Man-Made Vitreous Fibres

25 years of epidemiological research on mortality
and cancer incidence

Charles E. Rossiter

Arbetslivsinstitutet
National Institute for Working Life

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by the National Institute for Working Life. The series presents research by the Institute's own researchers as well as by others, both within and outside of Sweden. The series publishes scientific original works, dissertations, criteria documents and literature surveys.

Arbete och Hälsa has a broad target-group and welcomes articles in different areas. The language is most often English, but also Swedish manuscripts are welcome.

Summaries in Swedish and English as well as the complete original text are available at www.niwl.se/ as from 1997.

Guest editor's preface

The author

Professor C. E. Rossiter was Professor of Occupational Health, University of London between 1984-1989, and is now Emeritus Professor of Occupational Health.

He has specialised in the epidemiological study of the health risks of exposure to airborne fibres, for most of his academic career. When the Joint European Medical Research Board (JEMRB) was founded in 1975 to fund research into the health effects of the insulation wools, he was appointed Secretary of the Scientific and Technical Committee advising that Board. He has been Chairman of JEMRB since 1988.

Professor Rossiter was honoured with the Freedom of the City of London in 1988.

The report

This report is a tale of the development of the epidemiological evidence base in risk assessments with respect to workplace exposure to Man Made Vitreous Fibres. The author reviews the recent three decades of occupational health history during which time the knowledge base has expanded and become strengthened through the efforts of research groups in many countries.

It is an important report. Epidemiological studies, when designed and executed with scientific rigour, provide heavyweight evidence in assessments of toxic properties of hazardous agents. The author has, through his affiliation as scientific advisor to the industrial body Joint European Medical Research Board (JEMRB) had close contacts with scientific projects and researchers around the world addressing the issues reviewed in this report.

The author leads the reader from the starting point of epidemiological studies in the early 1970's following it up scrutinizing the language used by the researchers in their reports over the years in their pursuit of evidence corroboration. This follow-up is brought to a conclusion with the International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of MMVF in 2002. In this evaluation by the IARC fibres of insulation glass wool, continuous glass filament fibres and rock- and slagwool fibres were declared as "not classifiable as to carcinogenicity to humans" marking an important reappraisal of previously made assessments of these materials.

It is a fascinating narrative, in its adherence to a time scale, starting with the incentives setting research efforts in motion in many European countries and also in the US and Canada. The reader is taken along with the author to explore and examine the evidence as it unfolds and to follow the research groups use of all

their ingenuity to find out ways to corroborate their previous findings in changing study designs and methods and in using new sources of information.

The basic study hypothesis was all along that workplace exposure to mineral fibres implies risk for cancer disease. This was based on a model of analogy with asbestos fibres. Asbestos was at the time, and is still, a natural basis of comparison in assessing toxic properties of fibres taking into account the well-known carcinogenic potentials of most asbestos fibres.

This report describes the efforts of the researchers to bring out the facts of the case. There is an element of an antique drama in this report, with events and interpretations developing over the time course. This also implies the monitoring of the researchers' use of language to frame their assessments of the balance of probabilities and uncertainties with regard to the MMVF as potential determinant of cancer risk. It has all the time as been necessary to remind of other possible explanations than MMVF exposure for the lung cancer incidences observed.

This is not only a report on the carcinogenic properties of a few specified types of MMVF fibres. It is also the narrative of how research groups in many countries of the world, in all their ingenuity resilience, in pursuit of a truly valid result position themselves in relation to new results. It is a tale of hard work, hard thinking and – more often than not – the search for new solutions to new problems, not stopping with work only half-done.

Peter Westerholm, MD FFOM, Professor Emeritus
National Institute for Working Life

Contents

1. The Research Trigger

This story starts a century ago. In 1901, Montague Murray recorded the death from lung fibrosis of a 33-year-old man who had worked in an asbestos carding mill for ten years. This he presented in 1907, as resulting from exposure to asbestos dust (HM Murray, 1907). By 1931, following several other reports (eg Merewether & Price, 1930), lung fibrosis resulting from exposure to asbestos had been named "asbestosis" and the first studies of working conditions in asbestos textile factories had been undertaken. These led to the British Government recognising the adverse effects of asbestos exposure, and the promulgation of the 1931 Asbestos Industry Regulations requiring dust suppression measures (Government of the United Kingdom, 1931).

Just as there were some two decades from the earliest published reports to the general acceptance that asbestos exposure caused lung fibrosis, so it was many years from the first hints to the broad acceptance that lung cancer could also be caused by such exposure. Prompted by the occasional case reports and a review by the UK Factory Inspectorate, the first epidemiological study was undertaken by Doll (1955) showing that workers with 20 or more years of exposure to asbestos dust had a ten-fold increased risk of lung cancer. This evidence of carcinogenic risk was strongly supported by the findings of marked excess of lung cancer among American insulation workers (Selikoff et al, 1965).

Early reports of mesothelioma cases were rather more quickly followed by confirmation. Wagner et al (1960) reported 33 cases of mesothelioma occurring in four years associated with crocidolite exposure in South Africa. This study was doubly important in that it showed that mesothelioma cases also occurred among those who lived near the crocidolite mines and processing mills.

In 1964, the UICC Working Group on Asbestos and Cancer (1965) recommended that epidemiological investigations should be conducted to determine the importance of asbestos fibre type on the risk of mesothelioma, lung cancer, fibrosis, and other cancers. This confirmed a general acceptance that asbestos-exposure could cause these conditions, but emphasized the need for further understanding.

For a full discussion of the above history, see for example Government of Ontario (1984) or Selikoff and Lee (1978). An IARC Working Group evaluation of Asbestos hazard (IARC, 1977) reviewed the human and experimental evidence up to 1976.

The turning point for extending the range of fibres of concern beyond asbestos occurred in 1972 with the publication of two experimental reports (Stanton & Wrench, 1972; Pott & Friedrichs, 1972). In the first of a series of studies, Stanton and Wrench used intra-pleural implantation of various asbestos fibres and fibrous glass to investigate mesothelioma induction. The results indicated that increased carcinogenicity of asbestos and fibrous glass was related to greater fibre length, finer diameter and higher length/diameter ratio rather than to the physicochemical

properties of the fibres. Pott and Friedrichs used intra-peritoneal injection, also of a range of fibres, including glass fibres. They reached a similar conclusion to Stanton and Wrench.

Interestingly, in further experiments, both research teams argued that durability of the fibres was important, in addition to fibrous shape and size. Stanton et al (1977) commented

> "Since neoplastic response to a variety of types of durable fibers, particularly asbestos fibers, was similar, our experiments reinforce the idea that the carcinogenicity of fibers depends on dimension and durability rather than physicochemical properties and emphasize that all respirable fibers be viewed with caution."

Pott et al (1976) had also reached a similar conclusion that a requirement for carcinogenic potential in the peritoneal cavity was that the fibres were insoluble there.

But this is taking us ahead in this history.

1.1 Asbestos and man-made vitreous fibres

Today, there is a general international consensus that the adverse health effects of respirable fibres are primarily related to three factors, often termed the three Ds:

- *Dose:* the amount of respirable airborne fibres to which people are exposed;
- *Dimensions:* the size of the airborne fibres, which governs how easily fibres may be inhaled, where they may be deposited in the lungs and the mechanisms by which they can be removed from the lungs;
- *Durability:* better termed "Biopersistence", that is, how long inhaled and deposited fibres will be retained in the lung.

Airborne fibres are unique in that they are the only airborne particles which can be inhaled but which may be too long for clearance by macrophages, the primary deep-lung clearance mechanism. The critical fibre size is longer than about 15 μm and finer than about 1 μm. Thus, fibres longer than those that can be engulfed by macrophages can only clear by dissolution or by transverse fracture into shorter pieces. This fracture, if it occurs, is only likely if there has been significant dissolution of the fibre. Fracture is much less likely for asbestos fibres, than for the man-made vitreous fibres (MMVFs). Asbestos fibres are crystalline, and tend to split longitudinally creating finer fibres, whereas MMVF[1] are amorphous, and cannot split longitudinally.

The fibres of most concern are those that are sufficiently durable to remain in the lungs for a sufficient period of time, are fine enough to enter the lungs in the

---

[1] Throughout this report I refer to "man-made vitreous fibres (MMVF)", the most commonly used term today. originally, "man-made mineral fibres (MMMF)" was in common use; "synthetic vitreous fibres (SVF)" is also used, particularly in Australasia.

first place, and are present in a high enough dose: erionite and crocidolite (blue) asbestos. Both these fibre types are very fine, with the majority of airborne fibres less than 0.2 μm in diameter. Such fibres can be inhaled easily, deposited readily in the lung, and are very biopersistent. In use, asbestos exposure levels have often been higher than 100 f.ml^{-1}, and exposures have been reported above 1,000 f.ml^{-1} (NIOSH, 1976; Harries, 1971). Erionite exposures, such as those which occurred at Karain, Turkey, were rather lower, but this environmental exposure was continuous, effectively increasing the dose. For these fibre types (and for amosite and chrysotile asbestos), there is clear human evidence of the causation of the other three Ds: Disability, Disease and Death, from mesothelioma, lung cancer and lung fibrosis (IARC, 1977).

Airborne asbestos fibres are rather short, but studies from the Institute of Occupational Medicine (Cullen et al, 2000; Davis et al, 1986) have shown that there are enough long fibres present for there to be free non-soluble fibres in the lung tissue available to cause lung damage. There may be additional cytotoxicity enhancing the adverse effects of these fibre types.

At the other end of this continuum of mineral fibres come the MMVF. The term MMVF includes the insulation wools (fibre glass, stone [rock] wool, slag wool), refractory ceramic fibres and some speciality glass fibres. Some exposures to refractory ceramic fibres have been recorded up to about 20 f.ml^{-1}, but that is an uncommon occurrence. Occupational exposures to fibre glass, stone and slag wool have rarely exceeded about 5 f.ml^{-1} under the dustiest conditions (IARC, 1988).

The fibre diameters of most MMVF are much larger than those of asbestos fibres, with few MMVF less than 1 μm and virtually none less than 0.2 μm in diameter. However, airborne respirable MMVF can be much longer than asbestos fibres. The other major difference between asbestos fibres and MMVF is in their biopersistence. For example, Hesterberg et al (1996, 1998) compared, by inhalation, the biopersistence of crocidolite, amosite and several MMVFs. One year after the end of exposure, 17 per cent of the crocidolite fibres and 70 per cent of the amosite fibres longer than 20 μm had been cleared from the rat lungs. For the most biopersistent MMVF, 90-95 per cent of long fibres had been cleared and for the least biopersistent, most soluble fibre types, more than 99 per cent of long fibres were cleared.

1.2 Initial research programme on MMVF

The research reports by Stanton and Wrench, and Pott and Friedrichs in 1972 triggered the European and American insulation wool trade associations to consider what research should be supported following the findings of carcinogenicity of fibres implanted or injected into the pleural and peritoneal cavities of rats. The trade associations required that supported research should be carried out by independent research teams, with publication expected in the peer-reviewed literature.

In late 1975, EURIMA (European Insulation Manufacturers Association) and CIRFS (Comité International de la Rayonne et des Fibres Synthétiques) agreed to cooperate in a research programme. They created the Joint European Medical

Research Board (JEMRB). This is an English charity advising the industry and sponsoring relevant research. The initial sponsorship was for a cohort mortality study of production workers, for industrial hygiene studies, and for animal experimental research (Cameron, 1977). At the same time in USA, TIMA (Thermal Insulation Manufacturers Association of America) initiated a similar sponsored research programme.

In Europe, the epidemiological studies were undertaken at the International Agency for Research on Cancer, Lyon, France (IARC) with the associated industrial hygiene being carried out by the Institute of Occupational Medicine, Edinburgh (IOM). The epidemiological research in USA was undertaken at the University of Pittsburgh, in the Department of Biostatistics and the Center for Environmental Epidemiology. The industrial hygiene programme was also conducted in the same University, in the Department of Industrial and Environmental Health Sciences.

These studies initially included around 22,000 production workers in the European study, and 17,000 in the American study. These are among the larger cohort studies ever undertaken. There are some differences between these two studies, of which the reader should be aware. The European study included production workers in most factories who had had less than one-year of employment. In the American study, the lower employment limit was one-year in 15 factories, and six months in the other two. The American term "mineral wool" is equivalent to the previous European term "rock/slag wool" and the current term "stone/slag wool". The European study concentrated on lung cancer, whereas the American study considered respiratory system cancer, which is typically about four per cent higher.

There have been no published mortality or cancer incidence studies of refractory ceramic fibre workers, in production or use, so this group of MMVF is not considered further in this review.

2. The Years from 1975 to 1987

2.1 First WHO European Office Workshop on MMVF

An early initiative by JEMRB was the sponsorship of a Workshop at the WHO Regional Office for Europe in October 1976. This workshop (WHO Regional Office for Europe, 1977) considered the then present knowledge and research on the biological effects of exposure to man made vitreous fibres (MMVF).

At this time, the consensus was that there was very little evidence of adverse health effects of occupational exposure to MMVF (other than transient mechanical skin irritation), although the intra-cavitary studies published four years earlier did raise questions needing resolution (Gilson, 1977). In discussion, the production industry was described as "an industry searching for a problem".

2.2 Second WHO European Office Symposium on MMVF

But the picture was changing. At the second WHO meeting in 1982, evidence was presented of a small excess of lung cancer among production workers with more than 30 years since first employment. Workers producing stone/slag wool had a greater excess than those producing glass fibres in both the major European and American mortality studies, but the pattern of excess lung cancer did not appear to be related to length or intensity of exposure (Enterline & Marsh, 1984; Saracci et al, 1984).

For example, Table 1 presents the lung cancer mortality analysis for the follow-up to 1977–1979 (dependent on country) from the European study (Saracci et al, 1984) sub-divided by type of fibre produced. For each type of fibre, the SMR was highest for those with 30 or more years since first employment, although none of the SMRs was statistically significant at the conventional five per cent significance level. Unlike the extended follow-up investigations, this first study only determined the SMRs by reference to the national populations.

"Years since first employment" has been used in most of these epidemiological studies as a surrogate for exposure, as no individual estimates of exposure to respirable fibres have been available. In these early years, estimates of airborne respirable fibres could be determined for the various production areas in each factory, but not assigned to the individual workers as the employment records were inadequate for epidemiological purposes. "Duration of employment" has also been used, but the research teams have generally preferred "years since first employment" as the primary surrogate measure. Where relevant, this review has used this latter index.

However, any index based solely on time cannot provide any differentiation in response related to exposure to respirable fibres. The most recent studies, discussed in sections 4.1 and 4.2, have included assessments of fibre exposure for individual workers.

Table 1. European Cohort Study: mortality analysis up to 1977-1979. Deaths from cancer of the trachea, bronchus and lung, SMRs, and 95% confidence intervals. (Males only. Expected deaths based on national reference populations.)

		Years since first employment			
Production		<20 years	20–29 years	30 + years	Total
Glass wool	Deaths	30	10	4	44
	SMR	**96**	**76**	**157**	**94**
	95% ci	*65–137*	*37–140*	*43–402*	*68–126*
Stone/slag wool	Deaths	27	12	11	50
	SMR	**91**	**124**	**195**	**111**
	95% ci	*60–132*	*64–217*	*97–348*	*82–146*
Continuous filament glass	Deaths	11	2	2	15
	SMR	**139**	**104**	**333**	**143**
	95% ci	*69–248*	*13–374*	*40–1204*	*80–236*

From: Saracci et al (1984)

Environmental surveys (Esmen, 1984; Ottery et al, 1984) showed that the levels of fibre exposure were low, providing very little support for suggestions that the excess of lung cancer was related specifically to the fibre exposures. Cherrie et al (1986) reported on their re-assessment of the exposure levels in conformity with the then new standard for fibre counting (WHO/EURO Technical Committee, 1985). Although using the new standard approximately doubled the fibre counts, they were still considered by the authors to be low: generally <0.1 f.ml^{-1} (fibres per millilitre) for stone/slag wool; <0.05 f.ml^{-1} for glass wool; and <0.01 f.ml^{-1} for continuous filament. In one of the stone/slag wool secondary process groups, fibre counts reached an average of 0.67 f.ml^{-1}. The very few workers in the process which produced fine glass fibre ear plugs had exposures averaging 1.0 f.ml^{-1}. It should be noted that continuous glass filaments rarely have diameters under about 5 μm. So these are not included as respirable fibres, under any of the fibre counting rules for assessing exposure levels.

