2. Studies of Cancer in Humans

The epidemiological studies of MMVFs published before 1987 were reviewed by IARC (1988). These studies are reviewed here only briefly if no updates have been published since. The epidemiological studies reported since 1988 include updates of previously published studies, notably two large cohort studies from the United States of America (United States University of Pittsburgh study) and Europe, as well as new studies. Studies conducted within the MMVF industry have attempted to separate the different types of MMVF, although this was not always possible, in particular for rock (stone) wool and slag wool, and for glass wool and continuous glass filament. The results of studies of workers exposed to both glass wool and continuous glass filament were considered more relevant to glass wool, which is the predominant source of exposure in these plants. In most studies of installers and studies conducted in the general population, no reliable differentiation between different types of MMVF was possible and they are generally included in section 2.5. The studies described in sections 2.1–2.4 were carried out on production and maintenance workers. The epidemiological studies available have not directly addressed the issue of biopersistence of MMVFs. However, indirect information can be obtained by considering the results according to the types of fibre manufactured in specific plants (e.g. special-purpose glass fibres are produced in plants 6 and 10 of the United States University of Pittsburgh study).

2.1 **Glass wool** (see Table 52)

Two major mortality studies have been conducted on glass wool and continuous glass filament workers, one in the USA and one in Europe. The results published before 1987 were reviewed by IARC (1988). The results of the updates of these studies and of the new studies have been evaluated below. A study in Canada of a cohort of 2557 male glass wool workers was also reviewed in the 1988 *IARC Monographs*, but has not been updated since (Shannon *et al.*, 1984, 1987). From these studies, there was *inadequate evidence* for the carcinogenicity of glass wool in humans (IARC, 1988).

Table 52. Studies of the health effects of exposure to glass wool

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
US University of Pittsburgh						
Cohort studies						
					SMR	Local rates
Marsh *et al.* (1990) 8 plants	11 380 male workers[a] employed 1945–63, follow-up 1946–85	340 deaths from respiratory cancer	'Glass wool'		1.12 [1.00–1.24]	
			Time since first employment			
			< 10 years	11	0.92 [0.46–1.64]	
			10–19 years	49	1.08 [0.81–1.44]	
			20–29 years	118	1.11 [0.92–1.33]	
			≥ 30 years	162	1.15 [0.98–1.34]	
			Duration of employment			
			< 10 years	190	1.21 ($p < 0.05$)	
			10–19 years	56	0.98	
			20–29 years	62	1.09	
			≥ 30 years	32	0.97	
					SMR	Local rates
Marsh *et al.* (2001a) 8 plants (same as above)	26 679 male and female workers[a] employed 1945–78, follow-up 1946–92	733 deaths from respiratory cancer	'Glass wool'		[1.07 (0.99–1.15)]	
			Special-purpose glass fibres	81	[1.09 (0.87–1.36)]	
			Mostly glass wool[b]	243	1.18 (1.04–1.34)	
			Long-term workers (≥ 5 years)	138	1.06 (0.90–1.26)	
		63 deaths from buccal cavity and pharynx cancer	'Glass wool'		1.11 (0.85–1.42)	
		64 deaths from cancer of the bladder and other urinary organs	'Glass wool'		1.07 (0.82–1.37)	

Table 52 (contd)

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Nested case–control studies						
					Odds ratio	
Marsh *et al.* (2001a); Stone *et al.* (2001) 10 plants (Glass fibres including continuous glass filament plants)	631 deaths from respiratory cancer[a] diagnosed 1970–92 (men)	570 controls	Ever exposed to respirable fibres	622	1.37 (0.55–3.42)	Adjusted for smoking
			continuous glass filament		1.0	
			glass wool + continuous glass filament[b]	356	1.01 (0.69–1.47)	Adjusted for smoking
			mostly glass wool[b]	183	1.06 (0.71–1.60)	Adjusted for smoking
Chiazze *et al.* (1992, 1993) plant 9 of Marsh *et al.* (2001a) glass wool + continuous glass filament plant[b]	166 deaths from lung cancer[a] diagnosed 1940–82 (men)	387 controls			Odds ratio	Adjusted for smoking and other potential confounders
			< 100 fibres/cm^3–day	98	1.0	
			100–299.99 fibres/cm^3–day	37	1.72 (0.77–3.87)	
			≥ 300 fibres/cm^3–day	27	0.58 (0.20–1.71)	

Table 52 (contd)

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
European study						
Cohort studies						
					SMR	Local rates
Plato *et al.* (1995c) Sweden; one glass wool plant included in Boffetta *et al.* (1997)	1970 male and female workers[a] employed before 1978, mortality follow-up 1952–90	14 deaths from lung cancer			0.97 (0.57–1.69)	
			Duration of employment with 20-year lag			
			< 2 years	5	2.24 (0.73–5.23)	
			2–9 years	5	1.14 (0.37–2.66)	
			10–19 years	0		
			≥ 20 years	1	0.94 (0.02–5.21)	
			Total	11	1.21 (0.68–2.30)	
	Incidence follow-up 1958–89	17 cases of lung cancer	Duration of employment		SIR	
			< 2 years	3	0.72 (0.15–2.12)	
			2–9 years	11	1.15 (0.57–2.05)	
			10–19 years	1	0.31 (0.01–1.74)	
			≥ 20 years	2	1.45 (0.18–5.24)	
			Total	17	0.93 (0.54–1.48)	

Table 52 (contd)

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
					SMR	National rates
Boffetta *et al.* (1997) 5 glass wool plants in Finland, Italy, Norway, Sweden and United Kingdom	6936 male and female workers[a] employed 1933–77, follow-up until 1992	140 deaths from lung cancer			1.27 (1.07–1.50)	
			Technological phase			
			early	19	1.07 (0.64–1.67)	
			intermediate	100	1.40 (1.14–1.70)	
			late	21	1.02 (0.63–1.56)	
		10 deaths from cancer of the buccal cavity and pharynx			1.47 (0.71–2.71)	
					SIR	National rates
Boffetta *et al.* (1999) 3 glass wool plants in Finland, Norway and Sweden; included in Boffetta *et al.* (1997)	2611 male and female workers[a], follow-up until 1995	40 cases of lung cancer			1.28 (0.91–1.74)	
			Time since first employment		Relative risk	Adjusted for age, gender, country and technological phase
			≤ 19 years	10	1.0	
			20–29 years	15	1.9 (0.8–4.8)	
			≥ 30 years	15	2.3 (0.6–9.2)	*p* for linear trend = 0.2
			Duration of employment			
			1–4 years	23	1.0	Adjusted for age, gender, country, technological phase and time since first employment
			5–9 years	8	0.8 (0.3–2.0)	
			10–19 years	4	0.8 (0.3–2.4)	
			≥ 20 years	1	0.7 (0.08–5.3)	*p* for linear trend = 0.5
			Technological phase			
			early	20	0.6 (0.2–1.9)	Adjusted for age, gender, country and time since first employment
			late	20	1.0	

Table 52 (contd)

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Nested case–control study						
Gardner *et al.* (1988) 1 United Kingdom glass wool plant from the European study	73 deaths from lung cancer employed 1946–78, follow-up until 1984	506 controls			Odds ratio	Potential asbestos exposure odds ratio, 1.5 (0.8–2.5)
			Super-fine glass wool	2	1.3 (0.3–5.8)	
			Glass wool	31	1.1 (0.7–1.9)	
Other studies						
Cohort studies						
Shannon *et al.* (1984, 1987) Canada	2557 male workers employed 1955–77, ≥ 90 days, follow-up until 1984	Plant-only workers 19 deaths from lung cancer			SMR	Local rates
			All cases	19	1.99 [1.20–3.11]	
			Exposed ≥ 5 years and ≥ 10 years since first exposure	13	1.82 [0.97–3.11]	
			Duration of employment		SMR	Local rates
			< 5 years	6	2.91	
			5–< 10 years	3	2.88	
			10–< 15 years	3	1.79	
			15–< 20 years	2	1.16	
			20–< 25 years	1	0.86	
			25–< 30 years	2	1.59	
			≥ 30 years	2	3.25	

Table 52 (contd)

Reference, plants	Description, employment period, follow-up, definition of cases	No. of deaths or cases, type of cancer, controls	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Shannon *et al.* (1984, 1987) (contd)			Time since first employment		SMR	Provincial rates
			< 5 years	1	4.31	
			5–< 10 years	1	1.68	
			10–< 15 years	2	2.11	
			15–< 20 years	3	1.91	
			20–< 25 years	2	1.04	
			25–< 30 years	5	2.09	
			≥ 30 years	5	2.70	
Moulin *et al.* (1986) France	1374 male workers [a] employed 1975–84				SIR	Regional rates
		5 cases of lung cancer	Production workers		0.74 (0.24–1.72)	
			duration of exposure			
			1–9 years	2	1.82 (0.22–6.57)	
			10–19 years	1	0.63 (0.02–3.48)	
			≥ 20 years	1	0.56 (0.01–3.10)	
		19 cases of 'upper respiratory and alimentary tract' cancer			2.18 (1.31–3.41)	

SMR, standardized mortality ratio; SIR, standardized incidence ratio; respiratory cancer, ICD8, 160–163
[a] Workers employed for ≥ 1 year
[b] For this review, workers exposed to 'mostly glass wool' or 'glass wool and continuous glass filaments' are considered as being exposed to glass wool, because the pattern of exposure among these groups results predominantly in exposure to glass wool.

2.1.1 *United States University of Pittsburgh cohort*

(*a*) *Cohort studies*

The United States (US) University of Pittsburgh cohort consists of male workers employed for 1 year or more between 1945 and 1963 in production or maintenance at one or more of 11 glass fibre and six rock (stone) wool and slag wool plants (Table 53). Of the 11 glass fibre plants, three produced continuous glass filament, two glass wool and continuous glass filament and six mostly glass wool. The original report and the updates presented the mortality statistics collected until 1982 (Enterline *et al.*, 1983; Enterline & Marsh, 1984; Enterline *et al.*, 1987). The 1985 follow-up study was reported by Marsh *et al.* (1990) and included 16 661 workers. Death certificates were obtained for 96.2% of those identified as deceased. The data were analysed according to three different follow-up periods, time since first employment and duration of

Table 53. Characteristics of the plants participating in the study by the US University of Pittsburgh, USA, on MMVFs

Plant no.	Location	Principal product
Glass fibre plants		
1	Parkersburg, WV	Mostly wool[a]
2	Ashton, RI	Filament
4	Kansas city, KS	Mostly wool[a]
5	Huntington, PA	Filament
6	Santa Clara, CA	Mostly wool[a]
9	Newark, OH	Wool and filament
10	Waterville, OH	Wool and filament[b]
11	Defiance, OH	Mostly wool[a]
14	Shelbyville, IN	Mostly wool[a]
15[c]	Kansas City, KS	Wool and filament[b]
Rock (stone)/slag wool plants		
3	Alexandria, IN	Rock (stone)/slag wool[d]
7	Tacoma, WA	Rock (stone)/slag wool[d]
8	Wabash, IN	Rock (stone)/slag wool[d]
12	Birmingham, AL	Rock (stone)/slag wool[d]
13	S. Plainfield, NJ	Rock (stone)/slag wool[d]
17	Joplin, MO	Rock (stone)/slag wool[e]

Plants 6 and 10 produced special-purpose glass fibres (small-diameter, < 1.5 μm).
[a] Includes some filament operations
[b] Consists of one facility devoted to filament manufacturing and one devoted to wool.
[c] Two of the original glass fibre plants (plants 15 and 16) included in Marsh *et al.* (1990) were combined (as plant 15) in Marsh *et al.* (2001a) because the workers moved freely between the adjacent manufacturing sites.
[d] Extended follow-up: N-cohort
[e] Extended followup: O-cohort

employment. The expected numbers of deaths were based on cause-specific mortality rates for white men in the USA and on the rates from the county where the plant was located. In addition, Poisson regression modelling was used to investigate the dependence of standardized mortality ratios (SMRs) on possible combinations of exposure to fibres with potential confounding variables. The SMR for all malignant tumours for the whole cohort was 1.08 based on local rates.

