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Man-made mineral fibers and health

Answered and unanswered questions

by Rodolfo Saracci, MD¹

SARACCI, R. Man-made mineral fibers and health: Answered and unanswered questions. *Scand J Work Environ Health* 11 (1985) 215–222. An overall assessment of the epidemiologic evidence from 23 published studies on workers' health in the industry producing man made mineral fibers (MMMF) (21 studies) and in the user industry (2 studies) is presented. Three major studies recently published, one cross-sectional and two of the historical cohort type, conducted in the producer industry, have been singled out for closer examination and discussion. The combined evidence from the epidemiologic studies indicates that causal associations between MMMF occupational exposure, as it occurred in past decades, and lung cancer and chronic respiratory diseases cannot be excluded, neither does it offer clear support for such associations. Experimental data indicate clearly that a fibrogenic effect can be obtained by the intratracheal administration of MMMF and a carcinogenic effect by the intratracheal, intrapleural, and intraperitoneal administration of MMMF, while no appreciably fibrogenic nor carcinogenic effects have been detected in inhalation experiments. While it can be stated that no long-term pathological effects have been observed in MMMF workers in the first 20 years or so after first employment, the key scientific issue of whether MMMF are fibrogenic and/or carcinogenic in man when inhaled remains still open.

Key terms: chronic respiratory diseases, lung cancer, man-made vitreous fibers, multicentric studies, occupational epidemiology.

Relevance of the issue

Man-made vitreous fibers (MMVF), more commonly though less properly designated as man-made mineral fibers (MMMF), include a variety of inorganic synthetic wool products (glass wool, rock wool, slag wool) widely used as thermal and acoustic insulation, as well as filament products employed for textile manufacturing and for the reinforcing of plastic materials (37). Table 1 provides a schematic view of the varieties and of some key characteristics of these products, such as their nominal diameters and the diameters of the fibers airborne in workplaces. (The two differ, due to the greater propensity of coarser fibers to settle.) Short-term health effects manifested as acute and, with lower frequency, chronically persisting symptoms involving the skin and upper respiratory mucosae have long been recognized among workers exposed to man-made mineral fibers (3). However, it is the long-term effects, notably pulmonary fibrosis and respiratory (lung) cancer, which have mostly attracted attention in the last 10–15 years for a number of reasons.

First there is the size of the occupationally exposed populations. For instance, the workforce in the Western European producing industry could be estimated at around 30 000 at the end of the 1970s;

an even larger number of workers handle the products in user trades such as the building industry. The size of these populations is of course related to the volume of the man-made mineral fiber production, estimated to total about $46 \cdot 10^5$ t worldwide in 1973 (37).

The second cause of attention is the results of animal experiments clearly showing that man-made mineral fibers are capable of inducing cancer, namely, mesothelioma in the pleura and peritoneum, when directly deposited in these cavities and fibrosis when intratracheally administered (13, 19, 21, 30). These biological test systems may be regarded as rather special in respect to the route of administration, but no one has yet, to my knowledge, seriously questioned the validity by itself of these experiments. They demonstrate that, under a defined set of conditions, man-made mineral fibers are capable of eliciting pathological responses, like fibrosis and malignant neoplasia. It may not be inappropriate to remind in this context that, contrary to a superficial but not uncommonly heard opinion, not "everything" (for instance, any chemical) turns out to be carcinogenic if tested under suitable (and maybe very special) conditions. Indeed, out of more than 700 substances reviewed within the International Agency for Research on Cancer's (IARC's) monograph program on the carcinogenic risk of chemicals to humans, and which were purposely selected because of some pre-existing suspicion of carcinogenicity, only about 300 were evaluated as carcinogenic to humans, probably carcinogenic to humans, and/or with sufficient evidence of carcinogenicity for experimental animals (33).

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Table 1. Characteristics of man-made mineral fiber products and airborne fibers.

