The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Aluminium silicate fibres (refractory ceramic fibres, RCF)

MAK Value Documentation, supplement – Translation of the German version from 2019

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

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

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

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

Keywords

aluminium silicate fibres; lung; inflammation; carcinogenicity; lung tumours; mesotheliomas

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated aluminium silicate fibres considering all toxicological end points. Aluminium silicate fibres cause mesotheliomas and lung tumours in rats and hamsters. In epidemiological studies, cancer risk was not associated with exposure to aluminium silicate fibres. Tumour formation in animals is a result of chronic inflammation; therefore, aluminium silicate fibres are a candidate for Carcinogen Category 4. However, the re-evaluation showed that a maximum concentration at the workplace (MAK value) cannot be derived and aluminium silicate fibres thus remain classified in Carcinogen Category 2. Aluminium silicate fibres are not taken up via the skin in toxicologically relevant amounts. There are no studies of sensitization.

Citation Note:
Hartwig A, MAK Commission. Aluminium silicate fibres. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2021 Dec;6(4):Doc080.
DOI: https://doi.org/10.34865/mb0234fase6_4ad

Manuscript completed:
21 Mar 2018

Publication date:
30 Dec 2021

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

Note: Cristobalite can develop from aluminium silicate fibres used in building materials under thermal load. Exposure to cristobalite that occurs during the removal or demolition of these types of products is to be assessed separately.

Since the last documentation in 1993 (Greim 1997), numerous studies of aluminium silicate fibres have been published which make a re-evaluation necessary. The present documentation is based partly on the SCOEL documentation of refractory ceramic fibres (SCOEL 2011).

The name commonly used today is aluminium silicate fibres. As the publications cited use the older designation refractory ceramic fibres (RCF), it is also used in this documentation.

General characteristics

Aluminium silicate fibres/RCF are oxide ceramic materials of different composition based on SiO_2/Al_2O_3, which are used as heat protection (see Table 1). RCF consist of approximately 50% fibrous and 50% non-fibrous, largely non-inhalable material with a diameter of 1.2–3.5 µm and variable length (Fireman 2014). Unlike asbestos fibres, the fibres do not split longitudinally into thinner fibres (fibrils), but instead into fragments perpendicular to the longitudinal side of the fibre, down to particles of the dimension of granular dust (Mast et al. 2000 a).

Tab. 1 Physico-chemical properties and composition in percent of asbestos and ceramic fibres. Deviations in composition may occur according to product (Drummond et al. 2016; Schnegelsberg 1999; SCOEL 2011; Sonnenschein 2003; Tonnesen and Telle 2007). RCF4 fibres are produced from RCF1 fibres after sintering at 1300 °C for 24 hours.

	Chrysotile	Crocidolite	RCF1	RCF2	RCF3	RCF4[c)]
Chemical composition in %						
SiO_2	35–44	49–57	50–54	48–50	49–54	50–54
Al_2O_3	0–9	20–40	45	29	53	45
MgO	35–45	3–15	< 0.01	0.01	< 0.01	< 0.01
Fe_2O_3	0–9	20–40	0.97	< 0.05	< 0.2	0.97
Cr_2O_3	no data	no data	< 0.03	< 0.01	< 0.01	< 0.03
CaO	0–2	2–8	< 0.01	< 0.05	< 0.05	< 0.01
K_2O	no data	0.07–0.4	< 0.01	< 0.01	< 0.01	< 0.01
Na_2O	0–2	2–8	0.5	< 0.3	0.2	0.5
TiO_2	no data	0.01	2	0.04	0.02	2
ZrO_2	no data	no data	0.1	15–17	0.2	0.1

Tab. 1 *(continued)*

	Chrysotile	Crocidolite	RCF1	RCF2	RCF3	RCF4[c)]
Density (g/cm^3)	2.2–2.6	2.8–3.6	no data	no data	no data	no data
Fibre diameter	18–30 nm	60–90 nm	no data	no data	no data	no data
T_m (°C)[a)]	1500	1180	1800	1690	1800	1800
c[b)] (kJ/(kg × K))	1.1	0.8	no data	no data	no data	no data
Surface (m^2/g)	10–60	10	no data	no data	no data	no data

[a)] melting temperature
[b)] specific heat capacity
[c)] after service materials

RCF are divided into RCF types 1, 2, 3 and 4 according to their composition. RCF4 fibres are RCF1 fibres sintered at 1300 °C over 24 hours (see Section 5.7). RCF1 fibres can transform into RCF4 fibres over a longer period of time under high thermal load in technical applications. RCF1, RCF3 and RCF4 fibres consist of more than 50% silica and alumina. In RCF2, some of the aluminium oxide is replaced by zirconium dioxide. The differences in composition result in an increasing heat resistance of the aluminium silicate fibres of at least 1050 °C and higher, for the zirconium aluminium silicate fibres of at least 1424 °C and higher.

The main physical properties of RCF are low thermal conductivity, low bulk heat capacity and low density. RCF are produced and used in various technical forms such as bulk, and refractory thermal insulation material in the form of blanket, felt, putties, cements and textile (IARC 2002).

Exposure

Although some epidemiological studies have investigated the frequency and severity of health effects in exposed workers, it is difficult to derive a dose–response relationship from the data due to previous higher exposures and additional exposure to other dusts. One study describes the results of a hygiene report from the mid 1970s on the total amount of dust and RCF of the three largest production plants in the USA (Esmen et al. 1979). For the individual air samples, values between < 0.01 and 16 fibres/ml and average concentrations between 0.05 and 2.6 fibres/ml were obtained. The highest concentrations were found in factories and manufacturing plants without ventilation systems. The total dust load was between 0.05 and 100 mg/m^3, the average mean values were between 0.85 and 6.05 mg/m^3. The airborne fibres were < 4.0 µm in diameter and < 50 µm in length, with geometric mean values of 0.7 µm in diameter and 13 µm in length.

Recently, the concentrations determined in ongoing epidemiological studies in European and US workplaces between 2004 and 2008 were summarized (Table 2; SCOEL 2011). The concentrations were in the range of 0.146 fibres/ml during fibre production and 0.579 fibres/ml during kiln cleaning. These data are consistent with previous concentrations determined and show that, since 1993, concentrations have generally been below 0.6 fibres/ml.

Tab. 2 Summary of personal exposure data obtained from workplaces in Europe and the US between 2004 and 2009 (from SCOEL 2011, modified). 1482 studies from Europe and 2679 from the US (geometric mean) are available for the given period.

Workplace types	Description of workplace	Workplace concentration (fibres/ml)
Fibre production	all worksites producing bulk and blankets	0.146
Mixing/forming	wet-end production of shapes, boards, paper, mixing putties, compounds or castables	0.162
Finishing	cutting, sanding or machining products	0.322
Assembly	combining with other materials, e.g. module making, laminating, encapsulating	0.152
Installation	installation in furnaces, boilers, petrochemical plant and foundry equipment, electric power generators, includes maintenance, mould wrap and car builds	0.254
Removal	removal from industrial furnaces, boilers etc.; mould knock out, kiln car removal	0.579

1 Toxic Effects and Mode of Action

See the documentation from 1993 (Greim 1997) and the supplement entitled "Fibrous dusts, inorganic" from 2018 (Hartwig and MAK Commission 2019).

2 Mechanism of Action

The most important factors influencing the toxicity of RCF are length, diameter and biopersistence (Hartwig and MAK Commission 2019; IARC 2002; Mast et al. 2000 b). The longer a fibre can exert its irritant effect in a sensitive area of the lung or pleura, the greater the likelihood that the tissue at the affected site will degenerate, resulting in the formation of a tumour.

For ceramic fibres, the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been demonstrated both in cell-free systems and in cell systems such as alveolar macrophages of rats and guinea pigs, human polymorphonuclear leukocytes and human monocyte-derived macrophages (IARC 2002).

In humans and rodents, fibres deposited in the lungs are wholly or partially absorbed by phagocytes (macrophages and polymorphonuclear granulocytes). The incomplete phagocytosis of such fibres, the length of which exceeds the absorption capacity of the phagocytes, forms a strong inflammatory stimulus associated with the release of ROS and RNS and specific inflammatory mediators. This has also been demonstrated for ceramic fibres in several studies (Brown et al. 2005; Hartwig and MAK Commission 2019; IARC 2002; Mast et al. 2000 b).

The reactive species can induce DNA damage, which in turn, if not fully repaired, can cause secondary genotoxic effects. For ceramic fibres, such genotoxic effects have been demonstrated in vitro in CHO cells (a cell line derived from Chinese hamster ovary), hamster tracheal epithelial cells, pleural mesothelial cells of rats, Syrian hamster embryo cells, and human amniotic fluid cells (IARC 2002). However, these mutagenicity/genotoxicity data are considered to be of little relevance for RCF (Mast et al. 2000 a).

