

Retention Modeling of Refractory Ceramic Fibers (RCF) in Humans

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A mathematical retention model has been developed to predict the lung burden and size distribution of kaolin refractory ceramic fibers (RCF) in the pulmonary region of the human lung during exposure. Fiber dissolution, breakage, and differential clearance are considered in this model; rates for these processes are obtained by extrapolation from available data on laboratory rats. The lung burden predicted by this model is in general agreement with fiber counts from three factory workers. An important prediction from this study is that clearance of RCF is not significantly impaired at a fiber concentration beneath 10 f/cm³ during occupational exposure. © 1997 Academic Press

INTRODUCTION

When rats and hamsters were chronically exposed to refractory ceramic fibers (RCF) at high concentrations (30 mg/m³), lung fibrosis, lung cancer, and mesothelioma were induced in these animals (Mast *et al.*, 1995a,b; McConnell *et al.*, 1995). This raises a concern about the potential for adverse health effects in humans from inhalation of these fibers in the workplace, although available epidemiological data on present and former RCF workers do not show any evidence of these diseases. Since the rodent studies were performed at much higher concentrations than those encountered at the workplace, it is important to understand whether and how the animal data can be extrapolated to humans at the low concentrations (<1 f/cm³) typically found in the workplace. Such extrapolations require a knowledge of the comparative dosimetry of fibers in the respiratory tract of both species.

The health effects of inhaled fibers are related, inter alia, to the physical-chemical properties of the fiber and the number of fibers accumulating in the lung. In the exposure experiments with RCF conducted in rats and hamsters, the lung burden and fiber size retained in the lung as well as pathological effects were evaluated (Mast *et al.*, 1995a,b; McConnell *et al.*, 1995). In

principle, therefore, dose-response relationships can be developed in these animals based upon available data. The purpose of this paper is to develop a mathematical model for predicting the pulmonary accumulation of RCF during chronic human exposure. Such an analysis may provide useful guidance for selecting appropriate models for human risk assessment.

MODEL DEVELOPMENT

A mathematical model of RCF deposition and retention in the rat lung has been recently developed based upon bioassay data (Yu *et al.*, 1996). The model considered the removal of fibers from the lung by three simultaneous processes: alveolar macrophage-mediated clearance, dissolution of fibers in the lung fluid, and breakage of long fibers into shorter fibers. In addition, the macrophage-mediated clearance rate in this model was found to decrease with lung burden and with fiber length. The same deposition and retention logic is employed in this study for humans, except that different deposition and clearance rates are used. Table 1 compares several anatomical and physiological parameters relevant to respiratory deposition and clearance for humans and rats.

We consider the alveolar region of the lung as a single compartment in which there are $n(d_f, l_f, t) d(d_f) d(l_f)$ fibers in the diameter interval from d_f to $d_f + d(d_f)$ and in the length interval from l_f to $l_f + d(l_f)$ at time t . The kinetic equation which describes the time variation of $n(d_f, l_f, t)$ is (Yu *et al.*, 1996)

$$\begin{aligned} \frac{\delta n(d_f, l_f, t)}{\delta t} = & r(d_f, l_f, t) - \lambda_m(l_f, V)n(d_f, l_f, t) + 2k \frac{\delta n(d_f, l_f, t)}{\delta d_f} \\ & + \int_{l_f}^{\infty} m(l_f, l_f) \alpha(l_f, l_f) n(d_f, l_f, t) d(l_f) \\ & - \int_0^{l_f} \alpha(l_f, l_f) n(d_f, l_f, t) d(l_f), \end{aligned} \quad (1)$$

where $r(d_f, l_f, t)$ is the deposition rate, $\lambda_m(l_f, V)$ is the

TABLE 1

Comparison of Anatomical and Physiological Parameters of the Human and Rat Relevant to the Dosimetry Study

Parameter	Human	Rat	Ratio human/rat
Body weight (kg)	70	0.3	233
Lung weight (g)	10 ³	1.48	676
Airway volume (cm ³)	3.2 × 10 ³	6.5	492
Airway surface area (cm ²) ^a	6.27 × 10 ⁵	5.5 × 10 ³	114
Number of AM ^b	7 × 10 ⁹	2.6 × 10 ⁷	269
AM volume (μm ³) ^b	2.5 × 10 ³	10 ³	2.5
Total AM volume (mm ³) ^b	1.75 × 10 ⁴	26	673
Tidal volume (cm ³)	5 × 10 ²	2.74	182
Breathing frequency (min ⁻¹)	14	98	0.14
Minute ventilation (cm ³ /min)	7 × 10 ³	2.68 × 10 ²	26

^a Calculated from Weibel's model (1964) for humans and Yeh and Schum's model (1980) for rats.

