A Lung Retention Model Based on Michaelis–Menten-like Kinetics

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Lung clearance and retention of spherical particles was substantially quantified by the comprehensive model published by the Task Group on Lung Dynamics in 1966 (1). The model postulated that alveolar clearance involved multicompartamental linear processes. In the ensuing three decades, these underlying assumptions have been challenged by numerous investigations that point to nonlinear behavior of clearance as a function of lung burden. In particular, recent models of pulmonary retention and clearance of dusts have focused upon three nonlinear processes, namely, sequestration, overloading, and redistribution.

Sequestration, first recognized by Soderholm (2), describes a phenomenon whereby the alveolar clearance of very large lung burdens essentially ceases. This concept has been used to explain the clearance and retention behavior of diesel exhaust particles (DEP) (3–5), carbon black (CB) (6), quartz (7), titanium dioxide (7), photocopy test toner (PTT) (7), and amosite fibers (8). However, because the characteristics of particulate sequestration have not been fully elucidated, various types of models have been used to account for the phenomenon. For example, some investigations considered sequestration to be a process in which clearance ceased completely (3,4,8–11), while others regarded clearance as being merely very slow (5–7,12), or not applicable in cases involving low exposure (13).

Dust overloading, hypothesized first by Bolton et al. (14) and subsequently by Morrow (15,16), is a phenomenon in which the lung maintains its normal clearance rate until the burden reaches a threshold, whereupon clearance progressively slows. This phenomenon is based upon empirical observations that, above such a threshold, the alveolar clearance of exposed animals becomes significantly slower than those of control groups. As a result, compartmental models have included threshold values that defined the transition from normal to overloading conditions (5,9,10).

Finally, particle redistribution is a dynamic feedback process in which phagocytized particles are released from dying alveolar macrophages (AMs) into the alveolar space where they are phagocytized by newly recruited AMs. This feedback process has been demonstrated in various experiments (17–19) and has been incorporated into recent retention models (20–26).

Because clearance and retention models, which explicitly account for sequestration, overloading, and/or redistribution, have become increasingly complex, we propose herein an alternative nonlinear model based upon Michaelis–Menten (MM)-like kinetics. This model is consistent with the treatment by Smith (12), who implicitly recognized the appropriateness of MM-like kinetics for alveolar clearance. We previously presented the rationale underlying the clearance portion of this model and developed a linear relationship between pulmonary clearance half-time and lung burdens to evaluate the fit of the model to published data of PTT, antimony trioxide (Sb2O3), DEP, and polyvinyl chloride powder (27).

To further validate the full model (including both accumulation and elimination phases), we tested the model predictions of the temporal behavior of lung burdens, which were experimentally determined in a variety of inhalation studies in F344 rats.

Materials and Methods

Materials. We selected published data involving lung burdens measured over time in F344 rats exposed to Sb2O3 (29), PTT (8,30), CB (6), and DEP (4,5,31) by inhalation at various concentrations in either subchronic (12–18-week) or chronic (24-month) studies. Table 1 summarizes the protocols of these inhalation experiments. Note that some investigations studied only dust accumulation (6,8), some only elimination (6,31), and others both accumulation and elimination (5,29,30). These studies involved particles of both large diameters [PTT, mass median aerodynamic diameter (MMAD)= 4 μm; Sb2O3, MMAD = 3.5 μm] and small diameters (DEP, MMAD = 0.19–0.25 μm; CB, MMAD = 0.24 μm), as well as dusts of various densities (5.2 g/cm3 for Sb2O3, 2 g/cm3 for DEP and CB, and 1.2 g/cm3 for PTT).

Lung retention model. Insoluble particles are deposited in various portions of the rat lung and cleared by several mechanisms. Relatively large particles are likely to be deposited in the conducting airways and are then removed rapidly (over a period of hours to a few days) by mucociliary clearance. Smaller particles tend to be deposited in the alveoli and are then cleared predominately by AMs, which phagocytize the particles and transport them to the ciliated epithelium. A secondary mechanism for clearance in the deep lung involves transport to lung-associated lymph nodes, possibly mediated by AMs or via direct penetration of particles through the interstitium.