Chronic inflammation, which plays a crucial role in the development of fibrosis and tumours, has been found in numerous animal studies after exposure to ceramic fibres (IARC 2002; SCOEL 2011). Chronic inflammation is promoted by impairment of fibre clearance. Initially, macrophages, alveolar cells and mesothelial cells release pro-inflammatory chemokines and cytokines as well as growth factors and proteases, which in turn trigger cell proliferation and gradual degeneration of the "target" cells (Hartwig and MAK Commission 2019).

Interaction with the spindle apparatus leading to the loss of chromosomes or missegregations was found in several studies also for ceramic fibres, although no dose–response dependence could be demonstrated (Dopp et al. 1997; Dopp and Schiffmann 1998). Furthermore, fibres can induce the stimulation of cell receptors and inflammasomes, which activate intracellular signalling pathways and thereby set impulses for cell proliferation and apoptosis resistance. However, the effects of these mechanisms cannot be estimated on the basis of the current data.

In summary, it can be stated that tumour formation in the lungs and also in the pleura is mainly a consequence of chronic inflammation.

Ceramic fibres can induce malignant mesotheliomas and lung tumours in rodents after inhalation, intratracheal or intraperitoneal administration (Greim 1997; IARC 2002; SCOEL 2011). To date, only negative epidemiological findings are available regarding an association between exposure to ceramic fibres and the development of mesotheliomas or lung tumours in humans. Ceramic fibres, like asbestos and erionite fibres, induce pleural plaques in humans (IARC 2002; Lockey et al. 1996, 1998, 2002, 2012; Utell and Maxim 2010). Although it has not been proven that pleural plaques are a causal consequence of inflammatory processes, several studies provide evidence of inflammatory infiltrations in the area of the plaques. Pleural plaques should therefore be regarded as adverse effects (Brockmann 1991; Konstantinidis 2001; Roberts 1971). There are no reliable positive findings of the fibrosing effect of RCF in humans. There are, however, several animal studies that show that exposure to RCF leads to pulmonary fibrosis (IARC 2002; SCOEL 2011).

Biopersistence

The biopersistence of the fibres can be measured in vivo and in vitro. In the in vitro experiments, crocidolite fibres have the highest biopersistence, RCF have a biopersistence lower by one order of magnitude, and rock wool and slag wool are even less biopersistent (Zoitos et al. 1997).

The biopersistence of RCF in vivo has been repeatedly investigated in animal studies. Key influencing factors were the dose–time relationship for clearance, the presence of non-fibrous components and the amount of fibres absorbed. The arithmetic mean $WT_{1/2}$ (weighted half-time) for biopersistence in vivo was 59 days (Hesterberg et al. 1998). Another study reported an extension of the clearance half-time in rats from 50 to 100 days to about 1200 days (Creutzenberg et al. 1997). The fibre lung burdens after 24 months reached 5.6×10^4 to 27.8×10^4 fibres/mg dry lung tissue (Mast et al. 1995 a, b). The clearance rate of RCF1a, a fibre with specifically reduced particulate mass, was, however, normal ($t_{1/2} < 100$ days) (Mast et al. 2000 a).

This difference can be explained by the higher inflammatory potency of RCF1 compared with that of RCF1a. RCF1a were specially prepared for inhalation experiments in rats. Furthermore, several studies have shown that the biopersistence of RCF1 in the lungs of rats is approximately twice as high as that of RCF1a (Mast et al. 2000 a). The results also show that fibre exposures which do not cause inflammatory processes in the lungs also do not affect lung clearance.

3 Toxicokinetics and Metabolism

The removal of fibres by macrophages is an essential mechanism of fibre elimination from the lungs. This process of macrophage-mediated lung clearance is much slower in humans than in rats (Greim 1999).

The clearance function of alveolar macrophages was investigated by Bellmann et al. (2001). Female Wistar rats were exposed to RCF1 and RCF1a for 6 hours daily, on 5 days per week over a period of 3 weeks. The aerosol contained 125 fibres/ml with a length of more than 20 µm. The treatment was followed by a 12-month observation period. It was found that clearance was severely impaired by RCF1.

Clearance was not impaired by RCF1a (Drummond et al. 2016).

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

Respiratory symptoms, lung function, radiological findings, and mortality in worker cohorts in the USA and Europe were investigated in various studies (NIOSH 2006). The first commercial production of RCF and RCF products in the USA started in 1953; in Europe RCF production started in 1968. In 1986, the average longest duration of employment of a European cohort was 10.2 years (between 7.2 and 13.8 years) (Trethowan et al. 1995) and 13.0 years in 1996 (Cowie et al. 2001).

4.2.1 Effects in the lungs

4.2.2 Respiratory symptoms/questionnaire

In a retrospective cohort study, respiratory complaints and the lung function of 742 workers in five different US factories with a permanent exposure level below 1 fibre/ml were investigated. A questionnaire on the functioning of the respiratory system was developed to obtain information on chronic coughs, chronic phlegm, dyspnoea, wheezing, asthma, and pleuritic chest pain. The analysis covered various other parameters such as smoking, asbestos exposure, length of employment and the period between the survey and work at the last RCF workplace. The occurrence of dyspnoea after RCF exposure was the most commonly reported symptom. The OR (odds ratio) in male workers employed in production (n = 517) compared with those not employed in production (n = 80) was 2.9 (95% CI (confidence interval): 1.4–6.2) for one or more symptoms. The OR for female workers was 2.4 (95% CI: 1.1–5.3). In summary, the authors found that, in general, the number of respiratory responses was comparable to that of other populations exposed to dust (LeMasters et al. 1998).

In a cross-sectional study from 1995, the lung function of workers from all the companies in Europe producing RCF was examined. The fibre dust concentrations for the inhalable fraction were 1.7–3.4 mg/m^3 for primary production workers and 1.8–11.2 mg/m^3 for secondary production workers, and for respirable fibres 0.2–0.88 fibres/ml for primary production workers and 0.49–1.36 fibres/ml for secondary production workers. There was a correlation between the dust concentration and also the inhalable fibre concentration and the prevalence of respiratory symptoms, including a dry cough, nasal congestion, eye and skin irritation and shortness of breath (Burge et al. 1995). In addition, a significant increase in respiratory distress was reported for the above-mentioned workers with increasing cumulative exposure to RCF (2.88 to 6.83 fibre-years/ml) (Trethowan et al. 1995). In six of seven previously investigated factories (774 workers: 692 men and 82 women), the occurrence of chronic bronchitis, shortness of breath, the increased frequency of chest diseases and pleuritic chest pain were recorded as a response to previous cumulative exposure. Although rare, the occurrence of these symptoms was related to previous cumulative exposure to inhalable fibres (Cowie et al. 2001).

4.2.3 Lung function/spirometric measurements

In a lung function cross-sectional study, the dependence of the parameters FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), FEV_1/FVC or $FEF_{25–75}$ (forced expiratory flow), on RCF exposures was not found to be statistically significant. In current and past smokers (men) who had worked in RCF production for 10 years, a significant decrease in FVC of 165 ml and 156 ml, respectively, compared with 40.6 ml for non-smokers, was observed. There was a decrease in FEV_1 (135 ml per 10 years exposure) only in male smokers working in RCF production. No significant decrease was observed among non-smokers. A significant decrease in the FVC parameter was observed also among female non-smokers employed in RCF production. Previous fibre and dust exposure, the length of employment (stratified) and the duration of each type of activity determined the strength of the exposure–effect relationship. The median time-weighted average exposure was 0.03–0.61 fibres/ml for dry fabrication, 0.01–0.27 fibres/ml for wet fabrication, 0.01–0.47 fibres/ml for kiln operations and 0.02–0.62 fibres/ml for maintenance. The current fibre levels in this cohort were thus below 1 fibre/ml (LeMasters et al. 1998).

In five US plant sites, a long-term analysis was carried out in 361 male workers employed in production. Five or more spirometry tests were performed. They showed a decrease in FVC and FEV_1 parameters between the first (1987) and the last test (1994). The exposure–response relationship was modelled with two different exposure variables: years of work in a production job and cumulative fibre exposure (fibre-months/ml). Groups of workers in the non-production area and employees with a cumulative exposure up to 15 fibre-months/ml were used for comparison. A statistically significant decrease in FVC was found among workers employed in production jobs for more than seven years prior to the initial test. A similar, but not statistically significant result was obtained for FVC in workers with more than 60 fibre-months/ml cumulative exposure prior to the initial pulmonary function test. Similar results were obtained for FEV_1. Such findings were not obtained in the subsequent period after 1987. Lower RCF exposures since the 1980s may be responsible for the elimination of any further effect on pulmonary function. In summary, the authors concluded

that further short-term exposures from the late 1980s until 1994 did not cause a deterioration of FVC and FEV_1 (Lockey et al. 1998).

