

Recommendation from the Scientific Committee on Occupational Exposure Limits for Refractory Ceramic Fibres

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8-hour TWA:	(proposal 0.3 f/ml)
STEL (15 min):	Not assigned
Notation:	None
BLV:	Not assigned
SCOEL carcinogen group:	C (Genotoxic carcinogens for which a practical threshold is supported).

EU definition:

Refractory ceramic fibres with the exception of those species elsewhere in Annex VI to Regulation (EC) 1272/2008 (Man-made vitreous [silicate] fibres with random orientation with alkaline oxide and alkali earth oxide [Na₂O+K₂O+CaO+MgO+BaO] content less or equal to 18% by weight)

Synonyms: Vitreous siliceous fibres, alumino-silicate glass wools

Formula: (see table 1)

EU classification:

Carc. 1B Causes cancer by inhalation

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Introduction

RCFs are vitreous materials of variable composition and properties used for insulation at high temperatures. They are manufactured in the form of wool and typically contain approximately 50% fibre and 50% unfibred, largely non-respirable material. The fibres do not split longitudinally into thinner fibres as does asbestos but rather transversally, ultimately becoming granular dust (Mast et al 2000a).

The most important factors that affect toxic potential and potency of fibres are fibre length, diameter and bioavailability (rate of degradation in biological fluids). In humans, fibres with a diameter of $>3\mu\text{m}$ are essentially non-respirable, whereas pulmonary deposition is greatest for fibres of diameter of about $1\mu\text{m}$ and length of about $8\mu\text{m}$. Clearance of deposited fibres is also a function of length and diameter. Fibres with a length smaller than the diameter of the macrophages ($15\mu\text{m}$) are phagocytised and removed, either by transport via the mucociliary system or to local lymph nodes. Fibres longer than $15\mu\text{m}$ are partially engulfed by the macrophages. Since longer fibres are fractioned transversely they also become progressively removed.

Table 1: Chemical composition of the 3 mostly used types of RCF (see Mast et al 2000a) expressed in % weight.

Constituent	Kaolin aluminosilicate (RCF-1)	High-purity aluminosilicate (RCF-3)	Zirconia aluminosilicate (RCF-2)
SiO ₂	50-54	49-54	48-50
AlO ₃	44-47	46-51	35-36
K ₂ O	<0.01	<0.01	<0.01
Na ₂ O	0.5	0.2	<0.3
MgO	<0.01	<0.01	0.01
CaO	<0.01	<0.05	<0.05
TiO ₂	2	0.02	0.04
ZrO ₂	0.1	0.2	15-17
Fe ₂ O ₃	1	<0.2	<0.05
Cr ₂ O ₃	<0.03	<0.01	<0.01

The RCFs are distinguished in RCF types 1, 2, 3, and 4. RCF 4 fibres are RCF 1 fibres, which had been heated at 1300°C for 24 hrs represent "after service conditions". They have no commercial importance. Table 1 shows the composition of the 3 most widely used RCFs. It indicates that these fibres consist of about 50% each of silicium oxide and aluminium oxide (RCF 1 and 3). In zirconia aluminosilicate fibers (RCF 2) part of the aluminium oxide is substituted by zirconium oxide. The different composition results in increasing heat stability



from 1050° C or higher for the kaolin-based fibres to 1424° C or above for the zirconia-based material.

Studies in animals

Repeated dose studies

Inhalation

Due to methodological deficits most of the inhalation studies only allow to evaluate the carcinogenic potential rather than the dose response of effects.

In an experiment in which rats were exposed to ceramic fibres (95f/ml) by inhalation (Davis et al 1984) a statistically significant increase in the incidence of benign and malignant tumours of the lung was observed. Following 12 months exposure 5% fibrosis and 17% lung tumours have been observed, whereas Smith et al (1987) neither observed fibrosis nor tumours and only 2% mesotheliomas in hamsters after 24 months exposure of 200 f/ml. Two further inhalation experiments in rats and hamsters from the same laboratory (McConnell et al 1984) showed no increased tumour incidence in groups exposed to ceramic fibres. In the positive control groups, crocidolite produced a few lung tumours in rats, but not in hamsters. However, these studies had one or more technical limitations (Hesterberg and Hart 2001). In the McConnell et al study (1984) relatively short test fibres have been used. More than 70% of test fibres were shorter than 10 µm. In other studies (Pigott and Ishmael 1992) fibres tended to be too thick for rat respirability or data on fibre numbers and dimensions in aerosols and/or lung burdens were incomplete or not reported. Due to the less respirable fibres lung burdens were relatively small. In the Smith et al (1987) study (200 f/ml, 24 mo) in rats and hamsters lung burden were roughly 3×10^6 and 2×10^6 for RCF and JM 475 fibreglass-fibres, respectively as compared to $150\text{--}2000 \times 10^6$ fibres/lung in studies conducted after 1988.

In a long-term inhalation study with 4 types of RCF in rats at about 200 f/ml each, a statistically significant increase in the incidence of lung tumours and a few mesotheliomas were observed. Chrysotile asbestos was used as a positive control (Mast et al 1995a). In hamsters exposed to about 250 f/ml, no increase of lung tumours but a significant increase in the incidence of mesotheliomas was observed (McConnell et al 1995).

In more recent studies the fibres were rat respirable (geometric mean diameter about 1 µm or less with a large portion of long fibres (50% of the fibres had an arithmetic mean length of 20 µm) and representative for workplace exposure (Hesterberg et al 1993). Moreover, aerosolization and exposure by nose only inhalation have been improved (Hesterberg and Hart 2001).

Two long-term inhalation studies in rats exposed to RCF have been performed. One using a concentration of 30 mg/m³ (approximately 190 WHO-fibres/ml. WHO definition: length >5 µm, diameter <3 µm, ratio length/diameter <3:1) using 4 different types of RCF (RCF-1-4) (Mast et al 1995a) and a succeeding study using the same protocol (5 days/wk and 6 h/day for 104 weeks) at doses of 3, 9, or 16 mg/m³ RCF-1, which corresponded to 26, 75 and 120 WHO fibres/ml (Mast et al 1995b). The studies have been re-evaluated and summarized by Mast et al (2000b). To prepare rodent respirable fibre samples the commercial RCF was extensively milled and the animals were exposed to a fraction of a relatively high particle to fibre ratio of about 25% by weight and 10 particles per fibre (Turim and Brown 2003).