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Because these clearance mechanisms in the deep lung are relatively slow (working over a period of weeks to months), the vast majority of the total lung burden resides in the alveolar region following chronic exposure to insoluble dusts. Thus, our model treated the rat lung as a single compartment consisting exclusively of the pulmonary region (the alveoli and the supporting structures) and ignored a separate compartment for the tracheobronchial region, which contributes relatively little to the total lung burden (4). Experimental data reporting burdens of dusts in lung-associated lymph nodes were not used for testing our model.

In keeping with our earlier treatment of MM-like clearance (27), we defined the pulmonary clearance rate coefficient \( k \) as:

\[
k = \frac{k_{\text{max}} \cdot m_{1/2}}{m_{1/2} + m}
\]

where \( k_{\text{max}} \) represents the maximum rate coefficient of pulmonary clearance, \( m_{1/2} \) represents the characteristic burden at which \( k = \frac{1}{2} k_{\text{max}} \), and \( m \) represents the lung burden at which \( k \) is evaluated.

During the accumulation phase, when rats are continuously exposed to dust according to a particular exposure regimen (e.g., 30 hr/week for 13 weeks in the study by Newton et al. (29)), particles accumulate in the lung during the period of daily exposure (e.g., 6 hr), and the mass balance governing the lung burden is given by:

\[
\frac{dm}{dt} = V \cdot E \cdot A \cdot x - k \cdot m
\]

where \( V \) is the ventilation rate (a function of the animal’s age), \( E \) is the particle deposition efficiency, and \( x \) is the exposure concentration. Immediately following daily exposure, the lung reaches the initial post-exposure burden, designated \( m_0 \). During the period prior to the next daily exposure (e.g., 18 hr), the burden is cleared according to the following relationship:

\[
\frac{dm}{dt} = -k \cdot m
\]

Table 1. Inhalation experiments involving measurements of lung burden over time in F344 rats

| Dust   | MMAD (μm) | Specific density | Sex | Phase of study | Exposure concentration (mg/m³) | Exposure regimen | Reference |
|--------|-----------|------------------|-----|----------------|-------------------------------|------------------|-----------|
| Sb₂O₅  | 3.5       | 5.2              | M & F | Accumulation | 0.25, 1.08, 4.92, 23.46 | 30 hr/week for 13 weeks | (29)      |
|        |           |                  |      | Accumulation | 0.25, 1.08, 4.92, 23.46 | 30 hr/week for 90 days | (29)      |
| PTT    | 4         | 1.2              | M & F | Accumulation | 1.4, 16, 1.63, 2 | 30 hr/week for 24 months | (9)       |
|        |           |                  |      | Accumulation | 1.4, 16, 1.63, 2 | 30 hr/week for 24 months | (9)       |
| CB₆    | 0.24      | 2                | M    | Accumulation | 4.1, 6.7, 140 hr/week | 12 weeks       | (6)       |
| DEP    | 0.21      | 2                | M & F | Accumulation | 0.15, 0.94, 4.1 | 35 hr/week for 18 weeks | (31)      |
|        | 0.19      | 2                | M    | Accumulation | 5.91 | 140 hr/week for 12 weeks | (5)       |
|        | 0.25      | 2                | M & F | Accumulation | 0.353, 3.47, 7.08 | 35 hr/week for 24 months | (4)       |

Abbreviations: MMAD, mass median aerodynamic diameter; Sb₂O₅, antimony trioxide; M, males; F, females; NE, no exposure; PTT, photocoagulation test toner; CB, carbon black; DEP, diesel exhaust particulate.

*Combination of both males and females.

Agglomerated particles (primary size = 0.07 μm).

Concentrations and regimen were used to build up lung burdens.

Agglomerated particles (primary size = 0.04 μm).

Equations 3 and 1’ are also applicable during the weekends and after termination of exposure; the latter will be referred to hereafter as the elimination phase. Note that when particles are not deposited in the lung, \( k \) (in Equation 1’) is a function of \( m_0 \) and is independent of the postexposure time. Values of \( m \) were estimated during the accumulation and elimination phases by numerically integrating Equations 2 and 3, as described in Appendix A.

