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Potential Significance of Airborne Fiber Dimensions Measured in the U.S. Refractory Ceramic Fiber Manufacturing Industry

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Background *To determine dimensions of airborne fibers in the U.S. refractory ceramic fiber (RCF) manufacturing industry, fibers collected through personal air sampling for employees at RCF manufacturing and processing operations have been measured.*
Methods *Data were derived from transmission electron microscopy analyses of 118 air samples collected over a 20-year period.*
Results *Characteristics of sized fibers include: diameter measurements of < 0.19 to 1.0 μm, of which 75% are less than 0.6 μm; and length ranging from < 0.6 to > 20 μm, with 68% of fibers between 2.4 and 20 μm.*
Conclusions *Exposures in RCF manufacturing include airborne fibers with dimensions (diameter < 0.1–0.4 μm, length < 10 μm) historically associated with biological effects in pleural tissues. Air sampling data and a review of studies relating fiber size to pleural effects in animals and humans support the belief that information on fiber dimensions is essential for studies with synthetic vitreous fibers.* Am. J. Ind. Med. 36:286–298, 1999.

KEY WORDS: airborne fiber; electron microscopy; man-made vitreous fiber; occupational exposure; pleural plaque; refractory ceramic fiber; synthetic vitreous fiber

INTRODUCTION

Refractory ceramic fiber (RCF) is a synthetic vitreous fiber (SVF) used in industrial applications requiring lightweight and heat-resistant insulation (e.g., furnace and kiln insulation). Annual domestic production of RCF at the beginning of this decade was estimated at 85.7 million pounds [TIMA, 1990]; in 1997, U.S. production of RCF totaled approximately 107.7 million pounds [RCFC, 1998]. This amount comprises approximately 1–2% of the worldwide production of SVFs, which also include mineral wool and glass fiber. Increasing production of RCF and other types of SVF since the 1970s has created interest in investigating any potential respiratory effects for persons exposed to airborne fibers during manufacturing. While RCF differs from naturally occurring mineral fibers according to physical and chemical characteristics, one hypothesis supported by the literature is that fiber toxicity is determined by dose of durable fibers of specified dimensions reaching target tissues of the respiratory system [Davis, 1986; Harris and Timbrell, 1977; Lippmann, 1988; Mast et al., 1995a,b; Stanton et al., 1981]. The importance of

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describing fiber size distributions in occupational settings and quantifying the dose to target organs for exposed workers has been recognized as a priori risk criteria for assessing the biological activity of these fibers [Bignon et al., 1995].

Animal studies have indicated that inhalation of RCF at the maximum tolerated dose (approximately 220 fibers/cm^3) induces mesothelioma, lung cancer, and pleural and pulmonary fibrosis [Bunn et al., 1993; Mast et al., 1995a; McConnell et al., 1995]. In a retrospective cohort study of workers at RCF manufacturing sites, Lockey et al. [1996] showed a progressive relationship between cumulative fiber exposure and the occurrence of pleural plaques. Changes in pulmonary function have also been observed with occupational exposure to RCF [Lockey et al., 1998], and in a cohort from the RCF manufacturing industry (n = 742) the prevalence of one or more respiratory symptoms (e.g., cough, dyspnea, wheezing, asthma) among production workers was found to be two to five times higher than for non-production workers [Lemasters et al., 1998]. The increased prevalence of symptoms among production workers is consistent with that seen in comparable dust-exposed populations.

In this context, an investigation was conducted with the following objectives: (1) to describe airborne fiber size distributions derived from air samples collected at RCF manufacturing and processing facilities and analyzed by transmission electron microscopy; (2) to review current literature for studies of fiber dimensions as related to fiber toxicity and respiratory system effects, specifically pleural plaques; and (3) to assess the potential significance of the dimensions of airborne RCF as a factor affecting respiratory health.

MATERIALS AND METHODS

Description of Manufacturing Processes

Although individual production processes vary slightly by plant, all RCF products originate from the manufacture of ceramic fiber, shown in the flow diagram in Figure 1. This process begins with blending of raw materials, which may include kaolin clay, alumina, silica or zirconia in a batch house. The batch mix is then transferred manually or automatically to a furnace where the batch is melted at temperatures above 1600°C. After reaching a specified temperature and viscosity, the molten mixture drains from the furnace and is fiberized either through exposure to pressurized air (blowing process) or by flowing through a series of spinning wheels (spinning process) [Hill, 1983]. Fans are used to create a partial vacuum which pulls the fibers into a collection or settling chamber. RCF may then be conveyed pneumatically to a bagging area for packaging as bulk fiber; some bulk fiber may be used directly in this form, while it may also be processed to form textiles, felts, boards, cements, and other specialty products. Other RCF is formed into blankets as bulk fiber in the collection chamber settles onto a conveyor belt. The blanket passes through a needle felting machine which interlocks the fibers and compresses the blanket to specified thickness. From the needler, the blanket is conveyed to a tempering oven to remove

