

Mortality and incidence of cancer of workers in the man made vitreous fibres producing industry: an international investigation at 13 European plants

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ABSTRACT A total of 25 146 workers at 13 plants producing man made mineral fibres (MMMF) in seven European countries (Denmark, Finland, Federal Republic of Germany, Italy, Norway, Sweden, and United Kingdom) were studied in a historical cohort investigation. At 12 of the 13 plants an environmental survey was carried out to determine present day concentrations of airborne man made mineral fibres that showed levels of respirable fibres usually below 1 f/ml and most commonly in the range 0.01 to 0.1 f/ml. Workers were entered into the cohort at the moment of their first employment at one of the 13 factories (which started to operate between 1900 and 1955), and were followed up to at least 31 December 1977. Three per cent of the workers were lost to follow up. National death rates and national cancer incidence rates, where applicable, were used for each of the seven countries for comparison with the workers' cohort. A single death from mesothelioma was reported out of a total of 309 353 person-years of observation. No consistent differences (within and between plants) were noted between observed and expected numbers concerning individual causes of death or individual cancer sites, apart from lung cancer. For this cause a tendency was observed for the standardised mortality ratio (SMR) to increase with time from first employment. When the data from all the plants were pooled a statistically significant raised SMR of 192 (17 observed, 8.9 expected; 95% confidence interval 117-307) appeared in the group with 30 years or more since first employment. The relevance of this finding, to which different factors including uncontrolled confounders such as smoking habits may have contributed, cannot be established at present. The result is suggestive, however, of an increased risk associated with the man made mineral fibres working environment of 30 or more years ago.

Man made vitreous fibres (MMVF), usually referred to as man made mineral fibres (MMMF), include different inorganic synthetic wool products (slag wool, rock wool, glass wool) widely used as thermal and acoustic insulation material and as filament products used for textile manufacturing and for the reinforcing of plastic materials. Production of

MMMF had reached an estimated world annual total of 4.5m tons in 1973, thus being close to that of asbestos.¹ Biologically, experiments in animal systems have indicated that MMMF may have pathogenic actions²⁻⁴ (fibrogenic and carcinogenic), while pertinent epidemiological observations on pulmonary fibrosis (or more generally, chronic respiratory diseases) and on respiratory cancer in exposed subjects have been limited until recently.⁵

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We present and discuss here the results of an international epidemiological investigation, involving 13 factories producing MMMF in seven Western European countries, carried out with the coordination of the International Agency for Research on Cancer.

Methods

SELECTION OF PLANTS

All 72 MMMF production plants included in early 1976 in the roster of companies belonging to the European Insulation Manufacturers Association

(EURIMA) and to the Comité International de la Rayonne et des Fibres Synthétiques (CIRFS) in 15 European countries were considered as candidates for selection in a historical cohort study of their workforce. Criteria for selection were:

- (1) No loss or destruction of personnel records; total cohort identifiable;
- (2) MMMF production process operating for at least 20 years;
- (3) Facilities for follow up available with regard to mortality and, whenever possible, cancer incidence; and
- (4) Plants with a history of processing asbestos



Geographical distribution of man made mineral fibre producing plants included in the study.

materials excluded.

These requirements, together with other information of a general nature (plant address, approximate present workforce) were ascertained in a preliminary way by a mailed questionnaire. This was followed up by a direct site visit and inquiry at each plant: individual visits were made to 64 plants, eight having been discarded on the basis of the questionnaire reply only as obviously unsuitable for a historical study. As a result of the application of the selection criteria, 13 factories in seven countries (Denmark, Finland, Federal Republic of Germany, Italy, Norway, Sweden, United Kingdom (figure)) were chosen for the study. They included seven rock wool factories (labelled C, G, H, I, K, M, O), four glass wool factories (B, D, F, L), and two factories producing continuous glass filament (J and N): N had actually produced glass wool up to 1962. The letter labels of each factory correspond to those used in the environmental survey.⁶ The 13 factories, which started operations between 1900 and 1955, represented 18% of the total in the initial roster and 20% of the workforce in 1976.

ENVIRONMENTAL SURVEY

At 12 of the 13 plants a team from the Institute of Occupational Medicine, Edinburgh, conducted an environmental survey to measure present concentrations of fibres in air samples collected by personal samplers carried during an eight hour shift by workers operating in different jobs and plant areas.

No survey could be conducted at plant O which was closed at the time of the study.