Category of fiber	Material	Use/product	Approximate range of nominal diameters (μ)	Approximate range of median airborne diameters (μ)
Insulation wool	Rock Glass Slag	Thermal insulation	5–15	0.4–4.0 ^a
Continuous filament	Glass	Electrical insulation Reinforcing mat Chopped strands	5–15	0.3–2.0 ^a
Special purpose	Rock Glass Ceramic	Thermal insulation Aircraft insulation High efficiency filters	0.2–5.0	0.2–1.0 ^a

^a Taken from EURO Reports and Studies 81 (37).

Table 2. Epidemiologic studies^a on long-term effects of man-made mineral fibers.

Production workers	User workers
<ul style="list-style-type: none"> — 13 cross-sectional studies (6 countries) — 7 historical cohort studies (9 countries) <ul style="list-style-type: none"> — mortality (7 studies: 9 countries) — cancer incidence (1 study: 4 countries) — 1 autopsy study (1 country) 	<ul style="list-style-type: none"> — 1 study (case-referent and cross-sectional) in the building industry (1 country) — 1 cross-sectional study on sheet metal workers (1 country)

^a Include the studies cited by Saracci et al (23), plus studies cited by Grimm (10), Siebert (27), Sixt et al (28), and Valentin et al (34).

Table 3. Chronic respiratory diseases and respiratory cancers in the man-made mineral fiber (MMMF) producer industry and user industries.

Producer industry				User industries			
Studies	Size (in thousands)	Association with MMMF industry ^a	Causal association with MMMF ^a	Studies	Size (in thousands)	Association with MMMF occupations ^a	Causal association with MMMF ^a
<i>Chronic respiratory diseases</i>				<i>Chronic respiratory diseases</i>			
10 cross-sectional	37	—	No	1	<1 (23 subjects)	±	Possible
3 mortality				1		+	Possible
1 autopsy							
2 cross-sectional	5	±	Possible				
2 mortality							
2 mortality	17	±	Possible				
1 cross-sectional	1	+	Probable				
<i>Respiratory cancers</i>				<i>Respiratory cancers</i>			
3 mortality	2	—	No	1	135	+	Possible
1 autopsy							
2 mortality	21	±	Possible				
1 cancer incidence							
2 mortality	42	±	Possible				

^a See the text for an exact definition of the symbols or terms.

Third in the list of reasons for interest in the long-term effects of man-made mineral fibers is the possible outcomes of the epidemiologic studies on exposed workers prompted by the results of the animal experiments, essentially in the absence of any obvious evidence of pathological effects in humans. These results are in themselves worth notice. Large analytical epidemiologic studies have been started on man-made mineral fibers not, as has happened almost constantly in the past for other occupational exposures, after case reports of diseases in workers

have surfaced, but on the basis of animal experiments. One would hope that this course of events would cease to be the exception in the future. Whatever the outcomes of the epidemiologic studies, they should prove of considerable interest. Indeed, should the studies consistently show some long-term pathological effects on exposed workers, they would fall in line with the results from the animal experiments just mentioned. Should they instead indicate repeatedly and consistently no detectable effects, even in large study populations, one would then face

one of the few (maybe the only one up to now) well-documented cases of negative human evidence against *some* correctly and definitely positive animal evidence. This would be a result of import not only for the man-made mineral fiber question, but also in general, if one thinks that for several hundreds of chemicals with sufficient evidence of carcinogenicity in animals no conclusion about effects in humans can be drawn simply because there are no adequate (or none at all) epidemiologic data available (32).

Finally there is the contribution that the study of man-made mineral fibers, in man and in the laboratory, can make to the whole field of "fiber carcinogenesis" by helping to identify the characteristics — geometric, physical, chemical — which can confer a carcinogenic potential on a mineral fiber.

For these reasons, it is of interest first to examine the epidemiologic evidence on the health effects of man-made mineral fibers in exposed workers and then place this evidence in the frame of biological findings relevant to its interpretation. The focus throughout is on chronic respiratory diseases (a rather mixed bag of pathological and clinical conditions) and respiratory cancers (essentially lung), as the ensemble results of the epidemiologic studies present clear pointers to no other effects.