In the study using the three different exposure concentrations of 3, 9, or 16 mg/m³ of RCF-1) pulmonary clearance was considered to be unaffected for most of the exposure period at 3 mg/m³. No observable clinical signs were seen at all doses while time- and dose-dependent increases in lung weight and in lung to body weight ratio occurred at all



exposure levels. These increases became statistically significant at 16 mg/m³. Histopathological evaluation of lung tissue was started after 3 months of exposure. At this time dose-related influx of fibre-containing macrophages, minimal fibre-containing microgranulomas at the bronchoalveolar junction and early bronchiolization was seen with a minimal progression of the effects over time. At 3 mg/m³ these changes were considered to be minimal to mild within the 1 to 4 grading of lung fibrosis scale of Wagner. The effects correlated with the fibre lung burden (Mast et al 1995b). SCOEL notes that this 24 months inhalation study in rats resulted in a LOAEC of minimal effects in the rat-lung in a at 3 mg/ m³ RCF-1, which is equivalent to 26 fibres/ml (Table 2).

Table 2: 24 months inhalation study in rats resulting in a LOAEC of minimal effects in the rat-lung at 3 mg/ m³ RCF-1, which is equivalent to 26 fibres/ml . For details see text.

Fibre	Species/duration	Exposure	LOEL	Reference
RCF1	Rats, 24 mo 6h/d, 5d/w	3, 9, 16, 30 mg/m ³	3 mg/m ³ 26f /ml (LOEL)	Mast et al 1995b, 2000b

When studying the 3 different types of RCF that represented types of rodent respirable fractions of typical RCF compositions rats were exposed to a single concentration of 200 WHO fibers/ml for 24 months. An additional group has been exposed to RCF 4. High incidence of exposure-related pulmonary neoplasms (bronchoalveolar adenomas and carcinomas) were observed with RCF 1-3, not with RCF-4. A small number of mesotheliomas were observed in each of the fibre exposure groups (Mast et al 1995a). Using the same experimental design hamsters exposed to 30 mg/m³ (260 f/ml) for 18 mo developed lung fibrosis, a significant number of pleural mesotheliomas (42/102) but no primary lung tumours (McConnell et al 1995).

Intratracheal instillation

Intratracheal instillation of ceramic fibres did not produce lung or pleural tumours in one study in rats and hamsters given 5 weekly instillations of 2 mg Fibrefax and kept in study for the rest of their life (Smith et al 1987), while crocidolite produced a high percentage of benign and malignant lung tumours in hamsters but only a few in rats.

Intrapleural implantation

In one study, intrapleural implantation in rats of several kinds of ceramic fibres produced variable incidences of pleural mesotheliomas or sarcomas (Stanton et al 1981). Another study in rats produced equivocal results (Wagner et al 1973). Rats exposed to refractory ceramic fibres by intrapleural implantation 55, did not show a significant increase in tumour incidence (Pigott et al 1992, Carthew et al 1995).

Intraperitoneal injection

After intraperitoneal injection of ceramic fibres into rats in three experiments (Smith et al 1987, Pott et al 1987, Davis et al 1984), mesotheliomas were found in the abdominal cavity in two studies, while the third report (Pott et al 1987) had incomplete histopathology. Only a few mesotheliomas were found in the abdominal cavity of hamsters after intraperitoneal injection in one experiment (Smith et al 1987). However, the ceramic fibres tested were of relatively large diameter. When rats and hamsters were exposed via intraperitoneal



injection, tumour incidence was related to fibre length and dose (Smith et al 1987, Pott et al 1987, Miller et al 1999, Pott et al 1989).

On the basis of these studies IARC has classified RCFs as 2B carcinogens, with sufficient evidence in animals and insufficient evidence for humans (IARC 1987 (Vol 43) and 2002 (Vol 81). For details see Baan and Grosse (2004).

Genotoxicity of RCF

In acellular systems RCFs can directly cause oxidative DNA damage (Gilmour et al. 1995). RCF induce DNA adducts from end products of lipid peroxidation (Howden and Faux 1996).

In vitro RCF1, RCF2 and RCF3 caused DNA damage (breakage and cross-links) in human lung epithelial cell line A549 (one dose investigated) (Wang et al. 1999). Micronucleus formation and structural and numerical chromosomal aberrations were detected in human amniotic fluid cells (Dopp et al. 1997; Dopp and Schiffmann 1998) and structural chromosomal aberrations were noted in human embryonic lung cells after treatment with RCFs (Wang et al. 1999). In the presence of RCFs micronucleus induction and increased apoptosis were detected in Syrian hamster embryo cells (Dopp et al. 1995). Nuclear abnormalities (micronucleus and polynucleus formation) were detected in Chinese hamster ovary (K1) cells after treatment with RCFs (Hart et al., 1992, 1994). No abnormalities of anaphase or telophase were observed in rat pleural mesothelial cells treated with different samples of refractory ceramic fibres (Yegles et al. 1995). No deoxyguanosine hydroxylation was detected in reticulum-cell sarcoma cell line (J774) after treatment with refractory ceramic fibres (Murata-Kamiya et al. 1997). RCF1 did not induce HPRT mutation in human-hamster hybrid A₁ cells (Okayasu et al. 1999).

In vivo aneuploidy was observed in *Drosophila melanogaster* fed with different samples of refractory ceramic fibres (Osgood 1994). However, no dose-response relationships were reported in these assays.

In a more recent study it was shown that human mesothelial cells (MeT-5A) exposed to RCF showed significant direct DNA damage (DNA strand breaks) in the comet test and a marked reduction of microvilli on cell surface (Cavallo et al. 2004).

It can be concluded that RCFs cause mainly clastogenic effects in cells in vitro, as summarised by IARC (2002). The direct entry of fibres into cells and physical interference with chromosomal segregation followed by, or associated with cell division can produce chromosomal/nuclear abnormalities and genetic changes which may lead to cell transformation. Further studies conducted on rodent alveolar macrophages and human polymorphonuclear leukocytes exposed to refractory ceramic fibres show the production of reactive oxygen species. These reactive oxygen species may also damage DNA.

These studies and the information that inflammation is the underlying effect of fibre carcinogenicity (see mechanisms) strongly indicate that the genotoxic effects observed in the different studies are secondary. They result from the induction of reactive oxygen species and in case of cytogenetic effects from the interaction of the fibres with the spindle apparatus.

Factors that affect toxicity of RCF

The factors that affect the potential health effects of RCF have been summarised by Mast et al (2000a). In general, length, diameter and biopersistence in biological fluids are the most critical determinants. Fibres with a diameter of >3 µm are essentially nonrespirable and have no health significance except irritation in the upper airways and the skin. In the human pulmonary region fibres with a diameter of approximately 1 µm and a length of about 8 µm are deposited preferentially. Clearance of the deposited fibres also depends on diameter and length. Fibres shorter than 15 µm, the diameter of lung macrophages,



are phagocytised and removed by mucociliary clearance or transported to the local lymphnodes, so that fibre toxicity is specifically linked to fibres longer than 15 μm . Since RCF fracture transversely, originally longer fibres that are broken will also be cleared faster. Since durable fibres remain in the lung longer and by that are more biologically active, biopersistence also affects toxicological potency. Biopersistence can be measured in vivo and in vitro; the latter systems are seen appropriate to determine relative durability. In a series of experiments Zoitos et al (1997) showed that durability of crocidolite asbestos fibres had the highest durability, RCF were an order of magnitude less durable, rock wool and slag wool an order of magnitude less durable than RCF, and two glass wool formulations even less durable.

