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Pulmonary Deposition Modeling with Airborne Fiber Exposure Data: A Study of Workers Manufacturing Refractory Ceramic Fibers

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Increasing production of refractory ceramic fiber (RCF), a synthetic vitreous material with industrial applications (e.g., kiln insulation), has created interest in potential respiratory effects of exposure to airborne fibers during manufacturing. An ongoing study of RCF manufacturing workers in the United States has indicated an association between cumulative fiber exposure and pleural plaques. Fiber sizing data, obtained from electron microscopy analyses of 118 air samples collected in three independent studies over a 20-year period (1976–1995), were used with a computer deposition model to estimate pulmonary dose of fibers of specified dimensions for 652 former and current RCF production workers. Separate dose correction factors reflecting differences in fiber dimensions in six uniform job title groups were used with data on airborne fiber concentration and employment duration to calculate cumulative dose estimates for each worker. From review of the literature, critical dimensions (diameter <0.4 μm, length <10 μm) were defined for fibers that may translocate to the parietal pleura. Each of three continuous exposure/dose metrics analyzed in separate logistic regression models was significantly related to plaques, even after adjusting for possible past asbestos exposure: cumulative fiber exposure, $\chi^2 = 15.2$ ($p < 0.01$); cumulative pulmonary dose (all fibers), $\chi^2 = 14.6$ ($p < 0.01$); cumulative pulmonary dose (critical dimension fibers), $\chi^2 = 12.4$ ($p < 0.01$). Odds ratios (ORs) were calculated for levels of each metric. Increasing ORs were statistically significant for the two highest dose levels of critical dimension fibers (level three, OR = 11, 95%CI = [1.4, 98]; level four, OR = 25, 95%CI = [3.2, 190]). Similar associations existed for all metrics after adjustment for possible asbestos exposure. It was concluded that development of pleural plaques follows exposure- and dose-response patterns, and that airborne fibers in RCF manufacturing facilities include those with critical dimensions associated with pleural plaque formation. Analysis of additional air samples may improve estimates of the dose-response relationship.

Keywords Dose, Exposure, Man-Made Vitreous Fiber, Pleural Plaques, Pulmonary Deposition, Refractory Ceramic Fiber, Synthetic Vitreous Fiber

Refractory ceramic fiber (RCF) is a lightweight, heat-resistant material belonging to the larger group of synthetic vitreous fiber (SVF) that also includes glass fiber and mineral wool. Production of RCF and other types of SVF has increased rapidly since the 1970s, creating concerns about the potential for exposure to airborne fibers among workers and possible health effects. 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.[1–7] Animal studies indicate that inhalation of RCF at the maximum tolerated dose (approximately 220 fibers/cm^3) may induce mesothelioma, lung cancer, and pleural and pulmonary fibrosis.[6,8,9]

The industry group Refractory Ceramic Fibers Coalition (RCFC) has established an industry recommended exposure guideline for RCF of 0.5 fibers/cm^3 as an eight-hour time-weighted average (TWA). Early in 1996, the U.S. Occupational Safety and Health Administration (OSHA) placed SVFs on a list of priority areas requiring non-regulatory consideration. The National Institute for Occupational Safety and Health (NIOSH) set a recommended exposure limit (REL) for MMVF at 3 fibers/cm^3 TWA exposure for up to a 10-hour shift during a 40-hour work week.[10]

The American Conference of Governmental Industrial Hygienists (ACGIH®) Committee on Threshold Limit Values (TLVs®) assigned to RCF a rating of A2 (suspected human

carcinogen) and a TLV of 0.2 fibers/cm^3 as an eight-hour TWA.[11] The International Agency for Research on Cancer classified ceramic fiber as group 2B, or possibly carcinogenic to humans.[12] The EPA also has classified RCF as a probable human carcinogen based on animal data and has recognized the need for additional human exposure monitoring.[13] Currently airborne exposure levels encountered during production range from 0.66 fiber/cm^3 to below the limit of detection.[14]

To monitor for any potential respiratory effects among workers at RCF manufacturing facilities in the United States, researchers at the University of Cincinnati (UC) have been performing exposure assessment and medical surveillance since 1987 with the cooperation and support of the RCFC, formerly the Thermal Insulation Manufacturers Association (TIMA). In a retrospective cohort study of workers at two RCF manufacturing sites, the UC researchers reported a relationship between increasing cumulative fiber exposure and the occurrence of pleural plaques.[15] Historically, pleural plaques have been viewed predominantly as a marker of asbestos exposure. Plaques have been related to mild but detectable decreases in pulmonary function, but in general have not been associated with pulmonary impairment as measured by submaximal exercise testing.[16–20]

The aspect of the RCF study reported here involved the calculation of pulmonary deposition estimates of airborne fibers for former and current exposed workers based on air monitoring conducted during the production of RCF. The purpose of this investigation was to test the possible relationship between airborne fibers of specific dimensions and the development of pleural plaques in RCF workers. Procedures involved in performing this investigation included: 1) characterizing occupational exposure to RCF by reviewing and comparing air sampling data collected from multiple studies at RCF manufacturing and processing facilities; 2) calculating cumulative pulmonary doses of fibers for RCF production workers using a lung deposition model; and 3) calculating odds ratios (ORs) to evaluate the relationship between levels of cumulative pulmonary dose of critical dimension fibers and the formation of pleural plaques. In particular, this study sought to compare metrics of cumulative exposure measured by phase contrast microscopy alone and cumulative dose of fibers as determined by a combination of phase contrast and electron microscopy analyses. Pulmonary deposition estimates were used as a surrogate for dose, that is, the quantity of fibers reaching the smaller airway regions of the lungs. Obtaining this information on dose has been recognized as an essential step toward assessing the toxicity of inhaled SVF.[21]