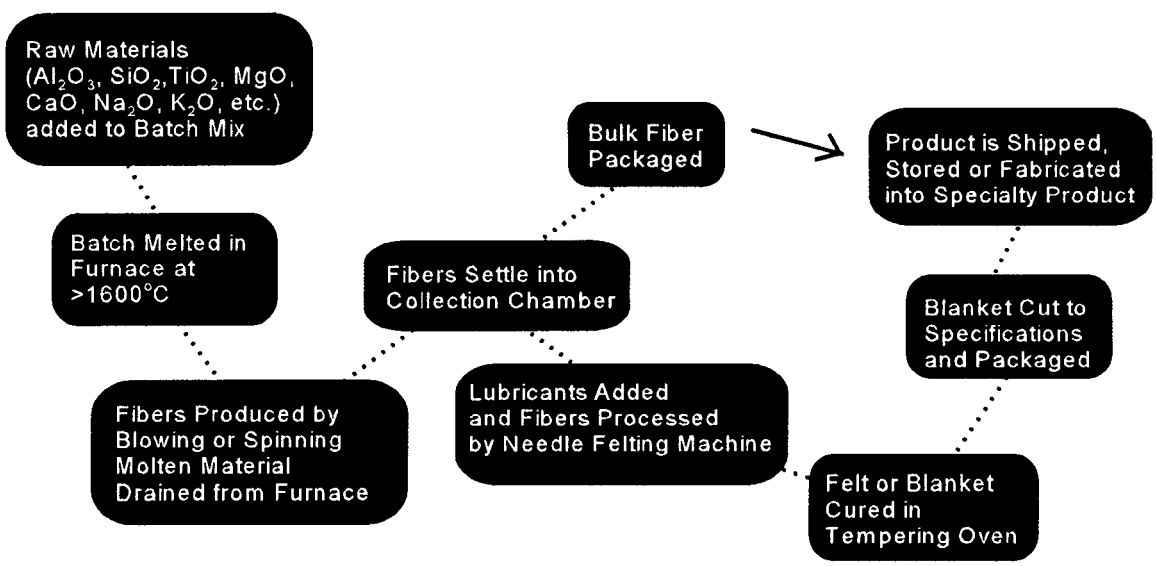


FIGURE 1. Process flow chart of RCF production.

lubricants which were added in the settling chamber. Finally, the blanket is cut to desired size and packaged. As with bulk fiber, RCF blanket may be fabricated into specialty products.

Many manufacturing processes are automated and are monitored by machine operators. Post-production processes (cutting, sanding, packaging, handling and shipping) are more labor intensive. Throughout production there is potential for exposure to airborne fibers. In the U.S., over 700 workers are employed in the manufacture of RCF and RCF products [RCFC, 1992].

Literature Review

A review of the literature was performed to identify studies of exposures to RCF and asbestos which provide information on fiber dimensions and pleural effects. The decision to include asbestos fibers in this review was based on the hypothesis that fiber toxicity is determined not by fiber type alone, but by dose of durable fibers of specified dimensions reaching target tissues of the respiratory system. The objective was to determine critical fiber dimensions which might be associated with effects in the respiratory system, and in particular the pleura.

Air Sampling Data

A total of 118 air samples analyzed by transmission electron microscopy (TEM) were available from three independent studies, all conducted at the same U.S. RCF manufacturing or processing plants between 1976 and 1995 [Esmen et al., 1979; MacKinnon et al., 1993; Maxim et al., 1997]. Although additional air samples analyzed by phase contrast microscopy (PCM) and scanning electron microscopy (SEM) were also available, only those analyzed by TEM were used, based on the ability of this method to detect the smallest diameter fibers. TEM has a resolving capability of 0.0003 μm, while the limits of resolution with PCM and SEM (0.25–0.4 μm) do not ensure that the smallest fibers will be detected and sized [Dement and Wallingford, 1990]. A photomicrograph of a refractory ceramic fiber (JEOL JEM 2000FX microscope, 7,500 × magnification) is presented in Figure 2. Air sampling materials and methods are described below for the three sampling studies conducted at RCF manufacturing plants in 1976, 1988–1991, and 1993–1995, and are summarized in Table I. A previous study has reported on changes in airborne concentration of fibers at these facilities over time related to process or ventilation modifications [Rice et al., 1996]. While too few data on

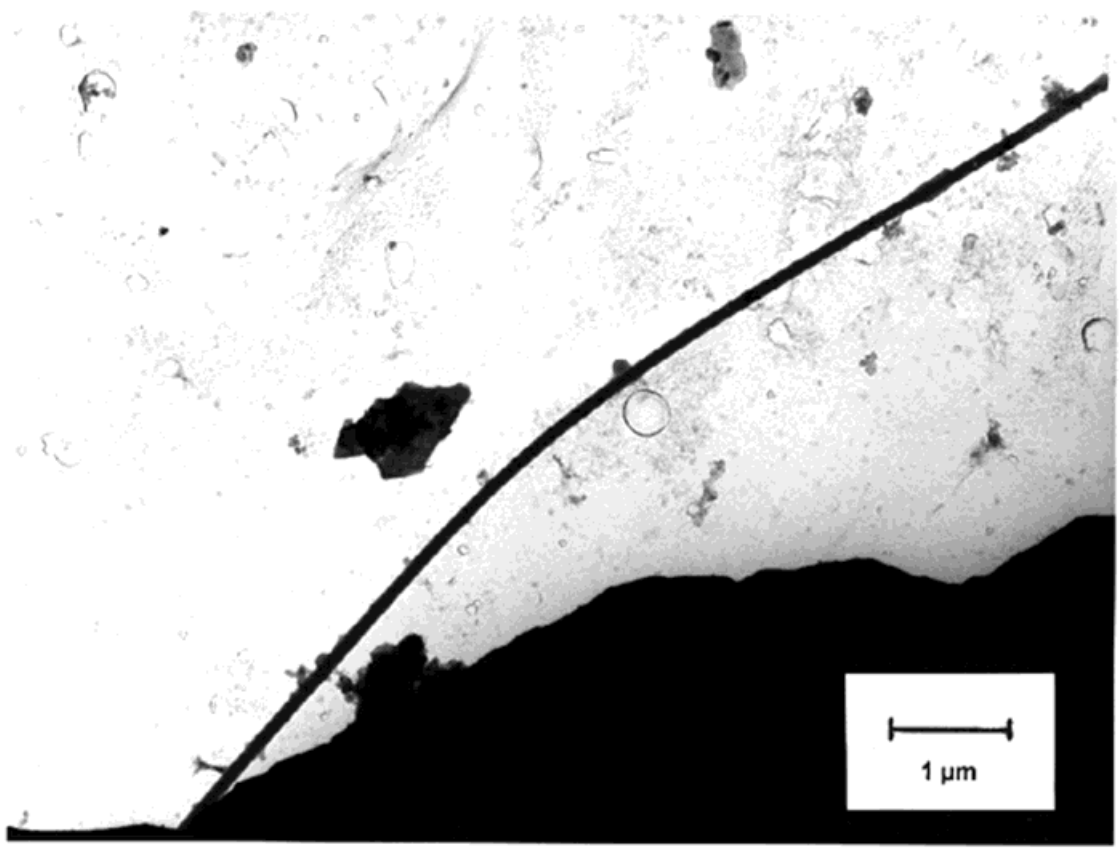


FIGURE 2. Photomicrograph of refractory ceramic fiber at magnification of 7,500 × (JEOL JEM 2000F × microscope).