The results are consistent with those from earlier higher exposure conditions from the 1950s (estimated maximum of 10 fibres/ml) compared with the most recent exposures, which were estimated to be in the range from 1 fibre/ml to below the detection limit (Rice et al. 1997).

In a cross-sectional study, the respiratory function of workers (n = 628) in seven European RCF manufacturing companies was investigated. The mean cumulative exposure was 3.84 fibre-years/ml. The mean duration of employment was 10.2 years. After adjusting for age, sex, height, smoking habits and previous exposure to respiratory hazards, a significant relationship was found between decreased FEV_1 and $FEF_{25–75}$ on the one hand and cumulative exposure in current smokers on the other hand. The same relationship was found for FEV_1 in ex-smokers. In contrast, no change in lung function after RCF exposure was seen in non-smokers (Trethowan et al. 1995).

In a study with 774 subjects, only a slight decrease in FVC and FEV_1 was observed in relation to cumulative RCF exposure for male active smokers, compared with the findings in the study by Trethowan et al. (1995) with 1987 subjects (Cowie et al. 2001). No exposure-related decrease in the FEV_1/FVC ratio or CO diffusion capacity was found in the lung function test. When the groups were separated with respect to smoking habits, effects were found only in current and ex-smokers. Lung function was found to be impaired by cumulative exposure to ceramic fibres only in current smokers. Thus, smoking seems to be an essential cofactor for the effects on lung function of ceramic fibre exposure.

On average, the study participants had worked at the plants for 13 years, mostly for around 8 years in production. The main estimated cumulative exposure index for respirable fibres was 4.9 (range 0.01–36) fibre-years/ml; for non-respirable fibres the exposure index was 0.7 (0.001–5.0) fibre-years/ml. Both values of fibre exposure were higher in the production jobs and among smokers and ex-smokers, proportionally more of whom worked in production jobs. The mean exposure for total dust was 15.9 (0.05–79) mg/m³ × years and for respirable dust 5.2 (0.02–45) mg/m³ × years. The occurrence of dust makes it difficult to assign the effects of fibre exposure in particular on the lungs (Cowie et al. 2001) (Table 3).

Tab. 3 Mean exposure to respirable and non-respirable fibres, [f/ml × years] respirable and total dust [mg/m³ × years] and average years of work in production (Cowie et al. 2001)

Years	Mean exposure to respirable fibres	Mean exposure to non-respirable fibres	Mean exposure to respirable dust	Mean total exposure to dust	Mean years in production jobs
before 1971	0.88	0.12	1.93	4.98	2.88
1971–1976	1.22	0.17	1.44	4.43	2.38
1977–1981	1.92	0.29	2.02	6.12	3.74
1981–1986	2.05	0.31	2.16	6.52	3.80
1987–1991	1.66	0.24	1.75	5.29	3.98
1992–1996	1.06	0.15	0.96	3.13	3.91

In a study from 2010, 933 male and 244 female current workers and a further group of 219 former workers exposed to certain cumulative RCF levels were examined and selected longitudinally by age group (McKay et al. 2011). The study followed workers from five RCF manufacturing locations for up to 17 years who were exposed to the exposure conditions described in Maxim et al. (2008). The tests were conducted annually from 1987 to 1994 and then every 3 years until 2004. No consistent decrease in FVC or FEV_1 could be attributed to the exposure.

4.2.4 Radiographic examinations

Radiological changes, such as the frequency of pleural plaques in workers exposed to RCF, were detected by chest imaging. In a study of 1008 individuals, the frequency of interstitial changes did not differ from that of workers exposed to other types of dust. Pleural changes were found in 27 workers exposed to RCF. In 22 cases, pleural plaques were

involved. Of the workers who had initially been employed in production and were examined after a latency period of > 20 years, or who had been employed in a production plant for 20 years, 16 and 5 workers respectively had pleural changes. Diffuse pleural thickening and pleural plaques with defined thickening were counted together as "pleural changes". Results from the cumulative exposure analysis (> 135 fibre-months/ml) yielded an OR of 6.0 (95% CI: 1.4–31.0) for pleural changes, for workers with exposure to > 45–135 fibre-months/ml an OR of 5.6 (95% CI: 1.5–28.1), related to workers with an exposure < 15 fibre-months/ml in each case. The authors concluded that RCF are significantly associated with pleural changes but without a statistically significant increase in interstitial changes (Lockey et al. 2002).

No relationship was found between category 1/0+ opacities and exposure. A weak association between category 0/1+, small opacities, and cumulative RCF exposure was noted, but the relationship was not further investigated. Pleural changes, after adjustment for age and previous exposure to asbestos, provided some evidence, although not statistically significant, of a relationship with time since first exposure to RCF (Cowie et al. 2001).

Thus, it can be concluded from the studies conducted in the USA that pleural plaques observed in the examined US cohort of RCF plants were related to cumulative exposure (Lockey et al. 2002). Similarly, some evidence of a relationship between latency and pleural plaques but not between the duration and level of RCF exposure was reported in the European studies (Cowie et al. 2001). No evidence of parenchymal disease was found in any of the studies.

The frequency of pleural plaques is significantly dependent on the cumulative RCF exposure. Individuals with pleural plaques do not exhibit other symptoms or limitations of lung function (Utell and Maxim 2010). However, this requires that the pleural plaques are of low frequency and do not exceed a critical thickness (Pairon et al. 2013).

4.3 Local effects on skin and mucous membranes

There are no new data available.

4.4 Allergenic effects

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

A retrospective cohort study examined the mortality from cancer of 942 male workers employed in two RCF factories between 1952 and 2000. Over the period 1987–1988, at the start of the study, the time-weighted average fibre dust concentrations were 0.03–0.61 fibres/ml in dry fabrication, 0.01–0.27 fibres/ml in wet fabrication, 0.01–0.47 fibres/ml in kiln operations and 0.02–0.62 fibres/ml in maintenance. Subsequently, the exposure levels remained relatively stable; the most recent time-weighted average exposure estimates were 0.03–0.57 fibres/ml in dry fabrication, 0.07–0.40 fibres/ml in wet fabrication, 0.11–0.12 fibres/ml in kiln operations and 0.05–0.53 fibres/ml in maintenance. Mortality was no higher for all causes of death (SMR = 69.8) than for deaths from all cancers (SMR = 94.2), for cancer of the lungs and respiratory tract including mesotheliomas (SMR = 78.8) and for diseases of the respiratory system (SMR = 106.8). A significant relationship between exposure and cancer of the urinary organs was found: SMR = 344.8 (95% CI: 111.6–805.4). When related to age and sex, there was no significant increase in deaths after exposure to RCF (LeMasters et al. 2003).

A parallel analysis with 10 years of exposure came to the same results. After comparing the categories of exposure with the initial exposure of < 1 fibre-month/ml with regard to age and sex, the risk levels were 1.35 (95% CI: 0.47–3.88), 1.45 (95% CI: 0.48–4.37), 1.90 (95% CI: 0.64–5.59) and 1.45 (95% CI: 0.46–4.59) for the categories > 1–15, > 15–45, > 45–135 and > 135 fibre-months/ml. A disadvantage of this study was that it was not suitable to show increased mortality from respiratory diseases due to the low age and the relatively small number of cohort members (942 male workers examined) (LeMasters et al. 2003).

Another study investigated whether RCF resemble asbestos in their carcinogenicity. The authors examined 605 persons employed in the production of these fibres from 1987 onwards for cancers associated with exposure. The participants were observed for an average of 27.8 years. In a total of 15 281 person-years, 12 lung cancer deaths were recorded, compared with 11.8 expected. The authors accordingly concluded that the exposure to aluminium silicate fibres did not lead to an increased incidence of lung cancer or mesotheliomas among the workers (Walker et al. 2012 a, b).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Groups of 140 male F344 rats were exposed nose-only to four different fibres, RFC1, RCF2, RCF3 and RCF4, each at a concentration of 30 mg/m^3 for 6 hours daily, on 5 days per week, for 24 months. A group of 80 rats exposed to 10 mg/m^3 chrysotile served as a positive control. At the end of exposure, the lung fibre content was 2.6 to 9.6×10^5 per mg dry lung tissue. Macrophage infiltration, bronchiolization of the alveoli, microgranulomas, interstitial fibrosis and minimal to mild focal pleural fibrosis, all dose-dependent, were detected histopathologically (Mast et al. 1995 a; see also Section 5.7).