Two other studies of relevance were published at this time. Shannon et al (1984) reported on a mortality study of glass wool production workers in a Canadian factory. They also reported raised lung cancer mortality, with seven deaths, giving an SMR of 166 (95% ci 67–342). From a more detailed analysis, they did not consider that the lung cancer mortality excess was due to fibre exposure. Meanwhile results of a study of Swedish construction workers who used MMVF regularly showed an increased incidence of respiratory cancer. However, only a small proportion of these cases were considered likely to be due to exposure to MMVF (Engholm et al, 1984), although the findings did suggest an association between respiratory cancer risk and MMVF exposure. It was not possible to determine which types of MMVF were being used by these construction workers. Many of these workers were also exposed to asbestos dust.

So there was a need to temper the observations of some excess of lung cancer with a recognition that not all the excess was likely to have been caused by exposure to MMVF. Clearly the epidemiological studies needed to be continued, to raise the power to detect lung cancer risk, and to permit analyses taking into account confounding factors.

2.3 Third WHO European Office Symposium on MMVF

The third WHO Conference on "Man-made mineral fibres in the working environment" was held at WHO, Copenhagen in October 1986. The epidemiological session included follow-up reports on the European and American studies, and on the smaller Canadian study of glass fibre production workers (Simonato et al, 1987, 1988; Enterline et al, 1987; Shannon et al, 1987). Engholm et al (1987) reported further on their study of respiratory cancer incidence in Swedish construction workers.

2.3.1 The European Study

In the IARC-coordinated European study, the follow-up was extended for a further four years. The pattern of lung cancer mortality by years since first

employment (Table 2) was similar to that shown in Table 1. For glass wool production workers, the lung cancer mortality was significantly raised overall, based on standardization to national rates, but the excess disappeared when standardized using local rates. For stone/slag wool production workers, the SMR for lung cancer for workers with at least 30 years since first employment (12 deaths) had reduced slightly to 185 with 95 per cent confidence interval (95% ci 95–322), based on local mortality rates, where available. The trend with increasing time from first employment remained evident. In practice, the use of local or national rates for standardization had little effect in the stone/slag wool sector. For continuous filament production, this report shows no deaths for those first employed at least 20 years previously, compared with four in the earlier study (Table 1). It must be presumed that these missing cases were all among the office workers excluded in this study, but included previously.

An important feature of this 1987 report is that the analysis was extended considerably in scope, in particular by analysing those with less than one-year of employment separately, by considering the technological development of the industry, and by assessing the effects of potential confounding exposures.

Those employed for less than one year in the production industry had a markedly higher SMR for all causes (SMR 142, 95% ci 132–153), based on 741 deaths, compared with an SMR of 102 (98–107) for those employed for one or more years, based on 1978 deaths. This excess mortality for the short-term workers existed for all major causes of death, except lung cancer, for which the SMRs were: short-term workers 113 (79–157); longer-term workers 128 (109–150).

Table 2. European Cohort Study: mortality analysis up to 1981-1983. Stone/slag wool production: Deaths from cancer of the trachea, bronchus and lung, SMRs, and 95% confidence intervals (both sexes, expected deaths based on local reference populations).

Production		**Years since first employment**			
		<20 years	20–29 years	30 + years	Total
Early technological phase	Deaths	0	4	6	10
	SMR	**0**	**317**	**295**	**257**
	95% ci	*0–620*	*86–812*	*108–642*	*123–473*
Intermediate technological phase	Deaths	3	7	4	14
	SMR	**79**	**164**	**217**	**141**
	95% ci	*16–230*	*66–338*	*59–556*	*77–237*
Late technological phase	Deaths	44	11	2	57
	SMR	**120**	**90**	**77**	**111**
	95% ci	*87–161*	*45–161*	*9–278*	*84–144*
Total, all phases	Deaths	47	22	12	81
	SMR	**114**	**124**	**185**	**124**
	95% ci	*84–152*	*77–187*	*95–322*	*99–154*

From: Simonato et al, 1987

The Historical Environmental Investigation (Cherrie & Dodgson, 1986) for the European MMVF cohort study extended the earlier exposure assessments (Ottery et al, 1984; Cherrie et al, 1986) to consider the effects of changes in production

methods over time. They identified three factors believed to be influential in reducing exposures to MMVF: addition of oil to the process of fibre production; increase in the nominal fibre size; and introduction of continuous production of insulation.

Based on the above factors, three technological phases were defined for the epidemiological analyses. In the early phase, batch production was in use and/or no oil was added to the fibres during production. In the late phase, production methods were judged to be similar to modern production techniques. An inter-mediate phase was identified in some factories. Table 2 shows ten deaths from lung cancer among those stone/slag wool production workers first employed during the early technological phase, resulting in a significantly raised SMR of 257 overall, and with high SMRs for those employed for 20 or more years. However, only 0.7 lung cancer deaths were expected for those with less than 20 years since first employment, so that any trend is possibly more apparent than real. For those workers first employed in the late production phase, a decreasing trend of SMR with increasing time since first employment appears, but there are too few people with a long time since first employment for this trend to be convincing.

Yet, the patterns of mortality in the margins of Table 2 show trends in lung cancer mortality by years since first employment and by technological phase. These univariate trends are consistent with the hypothesis that exposure to stone/slag wool was a cause of lung cancer. They are also, of course, consistent with the hypothesis that other factors related to employment in stone/slag wool production were a cause of lung cancer.

A similar analysis for glass wool production workers shows no evidence of an association of lung cancer mortality rates and time since first employment or with technological phase when mortality rates were calculated based on local reference populations.

In assessing these findings, the exposure levels should be considered. Based on a mathematical model of the effects of changing production conditions, Dodgson et al (1987) presented, for each technological phase and factory, upper and lower estimates for the time-weighted average exposure levels. For the glass wool plants, the authors concluded that mean airborne glass fibre levels in the early technological phase "were little different from current levels (about 0.1 [respir-able] f.ml^{-1} or less)".

For the stone/slag wool factories, taking the mid-point between these upper and lower estimates, the early phase exposures ranged between 0.15 and 1.2 f.ml^{-1}. By the late technological phase, these exposure levels had dropped to between 0.08 and 0.11 f.ml^{-1}. The differences between the phases accord reasonably with the results from an experimental simulation of past exposure conditions (Cherrie et al, 1987).

In addition to defining the technological phases, Cherrie and Dodgson (1986) also assessed other environmental risk factors (asbestos, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde, and arsenic). These risk factors, and the use of slag in the stone/slag wool production process, were

analysed by Simonato et al (1987, 1988). They reported a doubling of lung cancer mortality in stone/slag wool production when slag was being used, with no evidence of an excess otherwise. This is described as difficult to interpret as the periods with no slag wool use coincided with the late technological phase. Copper slag was used to some extent, showing an additional excess but based on only four deaths, so the possibility of arsenic-related lung cancers cannot be proven.

For asbestos, there was an apparently anomalous result, with an SMR in stone/slag wool below 100 when asbestos was in use, and about 170 when no asbestos was being used in production. However, the use of asbestos was one criterion for exclusion of a factory from the European cohort study, so no pattern should have been expected. For none of the other potential confounding exposures was there any evidence of an association with lung cancer mortality.

A cancer incidence study was also undertaken for the factories in those countries with adequate cancer registries. The results are very similar to those in the mortality study.

The only other causes of death to show a significantly elevated mortality rate was "Accidents, poisoning and violence", and its subset "Suicide". In the cancer incidence study, cancer of the buccal cavity and pharynx showed a just significant excess – the Standardized Incidence Ratio, based on 26 deaths, was 153 with 95% ci 99.9–224. The excess occurred in both stone/slag wool and glass wool production, but the pattern of the cancer incidence with time since first employment was irregular.

2.3.2 The American cohort study

As for the European cohort study, the University of Pittsburgh study of 16,661 workers in 17 factories extended the follow-up by a further five years. Table 3 presents a global overview of malignant neoplasm mortality rates for all factories combined. Separate data by type of production were not published, except for respiratory cancer presented in Table 4, and discussed below. There was a small excess of malignant neoplasms, which was higher and just statistically significant for those with more than 20 years since first employment. For buccal cavity cancer, the SMR was 122, raised equally independent of the number of years since first employment. This rate is also almost identical to the SMR of 123 (95% ci 65–210) in the European study.

For both respiratory cancer and lung cancer, the SMR was close to 100 for those with less than 20 years since first employment in MMVF production. However, for those with more than 20 years since first employment, the SMR was very close to being statistically significant.

Table 4 presents the mortality rates for respiratory cancer by type of production. As for the European study, the main excess respiratory cancer mortality occurred among the mineral wool (stone/slag wool) production workers, with a statistically significant excess overall, but no pattern by time since first employ-

Table 3. American Cohort Study: mortality analysis up to 1982. Deaths from selected causes, SMRs, and 95% confidence intervals. (Males only. Expected deaths based on local population.)

		Years since first employment		
		<20 years	20 + years	Total
All malignant neoplasms	Deaths **SMR** *95% ci*	312 **100** *89–112*	735 **108** *100–116*	1047 **105** *99–112*
Buccal cavity and pharynx	Deaths **SMR** *95% ci*	12 **122** *60–132*	23 **122** *64–217*	35 **122** *82–146*
Respiratory system	Deaths **SMR** *95% ci*	90 **100** *80–123*	301 **112** *99.7–125*	391 **109** *98–120*
Trachea, bronchus and lung	Deaths **SMR** *95% ci*	82 **97** *77–120*	288 **113** *100–127*	370 **109** *98–121*

From: Enterline et al, 1987.

ment. The fibrous glass filament production workers showed no evidence of an excess respiratory cancer rate, and so the two factories that produced both filament and glass wool have been included with the glass wool production factories in Table 4. There is a very slight trend of increasing mortality with time, but the evidence of an excess is weak, and similar in magnitude to that seen in the European study.

Table 4. American Cohort Study: mortality analysis up to 1982. Respiratory cancer deaths, SMRs, and 95% confidence intervals by production process and time since first employment. (Males only. Expected deaths based on local reference populations.)

		Years since first employment			
Production		<20 years	20–29 years	30 + years	Total
Fibrous glass filament	Deaths **SMR** *95% ci*	15 **66** *37–109*	36 **119** *83–165*	13 **80** *43–137*	64 **92** *71–118*
Fibrous glass wool (+ glass filament in 2 factories)	Deaths **SMR** *95% ci*	60 **105** *80–135*	104 **108** *88–131*	103 **114** *93–138*	267 **109** *97–123*
Fibrous glass – all	Deaths **SMR** *95% ci*	75 **94** *74–118*	140 **111** *93–131*	116 **109** *90–131*	331 **105** *94–117*
Ever produced small diameter fibrous glass	Deaths **SMR** *95% ci*	8 **113** *49–222*	8 **105** *45–206*	6 **198** *73–431*	22 **124** *78–187*
Mineral wool	Deaths **SMR** *95% ci*	15 **143** *80–236*	20 **126** *77–195*	25 **135** *87–199*	60 **134** *102–172*

From: Enterline et al, 1987

In five factories, small diameter fibres were produced, but in lower volumes than fibrous glass wool. These fibres are typically manufactured in low volumes for special purposes, such as aircraft insulation, to have diameters under about 1 μm. Workers employed in the manufacture of these small diameter fibres would also have been involved in fibrous glass production. So the workers in these factories were sub-divided into ever- and never-employed in small diameter fibre production. Table 4 shows that overall, the respiratory cancer SMR for the ever-producers, based on local rates, was 124 (78–187). This compared with 105 (90–121) for the never-producers. Those first employed in small diameter fibre production at least 30 years earlier had a raised SMR of 198, based on six respiratory cancer deaths.

The authors also reported that exposure levels to small diameter fibrous glass were about ten times higher than for exposure to other fibrous glass. They commented that "Data presented here are consistent with the notion that work in departments that produced small diameter fibres is associated with respiratory cancer".

A major feature of this American cohort mortality study is that fibre exposures have been estimated for all the production workers. Table 5 shows the mortality pattern by increasing levels of cumulative fibre exposure, for the same product groups as used in Table 4 (other than for ever-production of small diameter fibres, for which the data were not presented). Overall, there is a decrease in SMR with increasing cumulative fibre exposure, with this trend being very strong for the mineral wool sector. For fibrous glass wool, there is some reduction in the SMRs, as cumulative exposure increases, but the values are rather lower than for mineral wool. For fibrous glass filament, the SMRs are generally low, reflecting the overall SMR of 92 (Table 4).

To investigate the pattern of mortality further, Enterline et al (1987) nested a case-referent study within their cohort study, using respiratory cancer cases 1950-1982 as the cases, and a four per cent stratified random sample of non-cases as the referents, subject to exclusion criteria related to age, the specific dates, and mortality from respiratory cancer or non-malignant respiratory disease (other than influenza or pneumonia). Smoking information was sought from any of the controls still alive, and from knowledgeable informants. For fibrous glass, attempts to get smoking histories were successful for 242 of 330 respiratory cancer cases and for 387 of 529 referents. For mineral wool, the success rates were 45 of 60 cases and 49 of 67 referents.

For both fibrous glass wool and mineral wool, an analysis including a smoking index, never- or ever-smoker, showed a very highly significant relation of respiratory cancer to smoking, and no significant association with cumulative fibre exposure. However, for mineral wool, the association with cumulative fibre exposure was positive, and this was considered unexpected given the pattern of decreasing SMRs with cumulative fibre exposure alone (Table 5).

Table 5. American Cohort Study: mortality analysis up to 1982. Respiratory cancer deaths, SMRs, and 95% confidence intervals by production process and cumulative fibre exposure. (Males only. Expected deaths based on local reference populations.)

Production		Cumulative fibre exposure[1]			
		Lowest	Lower	Higher	Highest
Fibrous glass filament	Deaths	53	3	7	1
	SMR	**96**	**51**	**109**	**62**
	95% ci	*73–127*	*11–160*	*44–255*	*2–348*
Fibrous glass wool (+ glass filament in 2 factories)	Deaths	147	40	37	43
	SMR	**120**	**109**	**81**	**108**
	95% ci	*102–141*	*74–148*	*57–112*	*78–146*
Fibrous glass – all	Deaths	200	43	44	44
	SMR	**113**	**101**	**84**	**106**
	95% ci	*97–129*	*73–136*	*61–113*	*77–143*
Ever produced small diameter fibrous glass	Deaths	7	22	18	13
	SMR	**185**	**164**	**119**	**104**
	95% ci	*74–382*	*103–248*	*70–118*	*55–177*

Note: The cumulative fibre exposure groups are as follows (in f.ml^{-1}.months)
    Fibrous glass: <2.14   2.14−4.67   4.67−9.99   10 +
    Mineral wool: <4.67   4.67−21.88   21.88−99.99   100 +
From: Enterline et al, 1987

In further analyses, smoking was included in the analysis as duration of smoking and years since first smoking. For fibrous glass, the smoking history was complete enough for 211 cases and 374 referents. In these analyses, there remained no significant association of lung cancer risk with cumulative fibre exposure, but there was the expected pattern with duration of smoking.

For mineral wool, adequate smoking histories were available for 38 cases and 43 referents. The logistic regression analyses showed a significant association of increasing respiratory cancer risk with increasing cumulative exposure to fibres, as well as the expected association with cigarette smoking. The log odds ratio for time-weighted cumulative exposure (f.ml^{-1}.months) was 0.008 (P=0.009).

In contrast to this positive association, Table 5 shows for mineral wool a marked decline in respiratory cancer SMR with increasing estimated cumulative fibre exposure. Trying to reconcile these contrasting results, the authors analysed the data by year of hire, reporting higher respiratory cancer rates for those hired most recently, suggesting that this was concordant with the patterns of increasing smoking rates over time. The main conclusion of this reconciliation was that there was a marked confounding of the mortality patterns by smoking.

2.3.3 Other mortality studies

At this third symposium on MMVF, Shannon et al (1987) presented an update on the Ontario glass fibre workers study, as did Engholm et al (1987) on the Swedish respiratory cancer incidence study of construction workers.

The Ontario study of one glass fibre production factory covered 2,557 men, who had worked in the factory for at least three months. The only statistically

significant excess mortality rate was for lung cancer. The SMR for those who worked in fibre production was double expectation: 19 men; SMR 199; 95% ci 120–311. However, the authors point out that several of these lung cancer cases had been employed for a short period only, or had short latency. They also considered that the lung cancer mortality pattern in relation to either duration of employment or years since first employment was "not consistent with an occupational cause".

