Recommendation from the Scientific Committee on Occupational Exposure Limits for Man Made Mineral Fibres (MMMFs) with no indication for carcinogenicity

8 hour TWA: 1 fibre/ml
STEL (15 mins): -
Additional classification:

Background
In 2000 SCOEL has evaluated the health significance of workers exposed to MMMF10 fibres and proposed an OEL of 1 mg/m³ or 10 fibre/ml (10x10⁶ fibres/m³). This considered the well-defined NOEL of 30 fibres/ml, a LOEL at fivefold higher concentration, and the absence of a carcinogenic potential in long term inhalation studies. Subsequently, a general evaluation of available data on MMMF has been started to develop a procedure to regulate MMMF exposure at the workplace. When evaluating the literature it became apparent, that although a great amount of publications on MMMF are available only few have been designed to identify dose-response of the adverse effects including identification of NOAELs that can be used as a starting point to derive OELs. Since the number of MMMF is abundant and steadily increasing, SCOEL does not expect that long-term inhalation studies will be made available for each of the fibre materials. SCOEL concluded therefore that it is not appropriate to propose an OEL for each of the fibres, but to set a value that is applicable for all fibre materials. This only applies for fibres without indication of carcinogenicity, according to the criteria for fibre classification of the Annex II to Council Directive 67/548/EEC (see Appendix I). A deviation from such level is only possible when appropriate long-term exposure studies of the specific material is made available which allow identification of a NOEL. A similar approach has been made by DECOS (1995).

The main documentations used by the SCOEL in the evaluation of MMMFs were MAK (DFG 1993), DECOS (1995) and IARC (2002).
**Substance:**

Man-made mineral fibre (MMMF) is a generic name used to describe an inorganic fibrous material manufactured primarily from glass, rock, minerals, slag and processed inorganic oxides. The MMMFs produced are non-crystalline (glassy, vitreous, amorphous). Man-made mineral fibres are manufactured by a variety of processes based on the attenuation of a thin stream of molten inorganic oxides at high temperatures. All commercially important MMMFs are silica-based and contain various amounts of other inorganic oxides. The non-silica components typically include, but are not limited to, oxides of alkaline earth, alkalis, aluminium, boron, iron and zirconium. The MMMFs have a broad variety of chemical compositions (IARC 2002). Physical structure influences leaching of the fibres and their reactions to mechanical stress. Leaching favours dissolution and disintegration of the fibre and it changes the surface characteristics of the fibre, such as specific surface area, surface charge, the presence of Fe ions and the fibre dimensions. Fibre surface and fibre dimensions affect interactions with biological structures and the generation of ROS (Wagner et al. 1984, Davis 1986, LeBouffant et al. 1987, Hammad 1988, Fubini 1996, 1997, Greim 1997, Greim et al. 2001).

Fibre dimensions are of crucial importance regarding biopersistence and the toxic potential of (Hammad 1984, Bernstein et al. 1996; Hart et al. 1994). For regulatory purposes, particles are counted as fibres when they are the following dimensional characteristics: length L> 5 µm, diameter D< 3 µm and an aspect ratio L:D> 3:1, meeting the fibre definition criteria of WHO. They correspond to the respirable fraction of the fibrous dust limited to those being able to enter the alveolar region of humans (D< 3µm).

In 1988 IARC grouped MMMFs into five categories: glass filament, glass wool, rock wool, slag wool and ceramic. To reflect developments in the industry, IARC (2002) expanded the categories into: continuous glass filament, glass wool (insulation wool and special purpose wool), rock wool, slag wool, refractory ceramic and other and reached following overall assessment:

*Special-purpose glass fibres such as E-glass and ‘475’ glass fibres are possibly carcinogenic to humans (Group 2B).*

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

*Insulation glass wool, continuous glass filament, rock (stone) wool and slag wool are not classifiable as to their carcinogenicity to humans (Group 3).*

Refractory ceramic fibres, classified by the EU as R49 (may cause cancer by inhalation) are treated in SUM 165.
**Occurrence and Use**

