A Clearance Model of Inhaled Man-Made Fibers in Rat Lungs

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Abstract: A clearance model of inhaled man-made fibers (MMFs) was developed, and the calculated fiber numbers and dimensions were compared with the experimental ones using a glass fiber (GF), ceramic fiber (RF1) and two potassium octatitanate whiskers (PT1, TW). If the translocation rate by macrophages is constant and the effect of dissolution and disintegration can be ignored, the fiber number is expected to decrease exponentially with time. In the experimental study, however, the fiber number did not always decrease exponentially. In the case of RF1, the fiber number decreased almost exponentially and the diameter decreased linearly with the time. The clearance rate constant of GF during 3 to 6 months after the end of one-month exposure was greater than that during 1 to 3 months. On the contrary, the clearance rate constants of PT1 and TW during 1 to 6 months were greater than next six months. The diameter and the length of GF did not change significantly. The fiber length of PT1 tends to become longer with time although the diameter did not change significantly. Our theoretical model gives a satisfactory fit to these experimental results.

Key words: Glass fiber, Ceramic fiber, Potassium octatitanate whisker, Biopersistence, Clearance model, Dissolution, Translocation, Disintegration

Introduction

Biological effects of inhaled fibers are related to their biopersistence in lung. It is very important to investigate the clearance mechanism of the inhaled fibers in order to understand the biopersistence.

Fibers deposited in the lung are eliminated by several mechanisms, such as, translocation by phagocytosis of macrophages and by mucociliary elimination, dissolution into body fluid and disintegration or breakage1-3). In the previous paper4), we had found that the dominant factor of the clearance of a ceramic fiber (RCF) was translocation. Dissolution was also observed but the effect on the fiber number was small. However, the main influence must be different from fiber to fiber depending on the physical and chemical properties such as the shape, sizes, chemical structures, solubility and so on, of the fibers. Morris et al.5) shows that the in vivo fiber retention and morphometry data reflects the measured in vitro dissolution rate using three experimental glass fibers. Sear6) shows rapid reduction in the number of longer p-aramid fibrils and glass fibers due to disintegration.

In this study, a mathematical model is proposed to understand the clearance mechanism of fibers based on translocation, dissolution and disintegration. The results are compared with the experimental data after one-month exposure to man-made fibers (MMFs), that is, a glass fiber (GF), a ceramic fiber (RF1) and two potassium octatitanate whiskers (PT1, TW) in rat lungs.

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Theoretical

1) Translocation

Major mechanism of translocation of fibers in the lung is phagocytosis by macrophages and elimination by mucociliary action. Macrophages phagocytize the fibers and transport to lymph nodes or another excretion places. If the number and activity of the macrophages are assumed to be constant during the clearance period, the translocation rate by phagocytosis is in proportion to the number of fibers. If this is the case, the decreasing rate of the fiber number is shown as follows:

\[
- \frac{dn}{dt} = \alpha n
\]
(1)

where, \(n\) is the fiber number, \(t\) is the time (month), \(\alpha\) is the clearance rate constant.

By integrating Eq.(1):

\[
n = n_0 e^{-\alpha t}
\]
(2)

where, \(n_0\) is the initial fiber number.

(2) Dissolution

If a fiber is submerged in the body fluid, the fiber dissolves into the fluid and the rate of the dissolution should be proportional to the surface area. Therefore, the decreasing rate of the fiber volume is described by:

\[
- \frac{d(nD^2)}{dt} = k \left( \frac{\pi DL + 2\pi D^2}{4} \right)
\]
(3)

where, \(D\) is the fiber diameter (\(\mu m\)), \(L\) is the fiber length (\(\mu m\)), \(k\) is a constant depends on the dissolution (\(\mu m/\text{month}\)).

In Eq.(3), \(\pi D^2/2\), is usually much smaller than \(\pi DL\). Therefore, Eq.(3) can be simplified to:

\[
- \frac{D^2}{dt} = 4kD
\]
(4)

By integrating Eq. (4):

\[
D = D_o - 2k t = D_o - Kt
\]
(5)

where, \(D_o\) is the initial diameter of the fiber (\(\mu m\)), \(K\) is the dissolution rate constant (\(\mu m/\text{month}\)). Equation (5) indicates that the fiber diameter decreased linearly with the time.