*Estimation of model parameters.* The parameters to be estimated under the model, defined by mass balance Equations 2 and 3, are \( V, E, k_{\text{max}}, m_{1/2}, \) and \( m_0 \). Because \( V \) depends on the ages of the animals and, in part, on the particular laboratory where each inhalation study was conducted, we attempted to match the method of estimation to the published data as closely as possible. For the study by Strom et al. (5), we used the following function reported by the same authors (6) for male F344 rats:

\[
V_m \text{(ml/min)} = 278e^{-14.2(t)/i},
\]

where \( i \) is the animal’s age in days. Likewise, for the later study from the same laboratory (6), we used a similar relationship reported by the authors:

\[
V_m \text{(ml/min)} = V_M e^{-10.2(50)/i},
\]

where \( V_M \) represents the maximum ventilation rate. Since postexposure ventilation rates were reported to be 117, 123, and 154 ml/min among animals of the 1-week, 3-week, and 41-day groups, we adjusted \( V_M \) to values of 217, 202, and 227 ml/min, respectively, so that postexposure ventilation rates would correspond exactly to the reported values. In other studies, ventilation rates were not reported, so we used the published relationship of Guyton (32) between \( V \) and body weight (bw) in grams, at age \( t \) in days:

\[
V \text{ (ml/min) = (2.1)(bw)^{0.75}.}
\]

For the study by Newton et al. (29), body weight was estimated for male F344 rats from the following relationship given by Strom et al. (5) because it corresponded well to the published body weight curves of Newton et al. (29):

\[
bw (g) = 460e^{-0.2(t)/104},
\]

For female rats in the same study (29), the body weight from Equation 7 was adjusted by a factor of 84.5%, representing the estimated ratio of the average body weight of 7-week-old female rats to the corresponding males. Finally, for the studies by Wolff et al. (4), Bellmann et al. (9), Muhle et al. (30), and Griffiths et al. (31), we estimated body weights from the following relationships published by Bellmann et al. (8):

\[
bw (g) = 143 + (46.6)ln(t)
\]

for male rats, and

\[
bw (g) = 38 + (42.5)ln(t)
\]

for female rats.

The MM-like parameters were estimated from the following relationships given by Yu and Rappaport (27):
Table 2. Particle deposition efficiencies used to fit Michaelis–Menten (MM)-like retention models

| Dust        | Range of particle deposition efficiency (%) | Source of data used to fit the MM-like retention model |
|-------------|-----------------------------------------------|--------------------------------------------------------|
| Sb₂O₃       | 4.1–8.8                                       | Newton et al. (29)                                      |
| PTT         | 2.5–5.7                                       | Muhle et al. (30)                                      |
| PTT         | 2.8–4.1                                       | Bellmann et al. (9)                                    |
| CB          | 11–18                                         | Strom et al. (6)                                       |
| DEP         | 8–12                                          | Griffis et al. (31)                                    |
| DEP         | 11–15                                         | Wolff et al. (4)                                       |
| DEP         | 28–30                                         | Strom et al. (5)                                       |

Abbreviations: Sb₂O₃, antimony trioxide; PTT, photocopy test toner; CB, carbon black; DEP, diesel exhaust particulate.

\[
k_{\text{max}} = \ln(2)/\alpha
\]

and

\[
m_{1/2} = \alpha/\beta
\]

where \(\alpha\) (common to all dusts) and \(\beta\) (specific to each dust) are, respectively, the estimated values of the intercept and slope of the linear relationship between \(T_{1/2}\) and lung burden. The rationale for development of this linear relationship was discussed previously (27). From Equations 10 and 11, \(k_{\text{max}}\) was estimated to be 0.009/day for F344 rats (27) and \(m_{1/2}\) was estimated to be 0.69 mg for Sb₂O₃ (reported by Yu and Rappaport (27) from data of Newton et al. (29)), 0.97 mg for PTT (reported by Yu and Rappaport (27) from data of Muhle et al. (30)), 2.49 mg for DEP (reported by Yu and Rappaport (27) from data of Griffis et al. (31)), and 0.69 mg for CB [estimated in this study from data of Storm et al. (6)]. Note that values of \(m_{1/2}\) were derived from data obtained exclusively from the elimination phase of each experiment and that for PTT and DEP, values of \(m_{1/2}\) that were estimated from one study were applied to other studies involving the same dust.

Finally, \(E_A\) was determined empirically for each experimental data set by applying model predictions, dust, exposure concentration, duration (if applicable), and gender (if applicable) by fitting Equations 2 and 3 to the data after including all other terms in the model. Table 2 shows the estimated ranges of \(E_A\) for each of the data sets for the various experimental groups.