The Swedish study of the incidence of respiratory cancer among 135,000 construction workers was extended to the end of 1983. About ten years earlier all the workers had been interviewed, and *inter alia* questioned about whether they had ever worked with glass wool, mineral wool, or with materials containing asbestos. They were asked when they first did such work and for how long. Industrial hygienists graded each of the 160 tasks in the industry on a six-point scale of potential for exposure to MMVF (without differentiation by type of fibre) and asbestos. Tobacco smoking information was also collected.

Overall, there was an excess mortality from industrial accidents. For all causes, the SMR was 68, based on 7,356 deaths. For malignant neoplasms of the trachea, bronchus and lung, the SMR was also low, being 86 (95% ci 79–95), based on 444 deaths. Non-malignant respiratory disease mortality was even lower, with an SMR of 46 (40–53). The cancer incidence analysis found an excess of pleural mesothelioma, with 23 cases compared with eleven expected.

In the nested case-control study, each of the 424 incident lung cancer cases was matched to five control subjects alive for at least as long as the case since the date of original interview. The authors note that there was a poor relation between the hygienists' assessments of asbestos exposure, and self-reported exposure. Also, the analysis was limited by the very high correlation between the assessments of exposure to MMVF and asbestos. The final analyses showed a lung cancer relative risk for MMVF exposure, adjusted for asbestos exposure, smoking and population density of 1.21 (95% ci 0.60–2.47). For asbestos exposure, the adjusted relative risk was 2.53 (0.77–8.32). The conclusion was that "it would appear that there is a risk related to asbestos exposure but no evidence of a risk related to [MMVF] exposure after allowing for asbestos" but that because of the high correlation between the two exposures "the follow-up of this cohort so far provides insufficient data for an evaluation of risks associated with inhalation of [MMVF] fibres."

Moulin et al (1986) reported on a study of cancer incidence among some 1,400 stone wool producers in northern France over ten years. They found no excess of lung cancer, but they did find a statistically significant doubling of incident cancers of the upper respiratory and alimentary tract. However, the cancer registries used as the basis for the cancer incidence rates were not located in the area of the factory, and subsequently a follow-up study (Czernichow et al, 1989) did not confirm the original findings.

3. The IARC and IPCS reviews of the health effects of MMVF, 1987

Just before this third WHO Symposium discussed above, a supplement to the Scandinavian Journal of Work, Environment and Health was published, devoted to the European Study co-ordinated by IARC. The mortality study report (Simonato et al, 1986) was effectively identical to that presented in Copenhagen, and separate reports were made for the production factories in each of the seven countries of the study. This supplement was introduced by a review of the epidemiological evidence, and it is relevant to note that Saracci (1986) closes the review:

> "The 1982 follow-up was undertaken with the awareness that more observation may not necessarily bring about more clarity. However, after the exercise was completed, it appeared that the extended follow-up combined with the historical industrial enquiry could lead some steps further towards clarity – in my opinion, in two different directions. First, it endorses the indication from the previous follow-up (1977) that no adverse long-term health effects have been detectable in terms of mortality throughout almost all segments of the MMMF producing industry. This outcome is of paramount importance for the employees and management in this industry, notably if it receives reconfirmation in the future from longer observations of the workers exposed for longer periods. Second, it supports the inference that MMMF – as present in the environmental conditions of the early slag wool/rock wool production – may have played a role in the causation of lung cancer."

Thus, the scene was painted for the formal reviews of hazard, by IARC (1988), and of environmental risk, by the International Programme on Chemical Safety (IPCS, 1988).

3.1 IARC Evaluation of Carcinogenic Hazard, 1987

IARC convened a Working Group of 23 independent scientists in June 1987 to consider the hazard classification for the carcinogenicity of MMVF and of Radon (IARC, 1988) (Table 6). The report assessed the levels of MMVF exposure as published to that date, and noted that exposure levels in glasswool production have generally been 0.1 respirable $f.ml^{-1}$ or less, and about 0.2–0.3 $f.ml^{-1}$ in stone/ slagwool production. Airborne fibre concentrations in the production of fine glass fibres were some tenfold higher than in glasswool production, averaging 0.8 $f.ml^{-1}$. In ceramic fibre production factories, the average airborne fibre concentrations were yet a little higher, up to 3 $f.ml^{-1}$.

These exposure levels need to be viewed from the perspective of asbestos exposure levels at about the same time. In production, exposure levels ranged up to 200 $f.ml^{-1}$ in insulation production, up to 140 $f.ml^{-1}$ in asbestos textile production and around 20 $f.ml^{-1}$ in the production of other materials (IARC,

1977). These levels are some 100 times higher than the maximal exposures reported for those doing similar work during MMVF production and use.

Table 6. IARC (1988) Classification for the carcinogenicity of MMVF.

Man-Made Vitreous Fibres Evaluation			
Glass Wool & Fine Glass Fibres	**Glass Filaments**	**Rock (Stone) and Slag Wool**	**Ceramic Fibres**
Human carcinogenicity			
"There is inadequate evidence for carcinogenicity to humans"	"There is inadequate evidence for carcinogenicity to humans"	"There is limited evidence for carcinogenicity to humans"	"There are no data available on the carcinogenicity to humans"
Animal carcinogenicity			
"There is sufficient evidence for the carcinogenicity of glass wool in experimental animals"	"There is inadequate evidence for the carcinogenicity of glass filaments in experimental animals"	"There is limited evidence for the carcinogenicity of rock (stone) wool in experimental animals"	"There is sufficient evidence for the carcinogenicity of ceramic fibres in experimental animals"
Overall Evaluation			
2B	**3**	**2B**	**2B**
Possibly carcinogenic to humans	Not classifiable as to their carcinogenicity to humans	Possibly carcinogenic to humans	Possibly carcinogenic to humans
Extracted from: International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risks of humans. *Man-made vitreous fibres and radon*, vol 43. 1988.			

On the mortality and cancer incidence studies, the conclusions of the IARC Working Group were similar to those presented above, and particularly as expressed in the quotation from Saracci. Table 6 shows the classification of MMVF, as used by IARC (1988). The concern expressed that stone/slag wool may be carcinogenic, but without convincing evidence of an association with fibre exposure, is reflected in the classification of "limited evidence" of carcinogenicity to man.

Table 6 also shows the conclusions drawn by the IARC Working Group from the experimental studies, and the overall evaluation. All the fibre groups, except glass filaments, were considered to be "possibly carcinogenic to humans (Group 2B)".

3.2 IPCS Review of Environmental Risk, 1987

Three months after the IARC Working Group meeting, IPCS (1988) convened its own review by 19 independent scientists of environmental risk to humans through exposure to MMVF. The evidence considered was inevitably the same as in the IARC report; six of the scientists were also members of the IARC working group.

However, there was one key difference between the two reports: the grouping of fibre types differed, as may be seen in Table 7. In particular, special purpose glass fibres were separated from glass wool, on the basis of method of

manufacture, size and use. This is reflected in the higher fibre exposure levels for the finer fibres (Esmen et al, 1979). It is the IPCS grouping which has generally been followed in subsequent scientific reports and regulatory decisions.

Table 7. IPCS (1988) Classification of MMVF.

Man-Made Vitreous Fibres			
Continuous Filament	**Insulation Wool**	**Refractory Fibres**	**Special Purpose Fibres**
1) Glass	1) Glass wool 2) Stone wool 3) Slag wool	1) Ceramic 2) Others	1) Glass microfibres
Overall Environmental Assessment			
The overall picture indicates that the possible risk for the general population is very low, if there is any at all, and should not be a cause for concern if current low exposures continue			

The IPCS reviews are more concerned with risk, rather than hazard, and with a wider range of possible adverse health effects. For the occupationally exposed, the review considered dermatitis, eye irritation and non-malignant respiratory disease. For the first two of these, the data were considered insufficient to derive any exposure-response relation; for non-malignant respiratory disease, conclusions could not be drawn concerning the nature or extent of any association.

As for the IARC review, IPCS considered that for production workers, the lung cancer epidemiology was "consistent with the hypothesis that it is the airborne fibre concentrations that are the most important determinants of lung cancer risk". IPCS also noted that higher exposure levels could have occurred in the production of ceramic fibres and small diameter special purpose glass fibres, and in the application and spraying of insulation wool in confined spaces.

For the general population, IPCS noted that exposure levels were several orders of magnitude lower than exposures associated with lung cancer risks. The review concluded

> "Thus, the overall picture indicates that the possible risk for the general population is very low, if there is any at all, and should not be a cause for concern if current low exposures continue."

4. The Years from 1987 to 2002

At the start of this second half of these 25 years, there was public and regulatory concern about the possible health effects of exposure to MMVF. For example, the UK Health and Safety Executive (1986) published a Guidance Note on exposure to MMVF, which has been updated periodically. Also the UK Committee on Carcinogenicity (Health and Safety Executive, 1987) reviewed the evidence about workplace exposure, on the human evidence of lung cancer risk, and from experimental studies. Its statement advised that

> "it would be prudent to act on the basis that sufficient exposure to any form of MMMF in the production industry (or in the user industries) may increase the risk of lung cancer among the work force".

These concerns prompted a Resolution of the International Labour Office (ILO) in 1986 concerning health risks of occupational exposure to fibres. This formal resolution required ILO to convene a meeting of "Experts on Safety in the Use of Mineral and Synthetic Fibres", which was held in Geneva in April 1989 (ILO, 1989). The primary outcome was that a Code of Practice for Safety in the Use of Mineral and Synthetic Fibres should be prepared.

Among the Unions, the US AFL-CIO (1991) recommended to the US Environmental Protection Agency that there should be a permissible exposure limit of 1 f.ml^{-1} for respirable glass fibres, time-weighted average. The International Federation of Building and Wood Workers (1993) also recommended a draft policy on MMVF and a list of control measures. They demanded that MMVF dust should be declared a carcinogenic substance, and supported the ILO proposal for a Code of Practice.

The epidemiological research continued. The next sections consider the cohort mortality and cancer incidence studies; the case-control studies; and additional evidence from other epidemiology.

Miettinen and Rossiter (1990) argued at this time that the conclusions from the cohort study results were biassed *inter alia* by assuming that the national or regional comparison populations were actually comparable to the cohort populations, in particular in relation to smoking habits. Later in this review, we shall see that epidemiological approaches not dependent on SMR analyses may lead to a different conclusion about potential lung cancer risk.

4.1 Cohort mortality and cancer incidence studies

4.1.1 The European cohort study: Lung cancer mortality

Boffetta et al (1995, 1997) and Sali et al (1999) have reported on the update of the major European study, with a mortality update to 1990 and cancer incidence to 1994-1995. The findings and conclusions were essentially unchanged from the previous follow-up.

Although the number of person-years of follow-up increased by 34 per cent to nearly 500,000, there was little change in conclusion from the previous study (Simonato et al, 1987, 1988). For glass wool production workers, the lung cancer mortality remained significantly raised overall, based on standardization to national rates, but the excess reduced to an SMR of 112 (95% ci 95–131) when standardized using local rates. For stone/slag wool production workers, the number of lung cancer deaths for workers with at least 30 years since first employment increased from 12 to 42 deaths, but the SMR reduced slightly to 171 (95% ci 123–230), based on local mortality rates, where available. In practice, the use of local or national rates for standardization had little effect in the stone/slag wool sector. For continuous filament production, this report now shows six lung

cancer deaths for those first employed at least 20 years previously; this SMR is 93 (95% ci 34–203).

For the stone/slag wool sector in more detail, the trend with increasing time from first employment and technological phase remained evident (Table 8). However, comparison of this table with Table 2 for the previous follow-up period, shows that the trends are less marked. A more detailed analysis by period of follow-up led the authors to suggest that "the excess [lung cancer] risk may be concentrated among workers starting their employment in the industry more than 40 years ago", as more recent recruits have a lower SMR for lung cancer.

This extended follow-up again considered the possible confounding effects of exposure to other potential carcinogens in the working environment of the stone/slag wool production factories: asbestos, slag, bitumen, and formaldehyde. There were slightly higher SMRs related to asbestos, slag and formaldehyde exposures, but not for bitumen. These differences were small and not enough to account for the excess lung cancer mortality overall. However, the authors did record that there was additional evidence available indicating that all workers in the German factory could have been exposed to asbestos.

The importance of slag in this environment is that the metal slags that were used were from the production of lead and copper. These could lead to airborne exposures to arsenic, lead and cadmium.

To investigate further the relation of lung cancer risks to stone/slag wool exposure, Consonni et al (1998) undertook a multivariate Poisson regression analysis, using exposure estimates lagged by 15 years. These estimates of cumulative and maximal annual exposure to airborne respirable fibres were calculated for each worker, based on a mathematical model of exposure levels in each factory over time (Krantz et al, 1991). This model did not permit differential assessment of exposure by job or task.

Table 8. European Cohort Study: mortality analysis up to 1990. Stone/slag wool production: Deaths from Cancer of the trachea, bronchus and lung, SMRs, and 95% confidence intervals (both sexes, expected deaths based on local reference populations).

		Years since first employment			
Production		<20 years	20–29 years	30 + years	Total
Early technological phase	Deaths	0	4	7	11
	SMR	**0**	**317**	**175**	**187**
	95% ci	*0–605*	*87–813*	*70–361*	*93–335*
Intermediate technological phase	Deaths	3	8	9	20
	SMR	**78**	**152**	**149**	**132**
	95% ci	*16–228*	*66–299*	*68–282*	*81–204*
Late technological phase	Deaths	62	43	26	131
	SMR	**127**	**134**	**178**	**137**
	95% ci	*97–162*	*97–180*	*116–261*	*115–163*
Total, all phases	Deaths	65	55	42	162
	SMR	**122**	**142**	**171**	**139**
	95% ci	*94–155*	*107–185*	*123–230*	*118–162*

From: Boffetta et al, 1995, 1997

Table 9. European Cohort Study: mortality analysis up to 1990. Stone/slag wool production: Relative risks of death from cancer of the trachea, bronchus and lung, by exposure to respirable fibres (males only).

		Cumulative exposure to respirable fibres (f.ml^{-1}.years)			
Exposure groups		*0–0.007*	*0.008–0.136*	*0.137–1.367*	*1.368 +*
All workers	Deaths	39	40	40	40
	RR	**1**	**1.3**	**1.2**	**1.5**
	95% ci	*reference value*	*0.8–2.4*	*0.7–2.1*	*0.7–3.0*
Exposure groups		*0–0.139*	*0.140–0.729*	*0.730–2.622*	*2.623 +*
Workers employed > 1 year	Deaths	25	24	24	24
	RR	**1**	**0.9**	**0.8**	**1.0**
	95% ci	*reference value*	*0.4–2.0*	*0.3–1.9*	*0.4–2.7*

From: Consonni et al, 1998.

Table 9 shows the relative risks for four groups of estimated exposure to airborne stone/slag wool respirable fibres. These relative risks were standardized for country (Denmark, Sweden, Norway, Germany), age, calendar year, time since first employment and employment status.

For all male workers, there were 159 lung cancer deaths, and the exposure level ranges had been chosen to give equal numbers of deaths in each group. There was a slightly increasing trend (P=0.04) of relative risk with increasing estimated exposure to airborne respirable fibres (Figure 1). For maximal annual fibre exposure, there was no trend.