The US University of Pittsburgh cohort included eight glass fibre plants: two producing glass wool and continuous glass filament (start of production, 1938–50) and six producing mostly glass wool (start of production, 1946–52). The study population consisted of 11 380 male workers employed for 1 year or more (or for six months at two plants that produced small-diameter glass fibres (less than 1.5 μm)) between 1945 and 1963 (1940–63 for plant 9) in these eight plants. Results are presented for 'fibrous glass wool and both' combining 'fibrous glass wool' ('mostly glass wool') and 'fibrous glass both' ('glass wool and continuous glass filament'). For the purposes of this review, workers exposed to 'mostly glass wool' or 'glass wool and continuous glass filament' are considered as being exposed to glass wool, because the pattern of exposure among these groups results predominantly in exposure to glass wool. The SMR for respiratory cancer (ICDs 8 160–163) (including cancer of the larynx) for workers exposed to glass wool was 1.12 [95% confidence interval (CI), 1.00–1.24] (340 cases) based on local reference rates. The average exposure to fibres was 0.047 fibre/cm^3. The average exposure to (respirable fibres) < 3 μm diameter was 0.039 fibre/cm^3 for all glass fibre plants. There was no positive relationship between respiratory cancer and duration of employment (Marsh *et al.*, 1990).

The US University of Pittsburgh cohort study for the glass fibre plants was extended until 1992 and expanded to include a more complete characterization of the work histories and the racial composition of the cohort, a nested case–control study of respiratory cancer, a survey of tobacco smoking habits and a retrospective assessment of exposure (Buchanich *et al.*, 2001; Marsh *et al.*, 2001a,b,c; Quinn *et al.*, 2001; Smith *et al.*, 2001; Stone *et al.*, 2001; Youk *et al.*, 2001). The expanded cohort included female employees, workers employed after the original cohort end-date of 1963 and workers from additional manufacturing sites. Thus the study covered 10 glass fibre plants (two from the original cohort were combined), including eight plants that produced glass wool and two that produced continuous glass filament (see Table 53). This study examined the mortality experience between 1946 and 1992 of 32 110 production or maintenance workers (5431 workers exposed to continuous glass filament, 15 718 to glass wool and continuous glass filament and 10 961 mostly to glass wool) employed for at least one year between 1945 and 1978 with certain exceptions. Firstly, a six-month employment criterion was applied to male workers in the original cohort from two plants (6 and 10) where special-purpose glass fibres, relatively low-solubility glass fibres or quartz (pure silica) fibres (small-diameter (less than 1.5 μm)) were produced, and secondly, a starting date of 1940 was used for one plant (plant 9). The cause of 98.8% of deaths was identified and 0.6% of the study subjects were lost to follow-up. The whole cohort of glass fibre workers, including those who worked with glass wool and continuous glass filament covered 935 581 person–years and was about evenly divided between short-term (< 5 years; 47.9%) and long-term (≥ 5 years; 52.1%) workers. Of the glass-fibre workers, 5675 (17.7%) had been employed for 20 or more years and 15 766 (49.1%) were followed up for 30 or more years (Marsh *et al.*, 2001a).

As described by Smith *et al.* (2001) and Quinn *et al.* (2001), profiles for the historical exposure of individual workers were developed using an approach that integrated epidemiological methods with those used by industrial hygienists. Quantitative estimates of exposure were made for respirable fibres, formaldehyde and crystalline silica, and qualitative estimates for other agents such as arsenic, asbestos, asphalt, polycyclic aromatic hydrocarbons (PAHs) and styrene. The exposure was estimated from the date of plant start-up until closure or until 31 December 1987, which was the latest common work-history end-date. The median average intensity of exposure to respirable fibres computed across all individual workers was 0.035 fibre/cm^3. When calculated by plant, this value ranged from 0.001 fibre/cm^3 for workers in one plant that produced continuous glass filament to 0.167 fibre/cm^3 for workers in a plant that produced mostly glass wool. The median cumulative exposure was 1.441 fibres/cm^3–months for all workers, ranging from 0.086 to 6.382 fibres/cm^3–months. The average exposure of long-term workers (employed for at least 5 years) during their first five years of exposure was similar to that of short-term workers (employed for less than 5 years) (Marsh *et al.*, 2001a).

For the whole glass fibre cohort (10 plants) using local county rates, the SMR for all causes of mortality was reduced (SMR, 0.90; 95% CI, 0.88–0.92) as was that for all cancers (SMR, 0.94; 95% CI, 0.90–0.98) during 1960–92 (8436 deaths from all causes and 2243 deaths from cancer). For all workers, the local county-based SMRs for respiratory cancer increased with calendar time and time since first employment, but not with duration of employment. The short-term workers had an excess of respiratory cancer (SMR, 1.12; 95% CI, 1.01–1.24) (378 cases) compared with an SMR of 1.03 (0.94–1.12) (496 cases) for long-term workers. The SMRs for long-term workers did not increase with calendar time, duration of employment or time since first employment (Marsh *et al.*, 2001a).

An analysis restricted to the eight glass wool plants resulted in an SMR for respiratory cancer of [1.06 (95% CI, 0.99–1.14)] (733 deaths) (local county comparison). The SMR for respiratory cancer in the four plants producing special-purpose glass fibres (local county comparison) was [1.06 (95% CI, 0.97–1.15)] (490 cancer deaths). In general, comparison with national reference rates provided similar results (Marsh *et al.*, 2001a).

Buchanich *et al.* (2001) inferred from a survey of the tobacco-smoking habits of the US University of Pittsburgh cohort that male glass fibre workers had higher estimated point prevalence rates of ever smoking than the corresponding general US populations and than most of the states where the study plants were located. The method of Axelson and Steenland (1988) was used to make an indirect adjustment of the SMRs for respiratory cancer to account for potential confounding by smoking. The adjustments were based on data on smoking prevalence within the cohort estimated from a random sample of cohort members (Marsh *et al.*, 2001b) and the relative risk for ever versus never smoking as estimated from the nested case–control study of respiratory cancer (Marsh *et al.*, 2001a). The adjustment suggested that cigarette smoking may account for the excess in respiratory cancer observed for the cohort of male glass-fibre workers (SMR adjusted for age-adjusted prevalence of ever smoking and based on local county rates, 0.89). The same conclusion was reached regardless of which of several alternatives were used to adjust local county rate-based SMRs for respiratory cancer. All SMRs that were statistically significantly elevated when unadjusted were reduced to non-statistically significant levels when adjusted for smoking (Marsh *et al.*, 2001b).

As part of the on-going mortality surveillance programme for the US MMVF industry, mortality from mesothelioma [mesotheliomas were not identified before the 8th ICD revision in 1968] was investigated from the 1992 follow-up of the US University of Pittsburgh study (Marsh *et al.*, 2001c). A manual search of all death certificates of 9060 glass-fibre workers revealed that seven of the death certificates issued for the glass wool workers mentioned the word mesothelioma. A subsequent review of medical records and pathology specimens for one (plant 9) of the seven workers deemed this one death as having a 50% chance of being due to mesothelioma. Five of the seven workers who had died had potentially been exposed to asbestos while working in the glass fibre industry or in other jobs. No death coded as pleural cancer was observed in the glass wool cohort.

With the exception of respiratory cancer, no statistically significant excesses of mortality were observed among the cancer site categories 'buccal cavity and pharynx' (SMR, 1.11; 95% CI, 0.85–1.42; 63 cancer deaths) or 'bladder and other urinary organs' (SMR, 1.07; 95% CI, 0.82–1.37; 64 cancer deaths) (local county comparison) (Marsh *et al.*, 2001a).

(*b*) *Nested case–control studies*

Marsh *et al.* (2001a), Stone *et al*. (2001) and Youk *et al*. (2001) performed a nested case–control study as part of the US University of Pittsburgh cohort study of glass-fibre workers (10 plants) in which workers at the continuous glass filament plants represented the lower exposure groups. The investigators identified 713 men who had died from respiratory cancer during 1970–92 and one control per case. The potential controls were at risk during 1970–92 and alive and at risk at the age at which the case had died; controls were also matched by date of birth. A telephone interview was conducted with the study subject or a knowledgeable informant for [88.6%] of cases and 80.2% of controls (Stone *et al.*, 2001). [The proportion of respondent type was not given.] There were 516 matched sets for which data on smoking (631 cases and 570 controls) were available for analysis.

Marsh *et al.* (2001a) reported an increased risk for respiratory cancer for combined non-baseline levels of exposure to respirable fibres (odds ratio, 1.37; 95% CI, 0.55–

3.42), adjusted for smoking. The duration of exposure and cumulative exposure to respirable fibres (adjusted for smoking) did not appear to be associated with an increased risk for respiratory cancer and no apparent increase in risk with increasing time since first employment in the plant was noted. There was some evidence of an elevated risk for respiratory cancer associated with non-baseline levels of average intensity of exposure to respirable glass wool, but this was not statistically significant when adjusted for smoking and there was no apparent trend with increasing exposure. The analysis by product group ('continuous glass filament', 'glass wool and continuous glass filament' and 'mostly glass wool') used continuous glass filament as the baseline category. After adjustment for smoking, the odds ratios for the 'glass wool and continuous glass filament' and 'mostly glass wool' categories were close to unity when compared to the baseline for continuous glass filament, and were 1.01 (95% CI, 0.69–1.47) and 1.06 (95% CI, 0.71–1.60), respectively.

Youk *et al.* (2001) explored the possible exposure–response relationship between respiratory cancer and exposure to respirable fibres or formaldehyde using exposure-weighting. None of the categorized measurements of exposure to respirable fibres using time lags and unlagged/lagged time windows showed a statistically significant association with risk for respiratory cancer ($p > 0.49$ for each). All of the estimated odds ratios for exposure-weighted models were lower than the estimated odds ratio of 1.37 (95% CI, 0.55–3.42) for the unweighted model. No pattern of increasing risk for respiratory cancer with increasing levels of cumulative exposure or average intensity of exposure to respirable fibres was seen.

Stone *et al.* (2001) extended the exposure–response analysis within the case–control study to include quantitative measures of exposure to respirable fibre for the US University of Pittsburgh cohort. Quantitative measures of formaldehyde and crystalline silica (mainly quartz) were made as these substances were considered as potential confounders and effect modifiers. Neither the average intensity of exposure nor the cumulative exposure to respirable fibres showed a statistically significant association with risk for respiratory cancer in any of the hundreds of fractional polynomial models considered.

Chiazze *et al.* (1992) reported on a case–control study of male workers employed for one year or more between 1 January 1940 and 31 December 1962, and followed up until 1982, at one glass fibre plant (producing glass wool and continuous glass filament) in the USA. This plant is included in the US University of Pittsburgh cohort (plant 9). The investigators identified 166 deaths due to lung cancer. The controls were cohort members matched on year of birth (within 2 years) and survival to end of the follow-up period or death (within 2 years). The response rate was 88% for cases and 79% for controls. Interviews were completed with proxies for 144 of these cases. Eighty per cent of the interviews were conducted face-to-face and the remaining 20% by telephone. Moste of the interviewees were proxy respondents (88%), of whom 87% reported having been in contact with the subject at least once a month. Data available for analysis included information on work history, demographic information (including smoking habits) and Chiazze *et al*. (1993) added information on exposure for a profile constructed for the years 1934–87 that included estimates of cumulative exposure to respirable fibres. The odds ratio for smoking (> 6 months versus never) and lung cancer was 26.2 (95% CI, 3.32–207). The odds ratios for lung cancer adjusted for smoking and other potential confounders were 1.72 (95% CI, 0.77–3.87) and 0.58 (95% CI, 0.20–1.71) for cumulative exposure to respirable fibre categories of 100–299.99 fibres/cm^3–days and ≥ 300 fibres/cm^3–days, respectively. The lowest exposure category, < 100 fibres/cm^3–days, served as the reference group.