RCF MANUFACTURING AND RCF PRODUCTS

Production of RCF in the last four decades has experienced rapid growth, especially as RCF has gained acceptance as an economical, alternative, heat-resistant insulation material. This growth may also be attributed to the search for less hazardous man-made substitutes for naturally occurring mineral fibers that have been associated with adverse health effects.[22,23] In 1997, U.S. production of RCF totaled 107 million pounds, accounting for 1–2% of worldwide SVF production.[24] Approximately 30,000 workers in the United States are potentially exposed to RCF during its manufacture, distribution, installation, conversion, and end-uses.[25] Of these, slightly more than 700 workers are employed in the domestic manufacture of RCF and RCF products.[22]

RCF production begins with a mixture of raw materials, which includes kaolin clay or alumina and silica, in a batch house. The batch mix is transferred either manually or automatically to a furnace to be melted at temperatures exceeding 1600°C. Upon reaching a specified temperature and viscosity in the furnace, the molten batch mixture drains from the furnace and is fiberized either through exposure to pressurized air or by flowing through a series of spinning wheels.[26] Fans used to create a partial vacuum pull the fibers into a collection or settling chamber. RCF may then be conveyed pneumatically to a bagging area for packaging as bulk fiber; fiber may be used directly in bulk form, while it may also be processed to form textiles, felts, boards, cements, blankets, and other specialty items. Many processes are automated and are monitored by machine operators. Post-production processes (cutting, sanding, packaging, handling, and shipping) are more labor-intensive and may account for differences in airborne fiber concentrations, although potential for airborne fiber exposures exists throughout production.

Although RCF differs from naturally occurring mineral fibers by physical and chemical characteristics, the literature suggests that fiber toxicity also relates to fiber dimensions.[1,2,4,5,27,28] From a review of this literature, a definition of critical dimension fibers (diameter <0.4 μm, length <10 μm) was derived to describe the fiber dimensions believed to be associated with pleural plaques. This review and a characterization of airborne fiber dimensions measured in RCF manufacturing facilities were described previously.[29]

MATERIALS AND METHODS

Air Sampling Data

Sampling data at RCF manufacturing plants were derived from personal monitoring of airborne fiber exposures for workers from representative work areas or dust zones (DZs), characterized previously in industrial hygiene walk-through surveys.[30] Over 900 air samples have been collected at six facilities and analyzed according to NIOSH Method 7400 using phase contrast microscopy (PCM) to determine concentration of airborne fibers,[31] which provided the basis for calculating cumulative fiber exposure.[14,30] In addition, a set of 124 air samples was analyzed by scanning electron microscopy (SEM) or transmission electron microscopy (TEM) to obtain fiber sizing data.

The PCM and electron microscopy methods were intended for different purposes. Whereas the PCM was used to determine an index of exposure (i.e., airborne concentration of respirable fibers with length > 5 μm), the TEM method incorporates a much smaller lower limit for inclusion (fiber length > 0.5 μm)

and was intended for measuring fiber dimensions. A significant percentage of the fibers sized by TEM (many of those in the critical dimensions range) would probably be excluded using the PCM method. In an earlier publication comparing the distribution of airborne fiber dimensions for this study, ~40 percent of fibers identified by TEM met the critical dimensions criteria while ~1 percent of fibers identified by SEM met these criteria (with analytic capabilities and protocol comparable to PCM).[32]

Analyses of variance (ANOVA) for fiber size distributions by plant showed no statistically significant differences.[32] Additional fiber sizing data from TEM analyses were available from two independent sampling surveys, which were also collected at the same RCF manufacturing or processing plants. The combined air sampling data contained 118 samples analyzed by TEM, the only microscopy method capable of detecting all critical dimension fibers of importance to this study.[33] The three sources of TEM fiber sizing data included: Study A—air samples ($n = 67$) collected in June 1976;[34] Study B—air samples ($n = 28$) collected by UC researchers between June 1988 and January 1991;[32] and Study C—air samples ($n = 23$) collected by member companies at RCFC between 1993 and 1995 as part of a consent agreement between the RCFC and the U.S. Environmental Protection Agency (EPA).[25]

All air samples were obtained from workers in representative work areas and jobs using a personal sampling pump worn by the worker connected to a sampling cassette or cowl positioned in the breathing zone of the worker. Air was pulled through a membrane filter (0.45 or 0.8 μm pore size) on the sampling cassette at a rate between 0.5 and 2.5 liters per minute. Laboratory analyses of the filters were performed using TEM at a magnification of 10,000–25,000×. Fibers with an aspect ratio (length:width) greater than 3:1 were measured. Selected area electron diffraction (SAED) and energy dispersive x-ray analyses (EDXA) were used to verify that fibers were RCF according to crystallography patterns and chemistry. In total, 3711 fibers were identified and sized according to these criteria. Statistical analyses of fiber sizing data were performed using PC SAS, Version 6.03.[35]

FIBER CHARACTERISTICS BY UNIFORM JOB TITLE GROUPS

In combining information from the three studies, air sampling data were standardized under one set of categories to ensure a consistent classification system representative of exposures for groups of workers. Uniform job titles (UJTs) were used to describe a set of activities routinely performed by an individual with a specific job title within each facility.[14] Standardization involved determining from the sample number the job duties of the person sampled, the sampling date, and the plant identification, and then checking or reassigning the appropriate UJT and dust zone (DZ) classifications as necessary. A Kappa statistic was calculated to measure classification agreement between two independent reviewers for a subset of the samples (~25%). The Kappa statistic for the UJT assignments ($k = 0.89$) indicated a high level of agreement between the reviewers.[36]

Based on similarity of job functions and specific operations, UJTs were consolidated into UJT Groups to increase the number of exposure estimates for each group and to provide an estimate of concentration for individual UJTs not represented in the TEM sampling data. The UJT Groups consist of the following six categories: wet secondary processes; furnace; blanket line; dry secondary processes; maintenance; and other. ANOVA tests by UJT Group showed statistically significant differences for log diameter ($p = 0.03$) and log length ($p = 0.01$). Thus, differences in fiber size distributions existed among the UJT Groups at the exposure level; these differences might be magnified at the dose level due to differential deposition patterns reflected in the calculation of pulmonary deposition estimates.

