Health Council of the Netherlands

Refractory ceramic fibres

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Refractory Ceramic Fibers*
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Geachte staatssecretaris,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan vuurvaste keramische vezels.

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

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

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

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

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Evaluation of the carcinogenicity and genotoxicity

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

to:

the State Secretary of Social Affairs and Employment

No. 2011/29, The Hague, November 15, 2011

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

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

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

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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de Raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie vuurvaste keramische minerale vezels onder de loep.

Vuurvaste keramische minerale vezels zijn door de Europese Commissie gedefinieerd als “kunstmatige (silicaat)glasvezels met een willekeurige oriëntatie en een gehalte aan alkali- en aardalkali-oxiden (Na_2O + K_2O + CaO +MgO +BaO) van ten hoogste 18 gewichtsprocenten” (zie Richtlijn (EC) Nr. 1272.2008; index nr. 650-017-00-8). Ze worden ondermeer gebruikt voor hittebestendige isolatiedoeleinden en als versterkingsmateriaal.

De commissie concludeert dat vuurvaste keramische minerale vezels beschouwd moeten worden als kankerverwekkend voor de mens, en beveelt aan deze vezels te classificeren in categorie 1B*. De commissie gaat er vooralsnog vanuit dat de vezels werken via een niet-genotoxisch mechanisme.

* Volgens het nieuwe classificatiesysteem van de Gezondheidsraad (zie bijlage G). In richtlijn 1272/2008 van de Europese Unie, die op 20 Januari 2009 van kracht werd is bij keramische minerale vezels gemeld dat “indeling als kankerverwekkend niet noodzakelijk is voor vezels waarvan de lengte gewogen meetkundige gemiddelde diameter, minus tweemaal de meetkundige standaardfout, groter is dan 6 µm”.

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In this report, the Committee evaluated refractory ceramic fibres. These are defined by the European Commission as "man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali oxide ($Na_2O + K_2O + CaO + MgO + BaO$) content less or equal to 18% by weight" (see Regulation (EC) No. 1272/2008; Index No. 650-017-00-8). The fibres are mainly used for heat resistant isolation applications, and as strengthening material.

The Committee concludes that refractory ceramic fibres are presumed to be carcinogenic to man, and recommends classifying these fibres in category 1B*. Based on the available data, the Committee assumes that the fibres act by a non-genotoxic mechanism.

* According to the new classification system of the Health Council (see Annex G). In regulation 1272/2008 of the European Union, which entered into force on 20 January 2009, for refractory ceramic fibres, it is added that "the classification as a carcinogen need not to apply to fibres with a length weighted geometric mean diameter less two standard errors greater than 6 μm".

Chapter 1

Scope

1.1 Background

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

This report contains the evaluation of the carcinogenicity of refractory ceramic fibres. In 1995, the Health Council produced two advisory reports on the carcinogenicity and recommendation of a health-based occupational exposure limit, on man-made mineral fibres.[56,58] These reports included refractory ceramic fibres, of which a summary of the findings is given in Annex D. The findings are taken into account in deciding on the classification and carcinogenic mechanism of action in the present report.

1.2 Committee and procedures

The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B.

In 2010 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is standardly based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of refractory ceramic fibres, such an IARC-monograph is available. A summary of it is given in Annex E.

More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in June 2011. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physico-chemical properties

Refractory ceramic fibres (RCFs) are a large group of amorphous synthetically produced man-made mineral fibres.[63] Refractory fibres are produced from calcined kaolin clay, or from aluminium (Al_2O_3) and silicon (SiO_2) oxides, also known as kaolin-based or alumina-based ceramic fibres. Other oxides are added as stabilizers and binders, such as boron, titanium and zirconium oxides. Furthermore, although less commonly, non-oxide materials, such as silicon carbide or nitride, are sometimes added.[34,35,45,46] The European Commission defined refractory ceramic fibres as "man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali oxide ($Na_2O + K_2O + CaO + MgO + BaO$) content less or equal to 18% by weight" (see Regulation (EC) No. 1272/2008; Index No. 650-017-00-8). The Chemical Abstract Service defined RCFs (CAS No. 142844-00-6) as fibres with a weight percentage composition variable between 20 and 80% in alumina, 20 and 80% in silica, and low percentage of other oxides and with thermal resistance.[12]

RCFs have a white or slightly coloured appearance and are odourless. The softening point ranges between 1,700 to 1,800 °C, and the specific gravity (density) between 2.6 to 2.7 g/cm^3. The compounds do not dissolve in water.

Depending on its intended use, various RCFs are manufactured with different trade names (*i.e.*, Fibrefrax® bulk, long staple or HSA; Alumina bulk; Zirconia bulk; Fireline ceramic). In the literature, four types of RCFs are sometimes

described, numbered RCF1 through RCF4, according to their unique chemistry and morphology.[40,45] Their chemical composition is given below.

