GENERAL REMARKS ON MAN-MADE VITREOUS FIBRES

This eighty-first volume of *IARC Monographs* considers certain man-made vitreous (glass-like) fibres of highly variable composition that are widely used for thermal and acoustical insulation and to a lesser extent for other purposes. The generic term, man-made vitreous fibres (MMVFs), denotes non-crystalline, fibrous inorganic substances (silicates) made primarily from rock, slag, glass or other processed minerals. These fibres, also called man-made mineral fibres, include glass fibres (used in glass wool and continuous glass filament), rock (stone)/slag wool and refractory ceramic fibres. Rock (stone) wool, slag wool and glass wool are used extensively in thermal and acoustical insulation, typically in buildings, vehicles and appliances. The refractory ceramic fibres are designed for high-temperature applications, mainly in industrial settings. Continuous glass filament is used primarily in reinforced composite materials for the insulation, electronics and construction industries. These substances were evaluated by a previous IARC Working Group (IARC, 1988) (Table 1). Since these evaluations, new data have become available, which have been incorporated into the monograph and were taken into consideration in the present evaluations.

Man-made vitreous fibres have some physical similarities to asbestos, in particular, their fibrous character which gives them the same aerodynamic properties and leads to their deposition throughout the respiratory tract. Unlike amphibole asbestos, however, they are synthetic and amorphous, and generally have a lower biopersistence in lung tissues. Also, unlike serpentine asbestos, they tend to break transversely rather than cleaving along the fibre axis.

Inhaled asbestos fibres can cause two quite different malignancies in humans: malignant mesothelioma, which arises from the lining of the body cavities, and carcinoma of the lung, which arises from pulmonary epithelial cells (IARC, 1987). Epidemiological studies of human populations exposed to MMVFs have therefore focused on these two types of cancer.

The mechanisms of carcinogenesis by inhaled fibres and the use of data on these mechanisms in the identification of carcinogenic hazard have been reviewed by Kane *et al*. (1996).

Table 1. Previous evaluations[a] of agents (names as used in Volume 43) considered in this volume

Agent[b]	Evidence for carcinogenicity		Overall evaluation of carcinogenicity to humans
	Human	Animal	
Glasswool	I	S	2B
Glass filaments	I	I	3
Rockwool	L	L	2B
Slagwool		I	2B
Ceramic fibres	I (no data)	S	2B

S, sufficient evidence; L, limited evidence; I, inadequate evidence; Group 2B, possibly carcinogenic to humans; Group 3, cannot be evaluated as to its carcinogenicity to humans

[a] *IARC Monographs* Volume 43 (IARC, 1988)

[b] See section 1.1.1(*a*).

1. Composition, production and use

The compositions of individual MMVF products were historically driven by production technology, the availability of raw materials and, more importantly, the intended use and the temperature ranges over which the products were designed to operate. During the period 1940–1980, changes in product formulation were introduced as production methods were improved or alternative raw materials became available. Most of these changes represented minor modifications to basic product formulations, but more significant changes took place in the early 1990s. In recognition of concerns over the possible adverse health effects of the fibres released from MMVF products and in response to governmental regulations, some manufacturers altered the chemical compositions of their products to enhance their solubility in biological systems. Other manufacturers developed completely new products (e.g. alkaline earth silicate wools and high-alumina, low-silica wools) to achieve the same effect. These products have become commercially available so recently that no relevant epidemiological data have yet been published.

A large experimental database is available on many fibre compositions, although inevitably the number of epidemiological studies on fibres is limited. For new fibres with compositions that differ considerably from those of the older fibre types, studies of toxicity and determinations of biopersistence are required for evaluations of possible inhalation hazards.

2. Toxicity

The end-points used in short-term toxicity studies range from inflammation in experimental animals *in vivo* to cytotoxicity and cell activation *in vitro*. In-vitro assays vary in duration from hours to a few days at most. During long-term residence in the lung, some non-biopersistent fibres undergo changes that act to dissolve, shorten or otherwise decrease the biological activity of the long fibres. This decrease in biological activity would not be detected in short-term assays and it would be difficult to extrapolate these assays to predict long-term effects.

3. Chronic inflammation, fibrosis and cancer

Chronic inflammation and increased turnover of epithelial cells are features of human cancers that are associated with chronic infections in the liver, gastric mucosa and colon (IARC, 1999). Chronic or persistent inflammation, especially in the lung, is frequently accompanied by progressive fibrosis in humans with idiopathic pulmonary fibrosis (reviewed by Samet, 2000); a sevenfold increase in incidence of lung cancer was reported in a recent cohort study of a population with idiopathic pulmonary fibrosis, although confounding by cigarette smoking could not be ruled out (Hubbard *et al.*, 1999).

In chronic inhalation assays of particulate materials in rodents, chronic inflammation and fibrosis almost always precede the development of lung cancer (Davis & Cowie, 1990). Chronic inflammation may contribute to the initiation, promotion and progression of tumours by several mechanisms. Firstly, inflammatory cells release reactive oxygen and nitrogen species that may lead to DNA damage in adjacent parenchymal cells. Secondly, inflammatory cells may release mediators such as cytokines, growth factors and proteases that may alter proliferation, differentiation and migration of preneoplastic cells (reviewed by Coussens & Werb, 2001). Activated fibroblasts may play a role in tumour progression by increasing turnover of the extracellular matrix which may also alter the adhesion, differentiation, proliferation and motility of epithelial cells. Active fibrosis is often accompanied by angiogenesis that may provide a favourable local environment for growth and invasion of developing tumours (reviewed by Tlsty, 2001). Although the experimental evidence for these processes in the pathogenesis of human lung cancer is currently limited, these proposed mechanistic links between chronic inflammation, fibrosis and cancer provide a plausible biological mechanism for lung carcinogenesis by fibres.

