Strategies for Setting Occupational Exposure Limits for Particles

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To set occupational exposure limits (OELs) for aerosol particles, dusts, or chemicals, one has to evaluate whether mechanistic considerations permit identification of a no observed effect level (NOEL). In the case of carcinogenic effects, this can be assumed if no genotoxicity is involved, and exposure is considered safe if it does not exceed the NOEL. If tumor induction is associated with genotoxicity, any exposure is considered to be of risk, although a NOEL may be identified in the animal or human exposure studies. This must also be assumed when no information on the carcinogenic mechanism, including genotoxicity, is available. Aerosol particles, especially fibrous dusts, which include man-made mineral fibers (MMMF), present a challenge for toxicological evaluation. Many MMMF that have been investigated have induced tumors in animals and genotoxicity in vitro. Since these effects have been associated with long-thin fiber geometry and high durability in vivo; all fibers meeting such criteria are considered carcinogenic unless the opposite has been demonstrated. This approach is practicable. Investigations on fiber tumorigenicity/genotoxicity should include information on dose response, pathobiocchemistry, particle clearance, and persistence of the material in the target organ. Such information will introduce quantitative aspects into the qualitative approach that has so far been used to classify fibrous dusts as carcinogenic. The rationales for classifying the potential carcinogenicity of MMMF and for setting OELs used by the different European committees and regulatory agencies are described. — Environ Health Perspect 105(Suppl 5):1357–1361 (1997)

Key words: occupational exposure limits, classification of carcinogens, man-made mineral fibers, fibrous dust particles, regulations of man-made mineral fibers

Introduction

In discussing the strategies to regulate particulate material, especially at the workplace, one has to consider the two approaches usually applied. One is the evaluation of the carcinogenic potential, the other is the setting of an air control level.

Evaluation of hazards and risks of dusts including man-made mineral fibers (MMMF) by the different European expert groups and authorities varies greatly (1–3). In Germany a fibrous dust that contains critical fibers (as defined in "Germany") is considered a potential carcinogen. Other countries may consider carcinogenic only those fibers for which positive inhalation studies in animals are available. This is the major reason for differences among countries and/or regions in the hazard identification and risk assessment of dusts, especially of MMMF, in addition to insufficient information on the mechanisms involved. Current European classifications are discussed below.

Classification of Carcinogens

Different national and international bodies classify carcinogenic compounds on the basis of their carcinogenic potential (Figure 1). In general there is differentiation among carcinogens: there are human carcinogens, for which there is sufficient evidence from epidemiologic data; animal carcinogens, positive in studies in animals; and suspected carcinogens, which require further information for a final decision (4–6). There are proposals, however, to include the improved understanding of carcinogenic mechanisms in the classification, e.g., to differentiate between genotoxic and nongenotoxic carcinogens (7). For the latter, no observed effect level (NOEL) may be identified, below which no effects occur. Carcinogenicity of MMMF might be considered to have a threshold if this effect is due exclusively to the formation of reactive oxygen species. As long as no increase in reactive oxygen DNA–adduct formation is detectable, no carcinogenic effect may be expected. Impairment of lung clearance because of overwhelming phenomena may contribute to an increased rate of reactive oxygen formation. Furthermore, the carcinogenic potential on the basis of lifetime risk may be considered for a better classification, i.e., a differentiation between strong and weak carcinogens (Table 1) (8–13). Lifetime risk is defined as the additional probability over the background probability of getting cancer within a lifespan of about 80 years because of exposure (40 years; defined concentration for 8 hr/day) to a given compound.

However, expert commissions that classify carcinogens, e.g., the International Agency for Research on Cancer (IARC) or the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission, Maximal Arbeitsplatz-Konzentration [maximum workplace concentration]) usually do not propose exposure control levels such as OELs for human or animal carcinogens. In Germany such values—the technische Richtkonzentrationen (technical guidance values [TRK–Werte])—are proposed by the Commission for Dangerous Chemicals (Ausschuß für Gefahrstoffe [AGS]) of the Federal Ministry of Labor (14,15). Members are representatives of the scientific community, industry, labor unions, and federal and national regulatory agencies. This commission discusses proposals for classification from the MAK Commission and proposes occupational exposure limits (OELs) after consideration of the carcinogenic potentials of the

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Abbreviations used: AGS, Ausschuß für Gefahrstoffe (Commission for Dangerous Chemicals, German Federal Ministry of Labor); DECOS, Dutch Expert Committee on Occupational Standards; EU, European Union; IARC, International Agency for Research on Cancer; MAK, maximale Arbeitsplatz-Konzentration (maximum workplace concentration); MMMF, man-made mineral fibers; MMVF, man-made vitreous fibers; NOEL, no observed effect level; OEL, occupational exposure limit; TLV, threshold limit value; TRK, technische Richtkonzentration (technical guidance value).
Classification of Man-made Mineral Fiber Dust