An overview of the epidemiologic evidence

Two years ago I evaluated, with my colleague Dr L. Simonato, all the epidemiologic evidence at that time available, considering in some detail every study investigating chronic respiratory disease or respiratory cancer, or both. It would be redundant to repeat the exercise here. Rather, an updated and compact summary of the overview will be presented, followed by a closer examination of the three major studies available today and recently published. For the overview purposes each study considered individually, ie, not in relation to the others, has been rated in respect to the existence of an association of disease (chronic respiratory or respiratory cancer) with man-made mineral fiber industries/occupations, as well as in respect to the likelihood of the association being causally due to exposure to man-made mineral fibers. The rating for the existence of an association is — = no association; $\mp$ = association weak, isolated, or with an inconsistent pattern; $\pm$ = some association, neither strong nor entirely consistent, particularly in relation to the duration of employment in the industry; + = association internally consistent within a given study. The likelihood of an association being causally due to exposure to fibers is rated as follows: no = no suggestion of a causal association found; possible = data from the study suggest the possibility of a causal association; probable = exposure to man-made mineral fibers appears as one of the most likely explanations of the observed association; definite = exposure to man-made mineral fibers appears to be

the most likely explanation of the observed association; this "definite" rating level can only be reached within a study, considered individually, if it contains a substantial amount of internal consistent replication, ie, in a multicentric study.

Applying these rating criteria to the epidemiologic studies (table 2) in the producer industry (21 studies) and in the user industry (2 studies) has produced the results reported in table 3, an indication being given in the second and sixth columns of the table of the total size (in thousands of subjects) for each category of studies. This figure is reported in order to provide the reader with a first, and rough, orientation on the scale of the observations of different kinds available which involve workers exposed to man-made mineral fibers, although, obviously, information derived from observing, say, several hundred workers for 10 years, counting deaths, and their causes, is quite different from that derivable from having exactly the same number of workers undergo a series of explorations of respiratory function at a given point in time (and this even discounting possible differences in study quality). It can be seen immediately that for none of the studies in the table does the assessment of the causality of the association with man-made mineral fibers reach the level of "definite," and for only one study of chronic respiratory diseases in the producing industry does it reach the level of "probable." For this class of pathological effects the aggregate evidence from the producer and the user industry falls to a large extent into the category of "possible" causal association with man-made mineral fibers, but with a sizable proportion of studies showing no association at all. These are mostly cross-sectional investigations carried out on workers still employed, ie, on groups of "survivors" in the producer industry with a majority of subjects exposed for not more than 20 years. For the other class of pathological effects of interest, namely, respiratory (lung) cancers, the aggregate evidence from the producer and the user industries predominantly falls into the "possible" category of causal association with man-made mineral fibers.

A less superficial appreciation of the current status of the evidence can be gleaned by a closer look at the three major studies, recently published, on workers in the man-made mineral fiber producing industry. (The rating assessment for each of them has been included in table 3).

The first is a *cross-sectional investigation* (36), carefully designed and conducted, of the respiratory health of 1 028 male workers at seven plants (five glass fiber, ie, glass wool and/or continuous filament, two mineral wool, ie, rock wool and/or slag wool) in the United States. The median age of the workers was 46 years, the median length of employment 18 years. A questionnaire investigation of respiratory symptoms and a battery of pulmonary function tests did not show abnormal findings. On 941

evaluable chest radiographs the prevalence of small opacities in categories 0/1, 1/0, 1/1 in the classification of profusion of small opacities of the International Labour Organisation (ILO) was respectively 7, 3, and 1 % (no opacities > 1/1 having been found). After adjustment for age, smoking habits, and fiber type (ordinary and fine versus other) the prevalence of these borderline radiographic abnormalities was related to duration of employment in the man-made mineral fiber industry, but only among current smokers. This association can be regarded as genuine, along with its causal nature in respect to fiber exposure as "probable" (maybe in combination with smoking).