2.1.2 *European glass fibre cohort*

(*a*) *Cohort studies*

Plato *et al*. (1995c) investigated the mortality and cancer incidence in Sweden among 3539 male and female workers (1970 from a glass wool plant, 1187 from a large rock (stone) wool/slag wool plant and 382 from a small rock (stone) wool/slag wool plant), employed for at least one year before 1978. These plants were included in the European MMVF cohort study (see Boffetta *et al.*, 1997). Of the 3539 subjects, 245 had emigrated before the study and 41 were lost to follow-up. The mortality analysis was based upon the remaining 3253 subjects, 738 of whom died between 1952 and 1990. Cancer incidence was followed from 1958 to 1989. The SMR and SIR were analysed using regional and national reference rates. When compared with regional reference rates, there was a slightly increased excess for overall mortality (SMR, 1.02; 95% CI, 0.95–1.10) for the total cohort including the rock (stone)/slag wool component. Comparison with regional reference rates showed no increased risk for mortality from all cancers for workers at the glass wool plant (SMR, 1.00; 95% CI, 0.82–1.22; 102 cancer deaths) or from lung cancer (ICD-8 162) (SMR, 0.97; 95% CI, 0.57–1.69; 14 lung cancer deaths). Neither was there an increased risk for lung cancer mortality associated with a longer duration of employment (length of employment < 2 years, SMR, 1.47; 95% CI, 0.48–3.44; 2–9 years, SMR, 0.92; 95% CI, 0.37–1.90; 10–19 years, SMR, 0.39; 95% CI, 0.01–2.19, ≥ 20 years, SMR, 0.94; 95% CI, 0.02–5.21). There was an excess in lung cancer mortality for workers with 30 years of latency (SMR, 1.43; 95% CI, 0.74–3.05). [No data on smoking or co-exposure were available.]

Boffetta *et al.* (1997) extended the follow-up of cancer mortality for the European cohort study of MMVF production workers in 13 factories from 1982 (except for one continuous glass filament plant where it was until 1983) until 1990 in Denmark, Italy, Norway and Sweden, 1991 in Germany and 1992 in the United Kingdom (see Table 54). Information on work history was available until 1977. The population under study was the workforce (male and female) ever employed (i.e. with at least 1 year of employment in Sweden and in one of the two factories in the United Kingdom) between the year production started (1933–50) and 1977; follow-up was successful for 97.7% of the workers and the cause of 99.5% of deaths was known. Five factories (1 in Finland, 1 in Italy, 1 in Norway, 1 in Sweden and 1 in the United Kingdom) in which glass wool was

Table 54. Plants and populations included in the European MMVF study

Production process, plant no. and country	No. of workers
Rock (stone)/slag wool	
1 Denmark	4 585
3 Norway	473
4 Norway	460
5 Norway	875
8 Sweden	384
9 Sweden	1 194
12 Germany	2 137
Total, rock (stone)/slag wool	10 108
Glass wool	
2 Finland	924
6 Norway	644
7 Sweden	2 022
10 United Kingdom	4 145
14 Italy	600
Total, glass wool	8 335
Continuous glass filament	
11 United Kingdom (Northern Ireland)	1 837
14 Italy	1 722
Total, continuous filament	3 559
Total, cohort	22 002

From Boffetta *et al.* (1997)

produced employed a total of 8335 workers (6936 workers had ≥ 1 year of employment and contributed 167 675 person–years of observation). Exposure to asbestos occurred in one plant in Finland (1946–48) and one plant in the United Kingdom (1946–62) (Cherrie & Dodgson, 1986). No information on other potential sources of workplace co-exposure or on smoking habits were available. Among the cohort of glass-wool workers employed for one year or more, excesses for all causes of death (SMR, 1.05; 95% CI, 1.00–1.10; 1679 deaths) and all malignant neoplasms (SMR, 1.11; 95% CI, 1.01–1.22; 460 cancer deaths) were observed based on national mortality rates. There was an increased risk for lung cancer (SMR, 1.27; 95% CI, 1.07–1.50; 140 lung cancer deaths). An analysis of lung cancer mortality by technological phase in all workers and in workers employed for one year or more did not reveal a trend of higher risks during the earlier technological phases. No trend in lung cancer mortality was associated with duration of employment. The SMR for cancer of the buccal cavity and pharynx was 1.47 (95% CI, 0.71–2.71). One death from mesothelioma was observed in the glass-wool workers.

The cancer incidence of 2611 glass-wool production workers was followed up until 1995. The subjects had been employed for one year or more (68 523 person–years) in Finland, Norway or Sweden (3 plants from the Boffetta *et al.* (1997) study) (Boffetta *et al*., 1999), an increased incidence of lung cancer (SIR, 1.28; 95% CI, 0.91–1.74; 40 cases) was observed. A trend was suggested for time since first employment ($p = 0.2$), but not with employment during the earlier technological phases. The SIR for cancers of the oral cavity, pharynx and larynx was 1.41 (95% CI, 0.80–2.28; 16 cases).

(*b*) *Nested case–control study*

Gardner *et al*. (1988) reported a study of 73 employees (66 men and seven women) who had died from lung cancer and 506 matched controls through 1984 (as did Simonato *et al.* (1987) in their follow-up of the cohort) from a glass wool plant in the United Kingdom which was included in the European glass fibre cohort. Superfine fibres (diameters, 1–3 μm and 2–5 μm) had been manufactured at this plant for two periods between 1949 and 1968. Up to eight controls were matched for sex and year of birth (within 2.5 years) with each case. The controls were selected at random from all eligible workers who were alive and had been employed for one year or more at the time the case died. [The response rates and proportions of respondent type were not reported.] The odds ratios and CIs were computed by conditional logistic regression for matched case–control sets with a variable matching ratio. The odds ratio for employment in jobs entailing exposure to 'superfine glass wool' was 1.3 (95% CI, 0.3–5.8) and that for employment in jobs in which workers were exposed to glass wool was 1.1 (95% CI, 0.7–1.9). There was no evidence of a relationship between lung cancer and fibre diameter, duration of exposure or time since first exposure. The results by broad occupational group were similar to those from the cohort study. [The Working Group noted that the study did not indicate a differential risk for lung cancer in workers exposed to 'finer-diameter' (superfine) glass fibres; however, the exposure levels were low and the number of cases was small. Data on smoking and co-exposure were not available.]

2.1.3 *Other cohort studies*

Shannon *et al*. (1984, 1987) reported a cohort study of 2557 men who had worked for 90 days or more between 1955 and 1977 in a glass wool plant in Sarnia, Canada. The cohort was followed for deaths to the end of 1984 and 97% of the cohort was traced. No data on historical exposure were available, but samples taken since 1978 suggested that fibre concentrations were rarely > 0.2 fibre/cm^3 and the mean concentrations in most areas of the plant were < 0.1 fibre/cm^3. The cohort was divided into three groups of workers: plant only, office only and 'mixed exposure'. For the plant-only group, the SMR for lung cancer based on 19 deaths and provincial (Ontario) rates was 1.99 [95% CI, 1.20–3.11]. In the office-only and mixed-exposure groups combined, there were two deaths from lung cancer compared to [2.4 expected (SMR, 0.83; 95% CI, 0.10–3.01)]. For plant-only workers who had been exposed for five years or more and for whom ten or more years had elapsed since first exposure, there were 13 deaths from lung cancer (SMR, 1.82 [95% CI, 0.97–3.11]). There was no trend of increasing lung cancer risk with increasing duration of employment or time since first employment.

Moulin *et al.* (1986) reported a cohort study in France at a glass wool production factory. The cohort included 1374 male workers who were employed at any time during 1975–84 for at least one year. The incidence of cancer during this period was ascertained from the social insurance records of the company, and the diagnoses were obtained from various medical sources. Five workers with lung cancer were identified in the whole cohort (SIR, 0.74; 95% CI, 0.24–1.72). Nineteen cases of cancers of the 'upper respiratory and alimentary tract' were observed (SIR, 2.18; 95% CI, 1.31–3.41). In particular, there was an excess of cancers of the larynx (5 observed; SIR, 2.30), pharynx (5 observed; SIR, 1.40) and buccal cavity (9 observed; SIR, 3.01). The excess was limited to production workers, and among this group the SIR increased with duration of employment. A survey of the cigarette smoking habits of the 1983 workforce indicated slightly lower smoking levels than those reported in a survey conducted in France in 1979. [The Working Group noted that the study was initiated because 'an industrial physician had noted an excess of cancers in the upper respiratory and alimentary tracts' in the factory and that the authors did not report whether any case of 'upper respiratory and alimentary tract' cancer was identified in addition to the index cases. Both the observed and expected numbers of workers with at least 10 years of exposure who developed lung cancer were very small. The Working Group also noted that the reference population may not have been appropriate.]

2.2 Continuous glass filament (see Table 55)

In the studies until 1987 evaluated by the previous Working Group, there was *inadequate evidence* for the carcinogenicity of continuous glass filaments in humans (IARC, 1988) (see section 2.1).

(*a*) *United States University of Pittsburgh cohort*

Marsh *et al.* (1990) reported the 1985 follow-up of the cohort of MMVF workers in the USA (see description of the study in section 2.1). The US University of Pittsburgh cohort included three plants that produced continuous glass filament (start of production, 1941–51). This part of the study included 3435 male workers employed for one year or more between 1945 and 1963. The SMR for respiratory cancer for workers exposed to continuous glass filament was 0.98 (84 cases) based on local reference rates. The average concentration of fibres to which workers were exposed was 0.011 fibre/cm^3.

In the 1992 follow-up, in the study of 10 glass fibre plants in the USA (described in detail in section 2.1), two plants (2 and 5) mainly manufactured continuous glass filaments. The two plants taken together had an SMR for respiratory cancer of 1.04 (95% CI, 0.87–1.22) for all workers and an SMR of 0.96 (95% CI, 0.76–1.19) for long-term workers (≥ 5 years) (local county comparison) (Marsh *et al.*, 2001a). The SMRs

Table 55. Studies of cancer incidence in workers exposed to continuous glass filament

Reference, plants	Description, employment period, follow-up	No. of deaths or cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
US University of Pitsburgh						
Cohort studies						
Marsh *et al.* (1990) 3 plants	3435 male workers[a], employed 1945–63, follow-up 1946–85	84 deaths from respiratory cancer	Time since first employment		SMR	Local rates
			< 10 years	6	1.03	
			10–19 years	8	0.47	
			20–29 years	42	1.22	
			≥ 30 years	28	0.99	
			Duration of employment			
			< 10 years	51	1.13	
			10–19 years	12	0.61	
			20–29 years	18	1.21	
			≥ 30 years	3	0.54	
					SMR	Local rates
Marsh *et al.* (2001a) 2 plants	5431 male and female[a] workers, employed 1945–78, follow-up 1946–92	141 deaths from respiratory cancer			1.04 (0.87–1.22)	
			Long-term workers (≥ 5 years employment)	81	0.96 (0.76–1.19)	
Case–control study						
					Odds ratio	
Marsh *et al.* (2001a) 1970–92	Plant 2	61 deaths from respiratory cancer			1.60 (0.95–2.69)	Adjusted for smoking
Male workers	Plant 5	31 deaths from respiratory cancer			0.54 (0.31–0.94)	Adjusted for smoking

Table 55 (contd)

Reference, plants	Description, employment period, follow-up	No. of deaths or cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
European cohort study						
Boffetta *et al.*	1940 male and female				SMR	National rates
(1997)	workers[a]	Deaths from lung		14	1.11 (0.61–1.86)	
2 plants	employed 1946–61	cancer				
United Kingdom	follow-up until 1990	Deaths from cancer		2	1.63 (0.20–5.87)	
(Northern Ireland),		of the buccal cavity				
Italy		and pharynx				
US Georgetown University						
Chiazze *et al.*	2933 white male				SMR	Local rates
(1997)	workers[a]	47 deaths from lung			1.17 (0.86–1.55)	
Cohort study	employed 1951–91	cancer				
	follow-up until 1991	2 deaths from cancer			0.87 (0.11–3.16)	
		of the buccal cavity				
		and larynx				
Chiazze *et al.*	45 deaths from lung	122 controls	Cumulative exposure to		Odds ratio	
(1997)	cancer [a]		respirable glass fibres			
Case–control study	white men		0	35	1.0	
	1951–91		> 0.005 fibre/cm^3–days	10	0.91 (0.36–2.25)	
			> 0.005 fibre/cm^3–days	8	0.78 (0.28–2.20)	Smokers

Table 55 (contd)

Reference, plants	Description, employment period, follow-up	No. of deaths or cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
US Georgetown University (contd)						
Watkins *et al.* (1997) Cohort study					SMR	Local rates
	1074 white women[a]	4 deaths from lung cancer			0.72 (0.20–1.85)	
	494 black men[a], employed 1951–91, follow-up until 1991	2 deaths from lung cancer			0.30 (0.04–1.07)	
Canadian cohort study						
					SMR	Local Ontario rates
Shannon *et al.* (1990)	1465 men and women[a], employed 1951–86	11 deaths from lung cancer			1.36 [0.68–2.4]	
			Cumulative exposure to dust (≥ 15 years since first exposure)			
			< 5 years	1	1.38	
			5–9 years	2	1.56	
			10–24 years	2	1.71	
			≥ 25 years	2	0.67	

[a] Employed for ≥ 1 year
SMR, standardized mortality ratio; SIR, standardized incidence ratio; respiratory cancer, ICD-8, 160–163

for respiratory cancer for the two continuous glass filament plants were (male workers only): plant 2, 1.18 [95% CI, 0.96–1.44] and plant 5, 0.85 [95% CI, 0.60–1.10]. The results of the exposure–response analysis for the continuous glass filament plants were included in the study of glass-wool workers, described in section 2.1. Adjustment for smoking had very little effect (Marsh *et al.*, 2001b). One person had died from mesothelioma according to the death certificate, but this diagnosis was not confirmed by a review of medical records and pathology specimens (Marsh *et al.*, 2001c).

