J. Aerosol Sci., Vol. 22, No. 6, pp. 757–763, 1991.
Printed in Great Britain.

0021-8502/91 $3.00+0.00

INTRAPULMONARY DEPOSITION AND RETENTION MODELING OF CHRYSOTILE ASBESTOS FIBERS IN RATS

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(*Received* 1 *October* 1990; *and in final form* 11 *February* 1991)

Abstract—Previous experiments have shown that the number accumulation of chrysotile asbestos fibers in the alveolar tissue of the rat lung after a prolonged exposure is highly nonuniform. This nonuniformity arises from the asymmetry of the airway path. A theoretical model is presented to simulate the deposition and clearance processes of these fibers in an asymmetric lung in order to explain the observed nonuniformity. Calculations reveal that alveolar regions with fewer airway generations or bifurcations in their path will have a higher fiber retention and a larger mean fiber length. These results compare favorably with existing experimental data.

INTRODUCTION

Accumulation of asbestos fibers in the alveolar tissue makes the lung vulnerable to injury. The degree of injury is believed, however, to be closely associated with the number of fiber accumulated. Experiments have shown that the number accumulation of chrysotile asbestos fiber in the rat lung is highly nonuniform after a prolonged exposure with regions of high fiber concentration (Churg and Warnock, 1980; Churg, 1983; Pinkerton *et al.*, 1986). These regions stem from different airway paths from the trachea, characterized by different airway branch patterns (Pinkerton *et al.*, 1986). The purpose of this paper is to present a theoretical model of fiber deposition and clearance in the rat lung to illustrate why such regional differences of fiber accumulation in the lung tissue would occur. An attempt is made to correlate the theoretical results of fiber retention with experimental data of fiber concentration in the lung tissue.

A theoretical model of deposition and clearance for inhaled chrysotile asbestos fibers in the rat lung has been reported recently (Yu *et al.*, 1990). This model assumes that chrysotile asbestos fibers behave like uncharged, rigid, long ellipsoids and that the lung airways are symmetrical. The calculated retention of inhaled fibers in the alveolar space from this model is identical for different airway paths. In the present work, the symmetrical airway model is generalized to incorporate the airway asymmetry. However, only the difference in deposition resulting from different airway paths will be accounted for in the new model. The clearance rate of the fiber in the lung is assumed to be the same for all regions.

REGIONAL MODEL OF DEPOSITION AND CLEARANCE

Pinkerton *et al.* (1986, 1989) have made measurements of fiber concentration in various regions of the left lobe of the rat lung. Following the identical procedure, we have divided the left lobe of the rat lung into five alveolar regions, each stemming from a different airway path. Since these regions have different distances from the trachea, the terminal bronchioles leading to alveoli for each region are located at a different airway generation. Thus, each region in the lung model can be identified by either the path length or generation number of its terminal bronchioles. The five regions defined previously (Pinkerton *et al.*, 1986) are: dorsally at the end of the 6th generation, laterally at the end of the 8th generation, cranially at the end of the 10th generation, costolaterally at the end of the 15th generation, and caudally at the end of the 16th generation. We also assume that each alveolar region has identical structure. Therefore, within each region, the number of airways at a generation is

one-fifth of the total airway number in that generation described by the whole lung model. In addition, the conducting airways at each generation are assumed to have the same number and dimensions for all airway paths. Since each airway path has a different path length and consists of a different number of airways, the airflow through each path is different. We assume that each airway path follows a trumpet model as described by Yu (1978) and the airflow through each airway path is proportional to the total volume of that pathway. The uneven distribution of ventilation to different regions of the lung due to gravity is not considered in the model. Figure 1 shows a schematic diagram of the airway paths into different alveolar regions.

The deposition model of Asgharian and Yu (1989) for fibers and the lung data of Schum and Yeh (1980) at the total lung capacity were employed to calculate the deposition of chrysotile asbestos fibers in each alveolar region. In using Schum and Yeh's data, all linear dimensions of airway were scaled according to one third power of body weight. A body weight of 250 g was used for Fischer rats and the resting lung volume of the rat was assumed to be 40% of its total lung capacity. The respiratory condition used in the calculation was 1.68 cm^3 tidal volume at 98 breath min^{-1}.

