AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 39:262–275 (2001)

Asbestos and Man-Made Vitreous Fibers as Risk Factors for Diffuse Malignant Mesothelioma: Results From a German Hospital-Based Case–Control Study

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Background *This study examines the role of occupational factors in the development of diffuse malignant mesothelioma with special emphasis on the dose–response relationship for asbestos and on the exposure to man-made vitreous fibers (MMVFs).*

Methods *One hundred and twenty-five male cases, diagnosed by a panel of pathologists, were personally interviewed concerning their occupational and smoking history. The same number of population controls (matched for sex, age and region of residence) underwent similar interviews by trained interviewers. Odds ratios (OR) were calculated for an expert-based exposure index using conditional logistic regression.*

Results *Exposure to asbestos shows the expected sharp gradient with an OR of about 45 for a cumulative exposure > 1.5 fiber years (arithmetic mean 16 fiber years). A significant OR was calculated even for the lowest exposure category "> 0–≤ 0.15 fiber years". Although the mean cumulative exposure to MMVF is roughly 10% of the exposure to asbestos, an increased OR is observed in an ever/never evaluation. This observation is heavily hampered by methodical problems. A corresponding case–control study was performed using a lung tissue fiber analysis in addition to interviews. Both interviews and the lung tissue analysis yielded similar OR levels between the reference and the maximum exposure intervals.*

Conclusions *Despite a possible influence as a result of selection and information bias, our results confirm the previously reported observation of a distinct dose–response relationship even at levels of cumulative exposure below 1 fiber year. Moreover, the study confirms that asbestos is a relevant confounder for MMVF. A causal relationship between exposure to MMVF and mesothelioma could neither be detected nor excluded, as in other studies.* Am. J. Ind. Med. 39:262–275, 2001. © *2001 Wiley-Liss, Inc.*

KEY WORDS: mesothelioma; case–control; asbestos; MMVFs; occupational history; lung tissue

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Contract grant sponsor: Federal Ministry of Research and Technology; Contract grant number: 01 HK 076 A6.
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Accepted 25 July 2000

INTRODUCTION

Diffuse malignant mesothelioma (DMM) is predominantly caused by asbestos fibers [HEI-AR, 1991; Mark and Yokoi, 1991; Rösler et al., 1994; Spirtas et al.,1994; Gun, 1995]. In the past, its incidence in the general population was low, but it has been increasing for decades in industrialized countries and it may take another 20 years before its peak is passed [Peto et al., 1999]. In addition to asbestos exposure at the workplace, contact in the household and environmental exposure to asbestos are established causes of DMM [Hain and Dalquen, 1974; Vianna and Polan, 1978; Großgärten and Woitowitz, 1993; Rödelsperger et al., 1996; Schneider et al.,1996; Magnani et al., 1997; Rees et al., 1999]. It has been demonstrated that the time since initial exposure and the type of asbestos are important for the quantification of the risk [Doll and Peto, 1985]. A risk estimate based on accurate workplace measurements is not yet available. Nevertheless, it has recently been demonstrated that an increase of risk may occur even below a cumulative exposure of a few fiber years (fibers/mL × years) [Iwatsubo et al., 1998]. However, a reliable dose–response relationship between the concentration of long amphibole fibers and the risk of mesothelioma has been consistently established by several research groups on the basis of lung tissue fiber analysis, while no relationship was observed for chrysotile fibers [Rödelsperger et al., 1999]. This is true even though the amphibole fibers in the lung tissue do not seem to be a good indicator of the fiber content of the pleura, where chrysotile fibers are predominantly observed [Smith and Wright, 1996].

Animal experiments show that other kinds of fibers, with a minimal length above 5 μm, may also induce mesothelioma after direct application [Pott, 1991]. They confirm the hypothesis that fibers, which are sufficiently long, thin, and durable, are carcinogenic [DFG, 1997]. Besides asbestos sufficient evidence for this hypothesis in humans has only been obtained for erionite [IARC, 1988; DFG, 1997]. In inhalation experiments in rats only erionite fibers caused mesothelioma whereas asbestos and ceramic fibers, but not other man-made vitreous fibers (MMVF), provoked lung cancer. However, even for asbestos this effect was observed only at very high fiber concentrations, which are not feasible for MMVF, since they are much longer and thicker than asbestos fibers and would, therefore, require a much higher mass concentration. This model is, therefore, considered too insensitive for predicting carcinogenic effects in humans [Pott and Roller, 1993; Infante et al., 1994, 1996; Rödelsperger and Woitowitz, 1995]. The question of the carcinogenicity of MMVF is of utmost public health relevance. Epidemiological observations have revealed an increased lung cancer mortality in producers of glass, stone, and slag wool, but the causal relationship to MMVF remained unclear [Infante et al., 1994, 1996; DeVuyst et al., 1995; DFG, 1997]. The concentration of MMVF is higher for processing than for production [IARC, 1988; WHO, 1988; Corn et al., 1992]. However, epidemiologic investigations in craftsmen processing these fibers are difficult since they also process asbestos.