In a nested case–control study among male workers of this cohort (see section 2.1 for description of the study), the smoking-adjusted odds ratios for respiratory cancer for the two continuous glass filament plants compared with the baseline plant (plant 9) were: plant 2, 1.60 (95% CI, 0.95–2.69) and plant 5, 0.54 (95% CI, 0.31–0.94) (Marsh *et al.*, 2001a).

(*b*) *European cohort*

In the study by Boffetta *et al.* (1997), described in detail in section 2.1, separation into distinct technological phases was not applicable to the process of continuous filament production. For 1940 continuous filament workers employed for one year or more in one plant in the United Kingdom (Northern Ireland) or one in Italy, contributing 35 293 person–years of observation, the SMR for overall mortality was 1.22 (95% CI, 1.05–1.40; 191 deaths) and that for overall cancer mortality was 1.04 (95% CI, 0.76–1.39; 45 cases). The SMR for lung cancer was 1.11 (95% CI, 0.61–1.86; 14 cases) and a non-statistically significant increase in SMR was seen for cancer of the buccal cavity and pharynx, based upon two deaths (SMR, 1.63; 95% CI, 0.20–5.87).

(*c*) *United States Georgetown University cohort*

Chiazze *et al.* (1997) studied a cohort of 2933 white male production workers employed for one year or more between 1951 and 1991 in a continuous glass filament plant in the USA, which was followed up until 1991. B fibres (‘respirable fibres’) (average diameter, 3.5 μm) were produced only from 1963–68 and glass fibres of 10–12 μm diameter were produced throughout the study period. Three per cent of the cohort members were lost to follow-up and cause of 96.3% of deaths was known. Information on ‘respirable glass fibre’ and on potentially confounding exposure to asbestos, refractory ceramic fibres, respirable silica, formaldehyde, ‘total chrome’ [presumed to be chromium oxides] and arsenic was available. This information was not presented in the SMR analysis (only the results of the case–control study were presented using this information, see below). The SMRs were calculated using national and county mortality rates. For all causes of death and all malignant neoplasms, there were deficits in mortality when compared with local rates (SMR for all causes, 0.92; 95% CI, 0.84–1.01; all malignant neoplasms, SMR, 0.96; 95% CI, 0.78–1.18). The SMR for lung cancer in white males, based on local mortality rates, showed a non-statistically significant increase (SMR, 1.17; 95% CI, 0.86–1.55; 47 deaths) and a non-significant deficit in mortality due to malignant neoplasms of the buccal cavity and pharynx (SMR, 0.87; 95% CI, 0.11–3.16; 2 deaths).

In a nested case–control study of this cohort, Chiazze *et al.* (1997) reported a study of 47 white men who had died from lung cancer between 1951 and 1991. Controls were matched on year of birth (within 2 years) and survival to end of follow-up or death (within 2 years). Information on demographic factors, including smoking, was obtained from interviews, and a reconstruction of the historical working environment was used to identify the agents to which the workers were potentially exposed (such as asbestos, refractory ceramic fibres, total particulate matter, respirable silica, formaldehyde, total chrome [presumed to be chromium oxides] and resins (binder)). Information on exposure was available for 45 (96%) and information on smoking habits was available for 35 (75%) of the cases. The odds ratio for lung cancer among workers exposed to respirable glass fibres (B fibres) was below unity (odds ratio, 0.91; 95% CI, 0.36–2.25). For smokers, the odds ratio for lung cancer among workers exposed to respirable glass fibres was further reduced (odds ratio, 0.78; 95% CI, 0.28–2.20). None of the other substances to which workers at the plant were potentially exposed was associated with an increase in lung cancer risk for this population.

In the same cohort, Watkins *et al*. (1997) studied 1074 white women, 130 black women and 494 black men (with the same entrance criteria, follow-up and information on other potential sources of exposure as used by Chiazze *et al*., 1997). A total of 107 white women died during the period of investigation and relatively few deaths were attributable to any one specific cause. There were no significant excesses or deficits in mortality by cause, including cancer, among the white women, when compared with national mortality rates. For black men, the SMRs for all cancers combined were below unity when calculated using either national (SMR, 0.84; 95% CI, 0.46–1.41) or local county standards (SMR, 0.82; 95% CI, 0.45–1.38; 14 deaths). Based upon local rates, the SMRs for lung cancer were below unity for both white women (SMR, 0.72; 95% CI, 0.20–1.85; 4 cases) and black men (SMR, 0.30; 95% CI, 0.04–1.07; 2 cases). Only four of the black women died during the study period.

(*d*) *Canadian cohort*

Shannon *et al.* (1990) reported the results of a cohort study in Canada. The cohort consisted of 1465 men and women who had worked for a total of at least one year at a continuous glass filament plant in Guelph, Ontario between 1951 (when the operations began) and 1986. Ninety-six per cent of the potential study subjects were traced. Data on the history of exposure to ‘dust’ were not available for the plant until 1978 and previous dust concentrations were estimated. These estimates were made by two groups of employees who were asked to rank dustiness for individual jobs and departments over time on a scale from 0 (fresh air) to 5 (the dustiest conditions ever experienced). When there was disagreement the estimates were averaged. In dust samples taken between 1979 and 1987, the time-weighted averages were between 0.02 and 0.05 fibre/cm^3. The highest value observed for any sample was 0.91 fibre/cm^3. The SMRs were calculated based upon local (Ontario) mortality rates. The overall mortality risk was decreased for both men (SMR, 0.76 [95% CI, 0.60–0.94]; 82 deaths) and women (SMR, 0.95 [95% CI, 0.52–1.6]; 14 deaths), and there was also a deficit in risk for all cancers for both men (SMR, 0.99 [95% CI, 0.64–1.5]; 25 deaths) and women (SMR, 0.67 [95% CI, 0.18–1.7]; 4 deaths). A non-statistically significant increase in risk for lung cancer, based upon 11 deaths (SMR, 1.36 [95% CI, 0.68–2.4]) was reported for the total cohort. The risk for lung cancer was not associated with increasing estimates of cumulative exposure to dust. [The Working Group considered that the limitations of this study include small size of the cohort and the lack of data on industrial hygiene and smoking habits.]

2.3 **Rock (stone) wool and slag wool** (see Table 56)

2.3.1 *Cohort studies*

In their evaluation of the studies of the carcinogenicity of rock (stone) wool and slag wool, the previous Working Group considered that there was *limited evidence* for the carcinogenicity of rock (stone) wool and slag wool in humans (IARC, 1988) (see section 2.1). The studies from the USA indicated statistically significant excess mortality from respiratory cancer; however, there was no relationship with time since first exposure, duration of exposure or time-weighted measurements of fibre exposure. The European study showed an overall excess of lung cancer mortality that was not statistically significant and an increasing risk with time since first exposure. The highest (and statistically significant) excess of lung cancer was found after more than 20 years of follow-up in workers who had first been exposed to rock (stone) and slag wool during the early technological phase. In addition to the studies described in the previously evaluated papers, Boffetta *et al*. (1992) reported the results from a Poisson regression analysis of the European cohort followed up for mortality until 1982–83 which showed no significant association of lung cancer with surrogates for fibre exposure.

(*a*) *United States University of Pittsburgh cohort*

Two follow-up studies of this cohort have been published since 1988 (Marsh *et al.*, 1990, 1996). The 1985 follow-up used (Marsh *et al.*, 1990) (see section 2.1 for description of the study), data on 1846 male workers from six plants producing rock (stone) wool and slag wool. During the follow-up period, 73 cohort members died from respiratory cancer giving an overall SMR of 1.36 [95% CI, 1.06–1.71] when local rates were used. The average concentration of fibres of diameter < 3 μm was 0.351 fibre/cm^3. There was no positive relationship between respiratory cancer and duration of employment; men employed for less than 10 years had an SMR of 1.43 [95% CI, 1.01–1.96], 38 deaths. The Poisson regression analysis showed no statistically significant pattern of increasing risk associated with any of the indicators of exposure.

Table 56. Studies of cancer in workers exposed to rock (stone) wool and slag wool

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
US University of Pittsburgh						
Cohort studies						
					SMR	Local rates
Marsh *et al.* (1990) 6 plants	1846 male workers[a] employed 1945–63, follow-up 1946–85	73 deaths from respiratory cancer			1.36 [1.06–1.71]	
			Time since first employment			
			< 10 years	2	0.89	
			10–19 years	13	1.56	
			20–29 years	24	1.37	
			≥ 30 years	34	1.32	
			Duration of employment			Local rates
			< 10 years	38	1.43 [1.01–1.96]	
			10–19 years	15	1.46	
			20–29 years	11	1.18	
			≥ 30 years	9	1.18	

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Marsh *et al.* (1996) 5 plants	*N-cohort* (cohort participating in the new programme): 3035 male and female workers[a] employed 1945–78	71 deaths from respiratory cancer (68 in men)	Time since first employment			
			N-cohort (men only)		SMR	Local rates
			< 10 years	2	0.58	
			10–19 years	13	1.22	
			20–29 years	23	1.35	
			≥ 30 years	30	1.06	
			O-cohort			
1 plant	*O-cohort* (cohort from the original plant): 443 male workers[a] employed 1945–63	32 deaths from respiratory cancer	< 20 years	3	0.95 [0.20–2.78]	Asbestos exposure
			20–29 years	8	1.41 [0.61–2.78]	
			≥ 30 years	21	1.71 [1.06–2.61]	
			Duration of employment			
	Follow-up until 1989		*N-cohort (men only)*		SMR	
			< 10 years	39	1.14	
			10–19 years	15	1.34	
			20–29 years	8	1.07	
			≥ 30 years	6	0.89	
			O-cohort			
			< 10 years	15	1.32	
			10–19 years	7	2.02	
			≥ 20 years	10	1.61	

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Nested case–control study						
Marsh *et al.* (1996)						
5 plants	*N-cohort*	107 male	Cumulative exposure to			
	54 deaths[a] from respi-	controls	respirable fibres		Odds ratio	
	ratory cancer (men)		< 3 fibres/cm^3–months		1.0	Unadjusted for smoking
			3–14 fibres/cm^3–months		0.70	
			15–39 fibres/cm^3–months		0.59	
			≥ 40 fibres/cm^3–months		0.71	*p* for linear trend = 0.76
	54 deaths from	101 male	< 3 fibres/cm^3–months		1.0	Adjusted for smoking
	respiratory cancer	controls	3–14 fibres/cm^3–months		0.64	
	(men)		15–39 fibres/cm^3–months		0.55	
			≥ 40 fibres/cm^3–months		0.58	*p* for linear trend = 0.64
			Duration of employment		Odds ratio	
1 plant	*O-cohort*	47 controls	< 2 years		1.0	Unadjusted for smoking
	24 deaths[a] from respi-		2–4 years		1.62	
	ratory cancer (men)		5–19 years		0.23	
	1970–89		≥ 20 years		0.85	*p* for linear trend = 0.21
	18 deaths from respi-	31 controls	< 2 years		1.0	Smokers only
	ratory cancer		2–4 years		1.82	
			5–19 years		0.33	
			≥ 20 years		0.73	*p* for linear trend = 0.47
USA						
Nested case–control study						
					Odds ratio	NIOSH exposure classification
Wong *et al.* (1991)	55 men who died from	98 male	Exposed/unexposed	50	0.90 (0.23–3.49)	Unadjusted for smoking
9 plants	lung cancer[a]	controls who			0.94 (0.23–3.78)	Adjusted for smoking
slag wool workers	1970–89	had died from	Exposed ≥ 7 fibres/cm^3–months	27	0.86 (0.42–1.79)	Unadjusted for smoking
(4 plants also in Marsh *et al.*, 1990, 1996)		other causes	exposed < 7 fibres/cm^3–months		0.98 (0.47–2.04)	Adjusted for smoking