TABLE I. Materials and Methods Used for Air Sampling and Analysis in the Three Studies of Refractory Ceramic Fiber Workers, 1976–1995

Study period (years)	Sampling media	Flow rate (Lpm)	Microscopy technique	Identification and sizing protocol
Study period A (1976) 67 samples [Esmen et al., 1979]	Sampling cassette with 37 mm diameter membrane filter (0.8 μm pore size) and support pad	2.0	TEM at magnification of 10,000 ×	Fibers defined as having an aspect ratio > 3:1. TEM used to measure fibers ≤ 1 μm in diameter. EDXA[a] used to identify fiber chemistry
Study period B (1988–1991) 28 samples [Mackinnon et al., 1993]	50 mm cowl with 25 mm diameter MCE filter (0.45 μm pore size) and support pad	1.5–2.0	TEM at magnification of 20,000 ×	Fibers defined as having an aspect ratio ≥5:1 and length >0.5 μm were sized by TEM. SAED[b] and EDXA[a] used to determine crystallography and chemistry
Study period C (1993–1995) 23 samples [Maxim et al., 1997]	50 mm sampling cowl with 25 mm MCE filter (0.45 μm pore size) and support pad	0.5–2.5	TEM at magnification of 15,000–25,000 ×	Fibers defined as having an aspect ratio ≥3:1 and diameter < 3 μm. SAED[b] used for crystallography (no pattern) and EDXA[a] for identification by chemistry (i.e. aluminum to silica ratio between 1:1 and 4:10)

[a]Energy dispersive x-ray analyzer.
[b]Selective area electron diffraction.

airborne fiber dimensions at present preclude identification of changes in fiber size over time, analyses of archived air samples may eventually allow this type of investigation.

Study period A (1976)

The earliest exposure monitoring data were obtained from TEM analysis of 67 air samples collected in June 1976 at RCF manufacturing facilities. Sampling was performed using a strategy of grouping workers into representative exposure zones, or dust zones. A dust zone is defined as the characteristic grouping of workers based on their job similarity and the similarity of the environment in which they work [Corn and Esmen, 1979]. Examples of specific zones include: maintenance, in which persons with the job titles of electrician, mechanic, and millwright are classified; and shipping, under which the fork lift operator is classified. The purpose of the dust zone method is to reduce the number of required samples while increasing the confidence of identifying workers at similar risk. From the dust zones, workers were selected to wear a personal sampling pump connected to a sampling cassette positioned in the worker's breathing zone. Sampling cassettes were equipped with a 37 mm diameter membrane filter (0.8 μm pore size) and a support pad for collecting airborne fibers. Sampling flow rates averaged 2.0 liters per minute (Lpm). To determine size characteristics of airborne fibers, laboratory analysis of air samples included the use of both PCM and TEM techniques on sections of each sample filter. For sizing purposes, a fiber was considered to be any particle having an aspect ratio (length to width) equal to or greater than 3:1 according to conventional methods for identifying asbestos fibers [Edwards and Lynch, 1968; NIOSH, 1972]. Fibers measuring ≤1 μm in diameter were measured by TEM in order to identify the proportion of submicron diameter fibers which might otherwise be missed by PCM alone. The fiber size distribution for the study was then calculated by matching results obtained from TEM and PCM analyses of the same sample [Esmen et al., 1979]. Samples were analyzed by TEM at a magnification of 10,000 ×, and fibers measuring <0.2 μm in diameter were subjected to electron beam diffraction to determine if these were crystalline or amorphous. RCF are amorphous and therefore are identified by the absence of selective area electron diffraction (SAED) patterns which are visible in crystalline fibers. The chemical composition of a representative sample was also tested using SEM equipped with an energy dispersive x-ray analyzer (EDXA). Data from this early study were provided for this investigation by the sponsor, the Refractory Ceramic Fiber Coalition (RCFC), formerly the Thermal Insulation Manufacturers Association (TIMA).

Study period B (1988–1991)

Data from the second sampling period were derived from 28 personal air samples collected at U.S. RCF manufacturing facilities and analyzed by TEM to determine if airborne fiber concentrations included small diameter fibers. According to the sampling protocol, 10% of those persons sampled (or 1% of the entire workforce) were requested to wear a pump for collection of samples to be analyzed for fiber size distributions. Workers were randomly

selected for sampling each quarter using a weighted process to ensure that all job categories with potential for RCF exposure were represented [Rice et al., 1994]. Dust zones were defined at the onset of the study, after the practice used by Corn and Esmen [1979]. Sampling was conducted according to a modified NIOSH Analytical Method 7400 [NIOSH, 1989], using a personal sampling pump attached to cassettes positioned within the breathing zone of the worker being sampled. Air samples were drawn through the cassettes, which consisted of reusable, nickel-plated, conductive cowls and 25 mm diameter mixed cellulose ester (MCE) membrane filters (0.45 μm pore size) with support pads. The use of the special cowls was implemented based on observations that significant background populations of fibers can be found on unused electrically conductive plastic cowls [Cornett et al., 1989; Breysse et al., 1990]. Sampling flow rate ranged between 1.5 and 2.0 Lpm. Samples were shipped to an independent, accredited laboratory for analysis by TEM (magnification = 20,000 ×), and fibers were defined as having an aspect ratio ≥ 5:1 and length > 0.5 μm. Fibers were identified as RCF by analyses of the chemistry and crystallography of a representative sample using EDXA and SAED techniques.

