The Occupational Physician’s Point of View: 
The Model of Man-made Vitreous Fibers

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This article gives a detailed description of the procedure the occupational physician uses in interpreting the available scientific data to provide useful information for prevention of pulmonary diseases related to man-made mineral fibers, particularly lung cancer and mesothelioma. As it is difficult to reach definite conclusions from human data on the toxicity of specific fibers, an experimental approach is needed. Concerning animal data, we emphasize that adequate inhalation studies are the “gold standard” for extrapolating to humans. However, experiments using intracavitary injection or cells in vitro may represent indicative tests for a possible carcinogenic effect. Such tests should be used to assess the intrinsic carcinogenicity of fibers, but they must be confirmed by adequate inhalation models. Despite the present uncertainties, a proposal is made that could make it possible to classify fibers according to their toxicologic potential, grading them in accordance with physicochemical parameters, in vitro testing, and animal experiments. This procedure may be applicable to nonvitreous fibers and to organic fibers. — Environ Health Perspect 102(Suppl 5):31–36 (1994)

Key words: MMMF, diameter, length, carcinogenicity, in vitro, in vivo, animal, human data, classification

Introduction

One of the main objectives of a public health physician is to transform scientific data into information useful for prevention of disease. The occupational physician is a public health physician who specializes in occupational health. This presentation will focus on the consequences of exposure of workers to man-made vitreous fibers (MMVF) as seen from the occupational physician’s point of view.

This approach is based on the circumstances in which the problem is raised at the workplace. Usually the occupational physician is alerted by the presence of fiber-containing products at some level of work activity, either because of the introduction of a new product or because of any intervention by a worker on an old fiber-containing material. The physician then has to identify the fibers either from information obtained from the producer—such as the health and security data sheet or product label—or, especially in the case of old materials, from bulk analysis. The two main pieces of information that can be obtained are the chemical identification of the fibers and their diameter and length distribution. The next step is to assess the potential toxicity of the identified fiber. Here again, the physician uses available specific information. However, when such information is missing or incomplete, he has to make a risk extrapolation or initiate a toxicological evaluation. Depending on the toxicologist’s answer, the physician makes a risk assessment of the situation at the workplace, taking into account the level of exposure and the medical status of the workers. This is possible only if information is available on a dose-response relationship and, particularly, if threshold limit values apply. Finally, he can establish a prevention program.

The aim of this presentation is to determine how the occupational physician could use the available scientific information concerning MMVF. To answer this point, we will discuss the topics concerning fiber identification, fiber toxicology, and evaluation of fiber-containing products, including the possible interpretation of biopersistence relative to each topic. In the light of this discussion, we propose a systematic method of assessment of the carcinogenic potential of MMVF.

Fiber Identification

A major effort has been made to classify fibers. However, two questions must be posed: First, can existing classifications include any existing or newly developed commercial fiber? Second, are commercial and technical classifications compatible with toxicological data?

Three organizations have proposed classifications that are in use: The American Thermal Insulation Manufacturers Association (TIMA) has proposed a tree to define the man-made vitreous fibers, according to their origin, their physicochemical composition, and the process of production (1). The ultimate subdivision of man-made mineral fibers has been used by the International Programme on Chemical Safety (IPCS). However, this classification is built mainly on a commercial basis, and some glass fibers of the same chemical composition are found in different groups. In other cases, fibers with different chemical compositions can fall into the same category (2). The classification used by the International Agency for Research on Cancer (IARC) was intended to integrate toxicological and epidemiological information, but it will now be difficult to include new data relating, for example, to special purpose fibers (3). None of these classifications seems completely adapted to a precise identification of a fiber, or a close match with toxicological data.

Fiber Toxicology

Detailed toxicological results are discussed elsewhere in these proceedings. Here, we consider only the data that may pose problems to the occupational physician.

Human Mortality Studies

Data on mortality have been obtained exclusively among manufacturing industries (4–6). They have demonstrated a small excess of lung cancer in the groups with the longest duration of exposure, at least for those exposed to rockwool or slagwool and to some superfine glass fibers. It is, however, very difficult from those data to distinguish clearly the role of each type of fiber. This is particularly needed for the
rockwool and slagwool group. In addition, discussions concerning the influence of the confounding factors on the available results are not closed (7–10). In any case, two points have to be reassessed: First, industrial hygiene data suggest that the level of exposure could be higher among end-users than among workers in the manufacturing industry (11); and second, due to the short survey period on the one hand and, on the other, the relatively small number of person-years in the groups derived from workers for whom the duration since the beginning of exposure was more than 30 years, it would not be possible to detect a low but significant excess risk of mesothelioma on the basis of the available data.