EPIDEMIOLOGICAL INVESTIGATION

In each of the seven countries a national research team of investigators undertook, with IARC coordination, two main functions:

(1) Supervision of identification and transcription of workers' nominal rolls and job history records performed at the personnel offices at each plant. A worker was considered to have entered the cohort at the date of his first employment in one of the 13 factories, each of which had a different opening date ranging from 1900 to 1955. At four plants (B, D, K, M), after an initial examination of the available records, workers employed for less than one year were excluded from the cohort owing to the low quality of recorded information in the factory files (missing identification items, dates, incomplete occupational histories, etc).

(2) Follow up of workers with ascertainment of vital status, cause of death, and, whenever possible, occurrence of cancer as derivable from cancer registries. Follow up was implemented either through a central national facility, the national death register,

for example, or, when such a facility was not accessible, through a peripheral mechanism of multiple contacts and inquiries such as the town hall offices of a worker's last residence. All workers were followed up at least until 31 December 1977. In factories B and J the data collection was extended to 31 December 1978 and for factories N and O to 31 December 1979.

Whatever the tracing mechanism, causes of death were ascertained as on the death certificate, and the diagnosis of cancer as in the cancer registry files and coded according to the version of the International Classification of Diseases (ICD) in use at the national level at the time of the event (death or cancer diagnosis). For the purposes of the presentation of results all codes have been converted to those of the 7th version of the ICD. National death rates specific for calendar period, cause, sex, and age, and national cancer incidence rates (when applicable) specific for calendar period, site, sex, and age, were obtained for each of the seven countries in the study, either by the national collaborating investigators or, if more expedient, computed by IARC using the WHO mortality data bank. Quinquennial intervals were used both for age and for calendar year grouping.

The results, as presented below, derive from the analysis of the data performed centrally at IARC. A modified life table procedure and computing program were used to calculate person-years at risk, expected number of deaths (or expected number of cases of cancer) on the basis of the national reference rates, and ratios (standardised mortality ratio (SMR) or standardised incidence ratios (SIR)) between observed deaths (or cases of cancer) and those expected multiplied by 100. Ninety five per cent confidence limits for SMR and SIR were computed based on the Poisson distribution. Person-years and expected values were computed starting from the first year, variable from country to country, in which the national reference rates were available. For mortality rates the starting year ranged from 1942 (Italy) to 1953 (Finland and Norway) whereas for cancer incidence rates it ranged from 1943 (Denmark) to 1958 (Sweden). Within each factory jobs/plant areas were grouped into six main occupational categories: not specified; office; preproduction (including workers at the raw materials reception, weighing, and mixing sections of a factory); production (including workers at the raw material melting furnace and at the glass fiberisation and fibre curing section); secondary processes (including workers at a variety of dry processes, shaping the primary fibre product into forms usable in applications); and maintenance (in any section of the factory). The present day mean concentration of

respirable fibres was calculated for each category, based on the result of the environmental survey. Fibres, counted by phase-contrast microscopy, were defined as particles longer than 5 μm and with a length to diameter ratio of 3 to 1 or more, respirable fibres being considered as those with a diameter < 3 μm . For each worker a cumulative exposure index was created, multiplying the present day mean concentration of the respirable fibres for each occupational main categories by the duration of stay of the worker in that group, and by totalling the products. This was used to explore the existence of exposure (= cumulative index)-response (= SMR) relationships for male cases of lung cancer. In addition, the exposure-response relationship was examined through a case-control analysis of duration of exposure in dead cases of lung cancer and controls surviving to the case (up to a maximum of 40 per case) matched to him by factory and date of birth (± 2 years). Duration of exposure of the dead cases was compared with that of the controls up to the time of death of the former.

Results

CHARACTERISTICS OF THE WORKING POPULATION

The total number of workers in the cohort, the total number of recorded deaths, and the numbers and percentages of workers lost to follow up for each factory and separately by sex, are given in table 1. A small proportion of the workforce, less than 1% on average, could not be included in the cohort because one or more basic items (date of birth, sex, date of first employment) was missing. The rock wool type of production is the most represented in the study (50% of the total workforce). The range of the workforce in the individual factories is large, varying

from 485 in factory K to 5369 in factory C. Men are largely predominant with a M to F ratio of 4.7:1. The percentages of workers lost to follow up range from 0 to about 10%, the lowest percentages having been achieved where a central national tracing facility was available and the workforce was relatively small in size and included few foreign workers. Conversely, a sizeable number of short term immigrant workers affected the follow up of factory O.

The overall mean duration of employment was 5.1 years, ranging from 2.3 years to 11.3 for the workforce of different factories. The overall median duration was 2.2 years (range 0.5 to 4.6 years).

The number of person-years accumulated in the cohort for the mortality analysis and for the cancer incidence analysis for men and women and for three time intervals since first employment is shown in table 2. Of the total of 309 353 person-years for both sexes computed for mortality 9074 occurred 30 or more years after first employment. In this time interval 191 deaths took place.

