Appendix 7A

Rat-to-Human Dose Extrapolation

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7A.1 INTRODUCTION

As noted at the outset of Chapter 7, the 1997 revisions to the PM NAAQS (Federal Register, 1997) were largely based on newly emerging epidemiologic evidence that showed associations between (a) ambient PM measured at community monitoring stations and (b) increased risks for mortality and morbidity (especially cardiorespiratory-related) among human populations exposed to contemporary U.S. ambient concentrations. However, little experimental toxicology data from controlled laboratory animal or human exposure studies were then available that provided more direct evidence supporting the plausibility of the PM-mortality/morbidity relationships observed at relatively low ambient PM concentrations.

Since completion of the 1996 PM AQCD supporting the 1997 PM NAAQS decisions, numerous hypotheses have been advanced and extensive new toxicologic evidence generated with regard to possible pathophysiologic mechanisms by which PM exposures (even at low ambient concentrations) might induce increased morbidity and/or mortality. Much of the new toxicologic data (as addressed in Chapter 7) has involved either (a) experimental in vivo exposures of human subjects and/or laboratory animals via inhalation exposures and/or intratracheal instillation of PM materials or (b) in vitro exposures of various (mostly respiratory tract) cells or tissues to diverse types of PM. The exposure conditions used in these studies were typically different from those experienced through inhalation of ambient PM. Therefore, the relevance of the effects observed under experimental conditions compared to the effects observed in humans following ambient PM exposures needed evaluation.

To address this issue, the EPA has conducted an analysis of the relationship between rat and human lung doses predicted for various exposure scenarios ranging from ambient PM exposures to PM instillations into the lung. The appendix begins in Section 7A.2 by presenting basic principles such as the relationship between PM exposure and PM dose in the lung. This section then introduces the concept of determining PM exposures for rats which lead to PM doses in the rat lung equivalent to that received by humans. The mathematical model used herein for interspecies comparisons is discussed in Section 7A.3. Particle dosimetry in the lung was described in Chapter 6, however, additional details regarding differences in particle dosimetry between rats and humans are discussed in Section 7A.4. Section 7A.5 expands on the equivalent dose concept and illustrates the variability in PM exposure concentrations that could be required for rats to have the same dose as a human as a function of dose metric, normalizing

factor, and level of human exertion. Section 7A.5 provides information that can be used to estimate the exposure concentrations required to give a rat a dose equivalent to the dose that would be received by a human exposed to various levels of ambient PM. In Section 7A.7, the dosimetric modeling techniques discussed earlier are used to compare doses received by rats and humans from experimental exposures. That dosimetry alone cannot explain all differences in response between rats and humans is discussed in Section 7A.6 and again in Section 7A.8. Readers not interested in the comprehensive analyses of dosimetric issues presented in Sections 7A.2 through 7A.6 may wish to skip to Section 7A.7 where several specific studies are compared and contrasted and then further discussed in Section 7A.8. Finally, conclusions based on the analyses appear in Section 7A.9.

7A.2 QUANTITATIVE INTERSPECIES EXTRAPOLATION

Much of the information on the toxicity of PM comes from studies in which laboratory rats were exposed to PM by inhalation or instillation. For optimal use of this toxicologic data, estimates of PM exposures that would result in similar human doses are needed. The premise of such comparisons is that comparable doses should cause comparable effects. It is the tissue dose, rather than exposure per se, that is responsible for adverse responses, making it essential to first consider the dose to the lung that might occur during an exposure to PM.

The rate of deposition in a specific region of the respiratory tract resulting from the inhalation of PM may be given as

$$\dot{D}_r(t) = C(t) \times f(t) \times V_T(t) \times DF_r(t) \quad (1)$$

where: $\dot{D}_r$ is the rate of deposition per unit time in region r; C is the PM exposure concentration and may be expressed as particle mass, surface area, or number per unit volume; f is breathing frequency in breaths per unit time; V_T is tidal volume, i.e., the volume of air inhaled per breath; and DF_r is the fraction of inhaled particles deposited in region r.