In another study, groups of 140 F344 rats were exposed nose-only to three different exposure concentrations of RCF1 of 3, 9 or 16 mg/m^3 (about 36, 91 or 162 fibres/cm^3; geometric mean diameter 0.8 ± 1.96 µm; geometric mean length 16.5 ± 2.6 µm), for 6 hours a day, on 5 days a week, for 24 months. Lung clearance was unchanged over the exposure period in the rats exposed to 3 mg/m^3. A 35% increase in lung weights was observed in the animals exposed to 16 mg/m^3. The fibre lung burden at the end of exposure was 4.3×10^4 fibres/mg dry lung tissue for the animals exposed to 3 mg/m^3 and 22.1×10^4 fibres/mg dry lung tissue for the rats exposed to 16 mg/m^3. Histopathological examination of the lung tissue revealed a dose-dependent increase in fibrous macrophages, minimal fibrous microgranulomas at the broncho-alveolar junction and early bronchiolization with minimal progression of the effects over time. Interstitial fibrosis was observed in the animals exposed to 9 and 16 mg/m^3. On an intensity scale of 1 to 4, changes in the lungs were considered negligible for the animals exposed to 3 mg/m^3. The effects were dependent on the fibre lung burden (Mast et al. 1995 b).

5.2.2 Oral administration

There are no data available.

5.2.3 Dermal application

There are no data available.

5.2.4 Intraperitoneal injection

The studies are summarized in Section 5.7.

5.3 Local effects on skin and mucous membranes

There are no new data available.

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

There are no data available.

5.6 Genotoxicity

5.6.1 In vitro

In acellular systems, RCF can cause direct oxidative damage to DNA (Gilmour et al. 1995). RCF form DNA adducts from the end products of lipid peroxidation (Howden and Faux 1996).

Positive results in the in vitro micronucleus test and the in vitro chromosomal aberration test with human amniotic fluid cells and Syrian hamster embryo fibroblasts (SHE cells) have been reported for 0.5 to 10 µg/cm^2 amosite, chrysotile and crocidolite asbestos and ceramic fibres (Dopp et al. 1997; Dopp and Schiffmann 1998). In the presence of RCF, the induction of micronuclei and an increased rate of apoptosis were observed in SHE cells (Dopp et al. 1995). However, information on cytotoxicity was not given in these studies, although the authors describe that cells can remain capable of division (Dopp et al. 1997).

In vitro, RCF1, RCF2 and RCF3 caused DNA damage (breaks and crosslinks) in the human lung epithelial cell line A549 at a dose of 200 µg/ml (40 µg/cm^2). In addition, structural chromosomal aberrations were observed in human embryo lung cells after treatment with RCF. Also in this test, cytotoxicity was not examined and the genotoxic properties cannot, therefore, be evaluated. However, the inhibition of DNA repair was reported, indicating a possible mechanism of action (Wang et al. 1999 b).

Nuclear abnormalities (micronucleus and polynucleus formation) were found in Chinese hamster ovary (K1) cells after treatment with RCF (Hart et al. 1992, 1994). RCF1 concentrations of up to 40 µg/cm^2 did not cause HPRT mutations in human hamster hybrid A_L cells (Okayasu et al. 1999).

Investigations of human mesothelial cells (MeT-5A) with glass wool, rock wool, RCF and crocidolite revealed very little oxidative DNA damage for RCF compared with ferrous rock wool (about 8% Fe). On the other hand, comet tests with RCF revealed direct DNA damage (DNA strand breaks) and a marked loss of microvilli on the cell surfaces even at the lowest dose tested of 1 µg/cm^2, but without there being any further increase at higher doses up to 10 µg/cm^2 (Cavallo et al. 2004).

In summary, RCF can cause clastogenic effects in cells in vitro (IARC 2002). The uptake of the fibres into cells and a mechanical disruption of chromosomal segregation followed by or associated with cell division may cause chromosomal/nuclear abnormalities and genetic changes. A possible consequence is cell transformation. Furthermore, several studies showed that the treatment of alveolar macrophages of rodents and human granulocytes with RCF leads to the production of reactive oxygen species. The reactive oxygen species can damage DNA (IARC 2002).

5.6.2 In vivo

In Drosophila melanogaster, aneuploidy was observed after feeding with different ceramic fibre samples. However, no dose–response relationship was reported in these studies (Osgood 1994).

5.7 Carcinogenicity

Already in the documentation entitled "Fibrous dust" from 1993 (Greim 1997), inhalation experiments in hamsters and rats were mentioned which demonstrated the carcinogenicity of RCF. Both lung tumours and mesotheliomas were found in rats, only mesotheliomas in hamsters.

In more recent studies, rats were exposed to fibres by inhalation. The fibres had a geometric mean diameter of 1 µm or smaller, with a large proportion of long fibres; 50% of the fibres had an arithmetic mean length of 20 µm and were inhaled in a concentration representative of occupational exposure (Hesterberg and Hart 2001).

Two long-term inhalation studies with RCF were performed in F344 rats. One study used a concentration of 30 mg fibres/m^3 (an estimated 190 WHO fibres/ml for four different types of RCF (RCF1, RCF2, RCF3 and RCF4)) (Mast et al. 1995 a). Groups of 140 male rats inhaled the material for 6 hours daily, on 5 days per week, for 24 months. A group of 80 rats was exposed to 10 mg chrysotile/m^3. The rats were observed for up to an age of 30 months. The number of WHO fibres was determined to be 187 ± 53 for RCF1, 220 ± 82 for RCF2, 182 ± 66 for RCF3, 206 ± 48 for RCF4 and 1.06 × 10^4 fibres/m^3 for chrysotile. Table 4 shows the incidence of pulmonary and mesothelial proliferative lesions and tumours in the treated animals. An increased incidence of exposure-related tumours (broncho-alveolar adenomas and carcinomas) was observed with all four types of RCF (RCF1–4). A small number of mesotheliomas was also seen in the exposed animals (Mast et al. 1995 a).

The second study (same study design: 6 hours daily, on 5 days per week, for 24 months) was conducted with exposure concentrations of 3, 9 or 16 mg RCF1/m^3 corresponding to 26, 75 and 120 WHO fibres/ml). No statistically significant increase in lung neoplasms was observed. Only one animal exposed to 9 mg/m^3 developed a very small mesothelioma (Mast et al. 1995 b).

Subsequently, it was found that to obtain respirable fibre samples, the commercial RCF were extensively ground and therefore the animals were exposed with a relatively high particle to fibre ratio of 25% by weight and 10 particles per fibre (Turim and Brown 2003).

Tab. 4 Incidence of pulmonary and mesothelial proliferative lesions and tumours in male F344 rats exposed to RCF and chrysotile asbestos (percentages in brackets) (according to Mast et al. 1995 a)

Group	n[a)]	BAH[b)]	Adenomas	Carcinomas	Adenomas and carcinomas	Mesothelial proliferation	Mesotheliomas
Controls	130	5 (3.8)	2 (1.5)	0	2 (1.5)	0	0
Chrysotile	69	13 (18.8)	7 (10.1)	6 (8.7)	13 (18.5)	0	1 (1.4)
RCF1	123	17 (13.8)	8 (6.5)	8 (6.5)	16 (13.0)	9 (7.3)	2 (1.6)
RCF2	121	15 (12.4)	4 (3.3)	5 (4.1)	9 (7.4)	2 (1.7)	3 (2.5)
RCF3	121	15 (12.4)	10 (8.3)	9 (7.4)	19 (15.7)	13 (10.7)	2 (1.7)
RCF4	118	8 (6.8)	2 (1.7)	2 (1.7)	4 (3.4)	9 (7.6)	1 (0.8)

[a)] number of animals at risk (number of animals that had survived exposure for 12 months)

[b)] bronchioalveolar hyperplasia

In another long-term study, 140 male hamsters were exposed nose-only to 30 mg/m^3 (260 fibres/ml) by inhalation for 6 hours daily, on 5 days a week, for 18 months. In this study, the same RCF fibre type was used as in the studies by Mast et al. (1995 a, b). The exposed hamsters developed lung fibrosis and a significant number of pleural mesotheliomas (42/102, 41% of the animals), but no lung tumours. Animals (n = 80) exposed to 10 mg chrysotile/m^3 served as a positive

control group. These animals did not develop neoplasms in the lung and mesothelium, but did develop pronounced fibrosis (McConnell et al. 1995).