This cross-sectional study was carried out in a subset of seven plants of a larger group of American plants which has been included in a large *historical cohort study* of worker mortality (7). Across these factories overall (ie, overall measurements within a given plant) mean plant concentrations of respirable fibers (length $\geq 5 \mu$, diameter $< 3 \mu$), ranging from 0.003 to 0.427 fibers/ml, had been measured through a detailed ad hoc survey, and, under present-day conditions of operation, most average employee values (reflecting job-specific exposures) were below 0.5 fiber/ml (8, 9, 12). From this survey some estimates of general interest to the man-made mineral fiber producing industry, at least as it operates nowadays within the United States, were inferred and are shown in table 4. S fibers ("Stanton's fibers") denotes fibers with a diameter of $\leq 1.5 \mu$ and a length $\geq 8 \mu$, namely, those in the dimensional range which showed the highest activity in intrapleural carcinogenic tests in rats (30). The 17 factories in the historical cohort study included 11 glass fiber factories and 6 mineral wool factories. Workers at these factories had an average length of employment of 11 years and were followed-up with a tracing rate of 98 %, providing a total of 383 024 person-years of observation; 3 761 deaths were recorded.

In the glass fiber category of production there were 129 observed deaths in the category of nonmalignant respiratory disease against 99.5 expected, with a standardized mortality ratio (SMR) of 139 ($p < 0.01$). When the data are broken down by time from first exposure and duration of exposure, no relation with duration of exposure is discernible except for ≥ 30

years from first exposure. Overall there were 25 deaths observed in this category against 20.05 expected, with an SMR of 125 (statistically nonsignificant). Moreover no trend was detectable with cumulative exposure to fibers. For the mineral wool workers 21 observed deaths were reported, against 14.05 expected, with an SMR of 150 (not statistically significant). There was no overall trend with duration of exposure, but a trend was discernible for the period of ≥ 30 years from first exposure, for which there were 8 observed deaths versus 4.87 expected, with an SMR of 164 (not statistically significant). No clear trend with cumulative exposure to fibers was discernible either.

For respiratory cancer 202 deaths were observed against 203.5 expected over the whole period of observation, with an SMR of 99. For the period of observation of ≥ 30 years the SMR was 130 (47:36.0), not statistically significant. No relation was detectable with duration of exposure nor with cumulative exposure to man-made mineral fibers. For the mineral wool workers an overall ratio of 160 (45:28.1, $p < 0.01$) was reported, with no relation to duration of exposure except for the period of ≥ 30 years from first exposure (for which there were 14 observed deaths versus 8.11 expected, for an SMR of 179, not statistically significant). No clear relation to cumulative exposure to man-made mineral fibers was present. When a separate analysis is done for subjects with at least 20 years of exposure and ≥ 30 years of observation, it appears that the elevated ratios are concentrated in only two of the six plants (SMR of $210 = 7 : 3.35$ and $240 = 3 : 1.24$), while in the other four no deaths from respiratory cancer had occurred. On the other hand, the expected figures in these plants are very small (0.89 for all four combined), indicating that in these plants a small number of workers exposed for at least 20 years was followed for ≥ 30 years.

The second large *historical cohort study* recently reported (25, 26) was conducted in 13 plants — four glass wool, seven rock wool, and two continuous filament, one of which had initially produced glass wool, in seven Western European countries — with the coordination of the IARC.

An ad hoc industrial hygiene survey (17) documented an overall mean of respirable fiber concen-

Table 4. Typical expected fiber concentrations by type of man-made mineral fiber produced.