Component	***RCF1*** kaolin aluminosilicate fibre (in % w/w)	***RCF2*** zirconia aluminosilicate fibre (in % w/w)	***RCF3*** high-purity aluminosilicate fibre (in % w/w)	***RCF4*** *after-service* kaolin fibre (in % w/w)
Silicon dioxide (SiO_2)	47.7	50	50.8	47.7
Alumina (Al_2O_3)	48	35	48.5	48
Ferric oxide (Fe_2O_3)	0.97	< 0.05	0.16	0.97
Titatinium dioxide (TiO_2)	2.05	0.04	0.02	2.05
Zirconium dioxide (ZrO_2)	0.11	15	0.23	0.11
Calcium oxide (CaO)	0.07	0.05	0.04	0.07
Magnesium oxide (MgO)	0.98	0.01	< 0.01	0.08
Sodium oxide (Na_2O)	0.54	< 0.3	0.19	0.54
Potassium oxide (K_2O)	0.16	< 0.01	< 0.01	0.16

Adapted from Mast *et al*. (1995).[40]

Regarding the toxicity of fibres, the dimensions, dose, and durability are key factors to take into account, rather than their chemical composition.[5,45] In particular so called respirable fibres are of interest, because they are able to reach and deposit in the lungs. The World Health Organization (WHO) considers a fibre to be a particle with a diameter of less than 3 µm and a length of more than 5 µm, which has a length/diameter aspect ratio of at least 3.[63] Furthermore, the WHO considers fibres as respirable for humans when they have a median aerodynamic diameter of approximately 3.5 µm or less. Individual refractory ceramic fibres have a diameter ranging from 0.1 to 20 µm (average diameter of 2.2 to 5.0 µm; nominal diameter of 1.2 to 3 µm), and a length varying from about 40 to 250 µm. Depending on intended use and fibre type, the majority of the airborne RCFs sampled during RCF manufacturing activities, are reported to be in the thoracic and respirable size range.[45] The fibres do not split longitudinally into fibres with a smaller diameter, but they can break transversely into shorter segments.[63]

Refractory ceramic fibres are relatively durable. The durability is measured by the amount of time it takes the fibre to fragment mechanically into shorter fibres or to dissolve in biological fluids.[5,45] Based on *in vitro* tests using fluids simulating lung fluids, it has been shown that RCFs have a dissolution rate of 1 to 10 ng/cm^2 per hour (at pH 7.4). For comparison, glass wools have a dissolution rate of hundreds ng/cm^2 per hour, and chrysotile (most soluble form of asbestos) of <1 to 2 ng/cm^2 per hour.[45]

Because of their durability and chemical resistance, RCFs are considered biopersistent materials that remain in lung tissue for a prolonged period of time.[2,45,46] For instance, in rats the lung clearance half time of inhaled RCF1a with a fibre length of more then 20 µm, was calculated to be 55 days (95% confidence limit, 44 – 66 days); and, the number of days required for clearance of 90% of the fibres that were present in the lung one day after cessation of exposure was 227 days (95% confidence limit, 190-268 days).[29,31] RCF1a fibres are refined RCF1 fibres, in which the content of nonfibrous particles is reduced: 2% and 25% of the mass of RCF1a and RCF1, respectively. The half time for RCF1 fibres was calculated to be about 77 days.[3]

RCFs are produced in bulk material in the form of blocks, modules, or "mats". As the name indicates, RCFs are highly resistant to heat. They find use, for instance, as insulators for industrial plant components exposed to very high temperature; for the caulking of melting furnaces and in thermal treatment plants, where the temperature is generally more then 1,000 to 2,000 °C; and as insulators for ships and in firewalls to contain fires or in catalytic converters in the automobile industry and in aircraft or aerospace engines.[2,12,34,35,45,46] Potential occupational exposure to dust (for instance as respirable free fibres) originating from the bulk materials may occur due to complete or partial devitrification during normal service life of RCF products, and after heating the material (>1,000-1,200 °C).[12]

2.2 EU classification

The European Commission classified refractory ceramic fibres in category 1B (presumed to have carcinogenic potential for humans), and labelled the compounds with the hazard statement H350i (may cause cancer by inhalation) (see Annex VI to Regulation (EC) No. 1272/2008; Index No. 650-017-00-8). Also in the same regulation Note R was assigned to refractory ceramic fibres indicating that "the classification as a carcinogen need not to apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 µm".[22]

2.3 IARC classification

In 1988 and again in 2002, IARC concluded that there is inadequate evidence in humans for the carcinogenicity of refractory ceramic fibres, but that there is sufficient evidence in experimental animals (see Annex E).[34,35] Based on these con-

clusions, IARC classified these types of fibres as possibly carcinogenic to humans (Group 2B).