Germany

The German MAK Commission considers all inorganic fiber particles with a ratio of length to diameter greater than 3:1, that are longer than 5 μm, and that have a diameter less than 3 μm, potential carcinogens (category IIIB). This classification indicates that further information is needed for final evaluation (Table 2). The rationale is that carcinogenic effects have been demonstrated for almost all inorganic fibers tested, especially after intraperitoneal or intrapleural administration in rodents. Further evidence for a carcinogenic potential is seen in positive cell transformation assays and the induction of chromosomal aberrations (16-19). The criteria for classifications of critical MMMF by the MAK Commission are as follows:

- Classification as carcinogens is based on qualitative data only. Therefore, positive studies with intraperitoneal, intrapleural, or intratracheal applications lead to classification as animal carcinogens.
- Fiber particles with a ratio of length to diameter greater than 3:1, longer than 5 μm, and less than 3 μm in diameter are considered potential carcinogens because intraperitoneal or intratracheal studies, cytogenetic, and cell transformation assays of most critical fibers tested, have shown positive results.
- The mechanism of the carcinogenic effects is considered genotoxic, which excludes the assumption of an NOEL.
- Durability is a critical parameter. Fibers with durability of days to weeks and negative intraperitoneal, intrapleural, or intratracheal studies are considered non-carcinogenic and allow an OEL to be set.

The German MAK Commission did not propose OELs for MMMF because their carcinogenic potential is caused by unknown mechanisms. Exceptions are calcium sulfate and wollastonite (20). Both types of fibers showed negative results in the intrapleural test and low durabilities in the organism (Table 3). The AGS reevaluates and usually approves the proposals of the MAK Commission. These become legal after being published by the Federal Minister of Labor in Bundesarbeitsblatt. The AGS sets OELs for carcinogens by considering available chemicals as well as consideration of available techniques to minimize and control exposure.
technical measures to reduce exposure as well as relevant information from toxicology, occupational medicine, and hygiene. The AGS is required to apply the legal regulations of the European Union (EU) and therefore uses the EU criteria 1 or 2 and 3a or 3b to classify carcinogens (Figure 1).

For MMMF the AGS introduced a semiquantitative procedure based mainly on the results of the intrapritoneal test and the chemical composition of the fibers (15). The concept is as follows: chrysotile or crocidolite fibers at a concentration of 10⁷ to 10⁸ after intrapritoneal application clearly are carcinogenic. Therefore, any fibers that induce tumors at up to 10⁵ fibers are also considered animal carcinogens and are classified as category 2 carcinogens (Table 4), which is equivalent to the MAK classification A2. For example, the special purpose fiber M-475/104, which is similar to man-made vitreous fiber(s) (MMVF)11 and MMVF21, is classified as a category 2 carcinogen. Examples are listed by the Bundesministerium für Arbeit und Soziales (15).

Fibers for which equivocal results at 10⁶ fibers but for which clearly positive results at up to 5 × 10⁵ fibers are available are considered weak carcinogens and are classified as 3a carcinogens (Table 4). An example is the B-0,9-2,0 fiber. Negative results at 10⁶ fibers are not a criterion for classification. So far no examples are available for this group.

When no data from animal experiments are available, glass fibers are classified according to the so-called index of carcinogenicity (K) (15):

\[ K_i = \sum (Na_2O, K_2O, B_2O_3, CaO, MgO, BaO) - 2 \times Al_2O_3 \]

This is based on the observation that the content of Al₂O₃ affects the durability of a mineral fiber (21). A high content of Al₂O₃ correlates with high durability of a fiber.

The chemical composition (weight percent oxide) of various fibers and their semiempirically estimated carcinogenic potency were compared. Accordingly, fibers with an index of carcinogenicity below 30 are classified as category 2 carcinogens and those with an index between 30 to 40 as category 3 carcinogens: those with carcinogenic indices higher than 40 are not classified. This procedure has not yet been applied in practice (Table 5). However, the TRK of 500,000 fibers/m³ (0.5 fibers/ml) has been set by using technical data on the usual exposure concentration at different workplaces. This regulates the exposure concentrations of critical fibers (14).

International Agency for Research on Cancer

In 1988 the IARC classified glasswool, rockwool, slagwool, and ceramic fibers as possibly carcinogenic to humans (group 2B). This classification was made on the basis of the following:

- Sufficient evidence for the carcinogenicity of glasswool and ceramic fibers is provided by animal data; human data were evaluated inadequate for glasswool. No data were available for ceramic fibers.
- Limited evidence for the carcinogenicity of rockwool is provided by animal experiments and human data.
- Inadequate evidence exists for the carcinogenicity of slagwool in animal experiments; there is limited evidence from human data.