MMMFs do not occur in nature. Significant commercial production of man-made mineral fibres began in the early twentieth century. MMMF products can release airborne respirable fibres during their production, use and removal. According to IARC (2002) it was estimated that in 2001 over 9 million tonnes of man-made mineral fibres were produced annually in over 100 factories around the world. Most of these are used as thermal or acoustical insulation. Usage for this purpose is divided about equally between glass wool (about 3 million tonnes, used predominantly in North America) and rock (stone) and slag wool (about 3 million tonnes, used predominantly in Europe and the rest of the world). In recent years, high-alumina, low-silica wools (about 1 million tonnes) have been increasingly replacing rock and slag wools in this application. Special-purpose glass fibres are of limited-production, small-diameter fibre products are typically used for purposes other than insulation as in filtration media and batteries. Continuous glass filaments (2 million tonnes) are generally used in the reinforcement of plastics and in textiles but usually are of larger diameter and hence are not subject to classification according to EU criteria. Refractory ceramic fibres, first produced commercially in the 1950’s are widely used (about 150 thousand tonnes) in high-temperature applications such as furnace insulation. The more recently developed alkaline earth silicate wools (about 10 thousand tonnes) are replacing refractory ceramic in some applications. In any case, refractory ceramic fibres, which are classified by the EU as carcinogenic, are not on the scope of this recommendation.

**Health significance**

**Toxicokinetics**

The uptake of fibres into the body takes place via the respiratory tract. Transport and deposition of the fibres in the airways are determined by their aerodynamic behaviour. The fibre size, their chemical composition and the deposited dose in the lung define their retention kinetics. Fibres may be deposited in the respiratory air-ways by: impaction, sedimentation, interception and diffusion. The fate of deposited fibres within the respiratory system depends on both the site of deposition and the characteristics of the fibre. The main mechanisms of fibre clearance include mucociliary movement in the nasopharyngeal and tracheobronchial regions and alveolar macrophage phagocytosis in the alveolar region with subsequent removal.
towards the mucociliary escalator. In addition to these mechanisms, chemical dissolution and leaching, swelling and breakage, can occur.

Biopersistence is defined as the total of all physical and chemical processes leading to clearance of fibres from the respiratory tract in vivo. The biopersistence of fibres deposited in the respiratory tract results from a combination of physiological clearance processes (mechanical translocation/removal) and physico-chemical processes (chemical dissolution and leaching, mechanical breaking). Breakage of fibres may lead to temporary increase of fibre numbers in the lung. Dissolution and leaching are processes influenced by fibre composition and the pH of the surrounding milieu (Hesterberg et al. 1196b; Christensen et al. 1994; HVBG 1998; Guldberg et al. 1998; Knudsen et al. 1996). Consequently, biodurability depends on whether or not fibres are phagocytised by macrophages (intracellular pH about 5) or not (Luoto et al. 1995, 1998). Only fibres with lengths up to about 10 µm can be efficiently phagocytosed by rat alveolar macrophages, whereas long fibres (L> 20µm) lead to “frustrated phagocytosis” (Oberdöster 1991; Oberdöster and Lehnert 1991; Tran et al. 1996). With regard to fibres >20µm, Nota Q of EU Directive outlines specific criteria in relation to biopersistence that determine whether or not classification for carcinogenicity should be applied (Annex I). In addition Nota R states, that “classification as a carcinogen need not apply to fibres with length weighted geometric mean diameter less two standard geometric errors greater than 6µm”.

**Mechanism of action**

Inhalation of man-made vitreous fibres leads to both to inflammatory and fibrotic processes, as well as expression of genes linked to cell proliferation and antioxidant defense in a dose-related fashion. These processes are associated with the activation of alveolar macrophages, lymphocytes, polymorphonuclear cells, mast cells, and fibroblasts and the release of a number of cellular mediators, e.g. tumor necrosis factor α (TNFα), interleukin-1α (IL-1α), interleukin-6 (IL-6), and basic fibroblast growth factor (bFGF) and the upregulation of protooncogenes. Injury to alveolar epithelial cells is followed by hyperplasia and hypertrophy and occasionally by neoplastic transformation resulting in tumorigenesis (Driscoll 1996; Mossman and Churg 1998; Oberdörster and Lehnert 1991; Saffiotti 1998; Tsuda 1997). Fibre activated macrophages and other inflammatory cells generate reactive oxygen species (ROS), e.g. O₂⁻, H₂O₂, and NO (Wang et al. 1999 a). The hydroxyl radical (OH⁻), peroxynitrite, and nitronium ions may also be formed. ROS also can originate from redox reactions...
occurring at the fibre surface, e.g. by fibre iron catalysis, leading finally to generation of OH•. These oxidants induce oxidative stress in the target cells (Driscoll 1996; Fubini 1996; Kamp et al. 1992; Martin et al. 1998; Mossman and Churg 1998; Wang et al. 1999a, b; Zhu et al. 1998).