Results

Antimony trioxide. Newton et al. (29) investigated both accumulation (for 13 weeks) and elimination (for an additional 28 weeks) of Sb₂O₃ in rats exposed to four exposure concentrations in a subchronic inhalation study. Figure 1 shows accumulation and elimination of the dust over time in male (Fig. 1A) and female (Fig. 1B) rats using values of \(k_{\text{max}}\) and \(m_{1/2}\) that were estimated from the elimination phase of the same study. The model predicted the behavior of all experimental data quite well. Furthermore, the residuals were found to be unremarkable with no apparent gender effect on model predictions (Fig. 2).

Photocopy test toner. Muhle et al. (30) investigated PTT accumulation (up to 90 days) and elimination (for an additional 75 days), whereas Bellmann et al. (8) examined only accumulation of PTT (for 24 months). Figure 3 depicts the predicted and observed burdens in female rats exposed to different dust concentrations, Figure 4 shows the burdens in males exposed to various concentrations of PTT in the study by Muhle et al. (30), and Figure 5 shows the results from the study by Bellmann et al. (8). In each case, \(k_{\text{max}}\) and \(m_{1/2}\) were estimated from the elimination phase of the study by Muhle et al. (30). These results indicate good fits of all data to the model, with the possible exception of the data from Muhle et al. (30) at
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Figure 4. Elimination of photocopy test toner in F344 male rats exposed to 63.2 mg/m³ (A), 16.1 mg/m³ (B), 4.0 mg/m³ (C), and 1.0 mg/m³ (D) in a subchronic study by Muhle et al. (30). Solid lines represent model predictions; symbols represent experimental observations. (The Michaelis–Menten-like clearance parameters for the model were estimated from the elimination phase of the same study.)

Figure 5. Accumulation of photocopy test toner in F344 female (A) and male (B) rats in a chronic study by Bellmann et al. (9). Solid lines represent model predictions; symbols represent experimental data. (The Michaelis–Menten-like clearance parameters for the model were estimated from the elimination phase of the study by Muhle et al. (30).)

the lowest concentration (Fig. 4D). Again, no effect on model fit by gender was observed (data not shown). The model, given the $k_{\text{max}}$ and $m_{1/2}$, estimated from the elimination phase, accurately predicted the burdens during the accumulation and elimination phases in the same study by Muhle et al. (30). Furthermore, the parameters estimated from the study by Muhle et al. (30) accurately predicted lung burdens during the accumulation phase of the study by Vincent et al. (8), suggesting that the MM-like clearance parameters were valid between phases and between studies.

Carbon black. Strom et al. (6) investigated elimination of CB for 1 year following accumulation of a range of burdens in male F344 rats exposed at about 7 mg/m³ for 7–41 days. Results are shown in Figure 6, using values of $k_{\text{max}}$ and $m_{1/2}$ that were estimated from the same study. The overall fit of the model was good, despite some underestimation of lung burdens at early stages (<60 days) of the experiment in which the animals were exposed for 7 days.

Diesel exhaust particle. Three studies involved inhalation of DEP: Griffis et al. (31) investigated only elimination; Wolff et al. (4) studied only accumulation; and Strom et al. (5) examined both accumulation and elimination. Figures 7–9 depict these data and the corresponding model predictions where values of $k_{\text{max}}$ and $m_{1/2}$ were estimated from the study of Griffis et al. (31). Again, the model predictions compared favorably with the data. The parameters $k_{\text{max}}$ and $m_{1/2}$, which had been estimated from the elimination phase of the study by Griffis et al. (31), were valid in predicting burdens in both the accumulation and elimination phases of all studies. However, the model tended to underestimate burdens at later stages of the experiments (1 year after termination of exposure).

Discussion

As noted in the introduction, investigators have long sought to develop an accurate model for the retention of insoluble particles in the lung. Indeed, many retention models have been published for the rat lung which, as shown in Table 3, contain varying numbers of compartments (1–7) and clearance-related parameters (3–13). As computational power and speed have improved, complex physiologically based models have become increasingly popular because they
offer avenues for explaining the behaviors observed. However, in the absence of particularly rich and varied data resources, questions of accuracy tend to plague such highly parameterized models. Thus, when data are sparse, simple empirical models offer advantages for the accurate prediction of kinetic behavior, even if the reasons for such behavior remain elusive. Certainly our model (defined by Equations 2 and 3) falls into this latter category because it contains only a single compartment and two clearance-related parameters, $k_{\text{max}}$ and $m_{1/2}$. We previously showed that $k_{\text{max}}$ and $m_{1/2}$ are easily estimated and evaluated by applying simple linear regression techniques to modest amounts of clearance data (27). We regard this as a particular strength given the sparseness of data that can currently be used to assess the fit of any dust-retention model.