PULMONARY DEPOSITION MODELING

The models considered in Table I were judged against the following criteria: applicability to a human population (i.e., based on human lung anatomy and physiology); ability to simulate the aerodynamic behavior of RCFs, or fibers with similar physical characteristics; and availability of the model to the researchers and access to the facilities necessary to utilize it. For this study the Harris-Fraser model was chosen.[37] This model predicts deposition of fibrous dusts based on the regular dichotomous architecture of the lung described by Weibel and Gomez,[38] mechanics of air flow within the respiratory system documented by the ICRP Task Group on Lung Dynamics,[39] and assumes nose breathing.[40,41] The model, designed to predict the behavior and deposition of regular-shaped cylindrical rods, was previously used to evaluate a dose-response relationship among textile workers exposed to chrysotile asbestos,[28] an irregular-shaped fiber characterized by its curved shape and many frayed and projecting fibrils.[42]

Fiber sizing data were entered into the computer model according to bivariate sizing characteristics in matrix format as presented in Figure 1, with length categories on the horizontal axis and diameter categories on the vertical axis. Each cell in the matrix was assigned a value representing the number of fibers meeting the bivariate characteristics of that cell; for example, for the UJT Group of wet secondary processes, the cell characterized by midpoints of 0.30 μm for diameter and 2.10 μm for length contained 12 fibers as shown in Figure 1. The computer model calculates aerodynamic equivalent diameters for the fibers in each cell of the matrix according to fiber length and uses these data to provide pulmonary deposition estimates based on established deposition probability values.

The model was adjusted to reflect a tidal volume of 1450 cm^3 (associated with moderate exercise or work activities), RCF density of 2.65 g/cm^3,[6] and airborne exposures consisting of 100 percent single, straight fibers, to be consistent with the characteristics of work with RCF.[23] Critical dimension fibers were defined as having diameter <0.4 μm and length <10 μm.

TABLE I
A list of selected pulmonary deposition models, their applications, and features

Model authors	Lung anatomy	Particle geometry	Respiratory physiology	Other features
ICRP, 1966[39]	Few airway generations; early lung model of Findeisen, 1935[56]	Compact (spherical) particles	4 s breathing cycle (inspiration—1.74 s, pause—0.20 s, expiration—2.06 s) three tidal volumes: 750, 1450, 2150 cm^3	One of the first models; identified basic elements required for lung dosimetry; assumes nasal breathing
Beeckmans, 1970[57]	Weibel Model A	Prolate ellipsoids (Chrysotile asbestos)	3 s breathing cycle (0.3 s pause after inspiration and again following expiration) 1000 cm^3 tidal volume	Designed to estimate deposition of asbestos dust in the lower respiratory tract; does not specify breathing mode
Harris and Fraser, 1976[37]	Weibel Model A	Thin, straight rods	4 s breathing cycle (inspiration—1.74 s, expiration—2.06 s, pause—0.20s) three tidal volumes: 750, 1450, 2150 cm^3	A mathematical model designed to reflect aerodynamic behavior and deposition of thin rods (fibers) in the human lung; equations based on reported observations of fibers in human lungs; nasal breathing
Asgharian and Yu, 1988[58]	Weibel Model A	Fibers (RCF)	4.28 s breathing cycle (inspiration-1.86 s, pause—0.21 s, expiration—2.21s) 500 cm^3 tidal volume	A mathematical model for predicting deposition of RCF in human lungs; based on rat and hamster deposition models; assumes both oral and nasal breathing
Koblinger and Hofmann, 1990[59]	Stochastic lung model; various airway generations and geometries	Compact (spherical) particles	4 s breathing cycle (inspiration and expiration each 1.8 s, separated by pauses of 0.2 s) 1000 cm^3 tidal volume	A computer-based model in which geometry of airways traveled by the inhaled particles is randomly selected; deposition probabilities computed by deterministic formulae; can assume oral or nasal breathing
Sussman et al., 1991[60]	Cast of the tracheo-bronchial airways in a human	Fibers (asbestos)	Constant inspiratory flow rates of 7.5, 15, 30, and 60 L/min	Empirical model based on experimental data describing deposition of asbestos fibers in the TB region of humans

FIBER TYPE: refractory ceramic fiber
INDUSTRY: manufacturing
UJT GROUP: wet secondary processes

FIBER SIZE INTERVAL MIDPOINT (in μm)

	LENGTH						
	0.30	0.90	1.50	2.10	3.70	12.50	25.00
DIAMETER							
0.10	1	7	5	5	19	47	11
0.30	0	1	8	12	25	69	25
0.50	0	0	1	7	27	52	27
0.70	0	0	0	2	10	41	19
0.90	0	0	0	0	7	46	21
1.20	0	0	0	1	1	46	27

FIGURE 1
An example of the fiber sizing data matrix used for each of the six Uniform Job Title (UJT) Groups with the Harris-Fraser computer model to calculate pulmonary deposition. (Values in the matrix indicate numbers of fibers in each category according to length and diameter characteristics.)

Calculation of Cumulative Exposure and Dose Indices

The equation for calculating cumulative dose is similar to that for cumulative exposure, the difference being that dose is the fraction of exposure reaching a specific region or tissue. In general, the equation for cumulative dose can be expressed as:

$$\text{Cumulative Dose} = \Sigma D_i T_i, \quad [1]$$

where D_i = dose for conditions at *i*,
and T_i = duration over which these conditions at *i* exist.

Cumulative exposure is based on air sampling results from PCM analysis only. Cumulative dose estimates rely on a combination of air sampling results from analysis by PCM for exposure and electron microscopy for sizing data. The relationship of pulmonary dose to measured fiber exposure (as determined by sampling and analysis by NIOSH method 7400 and electron microscopy techniques) can be described as follows:

$$D_i = C[(f_i)/P] \quad [2]$$

where D_i = dose of fibers at site *i* (pulmonary region) per cm^3 of air breathed;
C = airborne fiber concentration as measured by PCM, (fibers ≥ 5 μm in length per cm^3 of air);
P = fraction of fibers ≥ 5 μm in length;
f_i = fraction of all airborne fibers deposited at site *i* (pulmonary region).