Figure 1. Cumulative exposure to MMVF and realtive Risk of Lung Cancer (from Consonni et al, 1998).
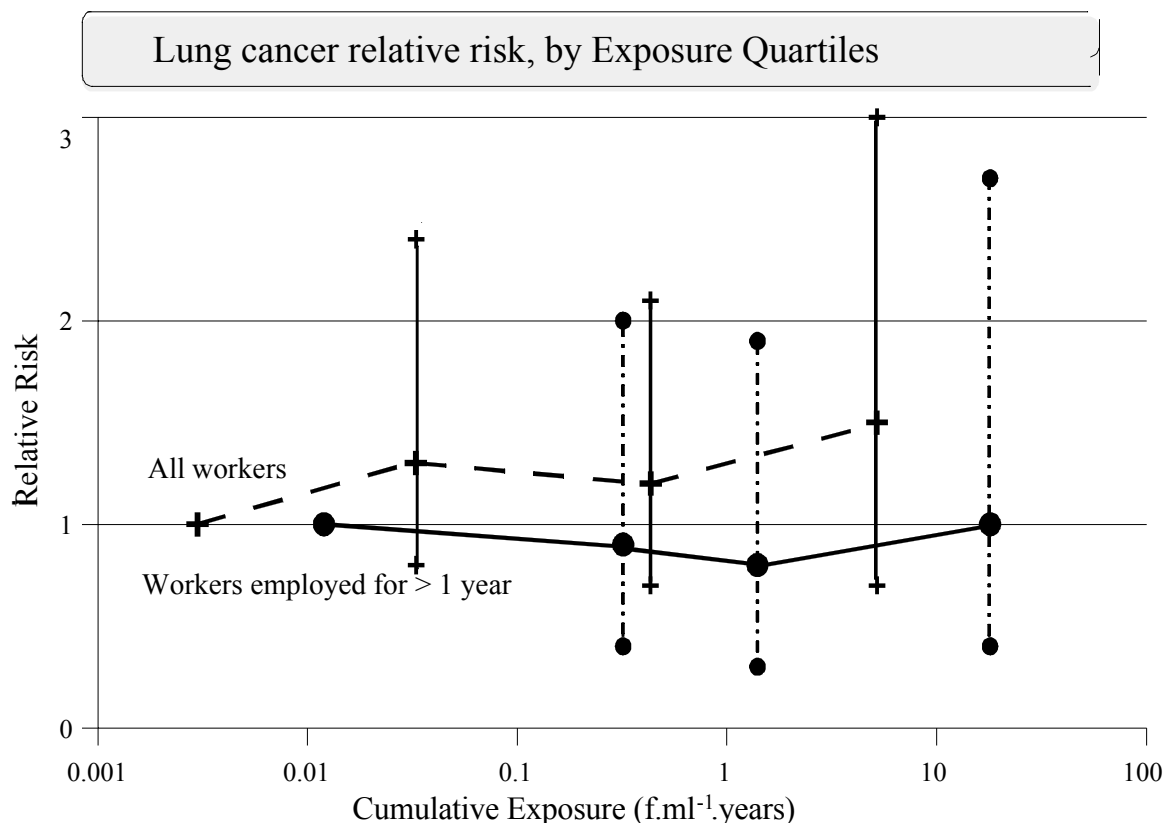
For the workers employed for at least one year, there was no trend at all with each relative risk equal to or less than unity (Figure 1). For maximal annual exposure, there was a tendency for the relative risk to decrease with increasing exposure level.

It is perhaps surprising that the authors concluded "We found a positive association ...", but they do continue

> "However, the lack of statistical significance, the dependence of the results on inclusion of short-term workers, the lack of consistency between countries, and the possible correlation between exposure to respirable fibers and to other agents reduce the weight of such evidence."

4.1.2 The European cohort study: Other causes of death

There were five mesothelioma cases; one in the glass wool sector, who had worked in one production factory for 25 years, but who had a considerable lung burden of asbestos fibres, believed not to be associated with employment in fibre glass production. Of the four in the stone/slag wool sector, two cases had worked for less than one year and had been employed there late in life. The other two had been employed in the German factory, and one of these had received compensation for asbestos-related disease. It seems unlikely that there is an association between MMVF exposure and mesothelioma, based on the evidence in this study.

The SMRs were raised, but not significantly, for cancers of the oral cavity, pharynx and larynx, for the pancreas, rectum, bones, and bladder. In each case there was little evidence to suggest any association with exposure to MMVFs. However there was a significant excess of neoplasms coded as "ill-defined and unspecified sites" which occurred in all three sectors of the production industry.

Sali et al (1999) reported separately on non-neoplastic mortality. They concluded that non-neoplastic mortality appears unrelated to employment in the European MMVF production industry. However, they did recommend further investigations on mortality from ischemic heart disease and non-malignant renal disease. The basis for the first recommendation was that there was an increase in ischemic heart disease for those with at least 30 years since first employment in the stone/slag wool and continuous glass filament sectors. However, most of this excess occurred for those employed for less than one year in MMVF production.

For renal diseases, the authors report a suggestive trend of increasing risk with duration of employment in the stone/slag wool sector and by technological phase. However, these observations are based on only six deaths in total in this sector of the production industry.

For cirrhosis of the liver, there was increased mortality among the stone/slag wool, primarily among the short-term workers. However for glass filament workers, those with more than one year of employment had a significantly raised SMR of 235 (95% ci 128–394) and there was a suggestion of an increasing trend with increasing duration of employment.

The above findings suggest that there may be lifestyle factors affecting non-neoplastic mortality rates, supported by the observations in the stone/slag wool

sector of high mortality rates for mental diseases. For short-term workers, the SMR was 467 (95% ci 313–671), but for the longer term workers, the SMR was also high (SMR 186, 95% ci 115–284). Death rates for accidents, poisoning and violence were also markedly raised, particularly but not only among the short-term workers.

4.1.3 The European cohort study: Cancer incidence

The cancer incidence study was extended to 1994 or 1995, dependent on country, for Denmark, Sweden, Norway and Germany (Boffetta et al, 1999). Those employed for less than one year were excluded. For lung cancer incidence, the results were similar to the mortality findings, as expected, but with fewer cases.

For both the stone/slag wool and glass wool sectors, lung cancer incidence increased with increasing years since first employment, with significance levels of 0.1 and 0.2 for trend, but with no individual relative risks significantly higher than 1. There was a slightly increasing trend in relative risk by duration of employment for stone/slag wool production workers, and a slightly decreasing trend for those on glass wool production. The results by technological phase show the greatest discrepancy relative to the SMR results, as for both sectors the relative risks for the early technological phase were less than 1, relative to the late technological phase.

4.1.4 The American cohort study: stone/slag wool sector

The follow-up of the University of Pittsburgh American cohort study was extended until 1989 for the stone/slag wool production sector, and up to 1992 for the glass wool and continuous filament sectors (Marsh et al, 1996; 2001).

An important aspect of these follow-up studies was that individual estimates were made of exposure to total airborne fibres, respirable fibres, formaldehyde and silica (Smith et al, 1994). In addition, for the stone/slag wool sector, qualitative estimates of the potential for exposure were also made for asbestos, arsenic, asphalt, PAHs, phenolics, radiation, and urea. The choice of potential exposures assessed was dependent on the history of the factory.

One stone/slag wool factory (number 17) had closed, and declined to participate further, and the analyses were consequentially limited. For this factory, lung fibre burden analyses found that four of six lung cancer cases had raised levels of amosite fibres in the lung, whereas no such excess was found for any other worker in this cohort study (McDonald et al, 1990). Historical evidence confirms that asbestos had been used for many years in this factory, at least as far back as the early 1930s (Merewether, 1932) shortly after the factory had opened in 1929.

This factory 17 has been designated by Marsh et al (1996) as the O-cohort. The other five stone/slag wool factories form the N-cohort.

The lower part of Table 10 shows the SMRs for respiratory cancer for the N- and O-cohorts. For the N-cohort, there were 71 respiratory cancer deaths, for whom 68 had known employment histories, and so are included in Table 10. There was no trend in SMR with increasing years since first employment. This

contrasts strongly with the results for the O-cohort, for which there was an increasing trend, with significantly raised SMRs overall and for the sub-group with more than 30 years since first employment.

Table 10. American Cohort Study: mortality analysis up to 1989 or 1992. Respiratory cancer deaths, SMRs, and 95% confidence intervals by time since first employment (expected deaths based on local reference populations).

		Years since first employment			
Production		<20 years	20–29 years	30 + years	Total
Fibrous glass – all	Deaths	132	219	523	874
	SMR	**92**	**99**	**114**	**106**
	95% ci	*77–110*	*87–114*	*105–125*	*99.5–114*
Fibrous glass >5 years employed	Deaths	63	124	309	496
	SMR	**74**	**96**	**115**	**103**
	95% ci	*57–95*	*80–115*	*102–128*	*94–112*
Mineral wool N-cohort	Deaths	15	23	30	68
	SMR	**106**	**135**	**106**	**114**
	95% ci	*60–175*	*86–203*	*72–151*	*89–145*
Mineral wool O-cohort	Deaths	3	8	21	32
	SMR	**95**	**141**	**171**	**152**
	95% ci	*20–278*	*61–278*	*106–261*	*104–214*

From: Marsh et al, 2001, 1996. (Fibrous glass: all workers; Mineral wool: males only.)

The difference between the two cohorts also is apparent for mortality from non-malignant respiratory disease (excluding influenza and pneumonia). For the main N-cohort, there were 39 such deaths (five per cent of all deaths) yielding an SMR of 127 (95% ci 90–174). Table 11 includes the 36 cases with known employment histories. In the O-cohort, there were 20 deaths (almost ten per cent of all deaths) and the SMR of 183 was statistically significantly raised (95% ci 112–283). For one of these 20 deaths, asbestosis was listed as cause of death.

There was one mesothelioma case reported, for a worker in factory 17, the O-cohort. This is consistent with the evidence of asbestos exposure in this factory.

The only other cause of death worth discussion is nephritis and nephrosis. In both cohorts, the SMR was above 200 and significantly higher than expected. The excess appeared unrelated to duration of employment. These results provide support for the recommendation by the IARC authors that renal diseases warranted further investigation.

As for the European study, logistic regression modelling of mortality rates was performed. However, in this study there were individual measures of exposure, as described above. For the males in the N-cohort, all of whom were employed for at least one year, the relative risks for respiratory system cancer were 1, 0.72, 0.94 and 0.83 with increasing estimates of cumulative exposure to respirable fibres[2]. This was based on all 68 respiratory system cancer cases with known employment history. After adjustment for all the potential co-exposures and for differences

---

[2]   Not enough details were provided to be able to calculate confidence intervals for the risk ratios.

between factories, the ratios became 1, 0.79, 1.01, and 0.93. This pattern is concordant with the results for those employed for more than one year in the European study (Table 9 and Figure 1). There is no evidence of any association of respiratory system cancer mortality and exposure to respirable fibres.

Table 11. American Cohort Study: mortality analysis up to 1989 or 1992. Non-malignant Respiratory Disease (excluding influenza and pneumonia): Deaths, SMRs, and 95% confidence intervals by time since first employment (expected deaths based on local reference populations).

Production		Years since first employment			
		<20 years	20–29 years	30 + years	Total
Fibrous glass – all	Deaths	42	117	281	440
	SMR	**76**	**102**	**92**	**92**
	95% ci	*55–103*	*82–113*	*82–103*	*84–102*
Fibrous glass >5 years employed	Deaths	21	68	163	252
	SMR	**64**	**95**	**88**	**88**
	95% ci	*39–97*	*76–125*	*75–102*	*77–99*
		Years since first employment			
		Short term (<5 years)		Longer term (≥5 years)	
Mineral wool N-cohort	Deaths	13		23	36
	SMR	**131**		**116**	**121**
	95% ci	*70–224*		*74–174*	*85–168*
Mineral wool O-cohort	Deaths	6		14	20
	SMR	**155**		**199**	**183**
	95% ci	*57–337*		*109–334*	*112–283*

From: Marsh et al, 2001, 1996. (Fibrous glass: all workers; Mineral wool: males only.)

4.1.5 The American cohort study: fibrous glass sectors: Respiratory cancer

All the original fibrous glass factories continued their participation (Marsh et al, 2001), although one factory had closed in 1984. As well as quantitative estimates of exposure to total and respirable fibres, formaldehyde and silica, qualitative estimates of the potential for exposure were also made for asbestos, arsenic, asphalt, epoxy, PAHs, phenolics, styrene and urea. The choice of potential exposures assessed was dependent on the history of the factory, as in the stone/slag wool sector.

The upper part of Table 10 shows the pattern of respiratory cancer by years since first employment for all workers, and for those employed at least five years in fibrous glass production. The present report does not provide detailed cross-tabulations of respiratory cancer mortality rates by production sector (fine fibrous glass, continuous filament, fibrous glass wool) and years since first employment. Detailed comparisons cannot be made with the data in Table 4, for the previous follow-up to 1982 (Enterline et al, 1987).

For all fibrous glass workers in the present follow-up, there is a pattern of increasing SMR with increasing time since first employment, and for those first employed at least 30 years earlier the SMR was raised significantly (P<0.05). For those employed at least five years, the overall SMR was 103 (95% ci 94–112).

The pattern of mortality by time since first employment was similar, except that the SMRs tended to be lower, in line with the general finding that shorter-term workers have the higher mortality rates. There is no such clear increasing trend of mortality rates with years since first employment, for all male fibrous glass workers followed to 1982 (Table 4).

In other univariate analyses of respiratory cancer mortality, Marsh et al found significantly raised SMRs for short-term workers, white males, the group of factories which produced both fibrous glass wool and glass filament, mortality during 1990-1992, those aged 30-39 when hired and those hired in 1950-1959. However, it is difficult to interpret these individual unstandardized observations.

4.1.6 The American cohort study: fibrous glass sectors: Other causes of death

There was a statistically significant deficit of all malignant neoplasms. In particular, neoplasms of the digestive organs and peritoneum, breast and prostate were all significantly low, and none was significantly raised.

There were no cases of mesothelioma among these fibrous glass production workers.

The non-malignant respiratory disease (excluding influenza and pneumonia) SMR was raised (SMR 110, 95% ci 101–121) based on the national mortality rates for the whole period of the study from 1946 (466 deaths). However when compared with local county rates for the period of their availability (1960-1992), the SMR was 92; 95% ci 84–102, based on 440 deaths (Table 11). There was no relation with years since first employment.

Most other non-malignant causes of death showed a statistically significant mortality deficit for either comparison period. The SMR for nephritis and nephrosis was 109 (95% ci 86–135) for the whole period (83 deaths), and 104 (95% ci 81–132) when compared with local rates (70 deaths).

4.1.7 Other cohort studies

The only other cohort studies of production workers during this period (1987-2000) were of glass filament producers. Shannon et al (1990) reported on a Canadian study of glass filament production workers. There were 96 deaths traced among the 1,465 workers who had worked for at least one year. There was a significant deficit in mortality overall (SMR 76). The lung cancer SMR was slightly raised (SMR 136; eleven deaths; 95% ci 68–243). However the authors concluded "Analysis by both duration of employment and cumulative exposure showed this increase to be inconsistent with an occupational aetiology".

Chiazze et al (1999) and Watkins et al (1997) studied a glass filament production plant, using methods described in more detail in section 4.2.4 below. In particular Watkins et al (1997) investigated a cohort which included 1,074 white women, 130 black women, and 494 black men who worked for a minimum of one year from the opening of the plant in 1951. Follow-up was until the end of 1991. White women had no significant excess mortality, except for motor vehicle

accidents. For black men, there was a significant deficit of heart disease. Lung cancer SMRs were below unity for both white women and black men.

Gustavsson et al (1992) studied a cohort of nearly 3,000 people in Sweden prefabricating wooden housing. More than 1,000 workers had been exposed to MMVF used for insulation. This group was selected as the authors considered that this exposure would not have been confounded by other exposures, unlike in MMVF production. Both mortality and cancer incidence were analysed.

The lung cancer incidence rate was low, with eleven cases observed and 23.3 expected (SIR 47, 95% ci 24–85). Lung cancer mortality was similarly low, and showed a trend of decreasing SMR with increasing years of employment: <10 years, SMR 92; 10-19 years: SMR 65; 20+ years, SMR 55.

Ischaemic heart disease rates were also significantly reduced. For the same three durations of employment, the SMRs were 78, 82 and 81.

Exposure levels for the workers exposed to MMVF were estimated to be up to 0.25 f.ml^{-1}. The authors concluded that "the exposure levels that have prevailed do not seem to be associated with an increased lung cancer rate".

4.2 Case-control studies

The cohort study analyses discussed in section 4.1 had increased the number of person-years at risk considerably, but had done little to clarify the evidence of risk. There remained raised mortality rates for lung cancer, but the authors could not conclude that the relation to fibre exposure was causal. Boffetta et al (1995) in Europe considered that "a carcinogenic effect of exposures occurring in the [stone/slag wool sector] working environment is a credible explanation", and that cigarette smoking, social class effects and co-exposures were unlikely to explain all the excess lung cancer mortality.

In the USA, Marsh (1991) took the opposite view. In a Research Memorandum, he explained that he did not consider the statistically significant 12 per cent excess of respiratory cancer deaths (Marsh et al, 1990) carried much weight for several reasons: marginal statistical significance; and lack of control for confounders such as cigarette smoking, lifestyle characteristics, racial composition, and occupational or non-occupational exposures to agents other than fibres.

In the other studies, Shannon et al (1990) did not consider that the lung cancer excess in their study of glass filament producers had an occupational aetiology. The wooden house fabricators had a significant deficit of lung cancer incidence (Gustavsson et al, 1992).