Morbidity Data
The most pertinent morbidity data are for workers exposed to insulation wool and refractory ceramic fibers. Results from the update of the American "insulation wool" study still are not available (12,13), while conflicting results are reported among the two European and American "ceramic" cohorts. Preliminary findings of an excess of pleural plaques in the American cohort seems to be very important in view of the relatively short duration of exposure in that cohort and the small numbers involved (14). An updating of the European cohort 5 years after the first survey should be very informative (15).

Human Data on Biopersistence
These data are still difficult to interpret. On the one hand, in the study made with the available lung tissue taken at autopsy from the American cohort, mineral vitreous fibers were so modified that it was impossible to make a precise identification of the siliceous fibers (16). On the other hand, only very preliminary data have been reported on bronchoalveolar lavage of ceramic fiber workers. An interesting feature, however, is the discordance between human data, which showed a marked chemical modification of ceramic fibers that had been deposited in the lung, and animal data, which did not indicate any significant modification during a retention period of 2 years (17).

Animal Data
Animal data are still the most detailed data available, and it is most important to consider the significance of the different models of administration used in animal experiments—inhalation models, intracavitary models and other mechanicial models.

Inhalation Models
A recent meeting organized by the World Health Organization emphasized the importance of adequate inhalation models for hazard assessment of fibers. To date, only the recent and ongoing studies carried out in the Research and Consulting Center (RCC), Geneva, fulfilled the recommendations elaborated at this meeting and by the U.S. Environmental Protection Agency (18,19). Results already have been presented. Only a limited number of chemically different MMVF have been tested, two very similar glass fibers (MMVF10 and 11) used in commercialized glasswool, a slagwool (MMVF22) and a rockwool (MMVF 21) with an intermediate content of iron oxide. In the ceramic group (RCF 1–4), the list of commercial vitreous fibers is nearly complete. Even what is called an "after-service fiber" has been tested. In this group, results from two studies, one published in 1987 (20), the other in 1992 (21), show that a very slight shift in fiber dimension and dose of a ceramic fiber can lead to very different results (Table 1). This finding emphasizes the importance of standardized criteria for an adequate inhalation model.

Intracavitary Models
Some of the same fibers as those used in the RCC (Geneva), study have been tested in intracavitary models. Even though comparison is difficult because fibers were not of the same origin, the studies reported in Table 2 using intrapleural administration have confirmed that ceramic fibers were more toxic than the others (22–25).

Classification of the results as negative, doubtful, or positive was made according to criteria proposed elsewhere (26).

More interesting are the results observed with intraperitoneal administration (Table 3). The results show a strongly positive response from ceramic fiber and an intermediate response from the rockwool fibers tested. These perhaps were not the same fibers as those used in the inhalation study, but the two results may still be considered complementary (20, 27–30).

If this estimation is confirmed, it could increase the significance of results obtained with fibers tested only with intracavitary models. In the case of "JM special purpose fine fibers" (Table 4), positive finding of both intrapleural and intraperitoneal studies should be considered significant even if inadequate inhalation studies showed no carcinogenic effect (20, 24, 27, 29, 31–36).

However, available information concerning the characterization of the fibers used in those studies is very limited, which makes it difficult to analyze the precise role of each parameter of the fibers.

Biopersistence
The only reproducible attempt made to correlate biopersistence rather than durability, and biological effect, was in the Geneva inhalation studies (37,38). The existing data show that ceramic fibers are more biopersistent than the glass fibers tested; rockwool is more biopersistent than slag-and glasswool and less biopersistent than ceramic fibers.

Are these results sufficient to draw conclusions regarding the role of biopersistence in the biological effects in animal models? Even if the answer to this question is positive, there are three other questions remain: Is there a threshold below which the biopersistence of the fiber is insufficient to initiate an irreversible disease? What should be a recommended experimental model to assess the level of biopersistence? What are the predictive parameters of fiber biopersistence (dimensions, chemical composition, polyatomic structure, surface characteristics)?