Fiber type	Nominal product diameter (μ)	Concentration (fibers/ml)		
		Detected by optical microscopy	Estimated total	Estimated S fibers
Continuous filament	2—100	< 0.003	< 0.003	$\cong 0$
Coarse	> 10		0.001—0.005	10^{-5} — 10^{-4}
Ordinary fibrous glass insulation	6—8	0.001—0.005	0.01—0.05	10^{-3} — 10^{-2}
Mineral wool	6—8	0.01—0.05	0.2—2	5×10^{-2} — 5×10^{-1}
Special purpose — fine	1—3	1—2	1—2	0.5—1
Special purpose — very fine (microfiber)	< 1	1—50	1—50	0.5—20

trations of 0.02 fibers/ml for glass wool plants, 0.04 fibers/ml for rock wool plants, and 0.004 fibers/ml for continuous filament plants. The highest concentrations were recorded in secondary processes, group averages ranging from 0.03 to 0.45 fibers/ml.

A total of 25 146 workers was included in this study, with a mean length of employment of about five years. The tracing rate was 96.1 %, and, for the total number of person-years of 309 353, 1 659 deaths have been recorded. One death from pleural mesothelioma was observed in a worker employed for 92 d, the death occurring about 11 years after first employment. No consistent differences (either within or between plants) were noted between observed and expected numbers concerning individual causes of death or individual cancer sites, apart from lung cancer. (In particular, no elevated SMR nor definite patterns with time from first employment were observed for chronic respiratory diseases.) For the three production categories of glass wool, rock wool, and continuous filament an SMR of 94 (44 deaths observed versus 46.9 expected), 111 (50 : 45.1), and 143 (15 : 10.5), respectively, was found, none being statistically significant. For the period of observation of 30 or more years since first employment, the SMR was elevated, but not statistically significant, for all three production categories: 157 (4 : 2.6) in the glass wool, 195 (11 : 5.7) in the rock wool, and 333 (2 : 0.6) in the continuous filament groups. A pattern of increasing SMR with time from first employment was clearly discernible in the rock wool industry: 91 (27 : 29.8) up to 19 years from first employment, 124 (12 : 9.7) for the 20- to 29-year period, and 195 (11 : 5.7) for the ≥ 30 -year period from first employment (none of these SMR values being statistically significant). This pattern was preserved (SMR 90, 148, 163 for the three time periods, respectively) if one factory, less well characterized environmentally and with some restricted asbestos use, was separated from the others. No relation of the SMR values was found with duration of exposure nor with cumulative exposure to man-made mineral fibers.

In addition to these three studies of workers in the man-made mineral fiber producing industry, results have also been recently published (5, 6) of a large study on 135 000 user workers in the building industry. The rating assessment of this study is included in table 3. As the attribution of exposure depended on questionnaire information, there remains some reservation about how successful the study was in separating exposure to man-made mineral fibers, asbestos, and other dusts present in the building trade.

Interpretation of the evidence

As one reviewer has commented (15), comparing the results from previous studies with those of the most recent ones, in particular from the two large histor-

ical cohort studies in the production industry in the United States and Europe just described, "Whereas previous studies of MMMF production workers have been essentially negative, the same cannot be said confidently of the new sets of data." This comment refers to the lung cancer excess observed both in the American study and in the European study, which appears at a site — the lung — and after a time — 20, 30, and more years since first exposure (actually, in most cases since first employment) — when it would a priori be expected to show up. Table 5 brings together, side by side and pooled, the results for respiratory cancer in the American and European studies separately for glass fiber and mineral wool. An excess, ie, an elevated SMR, is already seen for mineral wool in the interval 20–29 years from first employment. It is more marked at 30 and more years, and a pattern of increase in SMR with time is also discernible, more neatly in the mineral wool industry. At any rate, no SMR exceeds the value of 200. No information on smoking habits, the major potential confounder in lung cancer etiology investigations, was available in these two studies (nor, in fact, in any other of the cohort studies in the production industry included in the overview table 3). On the conservative assumption that smoking would actually be a confounder in these data sets, it is unlikely — unless an extreme and uncommon situation had materialized — that it would account for the whole of the observed elevations in SMR. [An increase of up to 150 is often regarded as a reasonable upper limit for an uncontrolled confounding effect of smoking (1, 4).]

