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Malignant Mesothelioma and Occupational Exposure to Asbestos: A Clinicopathological Correlation of 1445 Cases

Victor L. Roggli, MD
Anupama Sharma, MD
Kelly J. Butnor, MD
Thomas Sporn, MD
Robin T. Vollmer, MD

Department of Pathology, Durham Veterans Administration and Duke University Medical Center, Durham, North Carolina, USA

Asbestos exposure is indisputably associated with development of mesothelioma. However, relatively few studies have evaluated the type of occupational exposure in correlation with asbestos fiber content and type. This study reports findings in 1445 cases of mesothelioma with known exposure history; 268 of these also had fiber burden analysis. The 1445 cases of mesothelioma were subclassified into 23 predominant occupational or exposure categories. Asbestos body counts per gram of wet lung tissue were determined by light microscopy. Asbestos fiber content and type were determined by scanning electron microscopy and energy dispersive x-ray analysis. Results were compared with a control group of 19 lung tissue samples. Ninety-four percent of the cases occurred among 19 exposure categories. Median asbestos body counts and levels of commercial and noncommercial amphibole fibers showed elevated levels for each of these 19 categories. Chrysotile fibers were detectable in 36 of 268 cases. All but 2 of these also had above-background levels of commercial amphiboles. When compared to commercial amphiboles, the median values for noncommercial amphibole fibers were higher in 4 of the 19 exposure groups. Most mesotheliomas in the United States fall into a limited number of exposure categories. Although a predominant occupation was ascertained for each of these cases, there was a substantial overlap in exposure types. All but 1 of the occupational categories analyzed had above-background levels of commercial amphiboles. Commercial amphiboles are responsible for most of the mesothelioma cases observed in the United States.

Keywords mesothelioma, asbestos, fiber analysis, occupation, amosite, tremolite, chrysotile

The association between mesothelioma and prior asbestos exposure is undisputed. A wide variety of occupational and environmental exposures have been implicated as the source of this exposure. In the past, insulation workers and shipyard workers were exposed to high levels of asbestos dust and decades later were found to have a markedly elevated rate of mesothelioma. Bystanders working in the vicinity of those directly handling asbestos products were also found to be at risk. In addition, household contacts of asbestos workers and those living in the vicinity of an asbestos manufacturing plant also developed mesotheliomas [1–3]. Such studies have led to the conclusion that mesothelioma may be related to brief, low-level, or indirect exposures to asbestos.

Although numerous reports document mesothelioma risk associated with particular exposures, there are relatively few studies that have examined the distribution of occupations in a large series of mesothelioma cases. Otto reported the occupational categories in 71 patients with asbestos-related mesothelioma and 37 ‘‘spontaneous’’ or idiopathic cases [4]. The Australian Mesothelioma Register provides biennial reports on the occupational categories of the mesothelioma cases collected by the registry in Australia [5]. It is difficult, however, to find detailed analyses of lung mineral fiber content in a series of mesothelioma patients that also contain detailed information regarding occupational or environmental exposures to asbestos.

We have previously shown that amosite asbestos is the most common fiber type identified in the lungs of

Address correspondence to Victor L. Roggli, MD, Department of Pathology, Durham Veterans Administration and Duke University Medical Center, Durham, NC 27710, USA.

patients with mesothelioma from the United States [6]. Furthermore, there is a significant correlation between lung fiber burden of asbestos bodies and commercial amphibole fibers with duration of exposure to asbestos [7]. For equal durations of exposure, individuals who directly worked with asbestos products have a higher lung burden than those who were indirectly exposed (i.e., bystander exposure), and shipyard workers have on average a higher burden than non-shipyard workers. The present study extends these observations by examining exposure information in more than 1400 cases of histologically confirmed mesotheliomas. In 268 of these cases, the exposure information could be correlated with the results of tissue mineral fiber analysis.

MATERIALS AND METHODS

The consultation files of one of the authors (VLR) were reviewed for all cases of mesothelioma for which information was available regarding possible exposure to asbestos. The diagnosis of mesothelioma was based on the gross distribution of tumor, histologic pattern, and the results of immunohistochemical studies as previously described [8]. In some cases, histochemical stains and ultrastructural studies were performed when indicated. Information was also obtained regarding the age, sex, primary site of the tumor (pleura vs. peritoneum), smoking history, presence of pleural plaques and/or calcification, and presence of histologic asbestosis [9, 10].

Patients were classified into one of the 23 exposure groups shown in Tables 1–3. Industries with known asbestos exposure are listed in Table 1, occupations in Table 2, and nonoccupational exposures in Table 3. The occupations listed in Table 2 are distributed across many of the industries listed in Table 1. For example, pipefitters may be employed in shipyards, oil refineries, power plants, etc. Many individuals worked in more than one of the categories indicated in the tables. However, for purposes of analysis, an attempt was made to place patients in a predominant category where the most intense exposures (based on previous analyses from our laboratory) were likely to occur (e.g., insulators or shipyard workers). When more than one category of exposure occurred, these separate exposures were recorded as well. When available, data were also collected regarding the duration of exposure for each of the categories indicated in Tables 1–3.

Fiber analyses were performed on formalin-fixed or paraffin embedded lung tissue specimens by using previously described methods [11]. Lung tissue was processed for digestion by using the sodium hypochlorite technique. The residue was collected on 0.4-μm pore-size Nuclepore filters. For light microscopic analysis, the filter was mounted on a glass slide for asbestos body quantification. Filters were counted at a magnification of $\times$400, and only bodies with typical morphology and thin, translucent cores were

TABLE 1 Mesothelioma Cases by Industry

	Single	Multiple	Total
Shipbuilding[a]	203	86	289
U.S. Navy[b]	91	84	175
Construction[c]	99	35	134
Insulation[d]	92	11	103
Oil and chemical	78	10	88
Power plant	50	10	60
Railroad	37	16	53
Automotive[e]	24	27	51
Steel/metal[f]	33	10	43
Asbestos mfg.[g]	34	5	39
Papermill	7	0	7
Ceramics/glass	6	0	6

[a]Includes joiner, shipwright, rigger, sandblaster, shipfitter, electrician, painter, and welder.
[b]Includes merchant marine seamen.
[c]Includes construction worker, laborer, carpenter, painter, dry wall/plasterer.
[d]Includes pipecoverer, insulator, asbestos sawyer, asbestos sprayer.
[e]Includes auto mechanic, brake repair worker, brake line worker.
[f]Includes steel, aluminium, and iron foundry workers; furnace worker; potroom worker.
[g]Includes asbestos textile, asbestos manufacture, asbestos plant worker.

TABLE 2 Mesothelioma Cases by Occupation

	Single	Multiple	Total
Pipefitter[a]	159	28	187
Boilermaker[b]	81	31	112
Maintenance[c]	75	15	90
Machinist	62	27	89
Electrician	59	22	81
Sheetmetal	17	5	22
Other asbestos[d]	23	0	23

[a]Includes welders.
[b]Includes boiler worker, boiler maker, boiler mechanic, boiler repairman, steamfitter.
[c]Includes mechanical engineer.
[d]Includes millwright, brick mason/mason, bagging machine operator/bagger, asbestos worker (not otherwise specified).