^b Adopted from Dethloff and Lehnert (1987).

macrophage-mediated mechanical clearance rate, k is the dissolution rate, $\alpha(l_f, l_f)$ $d(l_f)$ is the rate at which a fiber in the length interval l_f and $l_f + d(l_f)$ breaks into a length l_f with number of segments $m(l_f, l_f)$, and $\alpha(l_f, l_f)d(l_f)$ is the rate at which a fiber of length l_f breaks into the length interval l_f and $l_f + d(l_f)$.

In general, the parameters λ_m and α in Eq. (1) depend upon both fiber length l_f and fiber diameter d_f . The dependence on fiber diameter is less obvious and cannot be derived directly from the rat data. We neglect this dependence in the present formulation. However, the rat data show that λ_m also varies with $V(t)$, the total accumulated fiber volume in the lung, and $V(t)$ is given by

$$V(t) = \int_0^\infty \int_0^\infty n(d_f, l_f, t) \frac{\pi}{4} d_f^2 l_f d(d_f) d(l_f). \quad (2)$$

We assume that λ_m for humans has a similar dependence on $V(t)$ in the formulation. The dissolution rate k in Eq. (1) is a constant, obtained from the rat data. The dissolution term in this equation states that all fiber diameters decrease with time at rate k . A fiber will disappear only when it passes through zero diameter. For RCF, the value of k is very small and fiber removal from the lung by dissolution is insignificant over the lifetime of a rat. Because the macrophage-mediated clearance is much slower and the lifetime is much longer, dissolution may become a contributor to the overall fiber removal process in humans.

The deposition rate $r(d_f, l_f, t)$ in Eq. (1) can be calculated from the expression

$$r(d_f, l_f, t) = TV \times BF \times C(d_f, l_f, t) \times \eta(d_f, l_f), \quad (3)$$

where TV is the tidal volume, BF is the breathing fre-

quency, $\eta(d_f, l_f)$ is the alveolar deposition fraction of a fiber with diameter d_f and length l_f , and $C(d_f, l_f, t)$ is the fiber concentration at time t . Mathematical models have been proposed to calculate the alveolar deposition fraction $\eta(d_f, l_f)$ for rats and humans (Yu *et al.*, 1994, 1995). The results showed significant differences between the two species, caused by the differences in extrathoracic airway structure, lung morphometry, and ventilation parameters. For an exposure to RCF with a given size distribution, the size distribution of deposited RCF in the alveolar region of the lung is obtained by multiplying the size distribution of airborne RCF by $\eta(d_f, l_f)$. Figures 1b to 1d compare the deposited fiber size distribution in rats and humans at nose and mouth breathing for a typical workplace airborne RCF with a bivariate lognormal size distribution reported by Hori *et al.* (1993), as shown in Fig. 1a. The geometric mean diameter and length of the airborne RCF for this case were, respectively, 0.86 and 11 μm with the corresponding geometric standard deviations of 1.9 and 2.6. Data on the size distribution of airborne RCF found in the workplace are also reported by Everest Consulting Associates (1995). Based upon transmission electron microscopy (TEM) measurements of over 3300 fibers distributed among 98 samples, the geometric mean diameter and length of RCF workplace samples were 0.8 and 14.1 μm, respectively, in broad agreement with the findings of Hori *et al.* (1993).

Because of a smaller filtration by the extrathoracic and tracheobronchial airways, the average number deposition fraction [the value of $\eta(d_f, l_f)$ averaged over the airborne size distribution of RCF] and the deposited fiber sizes in humans are considerably greater than those in rats. Human mouth breathing also leads to a greater deposition fraction and a larger deposited fiber size than human nose breathing. Table 2 summarizes the calculated deposition results for rats and humans from the deposition models (Yu *et al.*, 1994, 1995) for an airborne RCF size distribution shown in Fig. 1a.