The original aim of this study was to investigate not only asbestos, but also MMVF and other inorganic fibers as causal factors of the DMM [Woitowitz et al., 1993; Rödelsperger, 1996; Rödelsperger et al.,1998, 1999]. Since it was necessary to carry out a lung tissue fiber analysis, in addition to recording occupational histories, patients undergoing surgical resection for a diagnosis other than mesothelioma were selected as controls in the participating hospitals. Most of them suffered from lung cancer. In addition, a suitable group of population controls was recruited for the cases from the area of Hamburg. The results obtained for pairs of cases and population controls from the area of Hamburg are reported in this paper. It was from the first results of this study that there was a strong association between exposure to asbestos and to MMVF. Hence, it was first necessary to make a thorough examination of the influence of asbestos. Meanwhile, in connection with the study of Iwatsubo et al., [1998], a critical commentary on the use and the methodological problems of population-based mesothelioma case–control studies has emphasized the importance of direct risk estimation in a low-dose population [Siemiatycki and Boffetta, 1998]. Accordingly, we have examined the relationship between exposure to asbestos and the risk of mesothelioma and compared this with the relationship which was obtained from lung tissue fiber analysis [Rödelsperger et al., 1999].

MATERIAL AND METHODS

Subjects

The 415 incident patients with suspected diagnosis of diffuse malignant mesothelioma (DMM), recruited between January 1, 1988 and December 31, 1991 from clinics in Hamburg, Heidelberg, Essen, Munich, and Berlin, included 324 cases (275 male, 49 female) with a definite diagnosis confirmed by a panel of pathologists.

The present study was restricted to cases from Hamburg, which were individually matched to population controls. They had to be of German nationality, willing and able to give a personal interview and to provide written informed consent. Of 137 male and 37 female cases (almost all patients of DMM being treated in two specialized hospitals in Hamburg during the recruitement period) it was possible to include 125 male cases in the final analyses after matching with controls (according to region of residence, sex, year of birth ± 5 years). Females were not included on account of the small sample available. Population controls

TABLE I. Characteristics of Male Cases and Controls from Hamburg

	Cases	Controls
No.	**125**	**125**
Age (years)		
Median	62.0	64.0
Mean	62.6	64.2
SD	9.4	10.0
No. of jobs		
Median	6.0	6.0
Mean	6.0	5.8
Ever smoked	99 (79.2%)	107 (85.6%)

were randomly drawn from the mandatory registries of suitable administrational units [Woitowitz et al., 1993]. The response rate was 63%. One case/control pair had a year-of-birth difference >5 years. However, this did not influence the results presented in this paper. Some basic characteristics of cases and controls are shown in Table I.

Data Collection

In the first step, a structured questionnaire was used by trained interviewers to obtain information on job history and, in a second step, to obtain further specific information on occupational exposure to asbestos, MMVF, and other mineral fibers. Additionally, smoking, residential exposure, medical history, leisure-time activities and basic demographic characteristics were registered. Interviewers participated in several intensive training seminars during the recruitment phase. In a subset of variables from the questionnaire—(e.g., the duration of the interview and the number of job periods) the data were entered immediately in order to monitor and reduce possible interviewer effects.

Quantification of Occupational Exposure to Asbestos and MMVF

The description which in the first step was obtained for every job held (duration of at least 12 months) was supplemented with information from the second step (without limit of duration) and an expert industrial hygienist used these data to assess the cumulative dose of exposure to Asbestos and to man-made vitreous fibers.

Expert judgment was obtained blind with respect to the case–control status. Fiber concentration was quantified by assignment to one, two or even three of five exposure categories (Table II).

The geometric mean of the experts' estimate of the maximal and minimal value of fibers/ml per working shift

TABLE II. Definition of the Categories of the Asbestos Fiber Concentration and the Reproducibility of the Estimates of Two Experts

Categories of fiber concentration: definition by concentration intervals

Category	**Fiber concentration fibers/ml**				
	None	Low	Middle	High	Very high
Minimal value	0	0.005	0.025	0.25	2.0
Maximal value	0	0.025	0.25	2.0	10.0
Expert 1	**Expert 2**				
	none	low	middle	high	**total**
	Estimation of the minimal concentration value[a]				
None	191	10	4	—	**205**
Low	10	18	6	3	**37**
Middle	1	2	7	2	**12**
High	1	2	8	—	**11**
Total	**203**	**32**	**25**	**5**	**265**
	Estimation of the maximal concentration value [a]				
None	191	—	9	5	**205**
Low	3	1	—	3	**7**
Middle	6	2	7	4	**19**
High	3	1	6	24	**34**
Total	**203**	**4**	**22**	**36**	**265**

[a] Number of job periods per exposure category. If the experts were not able to assign the exposure to a certain category, they were allowed to combine two or more of them. In this case the minimal value resulted from the lowest and the maximal value from the highest category. Agreement is 82% for minimal and 84% for maximal concentration value.

was multiplied by the number of the working shifts with exposure. Integrating over the life span of each individual yielded the cumulative exposure to fibers (fiber years). For job periods with exposure to both asbestos fibers and MMVF the duration of exposure was only recorded once for both fiber species together. Because of the large differences between the minimal and maximal value of the concentration estimate and of the category of the frequency of working shifts with exposure, the arithmetic mean concentration, averaged over all job periods and correspondingly the cumulative exposure in fiber years, is taken as five times the geometric mean value (compare Table III and the section "Error of the Expert Estimate of the exposure to asbestos").

The quantitation is based on our own experience in measurement [Woitowitz and Rödelsperger, 1983; Arhelger et al., 1984; Rödelsperger et al., 1980, 1986, 1991], the international literature for asbestos [Woitowitz et al., 1983] and for man-made fibers [Walton and Coppock, 1987; IARC, 1988; WHO, 1988]. A second industrial hygienist reevaluated 265 job periods of 50 patients in order to check the reproducibility of the concentration estimates. The agreement for both rates is described in Table II.

