growth medium were added at concentrations of 0.1, 1.0

and 2.0 µg/ml to the cell cultures. As a measure of toxicity mitotic indexes were determined by evaluating the relationship between binucleated and mononucleated cells of 1,000 scored cells. The authors also evaluated the amount of micronuclei with a kinetochore, which allows the discrimination between whole chromosome or a centric fragment as the origin of the micronucleus.

A rise in the number of cells with micronuclei with increasing concentration was observed for all fibres. Chrysolite was most effective in micronucleus induction, followed by silicon carbide. A depression of the mitotic index was observed upon silicon carbide treatment. An evaluation of the amount of micronuclei with a kinetochore indicated that the relative portion of kinetochore-positive micronuclei was in the range of the untreated control for silicon carbide. It may be concluded that the substance is clastogenic and not aneugenic.

In vivo

No in vivo data (from humans and experimental animals) on genotoxicity of silicon carbide have been recovered from public literature.

4.1.3 Miscellaneous

In vitro

Brown et al.[35] studied the intrinsic hydroxyl radical activity of several types of man-made fibres, including silicon carbide, by supercoiled plasmid DNA scission and high-performance liquid chromatography using a hydroxyl radical trap salicylate. The authors used rat lung lining fluid to coat the fibres to determine whether the oxidant-generating ability could be modulated by modifying the fibre surface reactivity. The role of iron in mediating hydroxyl radical production was assessed by the use of the chelator desferrioxamine-B, and the hydroxyl radical scavenger mannitol was utilized in some assays. The concentration used in the experiments was adjusted to equal 8.24×10^7 fibres/mL, as this concentration was found to be non-toxic to cells in the culture. The length distribution in silicon carbide fibres was as follows: 60.86% had a length above 10 µm and 27.6% had a length above 20 µm.

All tested fibres displayed some free radical activity; however, except of long-fibre amosite asbestos, which caused 55% depletion of supercoiled DNA, it ranged from 5 to 20% and was not significantly different from control. The effects of the hydroxyl radical scavenger and rat lung surfactant were examined

therefore only for amosite asbestos. The introduction of these agents in the assay resulted in supercoiled DNA depletion being limited to a level that was not significantly different from the control. Silicon carbide also did not exhibit hydroxyl radical generation in salicylic acid assay. The authors concluded that free radicals are either not involved in silicon carbide carcinogenicity, or that the assay conditions were not sensitive enough to detect free radical generation in this case.

Vaughan et al.[36] studied DNA synthesis after exposure to SiC whiskers in BALB/3T3 embryonic mouse cells (clone A31). Two types of whiskers were used, one (SiCW-1) with a diameter of 0.8 (SD = 0.3) μm, average length of 18.1 (SD = 14.3) μm and aspect ratio of 23.3 (SD = 18.7), and another (SiCW-2) with the diameter of 1.5 (SD = 0.6) μm, average length of 19.0 (SD = 11.0) μm and aspect ratio of 15.3 (SD = 11.2). Crocidolite was used as a positive control, while saline vehicle was used as a negative control. The rate of DNA synthesis in cells exposed to fibres was determined by measuring the incorporation of [^{3}H]thymidine (100 μCi/mM) into DNA. The cells were exposed to test materials suspended in complete medium at concentrations ranging from 0.0 to 2.0 μg/cm^2 followed by 2 hours exposure to [^{3}H]thymidine (2.0 μCi/mL). The amount of [^{3}H]thymidine incorporated into DNA was determined by liquid scintillation counting. Cells were also scored for multinuclearity after incubation with the test material at 5 μg/cm^2 for 48 h.

The authors found that DNA synthesis rates in fibre/whisker-exposed cells were generally elevated relative to the controls, often by a factor of as much as 2.5, but the results were inconsistent. Significant increases in total cellular DNA content were consistently observed 10-20 generations after treatment, with cells treated with SiCW-1 having a 39% and cells treated with SiCW-2 a 42% increase in comparison to the negative control. Cells treated with the positive control crocidolite showed a 75% increase of total cellular DNA content.

In vivo

No relevant in vivo data (from humans and experimental animals) were retrieved from public literature.