Biopersistence of RCF in vivo as measured in chronic animal studies depends on the extent of exposure that affects clearance rate, the presence of non-fibrous particles and the dissolution rate of the fibres. Creutzenberg et al (1997) reported a prolongation of the clearance half-lives of 50-100 days in normal rats to about 1200 days when the lung burden of RCF-1 approached 30×10^6 fibres in the Mast et al studies (Mast et al 1995a, 1995b). This lung burden was reached approximately 48, 24 and 17 weeks at the exposure levels of 9, 16 and 30 mg/m^3 , respectively. Clearance rate in presence of RCF-1a (a fibre with reduced particle mass, reflecting the workplace dust) was almost normal (HL of about 100 days). This difference is explained by the higher inflammatory potency of RCF-1 as compared to RCF-1a, which is closer related to fibres inhaled at the workplace than RCF-1. The latter has been specifically prepared for the rat inhalation experiments. Moreover, several studies have shown that the durability of RCF-1 in the rat lung is about twice that of RCF-1a (see Mast et al 2000a). The results also imply that fibre exposures, which do not induce inflammatory reactions in the lung, do not impair lung clearance.

Studies in humans

Several studies on cohorts of employees in the US and Europe have investigated respiratory symptoms, pulmonary function, radiological findings, and mortality. NIOSH (2006) reports that the earliest commercial production of RCFs and RCF products began in the United States in 1953; in Europe, RCF production began in 1968. In 1986 the mean duration of employment in the European cohort was 10.2 years (range 7.2 to 13.8 years) (Trethowan et al. 1995) and 13.0 years in 1996 (Cowie et al. 2001). The U.S. study reports the mean duration of employment for 23 workers with pleural plaques as 13.6 years, the median is 11.2 years (range 1.4 to 32.7) (LeMasters et al. 1998).

Between 1987 and 1989, LeMasters et al (1998) examined 742 workers from 5 different plants in the US where current exposure to RCF was below 1 fibre/ml, and administered a standard questionnaire on respiratory symptoms to collect information on chronic cough, chronic phlegm, dyspnea, wheezing, asthma, pleurisy, and pleuritic chest pain. The analysis considered several independent variables, including smoking, asbestos exposure, duration of production employment, and time since last RCF employment. The authors reported an association between the prevalence of dyspnoea and RCF exposure. This symptom occurred more frequently among production employees. The prevalence rates in male production workers ($n=517$) compared to non-production workers ($n=80$) reporting one or more respiratory symptoms was 29.6% and 11.3%, respectively, with an adjusted odds ratio of 2.9 (95% confidence interval 1.4-6.2). In female workers the prevalences were 40.7 and 20.3, respectively, with an adjusted odds ratio of 2.4 (95% confidence interval 1.1-5.3). The authors concluded: "In general, the prevalence of respiratory symptoms here is similar to that reported in other dust-exposed populations."

In Europe, Burge et al. (1995) examined workers from all the manufactures of RCF and concluded that current exposure to both inspirable (inhalable) gravimetric dust (1.7 to 3.4 mg/m^3 for primary production workers and 1.8 and 11.2 mg/m^3 for secondary production



workers) and respirable fibres (0.2 to 0.88 f/ml for primary production workers and 0.49 to 1.36 f/ml in secondary production workers) were related to the prevalence of respiratory symptoms, including dry cough, stuffy nose, eye and skin irritation, and breathlessness. In addition, Trethowan *et al.* (1995) reported, in the same cohort, a statistically significant increase in the prevalence of breathlessness (both grades) with increasing cumulative exposure to RCF (2.88 to 6.83 f. year/ml). In 6 out of the 7 plants previously examined, Cowie *et al.* (2001) analyzed chronic bronchitis, breathlessness, recurrent chest illness and pleuritic chest pain as a function of recent and cumulative exposure. The authors noted that the prevalence of symptoms in the study group was generally low but significantly associated with recent or cumulative exposure to respirable fibres.

Pulmonary function

In the European cohort mentioned above (Cowie *et al.* 2001), a cross-sectional study of pulmonary function revealed no statistically significant association with RCF exposure for FEV₁/FVC or FEF 25-75. For men, there was a statistically significant decline in forced vital capacity (FVC) for 10 years of working in the production of RCF, amounting to 165mL and 156mL, in current and past smokers, respectively. Only those men who worked in RCF production and smoked showed a decline in FEV₁ (135 ml per 10 years exposure). There was no significant decline among non-smokers. A significant FVC decline associated with employment in the production of RCF was also detected in non-smoking women. Two surrogate measures of past fibre and dust exposure, duration of employment and categorical duration of employment status, provided strength as to an exposure effect relation. The median time weighted average exposure estimate was 0.01-1.04 fibres/ml for the blanket line, 0.03-0.61 for dry fabrication, 0.01-0.27 for wet fabrication, 0.01-0.47 for furnace operations, and 0.02-0.62 for maintenance, which indicates that the current fibre levels had been below 1 fibre/ml in this cohort.

In the 5 US plants, a longitudinal analysis of 361 male production workers who provided 5 or more spirometry tests examined declines in FVC and FEV₁ between the initial (1987) and the final test (1994) (Lockey *et al.* 1998). The exposure-response relationship was modelled with two exposure variables: years in a production job, and cumulative fibre exposure (fibre-mo/ml). Comparison groups were non-production workers and workers with up to 15 fibre-mo/ml cumulative exposure. A statistically significant decrease in FVC was demonstrated among workers employed in production jobs more than 7 year prior to initial test. A similar but non-statistically significant result was demonstrated for FVC in workers with greater than 60 fibre-mo/ml cumulative exposure prior to initial pulmonary function test. Similar but non-statistically significant results were obtained for FEV₁. These findings, which primarily reflect workers employed before 1980, did not persist with analysis of follow-up production years and accumulated RCF exposure from initial pulmonary function test (after 1984). Lower RCF exposure levels since the 1980s may be responsible for eliminating any further effect on pulmonary function. The authors concluded that more recent exposures from the late 1980s until 1994 had no deleterious impact on the longitudinal trend of FVC and FEV₁. The results corresponded to the historically higher exposure levels in the 1950s (estimated maximum 10 fibers/cc in carding) in comparison to more recent exposures that ranged from approximately 1 fiber/cc to below the limit of detection (Rice *et al.* 1997).