The experts agreed in assigning the category "none" for 191 job periods (72%). For 48 periods (18%) asbestos exposure was scored by both while 26 times (10%) this was scored by only one of them. In all, the experts scored asbestos exposure for 74 job periods. When these are evaluated separately only 34% of the minimal values and 43% of the maximal values are classified in the same exposure category, while 15% of the minimal and 36% of the maximal values differ for more than one category. The weighted κ values are 0.61 (95% CI 0.53–0.70) and 0.68 (95% CI 0.59–0.78) for the minimal and maximal concentration values, respectively, (SAS-procedure proc freq). If distinction is only made between exposed and unexposed people, both values increase to 0.72 (95% CI 0.62–0.82). For each expert the number of overestimates was nearly equal to the number of underestimates. Finally, the following parameters were selected for each person:

- Time since first exposure (years) defined as years since the beginning of the first job period with exposure to asbestos.
- Duration of an asbestos exposure (years) defined as duration of all job periods with exposure to asbestos.
- Highest intensity of asbestos exposure (f/ml) estimated during any period of the working life.
- Cumulative exposure to asbestos and MMVFs (f/ml × years) defined as fiber dose. For asbestos the cumulative exposure was calculated until the date of the interview and to time points 10 and 20 years previously.

Statistical Analysis

Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated by conditional logistic regression using the SAS procedure PHREG [SAS institute, 1992]. Occupational risks were analyzed separately for job categories and industries, and for the parameters of exposure.

Job titles and industries were coded according to standard classifications [Statistisches Bundesamt, 1975, 1979]. The analysis of job histories was based on these

TABLE III. Frequency of the Geometric Mean Fiber Concentrations per Working Shift with an Exposure to Asbestos, Estimated for 454 Single Job Periods with an Exposure to Asbestos. Possible Concentrations are Obtained from Table II by Taking the Geometric Mean Values for Various Combinations of Lower and Upper Limits of the Concentration Ranges

Job periods				Cases		Controls	
				n	%	n	%
All periods				746		697	
Periods with exposure to asbestos							
No.	GM f/ml	Range f/ml		324	100	130	100
1	0.0112	0.005	0.025	108	33.3	51	39.2
2	0.0354	0.005	0.25	99	30.6	47	36.2
3	0.0791	0.025	0.25	25	7.7	8	6.2
4	0.1	0.005	2	12	3.7	4	3.1
5	0.2236	0.025	2	41	12.7	13	10.0
6	0.5	0.025	10	16	4.9	0	0.0
7	0.7071	0.25	2	1	0.3	0	0.0
8	1.581	0.25	10	22	6.8	7	5.4
9	4.472	2	10	0	0.0	0	0.0

codes which were grouped into 32 job categories and 21 branches of industry [Jöckel et al., 1994, 1998]. An ever vs. never exposure concept was used, in addition to information on the longest-held job, which had been commenced at least 20 years before the onset of disease; on evaluation this yielded comparable results.

In order to adjust for the established impact of asbestos on mesothelioma risk, 4–5 categories of the different parameters of exposure were set up and included into the logistic regression as additional dummy variables. Five categories of cumulative exposure were used for MMVFs in a similar manner. An ever/never evaluation was also performed.

RESULTS

Job History

The mean duration of lifetime employment was 42 years for cases and 43 years for controls. Asbestos exposure was registered for 454 of a total of 1,443 single job periods of cases and controls. Table III gives the geometric mean value (GM) and the corresponding range of fiber concentration per shift for the five categories of exposure defined in Table II and their combinations together with the number of job periods assigned to these categories. The percentage of the job periods with asbestos exposure amounts to 43.4% for cases compared to 18.3% for controls. The frequency distribution of job periods with asbestos exposure is similar for cases and for controls.

Table IV gives the percentage of job periods with asbestos exposure, the duration of exposure and the arithmetic mean fiber concentration calculated as five times the GM value. After 1950 the frequency of exposure and fiber concentration, but not the mean duration of exposure, are higher for the cases than for the controls.

Tables V and VI show the number of cases and controls together with the odds ratios (ORs) for 22 of the 32 predefined occupations and for 20 of the 21 predefined industries, where at least five cases or five controls were exposed. Again the percentages of job periods with asbestos exposure and the estimate of the arithmetic mean fiber concentrations during these periods are also presented.

Significantly increased ORs and the highest numbers of mesothelioma cases were observed for the occupation of mechanics, fitters, and plumbers (n = 62), and in the industry of engine and vehicle building (n = 82).

TABLE IV. Job Periods Starting During Different Periods of Calendar Time

Time period	Cases		Controls	
Number of job periods and % with asbestos exposure				
Before 1950	343	39.7%	340	14.1%
1950–1970	352	50.3%	281	24.6%
1970–	51	21.6%	76	17.1%
Mean duration of exposure (years)				
Before 1950	6.02		6.14	
1950–1970	10.94		10.04	
1970–	5.85		7.29	
Mean fiber concentration (fibers/ml)				
Before 1950	0.75		0.97	
1950–1970	1.08		0.51	
1970–	0.90		0.33	

Characterisation of job periods according to the percentage with an asbestos exposure, the mean duration of exposure and the estimate of the (arithmetic) mean of the fiber concentration, which is averaged among all shifts with an exposure.