CHARACTERISTICS OF THE WORKING ENVIRONMENT

The results of the environmental survey have been reported elsewhere by Ottery *et al.*⁶ For the six plants producing rock wool the average concentration of respirable fibre for the main occupational groups was 0.04 fibres/ml; the corresponding concentration for the four glass wool plants was 0.02 fibres/ml. The average respirable fibre concentration for the same occupations at the two continuous fibre plants was 0.006 f/ml. The highest fibre concentrations were usually observed in secondary processes, particularly in plants producing fine fibres. For these secondary processes the group average fibre concentration ranged from 0.03 f/ml to 0.45 f/ml. The highest respirable fibre concentration recorded

Table 1 Total number of workers: deaths and lost to follow up by factory and by sex

Factory	Workforce			No of deaths			No and % lost to follow up		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Rock wool									
C	4 931	438	5 369	276	6	282	35 (0.7)	0	35 (0.7)
G	881	27	908	82	0	82	0	0	0
H	456	39	495	32	0	32	0	0	0
I	477	8	485	23	0	23	0	0	0
K	427	90	517	70	6	76	16 (3.7)	4 (4.4)	20 (3.9)
M	1 462	265	1 727	82	2	84	39 (2.7)	11 (4.2)	50 (2.9)
O	2 096	41	2 137	241	2	243	199 (9.5)	8 (19.5)	207 (9.7)
Glass wool									
B	3 538	1 185	4 723	310	63	373	92 (2.6)	66 (5.6)	158 (3.3)
D	2 044	782	2 826	79	13	92	79 (3.9)	15 (1.9)	94 (3.3)
F	617	325	942	60	29	89	7 (1.1)	6 (1.8)	13 (1.4)
L	546	134	680	38	1	39	0	0	0
Continuous filament									
J	1 195	713	1 908	68	8	76	37 (3.1)	37 (5.2)	74 (3.9)
N	2 096	333	2 429	144	24	168	83 (4.0)	11 (3.3)	94 (3.9)
All	20 766	4 380	25 146	1 505	154	1 659	587 (2.8)	158 (3.6)	745 (3.9)

Table 2 Person-years at risk by time since first employment, by factory, and by sex (for mortality and incidence analysis)

Factory	Men				Women			
	≤19	20-29	≥30	Total	≤19	20-29	≥30	Total
Rock wool								
C	45 197	2 164	436	47 797	3 529	356	118	4 003
	46 180	2 177	442	48 799	3 712	356	118	4 186
G	9 568	685	20	10 273	205	0	0	205
	9 568	685	20	10 273	205	0	0	205
H	3 857	755	264	4 876	267	0	0	267
	3 857	755	264	4 876	267	0	0	267
I	4 062	216	66	4 344	77	8	0	85
	4 062	216	66	4 344	77	8	0	85
K	4 613	786	1 202	6 601	1 112	329	36	1 477
	3 911	702	889	5 501	830	329	36	1 195
M	15 301	2 237	784	18 322	2 423	193	37	2 653
	13 385	2 214	777	16 376	2 263	193	37	2 493
O	26 832	4 437	1 141	32 410	503	73	14	590
Glass wool								
B	42 535	5 301	354	48 190	16 615	2 913	176	19 704
D	17 340	3 379	1 340	22 059	5 605	2 437	1 993	10 035
	14 748	3 270	1 340	19 358	4 066	2 197	1 993	8 256
F	6 089	624	40	6 753	3 393	1 159	161	4 713
	6 089	624	40	6 753	3 393	1 159	161	4 713
L	4 286	470	83	4 839	861	134	13	1 008
	4 286	470	83	4 839	861	134	13	1 008
Continuous filament								
J	14 557	437	58	15 052	9 003	661	129	9 793
N	24 510	2 025	387	26 922	5 226	934	222	6 382
All	218 749	23 516	6 175	248 438	48 819	9 197	2 899	60 915
	106 086	11 113	3 921	121 120	15 764	4 376	2 358	22 408

Table 3 Mortality analysis by cause of death for the total period of observation (men)