Cumulative dose was calculated by multiplying the expression above by the duration (T_i) of the dose under conditions at each *i* and summing for all *i*'s. Alternatively, calculation of cumulative dose involves multiplying the product of C_iT_i by $[(f_i)/P]_i$ and summing for all *i*'s. The value defined by $[(f_i)/P]_i$ or k_i is also referred to as the dose correction factor.

The above expression was modified to determine the "effective dose" of the critical dimension fibers (<0.4 μm in diameter and <10 μm in length). Calculating the effective dose based on the parameters of the critical dimension fibers involved use of the following formula:[28]

$$D_{Ei} = C\{[(S)(f_{is})]/P\} = C(k_{is}) \quad [3]$$

where D_{Ei} = dose of critical dimension fibers at site *i* (pulmonary region) per cm^3 of air breathed;
C and P are the same as in the previous expression;
S = fraction of all airborne fibers meeting the definition of critical dimension fibers (i.e., diameter $< 0.4\mu$m and length $< 10\mu$m);
f_{is} = fraction of critical dimension fibers deposited at site *i* (pulmonary region);
$k_{is} = [(S)(f_{is})]/P$ = dose correction factor for site *i*.

Dose correction factors for all fibers (k_i) and for critical dimension fibers (k_{is}) calculated for each of the six UJT Groups

were as follows: Wet secondary processes ($k_i = 0.19$, $k_{is} = 0.034$); furnace ($k_i = 0.23$, $k_{is} = 0.057$); blanket line ($k_i = 0.24$, $k_{is} = 0.071$); dry secondary processes ($k_i = 0.25$, $k_{is} = 0.058$); maintenance ($k_i = 0.22$, $k_{is} = 0.053$); and other ($k_i = 0.24$, $k_{is} = 0.063$). The appropriate dose correction factors were then applied to the cumulative exposure algorithm in an SAS computer program to calculate cumulative dose. Modification of the cumulative exposure algorithm resulted in the following equation:

$$\text{Cumulative Dose} = \sum(k_i \text{ or } k_{is})C_iT_i = \Sigma D_iT_i, \qquad [4]$$

where C_i is the exposure level (concentration) for a given UJT,
T_i is the duration of the exposure in months,
and k_i or k_{is} is the appropriate dose correction factor for the UJT Group associated with the UJT.

Screening for Pleural Plaques

Former and current RCF production workers at two facilities participating in the study who agreed to medical monitoring ($n = 652$) underwent chest x-rays (one posteroanterior and two oblique views).[15] Personal identifiers on the chest films were masked and these x-rays were mixed with normal films from nonexposed workers as a quality control measure. The additional films were from an industrial population with no known fiber exposure and were taken at one of the two medical facilities from which the study films were obtained. The films were interpreted independently by three radiologists who are certified B-readers using the ILO 1980 International Classification of Radiographs of the Pneumoconiosis.[43] Agreement between at least two of the three radiologists was required to determine whether or not a set of chest films demonstrated pleural changes consistent with pleural plaques. Following this protocol, 20 pleural plaque cases were identified among 652 participants (3.1%).

Statistical Analyses of Pleural Plaque Status and Exposure/Dose Variables

Three measures of exposure/dose were examined for their association with pleural plaques: cumulative exposure; cumulative pulmonary dose of all fibers; and cumulative pulmonary dose of critical dimension fibers. Each of these measures was treated as a continuous variable in an analysis of pleural plaque status with each variable in separate logistic regression models (Proc Logistic) using PC/SAS, Version 6.03.[35] Because the values for these variables were highly skewed, each was $\log_e$-transformed prior to statistical analysis. Each analysis included adjustment for years since first asbestos exposure (latency), the major known risk factor for pleural plaques, calculated using information obtained from employee interviews. RCF latency, or months since first RCF production job, was also considered as a separate variable, based on previous analyses that showed this variable to be associated with pleural plaques.[15] This variable was found to be correlated with the exposure/dose variables (Pearson correlation coefficients range from 0.6–0.9).

Four categories of dose levels were created to allow for comparison of plaque status according to different levels of pulmonary dose of critical dimension fibers. Categorical variables were also created from the variables of cumulative exposure and cumulative pulmonary dose of all fibers. Dose categories were determined by dividing the log-transformed cumulative pulmonary dose into four levels, each containing approximately 25 percent of the study cohort (quartiles).[44] Geometric means of each category were compared by ANOVA and found to differ significantly ($p < 0.01$) overall, as well as in all individual comparisons using the Scheffé test. Determining categories according to quartiles for each exposure/dose metric ensured a consistent approach to creating categorical variables for the three measures.

Calculation of Odds Ratios (ORs)

ORs for developing pleural plaques were calculated among the quartile groups of study subjects at increasing cumulative pulmonary dose levels. The lowest two cumulative dose categories were combined to be the referent group used for comparison with each of the two highest cumulative dose groups. The same procedure was followed for the variables of cumulative exposure and cumulative pulmonary dose of all fibers. For each OR, the 95 percent confidence interval (CI) was also calculated to determine statistical significance using maximum likelihood estimates (parameter estimate and standard error) for each category to calculate the upper and lower bounds. To account for a possible effect from past asbestos exposure, adjusted ORs were also calculated in an analysis that included the variable of years since first asbestos exposure.

RESULTS

Exposures of Workers by Pleural Plaque Status

In Table II, the arithmetic mean values for cumulative exposure, cumulative pulmonary dose of all fibers, cumulative pulmonary dose of critical dimension fibers, cumulative pulmonary dose of non-critical dimension fibers, asbestos latency, and RCF latency are presented for plaque cases, all non-plaque participants in the study, and all study participants combined. Mean values for each variable are higher among the plaque cases.