Public and regulatory concern still existed. In Europe for much of the 1990s decade, the European Commission Committee on the Classification of Dangerous Substances debated the classification of MMVFs, only reaching a decision in late 1997 (European Commission, 1997). Even this decision was a cause of controversy, as the German Government disagreed strongly and introduced more stringent control regulations.

Regulatory discussions were also actively taking place in USA, Australia, New Zealand and several other countries.

These concerns and discussions were a strong encouragement for continuing the research on MMVF production workers, using nested case-control studies within the two large cohort studies (Boffetta et al, 2000; Marsh et al, 2001) to provide clear conclusions, if such could exist. These case-control studies followed several earlier ones among production workers, which will be discussed first.

4.2.1 Case-control study: English glass fibre factory

Gardner et al (1988) conducted a case-control study in an English glass fibre production factory, comparing 73 lung cancer cases with 506 controls, matched by sex and date of birth. They found a slightly raised relative risk of 1.2 (95% ci 0.7–2.0). By type of product, the RR for superfine glass fibres was 1.3, for continuous filament 1.2, and for glass wool 1.1. Some individual relative risks were significantly raised, but always based on very small numbers of cases.

A major limitation of this study is that no records of smoking habits were available, and so confounding by tobacco smoking is possible.

4.2.2 Case-control studies: US stone/slag wool producers

Wong et al (1991) identified a cohort of 4841 men who had worked for at least one year at nine stone/slag wool production factories in the USA. Four of these factories were also included in the N-cohort of the University of Pittsburgh studies (Marsh et al, 1996). There were 504 deaths between 1970 and 1989, 61 of which were ascribed to lung cancer. Individually matched controls (usually two per lung cancer case) were selected from the other deaths. As no surviving families could be traced for three cases, nor for the controls for a further three cases, the final analyses included 55 lung cancer deaths, with 98 controls.

Estimates of exposure to airborne respirable stone/slag wool fibres were made for each case and control individually, using employment records and industrial hygiene surveys. Information was collected on tobacco smoking from telephone interviews with the families, and from personnel data.

This case-control analysis assessed relative risks for tobacco smoking and exposure to airborne respirable fibres. All the lung cancer cases were tobacco smokers and they had smoked on average 50 per cent more than the controls. There was a 33-fold lung cancer mortality relative risk for heavy tobacco smokers, relative to non-smokers. There was no association of lung cancer risk with cumulative fibre exposure (f.ml^{-1}.months), when adjusted for smoking habits. Workers exposed to stone/slag wool fibres were found to have a lung cancer risk effectively the same as non-exposed workers, with a relative risk (RR) of 0.94.

Marsh et al (1996) nested a case-control study within their follow-up study of stone/slag wool producers (see section 5.1.4 above). This was largely limited to the N-cohort, because of the lack of continued participation of factory 17 (the O-cohort), for which exposure data and employment histories were thus incomplete.

This case-control analysis was restricted to mortality for the limited period 1970-1989, because of expected problems in contacting families of people who had died more than 25 years ago, and because of doubts about their recall of

smoking habits. In this 1970-1989 period, there were 54 respiratory system cancer deaths, and all except one person were smokers. These cases were individually matched with two controls, born within two years of the case.

Adjusted for smoking, the relative risks for respiratory system cancer with increasing cumulative respirable fibre groups showed a decreasing trend: 1, 0.64, 0.55, 0.58. Similar trends were present when the analysis was unadjusted for tobacco smoking, or when the analysis was limited to smokers only. In each case, those with less than 3 f.ml^{-1}.months of exposure to airborne respirable fibres had the highest risk, typically 60-70 per cent higher than the more heavily exposed workers.

Considering only smoking cases, and excluding three cases with all non-smoking controls, the analysis was extended to assess the effects of the other occupational exposures (formaldehyde, silica, asbestos, arsenic, asphalt, and urea) and to adjust for differences between factories. In this analysis, the relative risk trend with increasing cumulative respirable fibre exposure strengthened: the relative risks were 1, 0.46, 0.33, 0.50.

For non-malignant respiratory disease, excluding influenza and pneumonia, the authors reported for the N-cohort that there was "no consistent evidence of a positive association with any of the exposure measures considered".

Because of the lack of exposure data, the relative risk analyses for the O-cohort used duration of employment as a surrogate measure of exposure. The analysis adjusted for smoking gave relative risks by increasing duration of employment of 1, 1.82, 0.33 and 0.73, based on 18 cases and 31 controls. The first two relative risks are for the "short-term workers" and the lower values are for those employed five or more years.

4.2.3 Case-control studies: European stone/slag wool producers

Boffetta et al (2000), Kjærheim et al (2001, 2002) set up a nested case-control study within the IARC-coordinated cohort study (see section 4.1.1), but limited to stone/slag wool producers, being the group which showed evidence of a raised lung cancer rate. In their report on the cohort mortality study, Boffetta et al (1995) concluded that

> "the issue of confounding by tobacco smoking and other occupational exposures should now be addressed, combined with an as accurate as possible assessment of past individual exposures to respirable fibres, in a case-control analysis nested in the [stone/slag wool] subcohort".

The lung cancer cases reported in the cancer incidence study (Boffetta et al, 1999) were those selected for the case-control study, excluding 46 cases that occurred before 1971. The follow-up was extended to 1996 in Denmark, giving a total of 196 cases of lung cancer.

First, each lung cancer case was matched individually with two series of controls. In the first control series, for each case there were up to four controls selected, being alive at time of diagnosis of the case but deceased at study time, and matched as closely as possible on date of birth, limited to within three years,

and matched on factory (or on country for Norway where the factories were small). In the second series of controls, each case was matched to up to three controls as in series I, except that the control did not need to be deceased at the date of study.

Before proceeding with the full study, a feasibility study was conducted of the multi-lingual questionnaire designed specifically to gather life-style information and working history outside the MMVF production industry. Hansen et al (1997) concluded

> "In general, the quality of information obtained from relatives appeared good. However, information on specific occupational exposures may be improved by supplementing the information from relatives with details obtained from colleagues, occupational hygiene experts or occupation-exposure matrices".

Unlike the University of Pittsburgh study, in the IARC cohort study there were no individual exposure assessments and factory-based exposure estimates were only available up to 1977. Hence a primary component of the study was to develop individual exposure assessments. Expert panels were set up in each factory, consisting of experienced managers, foremen and workers. Where possible, they reconstructed the employment and smoking history (job titles, dates, work areas, work tasks, and tobacco smoking habits) for each case and control. The information on job tasks was passed to the Institute of Occupational Medicine, Edinburgh, where hygienists grouped similar jobs. The group list was reviewed by the Expert Panels who then described the activities and work environment for each task, in each time period.

Based on this information and knowledge of technological changes in the factories, individual exposures were assigned to each task, for respirable fibres and for several possible confounding exposures. These data were then combined at IARC into exposure indices for each individual. Similar indices were developed for relevant exposures occurring in other occupations outside MMVF production.

Interviews were completed for 133 cases, all of whom were included in the analyses, and for 601 controls, of whom 513 were included. Detailed analyses were conducted using each of the two series of controls, but all results were effectively the same; so the two control series were combined.

Only two cases (1.5 per cent) had never smoked, compared with 72 (14 per cent) of the controls. To provide a better baseline for the regression analyses, ex-smokers who had smoked less than 200 kg of tobacco were included in the "never/light previous" base-line group.

As expected, the analyses showed highly significant odds ratios, and trends, for lung cancer with increasing amount smoked. Compared with the base-line group, the odds ratio for current smokers who had smoked more than 400 kg of tobacco was 8.8 (95% ci 3.9–19.8). Considering only those employed for more than one year, this odds ratio was 10.0 (3.4–29.1).

Table 12 shows the odds ratios for some of the exposure indices. For cumulative exposure to respirable fibres, there was a slight downward trend in odds

ratio with increasing exposure, statistically significantly reduced in the highest exposure group. For the longer-term workers only, the odds ratio for the second quartile was increased, based on three lung cancer cases only.

The authors considered it appropriate to consider respirable fibre exposure lagged by 15 years to allow for the latency between the initial development of the tumour and consequent death. For this index of lagged cumulative exposure to respirable fibres, there remained a slight, but less strong, downward trend in odds ratio with increasing exposure. When this was limited to those who had been employed for more than one year, the odds ratio for the second quartile was again increased, also based on small numbers.

Table 12. European Nested Case-Control Study. Stone/slag wool production: Odds ratios of death from cancer of the trachea, bronchus and lung, for various exposure indices, adjusted for smoking habits. (Males only. The numbers are shown as cases/controls.)

		Quartiles of exposure of all cases			
		Cumulative exposure to respirable fibres			
All workers	Case/Ctrl	33/100	32/107	33/111	34/191
	OR	**1**	**0.86**	**0.91**	**0.51**
	95% ci	*reference value*	*0.47–1.56*	*0.51–1.63*	*0.28_0.93*
Workers employed > 1 year	Case/Ctrl	12/42	3/12	26/92	34/188
	OR	**1**	**2.08**	**0.85**	**0.52**
	95% ci	*reference value*	*0.36–11.91*	*0.34–2.15*	*0.21_1.30*
		Cumulative exposure to respirable fibres, lagged 15 years			
All workers	Case/Ctrl	36/115	36/111	30/108	30/174
	OR	**1**	**1.25**	**1.02**	**0.67**
	95% ci	*reference value*	*0.66–2.34*	*0.54–1.93*	*0.35–1.27*
Workers employed > 1 year	Case/Ctrl	23/76	3/92	18/69	29/167
	OR	**1**	**2.00**	**0.76**	**0.63**
	95% ci	*reference value*	*0.41–9.83*	*0.27–2.17*	*0.28–1.42*
		Approximate tertiles of exposure			
		Cumulative asbestos exposure, lagged 15 years			
All workers	Case/Ctrl	49/175	11/52	11/79	
	OR	**1**	**2.15**	**1.13**	
	95% ci	*reference value*	*0.61–7.60*	*0.34–3.83*	
Workers employed > 1 year	Case/Ctrl	25/120	9/34	10/76	
	OR	**1**	**2.44**	**1.09**	
	95% ci	*reference value*	*0.59–10.12*	*0.25–4.77*	
		Cumulative exposure to silica, lagged 15 years			
All workers	Case/Ctrl	69/246	8/13	9/44	
	OR	**1**	**2.49**	**0.96**	
	95% ci	*reference value*	*0.86–7.14*	*0.38–2.41*	
Workers employed > 1 year	Case/Ctrl	39/164	6/12	9/37	
	OR	**1**	**2.08**	**1.12**	
	95% ci	*reference value*	*0.67–6.46*	*0.42–2.98*	

From: Kjærheim et al (2001); Boffetta et al (2000).

Table 12 also shows the pattern of odds ratio for cumulative asbestos and silica exposures, also with exposure lagged 15 years. For asbestos, there was a slight upward irregular trend whether based on all workers or those employed in the production industry for more than one year. The pattern for silica was very similar to that for asbestos. For PAH exposure, lagged 15 years, the highest exposed group had the lowest odds ratio. For the other indices of exposure (welding fumes, arsenic, formaldehyde, and various exposure outside MMVF production) there were no statistically significant patterns. The highest odds ratio was 4.5 (95% ci 0.7–29.5) for those ever exposed to arsenic among the longer-term workers.

Kjærheim et al (2001) concluded that "This study provides no evidence of a carcinogenic effect of [stone/slag wool exposure] on the lung under exposure conditions as experienced in the production industry during the last decades". The conclusion from Kjærheim et al (2002) was almost identical:

> "This study provides no evidence of a carcinogenic effect of rock and slag wool on the lung under exposure circumstances in the production industry during the last four to five decades".

4.2.4 Case-control studies: US fibrous glass producers

Chiazze et al (1992, 1993, 1995) undertook a case-control study of respiratory disease in the largest US factory in the University of Pittsburgh studies. The study population was as defined by Enterline et al (1987). The company undertook an historical environment reconstruction, from which a database of task-based exposure to various environmental substances was developed. Demographic information, occupational history, smoking history, residence, hobbies and medical history were collected using a questionnaire designed for response by an individual or by a proxy.

There were 166 cases with lung cancer, and 112 cases with non-malignant respiratory disease. These were matched to 406 and 270 controls respectively. It proved impossible to interview several people, so that there were 144 and 102 cases available for analysis with their 299 and 201 controls.

For lung cancer, univariate analyses showed significant associations of risk with various indices of tobacco smoking. For example, the odds ratio for those who had smoked less than 40 pack-years was 10.4 (95% ci 1.3–81.6), and for the heavier smokers it was 13.9 (1.8–106.4). There was also evidence that those with the longest period of education had the lowest lung cancer risk.

Analysis of risk related to exposure indices showed that those first hired before 1945 had twice the risk of those hired later. Otherwise there was no association of lung cancer risk with duration of employment, age when first hired, or cumulative exposure to airborne respirable fibre, asbestos, talc, formaldehyde, respirable silica, asphalt fumes or total particulates. When the odds ratio analyses were adjusted for tobacco smoking, the odds ratio for lung cancer of ever having smoked was 26.2 (95% ci 3.3–206.5). The only other statistically significant finding was a lower odds ratio for those with longer periods of education. For cumulative respirable fibre, talc and respirable silica, the pattern of odds ratio was

irregular, but with no significantly raised risks. For asbestos and formaldehyde, the trend was for decreasing risk with increasing exposure. Those with any exposure to asphalt fumes had an odds ratio of 1.13.

For non-malignant respiratory disease, there was a smaller, but still statistically significant effect of tobacco smoking. The odds ratio for those who had smoked less than 40 pack-years was 1.9 (95% ci 0.4–10.0), and for the heavier smokers it was 9.4 (1.2–74.5). There was no other non-exposure index showing a relation of disease risk.

The multivariate analyses showed that the non-malignant respiratory disease odds ratio for the ever smokers was 2.6 (95% ci 1.1–6.1). No other demographic or exposure variable showed a significant association. However, the disease risks relative to those not exposed to respirable silica all exceeded 2.2 and the results are suggestive of an adverse effect. Also the odds ratios for the highest exposure levels of respirable glass fibres, asbestos and asphalt fumes are all raised, even though non-significantly.

Chiazze et al (1999) also specifically investigated mortality from nephritis and nephrosis, using data from the occupational health surveillance programme of the largest US producer of fibrous glass products. There were 15 deaths with under-lying cause of nephritis or nephrosis, and a further 36 with nephritis or nephrosis listed as a contributory cause of death. These cases were matched by year of birth, factory and survival, giving 48 controls for the primary cases, and 172 controls for the full series.

This study was particularly addressed towards questions posed by Goldsmith and Goldsmith (1993); they had suggested that an excess of nephritis or nephrosis could be related to respirable silica exposure among MMVF production workers. Hence, Chiazze et al specifically studied nephritis and/or nephrosis in relation to estimates of cumulative respirable fibre exposures and of cumulative respirable silica exposures. These estimates were determined from the company's associated historical environmental reconstruction database. Socio-demographic information was collected by interview.

For the analyses of the cases with nephritis or nephrosis as an underlying cause of death, the paucity of data means that the confidence intervals were very wide, and the analyses essentially uninformative. Based on the combined series of cases (underlying and contributory causes), case-control analyses showed a downward trend in odds ratio with increasing exposure to respirable fibres, no association with cumulative silica exposure and no association with education level, marital status, income level, tobacco smoking or alcohol consumption.

The authors conclude that it is appropriate to consider contributory as well as underlying cause of death. They also stated

> "Although these results do not prove that there is no association between nephritis or nephrosis and exposure to fibreglass or silica [...] they do not support the assertion that such an association exists".

Marsh et al (2001) nested a case-control study of fibrous glass producers within the cohort study considered in sections 4.1.5 and 4.1.6 above. The cases were all

716 male deaths from respiratory system cancer during the period 1970-1992. For each case, one control was selected born within one month of the case and alive at the date of death of the case. Cases were not matched by race or factory.

Tobacco smoking information was collected for each case and control, using a structured questionnaire administered by telephone with the person himself, or with someone who knew the person. This was usually a family member. Smoking information was available for more than 80 per cent of the cases and the controls. Interview records were available for 502 case-control pairs. To maximise the size of the database, unmatched cases and controls were combined with closely matched pairs, or to form additional matched sets, resulting in 519 matched sets of cases and controls for statistical analysis.

As expected, tobacco smoking was a highly significant predictor of respiratory cancer mortality. Compared with the never-smokers, the odds ratio for ever-smokers was 13.1 (95% ci 7.0–24.3). Unadjusted for tobacco smoking, the respiratory cancer odds ratio showed a slight downward trend with increasing duration of employment, concordant with the findings that the short-term workers had higher SMRs for respiratory system cancer. There was no trend of odds ratio with years since first employment.