Cause of death (7th ICD revision)	Obs	Expected	SMR	95% Conf int
All causes	1505	1666.4	90	86-95
All neoplasms (140-205)	373	391.9	95	86-105
Buccal cavity and pharynx (140-148)	6	6.6	91	33-198
Oesophagus (150)	8	8.0	100	43-197
Stomach (151)	46	51.3	90	66-120
Intestine, except rectum (152, 153)	24	25.6	94	60-139
Rectum (154)	16	17.8	90	52-146
Larynx (161)	7	4.2	167	67-345
Trachea, bronchus, and lung (162, 163)	109	102.6	106	87-128
Prostate (177)	14	25.9	54	30-91
All other and unspecified sites (155-160, 164, 165, 170, 175, 176, 178-181, 190-199)	115	113.9	101	83-121
Leukaemia and aleukaemia (204)	12	14.6	82	43-144
Lymphosarcoma and other neoplasms of lymphatic and haematopoietic system (200-203, 205)	16	20.5	78	45-127
Benign neoplasms and neoplasms of unspecified nature (210-239)	12	9.2	131	68-229
Circulatory system (400-468)	538	715.1	75	69-82
Respiratory system (470-527)	96	112.4	85	69-104
Bronchitis, chronic and unqualified, asthma (501, 502, 241, 527.1)	36	50.7	71	50-98
Accidents, poisonings, and violence (E810-E999)	246	205.8	120	105-135
All other causes	240	232.0	103	31-117

among all samples was 1.89 f/ml in one specialised section of a secondary process. All these airborne fibre concentrations reflect present day conditions: environmental data from one production line operating without "binders" (which favour fibre adhesiveness), as practised in the early periods of the industry, suggest that in the past concentrations may have been higher (one order of magnitude?). The differences between the average respirable con-

centration in the different production processes (rock wool, glass wool, continuous filament) provide a rationale for a separate analysis of the corresponding epidemiological data.

MORTALITY

In table 3 the number of observed and expected deaths, their ratios (SMR), and confidence intervals for a selected number of causes of deaths are shown

for men in the whole cohort (13 factories). The mortality from all causes and from the major causes of death is lower than expected on the basis of the general population experience, this deficit being particularly pronounced for the diseases of circulatory system (ICD 400-468). A statistically significant excess of deaths from accidents, poisonings, and violence (E810-E999) is observed. The excess does not appear to be directly related to the working environment as the specific causes of death for industrial accidents (E910-E918) are not in excess.

Scattered excesses based on small numbers are found for cancer of the larynx and benign neo-

plasms. The excess of laryngeal cancer is limited to one of the 13 factories where four cases were observed versus 1.0 expected (SMR: 408; 95% CI: 111-1024).

Table 4 gives the results for women in the whole cohort. The mortality from all causes is significantly lower than 100 and most of the specific causes of death show a deficit. The numbers of expected deaths, however, is very small for most of the specific sites of cancer and in particular for the sites of interest in this analysis. Results for women were consequently excluded from subsequent tables.

The results of the mortality analysis by time since

Table 4 Mortality analysis by cause of death for the total period of observation (women)

Cause of death (7th ICD revision)	Obs	Expected	SMR	95% Conf int
All causes	154	219.6	70	59-82
All malignant neoplasms (140-205)	49	70.1	70	52-92
Buccal cavity and pharynx (140-148)	0	0.7	0	0-535
Oesophagus (150)	0	0.8	0	0-439
Stomach (151)	6	5.5	110	40-239
Intestine, except rectum (152, 153)	0	5.1	0	0-72
Rectum (154)	1	2.3	43	1-240
Larynx (161)	0	0.1	0	0-369
Trachea, bronchus, and lung (162, 163)	3	4.9	61	12-178
Breast (170)	11	14.7	75	37-134
Cervix (171)	2	4.3	46	6-167
Uterus others (172-174)	3	2.8	106	22-310
All other and unspecified sites (155-160, 164, 165, 175, 176, 178-181, 192-195, 198, 199)	19	19.2	99	59-154
Leukaemia and aleukaemia (204)	0	2.3	0	0-161
Lymphosarcoma and other neoplasms of lymphatic and haematopoietic system (200-203, 205)	2	2.9	70	8-253
Benign neoplasms and neoplasms of unspecified nature (210-239)	1	1.7	60	1-337
Circulatory system (400-468)	44	76.9	57	42-77
Respiratory system (470-527)	8	12.9	62	27-122
Bronchitis, chronic and unqualified, asthma (501, 502, 241, 527.1)	1	3.8	26	1-145
Accidents, poisonings, and violence (E810-E999)	12	15.5	77	40-135
All other causes	40	42.5	94	67-128

Table 5 Mortality analysis by time since first employment: rock wool production process (men)

