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Review Article

Man-made Vitreous Fibers: Present Status of Research on Health Effects

Paul Gross

The Industrial Health Foundation, 5231 Centre Ave., Pittsburgh, PA 15232, USA

Summary. Concerns engendered by inappropriate extrapolation from rat intracavitary cancer experiments stimulated the initiation of new retrospective and prospective epidemiologic studies of man-made vitreous fibers (**MMVF**). The results of these new studies have confirmed those of previous investigations that MMVF exposure had not caused an increased risk to develop lung cancer or nonmalignant respiratory disease.

In contrast to the high pathogenic potential of MMVF (thin long fibers) when injected into the body cavities of rats, the pulmonary reaction of rodents *inhaling* such fibers has been that of a nuisance-type dust. The results of new experimental inhalation studies have not yet been published.

In vitro studies have demonstrated cytotoxicity of thin long MMVF. Although there is a parallelism between the in vitro cytotoxicity results of MMVF and those of the in vivo intracavitary carcinogenesis studies with the same fibers, it is difficult to attach significance to this parallelism insofar as man is concerned because the rat intracavitary carcinogenesis results have no relevance to man.

Key words: Man-made vitreous fibers – Pulmonary reaction – Nuisance-type dust – Rat intracavitary carcinogenesis

Heretofore the climate of opinion regarding the health risk of fiberglass dust was best expressed by the following conclusion in "Documentation of the Threshold Limit Values for Substances in Workroom Air," a highly respected and authoritative publication:

> In light of the preponderant evidence to date, although admittedly still not complete in all detail, of the lack of adverse effects on health of fibrous glass dust of respirable size, a TLV (threshold limit value) of a *nuisance-type dust* of 10 mg/m^3 is recommended ... [6] (emphasis supplied).

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However, with the discovery that the intracavitary implantation of man-made vitreous fibers (MMVF) in rats caused the production of cancers [25], opinions regarding health effects of MMVF became controversial. The specific conclusions were derived from the results of the experiments involving the implantation or injection of insoluble mineral fibers into the chest cavity or abdomen of rats: regardless of chemical composition, the fibers were carcinogenic if their dimensions were within certain limits, i.e., their diameters were less than 1.5 μm and their length longer than 8 μm [25]. Although the development of cancers was limited to rodents, some professionals extrapolated the results to man, thereby generating considerable alarm. Objections that appeared persuasive and valid were made against the extrapolation to man of the rat intracavitary cancer results [14]. Nevertheless, regulatory agencies viewed MMVF with more than suspicion on the basis of admittedly inappropriate extrapolations [22, 23].

The appropriateness of extrapolating from the above intracavitary injection or implantation experiments to man has been contested on the ground that the development of cancer in rats under these circumstances is an example of "solid-state carcinogenesis" which is recognized to have no relevance to man [13]. This denial of relevance of intracavitary cancer production in rodents to man was supported by the Ad Hoc Committee of the National Cancer Institute [20]:

> Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man. *Exceptions should be considered only where the carcinogenic effect is clearly shown to result from physical rather than chemical induction, or when the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure* (emphasis supplied).

NIOSH and OSHA, separately, have also agreed that extrapolation to man from the intracavitary cancer experiments on rodents was inappropriate [22, 23], NIOSH states: "It is not valid to extrapolate from the results of the intracavitary exposures in animals to humans in the workplace."

OSHA's renouncement of the validity of extrapolating from the intracavitary rat cancer experiments is found in the Federal Register of January 22, 1980 [23] where the following statements are found:

> (2) *Tumors induced at site of administration.* Arguments that tumors at the site of administration should not be considered will be considered only if: (i) The route of administration is not oral, respiratory or dermal; and (ii) Evidence is provided which establishes that induction of local tumors is related to the physical configuration or formulation of the material administered (e.g., crystalline form or dimensions of a solid material, or matrix of an impregnated implant) and that tumors are not induced when the same material is administered in a different configuration or formula.

Because of the apprehensions and concern created by the inappropriate extrapolations that were made to man from the rat-intracavitary experiments, new retrospective and prospective epidemiologic studies were initiated on the health of thousands of workers who had been exposed to MMFV; some, for as long as 40 years [7, 8, 19, 21, 24]. In addition, new experimental studies were begun to determine if *inhalation* of thin long MMVF would also result in mild peribronchiolar fibrosis as did the intratracheal injection of such fibers [17], and in vitro studies on the effects of MMVF on cultures of various types of mammalian cells were started [2, 4–6, 10].

