

A review of experimental evidence for the carcinogenicity of man-made vitreous fibers

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DAVIS JMG. A review of experimental evidence for the carcinogenicity of man-made vitreous fibers. *Scand J Work Environ Health* 12 (1986): suppl 1, 12—17. This paper reviews experimental studies on the carcinogenicity of man-made vitreous fibers. Long-term inhalation studies using several animal species and dust preparations of fibrous glass, rock wool or slag wool have produced little evidence of pulmonary fibrosis or pulmonary tumors. While some intratracheal injection studies found almost no pathological changes in lung tissue, some showed that pulmonary fibrosis can occur. Only one intratracheal injection study has reported that vitreous fibers can be carcinogenic; in contrast, many workers have reported that, following intrapleural or intraperitoneal injection, man-made vitreous fibers are highly carcinogenic, and tumor production appears to be closely related to fiber size. In vitro tests confirm that vitreous fibers can be toxic and can cause neoplastic transformation of cultured cells. The discrepancies between some experimental studies probably result from the relatively high solubility of most vitreous fibers. It seems likely that, while these fibers can survive in body cavities long enough to cause tumor production, they dissolve in lung tissue fast enough to have relatively little harmful effect. Rock-wool fibers appear more durable than glass- or slag-wool fibers, and, with similar fiber numbers and sizes in any dust cloud, this material is the most likely to have harmful potential.

Key terms: experimental studies, mineral fibers, man-made.

Following the realization that exposure to high concentrations of asbestos fibers could result in the development of pulmonary carcinomas and mesotheliomas in humans, many industrial users of asbestos began to consider the replacement of this group of minerals with a variety of substitutes. Of necessity most of the substitutes had to retain a fibrous form similar to asbestos, and it was important to determine whether or not their industrial use would also represent a hazard. This problem became particularly important following publication of a report by Stanton & Wrench (39) on pleural implantation studies with a number of fibrous dusts. This work suggested that the shape of fibers was the main factor in carcinogenesis and that glass fibers were as carcinogenic as similarly sized asbestos. This was not the first experimental study involving nonasbestos fibers, but its findings did stimulate a very large amount of new experimental work on the effects of man-made mineral fibers (MMMF) which has continued until the present day. This review examines the data so far accumulated and discusses the likely implications of the findings in relation to human industrial exposure.

Long-term animal inhalation studies

Inhalation studies in which experimental animals are exposed to mineral fibers for a long period and then followed for the rest of their life-span represent the most realistic method of examining the carcinogenic potential of any fiber. This type of study is, however, complicated and expensive to undertake, and to date relatively few workers have used the technique to examine the effects of man-made vitreous fibers.

The earliest inhalation studies were reported by Schepers (29), and the work was continued for a number of years with further publications in 1959 (30, 31), 1961 (32), and a final résumé in 1976 (33). Rats, guinea pigs, rabbits, and monkeys were exposed to dust from glass-wool or glass-fiber reinforced plastics at dose levels from 0.1 to 5 mg/m³. Mean fiber diameters were close to 5 µm although 20 % of the fibers were < 2 µm in diameter, and of these 70 % were longer than 5 µm. No pulmonary tumors were reported in any species, and it was claimed that the dusts were not fibrogenic. In all cases however there was some infiltration of alveolar walls by macrophages containing glass fibers, and in areas where this infiltration occurred there was septal thickening with an increase in reticulin staining.

Gross and his co-workers (12, 13), in 1970 and 1976, reported studies in which rats and hamsters were exposed for two years to very high doses of glass fiber (100 mg/m³). Uncoated glass, as well as samples coated with resin or stock binder, was tested, and the fibers in the dust cloud had a mean length of 10 µm and a mean diameter of 0.5 µm. No fibrosis or pulmonary tumors were found with any of the dusts, and histo-

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logical changes were limited to those expected from an inert dust, the lung macrophages containing many glass fibers.