Time since first employment (years)	Observed	Expected	SMR	95% Conf int
All causes				
≤19	515	524.4	98	90-107
20-29	168	171.4	98	84-114
≥30	123	119.8	103	85-123
Total	806	815.6	99	92-106
All neoplasms				
≤19	126	128.8	98	82-117
20-29	48	41.4	116	85-154
≥30	35	27.5	127	87-117
Total	209	197.8	106	92-121
Cancer of the trachea, bronchus, and lung (162, 163)				
≤19	27	29.8	91	60-132
20-29	12	9.7	124	64-217
≥30	11	5.7	195	97-348
Total	50	45.1	111	82-146
Diseases of the respiratory system (470-527)				
≤19	18	25.9	69	41-110
20-29	9	11.3	80	37-151
≥30	11	8.3	133	66-238
Total	38	45.5	83	59-115

first employment for the four causes or groups of causes of particular interest for the study—namely, all causes, all neoplasms (140–205), cancer of trachea, bronchus, and lung (162, 163), and for diseases of the respiratory system (470–527) are shown by type of production in tables 5–7. The mortality experience of that part of the cohort engaged in rock wool production (table 5) does not show any trend for all causes with time since first employment, but an increasing trend appears for the diseases of the respiratory system with a small excess, statistically not significant, after 30 or more years of observation.

A pattern of increase in SMR is also present for all neoplasms. The excess after 30 or more years since first employment is mainly due to an excess of

lung cancer in that period. A clear pattern of increase in SMR is discernible for this site with time since first employment.

The data derived from the analysis by time since first employment in the glass wool production factories are shown in table 6. No clear pattern or trend is discernible for any of the four causes or groups of causes of death. An excess of lung cancer, statistically not significant, is present after 30 or more years of observation.

The part of the cohort which had a working experience in the continuous filament production processes showed a 24% excess in total mortality, which is statistically significant (table 7). A large part of this excess is accounted for by a statistically significant excess for accidents, poisonings, and viol-

Table 6 *Mortality analysis by time since first employment: glass wool production process (men)*

	<i>Observed</i>	<i>Expected</i>	<i>SMR</i>	<i>95% Conf int</i>
All causes				
≤19	322	417.3	77	69–86
20–29	126	200.1	63	52–75
≥30	39	61.7	63	45–86
Total	487	679.2	72	66–78
All neoplasms				
≤19	82	97.5	84	67–104
20–29	28	45.0	62	41–90
≥30	9	12.9	70	32–132
Total	119	155.5	77	63–92
Cancer of the trachea, bronchus, and lung (162, 163)				
≤19	30	31.2	96	65–137
20–29	10	13.2	76	37–140
≥30	4	2.6	157	43–402
Total	44	46.9	94	68–126
Diseases of the respiratory system (470–527)				
≤19	30	33.2	90	61–129
20–29	15	17.9	84	47–138
≥30	3	4.7	64	13–187
Total	48	55.9	86	63–114

Table 7 *Mortality analysis by time since first employment: continuous filament process (men)*

	<i>Observed</i>	<i>Expected</i>	<i>SMR</i>	<i>95% Conf int</i>
All causes				
≤19	173	137.1	126	108–146
20–29	26	26.1	100	65–146
≥30	13	8.3	156	83–268
Total	212	171.6	124	108–141
All neoplasms				
≤19	30	29.7	101	68–144
20–29	9	6.8	133	61–252
≥30	6	2.1	289	106–628
Total	45	38.6	117	85–156
Cancer of the trachea, bronchus, and lung (162, 163)				
≤19	11	7.9	139	69–248
20–29	2	1.9	104	13–374
≥30	2	0.6	333	40–1204
Total	15	10.5	143	80–236
Diseases of the respiratory system (470–527)				
≤19	7	8.3	85	34–175
20–29	1	2.0	49	1–275
≥30	2	0.7	286	35–1032
Total	10	11.0	91	44–167

Table 8 Mortality for cancer of the trachea, bronchus, and lung by cumulative levels ($f \times \text{years/ml}$) of exposure in workers with 20 or more years of observation

	Observed	Expected	SMR	95% Conf int
Rock wool				
Non-exposed	0	0.5	0	0-738
0-0.04	0	0.7	0	0-527
0.04-0.16	2	1.0	200	24-723
≥ 0.16	5	4.1	122	40-285
Total	7	6.4	109	44-225
Glass wool				
Non-exposed	0	1.4	0	0-264
0-0.04	4	3.1	142	35-330
0.04-0.16	5	4.0	125	41-292
≥ 0.16	4	6.1	66	18-168
Total	13	14.8	88	47-150
Continuous filament				
Non-exposed	0	0.3	0	0-1230
0-0.04	0	0.5	0	0-738
0.04-0.16	3	0.8	375	77-1096
≥ 0.16	1	0.9	111	3-619
Total	4	2.4	167	45-427
Total				
Non-exposed	0	2.2	0	0-168
0-0.04	4	4.3	93	25-238
0.04-0.16	10	5.8	172	83-317
≥ 0.16	10	11.1	90	43-166
Total	24	23.6	102	65-151