Chapter 3

Carcinogenicity

3.1 Observations in humans

The number of observational studies in workers is limited.[59] In the USA, a prospective cohort study of workers involved in RCF manufacturing was initiated in 1987 and is still ongoing.[37,38,53,61] The latest data on cancer mortality were reported in 2003 by LeMasters *et al*.[37] No increases in lung cancer and pleural mesothelioma were observed among 942 male RCF production workers (SMR 78.8; 95% CI, 36.0 – 149.7). However, a statistically significant association between exposure and cancers of the bladder was found (SMR, 344.8; 95% CI, 116.6 – 805.4). There were no increased malignancies at other sites or organs of the body. The authors pointed out that the relatively small and young study population may limit the study interpretation. Also they remarked that the study was not designed to detect bladder cancer.

Chiazze *et al*. (1997) reported on a nested-case-control study of an historical cohort mortality study in a continuous filament fibreglass manufacturing plant.[11] The risk of lung cancer was lower in workers exposed to RCF compared to non-exposed workers. Since the number of reported cases was small, and other sources of exposure may have affected the outcome, it is difficult to assess the value of the findings for the contribution of RCF exposure.

A few epidemiological studies have demonstrated the presence of pleural plaques, and mild respiratory symptoms among workers who were occupation-

ally exposed to RCFs.[37,45,59] However, it is uncertain whether a correlation exists between these abnormalities and the development of for instance mesotheliomas.

Overall, the investigations on the association between occupational exposure to RCFs and cancer development in humans are insufficient to draw a definite conclusion.

3.2 Carcinogenicity studies in animals

A number of animal carcinogenicity studies has been performed using different types of refractory ceramic fibres (specified as RCF1 to RCF4, or as trade names). A summary of the findings by route of exposure is given below. Study details are given in Annex F. Reviews on these studies have also been made by IARC and NIOSH.[35,45]

Several of these studies were performed in hamsters. The Committee emphasizes that it is under discussion whether hamsters are an appropriate animal model for assessing the hazard of ceramic mineral fibres in humans.[4,5] One of the reasons being the architecture of the hamsters' lung, the excessive sensitivity of the hamsters' pleura, and the fact that hamsters do not develop lung cancer when exposed to mineral dusts or bio-durable fibres. Also, the oxidative capacity of alveolar macrophages of rats was found to be five-fold greater than that of hamsters, whereas the antioxidant capacity is comparable in the two species.[21,30] This could partly explain why hamsters and rats differ in their response. Although there is discussion on this subject, hamster data cannot be ignored.

Whole-body inhalation exposure

A group of 48 Wistar rats were exposed to about 10 mg/m^3 respirable dust from a bulk fibrous ceramic aluminium silicate glass (corresponds to 95 WHO* fibres/m^3) for 7 hours per days, five days per week, for 12 months.[15,35] Approximately 90% of the fibres met the criteria for respirable-sized fibres. Eight animals developed pulmonary neoplasms, whereas in none of the control animals pulmonary tumours were observed. Of the tumours found eight were benign, eight malignant, and one was diagnosed as a mesothelioma. No details were given on animal strain and sex, and treatment of controls.

* WHO: respirable fibres as defined by the World Health Organization as having a length of > 5 µm, a diameter of < 3 µm, and an aspect ratio of > 3:1.

Nose-only inhalation exposure

Rats or hamsters were exposed nose-only to Fibrefrax® (composition not given) or to RCF1 to RCF4, 6 hours per day, 5 days per week for a maximum of two years. The number of animals varied between 55 and 140 per group. Smith *et al*. did not observe tumours in any of the Fibrefrax®-treated and control animals, which were exposed to approximately 10 mg/m^3.[54] Mast *et al*. reported on significant increases in incidence of lung tumours (adenomas and carcinomas) in treated rats compared to controls.[40] Also treatment resulted in development of pleural mesotheliomas in some animals, whereas no such tumours were observed in any of the control animals. Exposure concentration was 30 mg/m^3, which corresponded to approximately to 182 or 220 fibres/cm^3, depending on the type of RCF. At the same exposure level, also McConnell *et al*. found cases of pleural tumours in hamsters exposed to RCF1.[42] However, they did not observe lung tumours in any of the animals. The latter study is, on the other hand, difficult to interpret because all animals were treated with tetracycline to cure an intestinal infection that developed during study.

The Committee remarks that "spontaneous" malignant mesotheliomas are rare in laboratory animals as well as in humans.