Once chrysotile asbestos fibers are deposited on the alveolar surface, they will be removed from the deposition site by phagocytosis and macrophage migration. In addition, the fiber will be subjected to a longitudinal splitting process which reduces its diameter (Roggli and Brody, 1984; Bellmann *et al.*, 1986). The reason for the fiber splitting is not clear. It may be caused by the reaction with surfactants. We assume that the rate of splitting depends upon the fiber diameter while the clearance rate is a function of the fiber length alone, the differential equation describing the fiber kinetics in any given region is (Yu *et al.*, 1990)

$$\frac{dn(d_f, l_f, t)}{dt} = r(d_f, l_f, t) + \int_{d_f}^{\infty} \gamma(d'_f, d_f)\, n(d'_f, l_f, t)\, d(d'_f) - \int_0^{d_f} \gamma(d_f, d'_f)\, n(d_f, l_f, t)\, d(d'_f) - \lambda(l_f) n(d_f, l_f, t), \quad (1)$$

where $\gamma(d_f, d'_f)$ denotes the splitting rate of fibers of diameter d_f into fibers of diameter d'_f, $\gamma(l_f)$ is the clearance rate at which fibers of size (d_f, l_f) are removed from the lung, $n(d_f, l_f, t)$ is the number of the fibers in a region at time t and $r(d_f, l_f)$ is the fiber deposition rate when the rat is exposed to a constant fiber concentration. The expressions for γ, λ and r are given by Yu *et al.* (1990) as

$$\gamma(d_f, d'_f) = 0.0047\left[1 - \left(\frac{d'_f}{d_f}\right)^2\right], \quad (2)$$

$$\lambda(l_f) = 0.054 \exp(-0.12\, l_f) + 0.016, \quad (3)$$

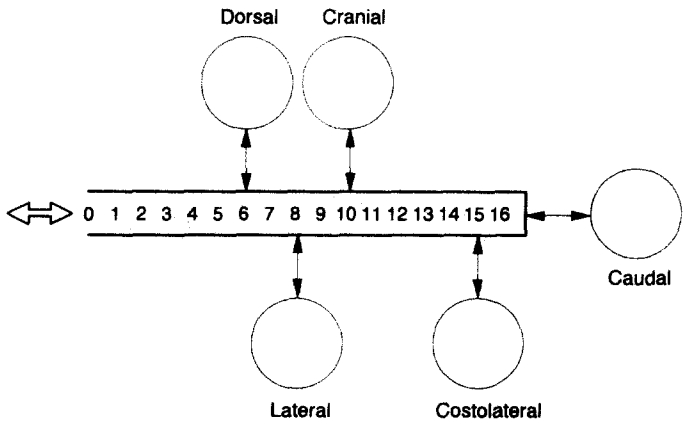


Fig. 1. Schematic diagram of the airway paths into different alveolar regions.

$$r(d_f, l_f, t) = \delta(d_f, l_f) \times \begin{pmatrix} \text{minute} \\ \text{volume} \end{pmatrix} \times \begin{pmatrix} \text{fiber} \\ \text{concentration} \end{pmatrix}, \quad (4)$$

where $\delta(d_f, l_f)$ is the deposition fraction in each alveolar region for a breathing cycle. In equation (1) the second term on the right-hand side represents the gain in the number of fibers of size (d_f, l_f) due to the splitting of the fibers with diameters larger than d_f, while the third term represents the loss due to fiber splitting from diameter d_f into smaller diameters. The last term on the right hand side of equation (1) denotes the loss of fibers due to clearance. Equations (2) and (3) were derived from the experimental data of Abraham *et al.* (1988) for Jeffery Mine chrysotile asbestos fibers. It is clear from equation (3) that λ decreases with the fiber length l_f but remains to be a finite even at very large l_f. The splitting rate γ and clearance rate λ may be different for different types of fibers (Leadbetter and Corn, 1972; Berstein *et al.*, 1980; Morgan *et al.*, 1982).