In summary, in spite of the difficulties of interpreting the current data based on methods that are either poorly standardized or not standardized at all, or on incomplete results, it is still necessary for the occupational physician to have some basis available for assessing the carcinogenic potential of each type of fiber and of any incorporated substances. In the light of the preceding discussion, we propose to develop a system in two stages that will be valid for all fibers that might be inhaled, whatever their origin.

Proposal for a Systematic Assessment of the Carcinogenic Potential of a Fiber Resulting from a Given Manufacturing Process
Basis for the Classification of an Elementary Fiber

Chemical Characterization. Each process is defined by the raw material used in it, and the type of fiber that results will have a chemical composition that will vary within a fixed range. This variation is related to the inherent variations found in each batch of raw material used for a given type of manufacture. It will be necessary to check whether the fluctuations in the composition are liable to produce significant modification of the biological response. Meanwhile, it has to be accepted that the assessment of carcinogenic potential be
made on a fiber, representative of each manufacturing process.

**Dimensional Characterization.** With the available experimental models, it is only possible to study fine fibers capable of penetrating into the bronchoalveolar region of the lungs. At present, it is accepted that fibers <1 μm in diameter are the only ones capable of being inhaled by the rodent species (rat, hamster) used in inhalation tests. As a result, only fibers with diameter ≤1 μm should be subject to an assessment. The available data on the model of erionite have similarly underlined the critical role of fiber length. The results obtained in inhalation tests show a drastic reduction in carcinogenic response if the fiber length is <5 μm. It would therefore seem legitimate to propose that only fibers ≥5 μm in length be subject to assessment.

These two proposals do not exclude the possibility that in the future an assessment could be made of fibers greater than 1 μm in diameter or less than 5 μm in length, if experimental data became available.

**Criteria for Assessment of Biological Effects.** It seems reasonable to propose a stage-four-algorithm (Table 5).

**First Stage: Physicochemical Criteria.** The physicochemical characteristics, in the absence of which no carcinogenic effect has been found in the inhalation model, could be considered the first criteria of selection. A fiber that does not correspond to these criteria would automatically not need to be classified. Conversely, a fiber that corresponds to at least one of them would be classified as "possibly carcinogenic" (European Community (EC) class 3), pending the results of the subsequent stages of the algorithm. Among the physicochemical criteria, the one that can be used at this stage is the dimensional criterion (diameter ≤1 μm and length ≥5 μm). Subsequently, parameters such as chemical durability in the appropriate media or the density of reactive sites capable of generating free radicals, could be considered. For each of these criteria, it would be necessary to establish standard methods and validated threshold levels, beyond which a parameter would be considered positive.

**Second Stage: Biological Screening Tests.** The response to these tests should distinguish between a negative response, which would justify a nonclassification of a tested fiber, and a positive response, which would indicate a classification of "possibly carcinogenic" (EC class 3) pending the results of the next stages of the algorithm. Tests, therefore, must be sufficiently reliable to not give false negatives while at the same time producing only a minimum of false positives. Such tests would include, first, certain in vitro tests, especially tests of genotoxicity, including cell transformation; and second, in vivo tests by intracavitary injection.

For each test, methods must be standardized and their sensitivity and specificity must be established by testing carcinogenic fibers identified in the inhalation model.

**Third Stage: Test by Confirmation in Animal Experiments.** The only test recognized to date as a reference test for respiratory carcinogenesis is the inhalation model meeting all the criteria defined by WHO (1992). A fiber that is so tested and

### Table 1. Comparison of two chronic inhalation studies of refractory ceramic fibers.

|                       | Los Alamos (20) | Geneva (21) |
|-----------------------|-----------------|-------------|
| Dose: 12 mg/m²-200 f/cc | Dose: 30 mg/m²-200 f/cc |
| Scanning electron microscopy | Optical microscopy |
| Mean D: 1.8 μm | Mean D: 0.96 μm |
| GMD: 0.9 μm | GMD: 0.82 μm |
| GML: 25 μm | GML: 15.9 μm |
| L>10 μm: 83% | L>10 μm: 60% |
| D<2 μm: 86% | D<2 μm: 80% (<1.5 μm) |

| Animal   | Rat   | Hamster | Rat   | Hamster |
|----------|-------|---------|-------|---------|
| No. of animals | 55    | 70      | 140   | 140     |
| No. with fibrosis | 3     | 2       | 4     | 4       |
| Lung tumors | 0     | 0       | 20(14.3%) | 0   |
| Mesothelioma | 0     | 1(1.4%) | 2(1.6%) | 60(42%) |

Abbreviations: D, diameter; GMD, geometric mean diameter; GML, geometric mean length; L, length.