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
European study						
Cohort studies						
					SMR	
Plato *et al.* (1995c) Sweden 2 plants (included in Boffetta *et al.*, 1997)	1569 male and female workers employed[a] before 1978, follow-up 1952–90 for mortality	13 deaths from lung cancer			[1.57 (0.83–2.68)]	Local rates
					[1.02 (0.55–1.75)]	National rates
			Duration of employment with 20-year lag:			Local rates
			< 2 years	1	1.10 (0.28–6.12)	
			2–9 years	5	2.69 (0.87–6.27)	
			10–19 years	1	0.87 (0.02–4.89)	
			≥ 20 years	2	1.43 (0.17–5.16)	
			Plant-specific cumulative fibre exposure (fibres/cm^3–years):		SMR	
			< 1	7	2.01 (0.81–4.13)	
			1–2	4	2.45 (0.67–6.21)	
			> 2	2	0.62 (0.08–2.24)	
						Local rates
	Follow-up 1958–89 for incidence	13 cases of lung cancer	Duration of employment:		SIR	
			< 2 years	1	0.69 (0.02–3.84)	
			2–9 years	7	2.12 (0.85–4.37)	
			10–19 years	3	1.63 (0.34–4.76)	
			≥ 20 years	2	1.61 (0.20–5.83)	
					SIR	Local rates
		13 cases of stomach cancer			1.71 (0.91–2.93)	

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Boffetta *et al.* (1997) 7 plants Denmark, Germany, Norway and Sweden Mortality study	4912 male and female workers[a] employed 1933–77, follow-up until 1990–91	97 deaths from lung cancer			SMR 1.34 (1.08–1.63)	National rates
			Time since first employment		Relative risk[b]	Adjusted for age, calendar year, country, technological phase and duration of employment
			≤ 9 years	10	1.0	
			10–19 years	26	1.3 (0.6–3.0)	
			20–29 years	29	1.2 (0.5–3.1)	
			≥ 30 years	32	1.4 (0.4–4.6)	*p* for linear trend = 0.67
			Duration of employment			
			1–4 years	31	1.0	Adjusted for age, calendar year, country, technological phase and time since first employment
			5–9 years	21	1.4 (0.8–2.4)	
			10–19 years	21	1.0 (0.5–1.8)	
			≥ 20 years	24	1.6 (0.8–3.1)	*p* for linear trend = 0.27
			Technological phase			
			Late	76	1.0	Adjusted for age, calendar year, country, duration of employment and time since first employment
			Intermediate	12	1.0 (0.5–2.3)	
			Early	9	1.1 (0.4–2.8)	
					SMR	National rates
		8 deaths from oral cancer + cancer of the pharynx			1.33 (0.57–2.61)	
		6 deaths from cancer of the larynx			1.96 (0.72–4.27)	
		8 deaths from cancer of the oesophagus			1.25 (0.54–2.46)	

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Consonni *et al.* (1998) Denmark, Germany, Norway and Sweden 7 plants	9603 male workers employed until 1977 follow-up until 1990–91	159 deaths from lung cancer	Cumulative exposure		Relative risk[b]	Adjusted for age, calendar period, country, time since first employment and employment status
			≤ 0.007 fibre/cm^3–years	39	1.0	
			0.008–0.136 fibre/cm^3–years	40	1.3 (0.8–2.4)	
			0.137–1.367 fibre/cm^3–years	40	1.2 (0.7–2.1)	
			> 1.368 fibres/cm^3–years	40	1.5 (0.7–3.0)	*p* for linear trend = 0.4
		97 deaths from lung cancer in workers with ≥ 1 year of employment	≤ 0.139 fibre/cm^3–years	25	1.0	
			0.140–0.729 fibre/cm^3–years	24	0.9 (0.4–2.0)	
			0.730–2.622 fibres/cm^3–years	24	0.8 (0.3–1.9)	
			> 2.622 fibres/cm^3–years	24	1.0 (0.4–2.7)	*p* for linear trend = 1.0
Boffetta *et al.* (1999)	3685 male and female workers[a] employed 1933–77 follow-up 1994–95	73 cases of lung cancer			SIR 1.08 (0.85–1.36)	National rates
			Time since first employment		Relative risk[b]	Adjusted for age, gender, country and technological phase
			≤ 9 years	7	1.0	
			10–19 years	21	1.8 (0.7–4.7)	
			20–29 years	25	2.4 (0.9–6.8)	
			≥ 30 years	20	3.0 (0.8–10.5)	*p* for linear trend = 0.1
			Duration of employment (15-year lag)			Adjusted for age, gender, country, technological phase and time since first employment
			1–4 years	33	1.0	
			5–9 years	11	1.0 (0.5–2.1)	
			10–19 years	10	1.2 (0.5–2.6)	
			≥ 20 years	5	2.0 (0.7–6.2)	*p* for linear trend = 0.4
			Technological phase			Adjusted for age, gender, country and time since first employment
			Late	50	1.0	
			Intermediate	14	0.8 (0.4–1.7)	
			Early	9	0.8 (0.3–2.0)	*p* for linear trend = 0.5
		31 cases of cancer of the oral cavity, pharynx or larynx			SIR 1.46 (0.99–2.07)	National rates

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Case–control study						
Kjaerheim *et al.* (2002) 7 plants	133 cases of lung cancer; rock (stone) wool/slag wool male workers employed 1937–76, follow-up 1971–96	513 male controls	Cumulative fibre exposure in quartiles		Odds ratio	Adjusted for age, country and tobacco smoking
			All workers			
			quartile 1	33	1.0	
			quartile 2	32	0.86 (0.47–1.56)	
			quartile 3	33	0.91 (0.51–1.63)	
			quartile 4	34	0.51 (0.28–0.93)	*p* for linear trend = 0.04
			Workers employed > 1 year			
			quartile 1	12	1.0	
			quartile 2	3	2.08 (0.36–11.91)	
			quartile 3	26	0.85 (0.34–2.15)	
			quartile 4	34	0.52 (0.21–1.30)	*p* for linear trend = 0.11
			Cumulative fibre exposure, in quartiles, lagged 15 years			
			All workers			
			quartile 1	36	1.0	
			quartile 2	36	1.25 (0.66–2.34)	
			quartile 3	30	1.02 (0.54–1.93)	
			quartile 4	30	0.67 (0.35–1.27)	*p* for linear trend = 0.17
			Workers employed > 1 year			
			quartile 1	23	1.0	
			quartile 2	5	2.00 (0.41–9.83)	
			quartile 3	18	0.76 (0.27–2.17)	
			quartile 4	29	0.63 (0.28–1.42)	*p* for linear trend = 0.19

Table 56 (contd)

Reference, plants	Description, employment, follow-up	No. of deaths, cases (controls), type of cancer	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Kjaerheim *et al.* (2002) (contd)			Duration of exposure in rock (stone)/slag wool industry		Odds ratio	
			All workers			
			Unexposed	7	1.0	
			1 year	58	1.24 (0.47–3.26)	
			2–6 years	32	0.86 (0.32–2.31)	
			7–40 years	35	0.85 (0.32–2.26)	*p* for linear trend = 0.23
			Workers employed > 1 year			
			Unexposed	6	1.0	
			1 year	2	0.51 (0.05–5.50)	
			2–6 years	32	0.60 (0.17–2.08)	
			7–40 years	35	0.65 (0.20–2.12)	*p* for linear trend = 0.63
			Duration of exposure in rock (stone)/slag wool industry, lagged 15 years			
			All workers			
			Unexposed	28	1.0	
			1 year	51	1.57 (0.82–2.99)	
			2–5 years	28	1.20 (0.61–2.34)	
			6–39 years	25	0.97 (0.48–2.00)	*p* for linear trend = 0.15
			Workers employed > 1 year			
			Unexposed	18	1.0	
			1 year	4	1.06 (0.21–5.30)	
			2–5 years	28	1.01 (0.44–2.34)	
			6–39 years	25	0.98 (0.39–2.47)	*p* for linear trend = 0.96

[a] Employed for ≥ 1 year
[b] Poisson regression analysis
SMR, standardized mortality ratio; SIR, standardized incidence ratio; respiratory cancer, ICD-8, 160–163

Marsh *et al*. (1996) extended the follow-up period for workers employed between 1945 and 1978 to 1989. The extended cohort (N-cohort) included 2762 men and 273 women who had been employed for one year or more in production or maintenance. One factory (plant 17) had closed and declined to participate further; this plant had evidence of exposure to asbestos and it was therefore designated to a separate subcohort (O-cohort). Vital status for the members of both cohorts was determined as of 31 December 1989. From the five other plants (the N-cohort), quantitative estimates of exposure to total airborne fibres, respirable fibres, formaldehyde and silica were computed together with qualitative estimates of potential exposure to asbestos, arsenic, asphalt, radiation and PAHs (Marsh *et al.*, 1993). The pattern of findings of respiratory cancer after the extended update was generally consistent with the results of the previous follow-up. Seventy-one workers from the five plants died from respiratory cancer. This increase was non-significant (SMRs, 1.24 [95% CI, 0.97–1.56] and 1.17 [95% CI, 0.91–1.48], based on US and local county comparisons rates, respectively). For the O-cohort (plant 17), however, 32 men died from respiratory cancer, resulting in statistically significant increases of the SMRs (SMRs, 1.91 [95% CI, 1.31–2.70] and 1.52 [95% CI, 1.04–2.15], using national and local county rates, respectively). There was no evidence of a positive association between mortality from respiratory cancer, duration of employment and year since first employment in the five plants (N-cohort), but in the O-cohort a positive association was seen with time since first employment (SMRs, 0.95, 1.41 and 1.71 [95% CI, 0.20–2.78, 0.61–2.78 and 1.06–2.61, respectively] in the groups with < 20 years, 20–29 and ≥ 30 years since first employment, respectively) (Marsh *et al*., 1996). Indirect adjustments for smoking (see section 2.1) reduced the SMR for respiratory cancer, among male workers in the six plants (N- and O-cohorts) taken together, from a statistically significant SMR of 1.24 [95% CI, 1.0–1.51] to an SMR of 0.96 [95% CI, 0.78–1.17] based on 100 observed deaths and using local county rates (Marsh *et al*., 2001b).

Relative risk regression modelling of internal cohort rates for respiratory cancer in the N-cohort revealed no consistent evidence of an association with any of the exposure indices for respirable fibre considered, with or without adjustment for potential confounding factors that included year of hire, plant and estimated co-exposure for individual workers (Marsh *et al*., 1996).

A manual search of death certificates of 1011 rock (stone) and slag wool workers from the N-cohort revealed two death certificates that mentioned the word 'mesothelioma'. A subsequent review of medical records and pathology specimens for one of the two cases deemed this death as definitely not due to pleural cancer. In a mortality analysis, only one of the two cases among rock (stone) and slag wool workers was coded as a pleural cancer (ICD-9 163.9) (this mesothelioma was seen in a worker from plant 17 where there was potential exposure to asbestos (Marsh *et al.*, 1996; Marsh *et al.*, 2001c)). [The Working Group noted the limitations of death certificates for the identification of mesothelioma diagnoses: deaths due to mesothelioma would not have been detected in this study if the word 'mesothelioma' had not appeared on the death certificate.]