Based upon the lung burden data, the macrophage-mediated clearance rate λ_m for rats was previously found to be (Yu *et al.*, 1996)

$$\lambda_m(l_f, V) = \begin{cases} \lambda_{mo} \exp \left[-a \left(\frac{V}{V_{AM}} \right)^b \right], & l_f \leq l_f^* \\ \lambda_{mo} \exp \left[-c \left(\frac{l_f - l_f^*}{l_{AM}} \right) \right] \exp \left[-a' \left(\frac{V}{V_{AM}} \right)^b \right], & l_f > l_f^*, \end{cases} \quad (4a)$$

$$(4b)$$

where $\lambda_{mo} = 0.013 \text{ day}^{-1}$ is the macrophage-mediated clearance rate of nonfibrous particles at low lung burden, $a = 7.2$, $a' = 17.4$, $b = 0.92$, and $c = 2.06$. $l_f^* = 2 \mu\text{m}$ is the fiber length below which the clearance rate

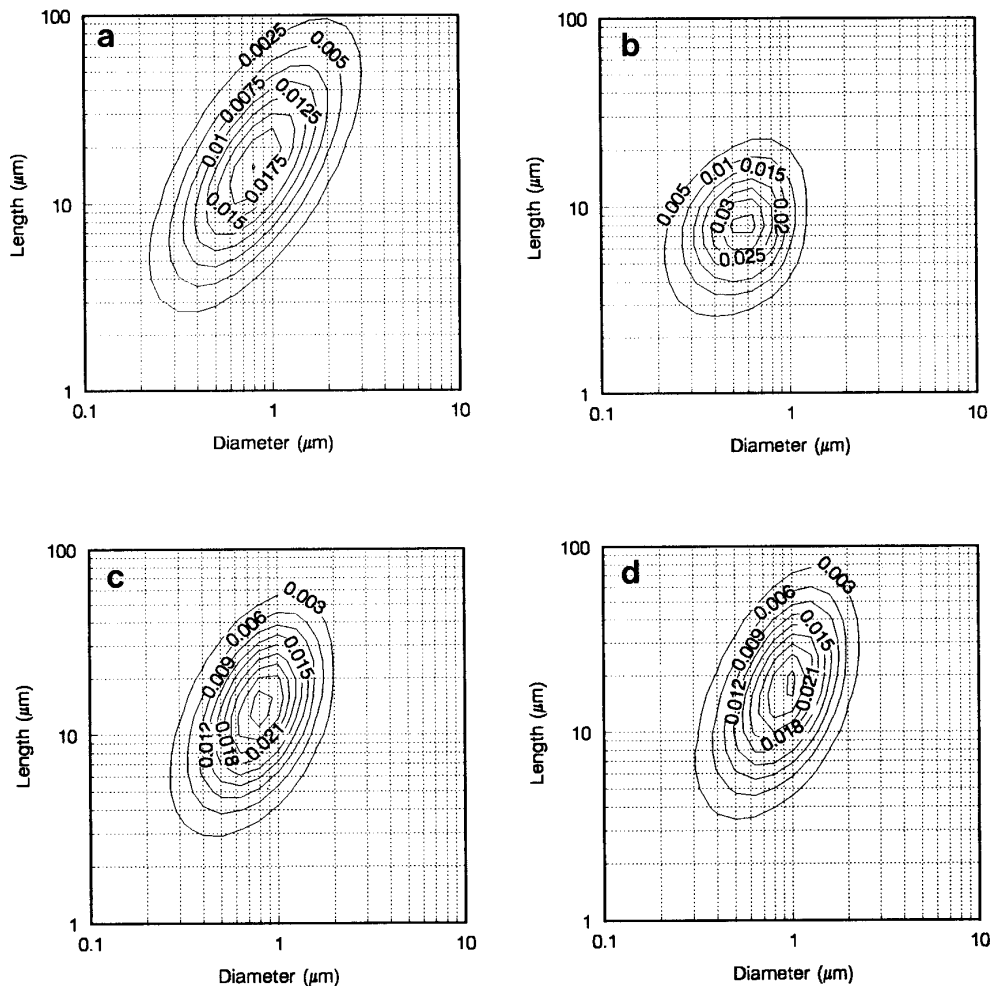


FIG. 1. Size distribution of deposited kaolin RCF in the pulmonary region of the lung. (a) Aerosol, (b) rat, (c) human at nose breathing, and (d) human at mouth breathing.