ORs for Categorical Exposure/Dose Variables and Pleural Plaques

The distribution of all study subjects and pleural plaque cases among each of the four categories of cumulative exposure levels is presented in Table III(a). Similar distributions are presented among the categories of cumulative pulmonary dose of all fibers, Table III(b), and cumulative pulmonary dose for critical dimension fibers, Table III(c). ORs, as compared with the lowest exposure/dose categories, are shown for each exposure/dose metric, both with and without adjustment for asbestos latency.

TABLE II
Arithmetic mean values of exposure/dose metrics for plaque cases, all non-plaque participants, and all study participants combined

	Mean (range)					
Plaque status (SD)	Cum. exposure[A]	Cum. pulmonary dose—all fibers[A]	Cum. pulmonary dose—CD fibers[B]	Cum. pulmonary dose—non-CD fibers[C]	Asbestos latency[D]	RCF latency[E]
Cases (N = 20)[(15)]	140 (0.2–970)	79 (0.2–810)	65 (0.2–770)	13 (0–36)	32 (3–50)	259 (155)
All non-plaque (N = 632)	45 (0–840)	20 (0–655)	15 (0–655)	5.5 (0–170)	21 (0–54)	125 (119)
All combined (N = 652)	47 (0–970)	22 (0–810)	17 (0–770)	5.8 (0–170)	22 (0–54)	131 (124)

[A]In fiber-mo/cm^3 (range in parentheses).
[B]Critical dimension fibers (<0.4 μm in diameter and <10 μm in length) in fiber-mo/cm^3 (range in parentheses).
[C]Non-critical dimension fibers (>0.4 μm in diameter or >10 μm in length) in fiber-mo/cm^3 (range in parentheses).
[D]In years since first exposure (range in parentheses).
[E]In months since first exposure (standard deviation).

Logistic Regression Modeling of Exposure/Dose Metrics as Continuous Variables

Each of the three exposure/dose measures ($\log_e$-transformed) was analyzed as a continuous variable in separate regression models of all study subjects (n = 652), adjusted for asbestos latency. Results of these analyses are presented in Table IV, which includes the model parameter estimate, standard error, Wald χ^2 value, and p-value for each exposure/dose variable. The Wald χ^2 test statistic, commonly used with logistic regression models and derived from Abraham Wald's large sample hypothesis test construction method, is the default statistic used with PC/SAS logistic procedure.[(35)] Pleural plaques were found to be significantly related to all metrics ($p < 0.01$).

Tests for linear trend were performed when adjusted ORs were statistically significant; all linear trend tests were statistically significant ($p < 0.01$). Logistic regression modeling of all three exposure/dose metrics in one model showed that only the cumulative pulmonary dose of all fibers was statistically significant ($p < 0.01$).

TABLE III
Odds ratios (ORs), with and without adjustment for years since first asbestos exposure, for pleural plaques among quartile categories for exposure/dose variables with all (N = 652) study participants

Fiber-mo/cm^3 (Arith. mean [SD])	N	Plaque cases	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
a) Cumulative exposure				
0–2.3 (0.6 [0.6])	148	0	(This category was combined with the next to form baseline.)	
>2.3–15.7 (7.6 [3.8])	165	1	1.0 (–, –)	1.0 (–, –)
>15.7–50.8 (30.7 [9.9])	164	5	9.5 (1.1, 82)[A]	7.7 (0.9, 67)
>50.8 (150 [143])	175	14	26[A] (3.4, 200)	22[A] (2.9, 170)
b) Cumulative pulmonary dose—all fibers				
0–0.57 (0.17 [0.17])	148	0	(This category was combined with the next to form baseline.)	
>0.57–4.23 (1.9 [0.95])	165	1	1.0 (–, –)	1.0 (–, –)
>4.23–14.3 (8.5 [2.9])	164	6	11[A] (1.3, 95)	9.3[A] (1.1, 79)
>14.3 (78.1 [118])	175	13	24[A] (3.1, 190)	20[A] (2.6, 160)
c) Cumulative pulmonary dose—critical dimension fibers				
0–0.18 (0.05 [0.05])	147	0	(This category was combined with the next to form baseline.)	
>0.18–1.11 (0.54 [0.27])	168	1	1.0 (–, –)	1.0 (–, –)
>1.11–4.88 (2.5 [1.0])	164	6	11[A] (1.4, 98)	10[A] (1.2, 85)
>4.88 (63.1 [118])	173	13	25[A] (3.2, 190)	20[A] (2.6, 160)

[A]Statistically significant ($p < 0.05$).

DISCUSSION

Fiber toxicity has been identified with three factors: 1) fiber dimensions, 2) biologic durability, and 3) dose delivered to the target organ.[45] Although much less durable and biopersistent than amosite or crocidolite, RCF is the among the most durable of SVFs in biologic fluids, with a dissolution rate that approximates that of chrysotile. Durability and resistance to dissolution increase the biopersistence of a fiber in a target tissue, thereby affecting its potential toxicity. This study used carefully characterized fiber dimensions to estimate dose using a pulmonary deposition model. While the pulmonary dose estimate is not presumed to be the exact dose ultimately delivered to the parietal pleura, it is a surrogate characterization of the fibers that may induce pleural plaques.

The complete mechanism of pleural plaque formation is unknown. One hypothesis is that some fibers that traverse the respiratory airways and deposit in the alveoli are translocated through membranes into interstitial tissues. Deposited fibers may penetrate the lungs and the visceral pleura, enter the pleural cavity, and migrate into the parietal pleura.[46–48] It has also been proposed that fibers cleared from the lung via lymphatics are transported to the parietal pleura before reaching the mediastinal lymph nodes,[49–52] because sites of plaque formation coincide with pathways of lymphatic drainage of the pleura.[53] The function of alveolar macrophages in clearance has also been considered important for the translocation of deposited fibers.[54] It is probable that all these mechanisms contribute to clearing fibers deposited in the alveolar region to the pleura.[55]

Results of this study show an association between pleural plaques and increasing levels of cumulative exposure, cumulative pulmonary dose (all fibers), and cumulative pulmonary dose estimates for fibers of critical dimensions (diameter $<0.4\ \mu$m and length $<10\ \mu$m). Analyses controlling potential asbestos exposure showed the magnitude of the association was diminished but remained statistically significant at the highest dose levels.