A related point, at least to the extent that local (as opposed to national) lung cancer rates in the general population are a reflection of local levels of tobacco smoking (22), is that in both the American and the European study national rates were used as reference to compute expected figures. This practice may not be wholly appropriate, especially when, as in some countries in the European study, rates vary appreciably within a relatively large population and only one

Table 5. Male respiratory cancer deaths in the glass fiber and mineral (rock/slag) wool industries.

Time from first employment (years)	Standardized mortality ratio ^a		
	Europe	United States	Pooled
<i>Glass fiber industry</i>			
≤ 19	105	87	92
20–29	80	98	95
≥ 30	187	130	135
Total	103	99	100
<i>Mineral (rock/slag) wool industry</i>			
≤ 19	91 (90)	166	108 (111)
20–29	124 (148)	146	135 (146)
≥ 30	195 (163)	172	181 (170)
Total	111 (107)	160	130 (132)

^a The figures in parentheses represent the corresponding ratios excluding one factory where use of asbestos was reported.

factory located in an area of particularly high or low mortality is included in the study. For the three large countries (England, Federal Republic of Germany, Italy) in the European study local rates were also used or the local SMR (as adjustment factors) in complementary analyses of the data; these procedures indicated that the use of local rates tends to lower the overall SMR but does not affect the SMR in the longest period since first employment.

An important element is that the search for an exposure-effect gradient, both in terms of duration of exposure and of cumulative exposure to fibers, has provided negative answers in the American and European studies, and these would in themselves be regarded by some as decisive in discounting the possibility that the observed elevated SMR values may be causally related to man-made mineral fiber exposure. One should appreciate, however, that, while the presence of such a gradient can be taken, as a rule, as an argument supporting a causal relationship, its absence does not carry the same weight against it. This statement applies particularly to cumulative exposure to airborne fibers. Fiber levels were measured under present-day conditions of operation and may have been higher, perhaps one order of magnitude, in the past (though no adequate measurements are available). Use of present-day levels may thus have contributed to diminish quantitative differences between levels associated with different jobs, restricting the span and flattening the slope of the derived exposure-effect lines.

In summary, from a closer look at the two major cohort studies in the producer industry, the possibility that some excess of lung cancer (all or part of that showing up in table 5) may be causally related to exposure to man-made mineral fibers cannot be ruled out of the range of reasonable interpretations of the

epidemiologic evidence. It is appropriate to recall at this point that indeed the results of the overall assessment of all epidemiologic studies indicated in the aggregate a "possible" causal association of man-made mineral fibers with lung cancer, and with chronic respiratory diseases as well. These open results need to be further assessed within the total picture of the biological evidence pertinent to man-made mineral fibers.

The first kind of evidence is represented by the kinetics of the absorption, distribution, and elimination of fibers in the human body, of which figure 1 provides a much simplified summary. It is seen that some characteristics of the fibers act in opposite directions. For example, fiber length decreases respirability, but also alveolar clearance; increasing the diameter above $1\ \mu$ decreases respirability but increases durability. The net quantitative result of these factors has been to some extent documented in experimental systems (11, 16) but not in such a complete and consistent way as to exclude with confidence, on the strength of kinetic considerations, the possibility of pathological effects in humans. In any case, even if man-made mineral fibers are assumed to have appreciably less persistence within the body (lungs) than any of the asbestos varieties, this assumption cannot be equated with the absence of pathogenic potential, particularly if, as for cancer, "hit and run" mechanisms may be implied.