is the same as nonfibrous particles, $V_{AM} = 26 \text{ mm}^3$ is the total volume of alveolar macrophages in rats (Dethloff and Lehnert, 1987), and $l_{AM} = 10 \mu\text{m}$ is a character-

TABLE 2

Comparison of Average Number Deposition Fraction and Size of Deposited RCF in the Alveolar Region of the Lung between Rats and Humans

	d_{fg} (μm)	l_{fg} (μm)	DF
Rat	0.51	5.3	0.026
Human (mouth breathing)	0.91	11.6	0.163
Human (nose breathing)	0.80	9.4	0.092

Note. d_{fg} , geometric mean diameter; l_{fg} , geometric mean length; DF, average number deposition fraction over the airborne fiber size distribution. All calculations were based upon a bivariate lognormal size distribution of airborne RCF with $d_{fg} = 0.86 \mu\text{m}$, $l_{fg} = 11 \mu\text{m}$, $\sigma_{gd} = 1.9$, and $\sigma_{gl} = 2.6$.

istic linear dimension of a macrophage for rats. The exponential function of $l_f - l_f^*$ in Eq. (4b) simulates the differential clearance of fiber, i.e., long fibers are cleared slower than short ones and fibers with length less than l_f^* are cleared at the same rate as nonfibrous particles. The exact value for l_f^* is not known at this time. However, the use of a higher value of l_f^* than $2 \mu\text{m}$ in Eq. (4b) will lead to a lower value of c and only a minor change in $\lambda_m(l_f, V)$. The exponential function of V in Eqs. (4a) and (4b) describes the prolongation of the clearance rate at high particle burdens due to overload (Morrow, 1988).

To extrapolate Eqs. (4a) and (4b) to represent human clearance, two parameters in these equations must be changed, i.e., λ_{mo} and V_{AM} . From the data of Bailey *et al.* (1985a,b), $\lambda_{mo} = 0.0017 \text{ day}^{-1}$ for humans, which is about 7.6 times smaller than the value for the rat. However, the total alveolar macrophage volume of humans is much higher than that of rats because of a

greater number of alveolar macrophages (7×10^9 in humans versus 2.6×10^7 in rats) and a larger alveolar macrophage volume ($2500 \mu\text{m}^3$ for humans versus $1000 \mu\text{m}^3$ for rats). Thus, $V_{AM} = (7 \times 10^9) (2500) (10^{-6}) \text{mm}^3 = 1.75 \times 10^4 \text{mm}^3$ for humans. The use of a new V_{AM} in Eqs. (4a) and (4b) for humans implies that clearance retardation occurs in humans in the same manner as found in the rat when the fiber volume dose becomes a significant fraction of the total macrophage volume. The parameters I_r^* and I_{AM} in Eq. (4b) can also be replaced by the human values. Because the linear dimension of a macrophage differs only about 35% (from the difference of the cubic roots of 2500 and $1000 \mu\text{m}^3$) between rats and humans, the same values of I_r^* and I_{AM} given above for rats are used for humans.

There are no data for the dissolution and breakage rates of RCF in humans. These rates are assumed to be the same as those calculated for rats, i.e., $k = 0.065 \text{nm day}^{-1}$ and

$$\alpha(i,j) = \begin{cases} 5 \times 10^{-4} \text{day}^{-1}, & \text{for } i > 20 \mu\text{m}, \\ & 10 \mu\text{m} < j < 20 \mu\text{m} \\ 3.4 \times 10^{-4} \text{day}^{-1}, & \text{for } 10 \mu\text{m} < i < 20 \mu\text{m}, \\ & 5 \mu\text{m} < j < 10 \mu\text{m} \\ 1.7 \times 10^{-4} \text{day}^{-1}, & \text{for } 5 \mu\text{m} < i < 10 \mu\text{m}, \\ & j < 5 \mu\text{m} \\ 0, & \text{for all other } i \text{ and } j. \end{cases} \quad (5)$$

LUNG BURDEN RESULTS

The lung burden accumulation in humans during exposure can be calculated using Eqs. (1), (4a), and (4b). Figure 2 shows the predicted number of fibers per gram of wet lung for an exposure to 1f/cm^3 RCF for 8 hr/day, 5 days/week over a total exposure period of 2 years. The result calculated for rats (Yu *et al.*, 1996) is also shown for comparison. The model predicts that, per gram of lung, humans accumulate less than one-third of the number of fibers found in the rat lung after a 2-year exposure, despite a much higher deposition rate.