Intratracheal installation

No lung or pleural tumours were found in rats and hamster given five weekly intratracheal installations of 2 mg Fibrefrax® (chemical composition not given) and kept in study for the rest of their life.[54]

NIOSH reported on a study performed by the Manville Technical Center (US EPA).[45] In that study male Fischer rats (N=107-109 animals/group) were given 2 mg of RCF1, RCF2, RCF3, or RCF4 by intratracheal installation (0.2 mL of a 10 mg/mL suspension). The study included positive controls (chrysotile) en vehicle controls. Animals were sacrificed at 128 weeks with interim sacrifices at different time points. Exposure to the fibers resulted in lung tumour development. The lung tumour incidences were: 5.5%, 3.7%, 3.7%, 6.5%, 14.5%, and 0% for RCF1, RCF2, RCF3, RCF4, chrysotile (asbestos), and vehicle-treatments, respectively. No further details were given.

Intrapleural injections

In some rats, which were given a single intrapleural injection of various types of RCFs at a dose of 20 mg, and which were followed for a lifetime, treatment-

related pleural and abdominal mesotheliomas were found.[9,50,60] No lung tumours were observed.

Intraperitoneal injections

Rats and hamsters were given various types of RCFs by a single or repeated intraperitoneal injections, and kept for their natural lifespan.[15,43,51,52,54] Some of the animals developed abdominal mesotheliomas, whereas no such tumours were observed in non-treated animals. No lung tumours were found. In one recently published study, in genetically modified mice, which were prone to malignant mesothelioma development, a statistically significantly increased incidence in peritoneal mesotheliomas and fibrosis was observed compared to controls.[1]

3.3 Location of tumour development

The mechanism of toxicity of refractory ceramic fibres is mainly influenced by their dimensions, dose and durability.[2,34,35,45,46,63]

Due to the fibre characteristics and dimensions it is plausible that RCFs cause mainly local effects at the site of deposition rather than systemic effects.[8] This would explain why in animals tumour development was observed mainly at the site of exposure, and that observations in humans mainly concern adverse effects of the respiratory tract and lungs.[2,45,46]

After inhalation, tumours were found in the pleural mesothelioom, which may be explained by the fact that the length of some fibres is or becomes (by breakage or dissolution) small enough to be translocated through the lung interstitium and into the pleura.[2,46]

Chapter 4

Mode of carcinogenic action

In the scientific literature, based on some observations, several mechanisms of toxic action of refractory ceramic fibres are postulated. It is possible that all those different mechanisms are involved, both by direct and indirect action of the ceramic fibres. Potential modes of carcinogenic action are summarized below.

4.1 Genotoxicity

In vitro assays

In one study using RCF1, formation of malondialdehyde DNA-adducts have been found in the bacterial *Salmonella typhimurium* strain TA104, but not in isolated rat lung fibroblast cells.[33] In addition, formation of 8-hydroxydeoxyguanisine was reported in a mouse reticulum sarcoma (J744) cell line treated with RCF (not specified).[44] The relevance of the latter finding on human health evaluation is however unclear.

No treatment-related gene mutations were found at *hprt* locus and *S1* locus in human-hamster hybrid A_L cells, which were exposed to RCF1.[48]

RCF1, RCF2, and RCF3 have been reported to induce DNA breakage, DNA repair and DNA interstrand cross-linking in a commercial available human lung epithelial tumour cell line.[62]

Regarding clastogenic activity, treatment-related increased frequencies of nuclear abnormalities (*i.e.*, micro- or polynucleus formation, chromosomal aber-

rations or breakage) were found in various studies, using: RCF (not specified) in Syrian hamster embryo cells or human amniotic fluid cells[19,20]; RCF1 to RCF4 in Chinese hamster ovary cells[26,27]; and, RCF1 to RCF3 in human embryo lung cells.[62] A negative outcome was reported on induction of micronuclei in Chinese hamster ovary cells.[13] Another study reported on negative outcomes on anaphase/telophase abnormalities in rat pleural mesothelial cells.[64]

The Committee emphasizes that as yet it is uncertain whether the available *in vitro* genotoxicity assays are suitable in assessing the genotoxicity of fibres, because it is uncertain whether these fibres can reach the cell nucleus due to their structure.

In vivo assays

RCF1, RCF2, RCF3 and RCF4 increased the frequency of aneuploidy in adult *Drosophila melanogaster*.[49] Moreover, RCF1 and RCF3 also increased the frequency of aneuploidy in larvae of these flies. However, no aneuploidy was induced in larvae after RCF2 and RCF4 exposure under the same experimental conditions.[49] No other data on *in vivo* tests were available.

4.2 Relevant non-genotoxic mechanisms

When foreign inert materials are able to deposit at the epithelial surface of the respiratory tract and lungs, such as is the case for refractory ceramic fibres in airborne dust, the body tries to clear the material with a reaction, in which inflammatory cells, such as (alveolar) macrophages, are involved. This is a normal non-specific biological defense system that ends with recovery of the damaged tissue as soon as the material is cleared by elimination or dissolution and subsequent breakage. Macrophages are the first line in defense against inhaled material that deposit in the lungs, and therefore play an important role in the toxicity of RCFs.