These processes, being the underlying mechanism of fibre carcinogenicity, are considered to be thresholded. Cellular antioxidative systems including superoxide dismutase (SOD), catalase, and glutathion-S-transferase-dependent systems, protect against cellular injury and DNA damage as long as the release of reactive oxygen species is not sufficient to overwhelm this defence (Howden and Faux 1996; Marks-Konczalik et al. 1998; Oberdörster 1997). Consequently, the lung is able to deal with a considerable number of fibres without detectable molecular or pathogenic events, which has been shown in epidemiologic and experimental studies (Mossman and Churg 1998).

**Genotoxicity**

Several types of fibres have been shown to induce chromosomal aberrations, deletions, micronuclei, and aneuploidy in both rodent and human cells in culture (overview in Greim 1997; Jaurand 1997). Aneuploidy and polyploidy can result either by sterically blocking cytokinesis, by mitotic disturbances or by physical interaction between and chromosomes or and the spindle apparatus (Dopp et al. 1995, 1997; Jensen et al. 1996; Ong et al. 1997). Some limited in vitro data are available on the formation of oxidized DNA bases (e.g. 8-hydroxydeoxyguanosine, 8-OHdG) (Jaurand 1997). ROS (see section 3) also play a role in DNA and chromosomal breakage (Dopp and Schiffmann 1998). The induction of DNA strandbreaks, DNA-DNA crosslinks and of DNA repair has been demonstrated (Wang et al. 1999b). But these in vitro data have not been sufficiently validated in in vivo studies, with the exception of few in vivo studies (Unfried et al. 2002, Schürkes et al. 2004).

The extent of genotoxicity may depend on a cell's ability to adapt to oxidant stress. It has been suggested that a threshold fibre concentration should be exceeded in order to initiate a significant enhancement of abnormal anaphases/telophases and subsequent cell transformation (Okayasu et al. 1999; Yegles et al. 1995).

The major problem in the evaluation of the genotoxic potential of fibers is that currently no sufficiently validated in vitro tests for fibre genotoxicity exist. It would be necessary to establish test systems with conditions optimized for testing fibres and these should be evaluated for a range of different fibres. Little information is available on mechanisms of
genotoxic effects. Future research should be designed to evaluate the dose-dependence of genotoxic effects and the differentiation between primary and secondary mechanism (Greim et al. 2000).

**Carcinogenicity**

The results from the carcinogenicity studies in which animals have been exposed to MMMF are well documented in the literature. In the following only studies that can serve as the basis for the derivation of an OEL for MMMFs will be presented.

**Derivation of an OEL for Man Made Mineral Fibres**

**OEL for MMMF proposed by DECOS**

The Dutch Expert Committee on Occupational Standards (DECOS) evaluated the available information and proposed occupational exposure limits (OELs) for MMMF (DECOS 1995). The expert committee evaluated the carcinogenic potency of MMMF at the OEL (Tab. 1). For glass-wool fibres, DECOS used the rat study of LeBouffant et al. (1987), which showed that a 12- to 24-month exposure of respirable glass-wool fibres at a concentration of 5 mg/m$^3$ induced an alveolar macrophage reaction with a slight septal fibrosis. The effect was related to the duration of the exposure and tended to diminish after the exposure stopped. Applying a safety factor of 10 for the extrapolation of animal data to man, an OEL of 0.5 mg/m$^3$ (4.8 fibres/ml) for respirable glasswool fibres has been proposed (Table 1).

There are many physical and chemical similarities between special-purpose glass fibres and glasswool fibres. No human data are available. Animal data showed that 332 respirable special-purpose glass fibres/ml induces an effect (irritation and inflammation of the nasal mucous membranes) level. For this reason, DECOS proposed a safety factor of 50 for special-purpose fibres, 10 for the interspecies variation, and 5 for taking an effect level as the starting point, that means to compensate for the use of a LOAEL (Table 1).