In 1979 Lee et al (19) reported inhalation studies in which rats and hamsters had inhaled a glass-fiber preparation (average diameter 1.2 μm) for 90 d with a full life-span follow-up. The dust exposure levels were extremely high at approximately 400 mg/m^3 , but only 15 % of the dust particles were fibrous (aspect ratios $>3:1$), and most of these were $<5 \mu\text{m}$ in length. The major pathological lesion found in both species was alveolar lipoproteinosis. Very slight alveolar interstitial fibrosis occurred in a few old animals, but no pulmonary tumors developed. This work was updated in 1981 (20) when guinea pigs were included and two pulmonary adenomas were found in both the rats and guinea pigs treated with fiber glass.

In 1982 the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) sponsored a symposium on the biological effects of MMMF, and at this meeting the results of a number of long-term animal inhalation studies were presented. Le Bouffant et al (18) had treated rats with samples of French commercial glass wool and rock wool and an American-produced microfiber (Johns Manville code 100). The dose level was 5 mg/m^3 , and animals were exposed for either 12 or 24 months. Because of diameter differences and the proportion of particulate material present, the numerical concentrations of the fibers $>5 \mu\text{m}$ in length, as seen by light microscopy, varied from 11/ml with rock wool to about 300/ml with microfiber. All three dusts produced some areas of moderate septal reticulin fibrosis in old animals although these areas appeared less markedly with rock wool. One animal treated with glass wool developed a squamous carcinoma.

Smith et al (35) reported studies in which rats and hamsters had been treated by nose only exposure for 24 months to glass fiber (mean diameter 0.45 μm) at dose levels of 800 and 80 fibers/ml ($>5 \mu\text{m}$ in length by light microscopy). While small amounts of pulmonary fibrosis and bronchoalveolar hyperplasia were found in some animals, these did not exceed the levels in controls. No pulmonary tumors were found in the animals treated with glass fiber.

Wagner et al (44) reported a large series of studies in which rats were exposed for either 3 or 12 months to glass microfiber (Johns Manville code 100), glass wool, and rock wool. The respirable dust mass was 10 mg/m^3 in all cases. The number of fibers $>5 \mu\text{m}$ in length ranged from 227/ml for rock wool to 1 436/ml for microfiber. Small amounts of pulmonary fibrosis and an occasional pulmonary tumor (either one or two per test group of 48 rats) were found with all the MMMF types. In a closely linked study McConnell et al (22) treated rats with the same glass microfiber preparation but achieved only half the cumulative dose of Wagner's group. They found neither pulmonary fibrosis nor tumors.

While most researchers have limited their studies to small laboratory rodents, Goldstein et al (11) exposed baboons to respirable clouds of glass microfiber (Johns Manville code 102 and 104). The dose level was approximately 1 100 fibers/ml ($>5 \mu\text{m}$ in length by light microscopy), and dusting was continued for up to 35 months with a further survival period of at least 12 months. Slight but definite pulmonary fibrosis was found, increasing in severity with postexposure time, but no pulmonary tumors developed.

Injection studies

The earliest studies involving the injection of glass fiber were reported by Vorwald et al in 1951 (43). A preparation of glass wool had been included in a large series of dusts injected intratracheally into guinea pigs at a dose level of 50 mg. Twelve months after injection there were focal areas of pneumonitis but no pulmonary fibrosis. Schepers in 1976 (33) reported large studies in which rats, guinea pigs, rabbits, and monkeys had been given intratracheal injections of a number of glass-fiber preparations. A high mortality was found for the injected animals and a "severe lung reaction" occurred, particularly in the monkeys. Gross (12), in 1976, found no pathological changes other than macrophage accumulations in rats and guinea pigs injected intratracheally with glass fiber. In 1977 Wright & Kuschner (46) reported on a series of experiments involving the intratracheal injection of carefully sized glass fibers into guinea pigs. Long glass fibers (92 % $>10 \mu\text{m}$) produced a marked fibrotic reaction, while short glass fibers (93 % $<10 \mu\text{m}$) produced no tissue reaction other than macrophage aggregation in the alveoli.