The size distribution of chrysotile fibers in the aerosol state was reported by Pinkerton *et al.* (1983). For model calculation, we reclassified their fiber size distribution into three diameter intervals: $d_f < 0.22$ μm, $0.22\ \mu m \leq d_f \leq 0.31$ μm, and $d_f > 0.31$ μm as shown in Table 1. Equation (1) can then be written in the form

$$\frac{dn_1}{dt} = r_1 + \gamma_{31}\left(\frac{d_{f3}}{d_{f1}}\right)^2 n_3 + \gamma_{21}\left(\frac{d_{f3}}{d_{f1}}\right)^2 n_2 - \lambda(l_f) n_1, \quad (5a)$$

$$\frac{dn_2}{dt} = r_2 + \gamma_{32}\left(\frac{d_{f3}}{d_{f2}}\right)^2 n_3 + \gamma_{21} n_2 - \lambda(l_f) n_2, \quad (5b)$$

$$\frac{dn_3}{dt} = r_3 - \gamma_{32} n_3 + \gamma_{31} n_2 - \lambda(l_f) n_3, \quad (5c)$$

where n_1, n_2 and n_3 are the numbers of fibers of length l_f in each diameter interval, r_1, r_2 and r_3 are the respective deposition rates for $d_{f1} = 0.2$ μm, $d_{f2} = 0.25$ μm, and $d_{f3} = 0.5$ μm, which are median fiber diameters in each diameter interval. The set of equations (5a)–(5c) permits an exact solution once the values of γ and λ are known. This solution has been previously found (Yu *et al.*, 1990).

RESULTS

The lung burdens of fibers of different size ranges in each alveolar region of the rat lung was calculated for an exposure condition of 7 h day^{-1}, 5 days week^{-1} for a 12-month period. Table 2 gives the results of total fiber number and mean fiber length of the retained fibers in each region. It shows that regions with fewer airway generations in their path have a higher value of fiber retention and a longer mean length. This is consistent with the experimental observations of fiber accumulation in the lung tissue by Pinkerton *et al.* (1986, 1989). The smaller fiber accumulation in the region with high airway generation number is

Table 1. Size distribution (number in per cent) of Jeffery chrysotile asbestos fibers according to the data of Pinkerton *et al.* (1983). Numbers in parentheses are the mean values

Fiber length (μm)	Fiber diameter (μm)		
	<0.22 (0.2)	0.22–0.31 (0.25)	>0.31 (0.5)
0–0.99 (0.5)	17.9	0	0
1–1.99 (1.5)	0	26.7	0
2–4.99 (3.5)	0	32.6	0
5–9.99 (7.5)	0	14.3	0
10–19.9 (15)	0	5.5	0
20–29.9 (25)	0	0	1.7
30–49.9 (40)	0	0	0.7
50–99.9 (75)	0	0	0.6
>100 (150)	0	0	0.1

Table 2. Total number and mean length of fibers in different regions of the rat lung

Region	Generation	Total number (10^8)	Mean fiber length (μm)
Dorsal	6	3.01	13.12
Lateral	8	2.79	12.81
Cranial	9	2.55	12.59
Costolateral	15	1.16	11.52
Caudal	16	0.136	10.88

attributed to the greater loss by deposition along the airway path. Because deposition of fibers takes place mostly at airway bifurcations, an airway path ending at a higher airway generation number would have a larger deposition loss. Also, since long fibers have a higher deposition efficiency at the bifurcation than the short ones, a smaller fraction of long fibers will reach the alveolar space. The mean fiber length in a region of higher generation number is therefore smaller.

In the experiments of Pinkerton *et al.* (1986, 1989), asbestos fibers collected from the exposure chamber and from digested lung tissues were placed directly on 0.2 μm nuclepore filters, sputter-coated with a thin layer of gold and viewed using a scanning electron microscope. To establish the size distribution of aerosolized fibers in the chamber, several samples of fibers were drawn from the exposure chamber air, from which a total of 1000 fibers were randomly selected and measured (Pinkerton *et al.*, 1983). To determine fiber concentration and size distribution from each region of the lungs, tissue samples from each region were digested and a total of 200 fibers or 100 fields were counted (Pinkerton *et al.*, 1986, 1989). For counting and sizing of fibers, all fields were randomly selected. Only asbestos fibers whose midpoints fell within each field under observation were measured to insure that each fiber, regardless of size, would have an equal probability of being selected for measurement.