The length of the fibre plays a dominant role in the clearance rate from the lung, rather than its aerodynamic diameter. The latter is a major determinant of respirability and lung deposition.[6,30]

In case of RCFs, shorter fibres (<10-15 µm length) can be completely phagocytised by macrophages, and thus are more easily cleared from the lungs by mucociliar transport.[5] However, fibres with a longer length can persist for a long time at the surface of the respiratory tract and lungs, because they are not completely phagocytised and cleared. As a consequence the inflammation can become chronic and even permanent. On the long-term this can end in the devel-

opment of fibrosis and even in cancer, which are irreversible and life-threatening effects.

On a molecular level, due to inflammation, macrophages produce inflammatory mediators, such as cytokines (TNF and interleukines), lipid mediators (prostaglandins and leukotrienes), and reactive oxygen species.[16,45,55] Extra production of reactive oxygen species may lead to oxidative stress in the cells involved, causing oxidation of lipids, proteins and nucleic acids, with the formation of cytotoxic and mutagenic products.

A factor that contributes to the inflammatory reactions, is pulmonary overload or lung burden.[5,8,59,59] Overload is characterized by reduced clearance and increased persistence, resulting in accumulation of RCFs and thus in higher lung burdens. It is also a factor to take into account when extrapolating animal data to humans, because between rodents and humans distinct differences exist in respiratory tract and lung size, lung and macrophage anatomy, and geometry.[2,5,30,35,65] For instance, fibres with a diameter of more than 3.5 µm and an aspect ratio of more than 10 are not deposited in the alveoli of rats and hamsters, whereas in humans, fibres with an aerodynamic diameter of 5 µm can still reach the alveoli.[14,35] Based on models in which rodents and humans inhaled a same concentration, it is furthermore estimated that approximately 2.2% of fibres with an aerodynamic diameter of 2 µm are deposited in the alveolar region of the lungs of rats, whereas in humans it is estimated to be approximately 23%, a ten-fold difference.[14,35] If these differences are not taken into account, the human risk in developing cancer is underestimated when using animal data for quantitative risk assessment.

4.3 Comparison with other fibres

Concern about the possible occurrence of cancer following exposure to RCFs arose from investigations into the carcinogenicity of other fibres. In general, the mechanistic link between inflammation, fibrosis and cancer is considered a plausible biological mechanism for the development of lung carcinogenesis by fibres (*e.g.* special purpose glass fibres, glass wool, slag wool, asbestos fibres).[35] The induction of cancer via inflammation is considered a non-genotoxic mechanism.

Also other mechanisms of actions by fibres are proposed. For instance, investigations using asbestos fibres showed that these are able to directly induce reactive oxygen species (and reactive nitrogen species), due to the high iron content in the fibres.[25,28,36,39,47]. This finding would suggest that at least asbestos fibres possess also some stochastic genotoxic activity. However, the Committee considers this unlikely for RCFs, because of their very low iron content. So far, no oxi-

dative DNA-damage has been found for RCFs using *in vitro* assays.[7,10,17,18,23,24,32]

4.4 Conclusion

Overall, the Committee considers the induction of chronic inflammation as the most plausible mechanism of carcinogenic action of RCFs. This would imply a threshold mechanism of action. In addition, it is unlikely that RCFs possess stochastic genotoxic properties via direct production or reactive oxygen species, due to the very low iron content. However, the Committee emphasizes that the relevance of genotoxicity testing for fibres is limited due to a lack of *in vitro* assays suitable for fibres.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

The number of observational studies reporting on possible associations between occupational exposures to refractory ceramic fibres and cancer development in humans is limited. Overall, available data are insufficient to draw a conclusion whether RCF is carcinogenic to humans.

Several animal carcinogenicity studies have been performed using rats or hamsters, which were exposed to various types of RCFs by various routes of exposure. Positive findings on lung tumour development were reported after whole-body and nose-only exposure. RCFs were also able to induce formation of pleural mesotheliomas after nose-only exposure or intrapleural injections; and, abdominal mesotheliomas after intraperitoneal injections. However, not all studies were clearly positive. Also, interpretation of some results was restricted, due to limited reporting, or due to the presence of additional risk factors. Overall, however, the Committee concludes that data show carcinogenic activity in animals.

The Committee considers the induction of chronic inflammation as the most plausible mechanism of carcinogenic action of RCFs. In addition, it is unlikely that RCFs possess stochastic genotoxic properties via direct production or reactive oxygen species, due to their very low iron content.

5.2 Recommendation for classification

The Committee concludes that refractory ceramic fibres are presumed to be carcinogenic to man, and recommends classifying these fibres in category 1B*. Based on the currently available data, the Committee assumes that the fibres act by a non-genotoxic mechanism.