Asbestos Exposure

We considered years since first exposure, years of duration of exposure, highest intensity of exposure estimated during any period of the working life, and cumulative asbestos exposure as parameters of an occupational asbestos exposure (Table VII). None of these parameters has been adjusted for the effects of the others. Comparing exposed persons to not-exposed ones yields a significantly increased OR for any of the categories of any of these parameters. For each of the parameters, with the exception of time since first exposure, the OR even increases among exposed persons, when the lower intervals of exposure are compared to the higher ones. A steep risk gradient up to OR = 47 is observed for the highest intensity of exposure, for years of exposure, and for the cumulative dose estimate. This result does not alter very much by introducing cut-off points 10 or 20 years before the end of observation for the calculation of the cumulative exposure.

Exposure to MMVFs

Table VIII reveals that elevated risks have been found for three intervals of cumulative exposure to MMVFs, although their concentration range is lower, by a factor of 10, than the corresponding range for asbestos exposure (see Table VII). Adjustment for asbestos exposure, however, causes a distinct reduction of the OR and the results are no longer significant. Instead of analyzing on the basis of a dose estimation, an ever/never evaluation may be performed by comparing the first exposure group (0 fiber years = never) to the three upper groups altogether (= ever). In this case the OR remains significant even after adjustment for asbestos.

Additionally, in Table IX exposure estimates and ORs are compared for four different groups of persons with and without exposure to asbestos or MMVFs. A significantly increased OR is registered for cases and

TABLE V. Number of Cases and Controls and Odds Ratio from an Ever/Never Evaluation of 22 of 32 Occupations Where At Least Five Cases or Five Controls were Exposed. Within Each of the Occupations the Job Periods are Characterized by the Percentage of Jobs with an Asbestos Exposure and by the Arithmetic Mean of the Fiber Concentration

					Jobs periods of cases and controls		
					All periods	Only periods with an asbestos exposure	
Key[a]	Occupation[a]	Cases No.	Controls No.	OR[b]	% of all periods		Fiber concentration GM × SF/ml
11,41–43	Farmer	17	25	0.60	92	0	0.00
21–32, 44,52	Forestry worker, fisherman, Animal husbandry worker	4	6	0.67	15	13.3	0.10
12,51	Gardener, vineyard worker	2	5	0.40	16	0	0.00
71–91	Miner	6	8	0.75	21	0	0.00
141–150	Chemical processor and related worker	13	11	1.18	48	60.4	1.39
181–184, 501–504	Joiner, wood processing worker	9	8	1.12	79	21.5	0.34
191–252	Metal production and processing worker	26	14	2.09*	81	45.7	0.80
261–306	Mechanician, fitter, plumber	62	21	2.82*	359	72.1	0.79
311–315	Electrician	15	5	3.00*	88	37.5	0.41
391–433	Food production and processing worker	3	5	0.60	47	0	0.00
441–453	Carpenter, bricklayer, roofer	8	10	0.78	96	34.4	0.69
461–472	Road construction worker, pipe layer, well digger, Unskilled construction worker	17	17	1.00	96	15.6	0.73
481–492	Tile setter, plasterer, paviour, upholsterer	11	3	3.67*	30	63.3	2.94
531	Unskilled worker not elsewhere classified	5	8	0.57	19	31.6	0.14
541–549	Stationary engine and heavy equipment operator	19	7	3.40*	41	65.9	0.70
601–635	Technician engineer	19	9	2.25	89	46.1	0.28
681–706	Sales assurance agent	11	26	0.38*	80	3.8	0.06
711–744	Transportation & store worker	48	39	1.32	227	22.9	0.20
751–784	Administrative & organization clerk	34	49	0.57*	201	4.0	0.07
791–805	Protective service worker	59	71	0.56	240	7.5	0.09
861–893	Teacher, scientist, social worker	4	7	0.57	41	14.6	0.10
901–937	Housekeeper, cleaner, hairdresser, bartender	5	7	0.71	28	14.3	0.62

[a] A priori defined occupational groups, see [Jöckel et al., 1994, 1998], code according to standard classification of industries [Statistisches Bundesamt, 1975, 1979].
[b] Odds ratio matched for age and region of residence.
[c] Cases, population controls and control patients.
* $p < 5\%$, two-sided.

controls, which were exclusively exposed to MMVFs, if they are compared to those exposed to neither MMVFs nor asbestos.

DISCUSSION

Retrospective exposure assessment is one of the main problems arising from case–control studies [Finkelstein, 1995; Siemiatycki, 1996, 1997; Benké et al., 1997]. Exposure estimates are often based on job exposure matrices (JEM) where estimates describing probability, frequency, and intensity of exposure are not related to specific persons but to specific combinations of occupations and industries. Different types of exposures are often estimated side by side [Siemiatycki, 1996; Benke et al., 1997; Cocco, 1999]. The mesothelioma case–control study of Iwatsubo et al., [1998] for example, is based on this concept. In our study, however, the frequency and the upper and lower limits of intensity of exposure to asbestos and MMVFs were estimated semi-quantitatively for the single job periods of individual persons. Other types of fiber-containing materials, such as talc or attapulgite, were considered at least qualitatively. Besides asbestos, MMVF was by far the most frequent cause source of exposure to fibers and it was only for MMVF that