It should be noted that all of the variables in Equation 1 are potentially variable over time. The effect of activity or exertion level on V_T and f was presented in Tables 6-3 and 6-6. Within an individual, the variability in DF_r over time is largely attributable to variations in inhaled

particle size, f, V_T, and route of breathing, i.e., mouth versus nose (ICRP, 1994). Inter-subject and interspecies variability in DF_r is additionally affected by morphologic differences in the size and structure of the respiratory tract.

For acute exposures, associated effects may simply be a function of the deposited dose in a region (D_r), given by

$$D_r = \int_{\Delta t} \dot{D}_r(t)\, dt \qquad (2)$$

where Δt is the exposure time interval.

For chronic exposures, it is necessary to consider the retained dose. The PM dose retained in a region of the lung is determined by the balance between rate of input and the rate of removal. The PM burden (B_r) in a region of lung may be expressed as

$$dB_r(t)/dt = \dot{D}_r(t) - \lambda_r B_r(t) \qquad (3)$$

where λ_r is the clearance rate constant for region r. It should be noted that transfer into region r from another region may also occur. Such situations in which a region receives a portion of its burden from another region are common in the lung, e.g., the mucus clearance of the segmental bronchi into the lobar bronchi, which clear into the main bronchi, which in turn clear into the trachea. In addition, the clearance from one region can transfer burden into more than one other compartment, e.g., soluble particles in the airways may be cleared into the blood as well as via the mucus. The discussion herein of retention is mainly limited to highly insoluble particles. However, multiple pathways for clearance of insoluble particles exist such as from the alveoli into the lymph and into the terminal bronchioles via macrophages.

For instillations into the lung, the dose can be characterized fairly well. For inhalation studies, however, the dose is not always known and must instead be calculated using a dosimetric model that may be based on empirical relationships, theoretical calculations, or a combination. The following discussion is based on the application of dosimetry to interspecies extrapolation as given in the scientific literature (U.S. Environmental Protection Agency 1994, 1996; Jarabek, 1994, 1995).

For dosimetric calculations and comparisons it is useful to assume that PM concentrations and activity levels are constant over time. Further, it is convenient to separate the deposited dose into one factor that depends on the exposure-related variables and a second factor that depends on species, particle size, and activity level. Exposure, E, can be defined as

$$E = C \times \triangle t \quad (4)$$

where: C is PM exposure concentration and $\triangle t$ is exposure duration. A dose adjustment factor, DAF, can also be defined as

$$DAF = f \times V_t \times DF \quad (5)$$

where it is understood that DF refers to specific regions of the lung. Retained dose can be expressed similarly except that the DAF would include a retention fraction.

In order to compare a rat dose with a human dose that might have comparable biological effects, it is useful to introduce the concept of dose normalization. Examples of normalized doses are the dose per body mass, per lung mass, per lung area, per macrophage, or per other biological or physiological parameters. A normalized dose (ND) is the dose (D) to the lung or lung region divided by an appropriate normalizing factor (NF):

$$ND = \frac{D}{NF} = \frac{E \times DAF}{NF} \quad (6)$$

In Equation 6, ND and DAF refer to specific regions of the lung and could apply to either a rat or human. In the extrapolation modeling presented here, normalized doses are calculated for rats and humans. The concept of dose normalization is not new to interspecies extrapolation of toxicologic data. The ingested dose that produces no adverse effect in animals is normalized and used to estimate an acceptable human dose. Typically, a safety or uncertainty factor of 10 is applied to the estimated acceptable human dose unless a dosimetric adjustment is made. In which case, the safety factor is reduced to 3 (U.S. Environmental Protection Agency, 1994;

Jarabek, 1995). Thus, the acceptable human dose would be one-third the no-effect level dose for the animal.