Because DECOS considers the nature of the critical effects of the MMMF of rockwool, slagwool, glasswool, and special-purpose fibres to be very similar, it recommends an equal OEL of 3 respirable fibres/ml for these fibres. This is based on the NOEL for rockwool of 33 fibres/ml being the lowest NOEL of these fibres.
Table 1: **Occupational exposure limits for man-made mineral fibres (MMMF), as proposed by the Dutch Expert Committee on Occupational Standards (DECOS 1995).**

<table>
<thead>
<tr>
<th>Fibres</th>
<th>NOAEL Resp. fibres/ml</th>
<th>Resp. fibres/ml</th>
<th>Safety factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasswool</td>
<td>48 (LOAEL)</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Rockwool</td>
<td>33</td>
<td>3.3</td>
<td>10</td>
</tr>
<tr>
<td>Slagwool</td>
<td>210</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Special purpose glass</td>
<td>332 (LOAEL)</td>
<td>6.6</td>
<td>50</td>
</tr>
<tr>
<td><strong>Common OEL</strong></td>
<td><strong>3 (0.3 mg/m³)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chronic inhalation studies**

Between 1970 and 1987 several chronic rodent inhalation studies have been conducted. Seven studies of fibreglass and three studies of mineral wool were negative for fibrosis and tumorigenesis (Gross et al 1970, Lee et al 1981, McConnell et al 1984, Wagner et al 1984, Davis 1986, Le Bouffant et al 1987, Muhle et al 1987, Smith et al 1987). In two studies of refractory ceramic fibres (Davis et al 1984) 5% fibrosis and 17% lung tumors following 12 months exposure of rats have been observed, whereas Smith et al (1987) neither observed fibrosis nor tumors and only 2% mesotheliomas in hamsters after 24 months exposure. However, these studies had one or more technical limitations (Hesterberg and Hart 2001). In two studies (Wagner et al 1984, McConnell 1984) relatively short test fibres have been used. More than 70% of test fibres were shorter than 10 μm. In other studies 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 lung burden was 2x10⁶ for JM 475 fibreglass-fibres, as compared to 150-2000x10⁶ fibres/lung in studies conducted after 1988.

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). Using these techniques several inhalation studies on different MMMF have been performed.
Recent long term dose response inhalation studies (Table 2)

**Rock wool and slag wool**
To study dose related chronic inhalation toxicity and carcinogenic effects rats were exposed to rock wool at concentrations of 3, 16, and 30 mg/m$^3$ (∼30, 150, or 240 WHO fibres/ml) for 24 months or 3, 16, and 30 mg/m$^3$ (∼30, 130, or 210 WHO fibres/ml) for 24 months. Exposure to these fibres induced a dose-related inflammatory response, while rock wool produced minimal focal pulmonary fibrosis in addition to inflammatory response. Both rock wool and slag wool exposure did not show any neoplastic activity in the lungs or the pleura. In both studies the NOEL was 30 fibres/ml (McConnell et al 1994).

**Insulation fibreglass**
This type of fibres includes MMVF10 (JM 901) and MMVF11 (Hesterberg et al 1993). Rats were exposed to three fibres concentrations of 3, 16, and 30 mg/m$^3$ (approximately 250 WHO fibres/ml, including 73 to 90 fibres/ml longer than 20 μm). The 2 types of fibre-glass did not induce fibrosis nor tumors except transient lung inflammation that disappeared after a post-exposure recovery period, which was disputed however by Infante et al (1994). Hamsters exposed to MMVF 10a (JM 901 fibreglass) did not develop fibrosis or thoracic neoplasms at 30 mg/m$^3$ (McConnell et al 1999).

In the chronic inhalation study (Hesterberg et al 1995) rats were exposed to fibrous glass (MMVF10 and 11) rock wool or slag wool and to RCF1 and chrysotile as positive control. A significant increase in pulmonary fibrosis, lung tumors and mesotheliomas was observed in rats exposed to RCF1, while these tumor incidences were within normal limits after exposure to rock wool, slag wool and fibrous glass. A slight pulmonary fibrosis was observed in rats exposed to rock wool and RCF1.
Potassium Octatitanate Fibres (TISMO)