Parenchymal regions selected for fiber burden analysis were isolated by microdissection of the airways to a level within two to four generations of the terminal bronchiole. Areas examined were all within in the left lung. Prior to tissue digestion, the volume of each fixed tissue block was measured with the aid of a dissecting microscope to determine the dimensions of each block. Histologic analysis of adjacent tissue blocks from the same regions verified that all tissues were inflated to the same degree. Therefore, fiber concentrations in each region were expressed per unit volume (mm^3) of fixed lung tissue.

A comparison with the fiber concentration data of Pinkerton *et al.* (1986, 1989) was made on the ratio of the number of the retained fibers in different regions with respect to those in the cranial region. Table 3 shows such a comparison. It is seen that the calculated ratio agrees reasonably with the data except in the caudal region where the calculated ratio is too small. The discrepancy could be caused by the insufficient tidal volume used in the calculation, which does not lead to enough penetration of the airflow into the caudal region. An adjustment of the fraction of tidal volume into each region in the calculation can improve the comparison.

To further understand the distribution of fiber length in each alveolar region, we calculate the percentage of fibers in different length intervals. Figure 2 shows these results along with the data of Pinkerton *et al.* (1986, 1989). Due to the reason explained earlier, the percentage of long fibers in a region is found to decrease progressively as the airway generation number of that region increases. Both calculation and data show the same trend. However, the experimental data we have a larger percentage of short fibers and a smaller percentage of long ones as compared to the calculation. The disagreement may be due to the fact that the fragmentation of long fibers during clearance was not included in the model, although such a process does exist for some fibers (Arul and Holt, 1980).

SUMMARY

We have presented a theoretical model of deposition and clearance for inhaled chrysotile asbestos fibers in the rat lung based upon an asymmetric airway model which consists of

Table 3. Ratio of number of the retained fibers in different regions to those in the cranial regions. The experimental data are from Pinkerton *et al.* (1986, 1989)

Region	Generation	Calculated	Experiment
Dorsal	6	1.18	1.41
Lateral	8	1.09	1.14
Cranial	9	1	1
Costolateral	15	0.45	0.40
Caudal	16	0.053	0.19