TABLE VI. Number of Cases and Controls and Odds Ratio from an Ever/Never-Evaluation of 20 of 21 Industries Where at least Five Cases or Five Controls were Exposed. Within Each of the Industries the Job Periods are Characterized by the Percentage of Jobs with an Asbestos Exposure and by the Arithmetic Mean of the Fiber Concentration

					Jobs periods of cases and controls		
					All periods	only periods with an asbestos exposure	
Key[a]	Industries[a]	Cases No.	Controls No.	OR[b]	% of all n periods		fiber concentration GM × 5 f/ml
011–077	Fishing, forestry, farming and horticulture	20	31	0.58	124	1.61	0.10
100–118	Energy and mining	20	11	1.82	61	34.4	1.89
200–205	Chemical and oil industry	13	16	0.79	65	30.8	0.18
210–216	Rubber and plastics	9	7	1.33	36	83.3	1.62
221–227	Stone and glass	15	9	2.00	36	55.6	2.73
230–239	Metal production	20	9	3.20*	72	52.8	0.30
240–249	Engine and vehicle building	82	45	3.18*	351	65.5	1.01
250–259	Electrical and sheet metal	15	10	1.71	61	14.8	0.23
260–269	Paper, wood, and print	11	17	0.57	97	5.2	0.13
270–279	Leather and textile	6	7	0.86	19	10.5	0.65
281–299	Food and tobacco	16	14	1.17	77	2.6	0.06
300–308	Construction	36	36	1.00	232	25.9	0.43
310–316	Installation	27	9	4.00*	92	57.6	0.29
401–439	Trade	11	17	0.63	115	7.0	0.11
511–517	Transportation	36	29	1.33	152	32.9	0.18
551–555	Stock-keeping and shipment	14	12	1.18	74	32.4	0.26
600–657	Financial service and insurance	4	9	0.38	33	3.0	0.18
731–745, 98	Cleaning service, barbershop, house-keeping, waste disposal	4	8	0.50	25	16.0	0.59
751–799, 94, 96	Education, sport, health	11	20	0.53	75	12.0	0.20
811–990	Public service and non-profit organizations	73	80	0.74	352	9.9	0.11

[a] A priori defined industries, see [Jöckel et al., 1994, 1998], code according to standard classification of industries [Statistisches Bundesamt, 1975, 1979].
[b] Odds ratio matched for age and region of residence.
[c] cases, population controls and control patients.
* $p < 5\%$, two-sided.

an increased risk was estimated (Tables VIII, IX). However, exposure to MMVFs is heavily confounded with exposure to asbestos; therefore this result has to be discussed very carefully. First, a critical examination of the study design has to be performed [Siemiatycki and Boffetta, 1998] and in addition, comparisons may be made with results which have previously been obtained for a second series of hospital controls using the same method, and with results of lung tissue fiber analysis [Woitowitz et al., 1993; Rödelsperger, 1996; Rödelsperger et al., 1999].

Selection Bias

It has been argued that the diagnosis of mesothelioma may be made more probable if asbestos exposure is evident [Siemiatycki and Boffetta, 1998]. This diagnostic bias would increase the risk estimate for asbestos. In our study a panel of pathologists was installed to exclude diagnostic errors. Each diagnosis obtained by the pathologist of a participating hospital had to be confirmed by a member of this panel. The whole panel was then included in the decision for 24% of the diagnoses, where the decisions were discrepant. A total of 15% of the cases considered was discarded (5% in agreement between the two pathologists and 10% by a panel decision).

Selection bias for the selection of population controls is minimized by the matching procedure. In contrast, many of the hospital controls of our previous study suffered from lung cancer [Woitowitz et al., 1993]. which is well known to be caused by asbestos.

TABLE VII. Odds Ratios for the Relationship between Mesothelioma and Asbestos Exposure Together with the Number of Cases and Controls According to Different Parameters of the Asbestos Exposure

	125 Cases	125 Controls	Odds ratio [a]	95%-CI
Time since first exposure (years)				
not exposed	11	67	1	
≤30	12	4	22.5	4.3–119
>30-40	40	22	18.9	5.3–67.3
>40	62	32	19.6	5.7–67.2
Duration of exposure (years)				
not exposed	11	67	1	
>0–10	24	21	10.4	2.9–37.1
>10–20	22	14	16.5	4.1–65.6
>20–30	19	8	27.7	5.8–132
>30	49	15	43.7	10.8–177
Highest intensity of exposure[b]				
not exposed	11	67	1	
low	14	12	9.2	2.3–35.9
medium	37	25	17.9	5.0–64.4
high	63	21	46.3	12.1–178
Cumulative exposure up to end of observation (fiber years)				
not exposed	11	67	1	
>0–0.15	14	12	7.9	2.1–30.0
>;0.15–1.5	38	25	21.9	5.7–83.8
>1.5–15	46	16	47.1	11.5–193
>15	16	5	45.4	8.1–257
Cumulative exposure up to 10 years before end of observation				
not exposed	11	67	1	
>0–0.15	15	13	7.9	2.1–29.5
>0.15–1.5	39	24	24.0	6.2–93.0
>1.5–15	45	16	51.8	12.4–216
>15	15	5	42.6	7.3–249
Cumulative exposure up to 20 years before end of observation				
not exposed	14	68	1	
>0–0.15	15	13	9.2	2.4–35.0
>0.15–1.5	44	24	20.5	5.8–72.6
>1.5–15	40	16	32.2	8.5–122
>15	12	4	43.8	7.1–269

[a] Odds ratio matched for age and region of residence.
[b] "Low" (<0.1 fibers/ml), "high" (>1 fiber/ml) or "medium" (otherwise) according to five times the geometric mean fiber concentration given in Table III.