Table 9 Cancer incidence analysis by site for the total period of observation (men)

Cause of death	Observed	Expected	SIR	95% Conf int
All neoplasms (140-205)	309	342.9	90	80-101
Buccal cavity and pharynx (140-148)	14	12.1	116	63-195
Oesophagus (150)	4	4.2	95	26-242
Stomach (151)	32	30.6	105	72-148
Intestine, except rectum (152, 153)	20	23.4	86	52-132
Rectum (154)	21	17.2	122	76-187
Larynx (161)	4	5.1	79	22-203
Trachea, bronchus, and lung (162, 163)	51	51.1	100	74-131
Prostate (177)	27	41.1	66	43-96
Skin (190, 191)	27	31.8	85	56-124
Other and unspecified (155-160, 164, 165, 178-181, 192-195, 197-199)	85	98.3	87	69-107
Leukaemia and aleukaemia (204)	10	10.3	98	47-179
Lymphosarcoma and other neoplasms of lymphatic and haematopoietic system (200-203, 205)	14	17.8	79	43-132

SIR = Standardised incidence ratio.

Table 10 Cancer incidence analysis by time since first employment

	Observed	Expected	SMR	95% Conf int
Rock wool				
All neoplasms				
≤ 19	184	171.5	107	92-124
20-29	40	41.9	96	68-130
≥ 30	23	25.1	92	58-137
Total	247	238.6	104	93-120
Cancer of the trachea, bronchus, and lung (162, 163)				
≤ 19	29	27.6	105	70-151
20-29	12	6.2	193	99-337
≥ 30	3	3.3	92	19-267
Total	44	37.1	119	86-159
Glass wool				
All neoplasms				
≤ 19	32	54.4	59	40-83
20-29	19	34.4	55	33-86
≥ 30	11	15.5	71	35-127
Total	62	104.3	59	46-76
Cancer of the trachea, bronchus, and lung (162, 163)				
≤ 19	3	7.8	38	8-112
20-29	2	4.4	45	5-162
≥ 30	2	1.7	118	14-425
Total	7	14.0	50	20-103

ence (E810-E999) (55 observed ν 30.8 expected; SMR = 179; 95% CI = 135-233). A pattern of increase in SMR is present for all neoplasms, which display a statistically significant excess after 30 or more years since first employment. In particular, an excess, based on small numbers and statistically not significant, appears in this period for lung cancer. An excess is also present for diseases of the respiratory system. No trend of increasing SMRs, however, is discernible for these two causes of death with duration of observation.

Because of the excess shown in the previous tables, possible exposure-response relationships have been explored for cancer of the trachea, bronchus, and lung. This analysis has been confined to the part of the cohort with at least 20 years of observation as the most likely to show an effect, if any, from industrial exposure. The results in table 8 do not indicate an increasing trend of SMR with the index of cumulative exposure (as derived from present day airborne fibre concentrations); in fact the only raised SMR, close to statistical significance, is present in the group with medium cumulative exposure. None of the single industrial types of process exhibits a pattern of increasing SMRs with cumulative exposure, and scattered excesses which are present in some of the exposure subgroups are based on very small numbers. As may be inferred from the figures in table 8 compared with those in the previous tables, the size of the cohort suitable for the cumulative exposure-response analysis is smaller than the entire cohort. This is due to the absence of airborne fibre measurements in one factory and to missing information on the job type for a non-negligible number of individuals. In the additional case-control analysis of death from cancer of the trachea, bronchus, and lung no statistically significant trend of increasing risk with increasing duration of exposure (adjusted for time since first exposure) was found for any of the three production processes. For the three processes taken together the risk of cancer of the trachea, bronchus, and lung in men employed for six months to two years, two to seven years, and more than seven years, relative to the risk in men employed for less than six months were respectively 1.4 (95% CI = 0.60-3.24), 1.9 (95% CI = 0.87-4.14), and 1.7 (95% CI = 0.79-3.63).

INCIDENCE OF CANCER

The results of the analysis of cancer incidence in the nine factories in which it was feasible to carry this out are shown in tables 9 and 10. The SIR for all neoplasms is 90, and for specific sites tends to be below 100 apart from buccal cavity and pharynx and rectum, which exhibit small, non-significant excesses.

Only rock wool and glass wool factories are represented in the cancer morbidity analysis and in neither is there an indication of an increasing SIR with time since first employment (table 10). In the rock wool factories an excess of cancer of trachea, bronchus, and lung is present in the group with 20-29 years of observation, which is close to statistical significance.