### Table 2. Animal data of intracavitary studies. Summary of tests by intrapleural injection.

| Fiber                  | No. of groups | No. of animals | Negative results | Intermediate results | Positive results |
|------------------------|---------------|----------------|------------------|----------------------|-----------------|
| Glasswool              | 4             | 234            | 100              | 0                    | 0               |
| Slagwool               | 3             | 120            | 100              | 0                    | 0               |
| Rockwool               | 3             | 136            | 100              | 0                    | 0               |
| Refractory ceramic fiber | 1         | 31             | 0                | 100                  | 0               |

### Table 3. Animal data of intracavitary studies. Summary of tests by intraperitoneal injection.

| Fiber                  | No. of groups | No. of animals | Negative results | Intermediate results | Positive results |
|------------------------|---------------|----------------|------------------|----------------------|-----------------|
| Glasswool              | 0             | 0              | 0                | 0                    | 0               |
| Slagwool               | 0             | 0              | 0                | 0                    | 0               |
| Rockwool               | 9             | 385            | 33               | 33                   | 33              |
| Refractory ceramic fiber | 4           | 156            | 0                | 25                   | 75              |

### Table 4. Animal data of intracavitary studies: summary of tests on "JM Special Purpose Fibers" by intrapleural and intraperitoneal injections and inhalation.

| Route of administration | No. of groups | No. of animals | Negative results | Intermediate results | Positive results |
|-------------------------|---------------|----------------|------------------|----------------------|-----------------|
| Intrapleural injection  | 9             | 283            | 25               | 25                   | 50              |
| Intrapleural injection  | 22            | 1028           | 15               | 5                    | 80              |
| Inhalation              | In the rat    | 8              | 320              | 100                  |                 |
| In the hamster          | 4             | 129            | 100              |                      |                 |

Data from Smith et al. (20), Wagner et al. (24), Pott et al. (27,29), Le Bouffant et al. (31,32), McConnell et al. (33), Gross et al. (34), Mitchell et al. (35), and Wagner et al. (36). 

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that does not give a significant result would not be classified. Some authors propose that in such case the classification of the preceding stage should be maintained particularly when the result is not completely negative, as for example, when there is fibrosis in the absence of any significant excess of tumors. In contrast, a positive result will lead to a classification of "definitely carcinogenic in the animal" (EC class 2).

At present, there is still no consensus on the method of carrying out and interpreting inhalation tests. Must a dose-effect relationship be observed? How is it possible to eliminate artifactual responses produced by overload, which could give false positives? What is the lower limit of the internal dose (that is, of fibers retained in the parenchyma or in the parietal pleura) that would make it possible to avoid false negatives? How should intermediate responses be considered, and in particular, nonmalignant pathologies?

Fourth Stage: Epidemiological Studies. If inhalation tests are positive, it is ethically legitimate to carry out an epidemiological follow-up of the exposed population. Nevertheless, whatever the quality of these studies, at best they can only correspond to a particular situation of exposure observed in the manufacturing industry. For the users of material containing fibers, feasibility studies and data already published have shown their limitations, such as multiexposures, or the impossibility of making a satisfactory characterization of individual exposure. Further, even in the production industry, it would be difficult to have a sufficiently large and homogeneous population exposed to one type of fiber. Larger groupings than those required for the early stages of the algorithm would be necessary. These factors make it possible only to take account of positive results—according to IARC criteria—by applying them to all the types of fibers that might have been encountered in the groups of subjects where a significant risk of respiratory cancer has been demonstrated. These fibers would therefore be classified as "carcinogenic in humans" (EC class 1).

In contrast, in the absence of a positive result, including the absence of interpretable data, a classification of the preceding stage of the algorithm would be maintained.