The airborne fiber concentration of RCF in the workplace is variable. Hori *et al.* (1993) reported a range of 0.09 to 3.69f/cm^3 based upon personal sampler measurements in two factories. Maxim *et al.* (1994) [see also Everest Consulting Associates (1995)] analyzed RCF workplace concentration data collected as part of a Consent Agreement between members of the Refractory Ceramic Fibers Coalition (RCFC) and the United States Environmental Protection Agency (EPA). Under terms of this agreement, more than 700 samples are collected annually from eight domestic production and

processing plants operated by RCFC members and from numerous customer locations. Time-weighted-average (TWA) workplace RCF concentrations measured by phase-contrast optical microscopy (PCOM) were found to vary with job category, specific task being performed, and sector (primary producer versus processor). Average TWA fiber concentrations ranged from approximately 0.08f/cm^3 (assembly operations at primary production facilities) to 1.11f/cm^3 (insulation removal operations); approximately 90% of all TWAs were less than or equal to 1f/cm^3 , although some individual measurements were significantly higher. As with the Hori data, these data were collected during the 1990s and may not reflect conditions that prevailed in earlier years.

To estimate the number of fibers accumulated in the lungs of workers over this concentration range, we calculated the lung burden for both nose and mouth breathing for four assumed RCF concentrations of 0.01, 0.1, 1, and 10f/cm^3 , breathing at rest. The assumed exposure pattern of the workers was 8 hr/day, 5 days/week over a working lifetime of 40 years. The results, normalized by the exposure concentrations, are shown in Figs. 3 and 4. As expected, the lung burden for mouth breathing was found to be higher than that for nose breathing. However, for both breathing modes, a significant reduction of fiber clearance is predicted only in cases when the exposure concentration approaches 10f/cm^3 . This behavior is similar to the overload phenomenon observed in studies of nonfibers (Morrow, 1988). The predicted result may be relevant for risk analysis because (from animal bioassay data) the observed shape of the empirical exposure-response function is flat at low exposure concentrations and steeper at high exposure concentrations. Calculations also show that fiber removal by dissolution for RCF in humans is still not a significant contributor even for 40 years of exposure. However, this may not be the case for more soluble fibers.

Because fiber length is a key determinant for fiber-induced lung diseases, it is of interest to know the length distribution of RCF in the human lung during the course of chronic exposure. Figure 5 shows the results of fiber number accumulated in the lung for different length ranges ($I_f \leq 5 \mu\text{m}$, $5 \mu\text{m} < I_f \leq 10 \mu\text{m}$, $10 \mu\text{m} < I_f \leq 20 \mu\text{m}$, and $I_f > 20 \mu\text{m}$) at an exposure concentration of 1f/cm^3 . While the number of long fibers ($I_f > 20 \mu\text{m}$) is reduced over time by breakage, short fibers ($I_f \leq 5 \mu\text{m}$) are removed most efficiently because of the high macrophage-mediated clearance. Most RCF retained in the lung have a length in the range from 10 to $20 \mu\text{m}$.

COMPARISON OF MODEL PREDICTIONS WITH HUMAN EPIDEMIOLOGICAL DATA

The only available human data on RCF accumulation were collected at the University of Cincinnati (Lockey