Nested case–control studies

A nested case–control study of the six rock (stone) and slag wool plants in the US cohort identified 78 men who had died from respiratory cancer between 1970 and 1989. Controls were matched on age and time period and were randomly selected from men who had died during the period 1970–89. Information on smoking habits was available for all of the 54 cases and 94% of 95 controls in the five-plant N-cohort, and for 92% of the 24 cases and 87% of 37 controls in the asbestos-contaminated O-cohort. The odds ratios for cumulative exposure to respirable fibres in the N-cohort showed a decreasing trend (odds ratios, 1.00, 0.70, 0.59 and 0.71; global test p-value = 0.76) for cumulative exposures of < 3, 3–14, 15–39 and ≥ 40 fibres/cm^3–months, respectively. After adjustment for smoking, the odds ratios were 1.0, 0.64, 0.55 and 0.58 (global test p-value = 0.64) for the same exposure groups. Further adjustment for potential confounding by co-exposure revealed no evidence of an increasing trend in odds ratios for any of the levels of exposure to respirable fibre. In the O-cohort, the odds ratios for the categories for duration of employment (< 2, 2–4, 5–19 and ≥ 20 years) showed no evidence of an increasing trend when no adjustment was made for smoking or when calculated for smokers only (Marsh *et al*., 1996).

A case–control study nested in a cohort of 4841 men employed for one year or more in the rock (stone) wool and slag wool industry was reported by Wong *et al*. (1991). The workers studied were employed in nine plants, four of which were also included in the University of Pittsburgh study (Marsh *et al*., 1990, 1996). Most of the plants had started producing slag wool, or using slag wool in their products, in the 1940s. Altogether, 504 workers who had died between 1970 and 1989 were included; 61 of whom had died from lung cancer. It was not possible to locate relatives for three of the workers and three others were excluded because matching controls could not be found. The final analysis included 55 cases and 98 controls who had died from other causes. Data on exposure were obtained from two industrial hygiene surveys, one by the National Institute for Occupational Safety and Health (NIOSH) (Fowler, 1980); and the other by the Pittsburgh group (Esmen *et al*., 1979a). The estimates of exposure to airborne fibres calculated for each case and control ranged from 0–0.25 fibres/cm^3 according to the NIOSH model and from 0–0.21 fibres/cm^3 according to the Pittsburgh classification. Information on smoking habits was collected by interview. All cases had been cigarette smokers, but only 81% of the controls had been smokers. According to the NIOSH classification, 93% of the cases and controls had been exposed to slag wool. The odds ratio of ever versus never exposure to slag wool, adjusted for smoking, was 0.94 (95% CI, 0.23–3.78). When data were divided into two exposure groups (< or ≥ 7 fibres/cm^3–months), the odds ratio after adjustment for smoking was 0.98

(95% CI, 0.47–2.04). [The results were not adjusted for exposure to asbestos although four plants had used a limited amount of asbestos for a few years.]

(*b*) *European study*

Plato *et al*. (1995b,c) reported the results of the follow-up study from 1952–90 (for cancer mortality) and from 1958–89 (for cancer incidence) of three Swedish plants included in the European MMVF cohort (see Boffetta *et al.*, 1997 and section 2.1). This cohort comprised 1569 male and female workers employed for at least one year before 1978, in the two plants that produced rock (stone) wool and slag wool. The duration of employment was categorized as < 2, 2–9, 10–19 or ≥ 20 years. The cumulative exposure to fibres, specific for plant and job, was estimated for the period from 1938–90, for 1487 workers (1329 men and 158 women), contributing 34 392 person–years of observation, in rock (stone) and slag wool plants. Exposure to fibres was classified as low, medium or high, the cut-points used were 1.0 fibre/cm^3–years and 2.0 fibres/cm^3–years. Lags of 20 and 30 years were used. Both national and county rates were used in the external comparisons to produce standardized mortality ratios and standardized incidence ratios (SMRs and SIRs). A Poisson regression analysis with internal comparisons was also performed. The SMR for cancer at all sites for the two rock (stone) wool and slag wool plants combined, based on 66 deaths, was very similar when either national or regional rates were used for comparison [SMR, 0.96; 95% CI, 0.74–1.22 using regional rates; and SMR, 0.87; 95% CI, 0.68–1.11 using national rates]. Based on 131 cancer cases and regional rates, the SIR for cancer at all sites for the two plants combined was [1.15 (95% CI, 0.95–1.35)]. In contrast to the finding in the whole European cohort, the SMR for lung cancer was higher when compared with regional than national rates [SMR, 1.57; 95% CI, 0.83–2.68; and 1.02; 95% CI, 0.55–1.75, using regional and national rates, respectively, based on 13 deaths]. In the larger rock (stone) wool and slag wool plant, the SMR for lung cancer was 2.40 (95% CI, 1.24–4.19), based on 12 deaths and regional rates. No trend was seen with duration of employment when 20 years of latency and regional rates were used. Neither the plant-specific nor the job-group-specific estimates of exposure to fibres gave a monotonic increase in SMRs for lung cancer (the lowest SMRs of 0.62 (95% CI, 0.08–2.24) and 0.95 (95% CI, 0.20–2.78), were found in the groups exposed to the highest fibre concentrations using regional reference rates). Internal comparison also revealed no monotonic increase in the relative risks with increasing estimates of exposure. The SIR for lung cancer was 1.65 (95% CI, 0.88–2.83), based on 13 cases and regional rates. It did not increase with increasing duration of employment. Based on 13 cases and comparison with regional rates, an increased incidence of stomach cancer was seen (SIR, 1.71; 95% CI, 0.91–2.93).

In their extended follow-up of the European cohort (until 1990 in Denmark, Norway and Sweden and 1991 in Germany) Boffetta *et al*. (1997) (see section 2.1) included 10 108 rock (stone) wool and slag wool workers from seven plants (1 in Denmark, 3 in Norway, 2 in Sweden (see Plato *et al.*, 1995a,b) and 1 in Germany) contributing 221 871 person–years. The cohort included 4912 workers employed for one year or more who contributed 114 228 person–years; 29% of these person–years took place 20 years or more after the date of first employment. Three hundred and twenty-two of the rock (stone) wool and slag wool workers were first employed during the early technological phase of the industry (when exposure to fibres was estimated to be high), 603 were first employed during the intermediate phase and 9183 during the late phase (corresponding to modern technology). Copper slags were used periodically between 1940 and 1944 in Denmark, and there was potential exposure to asbestos (for a few workers in Denmark between 1962 and 1982, and for a large number of workers in Germany between 1941 and 1970) (Cherrie & Dodgson, 1986). A Poisson regression analysis of all male workers with known duration of employment showed that the SMR for overall mortality, in rock (stone) wool and slag wool workers employed for one year or more, was 1.04 (95% CI, 0.98–1.10; 1281 deaths), the SMR for cancer at all sites was only slightly elevated (SMR, 1.08; 95% CI, 0.97–1.21; 325 deaths) and the SMR for lung cancer was 1.34 (95% CI, 1.08–1.63; 97 deaths), compared with national mortality rates. The subcohorts from Denmark and Germany accounted for 70% of all observed deaths from lung cancer. The lung cancer mortality was highest among workers with the longest time since first employment (*p* for trend, 0.19). Only small differences in the SMRs were seen in the analysis by technological phase. Among workers employed for one year or more, the SMRs for the early, intermediate and late technological phases, respectively, were 1.51 (95% CI, 0.69–2.87; 9 deaths), 1.49 (95% CI, 0.77–2.60; 12 deaths) and 1.30 (95% CI, 1.02–1.63; 76 deaths) for lung cancer. In the group first employed in the early technological phase and with 30 years or more since first employment, the SMR for lung cancer was 1.46 (95% CI, 0.59–3.02; 7 deaths). Using the Poisson regression analysis the relative risks for lung cancer with increasing time since first employment (adjusted for duration of employment, technological phase, age, calendar year and country) were 1.3 (95% CI, 0.6–3.0), 1.2 (95% CI, 0.5–3.1) and 1.4 (95% CI, 0.4–4.6; *p* for linear trend, 0.67) (10–19, 20–29 and ≥ 30 years since first employment). After adjustment for time since first employment and duration of employment, no differences in relative risk according to technological phase were seen (relative risk, 1.0 (95% CI, 0.5–2.3) and 1.1 (95% CI, 0.4–2.8), using the late technological phase as the reference). Workers employed for 20 years or more had a relative risk for lung cancer of 1.6 (95% CI, 0.8–3.1; 24 deaths), but the trend with increasing duration of employment was not monotonic (*p*-value for trend, 0.27).

In this cohort, four deaths from mesothelioma were recorded (two among workers with < 1 year of employment and two in the factory from Germany [expected numbers of deaths were not given]). Statistically non-significant elevations were found for oral and pharyngeal cancer (SMR, 1.33; 95% CI, 0.57–2.61; 8 deaths); laryngeal cancer (SMR, 1.96; 95% CI, 0.72–4.27; 6 deaths) and oesophageal cancer (SMR, 1.25; 95% CI, 0.54–2.46; 8 deaths) (Boffetta *et al*., 1997). No associations with time since first employment or duration of employment were seen for these cancer sites.

Consonni *et al*. (1998) analysed mortality from lung cancer by estimated fibre exposure in the cohort described by Boffetta *et al*. (1997). Individual cumulative exposure to fibres (fibres/cm^3–years) and lifetime maximum annual exposure (fibres/cm^3) were calculated, for year-specific estimates of exposure based on measurements of the concentrations of respirable fibres made in six of the seven plants during 1977–80, in combination with reconstruction of historical work processes, theoretical considerations and results obtained from simulation experiments on fibre emissions (Krantz *et al*., 1991). These data were used to assign numerical coefficients to the factors that had been identified as exposure determinants (addition of oil as a dust-suppressing agent, production rate, presence of ventilation system and degree of manual handling). These numerical coefficients were tabulated over the years and combined in a multiplicative way with the current fibre concentrations to obtain estimates of past concentrations of fibres for every plant and year of production. These estimates were combined in turn with individual work histories to provide an individual exposure assessment for each year of employment, from which the estimates of the cumulative and maximum exposure were derived. A 15-year lag was applied to the cumulative exposure variable and, in alternative models, a clearance with a half-life of five years and two years, respectively, was taken into account. The overall mean concentration of respirable fibres was measured as 0.06 fibre/cm^3. There was a very high correlation between the estimates of cumulative exposure to fibres and duration of employment ($r = 0.92$), and an even higher correlation when lung clearance was taken into account ($r > 0.99$). Poisson regression models were adjusted for employment status, time since first employment (< 10, 10–19, 20–29, ≥ 30 years), country, age and calendar year (in quinquennia). The analysis was based on 159 deaths from lung cancer (97 in workers with ≥ 1 year of employment). The relative risk for lung cancer was independent of employment status, but increased with increasing time since first employment. [The Working Group noted that relative risks for time since first employment were not given.] No trend in risk for lung cancer was seen with cumulative exposure among workers employed for one year or more. In the analysis that included all workers, a non-significant trend in the relative risks was found. No trend was found associated with maximum annual exposure. The incorporation of pulmonary clearance rates did not change these results.

In the countries with national cancer registries, follow-up for cancer incidence was extended until 1994 (in Denmark) and 1995 (in Norway and Sweden) (Boffetta *et al*., 1999). The cohort included 3685 male and female workers employed in plants that produced rock (stone) wool and slag wool for one year or more, contributing 92 562 person–years; 32.5% of the person–years took place 20 years or more after the date of first employment. Completeness of follow-up ranged from 89.8% to 98.3% in the different plants. National cancer rates were used in the SIR analyses and when production started before these rates had become available, the rates were linearly extrapolated back to the date of first production. Internal comparison with Poisson regression was also performed. No elevation in risk for cancer at all sites was found in the rock (stone) wool or slag wool workers (SIR, 0.97; 95% CI, 0.88–1.06; 468 cases). The SIR for lung cancer was 1.08 (95% CI, 0.85–1.36; 73 cases). The analysis of risk by time since first employment showed a non-significant trend. No association between risk and duration of employment or technological phase was found. The overall SIR for cancer of the oral cavity, pharynx and larynx was 1.46 (95% CI, 0.99–2.07; 31 cases) for the six plants; at one plant in Norway the SIR was 2.72 (95% CI, 1.09–5.61; 7 cases). There was no clear relationship with time since first employment. [The Working Group noted that no similar increase was seen in other rock (stone) wool or slag wool plants and that 14 of the 31 cancers observed in the whole cohort were lip cancers.]