Glass filaments cannot be classified with regard to their carcinogenicity to humans (group 3) because of inadequate evidence from animal and human data (5).

The Netherlands

The Dutch Expert Committee on Occupational Standards (DECOS) proposed OELs for MMMF (2). DECOS evaluated the carcinogenic potency of MMMF at the OEL (Table 6). For glasswool fibers, DECOS used the rat study of LeBouffant et al. (22), which showed that a 12- to 24-month exposure of respirable glasswool fibers at a concentration of 5 mg/m³ 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 to this exposure concentration to account for the extrapolation from animal to man and for intrindvidual variations, an OEL of 0.5 mg/m³ (4.8 fibers/ml) for respirable glasswool fibers has been proposed (Table 6).

There are many physical and chemical similarities between special-purpose glass fibers and glasswool fibers. No human data are available. Animal data showed that 332 respirable fibers/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 fibers, 10 for the interspecies variation, and 5 for taking an effect level as the starting point (Table 6).

Because DECOS considers the nature of the critical effects of the MMMF of rockwool, slagwool, glasswool, and special-purpose fibers to be very similar, it recommends an equal OEL for respirable fibers/ml for these fibers. This is based on the lowest figure of 3.3 fibers/ml for rockwool.

DECOS considers refractory ceramic fibers, which do not exclude fibers of silicon carbide and silicon nitride, to be carcinogenic on the basis of positive long-term inhalation studies in rodents. Two approaches have been used to set an OEL. Assuming a

| Table 3. Two man-made mineral fibers proposed for occupational exposure limits by the MAK Commission. |
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| Fiber | Animal carcinogenicity | Genotoxicity | OEL mg/m³ |
| Calcium sulfate | — | — | ND 6 |
| Wollastonite | — | — | Not yet established |

Abbreviations: inhal, inhalation; ip, intraperitoneal; ir, intratracheal. Fiber durability of wollastonite is 1 to 2 weeks; calcium sulfate is similar.

| Table 4. German Commission for Dangerous Chemicals classification of man-made mineral fibers based on data from intraperitoneal studies. |
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| Category | Classification |
| Category 2 | Positive after ip application of up to 10⁷ fibers or positive inhalation experiments |
| Category 3 | Positive after ip application of more than 10⁷ up to 5 × 10⁹ fibers |
| Not classified | Positive after more than 5 × 10⁹ fibers |

| Table 5. German Commission for Dangerous Chemicals classification of vitreous man-made mineral fibers in the absence of experimental data. |
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| Category | Classification |
| Category 2 | Index of carcinogenicity ≤ 30 |
| Category 3 | Index of carcinogenicity > 30 to < 40 |
| Not classified | Index of carcinogenicity ≥ 40 |

| Table 6. Occupational exposure limits for man-made mineral fibers, as proposed by the Dutch Expert Committee on Occupational Standards. |
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| Fibers | Respirable fibers/ml | Safety factor |
| Glasswool | 4.8 | 10 |
| Rockwool | 3.3 | 10 |
| Slagwool | 6.6 | 50 |
| Special purpose glass | 3 (0.3 mg/m³) | |
| Common OEL | 1 (3 mg/m³) | 25 |
nongenotoxic mechanism, an OEL of 1 respirable fiber/ml is proposed, which is based on the no observed adverse effect level of 25 fibers/ml. A safety factor of 25 is used to take into account the seriousness of the critical carcinogenic effect. Assuming a genotoxic effect, the acceptable excess cancer risk of \(7 \times 10^{-4}\) corresponds to an occupational exposure of 1 respirable fiber/ml for 8 hr/day for 40 years.

**Evaluations by Other National and International Committees**

To date other committees have not intensively discussed classification or OELs for MMMF (Table 7).

**American Conference of Governmental and Industrial Hygienists**

In 1978 the Threshold Limit Value Commission set a threshold limit value-time weighted average of 10 mg/m\(^3\) for fibrous glass dust. The Commission intended to reconsider this decision when additional long-term data became available (23).

**U.S. National Institute for Occupational Safety and Health**

In 1977 the U.S. National Institute for Occupational Safety and Health set an OEL for fibrous glass dust of 3 fibers/ml for fibers with a diameter \(\leq 3.5\ \mu m\) and a length of \(\geq 10\ \mu m\). Concentrations of total fibrous glass dust are limited to 5 mg/m\(^3\). The Institute considered the carcinogenic effects of glass fibers in animals to be the result of physical rather than chemical factors (24).