* According to the new classification system of the Health Council (see Annex G). In regulation 1272/2008 of the European Union, which entered into force on 20 January 2009, for refractory ceramic fibres, it is added that "the classification as a carcinogen need not to apply to fibres with a length weighted geometric mean diameter less two standard errors greater than 6 µm".

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Annexes

Annex **A**

Request for advice

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

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

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

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

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

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

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

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

Annex **B**

The Committee

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

The Health Council and interests

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

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2010 for public review. The following organisations and persons have commented on the draft document:

- Mr. R.D. Zumwalde, National Institute of Occupational Health and Safety, Cincinnati, OH, USA
- Mr. U. Heidegger on behalf of ECFIA, European Association representing the High Temperature Insulation Wool Industry, Marseille, France

Annex **D**

Summary advisory reports of the Health Council published in 1995

Report No. 1995/02WGD: Man made mineral fibers. Health based recommended occupational exposure limits[58]

[Summary]

Based on some positive animal studies, refractory ceramic fibers are considered to be potentially carcinogenic. However, the mechanism underlying the carcinogenicity is unclear. The Committee [DECOS] has considered two situations, that both lead to comparable results.

- If a *non-genotoxic* mechanism underlies the carcinogenic potential, the Committee [DECOS] derives a HBR-OEL of 1 respirable fiber per ml, TWA-8 hour; this value is based on a NOAEL of 25 fibers/ml and a safety factor of 25 taking into account the seriousness of the critical effect (cancer);
- If a *genotoxic* mechanism underlies the carcinogenic potential, the Committee assumes a linear relationship between dose and response. Based on 40 years of occupational exposure and excess cancer risk of $4x10^{-3}$ appears to be associated with an exposure to 5.6 respirable fibers per ml. A cancer risk of $4x10^{-5}$ is associated with an exposure to 0.056 respirable fibers per ml. Applying a linear extrapolation, daily (8 h) occupational exposure to 1 respirable fiber per ml for 40 years appears to be associated with a cancer risk of $7x10^{-4}$.

Report No. 1995/18: Man made mineral fibers. Assessment of carcinogenicity[57]

[Carcinogenic properties]

Does the health Council consider that all man-made mineral fibers (MMMFs) are carcinogenic, and that there is no threshold beneath which they have no effect?

The Committee endorses the conclusion drawn by the Health Council DECOS (Publication No. 1995/02WGD) that there is presently only evidence that one of the six currently identified categories of man-made mineral fibre (continuous filaments, glass wool, rock wool, slag wool, special purpose fibre and refractory ceramic fibre), is carcinogenic, namely refractory ceramic fibre. This conclusion is based on research into the effect on people and on animals of prolonged exposure to man-made mineral fibres by inhalation. Thus, the Committee's assessment is valid for those fibres which can be inhaled, i.e. those with a diameter of less than 3µ m, a length of between 2 and 200 µm and a length/ diameter quotient of at least 3.

The Committee does not have sufficient data at its disposal to determine the mechanism by which ceramic fibres can induce cancer; no conclusion can therefore be drawn regarding the existence of a carcinogenic threshold.

Annex **E**

IARC evaluation and conclusion

Man-Made Vitreous Fibres
Refractory ceramic fibres (Group 2B)

VOL.: 81 (2002)

Human carcinogenicity data

Preliminary results from a US epidemiological mortality study of refractory ceramic fibre workers were available. However, the limited epidemiological data do not permit an adequate evaluation of the cancer risk associated with exposure to refractory ceramic fibres.

Results on mortality among refractory ceramic fibre workers have also been published since the previous *IARC Monographs* evaluation (1988). However, the epidemiological evidence for refractory ceramic fibres is still extremely limited. Radiographic evidence indicating pleural plaques has been reported for refractory ceramic fibre workers. Although the prognostic significance of pleural plaques is unclear, such plaques are also a common finding among asbestos-exposed workers.

Animal carcinogenicity data

In a well-designed, long-term inhalation study with refractory ceramic fibres in rats, a statistically significant increase in the incidence of lung tumours and a few mesotheliomas were observed. In a well-designed, long-term inhalation study of refractory ceramic fibres in hamsters, a significant increase in the incidence of mesotheliomas was observed.

After intratracheal instillation, two studies reported no excess in tumour incidence in rats. In three intrapleural studies in rats, no significant increase in tumour incidence was observed. In intraperitoneal studies in rats and hamsters, tumour incidence was related to fibre length and dose.

Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of refractory ceramic fibres.

There is *sufficient evidence* in experimental animals for the carcinogenicity of refractory ceramic fibres.

Overall evaluation

Refractory ceramic fibres are possibly carcinogenic to humans (Group 2B).