Despite its simplicity, our model reasonably described the mass-dependent behavior of lung burdens in rats exposed to four dusts ($\text{SiO}_2$, PTT, CB, and DEP) over a wide range of particle sizes and experimental protocols. Thus, we conclude that MM-like kinetics captured the essential features of saturable AM-mediated clearance, which largely governed both the accumulation and elimination of lung burdens in inhalation studies involving insoluble dusts.

During the accumulation phase of inhalation experiments, our model relies upon an empirically derived constant ($E_A$) to account for the efficiency of particle deposition in the lung. The ranges of $E_A$ that we obtained were generally consistent with published values obtained from rats exposed to a variety of aerosols, including aluminosilicate (4,36,37), DEP (38,39) [note that 66% of lung deposition was assumed to be in the alveolar region (39), Ga$_2$O$_3$ (4,40,41), PuO$_2$ (42), U$_4$O$_6$ and UO$_2$ (43), and an $^{198}$Au labeled aerosol (44). We included monodisperse particles, characterized by their aerodynamic diameters (36,37) as well as polydisperse aerosols characterized by their MMADs (4,38-43). As shown in Figure 10, these published values of $E_A$ displayed a decreasing trend with increasing size from about 20% for 0.1-μm particles to about 1% for 7-μm particles. All fits produced values of $E_A$ within the range of those observed from experimental studies, with the exception of the fit of our model to the data from Strom et al. (5), where the estimated values of $E_A$ ranged from 28 to 30% for DEP particles, with an MMAD of 0.19 μm. These values, however, were very similar to those reported by Strom et al. (26.5-38%) (5,6) and Stöber et al. (28.3%) (10). Thus, we conclude that the values of $E_A$ that we assigned to the various experimental groups should not have unduly influenced the behavior of our model predictions.

The validity of MM-like kinetic models is considered from three perspectives. First, reasonable agreement is to be expected between model predictions and observed lung burdens when the same data are used to estimate the clearance-related parameters and also to evaluate goodness of fit (as for $\text{SiO}_2$ in Fig. 1, for PTT in Fig. 3,4, for CB in Fig. 6, and for DEP in Fig. 7). Second, all of the pairs of $k_{\text{max}}$ and $m_{1/2}$ that were used to define clearance rate coefficients for the four dusts were obtained from the elimination phases of inhalation experiments after exposure had been terminated. Yet, we observed excellent agreement between observed lung burdens and model predictions during the accumulation phases of all experiments as well (Fig. 1,5,8,9). Third, more validity can be given to a model in which parameters estimated from one study successfully predict lung burdens from another, as was the case for PTT (Fig.
5) and DEP (Fig. 8.9). Such agreement of model predictions across studies for two different dusts strengthens the notion that MM-like clearance behavior may be generally applicable to insoluble particles.

We suspect that the parsimony achieved by applying MM-like kinetics to alveolar clearance relates to its underlying biological plausibility. Table 4 compares the main characteristics of traditional MM enzyme kinetics to the analogous process that we postulate to be operative in the lung. The key feature leading to the mathematical forms of both relationships rests in the inherent feedback systems, which are related to dissociation of enzyme-substrate complex on the one hand and to redistribution of phagocytized particles (associated with the deaths of AMs) on the other. Although the concept of particle redistribution has long been recognized and has often been included in retention models (10,20,22–25), we are apparently the first to recognize the parallel between redistribution and dissociation of the enzyme-substrate process and, thereby, to justify the mathematical simplicity of MM kinetics in this context.

The MM-like kinetics that underlie our model also lend substance to the notion of lung overload, where it is postulated that the clearance rate slows only after some critical threshold burden has been exceeded. From Equation 1 it is easily shown that when \( m \ll m_{1/2} \), linear (or first-order) kinetics prevail and the alveolar clearance rate coefficient \( k \) is approximately equal to \( k_{\text{max}} \). Thus, the threshold burden is defined by the condition where \( m \ll m_{1/2} \).