Information Bias

Information bias may be caused by the different situation of the interview for mesothelioma patients compared to that for the healthy reference population [Siemiatycki and Boffetta, 1998]. In the total for our population controls it is likely that there will be a great deal of information bias increasing the risk estimate while selection bias ought to be low. This may lead to an overestimate. In contrast, the interview situation should be comparable both for the cases and for the hospital controls of the previous study, who have been treated by pulmonary resection. Hence, information bias, which may increase the risk estimate, should be low, while selection bias, which is expected to decrease the risk, should be high. The overall result might be to underestimate the risk. In order to reduce this type of bias, biographical

TABLE VIII. Odds Ratios and Number of Cases and Controls in Males and Exposure to MMVF

Geometric mean × 5 (fiber years)	Cases	Controls	Odds ratio [a]	95%-CI	Odds ratio [b]	95%-CI
never = 0	**70**	**111**	**1.00**	—	**1.00**	—
>0–0.015	10	6	2.96	0.92–9.57	0.78	0.16–3.77
>0.015–0.15	11	4	4.19*	1.17–15.00	3.11	0.56–17.2
>0.15–1.5	20	1	26.28*	3.39–203.75	7.95	0.88–72.3
>1.5	14	3	6.50*	1.47–28.80	5.43	0.72–41.0
ever >0	**55**	**14**	**6.12***	**2.90–12.93**	**3.08***	**1.17–8.07**

[a] Odds ratio matched for age and region of residence.
[b] Odds ratio adjusted for asbestos fiber years by means of four indicator variables, as defined in Table III.
* $p < 5\%$, two-sided.

history of all job periods was obtained in a first step, then a check list of asbestos and other fibrous products, including brand names, working processes and photos, was presented in a second step, but only minor additions were obtained.

Exposure Assessment Bias

An underestimate of the higher past exposure levels may be caused by information bias or even by change in the methods of fiber counting [Doll and Peto, 1985; Siemiatycki and Boffetta,1998]. A magnification of the dose–response relationship may result. On the other hand, random errors as a result of misclassification of exposure usually bias the risk toward null value (no association) [Armstrong, 1998].

In Table IV, where exposure estimates of exposure to asbestos for different time periods are presented, the percentage of jobs with asbestos exposure, the mean duration of exposure, and fiber concentration for cases is higher between 1950 and 1970 than in the time periods before and afterwards. This pattern, apart from the fiber concentration, is similar for population controls. A similar pattern in time was observed in the French mesothelioma case–control study [Iwatsubo et al., 1998]. In this study the highest rate of job periods with asbestos exposure also was observed between 1950 and 1970, but the percentage of about 38% in cases and 20% in controls lies below the German results. In contrast, the prevalence of exposure is higher in France from 1970. This observation might be explained by the restrictions in the use of asbestos, which were introduced in Germany at the end of the 1970s.

In our study quantitative estimates may be subject to error by using only one common duration of exposure in job periods where asbestos and MMVFs were used side by side. For job periods with exposure to asbestos the percentage for an additional exposure to MMVFs was only 22% in cases and 9% in controls. In periods with an exposure to MMVFs the percentage of an additional asbestos exposure was 85% in cases and 67% in controls. Hence, an overestimate must be expected, particularly for the cumulative exposure to MMVFs.

TABLE IX. Exposure to Asbestos and MMVF in Males. Estimate of MMVF and Asbestos Fiber Dose, Numbers of Cases and Controls and Odds Ratio

Exposure	Mean fiber years	125 Cases	125 Controls	Odds ratio*	95%-CI
MMVF –	0	9	65	1.00	—
Asbestos –	0				
MMVF+	0.6	2	2	**15.1***	**1.05–218**
Asbestos –	0				
MMVF –	0	61	46	19.8*	4.7–83
Asbestos +	7.1				
MMVF +	2.4	53	12	61.3*	12.9–292
Asbestos +	16.2				

[a] Odds ratio matched for age and region of residence.
* $p < 5\%$, two-sided

Error of the Expert Estimate of the Exposure to Asbestos

According to Table III the factor between the GM value of fiber concentration per shift and the upper and lower limits, respectively, of the exposure category which corresponds to this GM value may vary between 2.2 (No.9), and 20 (No.4) with weighted mean values of 6.4 for cases and 5.5 for controls. This expert estimate of the range of uncertainty largely describes the random error for single job periods. The mean bias for the exposure estimates of all job periods should lie below these factors. A similar but lower uncertainty results from classifying the number of working shifts with exposure to asbestos into only three categories where the highest category, e.g., even everyday exposure which is registered as "more than once per week," only contributes half of the working days of a year.

For a single job period the cumulative exposure to asbestos is obtained by the years of duration of exposure normally multiplied with the arithmetic mean values (AM) of fiber concentration per shift and the rate of working shifts with the exposure. Here AM amounts to half the sum of the lower and the upper limit of the expert estimate and therefore, an upper limit much higher than the lower limit would yield an AM which is roughly half the upper limit. A better description of the range of uncertainty is obtained using the GM, but GM values are systematically lower than AM values. The AM of fiber concentration is estimated five times the GM in order to compensate this bias, which results from the uncertainties of the estimate of the fiber concentration (factor 3) and of the frequency of asbestos exposure (factor 1.5). The weighed average of the AM values for all jobs with exposure to asbestos is 0.93 f/ml for the cases while it is 0.66 f/ml for the controls (Table III).