Trethowan *et al.*, (1995) studied the respiratory function workers from the 7 manufactures of RCF in Europe in a cross-sectional design. The mean fibre concentrations ranged from 0.2 to 0.88 fibres/ml and 0.49 to 1.36 fibres/ml for primary and secondary (greater amount of handling RCFs) production workers, respectively, and the mean duration of employment was 10.2 years. There was a significant association between reduced FEV₁



and FEV50 and cumulative exposure in current smokers. A similar relationship was found for FEV1 in ex-smokers. No association between RCF exposure and lung function in non-smokers was found.

Eye and skin symptoms have been reported in all plants and increased significantly, as did breathlessness and wheeze, with increasing current exposure (Table 3).

Table 3: Adjusted odds ratios (OR) and their 95% confidence intervals (CI) from multiple logistic regression analysis of symptom prevalence compared with the group with exposures < 0.2 f/ml

Symptom	Current respirable fibre concentration (f/ml)		p value
	0.2 < 0.6	≥ 0.6	
Dry cough	2.55 (1.25-5.11)	2.01 (1.05-3.84)	< 0.05
Chronic bronchitis	1 (0.48-2.09)	1.02 (0.54-1.93)	NS
Wheeze	1.14 (0.59-2.19)	1.42 (0.81-2.49)	< 0.0001
Dyspnoea ≥ 2	1.26 (0.61-2.6)	2.66 (1.31-5.42)	< 0.05
Stuffy nose	2.06 (1.25-3.39)	1.23 (0.8-1.89)	< 0.05
Eye irritation	2.16 (1.32-3.54)	2.63 (1.7-4.08)	< 0.0001
Skin irritation	1.25 (0.74-2.11)	3.18 (2.01-5.03)	< 0.0001

Dry cough and stuffy nose were less common in the least exposed group but did not increase with increasing exposure. After adjustment for the effects of age, sex, height, smoking, and past occupational exposures to respiratory hazards, there was a significant decrease in both forced expiratory volume in one second (FEV1) and forced mid expiratory flow related to cumulative exposure in current smokers ($P < 0.05$) and in FEV1 in ex-smokers ($P < 0.05$). The authors conclude, that exposure to RCF is associated with irritant symptoms similar to those seen with other exposures to MMMF. Since all symptoms of the lower respiratory tract were more frequent in current smokers compared with ex or never smokers there is conclusion that cumulative exposure to respirable RCF may cause airways obstruction by promoting the effects of cigarette smoke.

In the follow-up study in 774 subjects (Cowie *et al.*, 2001) the effects were slightly smaller than those seen in 1987 (Trethowan *et al* 1995) but there were mild decrements in FVC and FEV₁ associated with estimated cumulative FCR exposure but only for male current smokers. There was no reduction in FEV1/FVC ratio or in diffusing capacity for carbon monoxide related to exposure, a test of lung function measured by these investigators. When the groups were separated for smoking the effect was only seen in current and ex-smokers. There is no evidence of an effect of cumulative exposure of ceramic fibres on the lung function of lifelong non-smokers. It therefore seems that smoking was an essential prerequisite for an effect of cumulative exposure to ceramic fibres on lung function. On average attendees had worked at the plants for 13 years, with average time in production jobs of around 8 years. The mean (range) estimated cumulative exposure index for respirable fibres was 4.9 (0.01-36) fibre-y/ml, and for non-respirable fibres it was 0.7 (0.001-5.0) fibre-y/ml. Both measures of fibre exposure were higher in production jobs and among smokers and ex-smokers, proportionally more of whom worked in production jobs. The mean (range) exposure for total dust was 15.9 (0.05-79) mg/m³ x years and for respirable dust it was 5.2 (0.02-45) mg/m³ x years. The presence of dust complicates the attribution of pulmonary effects to a specific fibre exposure (Table 4). Although no evaluation of



irritation has been made the authors conclude that the effects are due to an irritant effect of RCFs.

Table 4: Mean exposure to respirable and non-respirable fibres (fibres-y/ml), respirable and total dust and mean years in production jobs (Cowie et al 2001)

Period	Mean exp. resp. fibres x years	Mean exp. non-resp. fibres	Mean exp resp. dust	Mean exp. total dust	Mean duration production	Mean exp. resp. fibres/ml
Before 1971	0.88	0.12	1.93	4.98	2.88	0.33
1971-1976	1.22	0.17	1.44	4.43	2.38	0.42
1977-1981	1.92	0.29	2.02	6.12	3.74	0.27
1981-1986	2.05	0.31	2.16	6.52	3.80	0.53
1987-1991	1.66	0.24	1.75	5.29	3.98	0.42
1992-1996	1.06	0.15	0.96	3.13	3.91	0.27

Recently McKay et al (2010) published a study during which 933 currently employed males and females were each assigned a level of cumulative RCF exposure and modelled longitudinally by age groups. The study included workers at five RCF manufacturing locations and former workers followed up to 17 years, the exposure conditions of which have been described by Maxim et al (2008). The tests were performed yearly from 1987 to 1994 and then every three years through 2004. No consistent exposure related decline in FVC or FEV1 was found. Decreases in lung function have been associated with increasing age.

Radiological investigations

Investigations have been carried out to evaluate the prevalence of pleural plaques in workers exposed to RCFs (Lockey *et al.*, 2002), a radiological change frequently reported among workers exposed to asbestos fibres. Results were reported for 1,008 subjects. In this study the prevalence of parenchymal abnormalities did not differ from workers exposed to other types of dust. Pleural changes were seen in 27 workers. Of workers with > 20 years of latency from initial production job or 20 years of duration in a production job, 16 and 5 workers demonstrated pleural changes, respectively. The cumulative exposure analysis revealed an odds ratio of 5.6 (95% CI; 1.45-28.1) and 6.0 (1.4-31.0) for pleural changes in workers with an exposure > 45 and > 135 fibre-months/ml, respectively, relative to workers with less than 15 fibre months/ml. The authors conclude that RCFs are significantly associated with pleural changes (predominantly pleural plaques) without a statistically significant increase in interstitial changes.

Similarly Cowie *et al.* (2001) found no association between category 1/0+ opacities and exposure. A weak association between category 0/1+ small opacities and cumulative exposure to RCF was suggested, but not clearly established. Pleural changes, after adjustment for age and past exposure to asbestos showed some but not significant evidence of a relation between time since first exposure to RCF.

When evaluating the available studies in Europe and the US Lockey *et al.*, (2002) concluded that pleural plaques were observed in the RCF manufacturing cohort in the US and associated with cumulative exposure. Similarly, in the European study Cowie *et al.* (2001) reported some evidence of a relationship between latency and pleural plaques but



not with duration or intensity of exposure to RCF. In both studies no evidence of parenchymal disease has been seen.