Adjusted for smoking, the odds ratios for lung cancer showed no trend with increasing cumulative respirable fibres. For deciles of exposure, the odds ratios were 1 (reference value), 1.39, 0.95, 1.28, 1.30, 0.79, 0.96, 1.57, 1.24 and 1.18. None of these odds ratios was significantly more or less than unity. When the results were cross-tabulated by duration and average intensity of exposure to respirable fibres, there was some indication of an increasing odds ratio with increasing intensity of exposure. However, none of the odds ratios was significantly raised above unity.

Considering co-exposures, there was no evidence in this case-control study of an association between respiratory system cancer and exposure to arsenic, asbestos, asphalt, epoxy, PAHs, silica, styrene, urea or phenolics. For formaldehyde, there were non-significant trends of increasing odds ratio with years of exposure, average intensity of exposure and cumulative exposure. Some of the individual odds ratios were significantly raised above unity.

The authors concluded that

> "Our case-control findings to date suggest that duration and exposure to respirable fiber glass at the levels encountered at the study plants are not associated with an increased risk for [respiratory system cancer]".

This conclusion applied with or without adjustment for tobacco smoking, plant and several co-exposures.

4.2.5 Case-control studies: US continuous glass filament producers

Chiazze et al (1997) used similar methodologies to those described in their case-control studies of fibrous glass workers (section 4.2.4). For these glass filament producers, there was no evidence of any association between exposure to respirable glass fibres, refractory ceramic fibres, respirable silica, asbestos, total chrome

or arsenic. The authors concluded that none of the exposure indices was associated with an increase in lung cancer risk for this population.

4.3 Additional evidence from other epidemiology

Kjuus et al (1986) carried out a case-control study of lung cancer in south-east Norway. In this study the authors examined the relationship between lung cancer and occupational exposures as well as smoking in 176 male lung cancer patients and their matched controls between 1979 and 1983. Heavy smokers were found to have a lung cancer odds ratio of 32-fold. The investigators also analysed the data by occupational exposures, including rock and glass fibres. The authors reported an odds ratio of 1.2 for workers with such exposures without adjustment for tobacco smoking. However, when the analysis was adjusted for smoking, the odds ratio became 1.0 (95% ci: 0.4–2.5).

Brüske-Hohlfeld et al (2000) pooled two German case-control studies to search for associations between lung cancer risk and occupation. These studies were a matched case-control study of lung cancer and occupational risk factors, and a frequency-matched case-control study to study the impact of radon exposure on lung cancer risk. There was no discussion of the effect of pooling studies of different design.

Smoking, demographic and occupational histories were collected using a standardized questionnaire and the occupations were grouped by industry into 21 categories and by job title into 33 categories. Cumulative exposures were assessed using job exposure matrices for silica and PAHs, by written description for diesel exhaust, by written description and supplementary questionnaire for MMVF and by semi-automatic quantification for asbestos, with 17 job-specific supplementary questionnaires. For MMVF, the supplementary questionnaire asked "insulation installers and electrical and electronic fitters [...] whether they had installed or removed insulation and what kind of insulation material they had used".

There were 3,498 male cases and 3,541 controls. There was the expected strong association with tobacco smoking, with 1.5 per cent of cases and 17.4 per cent of controls being lifelong non-smokers. Using the self-reported exposures to MMVF, the authors found significantly raised lung cancer risks, adjusted for tobacco smoking and asbestos exposure (odds ratio 1.5, 95% ci 1.2–1.9), based on 304 cases and 170 controls who reported that they had worked with MMVF. The adjusted odds ratio was 2.0 for those exposed for more than 30 years.

The findings in relation to MMVF exposure have been published in more detail by Pohlabeln et al (2000). The numbers of subjects and the odds ratios are identical. However, this report describes two additional questionnaires for the assessment of MMVF exposure. Each questionnaire asked specifically whether they used glass or mineral wool fibres. It must be assumed that the same workers (construction industry insulation installers, removers; electrical and electronic fitters) were asked supplementary questions about asbestos exposure, although that is not stated in these reports.

This report also describes the estimation of MMVF exposure indices for a subset of 59 cases and 39 controls, who self-reported no exposure to asbestos. The median MMVF exposure was lower among the cases than among the controls (0.4 vs 0.5 MMVF fibre.years). The lower and upper quartiles were almost identical, but the mean for the cases was twice that for the controls (2.52 vs 1.21 fibre.years). Above the 90th percentile for MMVF exposure there were eight cases and two controls. These proportions do not differ significantly, and a Wilcoxon rank-sum test showed no difference between cases and controls (P=0.83).

Given the similarities in these distributions of exposures, it is very difficult to understand how the mean exposures were so different. A rough calculation suggests that there must have been three or four cases with exposure levels of the order of 25-30 MMVF fibre.years. It would be interesting to know the occupations of these few individuals.

Sub-dividing this group into two sub-groups on the basis of MMVF exposure yields odds ratios which are lower for the higher exposure group. None of the odds ratios for the group reporting only MMVF exposure are significantly raised above unity, although all three are raised.

These two publications do not discuss the extent to which self-reporting of exposures under-estimates exposure to asbestos. These results are in contrast with those of Engholm et al (1987) for Swedish construction workers, who also used self-reporting of exposures to asbestos and to MMVF. Engholm et al (1987) noted "that subjects in the cohort to some extent are unaware of their exposure to asbestos". Indeed 21 out of the 23 pleural mesothelioma cases did not self-report exposure to asbestos, yet it must be reasonable to assume that most of these were caused by asbestos exposure.

Rödelsperger et al (2001) described a case-control study comparing 125 male mesothelioma cases with the same number of matched population controls. The interviews were described as similar for the two groups. There was the expected very strong relation between exposure to asbestos and mesothelioma.

For MMVF, there was a significant association between mesothelioma risk and exposure. However, this became non-significant statistically when adjusted for exposure to asbestos. There were just two cases and two controls who were reported to have had exposure to MMVF, but not to asbestos. The authors commented

> "This observation is heavily hampered by methodological problems" [and]
> "A causal relationship between exposure to MMVF and mesothelioma could neither be detected nor excluded".

Marchand et al (2000) used the data from a French case-control study to assess the relation between laryngeal and hypopharyngeal cancer and exposure to asbestos and MMVF. The 528 cases were all newly diagnosed with squamous cell carcinoma of the larynx or hypopharynx between 1989 and 1991. There were 305 controls who were patients in the same hospitals with a non-respiratory cancer.

A detailed job history was recorded, as was information on tobacco smoking and alcohol consumption. A job-exposure matrix was used to estimate exposure to asbestos and to four types of MMVF: mineral wools; refractory ceramic fibres,

glass filaments and microfibres. It must be presumed that "mineral wools" included glass wool as well as stone/slag wool. The job-exposure matrix provided for each task both probability and intensity of exposure.

Without making any adjustments for tobacco smoking or alcohol consumption, the authors reported a raised odds ratio for laryngeal cancer for exposure to asbestos, and significantly raised odds ratios for hypopharyngeal and epilaryngeal cancer. The odds ratios were 1.80 (95% ci 1.08–2.99) and 2.22 (1.05–4.71) respectively. For mineral wool exposure, the odds ratio was also highest for epilaryngeal cancer (OR 1.85; 95% ci 1.08–3.17), and raised for hypopharyngeal and laryngeal cancer. When analyses included both asbestos and mineral wool exposures, all the odds ratios reduced.

For asbestos exposure, an analysis standardised for cigarette smoking showed approximately a four-fold risk related to higher smoking and about a 1.5-fold risk for higher asbestos exposure. No such analysis was reported for mineral wool exposures, nor were there analyses including alcohol consumption.

Only four cases and 1 control were assessed as having mineral wool exposure but not asbestos exposure. The authors concluded that the results "may also suggest that mineral wools may have a carcinogenic effect on the epilarynx and the hypopharynx, but the possibility of a confounding by asbestos exposure requires that these findings be interpreted cautiously", especially as so many mineral wool exposed people had previously been exposed to asbestos.

5. The IARC review of the health effects of MMVF, 2001

As discussed above, considerable new evidence on the carcinogenicity of MMVF had been published in the dozen years since the IARC Working Group on the Hazard Assessment of MMVF meeting in 1987.

By the end of the year 2000, it was clear that the two major studies, in Europe and in USA, were both going to publish results indicating lack of evidence of lung cancer risk from exposure to MMVF in MMVF production. When IARC published their Internal Report No. 00/004 (Boffetta et al, 2000), the IARC Collaborators in Norway and Denmark issued press releases on the results, highlighting the contributions of their scientists to the IARC-coordinated studies.

The press release from The Cancer Register of Norway (2000) stated

> "The earlier suspicion that mineral wool fibres can cause lung cancer was not confirmed in a new European study by WHO's International Agency for Research on Cancer in Lyon (IARC). The study shows that mineral wool fibres do not give rise to lung cancer in the workers in the Rockwool factories. The results are based on an extensive international investigation with participation of Denmark, Sweden, Germany and Norway".

The Danish Cancer Registry (2000) commented

> "The suspicion from earlier studies of mineral wool fibres as the cause of lung cancer cannot be confirmed among European Rockwool workers,

[adding] Perhaps surprisingly, the cause of cancer is presumably not to be found in the mineral fibres, but on the contrary possibly in the effects of the rest of the working environment and smoking".

Thus, the scene was again painted for the formal reviews of hazard, by IARC in 2001, but the scene was rather different from that in 1987.

5.1 IARC Evaluation of Carcinogenic Hazard, 2001

As discussed in section 3.1, IARC convened a Working Group in June 1987 to consider the hazard classification for the carcinogenicity of MMVF and of Radon (IARC, 1988). A further Working Group was convened in October 2001 to reconsider the hazard classification of MMVF, particularly to take into account the research conducted since 1987, not just in epidemiology, but also in experimental studies. The understanding of the roles of biosolubility and fibre size in the retention kinetics of MMVF has also proved important for hazard assessment.

For the October 2001 meeting, IARC appointed an expert panel of 19 scientists from the field of fibre science and epidemiology to review the updated scientific information (IARC, 2002). There were also five observers present, including the present author, but we did not take part in evaluating the evidence. The evaluation is summarised in Table 13.

On the human carcinogenicity data, the experts concluded that:

"Results from the most recent cohort and nested case-control studies of US workers exposed to glass wool and continuous glass filament and of European workers exposed to rock (stone) and slag wool have not provided consistent evidence of an association between exposure to fibres and risk for lung cancer or mesothelioma.

These studies, like all epidemiological investigations, have limitations that must be borne in mind when interpreting their results. Although the exposure assessment methods used in these studies are far better than in most epidemiological studies, there is still the potential for exposure misclassification. Notably these studies were not able to examine fully the risks to workers exposed to more durable fibres. Information on smoking and on the other potential confounders that were adjusted for in these studies are also subject to measurement error, which may have influenced the validity of the adjustments made for these factors.

Underascertainment and misclassification of mesothelioma may also be a concern in these studies, which primarily relied upon death certificate information. Finally, although these studies are very large by epidemiological standards, their sensitivity may be limited by the fact that fibre exposure levels were low for a large proportion of the study population."

Given these conclusions, based on the same research as reviewed in section 4 above, the IARC experts' evaluation was that "There is inadequate evidence in humans for the carcinogenicity" of each of the MMVF fibre types.

Table 13. IARC (2002) Classification for the carcinogenicity of MMVF

Man-Made Vitreous Fibres Evaluation				
Special-purpose glass fibres	**Insulation glass wool**	**Continuous glass filament**	**Rock (stone) wool Slag wool**	**Refractory ceramic fibres**
Human carcinogenicity				
"There is inadequate evidence in humans for the carcinogenicity of special-purpose glass fibres"	"There is inadequate evidence in humans for the carcinogenicity of insulation glass wool"	"There is inadequate evidence in humans for the carcinogenicity of continuous glass filament"	"There is inadequate evidence in humans for the carcinogenicity of rock (stone) wool/slag wool"	"There is inadequate evidence in humans for the carcinogenicity of refractory ceramic fibres"
Animal carcinogenicity				
"There is sufficient evidence in experimental animals for the carcinogenicity of special-purpose glass fibres"	"There is limited evidence in experimental animals for the carcinogenicity of insulation glass wool"	"There is inadequate evidence in experimental animals for the carcinogenicity of continuous glass filament"	"There is limited evidence in experimental animals for the carcinogenicity of rock (stone) wool and of slag wool"	"There is sufficient evidence in experimental animals for the carcinogenicity of refractory ceramic fibres"
Overall Evaluation				
2B	**3**	**3**	**3**	**2B**
Possibly carcinogenic to humans	Not classifiable as to their carcinogenicity to humans	Not classifiable as to their carcinogenicity to humans	Not classifiable as to their carcinogenicity to humans	Possibly carcinogenic to humans
Note: The working group also considered that there was inadequate evidence in experimental animals for the carcinogenicity of "certain newly-developed, less biopersistent fibres". However, no Overall Evaluation was made for these fibres.				
Extracted from: International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risks of humans. *Man-made vitreous fibres*, vol 81, 2002.				

The summary of the evaluation (Table 13) shows that, for carcinogenicity in experimental animals, there were differing assessments by fibre product group. In particular, for the two most common groups, insulation glass fibres and rock (stone) and slag wool, the evaluation was "There is limited evidence in experimental animals" for their carcinogenicity. This was unchanged from the 1987 evaluation of rock (stone) and slag wool, but a lesser evaluation for glass wool. However, in the 1987 evaluation, glass wool and the special-purpose fine fibres were considered as one group; in the 2001 evaluation special-purpose fine fibres were considered separately and evaluated as "sufficient evidence for carcinogenicity in experimental animals".

6. Comments and conclusions

The second half of these twenty-five years of epidemiological research has largely reversed the first half. Initially there was no evidence of disease, as few human studies had been conducted. But by the time of the IARC and IPCS reviews in 1988, there was justifiable concern that stone/slag wool fibres might be carcino-

genic to humans by inhalation. In IARC's language, for stone/slag wool: "There is limited evidence for carcinogenicity to humans". This interpretation remained reasonable with the results of the continued cohort studies over the next decade.

However, the nested case-control studies have shown little evidence of any lung cancer risk to MMVF production workers. Given that these studies used analyses adjusted for tobacco smoking, unlike the cohort studies, the case-control study conclusions should carry most weight in the assessment of the hazard and risk of exposure to airborne respirable fibres.

Yet, the apparently different conclusions of cohort and nested case-control studies need explanation and resolution. Social class effects, particularly tobacco smoking, are most relevant. The cohort approach uses mortality rates for all people in the reference population to calculate the expected number of deaths. Logan (1982) has shown higher age-specific total and lung cancer mortality rates for blue collar workers, with increasing differentials for lung cancer over time. The US Surgeon-General reported similarly (U.S. Department of Health and Human Services, 1985) and estimated that a 20 per cent higher prevalence of cigarette smoking was associated with a 20 per cent increase in mortality rates for lung cancer. Axelson (1978, 1989) has also estimated how much differences in smoking prevalences could affect mortality rates, concluding that "confounding from smoking would rarely explain risk ratios of more than about 1.5 for lung cancer".

The Copenhagen Male Study (Hein et al, 1992) on "Lung cancer risk and social class" showed that the lung cancer relative risk for blue collar workers decreased by just over 20 per cent when adjusted for tobacco smoking habits. They also recorded that the smoking adjustment did not account for more than about one-third of the social class differences in lung cancer mortality rates.

Thus, if a group of workers smokes more heavily than the national or regional average, then standardised mortality ratios for lung cancer will be higher by about 20 to 40 per cent, just because of the comparison with the national or regional population. The nested case-control approach avoids that bias, as the comparisons are like with like, in terms of socio-economic status. Thus it is unsurprising to have raised lung cancer SMRs for a heavily-smoking cohort, but no raised odds ratios or relative risks in the nested case-control studies.

Marsh et al (2002) reviewed their studies in North America to ask "Does fiber glass pose a respiratory system cancer risk in humans?". Much of the discussion considered the impact of tobacco smoking on the interpretation of the results. The authors concluded that the raised SMR for respiratory system cancer among male workers "appears to be entirely explained by positive confounding [of fibre exposure indices] by smoking".