Ikegami et al (2004) investigated potassium octatitanate fibres (TISMO) in a 2 years inhalation study in rats, combined with determination of lung burden and fibre clearance. Groups of 135 rats were exposed to 0, 20, 60, or 200 WHO fibres/cc 6h/day, 5 days/week for 24 months. Lung burdens have been determined by killing subgroups after 3, 6, 12, 18, and 24 months. The results indicated that at 20 fibres/cc the steady state of lung burden (equilibrium between lung burden and clearance) has been reached after approximately 18 months of exposure. At all times investigated 200 fibres/cc resulted in a disproportional increase in lung burden indicating saturation of lung clearance as a result of overloading, while a graduate increase was seen at 20 or 60 fibres/cc. To determine lung clearance subgroups were removed after 6 months of exposure and were killed 3, 6, 12, and 18 months later. Following the 6 months exposure the amount of fibres in the lung decreased with a half life of approximately 6 months at all exposures and were decreased by approximately 72%, 74%, and 79% in the 200, 60, and 20 WHO fibres/cc.

Based on the results of the lung burden study and histopathological observations, the exposure concentration of 20 WHO fibres/cc has been considered a NOEL. 60 fibres/cc induced lesions of a borderline level. At the highest fibre concentration some alveolar walls enclosing aggregates of TISMO laden alveolar macrophages were slightly thickened after 12 months of exposure and revealed slight alveolar fibrosis after 18 and 24 months of exposure. No exposure related pulmonary neoplasm or mesothelioma was observed in 24 months of exposure. The publication also describes the results of a health hazard evaluation on 27 current employees and 18 former employees at 14 designed production workplaces. The employment period of the current workers ranged from 7 months to 19.1 years, that of the former employees from 3 months to 14.8 years. The health hazard was evaluated by chest x-ray, lung function tests, utilizing forced spirometry and expiratory flow volume curves. The geometric means of airborne TISMO fibre concentration ranged from 0.2 to 1.6 WHO fibres/ml in 1994 and decreased to 0.10-0.14 WHO fibres/ml in 1999. No exposure related adverse effects have been observed.

Due to its excellent design this study in addition to a precise characterization of the fibres provides all necessary data on dose-response of effects, NOEL, body burden and clearance. However, an evaluation of the half-lives of fibre elimination from the lung has not been made. Since Ikegami et al (2004) described a half-life of about 180 (Table 4) the high biopersistence does not exclude carcinogenic potential of this fibre.
Table 2: Long term dose response inhalation studies not considered by DECOS (1995)

<table>
<thead>
<tr>
<th>Fibre</th>
<th>Species/duration</th>
<th>Exposure</th>
<th>NOEL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMVF10</td>
<td>Rats, 24mo, 6h/d, 5d/w</td>
<td>3, 16, 30 mg/m³</td>
<td>3 mg/m³</td>
<td>Hesterberg et al 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25 f/ml)</td>
<td></td>
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<tr>
<td>MMVF11</td>
<td>Rats, 24mo, 6h/d, 5d/w</td>
<td>3, 16, 30 mg/m³</td>
<td>3 mg/m³</td>
<td>Hesterberg et al 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25 f/ml)</td>
<td></td>
</tr>
<tr>
<td>MMVF10</td>
<td>Rats, 78 w, 6h/d, 5d/w</td>
<td>3, 16, 30, 45, 60 mg/m³</td>
<td>3 mg/m³</td>
<td>Hesterberg et al 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25 f/ml) (LOEL)</td>
<td></td>
</tr>
<tr>
<td>MMVF10.1</td>
<td>Hamster, 13 w, 6h/d, 5d/w</td>
<td>3, 16, 30, 45, 60 mg/m³</td>
<td>3 mg/m³</td>
<td>Hesterberg et al 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25 f/ml) LOEL</td>
<td></td>
</tr>
<tr>
<td>MMVF10a, MMVF33</td>
<td>Hamster, 78 w, 6h/d, 5d/w</td>
<td>30 mg/m³</td>
<td>No NOEL determined</td>
<td>McConnell et al 1999</td>
</tr>
<tr>
<td>MMVF21</td>
<td>Rats, 104 w, 6h/d, 5d/w</td>
<td>3, 16, 30 mg/m³</td>
<td>3 mg/m³</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(30 f/ml)</td>
<td></td>
</tr>
<tr>
<td>MMVF22</td>
<td>Rats, 104 w, 6h/d, 5d/w</td>
<td>3, 16, 30 mg/m³</td>
<td>3 mg/m³</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(30 f/ml)</td>
<td></td>
</tr>
<tr>
<td>MMVF21</td>
<td>Rats, 13-104 w, 6h/d, 5d/w</td>
<td>16, 30 mg/m³</td>
<td>No NOEL determined</td>
<td>Kamstrup et al 2001</td>
</tr>
<tr>
<td>MMVF34/HT</td>
<td>Rats, 13-104 w, 6h/d, 5d/w</td>
<td>30 mg/m³</td>
<td>No NOEL determined</td>
<td>Kamstrup et al 2001</td>
</tr>
<tr>
<td>TISMO</td>
<td>Rats, 24 mo 6h/d, 5 d/w</td>
<td>20, 60, or 200 f/ml</td>
<td>NOEL</td>
<td>Ikegami et al (2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 f/ml</td>
<td></td>
</tr>
<tr>
<td>X607</td>
<td>Rats, 24 mo 6h/d, 5 d/w</td>
<td>200 f/ml (=16 mg/m³)</td>
<td>200 f/ml (LOEL)</td>
<td>Hesterberg et al 1998</td>
</tr>
</tbody>
</table>