TABLE 3 Mesothelioma Cases with Nonoccupational Exposures

	Single	Multiple	Total
Household contacts	86	3	89
Building occupants	17	1	18
Other[a]	46	0	46
Environmental	5	0	5

[a]Includes architect, baker, bookkeeper, businessman, computer consultant, driver, dry cleaning/laundry business, dye and press setter, elevator repairman, forest service, furniture co., grinder, hairdresser, jewelry repair, Kent smokers, landscaper, industrial manager, minister, no known exposure, nurse, policeman, pressman, professor, resident construction, salesman, salt cake and carbon plant operator, school administrator, silica plant and pattern shop, status postradiation/chemotherapy, telephone installer, textile worker, tire manufacure.

counted as asbestos bodies [12]. Results were reported as asbestos bodies per gram of wet lung tissue (AB/g). The detection limit for a 0.3-g sample size is approximately 3 AB/g. For cases in which no asbestos bodies were detected in the sample, the value was recorded as less than the detection limit for that sample.

For scanning electron microscopic (SEM) analysis, the filter was mounted on a carbon disk with colloidal graphite, sputter-coated with gold or platinum, and examined in a JEOL JSM-6400 scanning electron microscope at a screen magnification of $\times 1000$ and with a screen size of 22.7×17.3 cm. Fibers 5 μm or greater in length were counted by using a protocol in which 100 consecutive fields or 200 fibers were counted, whichever came first. Fibers were defined as particles with an aspect ratio (length to width) of at least 3:1 and roughly parallel sides. The concentration of fibers for each case was calculated based on the fiber density (i.e., per mm^2) on the filter surface times the effective area of the filter, divided by the weight of the lung sample that was analyzed. The results were reported as total asbestos fibers (coated and uncoated) 5 μm or greater in length per gram of wet lung. The detection limit for a 0.3-g sample size is approximately 440 fibers/g. For cases in which no asbestos fibers were detected in the sample, the value was recorded as less than the detection limit for that sample.

Fiber types were determined by using a combination of fiber morphology as determined by SEM and elemental composition assessed by energy dispersive x-ray analysis (EDXA). Fibers were classified as amosite, crocidolite, tremolite, anthophyllite, actinolite, or chrysotile as previously described [11]. For purposes of analysis, amosite and crocidolite were grouped together as commercial amphiboles (AC). Tremolite, anthophyllite, and actinolite were grouped together as noncommercial amphiboles (TAA). The proportion of each fiber type and the total asbestos fiber concentration were used to determine the tissue concentration of AC, TAA, and chrysotile for each case. All other fibers were counted as nonasbestos mineral fibers (NAMF). For cases where no fibers of a particular type were detected, the value was recorded as less than the detection limit for that case. The results of fiber analysis for the mesothelioma cases were compared with 19 controls from our laboratory with macroscopically normal lungs, no evidence of asbestos-related disease, and no history of asbestos exposure.

For statistical analysis we used the log rank test to explore the relationship between age of diagnosis as a time of failure and industrial exposure and the Cox proportional hazard model for the final analysis of age. We also used Kaplan–Meier plots to illustrate age effects. We used a general linear model to relate the logarithmic transformation of fiber counts to industrial exposure, and fiber counts below the detection limit were arbitrarily set at half the detection limit. We used analysis of variance for exploratory analysis of continuous variables and chi-square tests for analysis of categorical variables. We used logistic regression analysis to relate binary variables to other, independent variables. Finally, all *P* values were for 2-sided test, and all analyses were done with S-PLUS software (MathSoft, Seattle, WA).

RESULTS

A total of 1445 cases of histologically confirmed mesothelioma were retrieved from the files of one of the authors (VLR). These included 1322 men and 123 women. The median age for the entire group was 67 years (range: 17–94 years). The site of origin was the pleura in 1309 cases and the peritoneum in 136 cases. The histologic types included 698 epithelial, 442 biphasic, and 292 sarcomatoid cases. For 13 cases, information was not available regarding the specific histologic pattern of the tumor. Information regarding smoking was available in 1112 cases: 830 were smokers or ex-smokers and 292 were nonsmokers. Information was available regarding the presence or absence or pleural plaques (PPP) in 778 cases. Plaques were present in 608 cases (78%). Information regarding the presence or absence of asbestosis was available in 577 cases. Asbestosis was present in 135 cases (23%).

Exposure Categories

Cases were classified into the 23 exposure categories indicated in Tables 1–3. The industry with the largest number of cases was shipbuilding, followed by U.S. Navy, construction industry, and insulation industry, each of which included 100 or more cases (Table 1). Among the 12 industries listed in Table 1, an exposure in some additional occupational setting was noted in 26% of the cases. The occupation with the largest number of cases was pipefitter, followed by boilermaker (Table 2). Among the 6 specific occupations listed, an exposure in some additional occupational setting was noted in 21% of the cases. The nonoccupational group with the largest number of cases was household contact of an asbestos worker (Table 3). Among the 4 nonoccupational groups, an exposure in an occupational setting was noted in 2% of the cases.

Two of the categories were fairly nonspecific, with "other asbestos" (Table 2) including several occupations for which there were few cases in any one subgroup, and "other" (Table 3) including a variety of occupations with no known exposure to asbestos. In addition, the "building occupant" group is known to be associated with tissue asbestos burdens that are oftentimes indistinguishable from background levels. Among the 4 cases with "environmental" or neighborhood exposures, only 1 was from the United States. When these 4 groups are excluded, the remaining 19 categories (12 industries, 6 occupations, and 1 nonoccupational exposure) accounted for 94% of the 1445 cases of mesothelioma included in this study.

Two of these exposure categories often have been considered as low-level exposures. These include household contacts of asbestos workers and environmental (neighborhood) exposures. There were 89 cases that were household contacts of an asbestos worker, and 10 of these had an additional occupational exposure to asbestos. Of these, 79% were women with an average age of 59 years. There were 4 cases with environmental exposure to asbestos. All were men with an average age of 67 years. None had any additional known exposure to asbestos. Three of these cases were from a region of Turkey where there was intense environmental exposure to tremolite–actinolite. The fiber burdens in these 2 groups are discussed below.

Gender, Exposure Duration, and Age

Over 90% of our cases of mesothelioma occured in men. In some occupational categories, all were men (Table 4). These included insulators, railroad workers, power plant workers, steel workers, brake repair workers, boiler workers, electricians, and machinists. A large percentage of the women with mesothelioma occurred in the household contact group, which, as noted above, consisted of 79% women. The building occupant group included about an equal number of men and women.

The median duration of exposure to asbestos is also provided in Table 4 for those cases where this information was available. For most categories, the median duration was 2 or 3 decades, with ranges as short as 1 month to as long as 56 years. Shorter duration was observed for shipbuilding, U.S. Navy, asbestos manufacture, and building occupants. The former 2 are related to large numbers of workers with shipyard employment or navy service limited to World War II, bringing down the median value for these groups. Shorter duration for asbestos manufacture may have been related to the very dusty environment with many workers quitting after a relatively short period of employment [12].