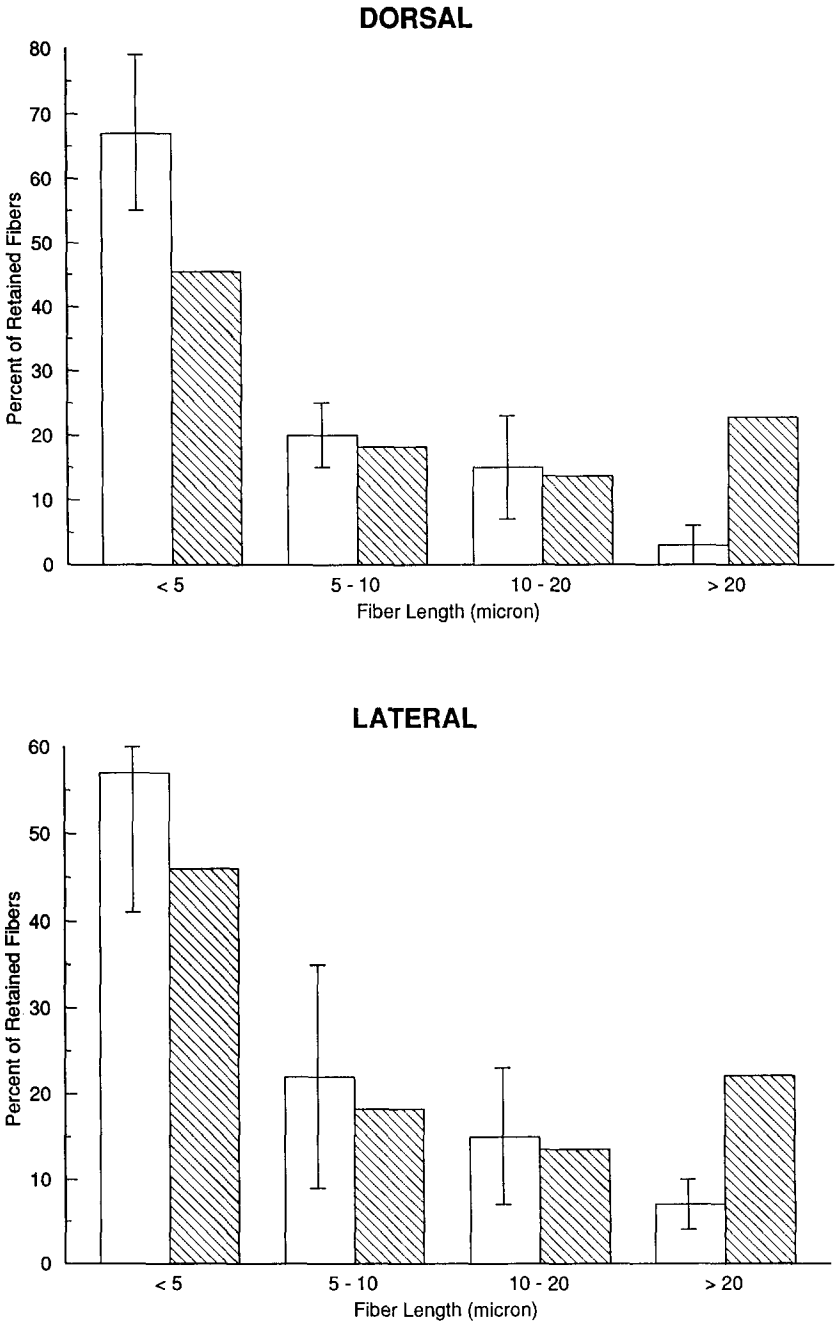
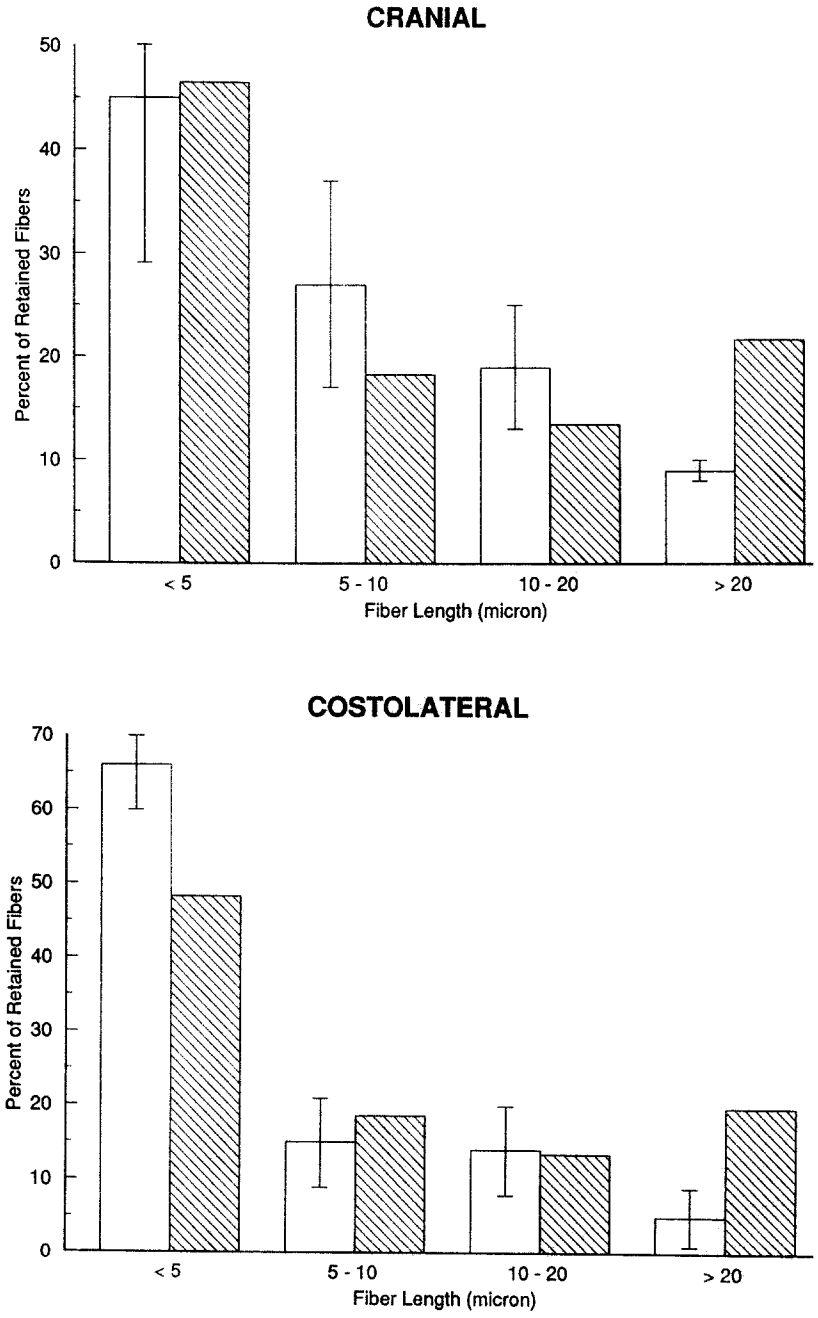