Consistency Between Exposure and Risk Estimates

OR significantly increases (Table VII) for each of the three parameters of cumulative exposure even within the first exposure interval > 0–≤ 0.15 fiber years. Exceptional behavior is observed for the time after first exposure. Here the OR remains constant, although a steep relationship should exist for this parameter. However, this discrepancy may be explained from study design: Controls were matched to cases with respect to the year of birth. There is a good correlation between cases and controls for the age and the time of first exposure.

In Tables V and VI, the percentage of job periods with asbestos exposure and the concentration estimate as parameters of exposure are compared to the OR. The correlation is better with the percentage of job periods with an asbestos exposure ($R = 0.810$ for occupations and $R = 0.769$ for industries, both $P < 0.001$) than with mean fiber concentration ($R = 0.765$, $P < 0.001$ and $R = 0.524$, $P = 0.018$). The most distinct discrepancy appears between the installation and the stone and glass industries. For the former, the highest OR of 4 (statistically significant) is associated with a small average concentration of 0.29 f/ml. For the latter, an OR of 2 (not significant) is associated with the highest concentration estimate of 2.7 f/ml.

In the "*installation industry*" a total of 56 job periods of *27 cases* and 21 job periods of *nine controls* was observed. They worked as tin smith or plumber (12 cases and 2 controls), carried out heating installation (5 cases and 3 controls), air conditioning installation (2 cases and 1 control) or worked as electrician (4 cases and 2 controls) or, interior designer or painter (4 cases and 1 control). In this industry working procedures were distributed homogeneously among cases and controls and, therefore, estimates of asbestos exposure were similar for both of them. The low exposure estimates are reliable since exposure mainly resulted from pipe insulation with asbestos, asbestos cement, welding protection, and sealing.

In the "*glass and stone*" *industries* a total of only 27 job periods of *15 cases* and *nine controls* was observed. Nine cases but only one control ($P = 0.02$) worked as insulators and definitely used asbestos in most periods; three times this was spray asbestos. One further case had mined asbestos in the Urals as a prisoner of war and two others had worked in the asbestos industry. The latter is also true for one control but he mainly worked inside the office as a designer. One of the remaining three cases was a boilerman in a glass factory. The other two worked as locksmiths in the cement industry. In contrast, the seven remaining controls worked in quarries ($n = 4$) and in concrete production ($n = 3$). The work periods of cases and controls are very obviously different in the "glass and stone" industry. While the high exposure estimate is convincingly justified by the work place descriptions of the cases, the OR is reduced by a large number of controls with places of work where a much lower degree of asbestos exposure should be expected.

Comparison with Lung Tissue Fiber Analysis

The fiber burden of the pulmonary tissue has been analyzed for a total of 66 cases (60 male and 6 female) and 66 hospital controls (primarily lung cancer cases) of the original study, among them 27 cases and 39 controls are from Hamburg as reported elsewhere [Rödelsperger, 1996; Rödelsperger et al., 1999]. The dose estimates for these cases on the average (AM) are 1.7 times higher, than for the cases from the present study. A subsample of 20 male cases was included in both studies, among them was the one with the highest exposure estimate of 167 fiber years.

For the patients of the lung tissue study, cumulative asbestos exposure, as derived from the interview, correlates with the concentration of asbestos fibers longer than 5 μm in

the lung tissue for amphibole ($R = 0.44$, $P < 0.001$), but not for chrysotile fibers [Rödelsperger, 1996]. Regression analysis reveals that a fiber dose of one fiber year roughly corresponds to a concentration of 80,000 amphibole fibers longer than 5 μm per gram dry lung tissue (g dry). This relationship is in good agreement with other estimates [Consensus Report, 1997].

A clear dose–response relationship could be observed between the concentration of these long amphibole fibers and the risk of mesothelioma [Rödelsperger and Woitowitz, 1995; Rödelsperger et al., 1999]. An OR of almost 100 was obtained from the almost linear relationship, when 10 of 66 cases (15%) in the reference interval < 50,000 fibers/g dry were compared to 29 of 66 cases (44%) in the uppermost interval ≥ 500,000 fibers/g dry.

Correspondingly, from the present study (Table VII) an OR of about 45 is observed, if the 11 cases (9%) of the reference interval (0 fiber years) are compared to the 62 cases (50%) of the two uppermost intervals ≥ 1.5 fiber years.

Within these uppermost exposure intervals the average dose estimate combined for cases and controls amounts to 25 fiber years for the lung burden study and to 16 fiber years for the interview study. Obviously, the results of both studies are very similar. This is true, though the OR of the lung burden study should be reduced in comparison to the present study because of the choice of hospital controls instead of population controls. On the other hand, the diminution of the OR by random error may be much stronger for the interview study.

Comparison With Other Case–Control Studies

In this study some 91% of the cases compared to 54% of the controls were occupationally exposed to asbestos (Table VII). Since only male individuals from Hamburg were included, the results are not representative for the German population as a whole. For example, higher exposure to asbestos can be expected in Hamburg due to shipyards and asbestos-processing industries [Hain and Dalquen, 1974]. The rates correspond to the upper limits of the ranges of 12–95% for mesothelioma cases and 2–48% for controls, which have been reported from international mesothelioma case–control studies [Brochard et al., 1993].