While these intratracheal injection studies failed to produce tumors, the result may have been due to the fact that the dust dose was administered by a single injection, and in some cases the animals were not followed for their full life-span. Pott et al (28) reported the production of both pulmonary carcinomas and mesotheliomas after the intratracheal injection of glass fiber, as well as after asbestos injection. In this series of experiments, however, the hamsters used received eight separate intratracheal injections of dust, a procedure which probably nullified the tendency of glass fibers to dissolve in lung tissue.

The majority of injection studies with glass fiber and other types of MMMF have involved the intrapleural or intraperitoneal injection of these dusts. This work was pioneered by Stanton's group in the United States, who published a series of reports in 1972, 1977, and 1981 (37, 38, 39). All these studies involved the intrapleural implantation of carefully sized samples of mineral fiber and a comparison of mesothelioma production with the number of injected fibers in each size range. The original conclusions suggested that the

most dangerous fiber size was a length of $> 8 \mu\text{m}$ and a diameter of $< 1.5 \mu\text{m}$, and glass fibers of this size range appeared to be as carcinogenic as asbestos. In later papers this work was refined, and by 1981 it was suggested that, provided the required length was maintained, fiber carcinogenicity continued to increase with reducing diameter to as little as $0.25 \mu\text{m}$. Other groups, including Pott and his co-workers (25, 26, 27), Davis (7), and Wagner et al (44, 45), soon confirmed that glass fiber was extremely carcinogenic when injected into the pleural or peritoneal cavities of experimental animals, and Pott and Wagner included samples of rock wool and slag wool in their later studies. The work of Pott in particular has confirmed the ideas of Stanton about the importance of long thin fibers in tumor production but has indicated that fiber durability, as well as the initial fiber dimensions, is important. From these animal studies it would appear that the glass fibers used were more carcinogenic than rock wool or slag wool. The results for rock wool were not surprising since the fiber diameter was quite large, but the slag-wool preparation contained over 90 % fibers in the supposedly most dangerous size range, and it was suggested that their relative failure to produce tumors was due to a lack of durability within the tissues.

In vitro studies

In vitro treatment of cells with dust particles has been used by many workers in exploring mechanisms of cell damage and in attempts to devise short-term tests to predict the relative pathogenicity of different mineral types. Glass fibers have been shown to produce hemolysis (40) and to be toxic to pulmonary and peritoneal macrophages (1, 2, 4, 6).

Tilkes & Beck (41, 42) showed that this macrophage toxicity was length dependent for a number of samples of glass fibers and obtained similar results using rat mesothelioma cells, which are also highly phagocytic. In vitro tests with phagocytic cells are usually considered to predict the initial toxic effects of mineral fibers and perhaps their fibrogenicity but do not necessarily relate to their carcinogenicity. Chamberlain & Brown (4), in 1978, tested a number of fiber samples including glass fiber (Johns Manville code 100 and 104) on nonphagocytic cells, as well as macrophages. They found that the colony-forming ability of V79/4 cells (Chinese hamster lung fibroblasts) was reduced by treatment with glass fiber and the mean cell diameter of A549 cells (human alveolar type II cells) was increased. Since these cells were not sensitive to quartz dust, which is extremely toxic to phagocytic cells, the authors suggested that the A549 and V79/4 test systems might be useful predictors of fiber carcinogenicity. That glass fiber, as well as asbestos, could cause chromosome aberrations in cultured cells was demon-

strated by Sincock et al (34), who reported chromosome damage in Chinese hamster cells following treatment with two glass preparations (Johns Manville code 100 and 110). Hesterberg & Barrett (15) found that thin glass fibers, as well as chrysotile and crocidolite asbestos, were able to induce a morphological transformation of Syrian hamster embryo cells in culture, and Oshimura et al (24) reported that these morphological changes were accompanied by chromosome abnormalities. In bacterial tests, Chamberlain & Tarmy (5) were unable to demonstrate mutagenicity in either *Escherichia coli* or *Salmonella typhimurium* following treatment with asbestos or glass fiber.