Study period C (1993–1995)

A third set of sampling data was made available by Everest Consulting through the sponsor, the RCFC. Air sampling data from 23 samples collected for TEM analysis during the third sampling period (1993–1995) were obtained using a sampling protocol developed to ensure monitoring of representative workers from eight functional job categories [Maxim et al., 1997]. Sampling equipment included 25 mm diameter MCE filters (0.45 μm pore size) with support pads in commercially available 50 mm long conductive cowls. Flow rate for sample collection averaged between 0.5 and 2.5 Lpm. Samples were shipped to an independent, accredited laboratory where these were analyzed using TEM at 15,000–20,000 × magnification. All fibers having an aspect ratio ≥ 3:1 and diameter < 3 μm were measured. Fibers were identified as RCF according to morphology (electron dense, blunt-ended, highly parallel sided, round in cross section); chemistry (aluminum to silica ratio between 1:1 and 4:10); and crystallography (no SAED patterns).

Data Analysis

Laboratory analyses of the airborne fibers provided data on the diameter and length of each fiber identified and sized. Bivariate (diameter and length) distributions of fibers were determined using SAS® software (version 6.03 for the personal computer) and graphed for comparison. Fibers were categorized according to size characteristics using the diameter and length categories which were established for the initial air sampling study [Esmen and Corn, 1979]. Fiber diameter was grouped according to five categories ranging from < 0.19 to 0.8–1.0 μm. Fiber length was divided into seven categories ranging from < 0.59 to >19.99 μm. Fibers with diameter >1.0 μm were present in the data sets from Study periods B and C, accounting for 20% and 33% of the total fibers in these sets, respectively. These were excluded from the data analysis to allow comparison with data from Study period A, which had an upper diameter limit of 1.0 μm for fibers identified and sized by TEM.

RESULTS

Review of Literature on Fiber Dimensions and Pleural Effects

Table II presents a summary of studies relating RCF and asbestos fiber dimensions to specific respiratory system effects. Asbestos fiber dimensions associated with pleural changes (pleural plaques, pleural fibrosis, pleural effusion, and mesothelioma) are listed for nine studies with humans or animals. Dimensions of fibers noted with these effects ranged from 0.03 to ≤1.5 μm in diameter and 0.85 to > 8 μm in length. In four studies with pleural plaques as the primary effect examined [Churg and DePaoli, 1988; Churg et al., 1993; Dodson et al., 1990; LeBouffant et al., 1973], associated asbestos fibers measured 0.03–0.23 μm in diameter and 0.85–3.0 μm in length. In two animal studies with RCF, fiber dose and size are related to pleural fibrosis, pleural inflammation and mesothelioma. RCF diameter ranged from 0.09–0.5 μm, and length ranged from 1.5 to 20 μm [Gelzleichter et al., 1996; Mast et al., 1995b].

Among studies in Table II, one analysis of pleural plaques revealed the presence of fine, short asbestos fibers (diameter < 0.03 μm, length < 2 μm) [LeBouffant et al., 1973]. In another study of 29 individuals with asbestos exposure, over 100 samples of lung parenchyma and parietal pleura tissues were analyzed for fiber content and size; mean fiber sizes in the pleura were 0.06 μm in diameter and 2.3 μm in length [Sébastien et al., 1979]. A predominance of short chrysotile fibers led researchers to conclude that fiber retention in the pleura was type- and size-related.

Churg and DePaoli [1988] examined four cases of pleural plaques found at autopsy in residents of Thetford Mines, Quebec, a chrysotile mining town. None of the cases had reported having worked in the chrysotile mining and milling industry. Fiber sizes and concentrations were examined for the cases and for nine control individuals without plaques. It is noted that fibers were identified in lung tissue samples from central and peripheral upper and lower lobes; no plaque tissue was examined. Fibers found in the lungs of cases and controls did not differ significantly in size. However, lung tissues of cases had a statistically

TABLE II. Studies of Exposures to Asbestos or RCF Which Include Fiber Dimensions and Pleural Effects.

Study authors	Experimental design	Fiber type	Critical dimensions	Pleural effects
Data from the asbestos literature				
LeBouffant et al., 1973	Clinical analysis of human pleural tissue	Asbestos	$L<2\ \mu m$; $D<0.03\ \mu m$	Pleural plaques
Sébastien et al., 1979	Clinical analysis of human pleural tissue	Asbestos (chrysotile)	$L = 2.3\ \mu m$; $D = 0.06\ \mu m$	Pleural effusion, pleural fibrosis, mesothelioma
Stanton et al., 1981	Implantation of fibers in pleural cavity of rats	Asbestos AlO_2 fibers	$L>8\ \mu m$; $D<0.25\ \mu m$ $L\geq 4\ \mu m$; $D\leq 1.5\ \mu m$	Pleural sarcoma
Churg and DePaoli, 1988	Clinical analysis of human pleural tissue	tremolite chrysotile	$L = 2.4\ \mu m$; $D = 0.15\ \mu m$ $L = 2.5\ \mu m$; $D = 0.03\ \mu m$	Pleural plaques
Lippmann, 1988	Review of scientific literature	Asbestos	$L>5\ \mu m$; $D<0.1\ \mu m$	Mesothelioma
Timbrell, 1989	Review of scientific literature	Asbestos	$D<0.1\ \mu m$	Mesothelioma
Dodson et al., 1990	Autopsy of lung and pleural tissue from former shipyard workers	Amphibole chrysotile	$L = 1.05\ \mu m$; $D = 0.14\ \mu m$ $L = 0.85\ \mu m$; $D = 0.06\ \mu m$ (Fewer than <10% of fibers in plaques had length $>5\ \mu m$)	Pleural plaques
Gibbs et al., 1991	Clinical analysis of human pleural tissue	Asbestos (all) Amosite	$L = 0.99\ \mu m$; $D = 0.06\ \mu m$ $L = 1.23\ \mu m$; $D = 0.17\ \mu m$	Pleural fibrosis
Churg et al., 1993	Clinical analysis of fiber types, dimensions in human lung tissue	Asbestos (tremolite)	$L = 3.0\ \mu m$; $D = 0.23\ \mu m$	Mesothelioma, pleural plaques
Data from RCF literature				
Mast et al., 1995b	Animal study utilizing rats exposed to fibers by nose-only inhalation	RCF	$L = 5$–$10\ \mu m$, 10–$20\ \mu m$ $D\leq 0.5\ \mu m$ (retained)	Pleural fibrosis, lung neoplasm, mesothelioma
Gelzleichter et al., 1996	Animal study utilizing rats exposed to fibers by nose-only inhalation	RCF	$L = 1.5\ \mu m$; $D = 0.09\ \mu m$	Pleural inflammation