Kjærheim et al (2001) reported that the controls in the IARC case-control study had a 20 per cent raised prevalence of ever tobacco smoking. There was a greater excess of ever-smoking among the workers in the University of Pittsburgh study (Buchanich et al, 2001). Standardised for the different numbers in each factory, male fibrous glass production workers with known smoking history at 1 January 1980 had a point prevalence of 75.7 per cent for ever-smoking, compared to a rate

of 51.0 per cent expected based on the local State smoking rates on the same date. For mineral wool producers, the ever-smoking point prevalence was similarly raised about 1.5 fold (73.8 vs 47.6 per cent).

Chiazze et al (1995) reviewed specifically lung cancer mortality in the largest of the US fibre glass production factories. The prevalence of ever having smoked tobacco among the production workers was 12 per cent higher than the US Male prevalence, adjusted to the same age distribution. Based on this difference in prevalence of ever smoking tobacco, the authors concluded that the smoking-adjusted lung cancer SMR was 107.8, 90 per cent of the unadjusted SMR of 119.6.

Wong and Musselman (1994) reported an extended analysis of their stone/slag wool case-control study (Wong et al, 1991). They estimated the increased risk due to coexposures, for various values of lung cancer relative risk and proportions of smokers in the exposed and comparison populations. For a relative risk of 5 for smoking, and smoking proportions of 0.7 in the exposed and 0.5 in the comparison populations, then the increased risk is 27 per cent. They concluded that "the modest increase in lung cancer reported previously in cohort studies of MMVF workers could easily be explained by a 20 per cent difference in smoking prevalence".

The combined case-control study reported by Brüske-Hohlfeld et al (2000) and by Pohlabeln et al (2000) did also include assessment of smoking habits. The results from this population-based study are somewhat more suggestive of an increased risk of lung cancer from exposure to MMVF. But the authors themselves have commented on the inadequacies of their studies, and did not conclude that there was evidence of causation.

In conclusion, in the two major cohort studies, the workers had a higher proportion of tobacco smokers than the national or regional comparison populations. In particular, the ever-smoking rate is higher by between ten and 50 per cent. These differences in tobacco smoking rates alone are large enough to account for the raised lung cancer mortality rates reported in the cohort studies, making the findings fully compatible with those of the case-control studies which have found no evidence of any lung cancer risk for these workers.

Thus, after 25 years of epidemiology, the conclusion should come back to its original state: there is no adequate evidence of an adverse risk, but today that conclusion is based on the results from well-conducted and extensive epidemiological research.

7. Summary

An intensive study of the possible adverse health effects of fibre glass and stone/slag insulation wools has taken place over the last 25 years. This review concentrates on the epidemiological research, particularly as it bears on lung cancer mortality and incidence. It also considers how the scientific evidence has affected public and regulatory opinion.

There have been two major cohort studies, one in Europe coordinated by The International Agency for Research on Cancer (IARC) and the other in USA, coordinated by the University of Pittsburgh. Each of these populations has been followed up three times, and case-control studies have been nested within the cohort studies. Several other cohort and case-control studies are also reviewed.

The trigger for this research programme was that in 1972, two studies were published reporting that implantation of fibres into the pleural or peritoneal cavities of rats produced mesothelial tumours. The production industry responded by funding independent epidemiological, animal experimental, and environmental research, which has continued for the last 25 years.

The cohort studies produced evidence suggestive of a possible lung cancer hazard among the insulation wool production workers. The strength of the evidence appeared to increase with continued follow-up. In 1988, IARC considered the evidence on rock and slag production workers to provide limited evidence of carcinogenicity, while the evidence on glass production workers was considered inadequate. When combined with the data on animal studies, especially the studies in which fibres were injected or implanted directly into the animals, IARC classified these insulation wools as possibly carcinogenic in humans. This was followed by increasing public concern and regulatory activity in many countries.

The cohort studies have been consistent in showing a raised Standardized Mortality Ratio (SMR), more so for the stone/slag wool producers. Even so, the evidence has never been reported by any of the cohort study authors as strong enough to conclude that a causal effect of fibre exposure existed. Yet, the case-control studies of production workers have produced little evidence of an adverse risk to exposed workers. These include the case-control studies nested within the major cohort studies; the results from the two study designs need resolution.

Subsequently, in 2001, IARC reviewed the latest evidence on the hazard of exposure to MMVF and classified the insulation wools produced from glass, rock and slag as "Not classifiable as to their carcinogenicity to humans" (Category 3). On the epidemiological evidence, the conclusion was that there is inadequate evidence in humans for the carcinogenicity of any of the MMVF.

It is postulated in this review that the resolution of these differences lies in large part in the smoking histories of the production workers. The prevalence of ever-smoking tobacco was 10 to 50 per cent higher among the production workers than among the national or regional populations used to calculate the SMRs. These higher smoking rates are enough to account for the higher risks estimated from the cohort studies. This is also the conclusion of the epidemiological experts on the IARC review.

8 Summary in Swedish

Charles E. Rossiter: *Man-Made Vitreous fibres – 25 years of epidemiological research on mortality and cancer incidence*. Arbete och Hälsa 2002:14, Arbetslivsinstitutet, Stockholm.

Frågan om oönskade hälsoeffekter av inandade mineralfibrer har ägnats stor uppmärksamhet under de senaste 25 åren. Denna litteraturgenomgång inriktas mot de epidemiologiska undersökningar av exponering för fibrer härrörande från glas- och sten/slaggmaterial som utförts och publicerats under denna tid. Den viktiga frågan har gällt fibrernas cancerframkallande egenskaper. I rapporten kommenteras också den påverkan som publicerat material och den härtill hörande vetenskapliga diskussionen har haft på den allmänna opinionen och på tillsynsmyndigheters förhållningssätt i dessa frågor.

Frågan om mineralfibrernas cancerframkallande egenskaper kom att uppmärksammas stort 1972 då två studier publicerades med rapporter om att mineralfibrer injicerade i bukhåla eller lungsäck hos försöksdjur framkallade elakartade mesoteliala tumörer, sk mesoteliom. Mineralfiberindustrins reaktion på detta var att initiera epidemiologiska studier, djurexperimentella undersökningar och miljökartläggningar utförda av i förhållande till industrin oberoende forskargrupper.

Rapporten följer framför allt två stora epidemiologiska undersökningar, den ena utförd i Europa – ledd och koordinerad av det internationella cancerforskningsinstitutet IARC (International Agency for Research on Cancer), Frankrike och den andra utförd i USA vid universitetet i Pittsburgh. Dessa undersökningar av stora kohorter har vardera följts upp vid tre tillfällen och även kompletterats med sk fall-referentstudier. Några andra i sammanhanget viktiga kohortstudier kommenteras också i rapporten.

Inledningsvis resulterade analyser av de stora kohortstudierna indikationer på ett tänkbart samband mellan exponering för fibrer av mineralull i tillverkningsindustrin. Risktalet föreföll öka vid förlängning av observationstiden. IARC utförde år 1988 en granskning av tillgänglig vetenskaplig bevisning och bedömde att i fråga om sten/slaggull fanns vissa indikationer på möjlig cancerrisk. Beträffande fibrer av glasull tillät det epidemiologiska bevismaterialet ingen sådan bedömning. Då IARC tog med i bedömningen djurexperimentella resultat från tester där fibrerna injicerats direkt i andningsvägar, bukhåla eller lungsäck blev slutsatsen då att fibrernas cancerframkallande egenskaper var möjlig ("possibly carcinogenic").

I de fortsatta uppföljningarna av de stora kohortmaterialen har de höjda dödlighetstalen (SMR) för anställda i sten/slaggullsindustri blivit kvar på samma nivå. Trots detta har de forskargrupper som svarat för undersökningarna inte tolkat iakttagelsen som varande ett orsakssamband. Bevisningen för detta bedömdes som otillräcklig. De fall-referentstudier som utfördes både i Europa och i USA gav inte

resultat som bekräftade eller styrkte misstanken om cancerframkallande egenskap hos de undersökta fibrerna.

IARC sammankallade en expertgrupp år 2001 för att återigen gå igenom tillgängligt bevismaterial i frågan om mineralfibrer och cancerrisk vilket ledde till bedömningen att isoleringsull av glas, sten och slagg inte var klassifierbara som cancerframkallande för människa ("not classifiable as to their carcinogenicity to humans). De hänfördes därför till IARC cancerklass kategori 3. Detta innebar en väsentligt mindre sträng bedömning än den som gjorts vid IARC granskning 1988.

Författaren lanserar i rapporten sin tolkning att de förhöjda risktalen för dödlighet och förekomst av lungcancer är till stor del att tillskriva tobakskonsumtionen i de undersökta kohorterna. Den var enligt författaren på tio till 50 procent högre nivå än i den allmänbefolkning som utgjorde jämförelsebas i beräkningarna av dödlighetstalen (SMR). Denna tolkning överensstämmer också med de bedömningar som gjordes av den epidemiologiska expertis som deltog i denna nya IARC genomgång.

IARC granskningsrapport av 2001 återfinns i litteraturförteckningen.

Acknowledgements

9. References

AFL-CIO (1991) *Man-made mineral fibers. Position paper of the Safety and Health Committee* Building and Construction Trades Department, AFL-CIO, Glass, Molders, Pottery, Plastics and Allied Workers International Union, Medina, PA 19063, USA, 1991.

Axelson O (1978) Aspects of confounding in occupational health epidemiology. *Scandinavian Journal of Work, Environment and Health.* 1978;4:85–89.

Axelson O (1989) Confounding from smoking in occupational epidemiology. *British Journal of Industrial Medicine* 1989;46:505–507.

Boffetta P, Andersen A, Hansen J, Olsen JH, Plato N, Teppo L, Westerholm P & Saracci R (1999) Cancer incidence among European man-made vitreous fiber production workers. *Scandinavian Journal of Work, Environment and Health* 1999;25:222–226.

Boffetta P, Kjærheim K, Cherrie J, Chang-Claude J, Eilber U, Ferro G, Hansen J, Olsen JH, Plato N, Proud L, Saracci R, Westerholm P & Andersen A (2000) *A case-control study of lung cancer among European rock and slag wool production workers*. IARC Internal Report No. 00/004to JEMRB, Lyon, IARC, 2000. 40pp + 78 Tables.

Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, Ferro G, Frentzel-Beyme R, Hansen J, Olsen J, et al (1997) Cancer mortality among man-made vitreous fiber production workers. *Epidemiology* 1997;8:259–268.

Boffetta P, Saracci R, Ferro G, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, Frentzel-Beyme R, Hansen J, Hemmingson T, Olsen J, Plato N, Teppo L, Westerholm P & Winter PD (1995) *IARC historical cohort study on man-made vitreous fibre production workers in seven European countries: extension of the mortality and cancer incidence follow-up until 1990*. IARC Internal Report 95/003. Lyon, International Agency for Research on Cancer, 1995. 56pp + 305 tables.

Brüske-Hohlfeld I, Mohner M, Pohlabeln H, Ahrens W, Bolm-Audorff U, Kreienbrock L, Kreuzer M, Jahn I, Wichmann HE & Jockel KH (2000) Occupational lung cancer risk for men in Germany: results from a pooled case-control study. *American Journal of Epidemiology* 2000;151:384–395.

Buchanich JM, Marsh GM & Youk AO (2001) Historical cohort study of U.S. man-made vitreous fiber production workers; V. Tobacco smoking habits. *Journal of Occupational and Environmental Medicine* 2001;43:793–802.

Cameron JD (1977) Man-made mineral fibres: Medical research – CIRFS/EURIMA initiative. *Annals of Occupational Hygiene* 1977;20,149–152.

Cherrie JW, Dodgson J, Groat S & Maclaren W (1986) Environmental surveys in the European man-made mineral fibre production industry. *Scandinavian Journal of Work, Environment and Health* 1986;12 Suppl 1:18–25.

Cherrie J & Dodgson J (1986) Past exposures to airborne fibers and other potential risk factors in the European man-made mineral fiber production industry. *Scandinavian Journal of Work, Environment and Health* 1986;12 Suppl 1:26–33.

Cherrie JW, Krantz S, Schneider T, Öhberg I, Kamstrup O & Linander W (1987) An Experimental Simulation of an Early Rock Wool/Slag Wool Production Process. *Annals of Occupational Hygiene* 1987;31:583–593.

Chiazze LJ, Watkins DK & Fryar C (1992) A case-control study of malignant and non-malignant respiratory disease among employees of a fibreglass manufacturing facility. *British Journal of Industrial Medicine* 1992;49:326–331.

Chiazze LJ, Watkins DK & Fryar C (1995) Adjustment for the confounding effect of cigarette smoking in an historical cohort mortality study of workers in a fiberglass manufacturing facility. *Journal of Occupational and Environmental Medicine* 1995; 37:744–748.

Chiazze LJ, Watkins DK & Fryar C (1997) Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. I. White men. *Journal of Occupational and Environmental Medicine* 1997;39:432–441.

Chiazze L, Watkins DK, Fryar C, Fayerweather W, Bender JR & Chiazze M (1999) Mortality from nephritis and nephrosis in the fibreglass manufacturing industry. *Occupational and Environmental Medicine* 1999;56:164–166.

Chiazze LJ, Watkins DK, Fryar C & Kozono J (1993) A case-control study of malignant and non-malignant respiratory disease among employees of a fiberglass manufacturing facility. II. Exposure assessment. *British Journal of Industrial Medicine* 1993;50:717–725.

Consonni D, Boffetta P, Andersen A, Chang-Claude J, Cherrie JW, Ferro G, Frentzel-Beyme R, Hansen J, Olsen J, Plato N, et al (1998) Lung cancer mortality among European rock/slag wool workers: exposure- response analysis. *Cancer Causes and Control* 1998;9:411–416.

Cullen RT, Searl A, Buchanan D, Davis JMG, Miller BG & Jones AD (2000) Pathogenicity of a special-purpose glass microfiber (E-glass) relative to another glass microfiber and amosite asbestos. *Inhalation Toxicology* 2000;12:959–977.

Czernichow P, Caillard JF, Fauré JJ, Maret Y & Paris C (1989) *Tumeurs de voies aerodigestives supérieures et exposition aux fibres minérales artificielles*. Presented at the Congrès International d'Epidémiologie de Langue Française, Bordeaux, September 1989.

Danish Cancer Registry (2000) Ny rapport svækker mistanke om Rockwool og lunge-kræft [New report weakens the suspicion of Rockwool and lung cancer. *Press Release*, 2000 December 08.

Davis JMG, Bolton RE, Donaldson K, Jones AD & Smith T (1986) The pathogenicity of long versus short fibre sample of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *British Journal of Experimental Pathology* 1986;67:415-430.

Dodgson J, Cherrie J & Groat S (1987) Estimates of past exposure to respirable man-made mineral fibres in the European insulation wool industry. *Annals of Occupational Hygiene* 1987;31:567–582.

Doll R (1955) Mortality from lung cancer in asbestos workers. *British Journal of Industrial Medicine* 1955;12;81–86.

Engholm G, Englund A, Fletcher AC & Hallin N (1987) Respiratory cancer incidence in Swedish construction workers exposed to man-made mineral fibres and asbestos. *Annals of Occupational Hygiene* 1987;31:663–675.

Engholm G, Englund A, Hallin N & von Schmalensee G (1984) Incidence of respiratory cancer and Swedish construction workers exposed to MMMF. In: *Biological effects of man-made mineral fibres,* Copenhagen, WHO, 1984. Vol 1. pp350–366.

Enterline PE, Marsh GM, Henderson V & Callahan C (1987) Mortality update of a cohort of U.S. man-made mineral fibre workers. *Annals of Occupational Hygiene* 1987;31: 625–656.

Enterline PE & Marsh GM (1984) The health of workers in the MMMF industry. In: *Biological Effects of Man-Made Mineral Fibres*, Copenhagen, WHO, 1984. Vol 1. pp311–339.

Esmen NA (1984) Short-term survey of airborne fibres in US manufacturing plants. In: *Biological Effects of Man-Made Mineral Fibres*, Copenhagen, WHO, 1984. Vol 1. pp65–82.

Esmen NA, Corn M, Hammad Y, Whittier D & Kotsko N (1979) Summary of measurements of employee exposure to airborne dust and fiber in sixteen facilities producing man-made mineral fibres. *American Industrial Hygiene Association Journal*. 1979; 40:108–117.

European Commission (1997) Commission Directive 67/89/EC of 5 December 1997 adapting to technical progress for the 23rd time Council Directive 67/548/EEC. *Official Journal of the European Communities*, L343/19.

Gardner MJ, Magnani C, Pannett B, Fletcher AC & Winter PD (1988) Lung Cancer among Glass Fibre Production Workers: A Case Control Study. *British Journal of Industrial Medicine* 1988;45:613–618.