4.2 Carcinogenic mechanism and comparison with asbestos

Brown and co-workers[37] studied a panel of mineral fibres, including silicon carbide, for their ability to cause translocation of the transcription factor NF-*k*B to the nucleus in A549 lung epithelial cells, as detected by immunofluorescent

staining. The authors hypothesize that translocation of NF-kB results in transcriptional activation of genes for pro-inflammatory cytokines. Treatment of A549 cells for eight hours with silicon carbide (1.3 to 16.48 x 10^6 fibres/ml) resulted in a concentration-dependent increase in positively stained cells. Silicon carbide proved more than twice as potent as other pathogenic fibres (amosite asbestos and refractory fibre 1) in this assay, while non-pathogenic fibres did not induce a significant effect. Based on these observations the authors conclude that nuclear translocation of NF-kB in A549 cells can be used as a short term in vitro assay to discriminate pathogenic and non-pathogenic fibres. In the same study Brown and co-workers showed that the positive effect of silicon carbide could be mimicked by hydrogen peroxide, while antioxidants such as curcumin and nacystelin blocked the effect of silicon carbide on NF-kB translocation. Based on these observations the authors conclude that silicon carbide exerts its activity by induction of oxidative stress and possibly a subsequent inflammatory response.

The same investigators (Brown et al.)[38] also studied the ability of several types of fibres, including silicon carbide, to deplete antioxidants glutathione and ascorbate in lung lining fluid and lung epithelial cells in vitro. Rat lung lining fluid was used. As positive control chemically produced oxidants, i.e. superoxide and hydroxyl radicals, were used. Also the ability to deplete glutathione and ascorbate in pure solutions was investigated for comparison.

The results indicate that silicon carbide, as well as other fibres, was able to deplete the glutathione contents in lung lining liquid; however, the most significant effects were observed with two glass fibres which were shown to be non-pathogenic in animal studies. The depletion of glutathione in lung lining liquid was clearly number dependent. The same glass fibres also significantly depleted the ascorbate levels in lung lining fluid. The authors concluded that antioxidant depletion in lung lining liquid in vitro is not a reliable discriminator of fibre pathogenicity.

Vaughan et al.[36] studied the cytotoxicity on and transformation of BALB/3T3 embryonic mouse cells (clone A31) upon exposure to SiC whiskers. Two types of whiskers were used, one (SiCW-1) with the diameter of 0.8 (SD = 0.3) μm, average length of 18.1 (SD = 14.3) μm and aspect ratio of 23.3 (SD = 18.7), and another (SiCW-2) with the diameter of 1.5 (SD = 0.6) μm, average length of 19.0 (SD = 11.0) μm and aspect ratio of 15.3 (SD = 11.2). Crocidolite was used as a positive control, while saline vehicle was used as a negative control. Cytotoxicity was determined by dye exclusion and by ^{51}Cr release. The effect of silicon carbide on cell proliferative ability was also studied by seeding 300 cells per 60-mm culture dish and incubating for 24 h before treatment with the test material at varying concentrations, with the subsequent colony counting by inverted phase

microscopy. Transformation frequency was determined after the exposure to the test material at 5 µg/cm^2 for 24 hours, by scoring foci exhibiting layered cell growth and the swirling pattern characteristic of transformed colonies as positive. In addition, total DNA content was estimated in fibre-exposed cells.

Within 24 h of being added to cell cultures, numerous fibres which could be detected by phase contrast were found associated with the cells, attached to cell surfaces, or internalized. Silicon carbide whiskers too large to be engulfed were found to be penetrating cell surfaces, often entering the cell on one side, and exiting on the other as if the cell were “skewered”.

Based on the dye exclusion studies, silicon carbide exhibited similar level of concentration-dependent cytotoxicity as crocidolite asbestos in the first 24 h. SiCW-1, SiCW-2 and crocidolite were found to induce, with eight generations of exposure, changes in cellular growth habits and structure generally held to be characteristic of cellular transformation. Transformation frequency of ca. $0.6 \cdot 10^{-2}$% was obtained as a result of exposure to 5.0 µg/cm^2 SiCW, in comparison to less than $0.1 \cdot 10^{-2}$% in saline control. Positive control crocidolite asbestos produced a transformation frequency of 0.0069% (SD = 0.0046%).