Discussion

The 13 factories which it proved possible to include in this historical study cover reasonably well, particularly by production type, the range of factories in the initial European roster of 72. Seven of the 15 countries in the initial roster are represented in the study. Two countries (Federal Republic of Germany and France), which included as much as one third of the plants in the initial roster, finished by being represented in the study by only one suitable factory. In both countries follow up was assessed as impossible or highly problematical. As a consequence of this type of impediment alone, five factories that could otherwise be included in the study had to be left out. It can be estimated that their inclusion would have increased the study population by some 30%.

Cumulative levels of exposure, as derived from airborne fibre concentration measurements under present MMMF production conditions are low, generally in the range of 0.1 to 1-2 $f \times \text{yrs/ml}$. As previously noted, however, environmental fibre concentrations *may* have been higher in the past, perhaps by one order of magnitude. As a term of comparison it may be recalled that in those studies of the health effects of asbestos fibres in which fibre concentrations have been measured, cumulative exposures in the range from ten to several hundred $f \times \text{yrs/ml}$ have usually been reported. Low exposure to an agent, while advantageous and desirable for workers' health, may make a biological response induced by the agent so inconspicuous as to be difficult or impossible to detect, even in a large study.

The mortality and cancer incidence analyses show no consistent departure across factories of the observed numbers from those expected on the basis of the general population experience for individual causes of death nor for individual cancer sites, with the exception of lung cancer (cancer of trachea, bronchus, and lung) discussed below. Only one death from mesothelioma was reported (factory C) out of a total of 309 353 person-years computed for men and women. This case was a man aged 65 (at death) who had been employed for 92 days at the factory: about 11 years elapsed between first employment and death.

Table 11 Lung cancer mortality by factory and by time since first employment (men)

Factory	≤19			20-29			≥30			Total		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
Rock wool												
C	11	16.8	66	5	2.7	182	2	0.9	225	18	20.4	88
G	3	2.6	114	0	0.6	0	0	0.0	0	3	3.2	93
H	3	0.6	484	2	0.3	606	0	0.2	0	5	1.2	435
I	0	0.6	0	0	0.1	0	0	0.0	0	0	0.7	0
K	2	1.0	194	0	0.5	0	0	1.2	0	2	2.7	74
M	2	1.8	110	1	1.2	85	3	0.8	395	6	3.8	160
O	6	6.4	94	4	4.3	94	6	2.6	233	16	13.2	121
Glass wool												
B	27	24.2	112	8	9.2	87	2	1.0	206	37	34.3	108
D	1	3.3	30	2	2.4	84	2	1.4	148	5	7.0	71
F	2	2.7	73	0	1.3	0	0	0.2	0	2	4.2	48
L	0	1.0	0	0	0.3	0	0	0.1	0	0	1.4	0
Continuous filament												
J	5	4.0	126	0	0.4	0	0	0.1	0	5	4.5	111
N*	6	4.0	151	2	1.5	132	2	0.5	392	10	6.0	167
Total	68	69.0	98	24	24.8	97	17	8.9	192	109	102.6	106

*Glass wool predominant till 1962, when discontinued.

The workforce of one factory (D) exhibit particularly low SMRs which contribute to the reduction, particularly for women, of all causes SMR for the entire cohort. This may be due to a pronounced "healthy worker effect," but before accepting this as the sole explanation, possible biases have been considered. Extensive checks of factory files make selection biases most unlikely, but incomplete ascertainment of death at old age in some subgroups of workers cannot be completely ruled out. Should this be the case, person-years and expected figures as reported in the present paper would somewhat overestimate and SMRs underestimate the corresponding true values.

If one takes all 13 factories together and pools the number of observed and expected deaths the risk of lung cancer appears to be increased 30 years after first employment, with an SMR of 192 (95% confidence interval: 117-307; the data for individual factories are displayed in detail in table 11). The meaning of this statistically significant increase is not obvious but non-occupational or occupational confounding factors not controlled for in the study might have contributed to it. Among non-occupational confounders a possible differential composition of the national reference population and of the workers' population in respect to urban/rural residence, socioeconomic status, or general conditions of living may be important. National reference rates have been used in the seven countries for computing the expected number of deaths but those may not be entirely appropriate when rates vary widely within a country and the factory under study happens to be located in an area of particularly high or low mortality. In these conditions overestimation or underestimation of SMRs may be produced. For three countries (England,

Federal Republic of Germany, and Italy), local rates or local SMRs to be used as adjustment factors for the national rates were also available and were used for complementary analyses. The results of these analyses indicate that the use of local rates tends to lower the overall SMRs but do not appear to affect the ratios in the longest periods since first employment. No attempt to adjust further the national or local rates, or both, for social class has been possible.