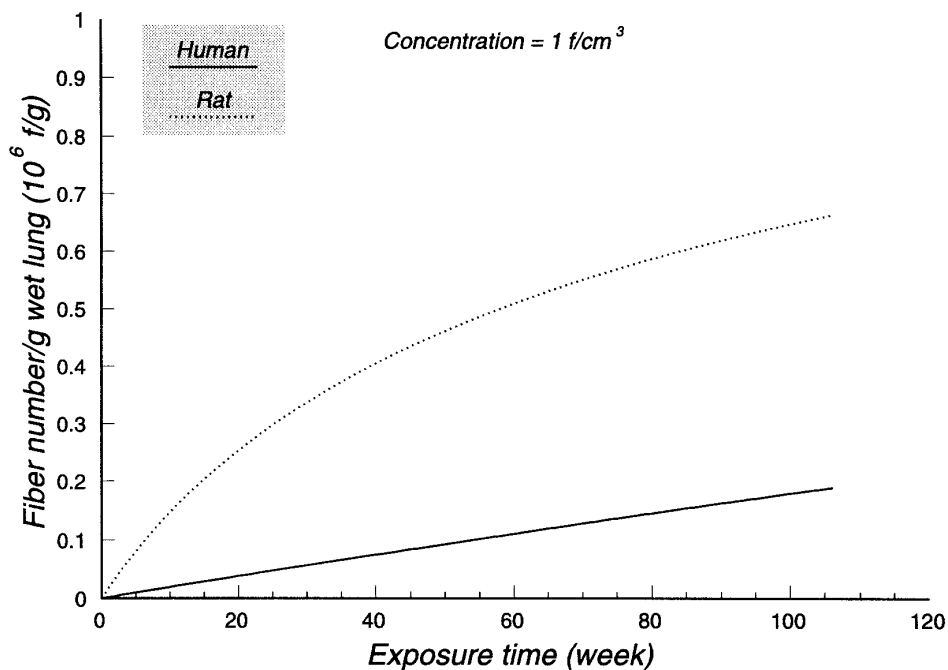


FIG. 2. Normalized lung burden of kaolin RCF in humans and rats as a function of exposure time. Exposure pattern is 8 hr/day and 5 days/week.

et al., 1993). These data were from three male workers who spent a total of 13, 16, and 17 years working in a RCF production facility. Lung tissue samples were

obtained from one individual at autopsy and from two workers at the time of elective surgery. Table 3 lists the job descriptions of these workers and the observed

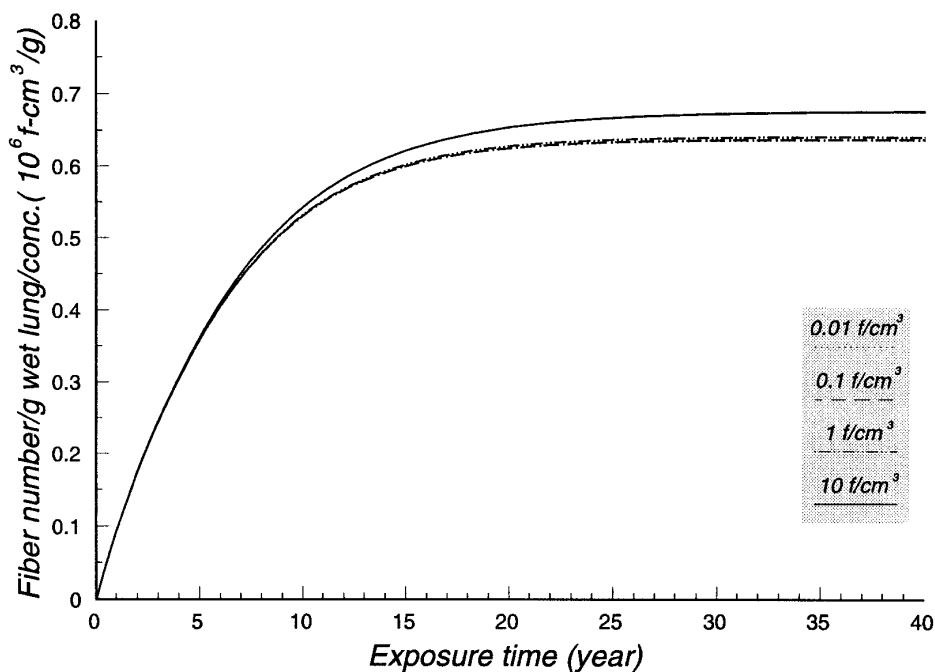


FIG. 3. Predicted normalized lung burden of kaolin RCF in humans at nose breathing as a function of exposure time. Exposure pattern is 8 hr/day and 5 days/week.