Previous evaluation: Vol. 43 (1988)

Annex **F**

Animal carcinogenicity studies

Animal characteristics	Fibre type	Exposure design [A,B]	Tumour development	Lung burden
Whole-body inhalation				
SPF Wistar AF/ HAN rats; 48 exposed, 40 unexposed; sex unspecified.[15]	Respirable dust from bulk fibrous ceramic aluminium silicate glass (composition not given)	10 mg/m^3 (95 f/cm^3 (WHO); 90% had a diameter of < 3 µm, and an aspect ratio of 4:1); 7 h/d, 5 d/w, 52 weeks; kept alive until 32 months	Lung tumours (adenoma, carcinoma, histocytoma): - exposed: 8/48 - control: 0/40 Pleural mesothelioma: 0 No other neoplasms reported.	-
Nose-only inhalation				
Male Fisher 344 rats; 140 animals per group.[40]	RCF1	30 mg/m^3 (187 f/cm^3 (WHO); GMD, ~0.8 µm; GML, 12.8-17.4 µm); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 16/123 (p<0.05) - control: 2/130 Pleural mesothelioma: - exposed: 2/123 - control: 0/130 No other neoplasms reported.	2-7 x10^5 (WHO) f/mg dry lung
	RCF2	30 mg/m^3 (220 f/cm^3 (WHO); GMD, ~0.8 µm; GML, 12.8-17.4 µm); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 9/121 (p<0.05) - control: 2/130 Pleural mesothelioma: - exposed: 3/121 - control: 0/130 No other neoplasms reported.	2-7 x10^5 (WHO) f/mg dry lung

	RCF3	30 mg/m^3 (182 f/cm^3 (WHO); GMD, ~0.8 µm; GML, 12.8-17.4 µm); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 19/121 (p<0.05) - control: 2/130 Pleural mesothelioma: - exposed: 2/121 - control: 0/130 No other neoplasms reported.	2-7 x10^5 (WHO) f/mg dry lung
	RCF4	30 mg/m^3 (206 f/cm^3 (WHO); GMD, 1.22 µm; GML, 9.8 µm); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 4/118 - control: 2/130 Pleural mesothelioma: - exposed: 1/118 - control: 0/130 No other neoplasms reported.	2-7 x10^5 (WHO) f/mg dry lung
Male Fisher 344 rats; 140 animals per group.[41]	RCF1	- 3 mg/m^3 (26 f/cm^3); - 9 mg/m^3 (75 f/cm^3); - 16 mg/m^3 (120 f/cm^3); WHO; GMD, 0.8 µm; GML, 14 µm); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed (3): 2 (1.6%) - exposed (9): 5 (3.9%) - exposed (16): 2 (1.6%) - control: 1 (0.8%) Pleural mesothelioma: - exposed (3): 0 - exposed (9): 1 (0.8%) - exposed (16): 0 - control: 0 No other neoplasms reported.	22.1 x10^4 (WHO) f/mg dry lung
Female Osborne Mendel rats; 55 animals per group.[54]	Fibrefrax® (chemical composition not given).	10.8 mg/m^3 (88 f/cm^3; GMD, 0.9 µm; GML, 25 µm; aspect ratio, 33:1); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 0/55 - control: 0/60 No other neoplasms reported.	2.18 x10^4 f/mg dry lung
Male Syrian golden hamsters; 70 animals per group.[54]	Fibrefrax® (chemical composition not given).	10.8 mg/m^3 (200 f/cm^3; GMD, 0.9 µm; GML, 25 µm; aspect ratio, 33:1); 6 h/d, 5 d/w, 104 weeks.	Lung tumours (adenoma and carcinoma): - exposed: 0 - control: 1/58 Pleural mesothelioma: - exposed: 1/70 - control: 0 No other neoplasms reported.	0.86 x10^4 f/mg dry lung
Male Syrian golden hamsters; 140 animals per group; animals were treated for intestinal infection during study.[42]	RCF1	30 mg/m^3 (215 f/cm^3 (WHO); GMD, 0.78 µm; GML, 15.9 µm); 6 h/d, 5 d/w, exposure period, 78 weeks; observation period, lifetime.	Lung tumours (adenoma and carcinoma): - exposed: 0 - control: 0 Pleural mesothelioma: - exposed: 42/102 - control: 0 No other neoplasms reported.	1.59 x10^5 f/mg dry lung