Epidemiologic Studies

Recent retrospective studies on the health of workers in factories producing MMVF [7, 8, 19, 21, 24] have reinforced the findings of previous investigations [16] on fiberglass workers by demonstrating conclusively that long-term exposures to MMVF in factories producing these fibers have caused no increased risk of lung cancer, nor have these exposures been associated with the development of mesothelioma—the cancer found in rats which had been subjected to the intracavitary deposition of MMVF.

A preliminary report of the mortality patterns and occupational exposures of a cohort of mineral wool production workers by a group of NIOSH investigators [21] was concerned with a cohort of 702 white males who had had at least 1 year of employment beginning January 1, 1940. They were traced through 1974. There were 199 deaths, of which 181 were traced. The SMR (Standard Mortality Rate) for all malignancies was found to be 98 and for nonmalignant respiratory disease (NMRD), 90. When these were broken down into specific diseases, it was found that there were excessive deaths, particularly in the category of NMRD other than influenza and pneumonia. However, none of the excessive deaths was statistically significant.

A new study of workers in a textile fiberglass plant in the United States included a cohort of 1,423 men who had worked 1 year or more from January 1, 1945 through December 31, 1963 [7]. There were 216 deaths for which death certificates were found (96%). The SMR for all causes was 88.3; for all cancers, 88.7; for NMRD, 48.3; and for respiratory tract cancer, 65.8. It was concluded that the workers exposed to fibrous glass suffered no excess in mortality from malignant or nonmalignant respiratory disease.

A report on the mortality among man-made vitreous fibers workers in the United States, still unpublished [8], involved a cohort of 7,049 males who had worked 1 year or more in manufacturing during 1945 through 1963 in three fiberglass plants and three mineral wool plants. Also included were men who had worked 6 months or more during that period in two plants producing glass fibers of very small diameter. The mortality was determined through 1973. A total of 1,006 deaths was identified, but death certificates were not located on 39 of these. The SMR for all causes was lower than expected based on U.S. white male mortality experience. The SMR for respiratory cancer was 88.6 based on 54 deaths. For one of the mineral wool plants which may have used asbestos in the manufacture of some products, the SMR for respiratory cancer was 393.7. The relationship between respiratory cancer and exposure to MMVF is therefore unclear in this group. There is no evidence of an excess in respiratory cancer related to MMVF in five fibrous glass plants and in two of the three mineral wool plants studied. There were 30 deaths caused by NMRD. The SMR for this category was 105.7. The SMR was 99.0 in the fiberglass plants and 129 in the mineral wool plants. The overall excess deaths among mineral wool plants was attributable to one plant (SMR 175.4). This was not the plant with the excess in respiratory tract cancer. None of the excess deaths from NMRD was statistically significant. There was no clear evidence of excess in NMRD related to MMVF. The deaths in two fiberglass plants producing very fine fibers provided no evidence that exposure to very fine fibers

was related to malignant or nonmalignant respiratory disease. However, this conclusion is somewhat tenuous because the number is small.

The fiber exposure of rock and slag mineral wool production workers at a plant which had been in operation since the early 1900s was studied by NIOSH investigators [24]. The authors concluded that their findings corroborated those of epidemiologists who had conducted an earlier mortality study of men employed in four mineral wool plants [7]. No excess in mortality from malignant or nonmalignant respiratory disease was found.

Another recent study of fiberglass production workers involved 6,536 men who had been employed for 10 or more years [19]. A special component of this study included 1,222 men with 20 or more years of employment and 30 or more years latency. It was concluded that the mortality pattern of the fiberglass production workers was considerably lower than comparable U.S. patterns. Long-term workers' mortality was similar to that of the men employed for shorter periods.

Animal Studies

Ten years ago it was reported that the inhalation of fiberglass caused no pulmonary fibrosis in rats or hamsters [10, 12]. The results of this investigation were often ignored because although the diameter of the fibers was well within the pathogenic range (0.6 μm), the average length of the fibers was only 10 μm, a length considered to be at the lower end of the spectrum capable of inducing fibrosis or carcinogenesis. Little or no consideration was given to important additional data included in the paper, namely, that the range of lengths extended from 5 μm to 20 μm and that the dust concentration was very high, about 95 mg/m^3. Since the average length of the fibers was 10 μm and the range of lengths was 5–20 μm, one-half of the fibers were 5–10 μm long and one-half, 10–20 μm long, the latter length generally believed to have considerable pathogenic potential. The significance of these data is that exposure to high concentrations of glass fibers with dimensions considered to be within the pathogenic range did not cause pulmonary fibrosis in animals *when inhaled.*