Table 4 provides the median and range of age for each category of exposure. A log rank test demonstrated that there was a significant relationship between the age at development of mesothelioma and type of industry or occupation (chi-square = 112, $P < .0001$). Table 5 provides detailed results of a Cox model analysis for the relationship between age and the key industries or occupations that had unusually high or low hazard rates. In the table, the relative hazard rates (column HR) provide the key result. Whereas values of HR above 1 (the reference for remaining undesignated cases) indicate a higher hazard and younger age for developing mesothelioma, values of HR below 1 indicate a lower hazard and older age for developing mesothelioma. For example, the highest relative hazard of 2.19 occured in those exposed in a nonindustrial

TABLE 4 Age, Gender, and Duration by Exposure Category

	Age[a]	M:F[b]	Exposure duration[c]
Industry			
Shipbuilding	69 (38–91)	37:1	10.5 (1 mo–46 yr)
U.S. Navy	67 (38–84)	55:1	9 (3 mo–56 yr)
Construction	66 (39–85)	96:1	30 (1–46)
Insulation	59.5 (37–78)	All men	26 (1 mo–50 yr)
Oil and chemical	70 (45–89)	40:1	30 (6 mo–45 yr)
Power plant	68 (39–81)	All men	30 (2–50)
Automotive	64 (31–83)	All men	23 (3–50)
Railroad	74 (45–94)	All men	30 (2–47)
Steel/metal	71 (44–81)	All men	31 (5 mo–45 yr)
Asbestos mfg.	64.5 (48–86)	6.8:1	8 (7 mo–40 yr)
Papermill	68 (51–77)	2.5:1	35.5 (13–42)
Ceramics/glass	64.5 (40–79)	5:1	30 (17–52)
Occupation			
Pipefitter	71 (38–91)	61:1	29 (6 mo–50 yr)
Boilermaker	67 (39–86)	All men	21 (6 mo–47 yr)
Maintenance	70 (39–88)	89:1	28 (2–56)
Machinist	68 (47–87)	All men	17.5 (1–51)
Electrician	69 (48–83)	All men	28.5 (1–49)
Sheetmetal	70 (52–76)	19:1	27.5 (1–43)
Other asbestos	60 (45–84)	All men	27 (5–40)
Nonoccupational exposure			
Household contacts	59 (25–93)	13:67	20 (1–45)
Building occupants	45 (17–78)	8:9	14 (1–26)
Other	63.5 (28–78)	27:11	NA
Environmental	67 (39–68)	All men	28 (18–38)

[a] Values represent median with range in parentheses.
[b] Ratio of men to women in given group.
[c] Values represent median duration of exposure in years with range in parentheses.
Note. NA, not applicable.

TABLE 5 **Cox Model Analysis of Age of Development of Mesothelioma**

Variable	HR	SE	*P* value
Nonindustrial	2.19	0.134	4.8×10^{-9}
Insulation	1.33	0.110	.010
Pipefitters	0.66	0.129	.0010
Rail workers	0.52	0.162	5.9×10^{-5}
Duration	0.99	0.002	2.3×10^{-10}
Female	0.70	0.143	.014

Note. Here, HR is the relative hazard, and SE provides the standard error for the regression coefficient, which can be calculated as log (HR).

setting (i.e., household contacts, building occupants, or other nonindustrial exposure). This result implied that this group experienced mesothelioma at an earlier age. Workers in the insulation industry also experienced a higher hazard rate, but pipefitters and railroad workers had lower hazard rates.

All these results were controlled for duration of exposure and female gender, because both were covariates in the analysis. Interestingly, longer duration was associated with increased rather than decreased age at diagnosis, and after controlling for category of exposure female gender was associated with a lower hazard and later age at diagnosis. The *P* values listed in the table provide the significance for the effect of each variable or group on the hazard for developing mesothelioma. Figure 1 illustrates these results further.

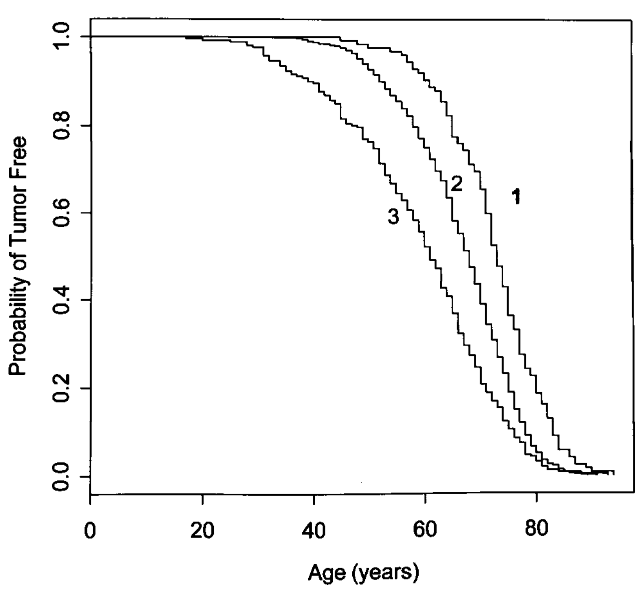

FIG. 1 *Kaplan–Meier plots of the probability of being tumor free versus age in years. Here age at diagnosis was treated as a failure time. Curve 1 provides the plot for pipefitters and railroad workers; curve 3 provides the plot for those in the insulation industry and those with nonindustrial exposure; and curve 2 provides the plot for the remaining groups of industrial/occupational exposures.*

In the figure are 3 Kaplan–Meier plots of the probability of being tumor-free versus age. Curve 1 combines pipefittes and railroad workers, who had the lowest hazards and developed mesothelioma at the oldest ages. Curve 3 combines those with nonindustrial exposure and those in the insulation industry, and this group developed mesothelioma at the youngest age. Curve 2 is for the remaining cases.

Tumor Location, Pleural Plaques, and Asbestosis

Approximately 90% of our cases arose in the pleura. The other 10% arose in the peritoneum. The highest percentage of peritoneal mesotheliomas occurred among insulators and absestos manufacturing plant workers (Table 6). In each of these groups, the ratio of pleural to peritoneal tumors was about 2:1. In the remaining groups, this ratio ranged from 8.6:1 in construction workers to more than 50:1 in shipyard workers. The low ratio of 1.8:1 in building occupants suggests that mesotheliomas in this setting are at or near the background rate of occurrence for these tumors.