CMS: Calcium-magnesium-silicate fibre
MVF10: 901 glass wool
MMVF10.1: 901 glass wool
MMVF10a: Typical building insulation fibre glass
MMVF11: Certain Teed glass wool
MMVF21: Traditional (rock) stone wool. HL 65 and 92 days (WHO, long fibres)
MMVF22: Slag wool
MMVF33: Special application fibre glass
MMVF34/HT: Biosoluble rock wool fibre. HL 25 and 6 days (WHO, long fibres)
TISMO: Potassium octatitanate fibres, HL ~ 6 months
X607: Calcium-magnesium-silicate fibre (similar to CMS)

MMVF10, MMVF10.a and MMVF10.1 are essentially the same (Hesterberg et al 1999). Due to production changes they slightly differ in their fluorine content. They have similar in vitro dissolution rates.
Table 3: NOELs and occupational exposure limits (OELs) for the non-carcinogenic man-made mineral fibres (see Table 2) proposed by applying safety factors (DECOS 1995).

<table>
<thead>
<tr>
<th>Fibres</th>
<th>NOEL Resp. fibres/ml</th>
<th>OELs Resp. fibres/ml</th>
<th>Safety factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMVF10 (glasswool)</td>
<td>25</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td>Rat, 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMVF10 (glasswool)</td>
<td>25 (LOEL) 1.3</td>
<td>20**</td>
<td></td>
</tr>
<tr>
<td>Rat, 78 w</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMVF10.1 (glasswool)</td>
<td>25 (LOEL) 1.3</td>
<td>20**</td>
<td></td>
</tr>
<tr>
<td>Hamster, 13 w</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMVF11 (glasswool)</td>
<td>25</td>
<td>2.5</td>
<td>10</td>
</tr>
<tr>
<td>Rat, 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMMMF21 (rockwool)</td>
<td>30</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Rat, 104 w</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMMMF22 (slagwool)</td>
<td>30</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Rat, 104 w</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X607(^1)</td>
<td>200 f/ml (LOEL)</td>
<td>10</td>
<td>20**</td>
</tr>
<tr>
<td>Rat, 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Common OEL**

1 X607: calcium-magnesium-silicate fibre

* No factor applied (SCOEL 2000)
** Factor 20 to consider LOEL
*** Factor 20 to consider LOEL and 12 months exposure instead of 24.
Clearance half-lives of fibres after inhalation exposure are given in Table 4. These data indicate that carcinogenic fibres like amosite, crocidolite, PTI or TISMO are relatively persistent having half-lives of several months and more whereas half-lives of the well-studied non-carcinogenic fibres are in the range of months or less.

**Table 4:** Elimination half-lives (HL given in days) of fibres after inhalation exposure in rats (modified from Hesterberg and Hart 2001).