On the other hand, an investigation published 6 years after the above inhalation study, dealing with intratracheal injections in guinea pigs of asbestos and glass fibers that had specified diameters and lengths, demonstrated that long, thin glass fibers caused slight peribronchiolar fibrosis compared with severe fibrosis resulting from asbestos fibers [17]. The diameter of the glass fibers was substantially below 1 μm and the length was longer than 10 μm in 92% of the fibers in one group and in 50% of the fibers in another group. This demonstration of mild peribronchiolar fibrosis in guinea pigs injected intratracheally with thin, long glass fibers is in apparent conflict with the reported lack of fibrosis in the lungs of rats and hamsters exposed by inhalation to high concentrations of glass fibers, 50% of which had dimensions generally held to be within the pathogenic range. The authors of the above guinea pig study suggested a possible explanation of the conflicting results:

> It must be conceded that the conditions of the experiment, that is, intratracheal injections, are highly artificial. (Indeed, as artificial as intrapleural instillation.) It produces an uneven dose and therefore an extraordinarily high local dose. It also produces aggregates which lodge unnaturally in larger air passages. Obviously, an inhalation experiment of improved design incorporating the use of carefully characterized fibers is now required [17].

New experimental studies have been initiated here and abroad to determine if rats exposed by inhalation to thin glass fibers of specified lengths (longer than 10 μm) would also suffer peribronchiolar fibrosis. Some of these studies have been in progress for more than 2 years but the results have not yet been published. One study, conducted at the Atomic Energy Research Establishment at Harwell, U.K., led to the conclusion that alveolar deposition decreases steeply (from about 13% to about 2%) as the aerodynamic diameter of fibers increases from 2 to 3 μm and that for fibers with the same diameter, this deposition decreases with increasing fiber length [18]. This finding is in agreement with the results obtained by Harris and Timbrell [15] and the graphs derived from their work [14] where the highest alveolar deposition was found to be about 18% by number for glass fibers 0.5 μm in diameter and 10 μm long. Glass fibers 20 μm long have an alveolar deposition probability of 2%, 4%, and 10% if their diameters are 2, 1.5, and 1.0 μm, respectively. Glass fibers 40 μm long have an alveolar deposition probability of only 1%, 2%, and 6% for diameters of 2, 1.5, and 1.0 μm, respectively.

Regardless of the dearth of information on the effects of inhaled long, thin glass fibers in the lungs of animals of the experiments now in progress, it appears that the intratracheal injection technique causes excessively high (extraordinarily high [17]) local deposits or aggregates that do not occur when the same fibers are inhaled. The peribronchiolar fibrosis obtained in guinea pigs by the intratracheal injection technique is also in conflict with the documented absence of increased risk of nonmalignant respiratory disease in man [7, 8, 19, 21, 24].

In Vitro Studies

The theory that the pathogenicity of insoluble fibers resides in their dimensions and not in their molecular composition has stimulated much interest in testing these fibers for cytotoxicity. In vitro studies, in general, have served to demonstrate by means of various criteria that thin long glass fibers are toxic to mammalian cell cultures. Comparisons of this toxicity with the available data on the potential of glass fibers to produce intracavitary cancers in rats, pointed to the conclusion that a positive relationship exists between the demonstrated cytotoxicity and the carcinogenic potential of these fibers for rats. Also, a parallelism has been suggested between the cytotoxicity of thin, long glass fibers and their ability to produce peribronchiolar fibrosis in guinea pigs upon intratracheal injection.

Although neither asbestos nor glass fibers caused mutagenesis in bacterial cultures [5], when tested against macrophage cultures, glass fibers produced an increase in cell-membrane permeability as measured by the amount of LDH in the medium [2]. The conclusion was:

> A non-specific effect on cell membrane due to the slow and sometimes incomplete process of ingestion of long fibers is probably a function of the morphology, particularly the length of the fibers.