Logistic regression modeling of all metrics in one model showed that all were successful at predicting the incidence of pleural plaques. Although it was hypothesized a priori that the cumulative dose metrics would be more predictive than cumulative exposure, no such difference in predictive ability of the models was observed (refer to Table IV.) Possible explanations for this include: 1) too few data to provide the statistical power to discriminate among exposure and dose metrics and models; 2) the exposure and dose metrics are too highly correlated to detect differences; 3) the inability of the deposition model to predict the effect of fiber clearance. With respect to the third explanation, some of the longer fibers (as compared to critical dimension fibers) deposited in the pulmonary region may be fractured, creating shorter fibers that eventually reach the pleura.

It is also possible that some fibers just beyond the "critical dimensions" defined by this study may reach the pleura. These fibers would be included in the cumulative pulmonary dose for all fibers and not the dose for the critical dimension fibers. Another possible explanation for the slightly weaker association with the dose of critical dimension fibers is misclassification of UJTs under UJT Groups. Precautions were taken to reduce the possibility of misclassification (i.e., using two independent reviewers and testing agreement between categorical assignments with a Kappa statistic); however, the effect of measurement errors could reduce the association.

TABLE IV

Separate logistic regression analyses[A] of pleural plaques for associations with three exposure/dose metrics for all (N = 652) study participants

Exposure/ dose metric[B]	Parameter estimate	SE	Wald X^2	p-value
Cumulative exposure	0.75	0.19	15.2	<0.01
Cumulative pulmonary dose (all fibers)	0.52	0.13	14.6	<0.01
Cumulative pulmonary dose (critical dimension fibers)	0.36	0.10	12.4	<0.01

[A] Adjusted for years since first asbestos exposure.
[B] Log_e transformation performed.

Air sampling data, obtained from both TEM and PCM analyses of airborne fiber samples, were important. Data from TEM analyses of airborne fibers provided information about fibers that would otherwise go undetected using the conventional exposure assessment method: namely, the fiber counting procedure described in NIOSH Method 7400. From the sizing data, it was determined that airborne fiber concentrations at RCF facilities include fibers that meet the critical dimensions associated with pleural plaques. The fiber counting procedure using PCM, on which the cumulative exposure metric is based, also proved to be an important method for evaluating the exposure-response relationship for RCF and pleural plaques. Fiber counting data, derived from more than 900 samples collected over roughly a 20-year period, indicate that airborne fiber concentrations have declined significantly to current levels below 0.5 f/cm^3.[14,25]

CONCLUSIONS

Size distributions of airborne RCF measured in the RCF manufacturing industry include fibers of dimensions that may be associated with pleural plaques.[29] Most of these critical dimension fibers would normally go undetected in air samples analyzed using NIOSH Method 7400, due to the limit of resolution for phase contrast microscopy and counting rules that preclude counting fibers shorter than five microns. Based on this realization, the use of TEM to measure airborne fiber size distributions may be an integral part of characterizing airborne RCF and the potential toxicity related to fiber dimensions.

Despite the limitations of the fiber counting method, cumulative exposure to RCF (calculated from airborne exposure data obtained using NIOSH Method 7400) was found to be

significantly related to pleural plaques, even after adjustment for asbestos latency. This is consistent with the earlier findings.[15] Estimates of cumulative pulmonary dose (all fibers and critical dimension fibers) were significantly related to pleural plaques, as was the simpler model based on cumulative exposure. This association between pleural plaques and cumulative dose estimates was apparent even given the limited amount of air sampling data from TEM fiber sizing analyses.

RECOMMENDATIONS

Areas for future research might include the evaluation, adaptation, and use of additional animal lung deposition and clearance models[61,62] that have become available since this study was initiated and performed. Advantages of such models, if adapted to simulate human lung parameters, include the integration of calculations to simulate the effect of clearance mechanisms (e.g., dissolution and breakage of fibers) on the cumulative lung burden of fibers in various size ranges.

With additional fiber sizing data, a more accurate characterization of the dose-response pattern for RCF and pleural plaques might also be obtained. Specifically, these data may help to identify potential differences in fiber size distributions that may be associated with specific dust zones or UJTs. More dose categories in an epidemiologic analysis would assist in the interpretation of any health risk at various levels.

Answers to the questions of whether and how pleural plaques relate to other possible health effects are elusive, indicating a need for additional experimental and epidemiologic research. Further study, presumably with animal models, may provide for a better understanding of the mechanisms by which deposited fibers ultimately reach the pleura and induce plaque formation.