The objective of the analysis set forth here is to specify an exposure for one species and determine an exposure for the second species such that both species will receive equivalent normalized doses,

$$ND_1 = ND_2 \quad (7)$$

where: subscripts refer to different species. An asterisk (*) is used to indicate exposures that give equivalent doses and subscripts to refer to species, thus

$$E_1^* \times (DAF_1 / NF_1) = E_2^* \times (DAF_2 / NF_2) \quad (8)$$

The equivalent exposure ratio (EqER) represents the ratio of species' exposure that give equivalent doses.

$$EqER = \frac{E_{1^*}}{E_{2^*}} = \frac{(DAF_2 / NF_2)}{(DAF_1 / NF_1)} \quad (9a)$$

The exposure for species 1, giving the equivalent dose for a specified exposure for species 2 is given by

$$EqE_1 = EqER \times SpE_2 \quad (10a)$$

where: SpE_2 is the specified exposure concentration for species 2 and EqE_1 is the equivalent concentration for species 1. EqER can be calculated directly from the DAF and NF for the two species provided that the dose is a linear function of time and concentration. If the exposure time is the same for both species, Equation 10a can be reduced to

$$EqC_1 = EqER \times SpC_2 \quad (11a)$$

where: SpC_2 is the specified exposure concentration for species 2 and EqC_1 is the equivalent concentration for species 1.

If species 1 is defined as rat and species 2 as human, then Equations 9a, 10a, and 11a become

$$EqER = \frac{E_R}{E_H} = \frac{DAF_H / NF_H}{DAF_R / NF_R} \quad (9b)$$

$$EqE_R = EqER \times SpE_H \quad (10b)$$

$$EqC_R = EqER \times SpC_H \quad (11b)$$

Thus, EqER is the factor by which a specified human exposure concentration must be multiplied to obtain the rat exposure concentration to yield an equivalent dose. If EqER is greater than 1, then the rat must receive a greater concentration than the human in order to receive an equivalent dose.

7A.3 THE MULTI-PATH PARTICLE DEPOSITION MODEL (MPPD)

The disposition (deposition and clearance) of particles in the human and rat respiratory tract was estimated using the publicly available Multiple Path Particle Deposition (MPPD) model.[1] The MPPD model was developed by the CIIT Centers for Health Research (CIIT), USA, in collaboration with the National Institute of Public Health and the Environment (RIM), the Netherlands, and the Ministry of Housing, Spatial Planning and the Environment, the Netherlands. Other models of deposition and clearance, which are not necessarily publicly available nor in a form easily suited for comparisons between particle disposition in rats and

[1] Some software problems encountered during the dosimetric modeling were fixed by the developers and a revised MPPD upgrade version is available on request from the CIIT Centers for Health Research (<asgharian@ciit.org>).

humans, were discussed in Chapter 6 (Sections 6.6.1 to 6.6.3). General information about the MPPD model was discussed in Chapter 6, Section 6.6.4.2; additional details relevant to this appendix are provided here. Comparisons between MPPD-predicted deposition fractions of monodisperse particles (0.01 to 10 μm) in humans during light exercise and in rats at rest were provided in Chapter 6, Section 6.6.4.3. Differences between rats and humans in deposition normalized to lung mass and lung surface were also provided. In this appendix, other normalizing parameters are considered as is the clearance of particles from the lung.

The MPPD model may be used to predict the deposition of particles between 0.01 to 20 μm in diameter in humans and rats. In the lung, the model considers deposition by the mechanisms of impaction, sedimentation, and diffusion. Although the lung geometries differ between species, the same mathematical formulation may be used to calculate particle deposition in the rat as well as in the human lung (Anjilvel and Asgharian, 1995). The extrathoracic particle deposition efficiencies used in the MPPD model were adopted from the ICRP (1994) for humans and from Zhang and Yu (1993) for rats. Model input parameters include airways morphology, particle properties (size distribution, density, concentration), and breathing conditions (tidal volume, breathing frequency, and mode of breathing). The effects of these parameters on deposition in rats and humans were reported by De Winter-Sorkina and Cassee (2002). The MPPD model also contains an optional correction for the inhalability of particles during nasal breathing which may be applied to both humans and rats (Ménache et al., 1995). This correction becomes increasingly important when particle size exceeds 1 μm (MMAD) for rats and 10 μm (MMAD) for humans. With reference to Equation 1, it should be noted that average exposure concentrations and average breathing patterns are used to estimate particle deposition fractions and lung doses over discrete time periods, i.e., the simulations presented herein do not consider temporal variations on a breath-by-breath basis as suggested by Equation 1.