Fig. 2. (*Continued*).



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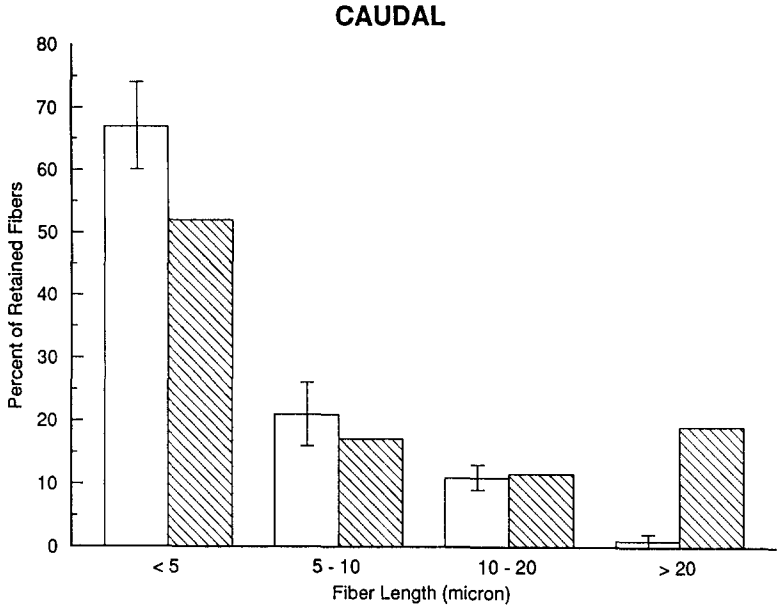

Fig. 2. Percentage of fiber distribution by length for given length intervals in different alveolar regions. Blank bars (mean values $\pm SD$) are the data from Pinkerton *et al.* (1986, 1989) and cross-hatched bars are the calculated results.

five alveolar regions in the left lobe. The calculated lung burden in different regions from the model shows that alveolar regions with fewer airway generations in their path have a greater fiber accumulation and a higher percentage of long fibers. These results are consistent with the experimental data of fiber concentration in the lung tissue. The high fiber accumulation in these regions is due to a small deposition loss of fibers along their airway path. The deposition and clearance modeling of chrysotile asbestos fibers in the rat lung presented can be applied to human if the clearance characteristics of these fibers such as that described by equations (2) and (3) in the human lung are known. The clearance characteristics of the fiber depend not only upon the fiber size which we discussed in our model, but also upon the fiber type and species under consideration.

Acknowledgment—This work was supported by Grant HL-38503 and Grant ES-04338 from NIH.

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