Previously (27), we estimated threshold burdens of 0.11, 0.16, 0.40, and 0.46 mg for \( Sb_2O_3 \), PTT, DEP, and polyvinyl chloride powder, respectively (whose values of \( m_{1/2} \) were estimated to be 0.69, 0.97, 2.49, and 2.90 mg, respectively). This implies that lung overload occurs when the lung burden exceeds about 16% of \( m_{1/2} \). The good fits of all experimental data to our model underscore the point that dust overloading is probably a manifestation of nonlinear kinetics of the MM type according to the relationship given in Equation 1.

Our model can also be interpreted in the context of particle sequestration, where it has been postulated that clearance stops completely for some portion of the lung burden (15,16). Yu et al. (35) argued that particle sequestration can be explained in practice by the effect of slowed alveolar clearance rather than a complete breakdown of the clearance process, given that animals have a finite lifetime. Our model offers a similar explanation in the sense that alveolar clearance, under Equation 1, is mass-dependent and, in the extreme, will

![Figure 10. Model-fitted (open symbols) and other published empirical values of pulmonary deposition efficiency of various particles in rats. MMAD, mass median aerodynamic diameter; DEP, diesel exhaust particulate; CB, carbon black; PTT, photocopy test toner.](image)

Table 4. Traditional Michaelis–Menten (MM) enzymatic kinetics versus the MM-like kinetics of alveolar clearance of dusts

| Characteristics                  | Enzyme kinetics | MM-like kinetics of dusts |
|----------------------------------|-----------------|---------------------------|
| Two-stage process                | Substrate       | Free particles            |
|                                  | Enzyme          | AM                        |
|                                  | Reaction product| Phagocytized particles    |
|                                  | Enzyme recycling| Cleared particles         |
| Feedback system                  | ES dissociation | Continuous supply of AM   |
| Overall kinetics                 | Saturable, nonlinear | from bone marrow |
| Kinetic variable                 | \( k \), rate of enzymatic reaction | Saturable, nonlinear |
| Kinetic parameters               | \( V_{\text{max}} \), maximal rate of enzymatic reaction | \( k_{\text{max}}, \) maximal alveolar clearance |
|                                  | \( k_m \), substrate concentration at which the rate is half of \( V_{\text{max}} \) | \( m_{1/2}, \) lung burden at which the clearance is half of \( k_{\text{max}} \) |
| Kinetic equation                 | \( v = \frac{V_{\text{max}}}{k_m + [S]} \) | \( k = \frac{k_{\text{max}}}{m_{1/2}} \) |
| Pseudo-linear condition          | \( [S] < k_m, \) leading to \( v \approx (V_{\text{max}}/k_m)[S] \) | \( m < m_{1/2}, \) leading to \( k \approx k_{\text{max}} \) |
| Parameter estimation            | Linear regression, e.g., Lineweaver-Burk method | Linear regression, \( T_{1/2} = \alpha + \beta m \), for \( k_{\text{max}} = \ln(2)/\alpha \) and \( m_{1/2} = \alpha/\beta \) |

Abbreviations: S, substrate; E, enzyme; AM, alveolar macrophages; ES, enzyme–substrate complex.
lead to radically diminished clearance coefficients. Thus, although conceptual differences remain in defining particle sequestration, in practice there is not much difference between our approach and that of Yu et al. (35). We also note that the most consistent bias observed between predicted and observed burdens under our model involved the underestimation of burdens of DEP (Fig. 9-11) during late stages of the experiments (times greater than about 1 year), where sequestration would be expected to play a more prominent role.

We conclude that MM-like clearance kinetics provide a reasonable basis for a general model describing the retention of insoluble particles in the lungs of F344 rats. We encourage others to investigate the suitability of our model for describing retention of other aerosols in the rat lung as well as for describing the behavior of insoluble dusts deposited in the lungs of other species, including humans.