Svensson et al. (1997)[39] investigated the toxicity of different fibrous silicon carbide (whiskers) and non-fibrous silicon carbide (powder) in comparison with crocidolite in a number of in vitro assays. All materials showed concentration-dependent inhibition of the cloning efficiency of V79 hamster fibroblast cells. The inhibition by the most toxic whiskers (EC_{50} 0.9 to 4.2 µg/cm^2) was in the same order of magnitude as that of crocidolite (1.4 µg/cm^2). Silicon carbide powder was less toxic (EC_{50} 31.4 µg/cm^2) than the whiskers. There was a high DNA breaking potential (nick translation assay) for crocidolite and silicon carbide whiskers and a rather low one for silicon carbide powder. Formation of hydroxyl radicals was found for crocidolite and one of the silicon carbide whiskers and not for the silicon carbide powder. Silicon carbide whiskers had the highest ability to stimulate human neutrophils to generate reactive oxygen species.

Silicon carbide fibers belong to a group of man-made mineral fibers. Asbestos fibres are of natural origin. Both fibre types differ chemically in their gross formula being SiC (silion carbide) and $Mg_3Si_2O_5(OH)_4$ (asbestos). In spite of these chemical differences both fibre types are respirable and biopersistent, although silicon carbide fibers are less biopersistent than asbestos fibers.[40]

The mechanism of asbestos carcinogenesis is not entirely clear at present. The direct or indirect action of asbestos on DNA and proteins can cause many different types of DNA and chromosomal damage. The main cellular functions

that are affected by asbestos fibres include oxidative stress response, inflammation, DNA damage repair, mitochondrial activity and apoptosis. Many genes and pathways involved in these functions have been identified.[40]

With the abovementioned studies in mind, the Committee is aware of some similarities between (carcinogenic) mechanisms of silicon carbide and asbestos, such as the development of lung tumours, the involvement of oxidative stress through free radicals, imbalance in oxidant-antioxidant levels, the involvement of NF-*k*B.(which is known to coordinate the inflammatory and proliferative response to asbestos).[40]

The Committee observes an important difference with asbestos in that, seen until now, silicon carbide exposure leads to mesotheliomas only in animals but not in humans.

4.3 Summary of the mechanistic data

Standard genotoxicity tests in vitro or in vivo were not available. Only Peraud and Riebe-Imre[34] reported on an in vitro micronucleus test, showing a concentration-dependent increase in the number of Syrian golden hamster epithelial lung cells with micronuclei, after treatment with SiC. In addition, an in vitro study focussed on the interaction of silicon carbide with DNA; Vaughan et al.[36] demonstrated whiskers to induce increased DNA synthesis and total cellular DNA content in embryonic mouse cells. Some similarities may exist between mechanisms of silicon carbide and asbestos.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Silicon carbide was not evaluated by IARC.

Summarizing the above, the following biological effects are observed:

- Epidemiological evidence indicates that inhalation exposure to silicon carbide fibres is responsible for an increased incidence of lung and stomach tumours in man[3-6] although the contribution of possible confounders can not be completely excluded.
- In one recent epidemiological study it was specifically argued that non-fibrous silicon carbide did not seem to contribute to the cancer risk.[6]
- Available animal studies demonstrate that silicon carbide fibres induce the development of various tumours, including mesotheliomas, after inhalation[17,18]. This was supported by similar findings after intraperitoneal and intrapleural administration. The inhalatory carcinogenicity appears to be dependent primarily on the fibre length, with fibres longer than 5 µm and diameter below 1 µm being carcinogenic. Non-fibrous forms of silicon carbide did not induce any adverse effects in a number of short term animal studies after inhalatory, intraperitoneal, intrapleural and intratracheal administration. However, due to the absence of long term exposure studies no conclusions can be drawn on the carcinogenicity of non-fibrous silicon carbide.