TABLE 6 **Site, Plaques, and Asbestosis by Exposure Category**

	Site[a]	PPP[b]	Asbestosis[c]
Industry			
Shipbuilding	52:1	144/177 (81%)	37/132 (26%)
U.S. Navy	54:1	12/57 (21%)	4/37 (11%)
Construction	8.6:1	14/41 (34%)	6/35 (17%)
Insulation	2.1:1	64/75 (85%)	34/59 (58%)
Oil and chemical	82:1	36/46 (78%)	5/29 (17%)
Power plant	17:1	23/27 (85%)	3/16 (19%)
Automotive	8:1	8/12 (67%)	0/12 (0%)
Railroad	38:0	20/24 (83%)	2/17 (12%)
Steel/metal	9.3:1	15/16 (93%)	3/11 (27%)
Asbestos mfg.	2.2:1	21/24 (87%)	1/17 (65%)
Papermill	6:1	5/6 (83%)	1/5 (20%)
Ceramics/glass	6:0	1/2 (50%)	0/2 (0%)
Occupation			
Pipefitter	50:1	103/119 (87%)	20/83 (24%)
Boilermaker	30:1	60/74 (81%)	11/46 (24%)
Maintenance	26:1	45/56 (80%)	7/35 (20%)
Machinist	22:1	32/44 (78%)	4/28 (14%)
Electrician	74:1	33/40 (83%)	8/30 (27%)
Sheetmetal	20:0	9/11 (82%)	1/7 (14%)
Other asbestos	5:1	2/6 (33%)	0/5 (0%)
Nonoccupational exposure			
Household contacts	4.3:1	20/35 (57%)	3/38 (7.9%)
Building occupants	1.8:1	3/7 (43%)	0/10 (0%)
Other	8.5:1	11/24 (46%)	2/21 (9.5%)
Environmental	4:10	0/1 (0%)	0/1 (0%)

[a]Ratio of pleural to peritoneal tumors.

[b]Number of cases with plaques divided by number of informative cases (percentage).

[c]Number of cases with asbestosis divided by number of informative cases (percentage).

When information was available regarding the presence or absence of parietal pleural plaques (PPP), it was found that a high percentage of cases did in fact have plaques (Table 6). Chest radiographs and even computed tomographic (CT) scans are somewhat insensitive for the detection of PPP[13], so cases where PPP were not mentioned in the radiographic reports and were not observed in surgical specimens were considered to be uninformative. Although logistic regression analysis demonstrated that there was a significant association between category of exposure and the presence of PPP ($P = .0015$), these categories explained just 5% of the noise in the data, and it was difficult to identify particular categories associated with PPP. In general, workers in insulation, pipefitting, and steel had increased prevalence of PPP, and those in nonindustrial-exposure situations had lower prevalence of PPP. On the subset of 199 cases with asbestos body counts, logistic regression analysis demonstrated that the prevalence of PPP was closely related to log (asbestos body counts) ($P < .0001$). In this subset of cases, industrial category explained an additional 11% of the noise in the data with a P value of .044. Having accounted for the effect of fiber burden, the auto industry seemed to have an increased prevalence of PPP, but the variance associated with the remaining exposure categories was too great to reach any conclusions about the remaining categories of exposure. Neither exposure duration nor gender was significantly related to the prevalence of PPP.

When information was available regarding the presence or absence of asbestosis, it was determined that a relatively low percentage of cases had histologically confirmed asbestosis (Table 6). Among occupationally exposed individuals, the percentage of cases with asbestosis ranged from 0% of glass and ceramic workers and friction product workers to as high as 67% of asbestos manufacturing plant workers. Asbestosis was rarely observed among patients with mesothelioma and nonoccupational exposures. None of the environmental exposures or building occupants had asbestosis, but asbestosis was confirmed histologically in 8.3% of household contacts of asbestos workers. Logistic regression analysis demonstrated that although the category of exposure was significantly associated with asbestosis ($P < .0001$), there was no pattern of one category or another that could be identified as having either a high or low prevalence of asbestosis. Furthermore, when the burden of asbestos bodies was accounted for by including log (asbestos body count) in the model, the industrial category was no longer associated with the prevalence of asbestosis. In other words, the influence of industrial category on prevalence of asbestosis appeared to be mediated entirely by differences in fiber burden.

Lung Fiber Burden Analyses

The results of tissue fiber analysis for each of the exposure groups are summarized in Table 7. The median asbestos body count in each of the 23 exposure categories exceeded our normal range of 0–20 AB/g, except for 2 categories: automotive brake repair workers and building occupants. The industry with the highest median asbestos body count was the insulation industry, and the occupation with the highest count was pipefitter.

Analysis of variance demonstrated that the category of industry or occupation was significantly related to the number of asbestos bodies ($P < .0001$), to the number of commercial amphibole fibers ($P < .0001$), to the number of noncommercial amphibole fibers ($P < .0005$), and to the number of chrysotile fibers ($P < .0001$). Furthermore, much of the industry/occupational differences were due to higher fiber levels in the insulation industry coupled with lower fiber levels in 3 industrial groups: those with nonindustrial exposure, those in the auto industry, and those who were machinists. This is illustrated in Figure 2, which provides box plots of the natural logarithm of fiber counts in these 4 categories versus an "other" group of all remaining cases. Simple visual comparison shows that the pattern for fiber counts is roughly the same for all 4 types of fibers, and general linear model analyses demonstrated that after controlling for gender and duration of exposure, the associations between fiber counts and these 4 industrial groups were significant (P values ranging from approximately 0 to .02) with one exception—the level of noncommercial amphibole fibers in the nonindustrial group ($P > .1$).

The predominant fiber type identified in each of the categories was commercial amphibole (mostly amosite with some crocidolite), except for 4 categories: automotive brake repair workers, household contacts, building occupants, and environmental (neighborhood) exposures (Table 6). In these instances, noncommercial amphiboles (mostly tremolite with some actinolite and anthophyllite) predominated over commercial amphibole fibers. Chrysotile fibers were detected less frequently, and for 7 categories were not detected at all. Nonasbestos mineral fibers were present in all groups in roughly similar amounts.

Further analyses were performed on the 12 exposure categories for which there were at least 10 analyses within the category (Figure 3). Commercial amphibole fibers were present in concentrations that exceeded the background level in all 12 categories, ranging from 57% (other) to 100% (insulators) of the individuals in any one category. Noncommercial amphibole fibers were also present in excess concentrations in all 12 categories, ranging from 13% (maintenance workers) to 68% (shipyard workers) of individuals in any particular category. However, the percentage of individuals in a category with elevated levels of noncommercial amphiboles exceeded 50% in only 2 categories: shipyard workers and electricians. Chrysotile was present in excess concentrations in 9 of the 12 categories (not in pipefitters, construction workers, or other), ranging from 5% to 23% of the individuals in any one category. In none of the categories was chrysotile found in elevated concen-