REFERENCES

1. Task Group on Lung Dynamics. Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys 12:173–207 (1966).
2. Soderholm SC. Compartmental analysis of diesel particle kinetics in the respiratory system of exposed animals. EPA Diesel Emissions Symposium, 1981, Raleigh, NC, Washington, DC:U.S. Environmental Protection Agency, 1981.
3. Vostál JJ, Schreck RM, Lee PS, Chan TL, Soderholm SC. Deposition and clearance of diesel particles from the lung. In: Toxico logical effects of emissions from diesel engines (Lewtas J, ed). New York:Elsevier, 1982:143–159.
4. Wolff RK, Henderson RF, Snipes MB, Griffith WC, Maudery JL, Cuddy KG, McClellan RO. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fundam Appl Toxicol 9:154–166 (1987).
5. Strom KA, Chan TL, Johnson JT. Pulmonary retention of inhaled submicron particles in rats: diesel exhaust exposures and lung retention model. Ann Occup Hyg 32(suppl 1):645–657 (1988).
6. Strom KA, Johnson JT, Chan TL. Retention and clearance of inhaled submicron black particles. J Toxicol Environ Health 26:183–202 (1989).
7. Vincent JH, Jones AD, Johnston AM, McMillin C, Bolton RE, Cowie H. Accumulation of inhaled mineral dust in the lung and associated lymph nodes: implications for exposure and dose in occupational lung disease. Ann Occup Hyg 31:375–393 (1987).
8. Vincent JH, Johnston AM, Jones AD, Bolton RE, Addison J. Kinetics of deposition and clearance of inhaled mineral dusts during chronic exposure. Br J Ind Med 42:707–715 (1985).
9. Bellmann B, Muhle H, Creuzenbergh O, Dusenbrock C, Kilpper R, MacKenzie JC, Morrow P, Merklestein R. Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats. Fundam Appl Toxicol 17:300–313 (1991).
10. Stöber W, Morrow P, Morawietz G. Alveolar retention and clearance of insoluble particles in rats simulated by a new physiolo gy-oriented compartmental kinetics model. Fundam Appl Toxicol 15:329–349 (1990).
11. Vincent JH, Donaldson K. A dosimetric approach for relating the biological response of the lung to the accumulation of inhaled mineral dust. Br J Ind Med 47:302–307 (1990).
12. Smith TJ. Development and application of a model for estimating alveolar and interstitial dust levels. Ann Occup Hyg 29:495–516 (1985).
13. Strom KA, Garg BD, Johnson JT, D'Arcy JB, Smiler KL. Inhaled particle retention in rats receiving low exposures of diesel exhaust. J Toxicol Environ Health 29:377–398 (1990).
14. Bolton RE, Vincent JH, Jones AD, Addison J, Beckert ST. An overload hypothesis for pulmonary clearance of UIICC amosite fibers inhaled by rats. Br J Ind Med 40:264–272 (1983).
15. Morrow PE. Possible mechanisms to explain dust overloading of the lungs. Fundam Appl Toxicol 10:369–384 (1988).
16. Morrow PE. Dust overloading of the lungs: update and appraisal. Toxicol Appl Pharmacol 113:1–12 (1992).
17. Hepplstein AG. The disposal of coal and hematite dusts inhaled successively. J Pathol Bacteriol 75:113–126 (1958).
18. Lehnert BE, Yolanda E, Valdez YE, Tieren GL. Alveolar macrophage-particulate relationships during lung clearance. Am J Respir Cell Mol Biol 1:145–154 (1989).
19. Lehnert BE. Alveolar macrophages in a particle “overload” condition. J Aerosol Med 3(suppl 1):S9–530 (1990).
20. Oberdörster G. Lung clearance of inhaled insoluble and soluble particles. J Aerosol Med 1:289–330 (1988).
21. Stöber W, Morrow P, Hoover MD. Compartmental modeling of the long-term retention of insoluble particles deposited in the alveolar region of the lung. Fundam Appl Toxicol 13:823–842 (1990).
22. Vacek PM, Hemenway DR, Absher MP, Goodwin GD. The translocation of inhaled silicon dioxide: an empirically derived compartmental model. Fundam Appl Toxicol 17:614–626 (1991).
23. Katsnelson BA, Konysheva KL, Privalova L, Morosova KL. Development of a multicompartamental model of the kinetics of quartz dust in the pulmonary region of the lung during chronic inhalation exposure of rats. Br J Ind Med 49:172–181 (1992).
24. Absher MP, Hemenway DR, Leslie KO, Trombley L, Vacek PM. Intrathoracic distribution and transport of aerosolized silica in the rat. Exp Lung Res 18:743–757 (1992).
25. Katsnelson BA, Konysheva KL, Sharapova NY, Privalova LI. Prediction of the compara-
29. Tran CL, Jones AD, Donaldson K. Mathematical model of phagocytosis and inflammation after the inhalation of quartz at different concentrations. Scand J Work Environ Health 21(suppl 2):50–54 (1995).