- Standard genotoxicity tests in vitro or in vivo were not available. Only Peraud and Riebe-Imre[34] reported on an in vitro study showing the potential of silicon carbide to induce micronuclei in Syrian golden hamster epithelial lung cells. Moreover, an experimental in vitro study demonstrated silicon carbide whisker's capability of inducing DNA synthesis and total cellular DNA content in embryonic mouse cells.[36]

This profile of fibrous silicon carbide has some resemblance with that of asbestos, which after inhalation can cause asbestosis (a type of pneumoconiosis), lung cancer, and malignant mesothelioma. Moreover, the in vitro assays described in this report with asbestos materials as positive controls, show some comparable intrinsic properties of the two particulates. On the other hand, the Committee observes an important difference with asbestos in that silicon carbide exposure leads to mesotheliomas only in animals but not in humans.

The Committee is of the opinion that, in general, test systems for the genotoxicity of fibres are ambiguous and that the data for silicon carbide are limited. The oxidative potential seems to be less important than for asbestos. Overall, the Committee considers it likely that fibrous silicon carbide acts via a non-stochastic mechanism. This implies that for further risk assessment and derivation of a health based reference value a threshold approach may be considered.

The Committee is of the opinion that during applications of non-fibrous silicon carbide the presence of fibrous structures in the workplace may not be excluded (see Section 2.1).[1] Therefore, employees may be exposed to a mixture of non-fibrous and fibrous forms and not just to the non-fibrous silicon carbide. These fibrous structures may, depending on their form and quantity, still increase the carcinogenic risk to humans.

The Committee is concerned about the question whether, in spite of the existing regulations, the commercial granular material is sufficiently free of fibrous forms to not pose a risk when used in the workplace. Therefore, the Committee advises to quantify the carcinogenic risk and to establish safe occupational exposure levels.

5.2 Recommendation for classification

Based on the available information, the Committee concludes that the fibrous forms of silicon carbide (fibers, whiskers) may cause cancer according to a non-stochastic genotoxic mechanism and should be classified as carcinogenic to humans (category 1A). The data on the non-fibrous form of silicon carbide are insufficient to classify the carcinogenic properties of this substance (category 3).*

* According to the classification system of the Health Council (see Annex E).

References

1 Rödelsperger K, Brückel B. The carcinogenicity of WHO fibers of silicon carbide: SiC whiskers compared to cleavage fragments of granular SiC. Inhal Toxicol 2006; 18(9): 623-631.

2 Skogstad A, Føreland S, Bye E, Eduard W. Airborne fibres in the norwegian silicon carbide industry. Ann Occup Hyg 2006; 50(3): 231-240.

3 Infante-Rivard C, Dufresne A, Armstrong B, Bouchard P, Theriault G. Cohort study of silicon carbide production workers. Am J Epidemiol 1994; 140(11): 1009-1015.

4 Romundstad P, Andersen A, Haldorsen T. Cancer incidence among workers in the Norwegian silicon carbide industry. Am J Epidemiol 2001; 153(10): 978-986.

5 Bugge MD, Kjuus H, Martinsen JI, Kjaerheim K. Cancer incidence among short- and long-term workers in the Norwegian silicon carbide industry. Scand J Work Environ Health 2010; 36(1): 71-79.

6 Bugge MD, Kjaerheim K, Føreland S, Eduard W, Kjuus H. Lung cancer incidence among Norwegian silicon carbide industry workers: associations with particulate exposure factors. Occup Environ Med 2012; 69(8): 527-533.

7 Føreland S, Bugge MD, Bakke B, Bye E, Eduard W. A novel strategy for retrospective exposure assessment in the Norwegian silicon carbide industry. J Occup Environ Hyg 2012; 9(4): 230-241.

8 Bugge MD, Kjuus H, Martinsen JI, Kjaerheim K. Cancer incidence among short- and long-term workers in the Norwegian silicon carbide industry. Scand J Work Environ Health 2010; 36(1): 71-79.

9 Romundstad P, Andersen A, Haldorsen T. Non-malignant mortality among Norwegian silicon carbide smelter workers. Occup Environ Med 2002; 59(5): 345-347.