(3) Disintegration

Disintegration of a fiber includes splitting into thinner fibers and breakage. If the fiber splits, the fiber diameter becomes small and there is no change in fiber length. When the fiber breaks, on the other hand, the length become short and there is no change in the fiber diameter. Because the fibers used in this study were hard to split, the major mechanism of disintegration would be breakage to shorter fibers.

Experimental

Wistar male rats were exposed to a glass fiber (GF), a ceramic fiber (RCF) and two potassium octatitanate whiskers (PT1 and TW) in exposure chambers made of stainless steel (volume 0.44 m³) for 6 hours a day, five days a week for one month. After the end of the exposure, the rats were sacrificed and the sizes and numbers of the fibers deposited in the lungs were measured periodically up to one year. The experimental conditions were summarized in Table 1.

Results and Discussion

Equation (2) indicates that the fiber number should be decrease exponentially if the mechanism of the clearance is only translocation and Eq.(5) shows that the fiber diameter must decrease linearly with time if the fiber dissolves into

<table>
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<tr>
<th>Table 1. Summary of experimental data used in this study</th>
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<tr>
<td>Exposure concentration (mg/m³)</td>
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<tr>
<td>MMAD ((\mu m))</td>
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<tr>
<td>Exposure period</td>
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<tr>
<td>Maximum clearance period</td>
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<td>GMD (GSD) ((\mu m))</td>
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<td>GML (GSD) ((\mu m))</td>
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MMAD: Mass median aerodynamic diameter of fibers in the exposure chamber, GMD: Geometric mean diameter, GML: Geometric mean length. GMD and GML are the values obtained from lungs just after the 1-month exposure.
the body fluid. The translocation and dissolution rates depend on many factors, such as, shape, sizes (length and diameter) and the chemical structure of the fibers. The geometric mean diameter (GMD) and the geometric mean length (GML) of fibers inhaled in rat lungs are also shown in Table 1. The diameter and length of these fibers were similar each other except that the diameter of RF1 is slightly larger than the others.

When the diameter of a fiber decreases by dissolution until below a detection limit, the fiber cannot be observed, which means the fiber number decreases. Figure 1 shows the effect of the dissolution rate constant on the change in fiber number when the initial diameter of the fibers has a log-normal distribution with GMD=0.52 µm and GSD=1.5. The fiber number decreased with the clearance time, and this is remarkable when the dissolution rate constant, K, was large.

Figure 2 shows the change in GMD of RF1. It decreased with the clearance time, and the dissolution rate constant, K, was 0.008. This value is so small that the decrease of the fiber number by dissolution is negligible. Therefore, the major clearance mechanism of RF1 is translocation. Figure 3 shows the clearance curve of RF1. The value of $\alpha$ in Eq.(2) was estimated to be 0.12. This value is in good agreement with the result of the previous study $^4$ ($\alpha$=0.11) using an another ceramic fiber (RCF).

The dissolution rate of GF into distilled water or saline was much larger than that of RF1 in vitro $^5$. Therefore, the effect of dissolution should be considered as well as translocation about the clearance of GF. In this study, $\alpha$=0.11 is also assumed for GF because the shapes and sizes of GF are similar to those of RCF. Comparison of the experimental fiber numbers with the calculated ones by Eq.(2) is shown in Table 2. The decreasing rate of the experimental fiber number was larger than the calculated ones especially during 3–6 months after the end of exposure. The reasons for this are, 1) the translocation rate of GF was greater than that of RCF, or 2) the fibers were disappeared by dissolution.

The translocation rate of GF might not be so different from that of RCF because the dimensions and the chemical compositions of GF and RCF are similar. On the other hand, the dissolution rate of GF in distilled water was much greater than that of RF1 as described above. Therefore, the major reason for this discrepancy would be the difference of the dissolution rate. We assume the dissolution rate constant...
of GF is 0.08, which is 10 times larger than that of RF1, and considering with the effects of dissolution and translocation, the fiber number at the clearance time $t$ is shown as:

$$n_t = n_0 \times e^{-\alpha t} \times \frac{N(D_0 | D_0 > 0.08t)}{n_0}$$

(6)

where, $N(D_0 | D_0 > 0.08t)$ is the number of fibers whose initial diameter ($D_0$) is greater than 0.08$t$ μm. The result is shown in Fig. 4. The calculated values are in good agreement with the experimental ones.