significant fourfold elevation in tremolite fiber concentrations. The authors concluded that the amphibole tremolite, and not chrysotile, was responsible for the plaques. Mean sizes of tremolite fibers in the lung tissue of cases were 0.15 μm (GSD ≈ 2.1) in diameter and 2.4 μm (GSD ≈ 1.9) in length. Mean sizes of the chrysotile fibers from lung tissue of cases were smaller in diameter [0.03 μm (GSD ≈ 1.2)], but were similar in length [2.5 μm (GSD ≈ 2.2)].

In another study of 94 long-term chrysotile miners in the same region, Churg et al. [1993] examined whether fiber type, concentration, and size from lung tissues correlate with the presence of asbestos-related disease. Again, lung tissues examined did not include the parietal pleura. The authors suggested that the tremolite fiber was responsible for airway fibrosis, asbestosis and probably mesothelioma, although no strong correlation was observed between these disorders and fiber dimensions. It was also concluded that mean fiber parameters (length and aspect ratio) appeared to be of importance only in the development of pleural plaques. Tremolite fibers associated with pleural plaques had a mean diameter of 0.23 μm, with a mean length of 3.0 μm.

The relative importance of asbestos fiber type (amphibole versus serpentine) in reaching target tissues and inducing biological effects was studied by Dodson et al. [1990], who examined autopsy samples from eight former shipyard workers. Amphibole and serpentine (chrysotile) fibers were found in lung parenchyma, tracheal lymph nodes and plaque tissue, with chrysotile being the predominant asbestiform mineral in plaques. Chrysotile fibers found in plaque tissues had a geometric mean diameter of 0.06 μm and geometric mean length of 0.85 μm. Only 3.1% of the

TABLE III. Distribution of Airborne Fibers by Diameter and Length (in μm) for Study period A (1976).

	D (μm)					
L (μm)	<0.19	0.19–0.39	0.4–0.59	0.6–0.79	0.8–1.0	Totals
<0.59	4 (0.1%)	0	0	0	0	4 (0.1%)
0.59–1.19	18 (0.6%)	10 (0.4%)	0	0	0	28 (1%)
1.2–1.79	35 (1.3%)	55 (2%)	21 (0.7%)	0	0	111 (4%)
1.8–2.39	53 (1.9%)	68 (2.4%)	48 (1.7%)	12 (0.4%)	0	181 (6.5%)
2.4–4.99	177 (6.3%)	214 (7.7%)	163 (5.8%)	83 (3%)	33 (1.2%)	670 (24%)
5.0–19.99	303 (11%)	370 (13%)	283 (10%)	185 (6.6%)	92 (3.3%)	1233 (44%)
>19.99	68 (2.4%)	168 (6%)	150 (5.4%)	126 (4.5%)	58 (2.1%)	570 (20%)
Totals	658 (24%)	885 (32%)	665 (24%)	406 (14.5%)	183 (6.5%)	2797 (100%)

TABLE IV. Distribution of Airborne Fibers by Diameter and Length (in μm) for Study period B (1988–1991).

	D (μm)					
L (μm)	<0.19	0.19–0.39	0.4–0.59	0.6–0.79	0.8–1.0	Totals
<0.59	5 (0.9%)	0	0	0	0	5 (0.9%)
0.59–1.19	36 (6.4%)	4 (0.7%)	0	0	0	40 (7.1%)
1.2–1.79	15 (2.7%)	26 (4.6%)	0	0	0	41 (7.3%)
1.8–2.39	11 (1.9%)	19 (3.4%)	5 (0.9%)	0	0	35 (6.2%)
2.4–4.99	25 (4.4%)	52 (9.2%)	35 (6.2%)	23 (4.1%)	9 (1.6%)	144 (26%)
5.0–19.99	19 (3.4%)	59 (10%)	42 (7.4%)	45 (8%)	76 (13%)	241 (43%)
>19.99	0	11 (1.9%)	12 (2.1%)	15 (2.7%)	21 (3.7%)	59 (10%)
Totals	111 (20%)	171 (30%)	94 (17%)	83 (15%)	106 (18%)	565 (100%)

TABLE V. Distribution of Airborne Fibers by Diameter and Length (in μm) for Study period C (1993–1995).

	D (μm)					
L (μm)	<0.19	0.19–0.39	0.4–0.59	0.6–0.79	0.8–1.0	Totals
<0.59	0	0	0	0	0	0
0.59–1.19	2 (0.6%)	2 (0.6%)	0	0	0	4 (1.1%)
1.2–1.79	0	7 (2.0%)	3 (0.8%)	0	0	10 (2.8%)
1.8–2.39	3 (0.8%)	3 (0.8%)	5 (1.4%)	2 (0.6%)	0	13 (3.7%)
2.4–4.99	9 (2.6%)	12 (3.4%)	13 (3.7%)	6 (1.7%)	4 (1.1%)	44 (12.6%)
5.0–19.99	10 (2.9%)	33 (9.4%)	55 (15.7%)	38 (10.9%)	62 (17.7%)	198 (56.7%)
>19.99	1 (0.3%)	9 (2.6%)	18 (5.1%)	15 (4.3%)	37 (10.6%)	80 (23%)
Totals	25 (7.2%)	66 (18.9%)	94 (26.9%)	61 (17.5%)	103 (29.5%)	349 (100%)

chrysotile fibers found in plaques were >5 μm in length. The amphibole fibers found in plaques had a geometric mean length of 1.05 μm and a geometric mean diameter of 0.14 μm. Of the amphiboles found in plaques, 10% were >5 μm in length.