10 Bugge MD, Føreland S, Kjaerheim K, Eduard W, Martinsen JI, Kjuus H. Mortality from non-malignant respiratory diseases among workers in the Norwegian silicon carbide industry: associations with dust exposure. Occup Environ Med 2011; 68(12): 863-869.

11 Jarvholm B, Thiringer G, Axelson O. Cancer morbidity among polishers. Br J Ind Med 1982; 39(2): 196-197.

12 Edling C, Jarvholm B, Andersson L, Axelson O. Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br J Ind Med 1987; 44(1): 57-59.

13 Jakobsson K, Mikoczy Z, Skerfving S. Deaths and tumours among workers grinding stainless steel: a follow up. Occup Environ Med 1997; 54(11): 825-829.

14 Masse S, Begin R, Cantin A. Pathology of silicon carbide pneumoconiosis. Mod Pathol 1988; 1(2): 104-108.

15 Funahashi A, Schlueter DP, Pintar K, Siegesmund KA, Mandel GS, Mandel NS. Pneumoconiosis in workers exposed to silicon carbide. Am Rev Respir Dis 1984; 129(4): 635-640.

16 Dufresne A, Loosereewanich P, Harrigan M, Sebastien P, Perrault G, Begin R. Pulmonary dust retention in a silicon carbide worker. Am Ind Hyg Assoc J 1993; 54(6): 327-330.

17 Davis JMG, Brown DM, Cullen RT, Donaldson K, Jones AD, Miller BG et al. A comparison of methods of determining and predicting the pathogenicity of mineral fibres. Inhalation Toxicol 1996; 8(8): 747-770.

18 Miller BG, Jones AD, Searl A, Buchanan D, Cullen RT, Soutar CA et al. Influence of characteristics of inhaled fibres on development of tumours in the rat lung. Ann Occup Hyg 1999; 43(3): 167-179.

19 Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 1981; 67(5): 965-975.

20 Paulussen JJC, Mahieu CM, Bos PM. Default values in occupational risk assessment. TNO report 1998; V98.390.

21 Johnson NF, Hahn FF. Induction of mesothelioma after intrapleural inoculation of F344 rats with silicon carbide whiskers or continuous ceramic filaments. Occup Environ Med 1996; 53(12): 813-816.

22 Vasil'eva LA, Pylev LN, Kiianenko VV, Nikolaishvili AA. [Carcinogenic properties of silicon carbide whiskers]. Eksp Onkol 1989; 11(2): 13-15.

23 Adachi S, Kawamura K, Takemoto K. A trial on the quantitative risk assessment of man-made mineral fibers by the rat intraperitoneal administration assay using the JFM standard fibrous samples. Ind Health 2001; 39(2): 168-174.

24 Miller BG, Searl A, Davis JM, Donaldson K, Cullen RT, Bolton RE et al. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. Ann Occup Hyg 1999; 43(3): 155-166.

25 Pott F, Roller M, Rippe RM, Germann P-G, Bellmann. Tumors by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In: Brown RC, Hoskins JA, Johnson NF, editors. Mechanisms in fibre carcinogenesis. NATO ASI Series (Series A Life Sciences Vol 223): New York: Plenum Press; 1991: 547-565.

26 Roller M, Pott F, Kamino K, Althoff GH, Bellmann B. Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. Exp Toxicol Pathol 1996; 48(1): 3-12.

27 Pott F, Roller M, Kamino K, Bellmann B. Significance of durability of mineral fibers for their toxicity and carcinogenic potency in the abdominal cavity of rats in comparison with the low sensitivity of inhalation studies. Environ Health Perspect 1994; 102 Suppl 5: 145-150.

28 Akiyama I, Ogami A, Oyabu T, Yamato H, Morimoto Y, Tanaka I. Pulmonary effects and biopersistence of deposited silicon carbide whisker after 1-year inhalation in rats. Inhal Toxicol 2007; 19(2): 141-147.

29 Lapin CA, Craig DK, Valerio MG, McCandless JB, Bogoroch R. A subchronic inhalation toxicity study in rats exposed to silicon carbide whiskers. Fundam Appl Toxicol 1991; 16(1): 128-146.