Durability of man-made mineral fibers in tissue fluids

Some types of mineral fibers can survive in lung tissue for many years, but chrysotile asbestos appears to be much less durable than the amphiboles (14). This lack of durability probably explains the lower pathogenicity of this asbestos type for humans. Spurny et al (36) confirmed that glass fibers could dissolve in lung tissue, and at the WHO meeting on the biological effects of MMMF in 1982 a number of papers were presented which demonstrated that some MMMF are particularly prone to dissolution. Förster (10), Klingholz & Steinkopf (17), and Leineweber (21) all reported studies in which the behavior of MMMF in artificial physiological fluids and water was examined. It was reported that the rate of fiber dissolution showed a range of 40-fold over one series of experiments (21), some types of glass showing the highest solubility and refractory fiber the lowest. In another study (17) slag wool was the most reactive followed by glass wool, rock wool, and basalt wool. It appears that most types of MMMF are softened in physiological solutions, and a gel forms on the fiber surface. This gel is removed in stages and leaves the fiber core free for the next attack by the solution.

That similar reactions occur in lung tissue was confirmed by Morgan & Holmes (23), who reported that, following intratracheal injection of sized glass fibers, marked solubility of the fibers was found during a one-year period. The larger fibers (originally $60 \mu\text{m}$ in length) leached much faster than fibers of 5 and $10 \mu\text{m}$ in length. This phenomenon was attributed to differences in pH between the external environment (long fibers) and the intracellular phagosomes of macrophages which are able to engulf short fibers. In contrast to glass fiber, long rock-wool fibers appeared less soluble. Bernstein et al (3) reported very similar findings, long glass fibers dissolving faster than short ones after intratracheal injection. Similar "etching" of the surface of MMMF in lung tissue was reported by Le Bouffant et al (18) and Johnson et al (16) at the

same meeting. Both glass fiber and rock-wool fibers were etched, but the glass was markedly affected.

Conclusions

Animal studies involving the intrapleural or intraperitoneal injection of glass and other MMMF clearly demonstrate that these minerals can be extremely carcinogenic, and those *in vitro* studies that are thought to predict carcinogenicity confirm that the reaction of MMMF is similar to asbestos. However, long-term inhalation studies, which should give the best prediction of the harmful effects of industrial exposure, have produced less dramatic results. In these studies the MMMF tested show, at the most, very low levels of fibrogenicity and carcinogenicity compared to asbestos. These findings probably result from the low durability of MMMF in lung tissue, and the situation is comparable to that found with the different asbestos varieties. Human epidemiologic studies seem to demonstrate quite clearly that exposure to amphibole is the most hazardous, while experimental studies often suggest that chrysotile can be the most carcinogenic and fibrogenic type of asbestos. The reason appears to be that chrysotile can survive in rat lungs for a sufficient proportion of the animal's life-span to initiate disease, but it is removed from human lungs during the much longer period required for disease initiation in this species. Most asbestos workers are known to have been exposed mainly to chrysotile, yet at autopsy it is common to find mainly amphibole in the lung tissues (14). It would appear that fiber dissolution takes place more slowly following injection into the peritoneal and pleural cavities than in lung tissue, so that a maximum carcinogenic potential of any dust type can be demonstrated by these techniques. Even during the short life-span of laboratory rodents, however, significant dissolution of some fiber types can occur in the lung, and it is the most durable fibers that produce the most serious pathological change in inhalation studies (8, 9). The results of experimental studies with glass and other types of MMMF and epidemiologic studies of exposed human populations fit in well with what one would expect from fibers of dangerous size but low durability. Injection studies have shown high levels of carcinogenicity; inhalation studies have shown, at the most, low fibrogenic and carcinogenic potential, while there is relatively little evidence of significant hazard to humans. The experimental studies do suggest that rock wool might be slightly more hazardous than the less durable glass-wool and slag-wool fibers, but all these fiber types may be removed from human lungs quickly enough to present no hazard at modern exposure levels. If in the future a type of MMMF were developed with a fiber size and durability similar to amphibole asbestos, then it is likely that it would be extremely dangerous in industrial use.

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