**Sweden**

In Sweden the Criteria Group for Occupational Standards considers possible carcinogenic effects, primarily lung cancer, as the critical effects of occupational exposure to MMMF such as glasswool, rockwool, and slagwool. Levels of 0.2 to 2 fibers/ml are expected to be associated with increased risk of lung cancer, but this allows no conclusions about whether lower levels also imply increased risk. Carcinogenicity of ceramic fibers is also considered a probability. An OEL of 1 fiber/ml has been set (25).

**United Kingdom**

The Health and Safety Executive of the United Kingdom recommended a maximum exposure limit of 5 mg/m\(^3\) in 1992. For superfine fibers the limit is 1 fiber/ml. No details are given (3).

**Outlook**

At present, classification of MMMF dusts and proposals for exposure control levels are rarely scientifically based. In most instances classification as a carcinogen is qualitative and does not consider the carcinogenic potential of the material. Proposals for OELs are based on the NOELs observed in inhalation studies. In both instances neither toxic mechanisms nor species/species extrapolations from rodents to man are considered. To date the scientific community has contributed little toward improvement of these criteria. Although many short- and long-term experiments using different routes of exposure have been performed, only a few have investigated mechanisms of the lesions observed and the dose-response relationship. Evaluations of the carcinogenic potentials of dusts and the relevance of such effects on humans exposed at the workplace or in the environment will be considerably improved when more information becomes available in the following areas.

**Toxic and Carcinogenic Mechanisms**

There is evidence that pulmonary inflammation-generated reactive oxygen species is one of the primary events of fiber toxicity. These reactive oxygen species might originate by Fenton reactions in the presence of iron liberated from the inhaled material or from ingestion of fiber material by macrophages. Since cellular systems efficiently inactivate reactive oxygen species, the inactivating capacity of this system could be overwhelmed by increasing amounts of fiber material, which could explain dose-dependent biological responses observed in both animal inhalation and injection studies. A better understanding of these processes as well as of lung clearance mechanisms and molecular biological responses to inhaled particles could improve the scientific basis for evaluating the relevance of data from animal experiments as related to man (26).

**Standardized Diagnosis of Toxic Lesions**

Dusts of particles and other inert materials, e.g., talc, titanium oxide, quartz, diesel exhausts, and certain fibers, induce keratinizing lesions in the rat lung with many morphological similarities. On the initiative of the German MAK Commission and with the support of the Deutsche Forschungsgemeinschaft, a group of pathologists reviewed and discussed the histopathologic alterations found in 13 long-term inhalation studies on 11 different materials. The outcome of this review has recently been published (27), and will lead to reevaluation of the studies using commonly applied diagnostic criteria. A reevaluation of the \(p\)-Aramid-induced lesions in rat lung has already been carried out (28).

**Role and Definition of Durability**

Durability of fibrous material in the organism is considered a determinant of carcinogenic potency. A better understanding of the parameters that affect durability and durability's impact on the carcinogenic efficiency of the material is required before these criteria can be applied for risk assessment.

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**Table 7. Levels of occupational exposure to man-made mineral fibers established by different committees.**

| Committee | Occupational exposure level | Remarks |
|-----------|----------------------------|---------|
| American Conference of Governmental and Industrial Hygienists, 1978 | 10 mg/m\(^3\) | Fibrous glass dust |
| National Institute for Occupational Safety and Health, 1977 | 5 mg/m\(^3\) | Total fibrous glass |
| | 3 fibers/ml | Fibrous glass (diameter \(\leq 3.5\ \mu m\); length \(\geq 10\ \mu m\)) |
| Germany, 1995 | 0.5 fibers/ml | Fiber dusts (diameter \(< 3 \ \mu m\); length \(> 5 \ \mu m\); length/diameter \(> 3:1\)) |
| Sweden, 1988 | 1 fiber/ml | Synthetic inorganic fibers |
| United Kingdom, 1992 | 2 fibers/ml | MMMF |
| | 1 fiber/ml | Superfine fibers |
| The Netherlands, 1995 | 3 fibers/ml | Respirable fibers (length 5–200 \(\mu m\); diameter \(< 3 \ \mu m\); length/diameter at least 3:1) |
| The Netherlands, 1995 | 1 fiber/ml | Refractory ceramic fibers |
Role of Chemical Composition

The release of ions, such as iron, attached to the material or during solubilization may contribute to toxic effects (29). A better understanding of the role of these factors in fiber toxicity will greatly improve the understanding of mechanisms involved.

Much information on these aspects is already available and has been presented during this symposium. Unfortunately, most of the information is qualitative and usually describes effects at very high exposure concentrations to unequivocally observe the effect. Such information will become useful for toxicologic evaluation when additional data on the dose response is available for understanding the susceptibility of the biologic system to toxic stress and possibly for identifying an NOEL.

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