Several types of normalized deposition data are available using the MPPD model. Particle deposition fractions normalized to airway surface area provide an index of the average dose of particles to epithelial cells. These data are useful in assessing generation-to-generation variability but do not consider dose variability within a generation, e.g., between the carina and airway wall. For this normalization, the MPPD model calculates the surface area of the airways based on the diameter, length, and number of airways in a generation. These data are most useful for the tracheobronchial airways since alveolar surface area is not included in the model's

calculations. For the alveolar region, the MPPD model calculates particle mass and number deposited per alveolus and per macrophage. From Mercer et al. (1994), the model assumes 4.86×10^8 alveoli in humans and 1.97×10^7 alveoli in rats. From Miller (2000), the number of alveolar macrophage (AM) per alveolus assumed in the model is 12.3 in humans and 1.5 in rats. However, an influx of monocytes and macrophage into the alveoli occurs following acute exposures to numerous pollutants, e.g., PM, ozone, and NO (Oberdörster, 1988; Mercer, 1999; Driscoll, 1988). Furthermore, the volume (and capacity) of a human AM is about 1.5 times that of a rat macrophage (Miller, 2000). Hence, it is difficult to interpret a dose metric like the predicted number of particles deposited per macrophage.

The balance between deposition and clearance affects tissue dose and lung burden. The MPPD model considers the lung clearance of insoluble particles as a two-phase process. The rapid first phase, tracheobronchial clearance, occurs via the action of the mucociliary escalator. The second clearance phase is the slow removal of particles that have deposited in the alveolar region of the lung.

The MPPD model estimates mucus clearance of insoluble particles in the human and rat lung by assuming a mass balance between the volume of mucus produced in the terminal bronchioles and the volume exiting the trachea, i.e., there is no net absorption or secretion of mucus during transport. By further assuming that the production of mucus is the same in all terminal bronchioles, the mucus velocity in terminal bronchioles may be determined given tracheal mucus velocity, tracheal diameter, and the number and diameter of terminal bronchioles. Moving proximally from the terminal bronchioles, the mucus velocity in each parent airway is based on its diameter and daughter airways' diameters and mucus velocities. An implicit assumption in this mucus clearance model is that particles are transported with the mucus blanket, i.e., there is no particle size-dependent slow-cleared fraction from the airways as in the ICRP (1994) model. A more detailed description of the MPPD mucus clearance model appears elsewhere (Asgharian et al., 2001; Hofmann and Asgharian, 2003). Model simulations of tracheobronchial clearance, presented herein, assumed tracheal mucus velocities of 1.9 mm/min in rats (Felicity et al., 1981) and 5.5 mm/min in humans (ICRP, 1994).

Clearance from the alveolar region of the lung is treated somewhat differently between humans and rats by the MPPD model. For humans, the alveolar clearance model was adopted from the ICRP (1994). In that model, the alveolar region consists of three compartments which