A case–control study nested in this cohort (Kjaerheim *et al.*, 2002) included 133 of 196 cases of lung cancer in men (134 cases identified in the mortality study, 45 from the incidence study and 17 identified from the extended follow-up in Denmark) that occurred between 1971 and 1996 (in Denmark), 1995 (in Norway and Sweden) and 1991 (in Germany, deaths only). Two control groups (group 1, incidence density-sampled controls; group 2, matched to cases by year of death) were combined in the main analyses, and comprised 513 controls matched by age and plant. Information on residential and general occupational history and on tobacco smoking habits came from personal interviews with the patients and controls or their next of kin. The response rate was 67.9% for cases. The proportion of interviews performed out of the controls contacted was 59.2% out of the number of possible respondents contacted. Exposure assessments within the industries were based on information obtained from panels of experts and outside the industry on the basis of self-reported life-time occupational histories (Cherrie *et al.*, 1996; Cherrie & Schneider, 1999). Variables indicating ever exposure, ever high exposure, duration of exposure and cumulative exposure were calculated for seven agents within the rock (stone) wool and slag wool industry. Similar variables, excluding cumulative exposure, were calculated for six sources of co-exposure occurring both within and outside the industry and for a further 12 sources of exposure that were found only outside the industry. All conditional logistic regression models included adjustment for age group and plant; additional adjustments were made for tobacco smoking and potential occupational confounders to which a significant number of workers were exposed (i.e. asbestos, polycyclic aromatic hydrocarbons and silica). No association was found between exposure to rock (stone) or slag wool fibres and risk for lung cancer for cumulative exposure to fibres of rock (stone) or slag wool assessed with a 15-year lag; the smoking-adjusted odds ratios in the second to fourth quartile of exposure were 1.25 (95% CI, 0.66–2.34), 1.02 (95% CI, 0.54–1.93) and 0.67 (95% CI, 0.35–1.27). Similar results were obtained when only workers employed for more than one year were included, with other indicators (e.g. duration of exposure) of exposure to fibres of rock (stone) wool or slag wool, and after adjustment for co-exposure. [Only four of the 11 workers (Boffetta *et al.*, 1997) who died from lung cancer and were first employed during the early technological phase (among whom the SMR for lung cancer was particularly elevated) were included in the case–control study.] The 1985 age-adjusted prevalence of current smokers among controls was 20% greater than in the general population.

2.4 Refractory ceramic fibres (see Table 57)

2.4.1 *Cohort study*

A cohort study of workers at two plants in the USA that produced refractory ceramic fibres included 927 male workers employed for one year or more between 1952 and 1997. The mortality data were presented in a conference abstract (Lemasters *et al.*, 2001) and in a paper addressing risk analysis (Walker *et al.*, 2002). The estimated exposure ranged from 10 fibres/cm^3 (8-h TWA) in the 1950s to < 1 fibre/cm^3 in the 1990s. No significant increase in cancer mortality was reported. [The Working Group noted that neither the observed nor the expected numbers of cancers other than lung cancer were given.] Six deaths from lung cancer were observed versus 9.35 expected, SMR, 0.64 (95% CI [0.24]–1.27). No cases of mesothelioma were observed. [The Working Group noted that the details of cohort definition and period of follow up were not clear, and there was no analysis of risk in relation to time since first exposure or exposure surrogates. The small number of study subjects, especially those with adequate latency, limits the informativeness of the study.]

2.4.2 *Case–control study*

A case–control study including 45 men with lung cancer and 122 controls was nested within a cohort of 2933 white men employed in a plant manufacturing continuous glass filament (described in detail in section 2.2) (Chiazze *et al.*, 1997). Exposure to respirable glass fibres, asbestos, refractory ceramic fibres (used at the plant for high-temperature heat insulation, but not manufactured there), and a number of other sources of exposure was assessed by a procedure of reconstruction of historical exposure conditions. The risk of lung cancer was lower in workers exposed to a cumulative dose of refractory ceramic fibres of 0.01–1 fibre/cm^3–days (odds ratio, 0.36 (95% CI, 0.04–3.64); 1 case), and those exposed to 1–40 fibres/cm^3–days (odds ratio, 0.30 (95% CI, 0.11–0.77); 7 cases), than in workers not exposed to fibres. The odds ratios were not adjusted for exposure in the workplace to other fibres or for tobacco smoking, but the trends in odds ratios were similar when the analysis was restricted to smokers. [The Working Group noted that exposure to refractory ceramic fibres may have been difficult to separate from other sources of exposure in the workplace in view of the small number of cases and the large number of sources of exposure.]

2.5 MMVF (not otherwise specified) (see Table 58)

A number of epidemiological studies in MMVF user industries and in the general population have provided information on cancer risk following exposure to MMVFs, but the ability of these studies to distinguish between exposure to the different types of MMVF was limited.

Table 57. Studies of lung cancer in workers exposed to refractory ceramic fibres

Reference	Description, employment, follow-up	Type of cancer, no. of deaths/ cases (controls)	Exposure categories	No. of cases	Relative risks (95% CI)
USA studies					
Cohort study					
Lemasters *et al.* (2001); Walker *et al.* (2002)	927 male workers[a] employed 1952–97	6 deaths from lung cancer			0.64 ([0.24]–1.27)
Case–control study					
Chiazze *et al.* (1997) Co-exposure in continuous glass filament plant	45 men with lung cancer[a]	122 controls (white men)	Cumulative exposure		
			< 0.01fibre/cm^3–days	37	1
			0.01–0.999 fibre/cm^3–days	1	0.36 (0.04–3.64)
			1.0–39.24 fibres/cm^3–days	7	0.30 (0.11–0.77)

[a] Employed for ≥ 1 year

Table 58. Studies of cancer in workers exposed to MMVF (fibre type not otherwise specified)

Reference, study population	Description, employment, follow-up	Type of cancer, no. of deaths/ cases (controls)	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Cohort study						
Gustavsson *et al.* (1992) Sweden Exposure to MMVFs 11 factories	1465 men employed[a] before 1972, follow-up 1969–88 (mortality)	14 deaths from lung cancer	Time since first exposure		SMR	Information on smoking habits was obtained for 73% of workers in 8 of 13 factories 1 lung cancer death with exposure level unknown
			< 10 years	1	0.59 [0.02–3.28]	
			10–19 years	4	0.70 [0.19–1.79]	
			≥ 20 years	9	0.75 [0.34–1.42]	
			Exposure to fibres during 8-h shift by occupational group			
			< 0.02 fibre/cm^3–years	9	0.78 [0.35–1.49]	
			0.02–0.08 fibre/cm^3–years	1	0.58 [0.02–3.28]	
			0.05–0.13 fibre/cm^3–years	1	0.33 [0.01–1.86]	
			0.05–0.17 fibre/cm^3–years[b]	2	0.85 [0.10–3.01]	
		22 deaths from stomach cancer	Time since first exposure			
			< 10 years	3	2.52	
			10–19 years	7	1.90	
			≥ 20 years	10	1.24	
			Duration of employment			
			< 10 years	11	2.16	
			10–19 years	3	0.98	
			≥ 20 years	6	1.25	
Nested case–control study						
					Odds ratio	
Martin *et al.* (2000) France Incidence	310 cases of lung cancer, 1978–89	1225 controls	33 cases exposed to MMVFs		0.73 (0.32–1.70)	Adjusted for socioeconomic status and exposure to asbestos

Table 58 (contd)

Reference, study population	Description, employment, follow-up	Type of cancer, no. of deaths/ cases (controls)	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Case–control studies						
Lung cancer						
					Odds ratio	Adjusted for smoking
Kjuus *et al.* (1986) Norway Incidence	176 cases of lung cancer, 1979–83	176 controls	Rock (stone) wool/glass fibre	13	1.0 (0.4–2.5)	
Siemiatycki (1991) Canada Population-based case–control study Incidence	857 cases of lung cancer, 1979–85	1360 cancer controls, 533 population controls	> 5 years of exposure		Odds ratio	90% CI, adjusted for age, smoking, other demographic factors and occupational exposure
			glass wool	11	1.2 (0.5–2.5)	
			rock (stone) wool and slag wool	10	1.2 (0.5–2.7)	
Brüske-Hohlfeld *et al.* (2000); Pohlabeln *et al.* (2000) Germany Incidence	3498 men with lung cancer, workers in several types of industry 1988–96	3541 controls	Ever versus never exposed to MMVF (rock (stone) wool/slag wool and glass wool)	304	1.48 (1.17–1.88)	Adjusted for smoking and exposure to asbestos
			Duration of exposure			
			0–3 years	51	1.68 (0.98–2.88)	
			3–10 years	69	1.38 (0.86–2.20)	
			10–20 years	76	1.17 (0.77–1.77)	
			20–30 years	61	1.69 (1.01–2.81)	
			≥ 30 years	47	2.03 (1.04–3.95)	
			Ever exposed to MMVF and never exposed to asbestos			Adjusted for smoking
			Cumulative exposure to MMVF (fibre·year)			
			0.1–0.4	30	1.41 (0.73–2.72)	
			> 0.4	29	1.20 (0.63–2.30)	

Table 58 (contd)

Reference, study population	Description, employment, follow-up	Type of cancer, no. of deaths/ cases (controls)	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Mesothelioma						
Rödelsperger *et al.* (2001) Germany	125 men with mesothelioma 1988–91	125 male controls	Ever exposed to MMVFs	55	3.08 (1.17–8.07)	Adjusted for exposure to asbestos
			Geometric mean (fibres–year)			
			≤ 0.015	10	0.78 (0.16–3.77)	
			> 0.015–0.15	11	3.11 (0.56–17.2)	
			> 0.15–1.5	20	7.95 (0.88–72.3)	
			> 1.5	14	5.43 (0.72–41.0)	
			Exposed to MMVFs without asbestos	2	15.1 (1.05–218)	Matched for age and region of residence
Larynx, hypopharynx						
Marchand *et al.* (2000) France Incidence	201 men with hypopharyngeal cancer 296 men with laryngeal cancer 1989–91	295 controls	Ever exposed			
			Rock (stone) wool/slag wool			Odds ratios adjusted for exposure to asbestos, age, smoking and alcohol habits
			Larynx cancer	130	1.23 (0.79–1.91)	
			Epilarynx cancer	51	1.61 (0.85–3.04)	
			Hypopharynx cancer	99	1.51 (0.90–2.52)	
			Continuous glass filaments			
			Larynx cancer	8	0.44 (0.15–1.31)	
			Hypopharynx cancer	8	0.91 (0.30–2.76)	
			Refractory ceramic fibres			Adjusted for age, smoking and alcohol habits
			Larynx cancer	16	1.28 (0.51–3.22)	
			Hypopharynx cancer	7	0.78 (0.26–2.38)	
			Microfibres			
			Larynx cancer	16	1.28 (0.51–3.22)	
			Hypopharynx cancer	7	0.78 (0.26–2.38)	

Table 58 (contd)

Reference, study population	Description, employment, follow-up	Type of cancer, no. of deaths/ cases (controls)	Exposure categories	No. of cases	Relative risks (95% CI)	Comments
Colon						
Goldberg *et al.* (2001) Canada Incidence (same study population as Siemiatycki, 1991)	497 men with colon cancer 1979–85	1514 cancer controls 533 population controls	> 5 years of exposure Rock (stone) wool/slag wool Glass fibres	 8 6	 1.9 (0.8–4.6) 1.9 (0.7–5.4)	Adjusted for age, smoking, occupational and non-occupational exposure
Registry-based studies						
Breast, ovary						
Weiderpass *et al.* (1999) Finland Incidence	23 638 women with breast cancer 1971–95		MMVF Postmenopausal women Medium-to-high exposure Low exposure		SIR 1.32 (1.05–1.66) 1.01 (0.90–1.12)	Adjusted for birth cohort, follow-up period, socioeconomic status, mean no. of children, mean age at delivery of first child and turnover rate for each job title
Vasama-Neuvonen *et al.* (1999) Finland Incidence	5072 women with ovarian cancer 1971–95		MMVF		1.3 (0.9–1.8)	

SMR, standardized mortality ratio; SIR, standardized incidence ratio
[a] Employed for > 1 year
[b] For this exposure category, the highest exposure that occurred in 1975–80 was estimated as 0.20–0.25 fibre cm^3–years.