Directly relevant among the potential non-occupational confounders are smoking habits, which could not be taken into account as smoking histories for past workers, forming the great majority of the cohort, were not available. Though a difference in the distribution of smoking habits in the general population and in the workers' population may indeed exist or have existed in the past or both, such a difference (unless it is extreme) is unlikely to account entirely for an observed SMR of nearly 200.⁸

Among occupational confounders, particular attention should in principle be given to possible exposures to asbestos. An absence of asbestos processing or production was one of the main criteria for inclusion of the factories in the study, and in the light of all available information this requirement has been met for all but one factory. For this single rock wool factory information was disclosed (after the study results became available) that during certain periods asbestos was used in processing some products. It is unfortunately not possible to separate the possible effect of exposure to asbestos from any other effect due to the working environment. As the rock wool type of production is the one exhibiting a trend of increasing SMR for lung cancer with time since first employment (table 5) an alternative

Table 12 Lung cancer analysis by time since first employment in the rock wool type of production excluding factory O in which use of asbestos was reported

	Observed	Expected	SMR	95% Conf int
Cancer of trachea, bronchus, and lung (ICD 162, 163)				
≤19	21	23.4	90	56-137
20-29	8	5.4	148	64-292
≥30	5	3.1	163	52-376
Total	34	31.9	107	74-149

analysis was performed excluding the factory in which asbestos was processed. The results are presented in table 12, from which it appears that an increasing trend of SMRs with time since first employment is still present. The numbers are, however, smaller and the pattern is less evident.

If the observed excess in lung cancer is not due solely to uncontrolled confounders such as those just discussed, one would expect to find a relation with duration and amount of exposure as assessed by cumulative exposure as derived from present day airborne fibre concentrations in the MMMF working environment. No such relations are observed, but this must be viewed against the fact that, so far as the relation with cumulative exposure is concerned, only a part of the cohort was suitable for study. In addition, the small number of subjects followed up for 30 years or more prevents the evaluation of an exposure-response relationship restricted to the one period in which the excess was observed, 30 years since first employment. Similar limitations apply to the incidence of cancer. In fact there is no consistent excess in the incidence of lung cancer, as opposed to mortality, but this may be due to the small numbers available because incidence data are not collected in all countries. As for mortality, one may note in table 11 that when the expected numbers of deaths (30 years since first employment) is not too small (in practice bigger than 0.50) the SMR appears systematically raised. This, and the fact that the observed excess occurs at a site (the lung) and at a time (several decades after first employment) in which an effect, if any, could be a priori expected to show up, points towards a causal role of MMMF or of the other exposures to, for instance, binders such as bitumen, mineral oils, and phenolic resins or to fumes occurring in the MMMF production industry or a combination of these.

These findings need to be placed against the background of the other scientific evidence at present available on the issue of the carcinogenic effect of MMMF. Three epidemiological studies of limited dimension have reported no excess in lung cancer mortality,⁹⁻¹¹ and two have reported rises of SMRs

that are not statistically significant. Shannon reports an observed/expected ratio for deaths from lung cancer of 1.4 (7/4.22),¹² and Morgan a ratio of 1.4 (37/27.3) with a ratio of 1.5 (9/5.91) for workers exposed at least 20 years and observed at least 30 years.¹³

An investigation similar to the present study and involving 16 730 workers at 17 MMMF producing plants has been carried out within the United States by Enterline and Marsh.¹⁴ The age structure of the workforce in their study is, however, somewhat older, and the follow up longer than in the present study; the total number of deaths observed in the United States study is 3761 v 1659 observed in the European study. The average duration of employment is about five years in our study and about 11 years in the United States investigation. In that study 202 deaths from lung cancer were observed among glass wool workers v 203.5 expected for the whole period of observation, and 47 deaths from lung cancer were observed v 36.0 expected for workers with at least 30 years of observation. The corresponding figures for slag wool/rock wool workers were 45 observed v 28.1 expected and 14 observed v 8.1 expected. No clear relation to cumulative exposure to man made mineral fibres was present.

Experimental data indicate clearly that a carcinogenic effect can be induced by direct intrapleural administration of MMMF,^{3,4} and one experiment suggests that tumours may also be produced by intratracheal administration (F Pott *et al* at 6th International Pneumoconiosis Conference, Bochum, September 1983). On the other hand, no carcinogenic effect has been detected in inhalation studies.¹⁵

Even when seen in the light of the ensemble of results from published reports, our study cannot settle the question as to whether the observed result of an excess of lung cancer 30 years after first employment can be attributed to exposure to MMMF. The result is, however, suggestive of an increased risk associated with the MMMF working environment of 30 or more years ago. Further follow up of workers and environmental investigations are already in progress to clarify this critical issue.

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