Airborne RCF Size Distributions

The dimensions of airborne fibers measured by TEM analysis are presented for Study periods A, B and C in Tables III, IV and V, respectively. From the 118 air samples,

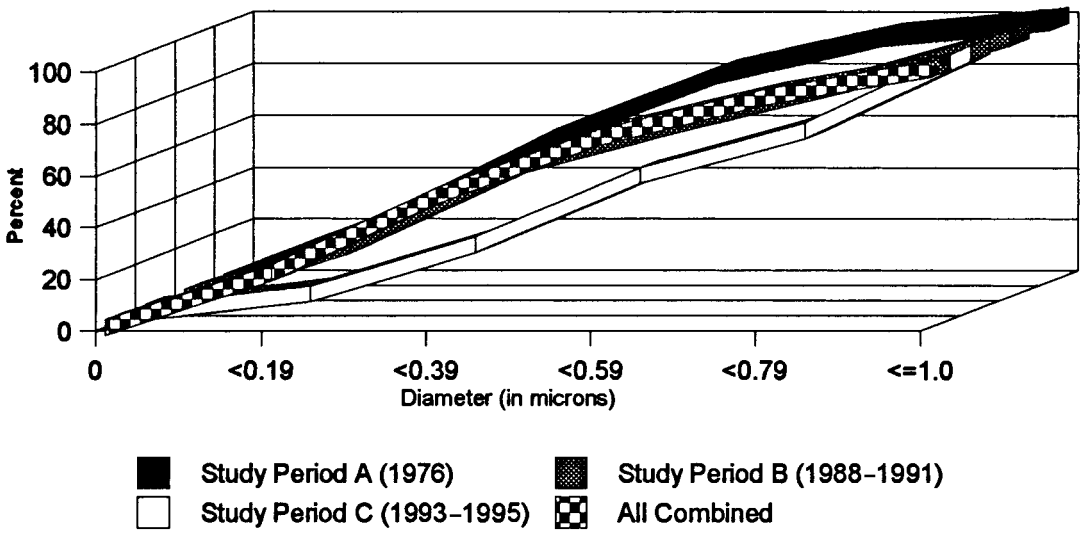
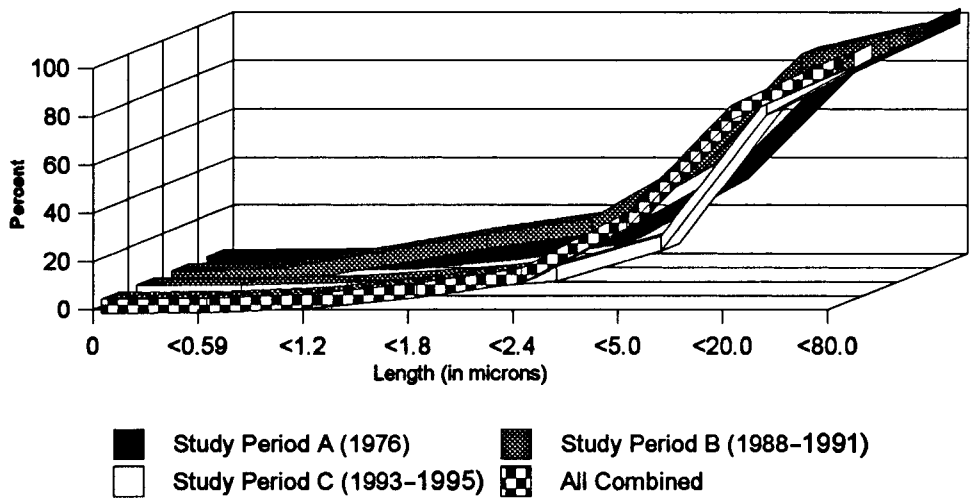


FIGURE 3. Cumulative distribution of fiber diameters by data set (TEM).



Note: Fibers with diameters > 1 μm excluded from the data sets graphed above.

FIGURE 4. Cumulative distribution of fiber lengths by data set (TEM).

a total of 3,711 fibers were identified and sized: 2,797 fibers were identified in 67 samples from Study period A; 565 fibers were identified in 28 samples from Study period B; and 349 fibers were identified in 23 samples from Study period C. Of all airborne fibers with diameter ranging up to 1 μm, 52% (1,916/3,711) had diameter < 0.4 μm, 75% (2,769/3,711) had diameter < 0.6 μm, and 89% (3,319/3,711) had diameter < 0.8 μm. The length of the fibers ranged from < 0.6 to > 20 μm, with only 19% (709/3,711) longer than 20 μm, and 68% (2,530/3,711) measuring between 2.4 and 20 μm in length. Among all fibers sized, 45% (1,659/3,711) measured < 0.4 μm in diameter and < 20 μm in length, with 47% (1,307/2,797), 48% (271/565), and 23% (81/349) of fibers meeting these characteristics in data sets from Study periods A, B and C, respectively. Cumulative distributions of fiber dimensions by size categories for all three study periods separately and combined are presented graphically for diameter in Figure 3 and length in Figure 4.