clear particles into the bronchioles at the rates of 0.02, 0.001, and 0.0001 day^{-1}. Of the particles deposited in the alveolar region, 30% was assumed in the fast compartment, 60% in the medium rate, and 10% in the slow compartment. The slow compartment also clears via lymphatic channels at a rate of 0.00002 day^{-1}. In rats, the MPPD model considers the overall alveolar clearance rate as the sum of the transport rates to the terminal bronchioles and to the lymph. The alveolar clearance rate constants are based on the pulmonary retention and lymphatic uptake of titanium dioxide particles (MMAD = 1.44 μm, σ_g = 1.71) following a 13-week exposure (6 hr per day, 5 day per week) to 10, 50, or 250 mg/m^3 (Bermudez et al., 2002). Average post-exposure alveolar rate constants of 0.00693, 0.00214, and 0.00083 day^{-1} and post-exposure pulmonary burdens of approximately 1, 8, and 41 mg were observed for the 10, 50, or 250 mg/m^3 exposures, respectively. Translocation into the lymph nodes increased in a concentration dependent manner. Based on these data, the MPPD model assumes that the overall alveolar clearance rate ($_A$) decreases with initial pulmonary burden (m_A). Specifically, $_A$ equals $[0.03341 \times \exp(-1.7759 m_A^{0.3123}) + 0.00072]$ day^{-1}. The assumed clearance rate from the alveoli to the lymphatic system is 0.00106 day^{-1}. The MPPD model, in effect, treats the clearance of particles from the alveolar surface (via macrophages) to the distal airways in rats as a pathway subject to saturation or overload.

The current version of the MPPD model does not offer the option of calculating clearance for exposures to multiple polydisperse aerosol modes or for multiple activity levels. Also, MPPD clearance calculations for rats during chronic exposures are quite time intensive, taking approximately 10 minutes on a Pentium computer (2.8GHz with 512 MB of RAM) to determine retention at 1 year of exposure. For such cases, alveolar clearance was calculated in a spreadsheet, instead of the MPPD model, using the deposition fraction (calculated using the MPPD model) and the same clearance rate constants as used by the model. Based on Equation 3, the alveolar burden in rats was calculated as

$$B_R(t) = \dot{D}_R(t-\Delta t)\Delta t + B_R(t-\Delta t)\exp(-_A \Delta t) \quad (12)$$

where: B_R is the alveolar burden in a rat; t is time; $\dot{D}_R$ is the dose rate to the alveolar region of the rat; Δt is the time increment for the calculations and was selected to be ~1% (or less) of the clearance half-time (i.e., 0.693 / $_A$); and $_A$ is the overall alveolar clearance rate in the rat.

Alveolar burden in humans was computed similarly for the three alveolar compartments (see above discussion) in humans as

$$B_H(t) = \sum_{i=1}^{3} \{F_{H_i} \dot{D}_H (t-\Delta t)\Delta t + B_{H_i}(t-\Delta t)\ \exp(-\lambda_{H_i}\Delta t)\} \quad (13)$$

B_H is the alveolar burden in a human; F_{H_i} is the fraction of alveolar deposition distributed to the i^{th} alveolar compartment; $\dot{D}_H$ is the dose rate to the human alveolar region; Δt is the time increment for the calculations and was selected to be ~1% (or less) of the fastest compartment's clearance half-time (35 days); B_{H_i} is the burden in the i^{th} alveolar compartment; and λ_{H_i} is the clearance rate constant for the i^{th} alveolar compartment.

7A.4 RAT AND HUMAN DOSIMETRY: INTERSPECIES DIFFERENCES

Before providing illustrative examples of how a dosimetric model may be used in rat-to-human extrapolation, it is useful to discuss some of the many differences between rat and human exposure and dosimetry.

7A.4.1 Anatomy

The structure and function of the respiratory tract differs in rats and humans in ways that affect the deposition of particles in the lung. Rats are obligate nose breathers whereas humans are oronasal breathers who breathe through the nose when at rest but who breathe increasingly through the mouth with increasing activity. It has been estimated that 13% of the human population are "mouth-breathers" (Niinimaa, 1981). This distinction is important because the nose is a more efficient filter than the mouth for preventing the penetration of particles into the lung. Thus, by breathing through the mouth, humans effectively increase the amount of inhaled particles reaching the lung. Even when breathing through the nose, humans have greater TB and A region deposition fractions for coarse particles compared to rats due to the lower inhalability of particles larger than 3 μm in the rat. The structure of the human and rat intrathoracic airways also differs in ways that affect the regional deposition pattern in the lung. The branching structure of the lung is monopodial in rats and symmetrically dichotomous in humans. A

monopodial structure has the potential to allow increased penetration of large particles into the A region. Rats also lack respiratory bronchioles, a site of early airway disease in humans.