The prevalence of pleural plaques is significantly associated with cumulative RCF exposure. However, according to Utell and Maxim (2010) persons with pleural plaques alone do not suffer any symptoms or material decrement in lung function. Similarly Browne (1997) in conclusion of the outcome of the workshop „Pathogenesis, diagnosis and clinical relevance of pleural plaques“ in asbestos workers stated: So, just as plaques do not imply any extra risk of other disease beyond that due to the exposure which caused them, so also they do not produce any symptoms“. As a consequence, the Industrial Injuries Advisory Council (IIAC 2009) did not recommend inclusion of pleural plaques among the list of prescribed diseases compensated under the IIDB Scheme.

The US Mine Safety and Health Administration claims that the prevalence of pleural plaques ranges from 0.53% to 8% in the environmental exposed population, excluding areas with known asbestos facilities or deposits. SCOEL notes that the prevalence of parenchymal abnormalities of 2.7% in the US cohort is in the range of prevalence of the environmental exposed population. Moreover, in the follow up studies in the US no additional pleural plaques have been diagnosed.

Mortality

Current and former male workers employed between 1952 and 2000 at two RCF manufacturing plants were investigated for any excess in mortality by LeMasters et al (2003). In 1987–1988, at time of study initiation, the ranges of time-weighted average exposure estimates were: 0.03–0.61 fibres/ml for dry fabrication, 0.01–0.27 fibres/ml for wet fabrication, 0.01–0.47 fibers/ cc for furnace operations, and 0.02– 0.62 fibres/ml for maintenance. Subsequently, exposure levels have remained relatively stable with the ranges of recent time-weighted average exposure estimates as follows: 0.03–0.57 fibers/cc for dry fabrication, 0.07–0.40 fibres/ml for wet fabrication, 0.11–0.12 fibres/ml for furnace operations, and 0.05– 0.53 fibres/ml for maintenance. There was no significant excess mortality for all deaths (SMR = 69.8), all cancers (SMR = 94.2), malignancies of respiratory system including mesothelioma (SMR = 78.8) and diseases of the respiratory system (SMR = 106.8). There was a statistically significant association with cancers of the urinary organs; SMR = 334.8 with a confidence interval at 95% (111.6-805.4). When adjusting for age and race (Cox's proportional hazards model) no elevated risk of death with cumulative RCF exposure (risk ratio 0.99, 95% CI = 0.85 – 1.16) became apparent. A parallel analysis that lagged exposure by 10 years led to similar conclusions. When comparing each of the exposure categories with the baseline (<1fibre-months/ml) while adjusting for age and race, the risk ratios were 1.35 (95% CI = 0.47–3.88), 1.45 (0.48– 4.37), 1.90 (0.64–5.59), and 1.45 (0.46–4.59) for the categories of >1–15, >15– 45, >45– 135, and >135 fibres months/cc, respectively. Major limitations of this study that failed to show any increase in mortality from respiratory system diseases are the relative youth of the cohort and its small size (942 male workers in analysis).

Previously Walker *et al.* (2002) performed a risk analysis based on the results of the just concluded study of this same cohort. The table 5 shows the correspondence between the proportional increase in lung cancer risk per unit cumulative dose (R_c) and the incremental lifetime risk of lung cancer if a worker is exposed to a fibre concentration of 0.5fiber/ml beginning at age 25 years and continuing for a 45-year period. A concentration of 0.5 fibre/ml was selected because the most workplace RCF measurements are below this value and because it is the RCF industry recommended exposure guideline.



Table 5: Incremental working lifetime lung cancer Risks (R_L)/1000 for various assumptions (Walker et al (2002))

Assumed potency R_L	In percentage terms $100 \times R_L$	Description of case	Lifetime incremental lung cancer deaths/100
0	0	Best current estimate from RCF epidemiology	0
1.54×10^{-5}	0.00154	Fyerweather et al (1997)	0.019
5.86×10^{-5}	0.00586	Best estimate from SII risk analysis for RCF	0.073
8.03×10^{-4}	0.0803	OSHA threshold for significant risk	1
1.00×10^{-3}	0.1	Hodgson & Darnton (2000) estimate for chrysotile	1.24
1.00×10^{-2}	1	OSHA estimate for "asbestos"	12.3
5.00×10^{-2}	5	Hodgson & Darnton (2000) estimate for amphibole	59.4

As table 5 shows, from the mortality study of LeMaster et al. 2003 (defined as the "best current estimate") the lung cancer risk (R_L) value is equal to zero since no increase in respiratory cancer risk was found, and equal to zero is also the estimated lifetime incremental lung cancer risk. The RCF risk estimate by Fayerweather et al. 1997 is based on rat bioassay data. The R_L for lung cancer for lifetime exposure to 0.5 fiber/ml is 1.54×10^{-5} and corresponds to incremental lung cancer deaths = 0,019/1000. Using the RCF risk estimate conducted by Sciences International Inc. (SII, see Moolgavkar et al. 1999, 2000), based on rat lifetime inhalation bioassay data, the incremental number of deaths becomes 0.073/1000. The estimated incremental risk for chrysotile is 1.24/1000 and for amphiboles 59.4/1000. They conclude that the lung cancer mortality in the RCF cohort is "incompatible" with the hypothesis that RCF is as potent as amphibole asbestos assuming identical cumulative exposure to the cohort, whereas the possibility that RCF is as potent as chrysotile asbestos could not be excluded.

Assuming a direct genotoxic effect the NIOSH report includes risk calculations for the OEL of 0.5 f/ml. This OEL corresponds to a lung cancer risk between 0.06/1,000 and 0.94/1,000 as described by Moolgavkar et al. (1999) and Yu and Oberdörster (2000). However, it has to be noted, that the epidemiological studies did not indicate an increased risk of lung cancer or mesothelioma.

Exposure over time

Although the epidemiological studies have followed up the prevalence and severity of health effects in exposed workers it is difficult to evaluate the dose response of effects, to what extent these result from previous higher exposures and the contribution of concomitant dust exposure. In 1979 Esman et al published the results of an industrial hygiene survey on the mid of 1970s' concentrations of total airborne dust and RCF in three facilities. The values for individual samples ranged between <0.01 and 16 f/ml with

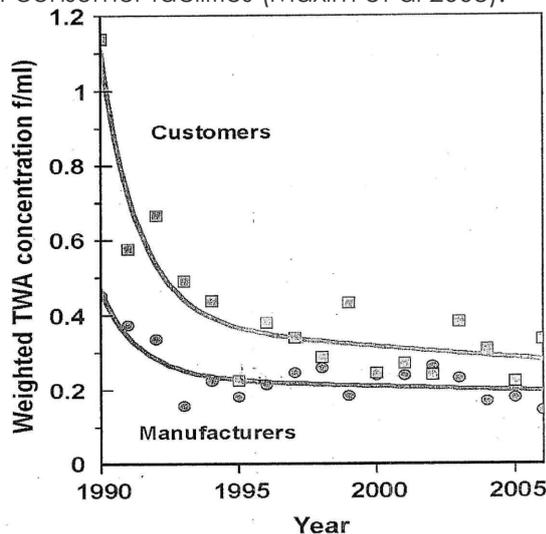


average mean concentrations from 0.05 to 2.6 f/ml. The highest concentrations have been found in manufacturing and finishing operations without ventilation. The total dust concentrations ranged from 0.05 to 100 mg/m³, the average mean values from 0.85 to 6.05 mg/m³. The airborne fibres were <4.0 µm in diameter and <50 µm long with a GM_D of 0.7 µm and a GM_L of 13 µm.