4. Studies of cancer in humans

Since the publication of the previous *IARC Monographs* on MMVFs (IARC, 1988), there have been substantial improvements in the quality of the epidemiological information available for the evaluation of the carcinogenicity of glass fibres,

continuous glass filament and rock (stone)/slag wool. The new investigations have addressed the limitations of the earlier cohort studies of workers exposed to MMVFs from the United States of America and Europe, particularly concerning the lack of adjustments in these studies of lung cancer risk to take into account concomitant risk factors such as smoking and other sources of occupational exposure.

These studies, like all epidemiological investigations, have limitations that must be borne in mind when interpreting their results. Although the methods of exposure assessment used in these studies are far better than in most, there is still the potential for exposure misclassification. Most notably these studies were not able to examine fully the risks to workers who were exposed to the more durable fibres, which appear to be more hazardous based on toxicological studies. Information on smoking and on the other potential confounders that were adjusted for in these studies was also subject to measurement error, which may have influenced the validity of the adjustments made. Underascertainment and misclassification of mesothelioma were possible in these studies, since they relied primarily upon information from death certificates. Finally, although these studies were very large by epidemiological standards, their sensitivity may have been limited by the low concentrations of fibres to which a large proportion of the study population was exposed.

There is some concern that workers in industries that use or remove products containing MMVFs (e.g. construction workers), may have experienced higher, but perhaps more intermittent exposure. The data available to evaluate risks for cancer from exposure to MMVFs in these workers are very limited.

The results of studies on mortality among workers in the refractory ceramic fibre industry have also been published since the last IARC Monograph. However, the epidemiological data for refractory ceramic fibres are still very limited. Radiographic evidence indicating pleural plaques has been reported for refractory ceramic fibres workers. Although the prognostic significance of pleural plaques is unclear, such plaques are common in workers exposed to asbestos.

5. Studies of cancer in experimental animals

The carcinogenicity of fibres in experimental animals has been studied using very different routes of administration, i.e. inhalation, intratracheal instillation or intracavitary injection. There is no general agreement on which of these routes of administration best predicts human cancer risk, but it is known that intraperitoneal injection allows high doses of fibres to reach the target organ.

Muhle and Pott (2000) analysed studies of asbestos inhalation and concluded that the rat inhalation model is not sufficiently sensitive to predict the cancer risk presented by fibre types other than asbestos for humans and proposed that the intraperitoneal injection test be used instead. In contrast, Maxim and McConnell (2001) reported that well-conducted inhalation studies of carcinogenicity are very sensitive and that rats may be more sensitive than humans in detecting the carcinogenic potential of MMVFs.

In a recent statistical analysis of the available data from studies that used intraperitoneal injection, chronic inhalation and measures of biopersistence, Bernstein *et al*. (2001a, b) showed that the studies that used intraperitoneal injection provide a ranking comparable to that obtained in studies of carcinogenicity following chronic inhalation of fibres of similar biopersistence and length.

6. Administration to experimental animals by inhalation

Before 1989, a number of inhalation studies on rodents had been conducted to evaluate the biological effects of the different types of MMVF. The results of many of these studies were negative for fibrosis and tumorigenesis even when relatively durable fibres were tested. For example, different results were obtained in two studies of refractory ceramic fibres — one study reported both fibrosis and tumorigenesis while the other reported neither fibrosis nor tumours in rats and mesothelioma in only 2% of hamsters. Many earlier studies did not appreciate the importance of fibre diameter in the respirability of fibres in the rat. In addition, fibres were often ground before administration; this procedure significantly shortened their length and often resulted in exposure of the test animals to primarily short fibres. Thus, it is not surprising that some inhalation studies of amphibole asbestos reported no tumours. The contradictory results of these studies led to a better understanding of the importance of respirability and length of fibres and to the development of new study designs (Hesterberg *et al*., 1993; Bernstein *et al*., 1995).

More recent inhalation studies in rodents have addressed the technological limitations of the earlier studies using test fibres prepared by new size-separation methods. Such fibres are respirable by rats and long enough to be biologically active, with nominal dimensions of 1×20 μm. An aerosolization system has been designed to create uniform, high concentrations of airborne fibres without destroying the biologically important long–thin fibre geometry.

In the chronic inhalation studies of MMVFs reviewed in section 3, the Working Group has clearly noted those studies that they considered to be ‘well-conducted long-term inhalation studies’ which meet the criteria summarized above.

7. Administration to experimental animals by intraperitoneal injection

The potential of asbestos fibres to produce mesothelioma was first demonstrated in animals by the implantation or injection of fibres into the pleural cavity of rats (Wagner, 1963; Wagner & Berry, 1969). Subsequently, Stanton and Wrench (1972) showed by implantation in the pleural cavity, and Pott and Friedrichs (1972) and Pott (1978) by injection into the peritoneal cavity, that fibre shape was important and that fibres can produce tumours if they are sufficiently long, thin and durable. Since then the intraperitoneal injection route has been used more often than pleural implantation due to its relative simplicity.

The intraperitoneal test, in which fibres are injected directly into the intraperitoneal cavity, bypasses the natural route of exposure. Because the lung is bypassed, the natural mechanisms by which the lung removes, dissolves or breaks fibres, thereby reducing or eliminating potential exposure of the pleural cavity, do not operate. Therefore the intraperitoneal test has no physiologically imposed maximum dose to which the animals can be exposed. The intraperitoneal test can indicate whether a fibre should be classified as a carcinogen if a proper positive control is used.

8. References

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