Iwatsubo et al. [1998] observed a pattern very similar to the results of Table VII for the different parameters of exposure, but in the uppermost intervals OR generally only reached 5 to 9 compared to about 45 in the German study. Again the OR remained almost constant for the time since first exposure. Its value is 2.2–2.8 in the French and 18.9–22.5 in the German study. The percentage of cases exposed is much higher for the German study (91% compared to 71%). In contrast, the rate of exposure among the German population controls is somewhat lower than for the French hospital controls (46% compared to 51%).

The ORs observed in our study fully support the well-established epidemiologic evidence for the carcinogenicity of asbestos with respect to mesothelioma. However, due to the low number of pairs with exposed controls and non-exposed cases, the absolute magnitude of the OR should be regarded with caution: the maximum OR decreased from about 100 in the original study [Woitowitz et al., 1993] to 45 in the present paper when the definition for "not exposed to asbestos" slightly was altered from "< 0.015 fiber years" to "0 fiber years" according to Iwatsubo et al., [1998]. According to Table VII the latter reference category contained 11 cases and 67 controls, among them eight pairs. The three remaining cases formed pairs with exposed controls.

Furthermore, if our results obtained for 125 population controls are compared to the results obtained for 125 additionally available hospital controls consisting primarily of lung cancer patients [Woitowitz et al., 1993], the maximum OR decreases from 100 to about 10. If, however, the matching is broken and a *stratified unconditional logistic regression* is applied the maximum OR decreases to 17 for the population controls while it remains almost constant for the hospital controls (OR = 9.4 in the maximum). A clear dose–response relationship is obtained even for these hospital controls and even for an exposure "> 0.15–1.5 fiber years" there is a significantly increased OR of 3.2 (95% CI: 1.7–6.1).

Asbestos Fibers and MMVFs

The estimate of the exposure to MMVFs is only about 10% of the exposure estimated for asbestos (Table IX) and, in addition, the effect of MMVF is greatly affected by this exposure. By adjusting for asbestos, a significantly increased OR only remains in the ever/never evaluation, which does not depend on the dose estimate (Table VIII). Considering the two cases and two controls, who were only exposed to MMVF but not to asbestos yield a significantly increased OR of 15.1 (Table IX). Despite the difference in fiber years the risk estimate is very similar for those exposed to asbestos alone. Therefore, MMVF even might be more hazardous than asbestos. However, this conclusion is severely hampered by the problems of estimation of exposure, which influence both the adjustment for asbestos exposure and the definition of non-exposed. In addition, the type of asbestos—chrysotile or amphibole—is unknown in spite of its well-known importance [Rödelsperger et al., 1999]. Further difficulties arise from the small sample size in cells with differing exposure with respect to either agent. Accordingly in the original report [Woitowitz et al. 1993], restriction to cases and controls without exposure to asbestos did not yield an increased OR since—as was discussed in the last section—the definition of the reference category was "< 0.015 fiber years" instead of "0 fiber

years." Therefore, in agreement with other studies, there is insufficient evidence to establish a causal relationship between the exposure to MMVF and mesothelioma. Nevertheless, even those studies, which do not show significantly increased incidence of mesothelioma, cannot exclude the possibility MMVF being carcinogenic with sufficient precision [Doll, 1987; Simonato et al., 1987; Marsh et al., 1990; Marsh et al., 1996; Boffetta et al., 1997].

In agreement with other studies [McDonald et al., 1990], our lung burden study did not reveal increased concentrations of MMVF, even after heavy exposure to glass or rock wool [Rödelsperger, 1996; Rödelsperger et al., 1998]. Yet, as for chrysotile, it cannot be excluded that these fibers may have caused a tumor, even if they are not present in lung tissue, when it is diagnosed [Baker, 1991; Woitowitz et al., 1991].

CONCLUSIONS

For all measures of asbestos exposure the OR increases significantly up to about 45 in the uppermost intervals. Even within the first exposure interval "> 0–≤ 0.15 fiber years" the OR significantly increases. This relationship may be influenced by information bias, exposure assessment bias, and the random error. Nevertheless, a stratified analysis, where matching is broken, and a further series of hospital controls yields a lower but still substantial OR.

The OR estimate shows a plausible relationship to the estimate of fiber concentration and to the percentages of jobs with asbestos exposure for different occupations and industries. The highest numbers of mesothelioma together with a significantly increased OR are found in "mechanics, fitters and plumbers" and for the "engine- and vehicle-building" industry. Discrepancies appear between the "glass and stone", and the "installation" industry since OR is reduced for the latter despite a much higher concentration estimate. This may be explained by a substantial difference in the type of exposure of cases and controls in this industry.

Although exposure to MMVF is much lower than the exposure to asbestos, an increased OR is observed in an ever/never evaluation. It even remains significant, if confounding by asbestos is considered by adjustment or if evaluation is restricted to cases and controls without any exposure to asbestos. However, when considering the problems of dose estimation and the sample size, a causal relationship can neither be proven nor excluded.

A further case–control analysis, based on lung tissue fiber concentrations in addition to the interview, yields similar ORs, if reference intervals and uppermost exposure intervals contain similar percentages of all cases. These results confirm the distinct dose–response relationship of the interview study even at a cumulative exposure below 1 fiber year. They clearly support the outcome of the French mesothelioma case–control study.

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