### Basis for Classification of a Product Containing Fibers

Any product containing fibers must be considered capable of releasing fibers into the air at some time during manufacture, utilization, or destruction. While waiting for the availability of a standard test capable of assessing the risk of a release of fibers into the air, it is reasonable to base the assessment on the classified fibers contained in the product.

### Products Containing Only One Chemical Variety of Fibers

Two steps are required for making an assessment. The first is to identify fibers <1 μm in diameter and secondly to determine the proportion of fibers <1 μm present in the product.

**First Stage.** The first stage is being codified. The method proposed by Schneider et al. (39) makes it possible to know the precise distribution of fiber diameters. This distribution is completely characterized by three parameters: geometric mean, median, and geometric standard deviation of the marginal distribution of the diameter. It is also possible to characterize the proportion of fibers <1 μm in diameter with the following parameters: the proportion of the accumulated lengths of fibers <1 μm in diameter in relation to the total cumulative length of all the fibers; and the proportion of the calculated mass of fibers (length × diameter × density) of <1 μm in relation to the total mass of the sample of the product, including nonfibrous particles. This latter parameter also takes account of the presence of nonfibrous particles, which can exceed 50% of the total mass of particles.

**Second Stage.** There is not, at present, a valid experimental basis for the second stage. It would be desirable to test experimentally the relationship between the parameters determined in the first stage and the proportion of fine fibers liable to be found

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**Table 5. Algorithm of fiber classification (substances).**

| Question                                                                 | Answers                                                                 | Proposed classification                                                                 |
|-------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| 1) Does the fiber possess a priori one of the criteria of risk?          | All criteria (confirmed) negative                                       | 0 (some would allocate 3b directly)                                                   |
| (Certain authors consider that these criteria are unworkable, and pass directly to question 2) | At least one criterion exists                                            | 3, pending other tests                                                                 |
|                                                                         | Results are negative, but incomplete                                    |                                                                                        |
| 2) Was a positive result obtained with a validated screening test?       | All the validated tests are negative                                    | 0                                                                                      |
|                                                                         | At least one test is positive                                           | 3, pending inhalation test                                                           |
|                                                                         | Results are negative but incomplete                                     |                                                                                        |
| 3) Did validated inhalation test give a positive result?                | Validated tests negative                                                | 0                                                                                      |
|                                                                         | At least one test positive                                              | 0 (some would propose maintaining 3 for fibers having a positive screening test)     |
|                                                                         | Results are negative but incomplete                                     | 2 (some would prefer 3 based on the strength of the result)                           |
|                                                                         |                                                                        | 3, pending complete inhalation tests                                                 |
| 4) Are there interpretable epidemiological results?                     | Studies negative                                                       | 0                                                                                      |
| The results apply to all the fibers likely to have been inhaled by the groups of subjects having a significant response | If the results were reproducible, effectively adapted to the risks, and representative levels of exposure | Maintain the classification based on experimental studies                           |
|                                                                         | Results doubtful                                                        | Maintain the classification based on experimental studies                           |
|                                                                         | Studies positive, according to IARC criteria                            | 1                                                                                      |
in the aerosol after the samples of the products under test have been suspended in air. While waiting for this validation, and by analogy with asbestos, it would seem desirable to determine, as a priority, the proportion of the mass of fibers <1 μm in diameter in relation to the total mass of sample. In conformity with the spirit of the European directive relating to labeling of preparations, a product containing more than 1 part per thousand by weight of class 2 fibers or one part per 100 of class 3 fibers should be so labeled.

Products Containing Many Fibers or Other Chemical Substances. The application of the "preparation directive of the EC" would make it possible to choose the correct label in accordance with the criteria already established for mixtures of substances.

Conclusion

The analysis of available data concerning MMVF shows that there are still a number of contradictions and gaps. Nevertheless, the uncertainty that results from these deficiencies must not be used as an excuse by the occupational physician for delay in setting up a preventive strategy. This is particularly true for fibers that are already available commercially.

For this reason, it seems possible to propose an algorithm of decisions leading to a classification of fibers and to labeling of products they contain. This algorithm is based on available data, on the condition that an effort is made to standardize the methods used. It must be usable for already existing fibers as well as for new fibers in preparation.

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