30. Yu RC, Rappaport SM. The relationship between pulmonary clearance and particle burden: a Michaelis–Menten-like kinetic model. Occup Environ Med 53:567–572 (1996).

31. Vincent JH. The fate of inhaled aerosols: a review of observed trends and some generations. Ann Occup Hyg 34:623–637 (1990).

32. Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, Rubin LF. Subchronic and chronic inhalation toxicity of anthracite trioxide in the rat. Fundam Appl Toxicol 22:561–576 (1994).

33. Muhle H, Bellmann B, Creutzenberg O, Fuhs R, Koch W, Mohr U, Takenaka S. Subchronic inhalation study of cotton in rats. Inhalation Toxicol 2:341–360 (1990).

34. Griffis LC, Wolff RK, Henderson RO, Griffith WC, Mokler BV, McClellan RO. Clearance of diesel soot particles from rat lungs after a subchronic diesel exhaust exposure. Fundam Appl Toxicol 3:99–103 (1983).

35. Guyton AC. Measurement of the respiratory volumes of laboratory animals. Am J Physiol 150:70–77 (1947).

36. Chan TL, Lee PS, Hering WE. Pulmonary retention of inhaled diesel particles after prolonged exposures to diesel exhaust. Fundam Appl Toxicol 4:624–631 (1984).

37. Yu CP, Jorgensen KM, Rappaport SM. Clearance of amosite asbestos fibers from the lungs. Inhalation Toxicol 1:97–107 (1988).

38. Raabe OG, Yeh HC, Newton GJ, Phalen RF, Velasquez DJ. Deposition of inhaled monodisperse aerosols in small rodents. In: Inhaled particles IV (Wolton WH, ed). Oxford: Pergamon Press, 1977:3–21.

39. Raabe OG, Al-Bayati MA, Teague SV, Rasolt A. Regional deposition of inhaled monodisperse coarse and fine aerosol particles in small laboratory animals. Ann Occup Hyg 32(suppl 1):53–63 (1988).

40. Chan TL, Lee PS, Hering WE. Deposition and clearance of inhaled diesel exhaust particles in the respiratory tract of Fischer rats. J Appl Toxicol 1:77–82 (1981).

41. Dutcher JS, Sun JD, Lopez JA, Wolf L, Wolff RK, McClellan RO. Generation and characterization of radiolabeled diesel exhaust. Am Ind Hyg Assoc J 45:491–498 (1984).

42. Wolff RK, Griffis LC, Hobbies CH, McClellan RO. Deposition and retention of 0.1 μm aggregate 67Ga2O3 aerosols in rats following whole body exposures. Fundam Appl Toxicol 2:195–200 (1982).

43. Wolff RK, Kanapilly GM, Gray RH, McClellan RO. Deposition and retention of inhaled aggregate 67Ga2O3 particles in beagles, Fischer-344 rats, and CD-1 mice. Am Ind Hyg Assoc J 45:377–381 (1984).

44. Craig DK, Buschhorn RL. The alveolar deposition of inhaled plutonium aerosols in rodents. Am Ind Hyg Assoc J 36:172–180 (1975).

45. Stokinger HE, Steadman LT, Wilson HB, Sylvester GE, Dziuba S, LaBelle CW. Lobar deposition and retention of inhaled insoluble particulates. Arch Ind Hyg Occup Med 4:346–353 (1951).

46. McMahon TA, Brain JD, Lemott S. Species differences in aerosol deposition. In: Inhaled particles IV (Wolton WH, ed). Oxford: Pergamon Press, 1977:23–32.

47. Yu CP, Agharian B. A kinetic model of alveolar clearance of amosite asbestos fibers from the rat lung at high lung burdens. J Aerosol Sci 21:21–27 (1990).

48. Yu CP, Yoon KJ, Chen YK. Retention modeling of diesel exhaust particles in rats and humans. J Aerosol Med 4:79–115 (1991).