30 Bruch J, Rehn B, Song H, Gono E, Malkusch W. Toxicological investigations on silicon carbide. 1. Inhalation studies. Br J Ind Med 1993; 50(9): 797-806.

31 Vaughan GL, Trently SA, Wilson RB. Pulmonary response, in vivo, to silicon carbide whiskers. Environ Res 1993; 63(2): 191-201.

32 Bruch J, Rehn B, Song W, Gono E, Malkusch W. Toxicological investigations on silicon carbide. 2. In vitro cell tests and long term injection tests. Br J Ind Med 1993; 50(9): 807-813.

33 Begin R, Dufresne A, Cantin A, Masse S, Sebastien P, Perrault G. Carborundum pneumoconiosis. Fibers in the mineral activate macrophages to produce fibroblast growth factors and sustain the chronic inflammatory disease. Chest 1989; 95(4): 842-849.

34 Peraud A, Riebe-Imre M. Toxic and chromosome-damaging effects of natural and man-made mineral fibres in epithelial lung cells in vitro. In: Dungworth DL, Mauderly JL, Oberdorster G, editors. Toxic and carcinogenic effects of solid particles in the respiratory tract. ILSI Monograph (Mohr U, editor-in-chief); Washington DC: ILSI Press; 1994: 569-574.

35 Brown DM, Fisher C, Donaldson K. Free radical activity of synthetic vitreous fibers: iron chelation inhibits hydroxyl radical generation by refractory ceramic fiber. J Toxicol Environ Health A 1998; 53(7): 545-561.

36 Vaughan GL, Jordan J, Karr S. The toxicity, in vitro, of silicon carbide whiskers. Environ Res 1991; 56(1): 57-67.

37 Brown DM, Beswick PH, Donaldson K. Induction of nuclear translocation of NF-kappaB in epithelial cells by respirable mineral fibres. J Pathol 1999; 189(2): 258-264.

38 Brown DM, Beswick PH, Bell KS, Donaldson K. Depletion of glutathione and ascorbate in lung lining fluid by respirable fibres. Ann Occup Hyg 2000; 44(2): 101-108.

39 Svensson I, Artursson E, Leanderson P, Berglind R, Lindgren F. Toxicity in vitro of some silicon carbides and silicon nitrides: whiskers and powders. Am J Ind Med 1997; 31(3): 335-343.

40 Nymark P, Wikman H, Hienonen-Kempas T, Anttila S. Molecular and genetic changes in asbestos-related lung cancer. Cancer Lett 2008; 265(1): 1-15.

41 Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.

A	Request for advice
B	The Committee
C	The submission letter
D	Comments on the public review draft
E	Carcinogenic classification of substances by the Committee

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemicals NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- G.B. van der Voet, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter

Subject	: Submission of the advisory report *Silicon carbide*
Your Reference	: DGV/MBO/U-932342
Our reference	: U-7475/BvdV/fs/246-S17
Enclosed	: 1
Date	: December 7, 2012

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to *Silicon carbide*.

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on the Classification of Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

In its advisory report the Committee has recommended separate classifications for fibrous silicon carbide (category 1A) and non-fibrous silicon carbide (category 3).

The Committee is concerned about the question whether, in spite of the existing regulations, the commercial granular material is sufficiently free of fibrous forms to not pose a risk when used in the workplace. Therefore, the Committee advises to quantify the carcinogenic risk and to establish safe occupational exposure levels.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,

(signed)
Professor W.A. van Gool
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in June 2012 for public review. The following organisations and persons have commented on the draft document:

- Mr. T.J. Lentz, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, USA
- Mr. J. Cherrie, Institute of Occupational Medicine (IOM), Edinburgh, UK
- Mr. C.L. König, ESD-SIC BV, Delfzijl, and Silicon Carbide Manufacturers Association (SiCMa), Luxembourg
- Mr. P.S. ter Haar, Vereniging voor Oppervlaktetechnieken van Materialen (VOM).

Annex **E**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category	
		(before 16 December 2008)	(as from 16 December 2008)
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[41]