TABLE 7 Lung Fiber Burden Analyses in 268 Mesothelioma Cases

	AB/gm[a]	AC[b]	TAA[b]	Chrys[b]	NAMF[b]
Industry					
Insulation	20.1 (0.12–1600)	246 (0.81–11900)	5.19 (1.11–19.7)	2.06 (0.87–124)	11.6 (2.24–19.7)
Asbestos mfg.	4.1 (0.9–322)	33 (14–755)	6.7 (1.7–90)	66.5 (43–90)	27 (3.2–54.1)
Shipbuilding	1.08 (0.006–436)	23.9 (0.24–2150)	4.56 (0.026–79.8)	4.8 (0.91–11)	10.3 (1.18–138)
Power plant	0.34 (0.013–21.9)	18.8 (0.92–200)	3.84 (0.73–2)	7.71 (1.19–14.2)	6.2 (2.4–19.5)
Construction	0.19 (0.002–83.5)	14.7 (0.48–268)	4.6 (0.48–15.7)	0.55 (0.48–0.6)	6.3 (0.6–85.2)
Steel/metal	0.48 (0.13–2.3)	8.4 (2.3–129)	2.6 (0.49–6.6)	ND	6.4 (0.49–23.9)
Oil and chemical	0.27 (0.018–2.8)	4.9 (1–39.3)	2.4 (0.67–6.9)	ND	6.4 (1.3–22.7)
U.S. Navy	0.17 (0.002–4.4)	4 (0.54–202)	3.3 (0.98–17.1)	3.1 (2–4.3)	8.3 (0.58–27.6)
Railroad	1.49 (0.005–5.7)	38.6 (2.95–48)	9.68 (8.85–27.3)	ND	17.7 (5.13–33.8)
Automotive	0.02 (0.003–1.5)	1.4 (0.12–17.3)	2 (0.24–9.8)	2.1 (0.72–2.18)	1.4 (0.34–18.5)
Papermill	NA	NA	NA	NA	NA
Ceramics/glass[c]	3.05	28.2	3.4	1.1	6.8
Occupation					
Maintenance	0.4 (0.013–15.9)	24.3 (0.32–316)	1.8 (0.63–17.1)	1.2 (1.19–1.26)	6.4 (1.3–18.5)
Pipefitter	2.2 (0.006–174)	24.2 (1.05–49.4)	5.2 (0.98–19.2)	ND	10 (0.85–31.7)
Boilermaker	1.68 (0.24–8.6)	21.3 (4.14–149)	8.49 (0.78–24.2)	1.45 (1.44–1.45)	7.3 (1.84–19.1)
Machinist	0.1 (0.002–1.8)	19 (0.98–48)	15 (2.9–27)	ND	5.1 (0.49–34)
Sheetmetal	0.78 (0.4–0.83)	6.2 (0.6–34.1)	5.8 (4.1–7.4)	ND	11 (7.4–18)
Electrician	1.4 (0.006–6.3)	5.5 (2.3–94.5)	5 (0.51–45)	5 (1.6–10.4)	6.7 (3.1–54)
Other asbestos	1.53 (0.1–3.9)	33.6 (2.0–33.7)	3.54 (0.66–17.3)	ND	4.0 (2.4–45)
Nonoccupational exposure					
Other	0.043 (0.001–11.5)	3.9 (1.02–54.9)	2.3 (1.05–43)	0.92	6.5 (0.48–28.1)
Household contacts	0.13 (0.002–14.1)	3.4 (0.45–116)	5.2 (0.98–22.4)	1.8	9.3 (0.24–14.6)
Building occupants	0.002 (0.002–1.1)	0.87 (0.38–43.8)	2.3 (1.1–4.1)	0.64	4.9 (1.5–36.8)
Environmental	0.7 (0.005–8.2)	ND	158 (1.7–455)	ND	5.1 (3.1–14.5)
Reference cases[d]	0.003 (0.002–0.022)	<0.6 (<0.1–<2.54)	<0.6 (<0.17–<2.54)	<0.6 (<0.1–<2.54)	<0.6 (<0.17–<2.54)

[a]Asbestos bodies per gram of wet lung tissue ($\times 10^3$) as determined by light microscopy. Values shown are medians with range in parentheses.

[b]Fibers 5 μm or greater in length per gram of wet lung tissue ($\times 10^3$) as determined by scanning electron microscopy and energy dispersive x-ray analysis. Values shown are medians for cases where fiber type was detected, with range in parentheses. When ranges are not shown, only one case had detectable levels of indicated fiber type.

[c]Tissue was available for fiber analysis in only one case of ceramics/glass plant worker.

[d]Ninteen cases with normal lungs, no history of asbestos exposure, and no evidence of asbestos related tissue injury at autopsy.

Note. AB, asbestos bodies; AC, commercial amphiboles (amosite + crocidolite); Chrys, chrysotile; gm, gram of wet lung; NA, no tissue available for analysis; NAMF, nonasbestos mineral fibers; ND, none detected; TAA, noncommercial amphiboles (tremolite + actinolite + anthophyllite).

trations in more than half of the individuals in that category.

Two of the categories deserve further comment. Household contacts of asbestos workers had tissue asbestos burdens that were similar to the median value for some occupational groups. For example, the median asbestos body count of household contacts (130 AB/g) was of the same order of magnitude as construction workers (190 AB/g). Hence, household contacts have tissue asbestos burdens that are on the average equivalent to mild to moderate occupational exposure [14, 15]. Wives tended to have higher lung asbestos burdens than daughters or sons. In contrast, the median asbestos body count for automotive brake repair workers was within our normal range. In many of these cases, the tissue asbestos content was completely within the limits of background. In those cases with an elevated tissue asbestos content, excess commercial amphibole fibers (mostly amosite) were invariably detected. Lung burden analyses in automotive brake repair workers reflect either a normal range tissue asbestos content or elevated commercial amphiboles [11, 17].

To further examine how the prevalence of plaques and asbestosis related to fiber burden, we used a logistic regression model to relate prevalence to the fiber burden of commercial amphiboles. The analysis demonstrated that both plaques and asbestosis were closely related to the natural logarithm of commercial amphibole counts ($P < .0001$), and the result allowed us to fit these relationships with 2 equations, one for the probability of plaques (Pplaq) and the second for the probability of asbestosis (Pasb). If we symbolize the logarithm of commercial amphiboles as Lca, then

$$\text{Pplaq} = \frac{1}{1 + \exp(3.36 - 0.393 * \text{Lca})} \quad (1)$$

$$\text{Pasb} = \frac{1}{1 + \exp(30.2 - 12.4 * \log(\text{Lca}))} \quad (2)$$

Figure 4 shows how these 2 compare over the range of Lca found in our cases. Clearly, this plot demonstrates that plques appear at lower fiber burdens