In the initial survey during the epidemiological studies initiated in 1987 the fibre concentrations ranged from <0.01 to 1.57 f/ml with a GM_D between 0.25 and 0.6 µm and a GM_L between 3.8 and 11 µm (Lockey et al 1998). By 1994 Rice et al (1994) had collected data from 484 fibre count samples from these 5 plants and 35 samples from persons working with raw materials. The fibre concentrations ranged between the analytical detection level to 1.54 f/ml. In 1997 Rice et al (1997) merged the exposure estimates of 1987-1991 with historic samples. The maximum exposure estimated was 10 f/ml in the 1950s for carding in a textile operation to below the analytic detection limit and 0.66 f/ml. The 10 years follow up sampling from 1991 to 2001 for 122 job titles at 5 facilities still active in 2001. The results are: ≤0.25 f/ml at 97 job titles, >0.25-0.5 at 17, and >0.5 at 8 job titles. Maxim et al (2000) summarized the data from a comprehensive workplace exposure-monitoring program for refractory ceramic fibres in the US factories.

In 2008 Maxim et al published the previous and current levels of RCF in the fibre industry. In the year 2006 95.8% of workers at RCF manufacturing plants were exposed to TWA concentrations below 0.5 f/ml. The figure shows the annual averages of RCF concentrations in manufacturing plants over the period between 1990 and 2006. These data clearly indicate that since about 1995 the fibre concentrations are about 0.2 f/ml. Since this fibre concentrations reflects the concentration in 1990 the weighted TWA concentrations were about 0.5 f/ml.

Figure 1: TWA concentrations between 1990 and 2006 for workers in RCF manufacturing plants and at consumer facilities (Maxim et al 2008).



Recently Maxim (2009) has summarized the concentrations, which have been measured during the ongoing epidemiological studies at European and US workplaces during 2004 and 2008 (see Table 6). The concentrations ranged between 0.146 f/ml at fibre production and 0.579 f/ml during furnace related removal. These data agree with the concentrations reported previously and indicate that since about 1993 the concentrations are below 0.5 f/ml.



Table 6: Pooled exposure data at European and US workplaces during 2004 and 2009 (modified from Maxim 2009) measured by personal samplers. Over this period there are 1,482 observations for Europe and 2,679 observations in the US (geometric mean).

Job category	Job description	Workplace concentration (fibres/ml)
Fibre production	All jobs 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 equipment, kilns, foundry equipment, electric power generators; includes maintenance, mould wrap and car builds.	0.254
Removal	Removal from industrial furnace, boiler etc; mold knock out, kiln car removal	0.579

Mechanisms of fibre carcinogenicity

The mechanism of fibre toxicity has been repeatedly discussed. IARC (2002) concludes that inflammation is the predominant manifestation of fibre toxicity and triggers several effects. Release of reactive oxygen from inflammatory cells leads to DNA damage. These cells also release mediators such as cytokines, growth factors and proteases that may alter proliferation, differentiation and migration of preneoplastic cells. Since it is well established that chronic inflammation contributes to cancer development (de Visser et al 2005) it can be concluded that inflammation is the relevant mechanism. Since lung inflammation is known to occur and persist only at sufficient particle (and fibre) doses (Schins 2002) it can be assumed that the basic carcinogenic mechanism of fibre carcinogenicity contains a threshold (Greim et al 2001). Previously, several review articles have evaluated and described this mechanistic principle of fibre toxicity and carcinogenicity (Jaurand 1997, Kane 1993, Fubini 1996, Churg et al 2000, IARC 2002). Especially the epidemiological studies in workers of facilities located in the US, which started RCF production in 1953 support the threshold concept of fibre carcinogenicity. Although originally workers have been exposed to relative high fibre concentrations of 10 fibres and more, no additional lung cancer cases have been observed even more than 30 years after onset of exposure, when concentration of 10 f/ml and more have been estimated (Rice et al 1997).

OELs for RCFs set in different countries are given in Table 7.



Table 7: Occupational exposure limits for RCFs in different countries

Country	OEL (f/ml)	Comments
Australia	0.5	
Austria	0.5	
Canada	0.2-1.0	Depending on state
Belgium	0.5	
Denmark	1.0	
France	0.1	Based on risk assessment
Germany	0.1	Tolerance level
Netherlands	1.0	LOEL 25 f/ml, AF 25 (DECOS 1995)
New Zealand	1.0	
Norway	0.1	
Poland	0.5 f/ml	0.5 f/ml also for RCF/MMMF mixtures
Sweden	1.0	
United Kingdom	1.0	
ACGIH	0.2	No justification given
NIOSH	0.5	0.25 f/ml action level

Recommendation

Occupational exposure to RCFs is associated with adverse respiratory effects as well as skin and eye irritation and may pose a carcinogenic risk based on the results of chronic animal inhalation studies. In these studies, exposure to RCFs produced an increased incidence of mesotheliomas in hamsters and lung cancer in rats. Mesotheliomas and sarcomas in rats and hamsters have also been induced after intrapleural and intraperitoneal implantation of RCFs. Intratracheal instillation induced lung tumours in rats. Epidemiologic studies have found no association between occupational exposure to airborne RCFs and an excess rate of pulmonary fibrosis or lung cancer.

The epidemiological studies in the US and in Europe showed an association between exposure and increased prevalence of respiratory symptoms and conditions such as dyspnoea, wheezing, chronic cough, decreases in pulmonary function, and skin, eye, and upper respiratory tract irritation. These findings, which primarily reflect workers employed before 1980, did not persist with analysis of follow-up production years and accumulated RCF exposure from initial pulmonary function tests. More recent exposures from the late 1980s until 2004 had no deleterious impact on the longitudinal trend of FVC and FEV1. During this time the RCF workplace concentrations constantly decreased below 1 f/ml. Since about 1993 the concentrations ranged around 0.2 f/ml in RCF fibre manufacture facilities and decreased from about 0.4 to 0.3 f/ml in customer facilities (see Figure 1). So far none of these studies provide information at what concentration the pulmonary effects are no longer seen. The common presence of other non-fibrous dust further complicates the evaluation of effects and their dose-responses at specific RCF workplace exposures. However, the studies indicate that the exposures since the late 1980s neither had deleterious impact on the lung function, nor diagnosed pleural plaques or mesothelioma. These exposures ranged from approximately 1 fibre/ml to below the limit of detection (Rice et al 1997).