<table>
<thead>
<tr>
<th>Fibres</th>
<th>HL (days)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amosite (asbestos)</td>
<td>418</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td>Crocidolite (asbestos)</td>
<td>817</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td>Crocidolite</td>
<td>246 - ∞</td>
<td>Rödelsperger 2004</td>
</tr>
<tr>
<td>MMVF10 (glass wool)</td>
<td>14.5</td>
<td>Hesterberg et al 1993</td>
</tr>
<tr>
<td>MMVF11 (glass wool)</td>
<td>9</td>
<td>Hesterberg et al 1993</td>
</tr>
<tr>
<td>MMMF21 (rock wool)</td>
<td>67</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td>MMMF21 (rock wool)</td>
<td>65 – 92</td>
<td>Bellmann et al 2001</td>
</tr>
<tr>
<td>MMMF22 (slag wool)</td>
<td>9</td>
<td>McConnell et al 1994</td>
</tr>
<tr>
<td>MMMF32 (E-glass)</td>
<td>79</td>
<td>Davis et al 1996</td>
</tr>
<tr>
<td>MMMF33 (475 glass)</td>
<td>49</td>
<td>McConnell et al 1999</td>
</tr>
<tr>
<td>X607 (hybrid fibre)</td>
<td>9.8</td>
<td>Hesterberg et al 1998</td>
</tr>
<tr>
<td>X607 (hybrid fibre)</td>
<td>32 – 107</td>
<td>Bellmann et al 2001</td>
</tr>
<tr>
<td>PT1 (Potassium octatitanate whisker)</td>
<td>60 – 360</td>
<td>Yamato et al 2003</td>
</tr>
<tr>
<td>TISMO (PT fibres)</td>
<td>~ 180</td>
<td>Ikegami et al 2004</td>
</tr>
</tbody>
</table>
Recommendation

The SCOEL considers properly conducted inhalation studies, preferentially in rats, using fibres of rat respirable size which upon long term exposure did not induce carcinogenic effects as the best basis for setting an OEL. Fibres longer than 5μm, shorter than 100 to 200μm of a diameter less than 3μm with a length/diameter ratio of at least 3:1 are considered respirable. Such studies have been performed with fibres of glass wool, rock wool, slag wool and calcium-magnesium-silicate (Table 3). In all these studies inflammation and subsequent fibrosis of the lung have been the critical effects. In the two years exposure studies in rats NOELs within the narrow range of 20 to 30 fibres/ml of inhaled air have been determined. Since there is no final conclusion whether humans are less sensitive to fibre exposure than rats or hamsters a species-species extrapolation factor of 10 is applied. After shorter exposure times (13 weeks in hamsters and 78 weeks in rats) 25 glass wool fibres/ml still induced inflammation.

To derive an OEL from this LOEL an extrapolation factor of 20 is applied. Based upon this information, the lowest OEL is 1.3 fibres/ml for glass wool fibres, which is adjusted to a general OEL of 1 fibre/ml. This OEL should be applied to all man made mineral fibres without indication of carcinogenicity (see Annex I).

When well-designed studies are available which allow identification of an NOEL, the OEL can be adapted by using the species-species extrapolation factor of 10 (see Table 3).

No difficulties on counting fibres are foreseen at the recommended OELs. Fibre counting shall be carried out in accordance with the 1997 World Health Organisation (WHO) recommended method "Determination of airborne fibre number concentrations by phase-contrast optical microscopy (membrane filter method)". Theoretically, the process of counting randomly distributed (Poisson) fibres yields a coefficient of variation (CV) of 10% for 100 fibres and 32% for 10 fibres, taking into account only statistical variation. In practice, however, the actual CV will be greater because of the additional component of variation associated with subjective differences within and between microscopists.
References


Howden PJ, Faux SP (1996) Glutathione modulates the formation of 8-hydroxydeoxyguanosine in isolated DNA and mutagenicity in Salmonella typhimurium TA100 induced by mineral. Carcinogenesis 17: 2275--2277


ANNEX I

Fibre classification
Classification of a fibre into the various categories is made according to the following criteria:

Category 1, known to be carcinogenic to man
Positive results from epidemiological studies
Category 2, should be regarded as if they are carcinogenic to man
Positive results from animal studies
Category 3, cause concern for man owing to possible carcinogenic effects, but in respect of which the available information is not adequate for making a satisfactory assessment

Based primarily on animal results
All inorganic with critical dimensions are suspected of having a carcinogenic potential and therefore are classified a priori as category 3 carcinogens. This classification need not apply if it can be shown that the fibre fulfills one of the following conditions (Nota Q):
a short-term biopersistence test by inhalation showing that the longer than 20 µm have a weighted half-life of less than 10 days;
or
a short-term biopersistence test by intratracheal instillation showing that the longer than 20 µm have a weighted half-life of less than 40 days;
or
an appropriate intraperitoneal test showing no evidence of excess carcinogenicity;
or
absence of relevant pathogenicity or neoplastic changes in a suitable long-term inhalation test.