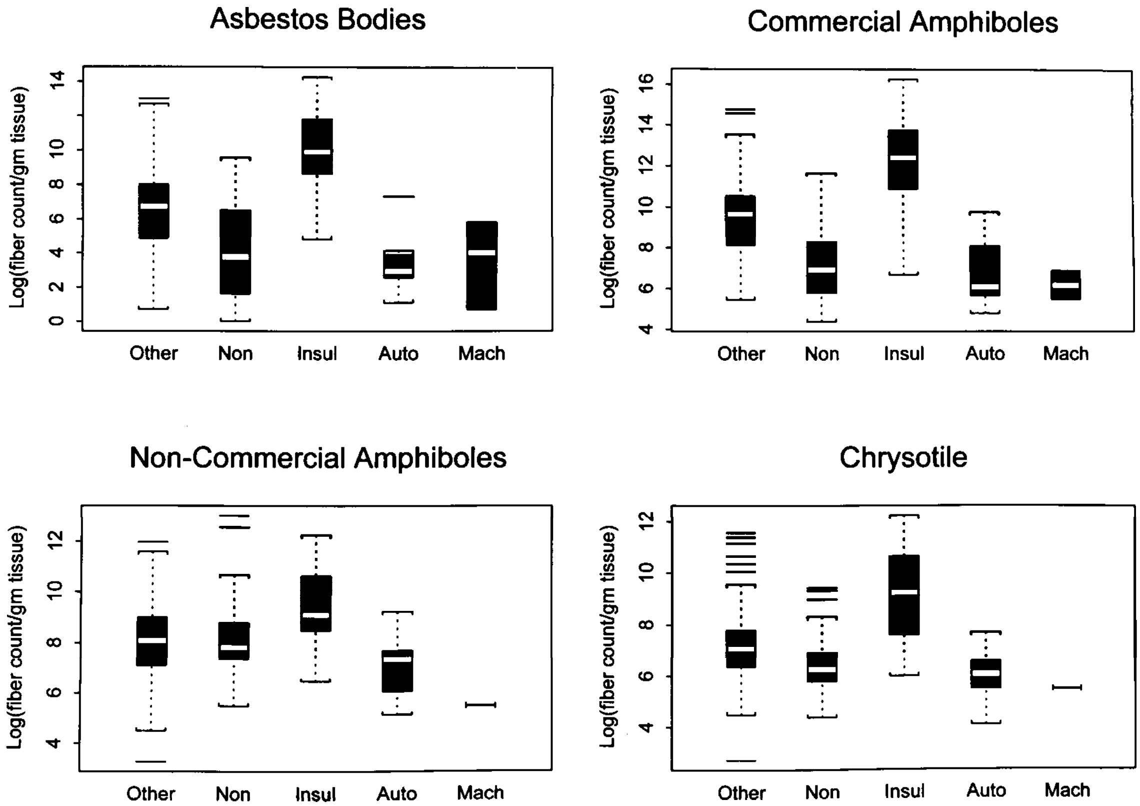

FIG. 2 *Boxplots of fiber burden for asbestos bodies* (upper left), *commercial amphiboles* (upper right), *noncommercial amphiboles* (lower left), *and chrysotile fibers. The vertical axis provides the fiber burdens in log* (number per gram), *and each plot provides the details for 5 industrial or occupational groups: nonindustrial exposure* (Non), *insulation industry* (Insul), *automobile industry* (Auto), *machinists* (Mach), *and all remaining groups* (Other). *The results inside the solid dark box provide the range from the 25th to 75th percentiles, and the white bars indicate the median value. The more distant brackets and lines above and below the solid boxes provide the full range and most peripheral values.*

than asbestosis. Asbestosis begins to become prevalent when the commercial amphibole fiber burden exceeds 22 000 per gram of tissue (Lca = 10). By contrast, at this level of amphiboles already 64% of cases have plaques. Thus, plaques are a sensitive marker for lower levels of fiber burden, and asbestosis does not occur until much larger fiber burdens. As a result of the above relationships among occupationally exposed individuals, the percentage of mesothelioma cases with asbestosis remained low at around 20% until the highest exposure category (insulators) was reached. At this point, the percentage increased to more than 60% of cases with histologically confirmed asbestosis. These findings indicate that there is a much higher threshold of asbestos exposure for asbestosis than for PPP, and this threshold is uncommonly met (about 20% of cases) for most exposure categories. The above models and equations suggest that with increasing fiber burden, all will eventually get asbestosis.

DISCUSSION

The current study extends our previous observations regarding mesothelioma and asbestos exposure by examining a large series of cases for which information was available regarding the patient's occupation or other exposure to asbestos. We have found that 94% of our cases had exposures in one or more of 12 different industries, 6 occupations, or 1 nonoccupational exposure. Exposure in more than 1 category was a common finding, observed in at least 26% of the industrial categories and 21% of the occupations. The most important nonoccupational exposure was as a household contact of an asbestos worker. The duration of exposure was typically on the order of decades, although we made no attempt in this regard to distinguish between intermittent and continuous exposures.

It could be argued that these cases are not representative of the types of exposures occurring in mesothelioma cases in the United States, since more than 90% of them are medicolegal cases. Therefore, it is of interest to compare our exposure groups with those obtained by the Australian Mesothelioma Surveillance Program [5]. The latter is a survey of all mesothelioma cases in Australia, and therefore does not suffer from any medicolegal selection bias. The top 14 groupings are shown arranged from greatest to least number of

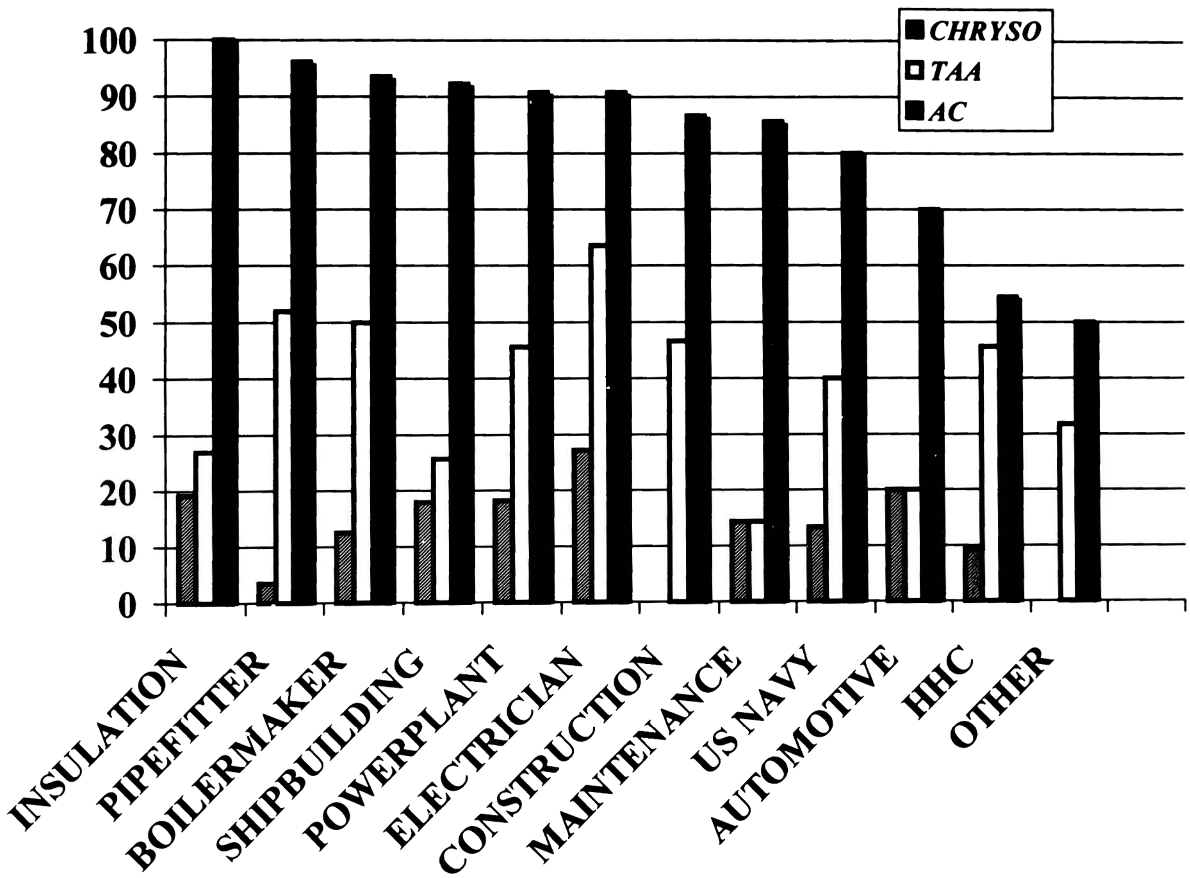

FIG. 3 *Histogram showing the percentage of cases in each category with elevated lung fiber burdens for commercial amphiboles* (AC)*, noncommercial amphiboles* (TAA)*, and chrysotile. Categories represented are those for which at least 10 cases with lung analyses in the given category were available. HHC, household contact.*

cases in Table 8. Carpenter/joiner would be included in our construction industry, as would builder/laborer. Waterside would be included in our shipbuilding industry, and plumber is included in our pipefitter occupation. Finally, asbestos dwelling is equivalent to our building occupant category, and brake lining to our automotive industry. It can be seen that, with the exception of mesothelioma cases related to working in the Wittenoom mine in Australia, the major categories of exposure are remarkably similar to those noted in our series of cases.