2.5.1 *Cohort studies*

Gustavsson *et al*. (1992) studied a cohort of 2807 male workers in Sweden (employed for at least 1 year before 1972) in 11 factories that produced prefabricated wooden houses. A total of 1465 of the workers had been exposed to MMVFs. The workers were assigned to one of four exposure categories: category 0, no exposure; category 1, background level (truck drivers, repairmen, transportation workers); category 2, full-time employment in locations where MMVF was handled, but without direct handling of MMVF (e.g. wood cutters); category 3, direct handling of MMVF during most of the working day (e.g. insulators). Current exposure to MMVF was measured and past exposure was estimated. Exposure varied from 0.02–0.25 fibre/cm^3 per 8-h shift. The follow-up period was from 1969 to 1988 for mortality and from 1969 to 1985 for incidence and was more than 99% complete. A deficit in mortality for lung cancer (SMR, 0.68; 95% CI, 0.37–1.13; 14 deaths) and incidence (SIR, 0.47; 95% CI, 0.24–0.85; 11 cases) was reported. An analysis of mortality from stomach cancer showed an excess (SMR, 1.59; 95% CI, 1.00–2.41; 22 deaths), based on local rates. An analysis of stomach cancer incidence based on national rates was concordant (SIR, 1.78; 95% CI, 1.15–2.63; 25 cases). Analysis by duration of employment showed that this excess of mortality from stomach cancer was seen mainly among workers who had been employed for less than 10 years.

A study on a cohort of 135 037 male construction workers in Sweden reported in 1987 and evaluated by the previous Working Group (IARC, 1988) has not been updated (Engholm *et al.*, 1987). In a nested case–control study, the relationship between lung cancer in 424 workers and their exposure to MMVFs and to asbestos was examined. After adjustment for smoking habits and population density in the area of residence, an odds ratio of 1.21 (95% CI, 0.60–2.47) was reported for exposure to MMVFs (adjusted for exposure to asbestos). Twenty-three cases of pleural cancer were observed among the cohort [SIR, 2.13; 95% CI, 1.35–3.20]. [The Working Group noted that misclassification of exposure to asbestos and the difficulty in differentiating exposure to asbestos from exposure to MMVFs may have resulted in residual confounding.]

Nested case–control studies

In a study of workers in French national electricity and gas companies, 310 workers with lung cancer and 1225 controls were included in a nested case–control study during 1978–89. Thirty-three of the cases were exposed to MMVF as opposed to eight of the controls. The odds ratio after adjustment for socioeconomic status and exposure to asbestos was 0.73 (95% CI, 0.32–1.70) (Martin *et al*., 2000).

2.5.2 *Population-based case–control studies*

Population-based case–control studies can be used to investigate exposure to MMVF in various circumstances. However, assessment of exposure in such studies is usually less valid and precise than in industry-based cohort studies.

(*a*) *Lung cancer*

Kjuus *et al.* (1986) conducted a case–control study of lung cancer (176 incident cases in men and 176 controls selected from one county in Norway) during 1979–83 and its association with occupational exposure and smoking habits. No association was seen between lung cancer and exposure to MMVF (rock (stone) wool or glass fibre) (odds ratio, 1.0; 95% CI, 0.4–2.5; 13 cases) after adjustment for smoking.

Siemiatycki (1991) conducted a population-based case–control study among male residents of Montreal, Canada, to explore associations between hundreds of occupational circumstances and cancer at several sites which had been diagnosed between 1979 and 1985. The study included interviews with 3730 patients with cancer at 11 major sites (response rate, 82%), including 857 patients with a pathologically confirmed diagnosis of lung cancer (response rate, 79.2%) from 19 hospitals in Montreal. Two sets of controls were selected: 1360 cancer controls (excluding patients with cancers at several sites that were anatomically contiguous), and 553 out of 740 potential population controls (response rate, 72%). Detailed job histories and information on relevant potential confounding variables were obtained during the interviews. The job histories were converted by a team of chemists and industrial hygienists into a history of occupational exposure. After adjustment for age, smoking, demographic factors and occupational exposure, the odds ratio compared with both control groups combined, for the group with substantial exposure to MMVF (i.e. > 5 years at medium or high frequency), for exposure to glass wool was 1.2 (90% CI, 0.5–2.5; 11 cases). The odds ratio for exposure to rock (stone) and slag wool was 1.2 (90% CI, 0.5–2.7; 10 cases).

Two population-based case–control studies were conducted at the Bremen Institute for Prevention Research and Social Medicine and the National Research Centre for Environmental Health in Germany during 1988 and 1996. Pooled analyses of exposure to fibres (mainly outside the MMVF production industry) were reported (Brüske-Hohlfeld *et al.*, 2000; Pohlabeln *et al.*, 2000). The final analysis included 3498 cases of lung cancer in men and 3541 controls. The response rates for cases were 69% and 77% and those for controls were 68% and 41%, for the Bremen Institute for Prevention Research and Social Medicine (1988–1993) and the National Research Centre for Environmental Health (1990–1996) studies, respectively. Both studies included pathologically confirmed cases of incident primary lung cancer. Information on smoking habits was obtained by standardized interview. Industries and job titles were grouped according to 21 industry codes and 33 job categories, respectively. The assessment of exposure was based on self-reported occupational histories obtained from personal interviews using a standardized questionnaire and two supplementary questionnaires to address exposure to MMVF. This information was used by two industrial hygiene experts to estimate cumulative exposure to MMVFs for a subset of the study group. A total of 304 cases and 170 controls were classified as ever exposed to MMVFs. The odds ratio after adjustment for smoking and exposure to asbestos was 1.48 (95% CI, 1.17–1.88) and a twofold risk was calculated for those who had been exposed for more than 30 years (odds ratio, 2.03; 95% CI, 1.04–3.95). The odds ratio for ever versus never self-reported exposure to MMVFs was 1.30 (95% CI, 0.82–2.07), after adjustment for smoking, in a subset of subjects who reported no exposure to asbestos (59 cases and 39 controls). No clear trend of increasing lung cancer risk with increasing cumulative exposure to MMVF was observed in this subset after adjusment for smoking. [The Working Group noted that the response rate of controls in the National Research Centre for Environmental Health study was low. The numbers of cases and controls reported in the two publications were inconsistent.]

(*b*) *Mesothelioma*

In a study designed to evaluate the association between occupational factors and mesothelioma, Rödelsperger *et al.* (2001) selected 137 German men with pathologically confirmed malignant mesothelioma recruited between 1988 and 1991 from clinics in Hamburg, Germany. Cases were matched on region of residence, sex, and year of birth (within 5 years) to controls selected randomly from population registries. The study team interviewed 125 patients almost all of whom were undergoing treatment at one of two specialized hospitals in Hamburg, and who were willing to grant a personal interview. The 125 controls were interviewed by trained interviewers using a similar protocol. [The Working Group noted that the response rates appear to have been higher for the cases (91%) than the matched controls (63%), but the basis for calculation of these participation rates was not provided.] The mean duration of lifetime employment was 42 years for cases and 43 years for controls. The self-reported job histories obtained from both cases and controls were used to estimate exposure to MMVFs and asbestos and to classify individuals as either exposed or not exposed to these fibres. The investigators did not differentiate between the types of MMVF to which the men were exposed. A statistically significant increase in risk for mesothelioma (odds ratio, 3.08; 95% CI, 1.17–8.07; 55 cases) was reported for individuals classified as ever exposed to MMVF (versus never exposed) and adjusted for exposure to asbestos. In addition, the odds ratios for MMVF exposure, adjusted for level of asbestos exposure, defined as geometric mean × 5 (fibre–year) showed an increased risk with increasing level of exposure to MMVFs. Of the 125 cases and 125 controls, the investigators estimated that only two cases and two controls were exposed to MMVFs alone (i.e. in the absence of exposure to asbestos) (odds ratio, 15.1; 95% CI, 1.05–218) compared with nine cases and 65 controls who reported no exposure to either asbestos or MMVFs.

[The Working Group noted the likely misclassification of exposure due to information bias and errors in exposure assessment in these analyses leading to possible imprecision in the adjustment for exposure to asbestos when examining an independent effect of MMVFs, and the potential imprecision in the risk estimates resulting from the small number of cases exposed to MMVFs only. Concerns about the catchment areas for cases and controls were also expressed.]

(*c*) *Cancer at sites other than the lung and pleura*

Marchand *et al*. (2000) studied hospital-based cases and controls in France to assess the relation between laryngeal and hypopharyngeal cancer and exposure to asbestos and MMVFs. The study subjects included 296 men with incident cancers of the larynx and 201 with incident cancers of the hypopharynx out of 664 patients newly diagnosed with squamous-cell carcinoma between 1989 and 1991. The 295 controls had been diagnosed with a non-respiratory cancer. A detailed job history and information on smoking and alcohol consumption were recorded. A job–exposure matrix was used to estimate exposure to asbestos and to four groups of MMVF (rock (stone) wool/slag wool/glass wool, refractory ceramic fibres, continuous glass filament and microfibres). In the group ever exposed to rock (stone) wool/slag wool and glass wool, the odds ratio for laryngeal cancer, after adjustment for smoking and alcohol consumption, was 1.33 (95% CI, 0.91–1.95; 130 cases) and the odds ratio for hypopharyngeal cancer was 1.55 (95% CI, 0.99–2.41; 99 cases). When the odds ratios were adjusted for exposure to asbestos, the highest odds ratio for rock (stone) wool and slag wool was for cancer of the epilarynx (odds ratio, 1.61; 95% CI, 0.85–3.04). For continuous glass filament, the odds ratios were 0.44 (95% CI, 0.15–1.31; 8 cases) for laryngeal cancer and 0.91 (95% CI, 0.30–2.76; 8 cases) for hypopharyngeal cancer. The odds ratios for exposure to refractory ceramic fibres were 1.28 (95% CI, 0.51–3.22; 16 cases) for laryngeal cancer and 0.78 (95% CI, 0.26–2.38; 7 cases) for hypopharyngeal cancer.

In the same study population as described for the Canadian case–control study of lung cancer by Siemiatycki (1991), Goldberg *et al.* (2001) investigated the association between exposure to MMVFs and colon cancer. The study included 497 male patients with a pathologically confirmed diagnosis of colon cancer, 1514 controls with cancers at other sites (excluding several sites including the lung and peritoneum) and 533 population-based controls, frequency matched on age during 1979–85. There was a non-significant increase in the risk for colon cancer (odds ratio, 1.9; 95% CI, 0.8–4.6; 8 cases), adjusted for age, smoking, demographic factors and occupational exposure and compared with both control groups combined, for the group with substantial exposure (i.e. > 5 years at medium or high levels) to rock (stone) wool or slag wool. For the same group, a non-significant increase in the risk of colon cancer was reported (odds ratio, 1.9; 95% CI, 0.7–5.4; 6 cases).

2.5.3 *Registry-based studies*

Weiderpass *et al.* (1999) and Vasama-Neuvonen *et al.* (1999) reported results from a study that linked incidence of breast cancer (23 638 cases) (Weiderpass *et al*., 1999) and ovarian cancer (5072 cases) (Vasama-Neuvonen *et al*., 1999) with 324 job titles from the 1970 census (for 892 591 Finnish women) during 1971–95. The job titles were classified with respect to 33 agents by means of a measurement-based, period-specific, national job–exposure matrix. The data were analysed by fitting Poisson regression models and adjusted for birth cohort, follow-up period, socioeconomic status, mean number of children, mean age at delivery of first child and turnover rate for each job title. For postmenopausal breast cancer, Weiderpass *et al.* (1999) reported an SIR of 1.32 (95% CI, 1.05–1.66) for medium to high levels of exposure to MMVFs. Vasama-Neuvonen *et al.* (1999) reported an elevated risk for ovarian cancer for women exposed to MMVFs (SIR, 1.3; 95% CI, 0.9–1.8). [The Working Group noted that the usefulness of the results was limited by potential misclassification of exposure and that the job–exposure matrix was not gender-specific and may not have reflected the relevant routes of exposure for the cancers under study.]