After intraperitoneal injection in rats, mesotheliomas occurred depending on the length and dose of the fibres (Miller et al. 1999). Groups of 24 male Wistar rats were treated once with different fibres (SiC whisker, amosite asbestos, man-made vitreous fibres MMVF10, MMVF21, MMVF22, MMVF100/475, and RCF1, RCF2 and RCF4) at a dose of 10^9 fibres. 88% of the rats exposed to amosite asbestos and RCF1 fibres developed mesotheliomas, as did 92% of the animals exposed to SiC fibres and 72% of the animals treated with RCF2 fibres. The animals that received an injection with RCF4 fibres did not develop mesotheliomas.

The risk of tumour occurrence was calculated using data from a long-term study in female Wistar rats after intraperitoneal administration. A total of 330 female F344 rats divided into 24 groups were given intraperitoneal injections with 5 to 20 mg of different fibres and observed for up to 2 years. All rats injected with 10 mg SiC whiskers developed mesotheliomas. In the chrysotile asbestos group, 85% of the rats developed mesotheliomas. Mesotheliomas also developed in 20% of the rats that received 20 mg RCF2, and in 10% of the animals that received 20 mg RCF1 (Adachi et al. 2001).

Biological effects of RCF1 ceramic fibres on the lungs and pleura of rodents were studied to clarify the transferability of the animal model to humans. For this purpose, 55 *Nf2*$^{(+/-)}$ mice (hemizygous for the tumour suppressor gene *Nf2* = neurofibromatosis-2) were given two intraperitoneal injections of 3 mg RCF1 fibres (22.4 ± 19.0 µm in length and 1.1 ± 0.8 µm in diameter) at an interval of 2 or 3 months (Andujar et al. 2007). In the control group, 33 mice received an injection of saline solution. The dosage was determined based on studies with mice exposed to crocidolite (Lecomte et al. 2005). The median survival of the treated animals was 478 days and 629 days for the control group. From day 233 onwards, 26 (55%) of the treated mice developed mesotheliomas. These were classified as 7 epithelial, 10 fusiform and 9 biphasic mesotheliomas. In contrast, the animals of the control group developed 2 biphasic mesotheliomas (7.1%) on days 450 and 676. As in humans, an association between ascites and mesotheliomas was found. However, *Nf2*$^{(+/-)}$ mice were not significantly more sensitive than the corresponding wild-type strain (Andujar et al. 2007).

On the basis of these studies, the IARC classified the ceramic fibres (RCF, aluminium silicate fibres) in carcinogen category 2B due to sufficient evidence in animals and insufficient evidence in humans (IARC 1988, 2002). Further information can be found in Baan and Grosse (2004).

So-called "after service materials (ASM)" represent a special case. These can be linings of kilns which have to be replaced after their service life has expired. It is known that RCF can crystallize if they are exposed to high temperatures over a longer period of time. This produces crystalline silica, cristobalite and other species that can be released when the kiln lining is removed. The transformation process takes place mainly at sustained temperatures of about 1300 °C, but also to a lesser extent at lower temperatures (Gualtieri et al. 2009). Fibres that are close to the surface of the kilns are completely crystallized. Since silica is a carcinogen, it was feared that these ASM could cause serious diseases after exposure to them. However, various in vitro studies have shown that the content of crystalline silica has little or no effect on the toxicity of heated RCF, and that heat-treated RCF are even less toxic than untreated RCF (Brown and Harrison 2014). The authors suggest that the silica in the process of crystallization is not formed on the surface of the fibres, but mainly inside the fibres, so that no interactions can occur and the fibres are accordingly toxicologically inactive. Other studies have, however, shown that this is not the case (Binde and Bolender 2002).

5.8 Other effects

The nuclear translocation of NFκB was investigated by immunohistochemical staining with an antibody against p50 (NFκB subunit) as a marker for oxidative stress and a potential activator of pro-inflammatory genes in human A549 lung epithelial cells. Hydrogen peroxide causes dose-dependent activation of NFκB. The RCF1 and SiC fibres yielded positive results, as did amosite asbestos (Brown et al. 1999).

In an in vitro experiment, the ability of different fibres to stimulate superoxide production and thus hydroxyl radicals in rat alveolar macrophages was examined (Hill et al. 1996). The cells were exposed to different fibre types (amosite asbestos, MMVF21, MMVF100/475, SiC and RCF1) and to fibres coated with rat immunoglobulin (IgG), a component of

the alveolar fluid. The "naked" fibres induced only a modest release of superoxide anion, while those with adsorbed IgG induced a higher release. RCF1 and MMVF21 fibres induced a strong release of superoxide, which correlated with their high affinity for IgG. The SiC whiskers and MMVF100/475 fibres showed a poor affinity for IgG and only a modest release of superoxide. Adsorbed amosite asbestos fibres generated a high release of superoxide, and thus hydroxyl radicals, despite a poor affinity for IgG.

In the acellular system, RCF can directly cause oxidative damage to DNA. RCF1–4 fibres were used to study free radical damage to a plasmid. The end point was the reduction of supercoiled DNA in the plasmid. The aluminium silicate fibres caused little damage (Gilmour et al. 1995). In another experiment, RCF1 formed small amounts of DNA adducts from the end products of lipid peroxidation (Howden and Faux 1996).

Anaphase or telophase aberrations could not be observed in rat pleural mesothelial cells treated with different high temperature ceramic fibres (Yegles et al. 1995). In the reticular cell sarcoma cell line J774, no deoxyguanosine hydroxylation occurred after treatment with high temperature ceramic fibres (Murata-Kamiya et al. 1997).

For genetic analyses, early passages of cell cultures obtained from ascites of 12 *Nf2*$^{(+/-)}$ mice exposed to RCF1 with mesotheliomas were used. *Nf2* was inactivated in all cultures, often together with the inactivation of genes of the *Cdkn* gene loci; these encode tumour suppressor proteins (see below), more rarely by co-inactivation by mutations in the *Trp53* gene (transformation related protein 53). The genetic analyses of the ascites cultures showed that inactivation of the *Cdkn2a/2b/2d* gene loci is frequent in mesotheliomas, mutations in the *Trp53* gene are less frequent. The authors suggest that these somatic cell transformations can determine different pathways of mesothelial cell transformation. Similar genetic alterations were shown in 12 ascites cultures from mice treated with crocidolite and 12 ascites cultures from mesothelioma patients (Lecomte et al. 2005). Thus, RCF1 fibres can induce tumours similar to human mesotheliomas in a way similar to that of crocidolite in *Nf2*$^{(+/-)}$ mice. The validity of the animal model is supported by similar genetic alterations in cell cultures obtained from ascites, equally from mice treated with RCF1 or asbestos fibres or from ascites of mesothelioma patients.

The uptake of fibres into cells and a mechanical disturbance of chromosomal segregation followed by or associated with cell division may cause chromosomal/nuclear abnormalities and genetic changes with the possible consequence of cell transformation. Furthermore, several studies showed that exposure to high temperature fibres led to the production of reactive oxygen species in alveolar macrophages of rodents and human granulocytes. These reactive oxygen species can damage DNA (Luoto et al. 1997; Wang et al. 1999 a).

Comparison of ceramic fibres with rock wool and slag wool

In a recent review, the toxic potential of ceramic fibres was compared with that of rock wool/slag wool (Greim et al. 2014). Ceramic fibres and rock wool/slag wool from different sources have similar diameters of 1.09–1.27 µm (arithmetic mean values) and similar lengths of 22.4–37.52 µm (arithmetic mean values). For biopersistence in vivo, the arithmetic mean $WT_{1/2}$ (weighted half-time) was 59 days for rock wool/slag wool and 41–64 days for ceramic fibres. The breakage behaviour of the two types of fibre is also similar. Both the ceramic fibres and the rock wool/slag wool do not split lengthwise, but transversely, resulting in fibre fragments with the same diameters. After inhalation, the ceramic fibres induced fibrosis and tumours of the lungs and mesotheliomas in rats, whereas the rock wool/slag wool induced only fibrosis but no tumours. In a long-term inhalation study, ceramic fibres induced mesotheliomas in hamsters. Inhalation studies with rock wool/slag wool in hamsters are not available. After intraperitoneal administration in rats, both rock wool/slag wool and ceramic fibres caused peritoneal mesotheliomas. Epidemiological studies show that ceramic fibres induced a dose-dependent increase in pleural plaques in the exposed persons, but not interstitial fibrosis. In epidemiological studies, no increase in the lung cancer and mesothelioma risk has been observed for ceramic fibres and for rock wool/slag wool. However, the available studies with rock wool/slag wool are of greater statistical power than the studies with ceramic fibres. The authors conclude that, based on the analogies with rock wool/slag wool, it is reasonable to believe that increases in lung cancer or any mesotheliomas are unlikely to be found in the RCF-exposed cohort.