More than 90% of our cases occurred in men, reflecting the predominance of males in those occupations and industries most commonly associated with asbestos exposure. Women predominated among household contacts of asbestos workers, related to the laundering of work clothes by the spouses of workers occupationally exposed to asbestos [15, 16]. The median age for most groups was the seventh or eighth decade, consistent with the long latency period for the development of mesothelioma and initial exposure during adulthood [8]. Exceptions to this included household contacts and insulators. The former is due to exposure of some household contacts during childhood. The latter suggests the possibility of an inverse relationship between dose and latency for mesothelioma. In addition, pipefitters and railroad workers were significantly older (Figure 1). The latter may be due to the fact that most railroad exposures occurred prior to 1958 (i.e., during the steam era).

The highest percentage of peritoneal mesotheliomas occurred among workers involved with the manufacture of asbestos products and insulation workers (Table 6). The percentages, however, did not reach the level reported by Selikoff et al., in which the ratio of peritoneal to pleural tumors among insulators was 3:1 [1, 2]. Insulators and asbestos plant workers also had the highest lung asbestos fiber burdens, which is consistent with the observation that, on the average, peritoneal mesotheliomas are associated with higher doses than are pleural mesotheliomas [7]. The observations are consistent with a model in which the pleural and peritoneal mesothelial cells are equally susceptible to the development of mesothelioma, and the probability is, in turn, related to the dose. At sufficiently high exposure levels, the dose to the peritoneum is high enough that the probability of a peritoneal origin approaches that of a pleural origin [18].

Pleural plaques were found in a high percentage of cases (78% of informative cases for the whole series),

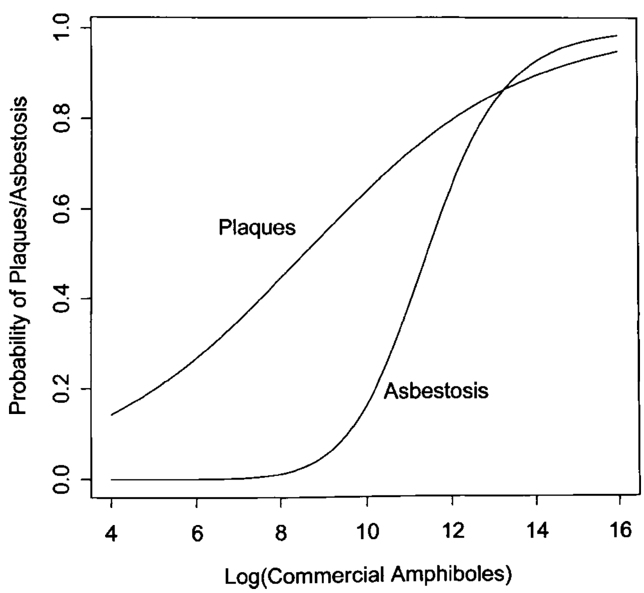

FIG. 4 *Plots of the probability of either observing pleural plaques or asbestosis on the vertical scale versus log* (commercial amphiboles) *found per gram of tissue on the horizontal scale. The lines provide a graphical picture of the results of two logistic regression equations* (see equations 1 and 2)*, one for the probability of observing plaques* (left curve, as noted) *and one for the probability of observing asbestosis* (right curve, as noted).

lending further support to the proposition that a high percentage of our cases are asbestos related. Furthermore, there was evidence for a dose response, with a higher percentage of plaques observed with increasing levels of commercials amphibole fibers

TABLE 8 Australian Mesothelioma Registry Report—1999

	Single	Multiple	Total
Carpenter/joiner	187	33	220
Wittenoom	189	25	214
Builder/laborer	150	27	177
Navy	100	43	143
Asbestos mfg.	99	33	132
Shipbuilding	79	53	132
Railways	89	36	125
Boilermaker	77	40	117
Power plant	76	39	115
Waterside	70	8	78
Plumber	62	13	75
Asbestos dwelling	66	6	72
Brake lining	58	12	70
Fitter/turner	51	16	67

Source. From [5].

(Figure 4). In contrast, asbestosis was observed less commonly (24% of informative cases for the whole series), again with evidence for a dose response (Figure 4). These findings are consistent with our prior observation that pleural plaques and mesothelioma require less exposure to asbestos than is typically associated with the development of asbestosis [11].

The results of fiber burden analysis are consistent with our prior observation that amosite is the most common fiber type associated with mesothelioma among U.S. workers [6]. Furthermore, the present study shows that amosite predominance extends over most occupational exposure groups (Figure 3), consistent with the widespread use of amosite-containing insulation products in these industries in the past. However, among nonoccupational exposures, noncommercial amphiboles predominated (Table 7). Chrysotile was infrequently identified in any exposure group, consistent with its tendency to break down into smaller fibrils that are more readily removed from the lungs [19].

Environmental or neighborhood exposures appear to be a very uncommon cause of mesothelioma, based on our observations. The 4 cases we studied in this category included 3 from the southern Anatolian region of Turkey that were exposed to high levels of tremolite and actinolite in the local environment[20]. The only U.S. case we studied had a fiber burden indistinguishable from background. Similarly, exposure to asbestos as a building occupant is also an infrequent cause of mesothelioma. Among the 6 cases of building occupants for which a fiber analysis was performed, 3 had a modestly elevated content of noncommercial amphiboles and 3 had levels indistinguishable from background. The finding of low levels of noncommercial amphiboles is consistent with an exposure to predominantly chrysotile asbestos in this setting [21].

Only 1 occupational exposure group contained on average more noncommercial amphibole fibers than commercial amphibole fibers. This was the category of automotive brake repair workers. In this group, fiber burden analyses performed on 11 cases showed either an elevated amosite content or an asbestos concentration indistinguishable from background. Workers in this category frequently were exposed to asbestos in other categories as well (Table 1), and none had asbestosis (Table 6). Among 15 workers exposed to brake dust who also had plaques, 10 had additional exposures in jobs or industries where commercial amphiboles predominated, and 3 additional cases had elevated commercial amphiboles in their lung tissue samples. Lung tissue was not available for analysis in the other 2. These findings are consistent with our prior observations of brake repair workers with mesothelioma [11, 17, 22], and with the nature of brake dust, which contains low levels of short chrysotile fibers [23]. These observations in combination with a negative case control study [24] indicate that brake dust is unlikely to cause mesothelioma.