Dust	Number of fibers per gram
110T	9×10^9
110R	25.2×10^9
100T	54.5×10^{10}
100R	78.2×10^{10}

Table 1[a]. Calculated number of glass fibers per gram in each of the four glass fiber samples

[a] Modified from Table 2 (ref. [4])
T = total fibers; R = respirable fibers
Code 110 fibers were coarser than Code 100. Approximately 70% of Code 100 fibers were $\leq 0.3\,\mu m$ in diameter whereas only 29% of Code 110 fibers were $\leq 0.3\,\mu m$ in diameter

In a more recent investigation two grades of glass fibers were tested for their effects on cell cultures [3]. The results indicated that Code 100T fibers with only 4.9% of the fibers $\geq 10\,\mu m$ long and $\leq 1.6\,\mu m$ thick were much more active than Code 110T fibers that had 41.67% of the fibers $\geq 10\,\mu m$ long and $\leq 1.6\,\mu m$ thick by the following criteria:

A. Greater cytotoxicity
B. Greater inhibition of growth (cloning)
C. Greater cell enlargement
D. Greater release of enzymes from cells (LDH and β glucoronidase)

Although these data seem to contradict the hypothesis that thin, long fibers are biologically more active, the authors calculated that Code 100T contained more than 60 times the number of fibers per unit mass than did Code 110T (Table 1). Therefore, on the basis of the number of fibers to which each cell was exposed, the results were considered supportive of the hypothesis. The authors concluded, "It is likely that in the system used in the present paper, fibers less than $10\,\mu m$ long are inactive."

In a conference report on an international workshop dealing with in vitro effects of mineral dusts [9], it was concluded that:

> The size of fibres which determined the *in vitro* activity was similar to those reported by Stanton and Layard (1978) as causing pleural tumours in rats.
>
> The absence of cytotoxicity in these cell cultures is probably indicative of the inert nature of a dust. However, a cytotoxicity response indicates that the dust may be fibrogenic.
>
> At present the validation of these tissue culture systems is based on empirical correlations with *in vivo* data. Clearly, before these systems can be generally accepted or relied upon, more work is necessary concerning the mechanism of interaction between dusts and cells both *in vivo* and *in vitro*.

Another recent study of vitreous fibers showed that glass wool as well as rock and slag wool are cytotoxic, although not as much as crocidolite [4]. The criterion of cytotoxicity was enlargement of the diameter of tissue culture cells greater than $25\,\mu m$. The conclusions were as follows:

> Our experience to date is that fibrous dusts which are cytotoxic in these *in vitro* systems are those which produce mesotheliomata in experimental animals; nonfibrous dusts are not toxic in these systems.
>
> At this state it is not possible to judge the significance of these results to the assessment of hazard to man, but we expect that these samples will produce a small number of tumours in experimental animals following intrapleural inoculation.

These conclusions appear reasonable inasmuch as these in vitro results obtained with glass fibers are incongruous with the results of an animal inhalation study with thin, longish fibers [16]. Considerable emphasis has been put on the parallelism between cytotoxicity of fibers and the production of mesotheliomata in rats by the intracavitary deposition of fibers. Since the production of intracavitary tumors in rats has no relevance to man [13, 22, 23], one can be sceptical of the significance or value of a test that relies so much on a comparison with results that are irrelevant.

Because of the obvious demonstrated differences in the results of epidemiologic studies on asbestos-exposed workers and the results of such studies on workers exposed to man-made vitreous fibers, it would be inappropriate to lump the health effects of these two different kinds of fibers regardless of similarities in their geometry. The statement that the cytotoxicity of a fibrous dust suggests that it may be fibrogenic to man is certainly correct for asbestos. However, there are recent investigations [7, 8, 19, 21, 24] which indicate that the suggested parallelism between the demonstrated cytotoxicity of glass fibers and their fibrogenicity is not applicable to man, even though mild fibrosis was produced in the lungs of guinea pigs by the intratracheal injection technique [17]. There is no question but that glass fibers, regardless of size, will cause a fibrogenic reaction when embedded in animal tissues. This, however, is a tissue reaction characteristic and common to all insoluble foreign solid materials, and it does not necessarily have any bearing on the reaction of the alveolar membrane to these materials when inhaled.

The insolubility and, hence, the durability of fine glass fibers in lung tissue has recently been questioned. The as yet unpublished results of investigations conducted at the Brookhaven National Laboratory have demonstrated that thin glass fibers undergo statistically significant reductions in diameter during an 18-month sojourn in the lungs of rats (DM Bernstein, Written communication to Jon L. Konzen, M.D., dated June 26, 1981). Earlier, Wright and Kuschner [27] had also questioned the durability of long, glass fibers compared to the durability of asbestos:

> In the experiments in which long glass fiber was introduced (into the lungs) a surprising amount of short fragments of fibers appeared in the lymph nodes. This fragmentation is confirmed by electron micrographic studies of ashed lung and lymph nodes of animals in which long fibers had been introduced.