6 Manifesto (MAK value/classification)

MAK value. Epidemiological studies have not demonstrated an association between workplace exposure to aluminium silicate fibres and an increase in pulmonary fibrosis. However, these studies have shown that high exposures in the past caused pleural plaques in workers. There is a dose–response relationship for pleural plaque formation. Pleural plaques can be considered an exposure marker, but are not a precursor for the development of mesotheliomas. Epidemiological studies from the USA and Europe show a correlation between exposure to aluminium silicate fibres and the frequency of respiratory symptoms such as dyspnoea, wheezing, chronic coughs, impairment of lung function, skin and eye irritation and irritation of the upper respiratory tract. These results, which mainly affected workers before 1980, could not be observed in subsequent production years because exposure has been reduced (Utell and Maxim 2010). Exposures since the 1980s until 2004 had no adverse health effects in the long-term development of the parameters FVC and FEV_1. During this period, RCF workplace concentrations have consistently fallen below 1 fibre/ml or below the detection limit (Rice et al. 1997). Since 1993, workplace concentrations have been around 0.2 fibres/ml in RCF manufacturing plants and 0.3 fibres/ml in processing plants. However, a concentration at which pulmonary effects are not observed cannot be derived from these studies.

In a cross-sectional study, a significant reduction of FVC and FEV_1 was found for exposed persons with the highest cumulative exposure of > 60 fibres × months/ml compared with exposed persons with < 15 fibres × months/ml. However, no significant decrease in lung function parameters was measured in a later longitudinal study in the same workers (McKay et al. 2011). SCOEL (2011) gives a value of 147.9 fibres × months/ml for the average cumulative exposure among all exposed persons in the group > 60 fibres × months/ml, based on a personal communication from the authors of the study by McKay et al. (2011). The average cumulative exposure value for exposed persons aged at least 60 years in this group was 184.8 fibres × months/ml. Assuming a 45-year exposure duration, these exposures result in average annual fibre concentrations of 0.27 and 0.34 fibres/ml, respectively, at which no effects on lung function are observed.

However, an exposure concentration at which no effects on lung function are to be expected does not protect against possible chronic inflammatory effects in the lung and pleura. Therefore, no MAK value can be established for ceramic fibres.

In rats, the NOAEC (no observed adverse effect concentration) for lung fibrosis is reported to be 3 mg/m³ (26 WHO fibres/ml) and for lung tumours 16 mg/m³ (120 WHO fibres/ml) (NIOSH 2006). These concentrations are much higher than the concentrations of aluminium silicate fibres determined at the workplace in recent years in production plants. They cannot be taken into account for the establishment of a MAK value because there are no NOAECs from experimental animal studies for chronic fibre-related inflammatory reactions in the lungs and pleura. NIOSH questions the extrapolation of data from experimental animals to humans because of their different sensitivity for fibre toxicity. NIOSH has recommended 0.5 fibres/ml as a TWA (time-weighted average) for up to 10 hours of exposure per day for 40 hours per week. At this limit value, the risk of developing lung cancer is reduced to values between 0.073/1000 and 1.2/1000. The risk of developing mesotheliomas is not quantifiable due to insufficient data. However, since no mesotheliomas have been observed in workers and pleural plaques are unlikely to occur at low exposure levels, the risk of mesotheliomas would be lower than the calculated risk for lung cancer (NIOSH 2006).

Carcinogenicity. Aluminium silicate fibres can induce malignant mesotheliomas of the pleura and lung tumours in rats and hamsters after inhalation, and intratracheal or intraperitoneal administration. Hamsters are more sensitive to mesothelioma formation than rats, but less sensitive to the formation of lung tumours. No dose–response relationship was found for mesotheliomas. To date, epidemiological studies have not provided evidence of a relationship between exposure to aluminium silicate fibres and the development of mesotheliomas or lung tumours in humans. However, the necessary latency period may not have been reached in these studies and the statistical power may be too low. So far, mesotheliomas in humans have been observed only after exposure to asbestos and erionite, but not after exposure to other artificial mineral fibres.

According to current knowledge, tumour development in the lungs and pleura of rats and hamsters is mainly a consequence of chronic fibre-related inflammatory processes. Rats and hamsters seem to differ in sensitivity. It is currently believed that exposure that does not lead to chronic fibre-related inflammation is not associated with an increased risk

of cancer. However, there are no long-term inhalation studies in animals available with a NOAEC for inflammatory changes in the lungs and pleura.

More recent epidemiological studies published since the last documentation in 1993 have not provided evidence that there is a need to deviate from the previous classification in Carcinogen Category 2. Animal studies have shown that aluminium silicate fibres persist in the lungs and pleura and induce tumour formation due to their length and biopersistence. There is evidence that pleural plaques are associated with inflammatory processes.

Aluminium silicate fibres therefore remain classified in Carcinogen Category 2.

Germ cell mutagenicity. From the available data for genotoxicity, aluminium silicate fibres are not suspected of having a mutagenic effect on germ cells. Therefore, classification in one of the categories for germ cell mutagens is not regarded necessary.

Absorption through the skin. Dermal absorption of aluminium silicate fibres is unknown. Designation with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) is therefore not required.

Sensitization. No data are available for sensitizing effects of aluminium silicate fibres on the skin and respiratory tract. Aluminium silicate fibres are therefore not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

Adachi S, Kawamura K, Takemoto K (2001) 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 39(2): 168–174. DOI: https://doi.org/10.2486/indhealth.39.168

Andujar P, Lecomte C, Renier A, Fleury-Feith J, Kheuang L, Daubriac J, Janin A, Jaurand M-C (2007) Clinico-pathological features and somatic gene alterations in refractory ceramic fibre-induced murine mesothelioma reveal mineral fibre-induced mesothelioma identities. Carcinogenesis 28(7): 1599–1605. DOI: https://doi.org/10.1093/carcin/bgm023

Baan RA, Grosse Y (2004) Man-made mineral (vitreous) fibres: evaluations of cancer hazards by the IARC Monographs Programme. Mutat Res 553(1–2): 43–58. DOI: https://doi.org/10.1016/j.mrfmmm.2004.06.019

Bellmann B, Muhle H, Creutzenberg O, Ernst H, Brown RC, Sébastien P (2001) Effects of nonfibrous particles on ceramic fiber (RCF1) toxicity in rats. Inhal Toxicol 13(10): 877–901. DOI: https://doi.org/10.1080/089583701752378151

Binde G, Bolender T (2002) Rekristallisation und Cristobalitbildung in Hochtemperaturglasfasern (AES) nach thermischer Belastung. Gefahrst Reinhalt Luft 62(6): 273–278

Brockmann M (1991) Asbestassoziierte Lungen- und Pleuraerkrankungen – pathologische Anatomie. Pneumologie 45(6): 422–428

Brown TP, Harrison PTC (2014) Crystalline silica in heated man-made vitreous fibres: a review. Regul Toxicol Pharmacol 68(1): 152–159. DOI: https://doi.org/10.1016/j.yrtph.2013.11.014

Brown DM, Beswick PH, Donaldson K (1999) Induction of nuclear translocation of NF-kappaB in epithelial cells by respirable mineral fibres. J Pathol 189(2): 258–264. DOI: https://doi.org/10.1002/(SICI)1096-9896(199910)189:2<258::AID-PATH410>3.0.CO;2-E

Brown RC, Bellmann B, Muhle H, Davis JMG, Maxim LD (2005) Survey of the biological effects of refractory ceramic fibres: overload and its possible consequences. Ann Occup Hyg 49(4): 295–307. DOI: https://doi.org/10.1093/annhyg/meh098

Burge PS, Calvert IA, Trethowan WN, Harrington JM (1995) Are the respiratory health effects found in manufacturers of ceramic fibres due to the dust rather than the exposure to fibres? Occup Environ Med 52(2): 105–109. DOI: https://doi.org/10.1136/oem.52.2.105

Cavallo D, Campopiano A, Cardinali G, Casciardi S, De Simone P, Kovacs D, Perniconi B, Spagnoli G, Ursini CL, Fanizza C (2004) Cytotoxic and oxidative effects induced by man-made vitreous fibers (MMVFs) in a human mesothelial cell line. Toxicology 201(1–3): 219–229. DOI: https://doi.org/10.1016/j.tox.2004.04.017

Cowie HA, Wild P, Beck J, Auburtin G, Piekarski C, Massin N, Cherrie JW, Hurley JF, Miller BG, Groat S, Soutar CA (2001) An epidemiological study of the respiratory health of workers in the European refractory ceramic fibre industry. Occup Environ Med 58(12): 800–810. DOI: https://doi.org/10.1136/oem.58.12.800