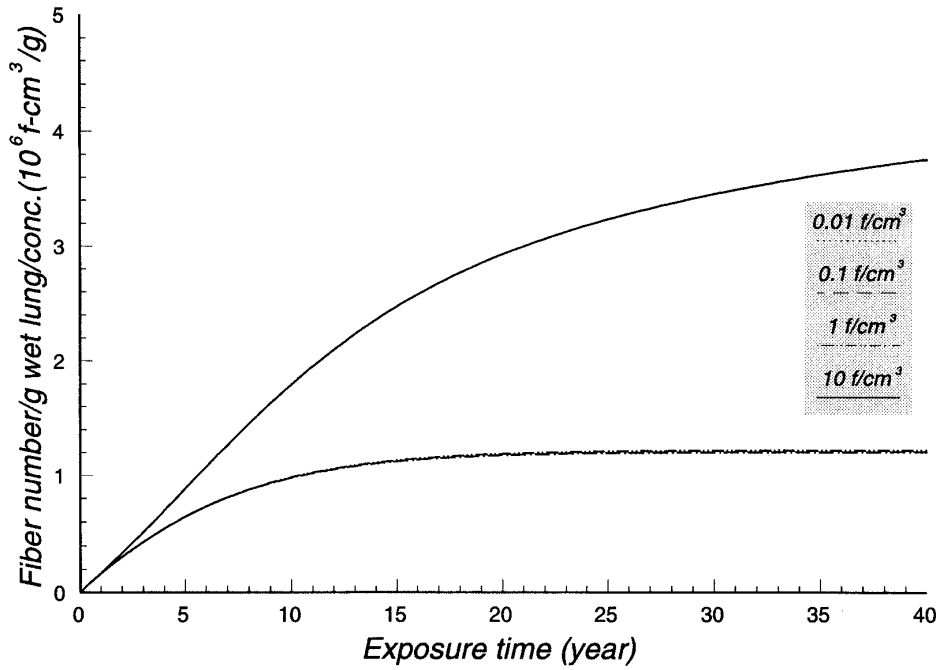


FIG. 4. Predicted normalized lung burden of kaolin RCF in humans at mouth breathing as a function of exposure time. Exposure pattern is 8 hr/day and 5 days/week.

lung burdens. The exposure concentrations and fiber sizes of these workers were not reported in the Cincinnati study. For this reason, it is not possible to provide

a rigorous test of the accuracy of the model presented here. However, there is some agreement between the model predictions and observed lung burden data (Fig.

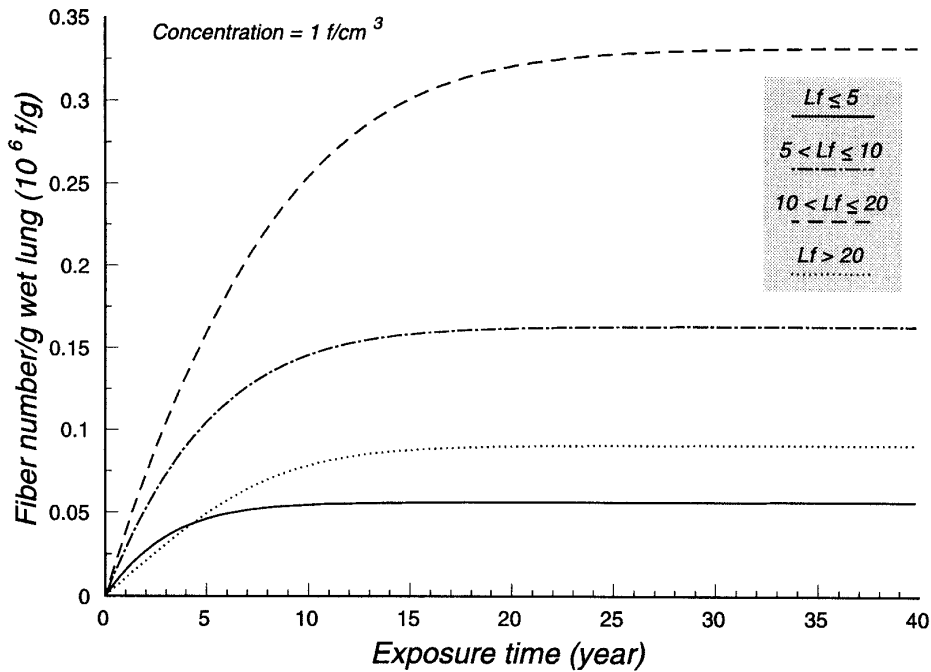


FIG. 5. Predicted lung burden of kaolin RCF in humans at nose breathing for different fiber length ranges as a function of exposure time. Exposure pattern is 8 hr/day and 5 days/week.