DISCUSSION

Fiber Exposure and Pleural Plaques

An industry-wide epidemiologic study of workers in U.S. RCF manufacturing plants found that latency and duration of employment in an RCF production job and

cumulative fiber exposure were associated with developing pleural plaques [Lemasters et al., 1994; Lockey et al., 1996]; this was once thought to be associated primarily with exposure to asbestos fibers. Pleural plaques are nodular fibrotic masses 0.5–1.0 cm thick [Raffle et al., 1987], most commonly found on the parietal pleura following the lines of the ribs and on the central tendon of the diaphragm [Herbert, 1986]. Plaques were initially considered benign and did not appear to inhibit normal lung function [Leathart, 1968; Lumley, 1977; Raffle et al., 1987]; however, several studies have shown small but recognizable changes in pulmonary function associated with pleural plaques [Bourbeau et al., 1990; Kilburn and Warshaw, 1990; Schwartz, 1991]. Early detection of biological changes such as plaques may allow intervention and thereby prevent serious respiratory conditions, such as interstitial fibrosis that has been associated with asbestos exposure [Hillerdal, 1994].

While some diseases of the lung, such as lung cancer and asbestosis, show a pronounced relationship to cumulative exposure in studies of asbestos-related effects, the relationship between pleural plaques and measures of asbestos exposure is less clear [Browne, 1994]. The presence of plaques does not correlate with asbestosis [Mollo et al., 1983], which may be explained by the fact that these disorders occur independently and are characterized by different pathophysiologic mechanisms. The relationship of plaques to the etiology of other lung disorders is also unclear. Most cases of pleural and peritoneal mesothelioma are accompanied by radiological evidence of benign pleural disease that is likely to have predated the development of mesothelioma [Lilis et al., 1987]. In reviews of evidence for an association between pleural plaques and lung cancer, Hillerdal and Henderson [1997] and Rudd [1996] cited several studies indicating that plaques are more than twice as common in chest x-rays of lung cancer patients as in chest x-rays of the general population. While pleural plaques may not be causally related to lung cancer, they are indicative of exposure which may increase the risk of developing lung cancer and other disorders.

Fiber Characteristics and the Pathology of Pleural Effects

Fiber dimensions play a significant role in determining the deposition site of a fiber in the lungs. Longer and thicker fibers are preferentially deposited in the upper airways by the mechanisms of impaction [Yu et al., 1986] or interception. Timbrell [1965] has suggested that direct interception plays an important role in the deposition of fibers, as part of the fiber comes into contact with the airway wall and is deposited. These fibers are generally cleared via the mucociliary escalator. Thinner fibers maneuver past airway bifurcations into smaller airways until their dimensions dictate deposition either by sedimentation or diffusion [Asgharian and Yu, 1989]. Another factor which may enhance deposition is the electrostatic charge a fiber can accumulate during dust-generating processes in occupational settings [Vincent, 1985].

Much as the dimensions of the airborne fiber influence its deposition in the respiratory tract, the chemical properties of a fiber can also dictate its clearance or retention once it reaches the alveolar region. Because biopersistence is an important determinant of fiber toxicity, the retention time of the fiber in the lungs and the efficiency of the clearance mechanism are factors in the prediction of biological effects. Accordingly, durable fibers which deposit in the gas exchange regions of the respiratory bronchioles and the alveoli become particularly important from a biological standpoint.

The anatomy of the pleura and the histology of pleural plaques are well-documented; yet, the exact mechanisms by which fibers reach the parietal pleura and induce the formation of plaques are not well understood. There is evidence that deposited fibers are translocated to the pleural tissues. One hypothesis to explain this is that respirable fibers may penetrate the lungs and the visceral pleura and enter the pleural cavity, where they are reabsorbed into the parietal pleura [Heard and Williams, 1961; Thomson, 1970; Zielhuis, 1977]. It has also been suggested that fibers cleared from the lung via lymphatics are transported to the parietal pleura before they reach the mediastinal lymph nodes [Brown, 1974; Hourihane, 1965; Oberdörster et al., 1988; Taskinen et al., 1973]. This explanation is supported by the recognition that the sites of plaque formation coincide with pathways of lymphatic drainage of the pleura [Herbert, 1986]. Clearance via alveolar macrophages has also been considered important for the translocation of deposited fibers [Oberdörster, 1994]. The relative roles of these mechanisms in fiber translocation are unclear; in probability, all contribute in clearing fibers from the alveolar region to the pleura [Browne, 1994].

Throughout the literature there are additional studies which support the theory that fiber toxicity is related to fiber dimensions [Davis, 1986; Harris and Timbrell, 1977; Lippmann, 1988; Timbrell, 1989]. Timbrell [1983, 1989] concluded that the thinner fibers with an upper diameter limit of 0.1 μm are more potent for producing diseases of the parietal pleura, specifically mesothelioma. Lippmann [1988] published a review suggesting that asbestosis, lung cancer and mesothelioma are each related to different-sized asbestos fibers. He concluded that lung cancer is associated with fibers longer than ∼10 μm and thicker than ∼0.15 μm, and asbestosis is most closely related to the surface area of fibers longer than 2 μm and thicker than 0.15 μm. Mesothelioma was determined to be associated with thin fibers (< 0.1 μm in diameter) with a lower limit for length of ∼5 μm.

The formation of pleural plaques may also be associated with shorter, thin fibers. Oberdörster [1994] has

studied the effects of both long (>∼10–16 μm) and short fibers (<∼10 μm) on alveolar macrophage function, concluding that both will lead to inflammatory reactions, although there is a distinct difference in the long-term effects due to differential clearance of fibers of different sizes. The ability of the macrophages to clear fibers has been observed to be size-dependent. Macrophages, which measure about 12 μm in diameter, are generally unable to ingest fibers longer than 10 μm [Morgan et al., 1982; Oberdörster et al., 1988; Oberdörster, 1994]. For fibers shorter than 10 μm, macrophage-mediated clearance predominates. From this review, it appears that the length of deposited fibers affects the uptake of fibers by macrophages, while diameter of retained fibers may also play a critical role based on the predominance of thinner (<0.1 μm) fibers with regard to impact on the parietal pleura [Timbrell, 1983].