Pulmonary function provides sensitive parameters to evaluate the effects of RCF exposure (see studies in workers in the US: Lockey *et al.*, 1998, 2002; LeMasters *et al.*, 1998; McKay 2010). The first cross-sectional pulmonary function study reported statistically (but not clinically) significant decrements in FVC and FEV1 for workers in the highest exposure category (> 60 fibres-months per cc) compared to those in the lowest exposure category



(≤ 15 f-m/cc), but later studies reported no significant decline in lung function in a longitudinal analysis of male workers providing pulmonary function tests over seven years.

Upon request the authors of the McKay *et al.* (2010) study provided the following additional information:

- The average cumulative exposure among all workers in the > 60 f-mo/ml group was 147.9 f-mo/ml, and
- When sorted by chronological age, those workers at age 60 in the > 60 f-mo/ml group experienced an average cumulative exposure of 184.8 f-mo/ml.

Assuming a 45 years exposure the average cumulative exposures of 147.9 and 184.8 f-mo/ml, respectively, result in an average fibre concentrations of 0.27 and 0.34 f/ml. Considering these values as no observed adverse effect levels SCOEL proposes an OEL of 0.3 f/ml.

From the available information it is concluded that the genotoxic effects observed in the different studies are secondary so that RCFs are classified as SCOEL Carcinogen group C carcinogens: Genotoxic carcinogens for which a practical threshold is supported.



References

- Baan R, Grosse Y (2004) Man-made mineral (vitreous) fibres: evaluations of cancer hazards by the IARC Monograph Programme. *Mutation Res* 553, 43-58
- Burge PS, Calvert IA, Trethowan WN, Harrington JM (1995). Are the respiratory health effects found in manufacturers of ceramic fibers due to the dust rather than the exposure to fibers? *Occup Environ Med* 52, 105-109.
- Carthew P, Edwards RE, Dorman BM, Brown RC, Young Y, Laskowski JJ, Wagner JC (1995) Intrapleural administration of vitreous high duty ceramic fibres and heated devitrified ceramic fibres does not give rise to pleural mesothelioma in rats. *Hum Exp Toxicol* 14, 657-661.
- Cavallo D, Campopiano A, Cardinali G, Casciardi S, De Simone P, Kovacs D, Perniconi B, Spagnoli G, Ursini C, Canizza C (2004) Cytotoxic and oxydative effects induced by man-made vitreous fibres (MMVFs) in human mesothelial cell line. *Toxicology* 201: 219-229
- Churg A, Wright J, Gilks B, Dai J (2000) Pathogenesis of fibrosis produced by asbestos and mn-made mineral fibers: What makes a fiber fibrogenic? *Inhalation Toxicol* 12, 15-26
- 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, 800-810
- Creutzenberg O, Bellmann B, Muhle H (1997) Biopersistence and bronchoalveolar lavage investigations in rats after subacute inhalation of various man-made mineral fibres. *Ann Occup Hyg* 41, 213-218
- Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Wright A (1984) The pathogenic effects of fibrous ceramic aluminium silicate glass administered to rats by inhalation or peritoneal injection. In: *Biological Effects of Man-made Mineral Fibres (Proceedings of a WHO/IARC Conference)*, vol. 2, Copenhagen, World Health Organization 303-322
- DECOS (Dutch Expert Committee on Occupational Standards) (1995) Man made mineral fibers. Health-based Recommended Occupational Exposure Limits. Publ No 1995/O2WGD. The Hague: Health Council of the Netherlands
- De Visser K, Korets L, Voussens I (2005) De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell* 7, 411-423
- Dopp E, Nebe B, Hahnel C, Papp T, Alonso B, Simko M, Schiffmann D (1995) Mineral fibers induce apoptosis in Syrian hamster embryo fibroblasts. *Pathobiology* 63: 213-221
- 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 fibres. *Mutat Res* 377: 77-87
- Dopp E, Schiffmann D (1998) Analysis of chromosomal alterations induced by asbestos and ceramic fibres. *Toxicol Lett* 96/96: 155-162
- Esman NA, Corn M, Hammd YY, Whittler D, Kotsko N, Haller M, Kahn RA (1979) Exposure of employees to man-made fibers: ceramic fiber production. *Environ Res* 19, 265-278
- Fayerweather WE, Bender JR, Hadley JG, Eastes W (1997) Quantitative risk assessment for a glass fiber insulation product. *Reg Toxicol Parm* 25, 103-120



- Federal Register (2005). Part II, Department of Labor, Mine Safety and Health Administration, 30 CFR Parts 56, 57, and 71. Asbestos Exposure Limit; Proposed Rule. Vol 70, No. 145, Friday, July 29, 2005, pp. 43950-43989
- Fubini B (1996) Use of physico-chemical and cell-free assays to evaluate the potential carcinogenicity of fibres. In: Mechanisms of fibre carcinogenesis. AB Kane, P Boffetta, R Saracci and JD Wilson (editors), IARC Scientific Publications, Lyon, 35-54
- Gilmour P, Beswick PH, Brown DM, Donaldson K (1995) Detection of surface free radical activity of respirable industrial fibres using supercoiled X174RF1 plasmid DNA. *Carcinogenesis* 16: 2973-2979
- Greim H, Borm PH, Schins R, Donaldson K, Driscoll K, Hartwig A, Kuempel E, Oberdörster G, Speit G (2001) Toxicity of fibres and particles. Report of the workshop held in Munich, Germany, 26-27 October 2000. *Inhal Toxicol* 13, 737-754
- 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: 317-326
- Hart GA, Kathman LM, Hesterberg TW (1994) In vitro cytotoxicity of asbestos and man made vitreous fibres: Roles of fibre length, diameter and composition. *Carcinogenesis* 15: 971-977
- Hesterberg TW, Miller WC, McConnell EE, Chevalier J, G, Hadley JG, Bernstein DM, Thévenaz P, Anderson R (1993) Chronic inhalation toxicity of size-separated glass fibers in Fischer 344 rats. *Toxicol Sci* 20, 464-476
- Hesterberg TW, Hart GA (2001) Synthetic vitreous fibers: a review of toxicology research and its impact on hazard classification. *Crit Rev Toxicol* 31, 1-53
- Howden PJ, Faux SP (1996) Fibre-induced lipid peroxidation leads to DNA adduct formation in *Salmonella typhimurium* TA104 and rat lung fibroblasts. *Carcinogenesis* 17: 413-419
- IARC (2002) International Agency for the Research of Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 81: Man-made vitreous fibres. Lyon
- Jaurand M-C (1997) Mechanism of fiber-induced genotoxicity. *Environ Health Perspect* 105, 1073-1084
- Kane AB (1993) Particle- and fiber-induced lesions: An overview. In: Toxic and carcinogenic effects of solid particles in the respiratory tract. DL Dungworth, JL Mauderly, G. Oberdörster (editors). ILSI Monographs, ILSI Press
- 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, 910-919
- LeMasters GK, Lockey JE, Yiin JH, Hilbert TJ, Levin SL, Rice CH (2003) Mortality of workers occupationally exposed to refractory ceramic fiber. *J Occup Environ Med* 45, 440-450
- 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, 1226-1233
- 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, 2044-2051
- Mast RW, McConnell EE, Anderson R, Chevalier J, Kotin P, Bernstein DM, Thevenaz P, Glass LR, Miller WC, Hesterberg TW (1995a) Studies on the chronic toxicity (inhalation) of four types of refractory ceramic fibers in male Fischer 344 rats. *Inhal Toxicol* 7: 425-467