Another group of interest is individuals exposed to crocidolite fibers from smoking Kent cigarettes, the micronite filters of which contained crocidolite for a

4-year period during the early 1950s [16]. We have performed fiber analyses on lung tissue samples from 4 such cases. For 3 of these, smoking Kents (or pretending to smoke Kent cigarette butts as a child) was the only known exposure to asbestos (these cases are included in the ''Other'' category in Table 3). One case that also had an exposure as a household contact had low levels of amosite in her lung samples. None of the 4 cases had detectable crocidolite. Based on these analyses, smoking Kent cigarettes seems to be an unlikely cause of mesothelioma.

Nonasbestos mineral fibers were found in roughly similar amounts among each of the exposure categories (Table 7). These include talc, silica, rutile, aluminium silicates, metallic fibers, apatite, and manmade mineral fibers [11, 25, 26]. There is no evidence that these fibers contribute to the development of mesothelioma [27]. A possible exception is refractory ceramic fibers, which have produced a high rate of mesothelioma in inhalation exposure studies and have been associated with the development of pleural plaques in humans [28, 29]. These fibers have a greater biologic persistence than most other manmade mineral fibers [30]. We have identified refractory ceramic fibers in lung tissue samples from 6 patients with mesothelioma, and in 2 cases, they were the most frequent fiber type identified. In both cases, however, commercial amphibole fibers were also present in excess amounts. Insufficient information is presently available to implicate manmade mineral fibers (including refractory ceramic fibers) as a cause of mesothelioma in humans [31].

REFERENCES

1. Selikoff IJ, Lee DHK. *Asbestos and Disease.* New York: Academic; 1978.
2. Selikoff IJ, Hammond EC, eds. Health hazards of asbestos exposure. *Ann NY Acad Sci.* 1979;330:1–811.
3. Landrigan PJ, Kazemi H, eds. The third wave of asbestos disease: exposure to asbestos in place: public health control. *Ann NY Acad Sci.* 1991;643:1–625.
4. Otto H. Das berufsbendingte Mesotheliom in der BRD. *Pathologe* 1980;2:8–18.
5. Australia Mesothelioma Register. *The incidence of Mesothelioma in Australia: Australian Mesothelioma Register Report, 1996, 1998, 1999. Camperdown, NSW: National Occupational Health and Safety Commission.*
6. Roggli VL, Pratt PC, Brody AR. Asbestos fiber type in malignant mesothelioma: an analytical scanning electron microscopic study of 94 cases. *Am J Ind Med.* 1993;23:605–614.
7. Roggli VL, Malignant mesothelioma and duration of asbestos exposure: correlation with tissue mineral content. *Am Occup Hyg.* 1995;39:363–374.
8. Roggli VL, Sanfilippo F, Shelburne JD. Mesothelioma. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases.* Boston: Little, Brown; 1992:109–164.
9. Greenberg SD. Benign asbestos-related pleural diseases. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases.* Boston: Little, Brown; 1992:165–187.
10. Roggli VL, Pratt PC. Asbestosis. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases.* Boston: Little, Brown; 1992:77–108.
11. Roggli VL, Pratt PC, Brody AR. Analysis of tissue mineral fiber content. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases.* Boston: Little, Brown; 1992:299–345.
12. Roggli VL. Asbestos bodies and nonasbestos ferruginous bodies. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases.* Boston: Little, Brown; 1992:39–75.
13. Roggli VL, Greenberg SD, Seitzman LH, et al. Pulmonary fibrosis, carcinoma, and ferruginous body counts in amosite asbestos workers: a study of six cases. *Am J Clin Pathol.* 1980;73:496–503.
14. Wain SL, Roggli VL, Foster WL. Parietal pleural plaques, asbestos bodies, and neoplasia: a clinical, pathologic, and radiographic correlation of 25 consecutive cases. *Chest.* 1984;86:707–713.
15. Gibbs AR, Griffiths DM, Pooley FD, et al. Comparison of fiber types and size distributions in lung tissues of papaoccupational and occupational cases of malignant mesothelioma. *Br J Ind Med.* 1990;47:621–626.
16. Roggli VL, Oury TD, Moffatt EJ. Malignant mesothelioma in women. In: Fechner RE, Rosen PP, eds. *Anatomic Pathology.* Chicago: ASCP; 1997:147–163.
17. Srebro SH, Roggli VL, Samsa GP. Malignant mesothelioma associated with low pulmonary tissue asbestos burdens: a light and scanning electron microscopic analysis of 18 cases. *Mod Pathol,* 1995;8:614–621.
18. Hodgson JT, Darnton A. The quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg,* 2000;44:565–601.
19. Roggli VL, Brody AR. Changes in numbers and dimensions of chrysotile asbestos fibers in lungs of rats following short-term exposure. *Exp Lung Res.* 1984;7:133–147.
20. Zeren EH, Gumurdulu D, Roggli VL, Tuncer I, Zorludemir S, Erkisi M. Environmental malignant mesothelioma in Southern Anatolia: a study of 50 cases. *Environ. Health Persp.* 2000;108:1047–1050.
21. Gaensler EA. Asbestos exposure in buildings. *Clin Chest Med.* 1992;13:231–242.
22. Roggli VL. Fiber analysis. In: Rom WN, ed. *Environmental and Occupational Medicine.* philadelphia, Lippincott-Raven;1998: 335–347.
23. Williams RL, Muhlbaier JL. Asbestos brake emissions. *Environ Res.* 1982;29:70–82.
24. Woitowitz H-J, Rodelsperger K. Mesothelioma among car mechanics. *Ann Occup Hyg.* 1994;38:635–638.
25. Churg A. Nonasbestos pulmonary mineral fibers in the general population. *Environ Res* 1983;31:189–200.
26. Roggli VL. Nonasbestos mineral fibers in human lungs. In: Russell PE, ed. *Microbeam Analysis—1989.* San Francisco: San Francisco Press; 1989:57–59.
27. McDonald JC, Armstrong B, Case B, et al. Mineral fibre content of lung in mesothelial tumours in North America. *Cancer.* 1989;63:1544–1547.
28. Miller WC, Hesterberg TW, Hamilton RD. Oncogenicity study of respirable refractory ceramic fibers (RCF) in hamsters. *MTC Report 092518.* Littleton, CO: Mountain Technology Center; 1991:1–69.
29. Lockey J, Lemasters G, Rice C, et al. Refractory ceramic fiber exposure and pleural plaques. *Am J Respir Crit Care Med.* 1996;154:1405–1410.
30. McConnell EE, Mast RW, Hesterberg TW, et al. Chronic inhalation toxicity of a Kaolin–based refractory ceramic fiber in Syrian golden hamsters. *Inhalation Toxicol.* 1995;7:503–532.
31. Rodelsperger K, Jockel J-H, Pohlabeln H, et al. Asbestos and manmade vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study. *Am J Ind Med.* 2001;38:1–14.