Creutzenberg O, Bellmann B, Muhle H (1997) Biopersistence and bronchoalveolar lavage investigations in rats after a sub acute inhalation of various man-made mineral fibres. Ann Occup Hyg 41(Suppl 1): 213–218. DOI: https://doi.org/10.1093/annhyg/41.inhaled_particles_VIII.213

Dopp E, Schiffmann D (1998) Analysis of chromosomal alterations induced by asbestos and ceramic fibers. Toxicol Lett 96–97: 155–162. DOI: https://doi.org/10.1016/s0378-4274(98)00063-0

Dopp E, Nebe B, Hahnel C, Papp T, Alonso B, Simkó M, Schiffmann D (1995) Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. Pathobiology 63(4): 213–221. DOI: https://doi.org/10.1159/000163954

Dopp E, Schuler M, Schiffmann D, Eastmond DA (1997) Induction of micronuclei, hyperdiploidy and chromosomal breakage affecting the centric/pericentric regions of chromosomes 1 and 9 in human amniotic fluid cells after treatment with asbestos and ceramic fibers. Mutat Res 377(1): 77–87. DOI: https://doi.org/10.1016/s0027-5107(97)00062-6

Drummond G, Bevan R, Harrison P (2016) A comparison of the results from intra-pleural and intra-peritoneal studies with those from inhalation and intratracheal tests for the assessment of pulmonary responses to inhalable dusts and fibres. Regul Toxicol Pharmacol 81: 89–105. DOI: https://doi.org/10.1016/j.yrtph.2016.07.019

Esmen NA, Corn M, Hammad YY, Whittier D, Kotsko N, Haller M, Kahn RA (1979) Exposure of employees to man-made mineral fibers: ceramic fiber production. Environ Res 19(2): 265–278. DOI: https://doi.org/10.1016/0013-9351(79)90054-9

Fireman E (2014) Man-made mineral fibers and interstitial lung diseases. Curr Opin Pulm Med 20(2): 194–198. DOI: https://doi.org/10.1097/MCP.0000000000000035

Gilmour PS, Beswick PH, Brown DM, Donaldson K (1995) Detection of surface free radical activity of respirable industrial fibres using supercoiled phi X174 RF1 plasmid DNA. Carcinogenesis 16(12): 2973–2979. DOI: https://doi.org/10.1093/carcin/16.12.2973

Greim H (ed) (1997) Fibrous dust. MAK Value Documentation, 1993. In: Occupational Toxicants, vol 8. Wiley-VCH, Weinheim, 141–338. Also available from DOI: https://doi.org/10.1002/3527600418.mb0243fase0008

Greim H (ed) (1999) General threshold limit value for dust. MAK Value Documentation, 1997. In: Occupational Toxicants, vol 12. Wiley-VCH, Weinheim, 239–270. Also available from DOI: https://doi.org/10.1002/3527600418.mb0230stwe0012

Greim H, Utell MJ, Maxim LD, Niebo R (2014) Perspectives on refractory ceramic fiber (RCF) carcinogenicity: comparisons with other fibers. Inhal Toxicol 26(13): 789–810. DOI: https://doi.org/10.3109/08958378.2014.953276

Gualtieri AF, Foresti E, Lesci IG, Roveri N, Gualtieri ML, Dondi M, Zapparoli M (2009) The thermal transformation of Man Made Vitreous Fibers (MMVF) and safe recycling as secondary raw materials (SRM). J Hazard Mater 162(2–3): 1494–1506. DOI: https://doi.org/10.1016/j.jhazmat.2008.06.066

Hart GA, Newman MM, Bunn WB, Hesterberg TW (1992) Cytotoxicity of refractory ceramic fibres to Chinese hamster ovary cells in culture. Toxicol In Vitro 6(4): 317–326. DOI: https://doi.org/10.1016/0887-2333(92)90021-i

Hart GA, Kathman LM, Hesterberg TW (1994) In vitro cytotoxicity of asbestos and man-made vitreous fibers: roles of fiber length, diameter and composition. Carcinogenesis 15(5): 971–977. DOI: https://doi.org/10.1093/carcin/15.5.971

Hartwig A, MAK Commission (2019) Fibrous dusts, inorganic. MAK Value Documentation, 2018. MAK Collect Occup Health Saf (4): 2054–2107. DOI: https://doi.org/10.1002/3527600418.mb0243fase6519

Hesterberg TW, Hart GA (2001) Synthetic vitreous fibers: a review of toxicology research and its impact on hazard classification. Crit Rev Toxicol 31(1): 1–53. DOI: https://doi.org/10.1080/20014091111668

Hesterberg TW, Chase G, Axten C, Miller WC, Musselman RP, Kamstrup O, Hadley J, Morscheidt C, Bernstein DM, Thevenaz P (1998) Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol 151(2): 262–275. DOI: https://doi.org/10.1006/taap.1998.8472

Hill IM, Beswick PH, Donaldson K (1996) Enhancement of the macrophage oxidative burst by immunoglobulin coating of respirable fibers: fiber-specific differences between asbestos and man-made fibers. Exp Lung Res 22(2): 133–148. DOI: https://doi.org/10.3109/01902149609050843

Howden PJ, Faux SP (1996) Fibre-induced lipid peroxidation leads to DNA adduct formation in Salmonella typhimurium TA104 and rat lung fibroblasts. Carcinogenesis 17(3): 413–419. DOI: https://doi.org/10.1093/carcin/17.3.413

IARC (International Agency for Research on Cancer) (1988) Man made mineral fibres. In: Man made mineral fibres and radon. IARC monographs on the evaluation of carcinogenic risks to humans, vol 43. IARC Press, Lyon, 39–170. https://publications.iarc.fr/_publications/media/download/1592/bddbe727065b1d7fddd8a42fa4e9e9cf758ce65e.pdf, accessed 08 May 2020

IARC (International Agency for Research on Cancer) (2002) Man made vitreous fibres. IARC monographs on the evaluation of carcinogenic risks to humans, vol 81. IARC Press, Lyon. https://publications.iarc.fr/_publications/media/download/2602/6d4cb1852bd2640e7efa05cd140ad44be02b5b42.pdf, accessed 08 May 2020

Konstantinidis K (2001) Hyaline Pleuraplaques: Rasterelektronenmikroskopische und immunhistochemische Befunde. Dissertation, Ruhr-Universität Bochum, Bochum. https://api.deutsche-digitale-bibliothek.de/binary/0b4b41e7-052f-4a2e-b4a9-c1b69457b1ef.pdf, accessed 19 Sep 2021

Lecomte C, Andujar P, Renier A, Kheuang L, Abramowski V, Mellottee L, Fleury-Feith J, Zucman-Rossi J, Giovannini M, Jaurand M-C (2005) Similar tumor suppressor gene alteration profiles in asbestos-induced murine and human mesothelioma. Cell Cycle 4(12): 1862–1869. DOI: https://doi.org/10.4161/cc.4.12.2300

LeMasters GK, Lockey JE, Levin LS, McKay RT, Rice CH, Horvath EP, Papes DM, Lu JW, Feldman DJ (1998) An industry-wide pulmonary study of men and women manufacturing refractory ceramic fibers. Am J Epidemiol 148(9): 910–919. DOI: https://doi.org/10.1093/oxfordjournals.aje.a009717

LeMasters GK, Lockey JE, Yiin JH, Hilbert TJ, Levin LS, Rice CH (2003) Mortality of workers occupationally exposed to refractory ceramic fibers. J Occup Environ Med 45(4): 440–450. DOI: https://doi.org/10.1097/01.jom.0000052968.43131.b5

Lockey J, Lemasters G, Rice C, Hansen K, Levin L, Shipley R, Spitz H, Wiot J (1996) Refractory ceramic fiber exposure and pleural plaques. Am J Respir Crit Care Med 154(5): 1405–1410. DOI: https://doi.org/10.1164/ajrccm.154.5.8912756

Lockey JE, Levin LS, Lemasters GK, McKay RT, Rice CH, Hansen KR, Papes DM, Simpson S, Medvedovic M (1998) Longitudinal estimates of pulmonary function in refractory ceramic fiber manufacturing workers. Am J Respir Crit Care Med 157(4 Pt 1): 1226–1233. DOI: https://doi.org/10.1164/ajrccm.157.4.9707131

Lockey JE, LeMasters GK, Levin L, Rice C, Yiin J, Reutman S, Papes D (2002) A longitudinal study of chest radiographic changes of workers in the refractory ceramic fiber industry. Chest 121(6): 2044–2051. DOI: https://doi.org/10.1378/chest.121.6.2044