Intratracheal installation				
Female Osborne Mendel rats; 22 animals per group.[54]	Fibrefrax® (chemical composition not given).	5 weekly installations of 2 mg; observation period, lifetime.	No lung or pleural tumours found in exposed and control animals. No other neoplasms reported.	-
Male Syrian golden hamsters; 25 animals per group.[54]	Fibrefrax® (chemical composition not given); elutriated from inhalation chamber.	5 weekly installations of 2 mg; observation period, lifetime.	No lung or pleural tumours found in exposed and control animals. No other neoplasms reported.	-
Intrapleural injection				
Male and female SPF Wistar rats; 31 animals per group.[60]	RCF (not specified).	Single injection of 20 mg (in 0.4 mL); ball mill grinding; observation period, lifetime.	No lung tumours found. Pleural mesothelioma: - exposed: 3/31	-
Male and female Alpk:AP Wistar derived rats; 24 male and 24 female animals.[50]	Fibre A: Kaolin; Fibre B: alumina and silica.	Single injection of 20 mg (in 0.2 mL); ball mill grinding and sieving; observation period, lifetime.	No lung tumours found. Pleural mesothelioma: - fibre A: 0 - fibre B: 1/48 - control: 0 Peritoneal mesothelioma: - fibre A: 0 - fibre B: 2/48 - control: 0	-
Male Wistar-Porton rats; 19 to 24 animals.[9]	High Duty® grade aluminosilicate, vitreous or devitrified.	Single injection of 20 mg (in 0.4 mL); not further specified; observation period, lifetime.	No pleural mesotheliomas found in exposed and control animals. No other neoplasms reported.	-
ntraperitoneal injection				
Heterozygous (*Nf2*$^{+/-}$) knockout mice; 55 exposed and 33 non-exposed mice; no data on sex given. Inactivation of *Nf2* gene has been reported in human malignant mesotheliomas.[1]	RCF1	3 mg (in 0.3 mL); average arithmetic length, 22.4 µm; average arithmetic diameter, 1,1 µm; two injections in a lag time of two months; observation period, lifetime.	Peritoneal mesotheliomas: - exposed: 25/55 (55%) - control: 2/33 (1.7%) Histopathological features of peritoneal tumours were similar to those observed in human malignant mesothelioma. No difference was found between exposed and control animals regarding other types of tumours in the lungs.	-
Wistar AF/HAN rats (sex not given); 32 animals per group.[15]	RCF (not specified).	Single injection of 25 mg (in 2 mL); length (90%), <3 µm; diameter, < 0.3 µm; observation period not given.	Peritoneal tumours: - exposed: 3/32 - control: 2/29 No other neoplasms reported.	-
Female Wistar WU/Kiβlegg rats; ~50 animals per group; 102 animals served as control.[51]	Fibrefrax® (chemical composition not given).	45 mg (in 2 mL); length, <8.3 µm; diameter, 0.91 µm; once a week for five weeks; observation period, 28 months after injection.	Peritoneal tumours: - exposed: 32/47 - control: 2/102 No other neoplasms reported.	-

	Manville (composition not given).	Single injection of 75 mg (in 2 mL); length, 6.9 µm; diameter, 1.1 µm; once a week for five weeks; observation period, 28 months after injection.	Peritoneal tumours: -exposed: 12/54 - control: 2/102 No other neoplasms reported. It is unclear whether histopathological examination was performed.	-
Male Wistar rats; 18 to 24 animals per group; no control animals included.[43]	RCF1	110 mg (in 2 mL); injections on two consecutive days; $228x10^6$ fibres, < 10 µm; observation period, lifetime.	Peritoneal tumours: 21/24	-
	RCF2	188 mg (in 2 mL); $320x10^6$ fibres, < 10 µm; injections on two consecutive days; observation period, lifetime.	Peritoneal tumours: 13/18	-
	RCF3	90 mg (in 2 mL); $81x10^6$ fibres, < 10 µm; injections on two consecutive days; observation period, lifetime.	Peritoneal tumours: 0/22	-
Female Osborne-Mendel rats; 25 animals per group.[54]	Fibrefrax® (chemical composition not given); elutriated from inhalation chamber.	Single injection of 25 mg (in 0.5 mL); observation period, lifetime.	Peritoneal tumours: - exposed: 19/23 (including one fibrosarcoma) - control: 0/25 No other neoplasms reported.	-
Female Syrian Golden hamsters; 56 animals per group.[54]	Fibrefrax® (chemical composition not given); elutriated from inhalation chamber.	Single injection of 25 mg (in 0.5 mL); observation period, lifetime.	Peritoneal tumours: - exposed: 7/36 - control: 0 High mortality rate in first month of experiment due to acute haemorrhagic peritonitis and vascular collapse.	-

[A] WHO: respirable fibres as defined by the World Health Organization as having a length of > 5 µm, a diameter of < 3 µm, and an aspect ratio of > 3:1.

[B] f/cm³, fibres per cm³; h/d, hours per day; d/w, days per week; GMD, geometric mean diameter; GML, geometric mean length; - not determined or relevant.

Partly adapted from IARC Monograph (2002).[35]

Annex **G**

Carcinogenic classification of substances by the Committee

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

Category	Judgement of the Committee (GRGHS)	Comparable with EU Category	
		67/584/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	1	1A
1B	The compound is presumed to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	Not applicable	Not applicable
(4)	The compound is probably not carcinogenic to man.	Not applicable	Not applicable

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