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REFERENCES

1. Timbrell, V.: Physical Factors as Etiological Mechanisms. In: Biological Effects of Asbestos, P. Bogovski, J.C. Gilson, V. Timbrell, J.C. Wagner, eds., pp. 295–303. IARC, Lyon (1973).
2. Harris, R.L., Jr.; Timbrell, V.: The Influence of Fibre Shape in Lung Deposition—Mathematical Estimates. In: Inhaled Particles IV, W.H. Walton, ed., pp. 75–88. Pergamon Press, Oxford (1977).
3. Stanton, M.F.; Layard, M.; Tegeris, A.; et al.: Carcinogenicity of Fibrous Glass: Pleural Response in the Rat in Relation to Fiber Dimension. JNCI 58:587–597 (1977).
4. Davis, J.M.G.: The Pathogenicity of Long Versus Short Fibres of Amosite. Br J Explor Pathol 67:415–430 (1986).
5. Lippmann, M.: Asbestos Exposure Indices. Environ Res 46:86–106 (1988).
6. Mast, R.W.; McConnell, E.E.; Anderson, R.; et al.: Studies of the Chronic Toxicity (Inhalation) of Four Types of Refractory Ceramic Fiber in Male Fischer 344 Rats. Inhal Toxicol 7:425–467 (1995).
7. Mast, R.W.; McConnell, E.E.; Hesterberg, T.W.; et al.: Multiple-Dose Chronic Inhalation Toxicity Study of Size-Separated Kaolin Refractory Ceramic Fiber in Male Fischer 344 Rats. Inhal Toxicol 7:469–502 (1995).
8. Bunn, W.B.; Bender, J.R.; Hesterberg, T.W.; et al.: Recent Studies of Man-Made Vitreous Fibers—Chronic Animal Inhalation. J Occup Med 35:101–113 (1993).
9. McConnell, E.E.; Mast, R.W.; Hesterberg, T.W.; et al.: Chronic Inhalation Toxicity of a Kaolin-Based Refractory Ceramic Fiber in Syrian Golden Hamsters. Inhal Toxicol 7:503–532 (1995).
10. National Institute for Occupational Safety and Health: NIOSH Criteria for a Recommended Standard: Occupational Exposure to Fibrous Glass. DHEW (NIOSH) Pub. No. 77-152. NIOSH, Cincinnati, OH (1977).
11. American Conference of Governmental Industrial Hygienists: Annual Reports of the Committees on Threshold Limit Values and Biological Exposure Indices. ACGIH, Cincinnati, OH (2001).
12. World Health Organization: Man-Made Mineral Fibers and Radon. In: International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 43. IARC, Lyon (1988).
13. Environmental Protection Agency. Federal Register. 56(225): 58693. H.S. Government Printing Office, Washington, DC (Nov. 21, 1991).
14. Rice, C.; Lockey, J.; Lemasters, G.; et al.: Estimation of Historical and Current Employee Exposure to Refractory Ceramic Fiber During Manufacturing and Related Operations. Appl Occup Environ Hyg 12:54–61 (1997).
15. Lockey, J.; Lemasters, G.; Rice, C.; et al.: Refractory Ceramic Fiber Exposure and Pleural Plaques. Am J Respir Crit Care Med 154:1405–1410 (1996).
16. Rosenstock, L.: Asbestosis and Asbestos-Related Pleural Disease. In: Textbook of Clinical Occupational and Environmental Medicine, L. Rosenstock, M.R. Cullen, eds., pp. 254–263. W.B. Saunders Company, Philadelphia (1994).
17. Borbeau, J.; Ernst, P.; Chrome, J.; et al.: The Relationship Between Respiratory Impairment and Asbestos-Related Pleural Abnormality in an Active Work Force. Am Rev Resp Dis 142:837–842 (1990).
18. Kilburn, K.H.; Warshaw, R.: Pulmonary Functional Impairment Associated with Pleural Asbestos Disease: Circumscribed and Diffuse Thickening. Chest 98:965–972 (1990).
19. Merchant, J.A.: Human Epidemiology: A Review of Fiber Type and Characteristics in the Development of Malignant and Nonmalignant Disease. Environ Health Perspect 88:287–293 (1990).
20. Schwartz, D.A.: New Developments in Asbestos-Induced Pleural Disease. Chest 99:191–198 (1991).
21. Bignon, J.; Brochard, P.; Brown, R.; et al.: Assessment of the Toxicity of Man-Made Fibres: A Final Report of a Workshop Held