The second kind of relevant biological evidence derives from the results of animal experiments testing the fibrogenicity and carcinogenicity of man-made mineral fibers. The experiments mentioned in the introduction to this paper, as well as subsequent ones, have shown that man-made mineral fibers administered intratracheally may be capable of eliciting pulmonary fibrosis in guinea pigs (13) and, to a less degree, in rats (2), and lung cancer and pleural mesotheliomas in hamsters (20). By pleural administration they have been clearly shown to induce mesotheliomas in rats (19, 30, 31), the same effect being obtained by intraperitoneal administration in rats (21). By inhalation, on the contrary, less than "minimal" pulmonary fibrosis was found in rats, and no detectable carcinogenic effect in rats and hamsters (in experiments involving a total of about 600 animals) (14, 29, 35).

Thus, while fibrogenic and carcinogenic actions of man-made mineral fibers have been demonstrated, it remains open whether they can indeed materialize into detectable effects by inhalation, a finding which duplicates, for animal data, the uncertainty of interpretation of the epidemiologic data.

Deposition:	{	— Respirable fibers $\leq 3\ \mu\text{m}$ diameter (S fibers: <1.5 diameter, $>8\ \mu\text{m}$ length)
		— Respirability varies with diameter (maximum $0.5\text{--}1\ \mu$) and decreases with length
Clearance:	{	— Tracheobronchial: <1 day half-time
		— Alveolar: 60—90 days half-time (ineffective for fibers $\geq 20\ \mu$ long)
Durability:		Amphiboles $>$ chrysotile/ MMMF Thicker $>$ thinner

Figure 1. Fiber kinetics oversimplified. (MMMF = man-made mineral fibers)

Conclusions: Answered and unanswered questions

From the results just discussed three questions can be singled out — one answered, one half-answered, one

unanswered.

The answered question derives from the observation that no long-term pathological effects on workers' health have been detectable in the first 20 years or so after first exposure in the industry producing man-made mineral fibers under the conditions of exposure then prevailing. Disagreement has been expressed on this point (18); it was however based, in my view (24), on a selective interpretation of some of the findings from the American historical cohort study, while the total epidemiologic evidence supports it. At least under present-day conditions of operation respirable fiber levels in the producing industry are generally low, on the order of 0.1 fibers/ml or even less. Intermittent higher levels may occur in some of the user industries, for instance, in the building trade, but the epidemiologic evidence from these is at the moment limited and does not alter the picture derived from the producing industry. It should also be noted that fine or very fine fiber production (diameters of 1–3 and less than 1 μ) started only in the 1960s and has been very limited in the past.

The half-answered question concerns the reporting of only one death from mesothelioma among all the man-made mineral fiber workers hitherto observed. This one death was that of a worker in the European historical cohort study, which by itself alone involved more than 300 000 person-years of observation. This finding needs, however, to be viewed against the relatively short period of exposure in most studies, the relatively small number of workers yet followed for long (three decades or more) periods, and the fact that death certificates may miss mesothelioma.

Finally, and most relevant, the unanswered question stems from inability to tell whether man-made mineral fibers are fibrogenic or carcinogenic, or not, when inhaled by man. In my view, to impose a positive or a negative conclusion on what appears to be a large, often good quality, but still unclear set of results, epidemiologic as well as experimental, is at present scientifically unjustified. In the immediate future (early 1985) further epidemiologic data will become available, from a five-year extended follow-up of the IARC historical cohort study in Europe, and a similar extension is expected for the American study. I am not so naive as to believe that more data will necessarily mean more clarity, though I am confident that, at the worst, we will be able to obtain a firmer footing regarding what we can and what we cannot expect to achieve by epidemiologic investigation in respect to man-made mineral fibers. *Should* man-made mineral fibers have long-term pathological, but "small," effects they may well end (particularly with the low levels of exposure current today in the producing industry and with the confounder exposures often present in user industries) by being very difficult or impossible to detect, even through the observation of large worker populations. The

scientific issue on the long-term health effects of man-made mineral fibers in man would then remain essentially pending, while the practical preventive issue would have to be resolved (as already today) on a largely judgmental basis, keeping prominent the protection of the exposed workers.

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