When relating the dimensions of airborne fibers to the dimensions of fibers found in the lungs, it is important to consider not only the preferential clearance of shorter fibers, but also the effects of fiber dissolution and breakage. These factors were evaluated in a study by Yu et al. [1996] which led to the development of a clearance model of RCF in the rat lung. Results of that study confirmed that longer fibers (>10–20 μm) are cleared more slowly than shorter ones (<10 μm) due to the incomplete phagocytosis of long fibers by macrophages. The preferential clearance of shorter fibers has also been documented in studies with chrysotile asbestos and other mineral fibers, where the average length of retained fibers has been shown to increase during a discrete period following deposition [Churg, 1994; Coin et al., 1992]. This increase might also be explained by the longitudinal cleavage pattern of asbestos fibers, resulting in long fibers of decreasing diameters [Coin et al., 1992]. By contrast, any breakage which may occur with RCF would occur perpendicular to the longitudinal plane, resulting in shorter fibers of the same diameter. For the clearance model developed by Yu et al. [1996], the effect of fiber breakage was also assessed from experimental data and incorporated into the model. It was concluded that the simultaneous effect of fiber breakage and differential clearance leads only to a small change in fiber size distribution in the lung. This would suggest that dimensions of airborne fibers (adjusted for deposition) are more closely related to the dimensions of fibers found in the lungs.

Results of animal studies by Mast et al. [1995a,b] also indicate that dose of respirable fiber, aerodynamic dimensions and in vivo durability are crucial determinants of RCF toxicity. Those studies demonstrated that after 21 months of recovery (post-exposure), approximately 20% of fibers were retained in the lungs of rats; most retained fibers had diameters <0.5 μm and lengths between 5 and 20 μm. Carcinogenic effects were recognized in animals at high doses; i.e., RCF demonstrated lung carcinogenicity at the maximum tolerated dose of 30 mg/m^3, but not at 3, 9 or 16 mg/m^3, suggesting the existence of a threshold below which tumors will not have time to develop within the animal's life span [Mast et al., 1995b]. In contrast, the dose-response relationship for mesothelioma was less pronounced, and may be more dependent upon fiber sizes. Due to the small number of animals studied, however, caution must be advised in interpreting the dose-response association demonstrated by these results.

In another animal study, pleural fiber burden determinations and analyses of biochemical and cytological responses in lavage fluids were used to examine the pleural tissue as a target organ of fiber toxicity separate and distinct from the underlying lung parenchyma [Gelzleichter et al., 1996]. For this investigation, rats were exposed by nose-only inhalation to RCF-1 (kaolin-based) at a concentration of 89 mg/m^3 six hours/day for five consecutive days. Animals were selected to be sacrificed and tissues were examined either immediately following the exposure period or 28 days post-exposure. Inflammatory biochemical responses in parenchymal tissue occurred rapidly after exposure in contrast to pleural responses which were delayed in onset. From these results, the researchers concluded that pleural injury may increase with time following exposure. Analysis of thoracic tissues to determine pulmonary and pleural fiber burdens showed that fibers can rapidly translocate to pleural tissues, as evident from pleural fiber burdens immediately following the exposure period. The geometric mean length (GML) and diameter (GMD) for fibers found in pleural tissues [GML = 1.5 μm (GSD ≈ 2.0), GMD = 0.09 μm (GSD ≈ 1.5)] were smaller than those in parenchymal tissues [GML = 5.0 μm (GSD ≈ 2.3), GMD = 0.3 μm (GSD ≈ 1.9)], indicating that the short, thin fibers are capable of translocating to pleural tissues to induce biochemical effects.

CONCLUSIONS

From a review of the literature, it appears that fibers with diameters from <0.1 to 0.4 μm and lengths ranging from <2 to 10 μm may have greater potency for inducing pleural plaque formation. Possible explanations involve the clearance of shorter, thinner fibers from the alveoli to the pleura via lymphatics, the enhanced ability of the fibers to penetrate directly through the respiratory epithelium, and the role of alveolar macrophages in fiber translocation. Caution must be taken in defining the critical dimensions of fibers responsible for inducing the outcome of interest (e.g., plaques), as the definition is derived from studies of different fiber types which, in some cases, are associated with different pleural effects. A major assumption is that the fibers of given dimensions found in plaque tissues are responsible for inducing the plaques. Based on the studies of breakage patterns by Yu et al. [1996], it seems probable that the critical dimension fibers deposited in the alveolar region

maintain their dimensions even after translocation to the parietal pleura. In addition, the durability [Luoto et al., 1995] and biopersistence [Hesterberg et al., 1991] of RCF meet the criteria established in the theory of fiber toxicity which is gaining wider acceptance: that fibers of appropriate respirable size and durability in sufficient quantities would be expected to produce biologic effects [Mast et al., 1995b; Stanton et al., 1981].

As evident from air sampling data [Esmen et al., 1979; MacKinnon et al., 1993; Maxim et al., 1997], exposures to airborne fibers with the dimensions that historically have been associated with biological effects in pleural tissues do occur in the RCF manufacturing industry. Based on this review and analysis of fiber sizing data, fibers with critical dimensions should be considered for their role in inducing plaque formation in studies with RCF. Future investigation of any potential respiratory effects which may be related to exposures to airborne RCF and other SVFs should involve exposure assessment with analyses for providing data on fiber size distributions. TEM analyses of air samples previously collected at RCF manufacturing facilities and currently archived could allow for investigation of changes in airborne fiber dimensions over time related to engineering controls or process changes. The use of fiber sizing data with pulmonary deposition models in epidemiologic studies may provide a better characterization of the exposure-dose-response relationship for workers with occupational exposures to SVFs. This type of investigation has been performed with occupational exposure data from the RCF manufacturing industry, and will be reported separately in an analysis of the critical fiber dimensions identified here and their association with pleural plaques.

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