Gilson JC (1977) Man-made Mineral Fibres: What Needs to be Known and Done. *Annals of Occupational Hygiene* 1977;20:175–178.

Goldsmith JR & Goldsmith DF (1993) Fiberglass or silica exposure and increased nephritis or ESRD (end-stage renal disease). *American Journal of Industrial Medicine* 1993;23:873–881.

Government of Ontario (Canada) (1984) *Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario*. Ontario Ministry of the Attorney General, (Ontario Ministry of Government Services, Publications Service Branch, 880 Bay Street, Toronto, Ontario Canada M7A 1N9)Toronto, Ontario, 1984, Volume 1, Chapter 2, Section E, pp104–111.

Government of the United Kingdom (1931) *Asbestos Industry Regulations (1931)* Statutory Rules and orders, 1931 No 1140. His Majesty's Stationery Office.

Gustavsson P, Plato N, Axelson O, Brage HN, Hogstedt C, Ringback G, Tornling G & Wingren G (1992) Lung cancer risk among workers exposed to man-made mineral

fibers (MMMF) in the Swedish prefabricated house industry. *American Journal of Industrial Medicine* 1992;21:825–834.

Hansen J, Boffetta P, Andersen A, Cherrie JW, Chang-Claude J, Eilber U, Frentzel-Beyme R, Hemmingsson T, Olsen JH, Plato N, Saracci R, Skare GB & Westerholm P (1997) Comparison of information on occupation and lifestyle habits obtained from European man-made vitreous fibre production workers and their relatives. *International Journal of Epidemiology* 1997;26:1009–1016.

Harries PG (1971) Asbestos Dust Concentrations in Ship Repairing: A Practical Approach to Improving Asbestos Hygiene in Naval Dockyards. *Annals of Occupational Hygiene*, 1971;14:241–254.

Health and Safety Executive (1986) *Exposure To Mineral Wools*. HMSO, 1986. (Guidance Note, Environmental Health/46) 4pp.

Health and Safety Executive Committee on the Carcinogenicity in Food, Consumer Products and the Environment (1987) *Work With Man Made Mineral Fibres*. Health and Safety Executive News Release. 24 Jun. 1987, no.E53, 1–6.

Hein HO, Suadicani P & Gyntelberg F (1992) Lung Cancer Risk and Social Class: The Copenhagen Male Study - 17-year follow. *Danish Medical Bulletin* 1992;39:173-176.

Hesterberg TW, Chase G, Axten C, Miller WC, Musselman RP, Kamstrup O, Hadley J, Morscheidt C, Bernstein D & Thevenaz P (1998) Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. *Toxicology and Applied Pharmacology* 1998;151:262–275.

Hesterberg TW, Miiller WC, Musselman RP, Kamstrup O, Hamilton RD & Thevenaz P (1996) Biopersistence of man-made vitreous fibers and crocidolite asbestos in the rat lung following inhalation. *Fundamental and Applied Toxicology* 1996;29:267–279.

International Agency for Research on Cancer (1977) IARC monographs on the evaluation of the carcinogenic risks of humans. *Asbestos*, vol 14. Lyon, France: IARC, 1977. 106pp.

International Agency for Research on Cancer (1988) IARC monographs on the evaluation of the carcinogenic risks of humans. *Man-made mineral fibres and radon*, vol 43. Lyon, France: IARC, 1988. pp1–171.

International Agency for Research on Cancer (2002) IARC monographs on the evaluation of the carcinogenic risks of humans. *Man-made vitreous fibres*, vol 81. Lyon, France: IARC, 2002. 418pp.

International Federation of Building and Wood Workers (1993) *Man-made mineral fibres in the building industry*. Discussion paper. International Federation of Building and Word Workers, Geneva 15, Switzerland, 1993.

International Labour Office (1989) *Safety in the use of mineral and synthetic fibres*. ILO Publications, International Labour Office, 1211 Geneve 22, Switzerland, 1989. 94pp.

IPCS International Programme on Chemical Safety (1988) Environmental Health Criteria 77. *Man-made mineral fibres*. Geneva, Switzerland: WHO, 1988. 165pp.

Kjærheim K, Boffetta P, Andersen A, Chang-Claude J, Cherrie J, Hansen J, Olsen J, Plato N, Saracci R & Westerholm P (2000) A case-control study of lung cancer among

European rock/slag wool production workers - Preliminary Results. Presented at *ICOH Conference*, Singapore, August 2000.

Kjærheim K, Boffetta P, Hansen J, Cherrie J, Chang-Claude J, Eilber U, Ferro G, Guldner K-H, Olsen JH, Plato N, Proud L, Saracci R, Westerholm P & Andersen A (2002) Lung cancer among rock and slag wool production workers. *Epidemiology* 2002: in press.

Kjuus H, Skjaerven R, Langard S, Lien JT & Aamodt T (1986) A Case-Referent Study of Lung Cancer, Occupational Exposures and Smoking. I. Comparison of Title-Based and Exposure-Based Occupational Information. *Scandinavian Journal of Work, Environment and Health*. 1986;12:193–202.

Krantz S, Cherrie JW, Schneider T, Öhberg I & Kamstrup O (1991) *Modelling of past exposure to MMMF in the European rock/slag wool industry*. Arbete och Hälsa 1991:1 56pp, National Institute for Working Life, Stockholm.

Logan WPD (1982) *Cancer mortality by occupation and social class 1851-1971*. IARC Scientific Publications No. 36, Lyon, IARC.

Marchand JL, Luce D, Leclerc A, Goldberg P, Orlowski E, Bugel I & Brugere J (2000) Laryngeal and hypopharyngeal cancer and occupational exposure to asbestos and man-made vitreous fibers: results of a case-control study. *American Journal of Industrial Medicine* 2000;37:581–589.

Marsh G, Stone R, Youk A, Smith TJ, Quinn MM, Henderson V, Schall L, Wayne L & Lee K (1996) Mortality among United States rock wool and slag wool workers: 1989 update. *Journal of Occupational Health and Safety of Australia and New Zealand* 1996;12:297–312.

Marsh GM (1991) Research Memorandum. *Response Statement - Health Effects of Exposure to Fibrous Glass Wool*. Graduate School of Public Heath, University of Pittsburgh, USA, 4pp.

Marsh GM, Buchanich JM & Youk AO (2001) Historical cohort study of U.S. man-made vitreous fiber production workers; VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. *Journal of Occupational and Environmental Medicine* 2001;43:803–808.

Marsh GM, Enterline PE, Stone RA & Henderson VL (1990) Mortality among a cohort of US man-made mineral fiber workers: 1985 follow-up. *Journal of Occupational Medicine* 1990;32:594–604.

Marsh GM, Gula MJ, Youk AO, Buchanich JM, Churg A & Colby TV (2001) Historical cohort study of U.S. man-made vitreous fiber workers. II. Mortality from mesothelioma. *Journal of Occupational and Environmental Health* 2001;43:757–766.

Marsh GM, Stone RA, Youk AO & Smith TJ (1998) Cancer mortality among man-made vitreous fiber production workers. *Epidemiology* 1998;9:218–220.

Marsh GM, Youk AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ, Churg A & Colby T (2002) Does fiber glass pose a respiratory system cancer risk in humans? Latest findings from the US cohort and nested case-control studies. *Annals of Occupational Hygiene* 2002;46 (Suppl 1):110–114.

Marsh GM, Youk AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ & Quinn MM (2001) Historical cohort study of U.S. man-made vitreous fiber workers. I. 1992 fiber glass cohort follow-up – Initial findings. *Journal of Occupational and Environmental Health* 2001;43:741–756.

McDonald JC, Case BW, Enterline PE, Henderson V, McDonald AD, Plourde M & Sebastien P (1990) Lung dust analysis in the assessment of past exposure of man-made mineral fibre workers. *Annals of Occupational Hygiene* 1990;34:427–441.

Merewether ERA & Price CW (1930) *Report on the Effects of Asbestos Dust on the Lungs and Dust Suppression in the Asbestos Industry*. Home Office, HMSO, London.

Meriwether FV (1932) *Report of dust investigation of the Eagle Picher rock wool plant at Joplin, Missouri*. Report No. 81384, Bureau of Mines, US Department of Commerce.

Miettinen OS & Rossiter CE (1990) Man-made mineral fibers and lung cancer: epidemiologic evidence regarding the causal hypothesis. *Scandinavian Journal of Work, Environment and Health* 1990; 16:221–231.

Miller BG, Jones AD, Searl A, Buchanan D, Cullen RT, Soutar CA, Davis JMG & Donaldson K (1999) Influence of characteristics of inhaled fibres on development of tumours in the rat lung. *Annals of Occupational Hygiene* 1999;43:167–179.

Moulin JJ, Mur JM, Wild P, Perreaux JP & Pham QT (1986) Oral cavity and laryngeal cancers among man-made mineral fiber production workers. *Scandinavian Journal of Work, Environment and Health* 1986;12:27–31.

Murray HM (1970) *Report of Departmental Committee on Compensation for Industrial Diseases. Minutes of Evidence*. Cd. 3946:127128. London, HMSO.

NIOSH (National Institute for Occupational Health and Safety) (1976) *Re-examination and update of information on the health effects of occupational exposure to asbestos*. Washington DC, US Department of Health, Education and Welfare.

Norwegian Cancer Registry (2000) Ny rapport svekker mistanke om en sammenheng mellom mineralull og lungekreft [New report weakens the suspicion of an association between mineral wool and lung cancer]. *Press Release*, 2000 December 08.

Ottery J, Cherrie J, Dodgson J & Harrison G (1984) A summary report on environmental conditions at 13 European man-made mineral fibre plants. In: *Biological effects of man-made mineral fibres,* Copenhagen, WHO, 1984. Vol 1. pp83–117.

Pohlabeln H, Jockel KH, Bruske-Hohlfeld I, Mohner M, Ahrens W, Bolm-Audorff U, Arhelger R, Romer W, Kreienbrock L, Kreuzer M, et al (2000) Lung cancer and exposure to man-made vitreous fibers: results from a pooled case-control study in Germany. *American Journal of Industrial Medicine* 2000;37:469–477.

Pott F & Friedrichs KH (1972) Tumoren der Ratte nach i.p.-Injektionen faser-förmiger Stäube. *Naturwissenschaften* 1972;59:318.

Pott F, Dolgner R, Friedrichs KH & Huth F (1976) L'effet oncogène des poussières fibreuses. L'expérimentation animale et ses relations avec la carcinogenèse humaine [The oncogenic effect of fibrous dust. Animal experiments and their relationship with human carcinogenesis] Annals of Anatomy and Pathology, Paris. 1976;21:237–246.

Rödelsperger K, Jöckel K-H, Pohlabeln H, Römer W & Woitowitz H-J (2002) Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study. *American Journal of Industrial Medicine* 2002;39:262–275.

Sali D, Boffetta P, Andersen A, Cherrie JW, Claude JC, Hansen J, Olsen JH, Pesatori AC, Plato N, Teppo L, et al (1999) Non-neoplastic mortality of European workers who produce man made vitreous fibres. *Occupational and Environmental Medicine* 1999;56:612–617.

Saracci R, Simonato L, Acheson ED, Andersen A, Bertazzi PA, Claude J, Charney N, Estève J, Frentzel-Beyme RR, Gardner MJ, Jensen OM, Maasing R, Olsen JH, Teppo LHI, Westerholm P & Zocchetti C (1984) The IARC mortality and cancer incidence study of MMMF production workers. In: *Biological Effects of Man-Made Mineral Fibres,* Copenhagen, WHO, 1984. Vol 1. pp279–310.

Saracci R (1986) Ten years of epidemiologic investigations on man-made mineral fibers and health. *Scandinavian Journal of Work, Environment and Health* 1986;12 Suppl 1:5–11.

Selikoff IJ, Churg A & Hammond EC (1965) The occurrence of asbestosis among insulation workers in the United States. *Annals of the New York Academy of Sciences* 1965;132:139–155.

Selikoff IJ & Lee DHK (1978) *Asbestos and Disease*. New York, Academic Press, 549 pp.

Shannon HS, Hayes M, Julian JA & Muir DC (1984) Mortality experience of glass fibre workers. *British Journal of Industrial Medicine* 1984;41:35–38.

Shannon HS, Jamieson E, Julian JA, Muir DCF & Walsh C (1987) Mortality experience of Ontario glass fibre workers – extended follow-up. *Annals of Occupational Hygiene* 1987;31:663–675.

Shannon HS, Jamieson E, Julian JA & Muir DCF (1990) Mortality of glass filament (textile) workers. *British Journal of Industrial Medicine* 1990;47:533–536.

Simonato L, Fletcher AC, Cherrie J, Andersen A, Bertazzi PA, Charnay N, Claude J, Dodgson J, Esteve J, Frentzel-Beyme R, Gardner MJ, Jensen OM, Olsen JH & Saracci R (1986) The Man-made Mineral Fiber European Historical Cohort Study. Extension of the Follow-Up. *Scandinavian Journal of Work, Environment and Health*. 1986;12 (Suppl 1):34–47.

Simonato L, Fletcher AC, Cherrie J, Andersen A, Bertazzi P, Bolander AM, Charnay N, Claude J, Dodgson J, Esteve J, Frentzel-Beyme R, Gardner MJ, Jensen O, Olsen J, Saracci R, Teppo L, Westerholm P, Winkelmann R, Winter PD & Zocchetti C (1988) Mortality among a cohort of man-made mineral fibres (MMMF) production workers in seven countries: extension of the follow-up until 1982. *Annals of Occupational Hygiene* 1988;32(Suppl 1):725–734.

Simonato L, Fletcher AC, Cherrie JW, Andersen A, Bertazzi P, Charnay N, Claude J, Dodgson J, Esteve J, Frentzel-Beyme R, Gardner MJ, Jensen O, Olsen J, Teppo L, Winkelman R, Westerholm P, Winter PD, Zocchetti C & Saracci R (1987) The

International Agency for Research on Cancer Historical Cohort Study of MMMF Production Workers in Seven European Countries: Extension of the Follow-Up. *Annals of Occupational Hygiene* 1987;31:603–623.

Smith TJ, Quinn MM, et al (1994) Extrapolation of past exposures in the production of man-made vitreous fibres. *Proceedings of the Ninth International Symposium on Epidemiology in Occupational Health,* Cincinnati, Ohio, 1992. US Department of Health and Human Services 1994:357–358.

Stanton MF, Layard M, Tegeris A, Miller E, May M & Kent E (1977) Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. *Journal of the National Cancer Institute* 1977;58:587–603.

Stanton MF & Wrench C (1972) Mechanisms of Mesothelioma Induction with Asbestos and Fibrous Glass. *Journal of the National Cancer Institute* 1972;48:797–821.

U.S. Department of Health and Human Services (1985) *The health consequences of smoking – Cancer and Chronic Lung Disease in the workplace: A report of the Surgeon-General*. Office on Smoking and Health, US Public Health Service, Rockville, MD, pp23–33.

UICC (Unio Internationalis Contra Cancrum) (1965) Report and recommendations of the Working Group on Asbestos and Cancer. *British Journal of Industrial Medicine* 1965;22:165–171.

Wagner JC, Sleggs CA & Marchand P (1960) Diffuse pleural mesothelioma and Asbestos Exposure in the North Western Cape Province. *British Journal of Industrial Medicine* 1960;17:260–271.

Watkins DK, Chiazze LJ & Fryar C (1997) Historical cohort mortality study of a continuous filament fiberglass manufacturing plant. II. Women and minorities. *Journal of Occupational and Environmental Medicine* 1997;39:548–555.

WHO/EURO Technical Committee for Monitoring and Evaluating Airborne MMMF (1985) *Reference methods for measuring airborne man-made mineral fibres (MMMF)*. World Health Organization, Regional Office for Europe, Copenhagen, pp 16-35 (Environmental Health No. 5).

WHO Regional Office for Europe (1977) The biological effects of man-made mineral fibres (MMMF). *Annals of Occupational Hygiene* 1977;20,149–187.

Wong O, Foliart D & Trent LS (1991) A case-control study of lung cancer in a cohort of workers potentially exposed to slag wool fibres. *British Journal of Industrial Medicine* 1991;48:818–824.

Wong O & Musselman RP (1994) An epidemiological and toxicological evaluation of the carcinogenicity of man-made vitreous fiber, with a consideration of coexposures. *Journal of Environmental Pathology, Toxicology and Oncology* 1994;13:169–180.