Lockey JE, Roggli VL, Hilbert TJ, Rice CH, Levin LS, Borton EK, Biddinger PW, Lemasters GK (2012) Biopersistence of refractory ceramic fiber in human lung tissue and a 20-year follow-up of radiographic pleural changes in workers. J Occup Environ Med 54(7): 781–788. DOI: https://doi.org/10.1097/JOM.0b013e31825296fd

Luoto K, Holopainen M, Sarataho M, Savolainen K (1997) Comparison of cytotoxicity of man-made vitreous fibres. Ann Occup Hyg 41(1): 37–50. DOI: https://doi.org/10.1016/S0003-4878(96)00031-2

Mast RW, McConnell EE, Anderson R, Chevalier J, Kotin P, Bernstein DM, Thevenaz P, Glass LR, Miiller WC, Hesterberg TW (1995 a) Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4): 425–467. DOI: https://doi.org/10.3109/08958379509015208

Mast RW, McConnell EE, Hesterberg TW, Chevalier J, Kotin P, Thevenaz P, Bernstein DM, Glass LR, Miiller W, Anderson R (1995 b) Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. Inhal Toxicol 7(4): 469–502. DOI: https://doi.org/10.3109/08958379509015209

Mast RW, Maxim LD, Utell MJ, Walker AM (2000 a) Refractory ceramic fiber: toxicology, epidemiology, and risk analyses–a review. Inhal Toxicol 12(5): 359–399. DOI: https://doi.org/10.1080/089583700196103

Mast RW, Yu CP, Oberdörster G, McConnell EE, Utell MJ (2000 b) A retrospective review of the carcinogenicity of refractory ceramic fiber in two chronic fischer 344 rat inhalation studies: an assessment of the MTD and implications for risk assessment. Inhal Toxicol 12(12): 1141–1172. DOI: https://doi.org/10.1080/08958370050198511

Maxim LD, Allshouse J, Fairfax RE, Lentz TJ, Venturin D, Walters TE (2008) Workplace monitoring of occupational exposure to refractory ceramic fiber–a 17-year retrospective. Inhal Toxicol 20(3): 289–309. DOI: https://doi.org/10.1080/08958370701866040

McConnell EE, Mast RW, Hesterberg TW, Chevalier J, Kotin P, Bernstein DM, Thevenaz P, Glass LR, Anderson R (1995) Chronic inhalation toxicity of a Kaolin-based refractory ceramic fiber in Syrian Golden hamsters. Inhal Toxicol 7(4): 503–532. DOI: https://doi.org/10.3109/08958379509015210

McKay RT, LeMasters GK, Hilbert TJ, Levin LS, Rice CH, Borton EK, Lockey JE (2011) A long term study of pulmonary function among US refractory ceramic fibre workers. Occup Environ Med 68(2): 89–95. DOI: https://doi.org/10.1136/oem.2009.048033

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

Murata-Kamiya N, Tsutsui T, Fujino A, Kasai H, Kaji H (1997) Determination of carcinogenic potential of mineral fibers by 8-hydroxydeoxyguanosine as a marker of oxidative DNA damage in mammalian cells. Int Arch Occup Environ Health 70(5): 321–326. DOI: https://doi.org/10.1007/s004200050225

NIOSH (The National Institute for Occupational Safety and Health) (2006) Criteria for a recommended standard: Occupational exposure to refractory ceramic fibers. DHHS (NIOSH) Publication No. 2006-123. NIOSH, Cincinnatti, OH. https://www.cdc.gov/niosh/docs/2006-123/pdfs/2006-123.pdf?id=10.26616/NIOSHPUB2006123, accessed 21 Mar 2018

Okayasu R, Wu L, Hei TK (1999) Biological effects of naturally occurring and man-made fibres: in vitro cytotoxicity and mutagenesis in mammalian cells. Br J Cancer 79(9–10): 1319–1324. DOI: https://doi.org/10.1038/sj.bjc.6690213

Osgood CJ (1994) Refractory ceramic fibers (RCFs) induce germline aneuploidy in Drosophila oocytes. Mutat Res 324(1–2): 23–27. DOI: https://doi.org/10.1016/0165-7992(94)90063-9

Pairon J-C, Laurent F, Rinaldo M, Clin B, Andujar P, Ameille J, Brochard P, Chammings S, Ferretti G, Galateau-Sallé F, Gislard A, Letourneux M, Luc A, Schorlé E, Paris C (2013) Pleural plaques and the risk of pleural mesothelioma. J Natl Cancer Inst 105(4): 293–301. DOI: https://doi.org/10.1093/jnci/djs513

Rice CH, Lockey JE, Lemasters GK, Levin LL, Staley P, Hansen KR (1997) Estimation of historical and current employee exposure to refractory ceramic fibers during manufacturing and related operations. Appl Occup Environ Hyg 12(1): 54–61. DOI: https://doi.org/10.1080/1047322X.1997.10389456

Roberts GH (1971) The pathology of parietal pleural plaques. J Clin Pathol 24(4): 348–353. DOI: https://doi.org/10.1136/jcp.24.4.348

Schnegelsberg G (1999) Handbuch der Faser: Theorie und Systematik der Faser. Deutscher Fachverlag, Frankfurt am Main

SCOEL (Scientific Committee on Occupational Exposure Limits) (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for refractory ceramic fibres. SCOEL/SUM/165. European Commission, Brussels. http://ec.europa.eu/social/BlobServlet?docId=7371&langId=en, accessed 21 Mar 2018

Sonnenschein G (2003) Werkstoffe zur Wärmedämmung unter Berücksichtigung des Einsatzes von Keramikfasern. Gefahrst Reinhalt Luft 63(5): 181–185

Tonnesen T, Telle R (2007) Influence of firing temperature and time on the quantitative phase formation and recrystallization behaviour of high temperature glass fibres (AES) and refractory ceramic fibres (RCF). RWTH Aachen, Institute of Mineral Engineering – Gesteinshüttenkunde, German Association of Manufacturers and Processors of High Temperature Wool, Aachen. https://www.yumpu.com/en/document/read/11660305/influence-of-firing-temperature-and-time-on-the-dkfgde, accessed 21 Mar 2018

Trethowan WN, Burge PS, Rossiter CE, Harrington JM, Calvert IA (1995) Study of the respiratory health of employees in seven European plants that manufacture ceramic fibres. Occup Environ Med 52(2): 97–104. DOI: https://doi.org/10.1136/oem.52.2.97

Turim J, Brown RC (2003) A dose-response model for refractory ceramic fibers. Inhal Toxicol 15(11): 1103–1118. DOI: https://doi.org/10.1080/08958370390228556

Utell MJ, Maxim LD (2010) Refractory ceramic fiber (RCF) toxicity and epidemiology: a review. Inhal Toxicol 22(6): 500–521. DOI: https://doi.org/10.3109/08958370903521224

Walker AM, Maxim LD, Utell MJ (2012 a) Are airborne refractory ceramic fibers similar to asbestos in their carcinogenicity? Inhal Toxicol 24(7): 416–424. DOI: https://doi.org/10.3109/08958378.2012.683892

Walker AM, Maxim LD, Utell MJ (2012 b) Corrigendum. Are airborne refractory ceramic fibers similar to asbestos in their carcinogenicity? Inhal Toxicol 24(13): 928–929. DOI: https://doi.org/10.3109/08958378.2012.736736

Wang QE, Han CH, Wu WD, Wang HB, Liu SJ, Kohyama N (1999 a) Biological effects of man-made mineral fibers (I)–Reactive oxygen species production and calcium homeostasis in alveolar macrophages. Ind Health 37(1): 62–67. DOI: https://doi.org/10.2486/indhealth.37.62

Wang QE, Han CH, Yang YP, Wang HB, Wu WD, Liu SJ, Kohyama N (1999 b) Biological effects of man-made mineral fibers (II)–their genetic damages examined by in vitro assay. Ind Health 37(3): 342–347. DOI: https://doi.org/10.2486/indhealth.37.342

Yegles M, Janson X, Dong HY, Renier A, Jaurand MC (1995) Role of fibre characteristics on cytotoxicity and induction of anaphase/telophase aberrations in rat pleural mesothelial cells in vitro: correlations with in vivo animal findings. Carcinogenesis 16(11): 2751–2758. DOI: https://doi.org/10.1093/carcin/16.11.2751

Zoitos B, DeMeringo A, Rouyer E, Thelohan S, Bauer J, Law B, Boymel P, Olson J, Christensen V, Guldberg M, Koenig A, Perander M (1997) In vitro measurement of fiber dissolution rate relevant to biopersistence at neutral pH: An interlaboratory round robin. Inhal Toxicol 9(6): 525–540. DOI: https://doi.org/10.1080/089583797198051