The fiber diameter will decrease with the clearance time due to dissolution but the shape of the size distribution should not change by the dissolution because the diameter of all the fibers decreases at constant rate as predicted by Eq.(5). Figure 5 shows the comparison of fiber length distribution at one day and six months after the end of exposure. The longer fibers decreased and the shorter fibers increased during the 6 months. Figure 6 shows a comparison of the calculated fiber length by the dissolution model with the experimental ones at 6 months after the end of the exposure. Compared with the calculated values, more shorter fibers (L<2 μm) and less longer fibers (L>6 μm) were observed in the experimental values. Possible explanations for these are whether the large fibers were easily translocated by phagocytosis or the fibers were disintegrated to the shorter fibers. The former explanation would not be acceptable. Therefore, the results of Figs. 5 and 6 suggest that the fibers were disintegrated to the shorter fibers.

The solubility of potassium octatitanate whiskers was very small in vitro, and these whiskers must not be easy to break. Therefore, the major clearance mechanism of PT1 and TW must be translocation. Figures 7 and 8 show the change in deposited amount of whiskers in the rat lungs. In these figures, the vertical axis is not the number but the mass of the whiskers because the counting was not always possible due to undigested tissues remaining on the filter. Break lines are the calculated values by Eq.(2) at $\alpha=0.11$. The calculated lines are not so different from the experimental values. However, the decreasing rates of PT1 and TW are

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**Table 2. Comparison of the experimental fiber numbers with the calculated ones by Eq.(2)**

<table>
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<tr>
<th>Clearance period</th>
<th>Experimental</th>
<th>Calculated</th>
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<tr>
<td>1 day</td>
<td>$2.95 \times 10^7$</td>
<td>$2.95 \times 10^7$</td>
</tr>
<tr>
<td>1 week</td>
<td>3.59</td>
<td>2.87</td>
</tr>
<tr>
<td>1 month</td>
<td>2.39</td>
<td>2.64</td>
</tr>
<tr>
<td>3 months</td>
<td>1.81</td>
<td>2.12</td>
</tr>
<tr>
<td>6 months</td>
<td>0.73</td>
<td>1.52</td>
</tr>
</tbody>
</table>

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**Fig. 4.** Change in the number of GF, ●: experimental value, ---: theoretical value calculated by Eq.(6).

**Fig. 5.** Comparison of experimental fiber length distribution between 1 day and 6 months after the exposure.

**Fig. 6.** Comparison of experimental fiber length distribution with calculated ones at 6 months after the exposure.
CLEARANCE MODEL OF INHALED FIBROUS PARTICLES

not linear but decreasing with time. This suggests that there are at least two different translocation mechanisms. According to the experimental results, we extend Eq.(1) as follows:

\[ m = m_0 e^{-\alpha t} + m_0 e^{-\beta t} \quad (\alpha > \beta) \]  

(7)

where, \( m \) is the mass of fibers (µg). Regression lines by Eq.(7) are also shown in the figures with solid lines. Although the shape of the clearance curves in PT1 and TW was different each other, the calculated lines are in good agreement with the experimental ones.

The physical meaning of these two terms were unclear. One possible explanation is that the first term is the clearance by macrophage mediated elimination and mucociliary elimination, and the second term is the clearance by transferring the fibers into interstitial tissues where the fibers were hard to be eliminated from the lung. Another explanation is that the activity of macrophages reduced with time because of high cytotoxicity of the fibers. Longer fibers that could not be phagocytized by macrophages are difficult to be removed from the lung. This should be also one reason why the clearance curve is concave.

Clearance curves for both whiskers showed similar tendency but the shapes of the curves were different between PT1 and TW. The reason for this is not clear because the chemical compositions of PT1 and TW were the same. Further investigations should be needed to clarify the difference of the clearance mechanism for these whiskers.

**Conclusion**

A mathematical clearance model was proposed for fibers inhaled in rat lungs considering with translocation, dissolution and disintegration. The experimental clearance curves of the fibers were linear for RFI, convex for GF and concave for PT1 and TW. Although the shape of the experimental clearance curves was different from fibers to fibers, the proposed model can explain them.

**References**