in Paris, France, 3–4 February 1994. Ann Occup Hyg 39:89–106 (1995).
22. Refractory Ceramic Fibers Coalition: Cost Impacts of a Potential Ban on Refractory Ceramic Fibre for Furnace Related Applications; Technical and Economic Analysis. Prepared by Everest Consulting Associates and Submitted to the U.S. Environmental Protection Agency, Washington, DC (1992).
23. Thermal Insulation Manufacturers Association: Health and Safety Aspects of Man-Made Vitreous Fibers. Report to NIOSH, Stamford, CT (July 10, 1990).
24. Refractory Ceramic Fibers Coalition: Refractory Ceramic Fiber. Review presented to the American Conference of Governmental Industrial Hygienists Chemical Substances TLV Committee, Cincinnati, OH (July 13, 1998).
25. Maxim, L.D.; Kelly, W.P.; Walters, T.; Waugh, R.: A Multi-Year Workplace Monitoring Program for Refractory Ceramic Fibers. Reg Toxicol Pharmacol 26:156–171 (1997).
26. Hill, G.W.: Fibres, Man-Made Glass and Mineral. In: Encyclopaedia of Occupational Health and Safety, L. Parmeggiani, ed., vol. 1, pp. 852–855. International Labor Organization, Geneva (1983).
27. Timbrell, V.: Review of the Significance of Fibre Size in Fibre-Related Lung Disease: A Centrifuge Cell for Preparing Accurate Microscope-Evaluation Specimens from Slurries Used in Inoculation Studies. Ann Occup Hyg 33:483–505 (1989).
28. Dement, J.M.; Harris, R.L.: Estimates of Pulmonary and Gastrointestinal Deposition of Occupational Fiber Exposures. DHEW (NIOSH) Publication No. 79-135. NIOSH, Cincinnati, OH (1979).
29. Lentz, T.J.; Rice, C.H.; Lockey, J.E.; et al.: Potential Significance of Airborne Fiber Dimensions Measured in the U.S. Refractory Ceramic Fiber Manufacturing Industry. Am J Indus Med 36:286–298 (1999).
30. Rice, C.; Lockey, J.; Lemasters, G.; et al.: Assessment of Current Fibre and Silica Exposure in the U.S. Refractory Ceramic Fibre Manufacturing Industry. Ann Occup Hyg 38(Suppl 1):739–744 (1994).
31. National Institute for Occupational Safety and Health: NIOSH Manual of Analytical Methods, 3rd ed., NIOSH, Cincinnati, OH (1989).
32. MacKinnon, P.A.; Lentz, T.J.; Rice, C.H.; et al.: Electron Microscopy Study of Refractory Ceramic Fibers. Appl Occup Environ Hyg 16:944–951 (2001).
33. Dement, J.M.; Wallingford, K.M.: Comparison of Phase Contrast and Electron Microscopic Methods for Evaluation of Occupational Asbestos Exposures. Appl Occup Environ Hyg 5:242–247 (1990).
34. Corn, M.; Esmen, N.; Hammad, Y.; et al.: Estimation of Employee Exposures to Total Suspended Particulate Matter and Airborne Ceramic Fibers at Carborundum Plant, Niagara Falls, New York. Report presented to the Medical and Scientific Committee of the Thermal Insulation Manufacturers Association (1977).
35. SAS Institute: SAS Procedure Guide, Release 6.03. SAS Institute, Inc., Cary, NC (1992).
36. Fleiss, J.L.: Statistical Methods for Rates and Proportions, 2nd ed., pp. 212–236, John Wiley & Sons, New York (1981).
37. Harris, R.L., Jr.; Fraser, D.A.: A Model for Deposition of Fibers in the Human Respiratory System. Am Indus Hyg Assoc J 73–89 (1976).
38. Weibel, E.R.; Gomez, D.M.: Architecture of the Human Lung. Science 137:577–585 (1962).
39. International Commission on Radiological Protection, Task Group on Lung Dynamics: Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract. Health Phys 12:173–207 (1966).
40. Swift, D.L.; Proctor, D.F.: Human Respiratory Deposition of Particles During Oronasal Breathing. Atmos Environ 16:2279–2282 (1982).
41. Niinimaa, V.; Cole, P.; Mintz, S.; Shephard, R.J.: Oronasal Distribution of Respiratory Airflow. Res Physiol 43:69–75 (1981).
42. Ayer, H.E.; Zumwalde, R.D.: Physical and Chemical Characteristics of Airborne Fibers. In: Generation of Aerosols and Facilities for Exposure Experiments, K. Willeke, ed., pp. 235–256. Ann Arbor Science Publishers, Inc., Ann Arbor, MI (1980).
43. International Labor Organization: Guideline for the Use of ILO International Classification of Radiographs of Pneumoconioses. Occupational Health Series 22 (Rev. 80), International Labor Office, Geneva (1980).
44. Imbernon, E.; Goldberg, M.; Bonenfant, S.; et al.: Occupational Respiratory Cancer and Exposure to Asbestos: A Case-Control Study in a Cohort of Workers in the Electricity and Gas Industry. Am J Indus Med 28:339–352 (1995).
45. Lippmann, M.: Man-Made Mineral Fibers (MMMF): Human Exposures and Health Risk Assessment. Toxicol Indus Health 6:225–246 (1990).
46. Heard, B.E.; Williams, R.: The Pathology of Asbestos with Reference to Lung Function. Thorax 16:264–281 (1961).
47. Thomson, J.G.: The Pathogenesis of Pleural Plaques. In: Pneumoconiosis—Proceedings of the International Conference, Johannesburg, 1969, H.A. Shapiro, ed., pp. 138–141. Oxford University Press, Capetown (1970).
48. Zielhuis, R.L.: Public Health Risks of Exposure to Asbestos. Report of a Working Group of Experts Prepared for the Commission of the European Communities, Directorate General for Social Affairs, Health and Safety Directorate, Pergamon Press, Oxford (1977).
49. Hourihane, D.O'B.: A Biopsy Series of Mesothelioma and Attempts to Identify Asbestos Within Some of the Tumors. Ann NY Acad Sci 132:647–673 (1965).
50. Taskinen, E.; Ahlmann, K.; Wiikerie, M.: A Current Hypothesis of the Lymphatic Transport of Inspired Dust to the Parietal Pleura. Chest 64:193–196 (1973).
51. Brown, A.: Lymphohematogenous Spread of Asbestos. Environ Health Persp 9:203–204 (1974).
52. Oberdörster, G.; Morrow, P.E.; Spurny, K.: Size Dependent Lymphatic Short Term Clearance of Amosite Fibres in the Lung. In: Inhaled Particles VI, J. Dodgson, R.I. McCallum, M.R. Bailey, D.R. Fisher, eds., pp. 149–156. Pergamon Press, Oxford (1988).
53. Herbert, A.: Pathogenesis of Pleurisy, Pleural Fibrosis, and Mesothelial Proliferation. Thorax 41:176–189 (1986).
54. Oberdörster, G.: Macrophage-Associated Responses to Chrysotile. Ann Occup Hyg 38:601–615 (1994).
55. Browne, K.: Asbestos-Related Disorders. In: Occupational Lung Disorders, 3rd ed., W.R. Parkes, ed., pp. 411–504. Butterworth-Heineman Ltd., Oxford (1994).
56. Findeisen, W.: The Deposition of Small Airborne Particles in the Human Lung During Respiration. Pfluegers Archiv fuer Die Gesamte Physiologie des Menschen und der Tiere 26:367–379 (1935).
57. Beeckmans, J.M.: The Deposition of Asbestos Particles in the Human Respiratory Tract. Intern J Environ Stud 1:31–34 (1970).

58. Asgharian, B.; Yu, C.P.: Deposition of Inhaled Fibrous Particles in the Human Lung. J Aerosol Med 1:37–50 (1988).
59. Koblinger, L.; Hofmann, W.: Monte Carlo Modeling of Aerosol Deposition in Human Lungs. Part I: Simulation of Particle Transport in a Stochastic Lung Structure. J Aerosol Sci 21:661–674 (1990).
60. Sussman, R.G.; Cohen, B.S.; Lippmann, M.: Asbestos Fiber Distribution in a Human Tracheobronchial Cast. II. Empirical Model. Inhal Toxicol 3:161–179 (1991).
61. Yu, C.P.; Ding, Y.J.; Zhang, L.; Oberdörster, G.; Mast, R.W.; Maxim, L.D.; Utell, M.J.: Deposition and Clearance Modeling of Inhaled Kaolin Refractory Ceramic Fibers (RCF) in Hamsters—Comparison Between Species. Inhal Toxicol 7:165–177 (1995).
62. Yu, C.P.; Ding, Y.J.; Zhang, L.; Oberdörster, G.; Mast, R.W.; Glass, L.R.; Utell, M.J.: A Clearance Model of Refractory Ceramic Fibers (RCF) in the Rat Lung Including Fiber Dissolution and Breakage. J Aerosol Sci 27:151–160 (1996).