- Mast RW, McConnell EE, Hesterberg TW, Chevalier J, Kotin P, P. Thévenaz P, Bernstein DM, Glass LR, Miller WC, Anderson R (1995b) Multiple-dose chronic inhalation toxicity study of size-separated kaolin refractory ceramic fiber in male Fischer 344 rats. *Inhal Toxicol* 7, 469–502.
- Mast RW, Maxim LD, Utell MJ, Walker AM (2000a) Refractory ceramic fibers: Toxicology, epidemiology, and risk analysis – A review. *Inhal Toxicol* 12: 359–99 (missing in the current list)
- Mast RW, Yu CP, Oberdörster G, McConnell EE, Utell M (2000b) A retrospective review of the carcinogenicity of refractory ceramic fiber in two chronic Fischer 344 rat inhalation studies: An assessment of the MTD and implication for risk assessment. *Inhal Toxicol* 12: 1141–1172
- Maxim LD (2009) Personal communication. Manuscript in preparation
- Maxim LD, Allshouse JN, Chen SH, Treadway JC, Venturin D, (2000) Workplace monitoring of refractory ceramic fiber in the United States. *Regul Toxicol Pharmacol* 32, 293-309
- 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, 289-309
- McKay RT, LeMasters GK, Hilbert TJ, Levin LS, Rice CH, Borton EK, Lockey JE (2010) A long term study of pulmonary function among U.S. refractory ceramic fiber workers. *J Occup Environ Med* (2011) *Occup Environ Med* 68, 89-95
- McConnell EE, Wagner JC, Skidmore JW, Moore JA (1984) A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM 100). In: *Biological Effects Of Man-Made Mineral Fibres (Proceedings of a WHO/IARC Conference)*, vol. 2, Copenhagen, World Health Organization pp. 234–252.
- McConnell EE, Mast RW, Hesterberg TW, Chevalier J, Kotin P, Bernstein DW, Thévenaz P, Glass LR, Anderson R (1995) Chronic inhalation toxicity of a kaolin-based refractory ceramic fiber (RCF) in Syrian golden hamsters. *Inhal Toxicol* 7, 503–532.
- Miller BG, Searl A, Davis JMG, 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, 155–166.
- Moolgavkar SH, Luebeck EG, Turim J, Hanna L (1999) Quantitative assessment of the risk of lung cancer associated with occupational exposure to refractory ceramic fibers. *Risk Anal* 19, 599-611
- Moolgavkar SH, Luebeck EG, Turim J, Brown RC (2000) Lung cancer risk associated with exposure to man-made fibers. *Drug Chem Toxicol* 23, 223-242
- 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 Environ Health* 70, 321-326
- NIOSH (2006) National Institute for Occupational Safety and Health. Occupational exposure to refractory ceramic fibers. DHHS (NIOSH) Publication No. 2006-123
- Okayasu R, Wu Y, Zhong BZ, Jones WG, Whong WZ (1997) Induction of micronucleated and multinucleated cells by man-made fibres in vitro in mammalian cells. *J Toxicol environ Health* 50: 409-414
- Osgood CJ (1994) Refractory ceramic fibres (RCFs) induce germline aneuploidy in *Drosophila oocytes*. *Mutat Res* 324: 23-27



- Pigott GH, Ishmael J (1992) The effects of intrapleural injections of alumina and aluminosilicate (ceramic) fibres. *Int J Exp Pathol* 73, 137–146.
- Pott F, Ziem U, Reiffer F-J, Huth F, Ernst H, Mohr U (1987) Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp Pathol* 82, 129–152.
- Pott F, Roller M, Ziem U, Reiffer F-J, Bellmann B, Rosenbruch R, F. Huth F (1989) Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. In: Bignon, J., Peto, J., Saracci, R., (Eds.), *Non-Occupational Exposure to Mineral Fibres* (IARC Scientific Publications No 90), Lyon, IARC Press pp. 173–179.
- Rice D, Lockey J, Lemasters G, Dimos J, Gartside P (1994) Assessment of current fibre and silica exposure in the U.S. refractory ceramic fibre manufacturing industry. *Ann Occup Hyg* 38, 739-744
- Rice D, Lockey J, Lemasters G, Levin L, 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, 54-61
- Schins RPF (2002) Mechanism of genotoxicity of particles and fibers. *Inhal Toxicol* 14, 57-78
- Smith DM, Ortiz LW, Archuleta RF, Johnson NF (1987) Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. *Ann Occup Hyg* 31, 731–754.
- Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A (1981) Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst* 67, 965–975.
- 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, 97-104
- Turim J, Brown RC (2003) A dose-response model for refractory ceramic fibers. *Inhal Toxicol* 15: 1103-1118
- Utell MJ, Maxim LD (2010) Refractory ceramic fiber (RCF) toxicity and epidemiology. *Inhal Toxicol* (in the press)
- Wagner JC, Berry G, Timbrell V (1973) Mesotheliomata in rats after inoculation with asbestos and other materials. *Br J Cancer* 28, 173–185
- Walker AM, Maxim LD, Utell M (2002) Risk analysis for mortality from respiratory tumors in a cohort of refractory ceramic fiber workers. *Reg Toxicol Pharmacol* 35, 95-104
- Wang Q, Han C, Yang Y, Wang H, Wu W, Liu W, Kohyama N (1999) Biological effects of man-made mineral fibers-their genetic damages examined by in vitro assay. *Ind Health* 37, 342-347
- 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: 2751-2758
- Yu CP, Oberdörster G (2000) Dose response and human cancer risk and non-cancer risk assessment of inhaled refractory ceramic fibers (RCF)
- Zoitos BK, De Meringo A, Rouyer E, Thélohan S, Bauer J, Law B, Boymel PM, Olson JR, Christenson VR, Guldberg M, Koenig AR, Perander M (1997) In vitro measurement of fiber dissolution rate relevant to biopersistence at neutral pH: An interlaboratory round robin. *Inhal Toxicol* 9, 525-540