It may be of interest to mention that a flaw has appeared in the hypothesis that only the geometry of a fiber and not its chemical composition determines its biologic activity. This flaw resides in the finding that when the magnesium content of chrysotile fibers is leached out, the fibers will have lost much of their pathogenic potential in spite of the fact that their geometry remains unchanged [19]. That the fiber geometry remained unchanged is suggested by the similarity of the side-by-side electron micrographs of the leached and unleached chrysotile as well as by the

observation that "there was no evidence that the leached samples fragmented more than the unleached *in vivo*" [19]. However, these relatively short-term observations from animal experiments (lifetime of the rat) do not necessarily controvert the suggestion that chrysotile fibers may fragment and disappear by dissolution in human lungs during a sojourn of decades.

Conclusions

Inappropriate extrapolation to man from intracavitary cancer experiments on the rat with man-made vitreous fibers raised concern and apprehension regarding the risk to health from the production and use of these materials. This concern stimulated new epidemiologic studies, which included workers not only from fibrous glass producing plants but also from those producing mineral wool; these studies involved many thousands of men who had been exposed to MMVF for as long as 40 years. These investigations confirmed the results of previous studies and concluded that exposure of workers to MMVF has not caused an increased risk to develop lung cancer or nonmalignant respiratory disease. Many of the experimental studies are still in progress.

Attention is drawn to a recent report which indicated that alveolar deposition of glass fibers decreases steeply as the aerodynamic equivalent diameter of the fibers increases from 2 to 3 μm and that for fibers with the same diameter, this deposition decreases with increasing fiber length. From the work of others it was determined that the probability of alveolar deposition of glass fibers 40 μm long is only 1% for fibers 2 μm in diameter; 2% for fibers 1.5 μm in diameter; and 6% for fibers 1.0 μm in diameter. The previous animal experiments were reviewed and the absence of pulmonary fibrosis when longish glass fibers were inhaled was emphasized. The development of slight peribronchiolar fibrosis when thin long fibers were injected intratracheally requires confirmation by inhalation studies which are not yet completed. The authors of the intratracheal injection study suggested that the peribronchiolar fibrosis may be caused by the unnatural technique employed.

In vitro studies have demonstrated that thin, long glass and other vitreous fibers less than 1.5 μm in diameter and longer than 8 μm are cytotoxic. Although there is parallelism between the cytotoxicity and the cancer production by the fibers in rats, caution is expressed by the investigators regarding extrapolation of the in vitro results to man.

Considerable emphasis or reliance has been placed on the parallelism between the cytotoxicity of fibers and the production of cancers by the intracavitary deposition of the fibers in rats. Inasmuch as the production of these intracavitary cancers in rats have been judged to have no relevance to man, reliance of cytotoxic test results on comparisons with results that are irrelevant can serve no useful purpose.

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Original Papers

Standards for Chemical Quality of Drinking Water: A Critical Assessment

R. L. Zielhuis

Coronel Laboratory, Chair of Occupational and Environmental Health, Faculty of Medicine, University of Amsterdam, The Netherlands

Summary. The author critically reviews present standards for the chemical quality of drinking water, particularly the limits proposed by the Commission of the European Communities (CEC) in 1979. Particularly, the general principles of standard setting are discussed. It appears that there exists a surprisingly high similarity in drinking water limits, issued by various national and international authorities, although for other environmental compartments important discrepancies exist. Usually, drinking water limits lack adequate documentation, and appear often to be copied from other existing lists. There is an apparent lack of logical consistency in limits set for food, ambient or workroom air, and drinking water, probably due to lack of communication between health experts and decision-making authorities. Moreover, there is a lack of toxicologic studies, explicitly aimed at setting limits. Extrapolation from the acceptable daily intakes (ADI) for food or the Threshold Limit Value (TLV)-Maximum Acceptable Concentration (MAC) for workroom air could be undertaken to derive tentative drinking water limits, as long as explicitly designed studies for drinking water are not yet available.

Key words: Drinking water standards – Acceptable limits

The Validity of Numerical Values

Regulatory or recommended operational standards (limits) for the chemical quality of environmental compartments (e.g., ambient or workroom air, food, drinking water) aim at preventing health risks. Critical assessment of the validity of such values requires to consider at least five questions: (1) What does the actual numerical value mean? (2) What is the scientific basis? (3) Which health effects are to be prevented, and in which groups at risk? (4) What value-judgements have been made in deriving a health-based recommendation? (5) What is the impact of economic and technologic constraints on the ultimate operational standard or recommendation?

Offprint requests to: Prof. R. L. Zielhuis, MD, 1st Const. Huygensstraat 20, 1054 BW Amsterdam, The Netherlands

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