TABLE 3

Lung Burden Data and Possible Exposure Concentrations of Three Workers in the Cincinnati Study (Lockey *et al.*, 1993)

Worker	Job description	Fiber number/ lung tissue ($10^6/g$)
W1	Textile machine operator (17 years)	0.401
W2	Production line operator (16 years)	0.154
W3	Production line operator and quality control technician (13 years)	0.357

6). For example, the predicted average workplace concentration from the model for worker 2 (production line operator) is 0.25 f/cm^3 . Based upon current workplace conditions, Hori *et al.* (1993) reported a range of fiber concentrations in Japanese plants of 0.09 to 0.72 f/cm^3 for workers in this functional job category. Average TWAs reported by Everest Consulting Associates (1995) for plants in the United States for the functional job category fiber manufacturer were 0.27 f/cm^3 in 1994 and 0.17 f/cm^3 in 1995. For workers 1 and 3, the predicted average workplace concentrations are higher than the above-reported values. This discrepancy is probably caused by the fact that these workers belong to different work categories for which exposure concen-

trations are higher. The appropriate test of the predictive power of the model, however, is to compare the observed lung burdens with the overall TWA exposures to the actual fiber size distribution for these particular workers during their working life.

CONCLUDING REMARKS

Assuming that the clearance rate in humans varies with the specific fiber dose to the total alveolar macrophage volume in the same way as was found in the rat and that dissolution and breakage rates are the same for both species, the model developed here predicts the removal rate of kaolin refractory ceramic fibers from the human lung for any fiber burden and fiber size. In conjunction with the deposition model of inhaled fibers in humans described in a previous study (Yu *et al.*, 1995b), this model enables calculation of the fiber burden in the human lung at various occupational exposure concentrations. The results are in general agreement with lung tissue fiber counts from a recent study. The modeling results also show that humans have a much lower fiber burden per gram of lung than rats over a 2-year exposure period, i.e., the approximate lifespan of a rat (Fig. 2). In contrast, exposure of workers over 40 years to the same fiber concentration leads to a higher fiber burden in their lungs. An important prediction from this study is that the clearance rate of kaolin RCF would not be significantly reduced in hu-

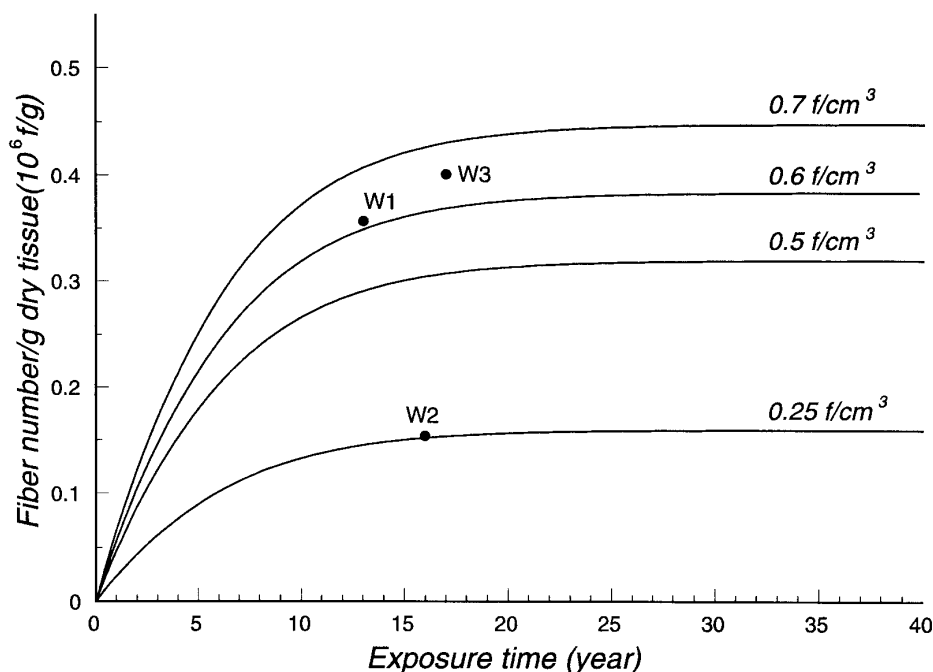


FIG. 6. Comparison of the human lung burden data and the modeling results at several concentrations. The dry lung weight was assumed to be 22% of the wet lung weight.

mans until exposure concentration approaches 10 f/cm^3 during occupational exposure.

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