7A.4.2 Exposure Scenarios

7A.4.2.1 Exertion Level. The amount of PM inhaled is influenced by the exertion level. Chapter 6 discussed how increasing exertion leads to greater deposition of PM in the human lung due to changes in the mode of breathing (nasal to oronasal to oral) as well as the inhalation of greater quantities of PM per unit time due to an increase in minute ventilation (breaths per minute times the tidal volume in L) (Figure 6-18). Humans typically experience a range of breathing patterns during exposure to ambient PM, including those experienced during light and heavy exertion as well as at rest and during sleep. In contrast, laboratory rats are commonly at rest when exposed to PM by inhalation. It is not clear which human breathing pattern is most appropriate for use in an extrapolation. However, just because the rat received its dose while resting does not mean that only the dose received by a resting human should be of interest. The quantity of PM inhaled during a specified time period is given by

$$\text{PM (Inhaled)} = C \times f \times V_t \times t = C \times \text{minute ventilation} \times t \qquad (14)$$

where C may be given in μg, μm^2, or particle number per m^3.

Breathing patterns used in subsequent dosimetric calculations are given in Table 7A-1. The minute ventilation, and therefore the mass of PM inhaled per unit time, will increase with exertion level.

7A.4.2.2 Size Distribution

The atmospheric aerosol to which people are exposed may be thought of in terms of three particle classes: coarse particles (greater than about 1 μm in diameter), accumulation mode particles (about 0.1 to 2.5 μm in diameter), and ultrafine particles (< 0.1 μm in diameter, including the nucleation and Aitken modes [see Chapter 2]). However, laboratory rats are not normally exposed to all three size classes. Some experimental studies reported in the literature use diesel exhaust (ultrafine particles but with some coagulation into the accumulation mode size

TABLE 7A-1. HUMAN AND RAT BREATHING PATTERNS USED IN DOSIMETRIC CALCULATIONS

	Human					Rat
Activity	awake rest [a]	slow walk [a]	light exertion [a]	moderate exertion [a]	heavy exertion [b]	awake rest [a]
Breaths/min	12	16	19	28	26	102
Tidal volume, mL	625	813	1000	1429	1923	2.1
Minute ventilation, L/min	7.5	13	19	40	50	0.214

[a] De Winter-Sorkina and Cassee (2002), [b] ICRP (1994).

range), concentrated accumulation mode particles (concentrated air particles [CAPs]), or particles with a narrow size range within the accumulation mode size range (e.g., studies of acid aerosol). A more recent development is the ultrafine concentrator in which ultrafine particles are separated from larger particles, grown by humidification, concentrated, and dehydrated to reconstitute ultrafine particles. In other studies, rats have been exposed to particles produced by resuspension of bulk material or resuspension of particles previously collected from specific sources (e.g., resuspended oil fly ash, ROFA, or from ambient air). Particles produced by resuspension are frequently passed through an inertial separator (cyclone or impactor) to remove particles > 2.5 μm diameter, thus leaving particles with a nominal MMAD between 1 and 2 μm. The particle size distribution is important because the deposition fraction and the region of deposition in the lung varies with particle size.

Some studies suggest that particle surface area (Oberdorster et al., 1994; 2000) or possibly particle number (Wichmann and Peters, 2000; Wichmann et al., 2000) may be as (or more) important than mass in determining the extent of health effects. Figure 7A-1a shows the mass size distribution of a representative resuspended dust (MMAD = 2 μm, σ_g = 2) overlaid on an atmospheric mass size distribution. Figures 7A-1b and 7A-1c show the distribution of particle surface area and number, respectively. The coarse mode and the resuspended PM mode contribute little to the total particle surface area and contribute minimally to the particle number concentration (note the logarithmic scale for number concentration). Particle characteristics

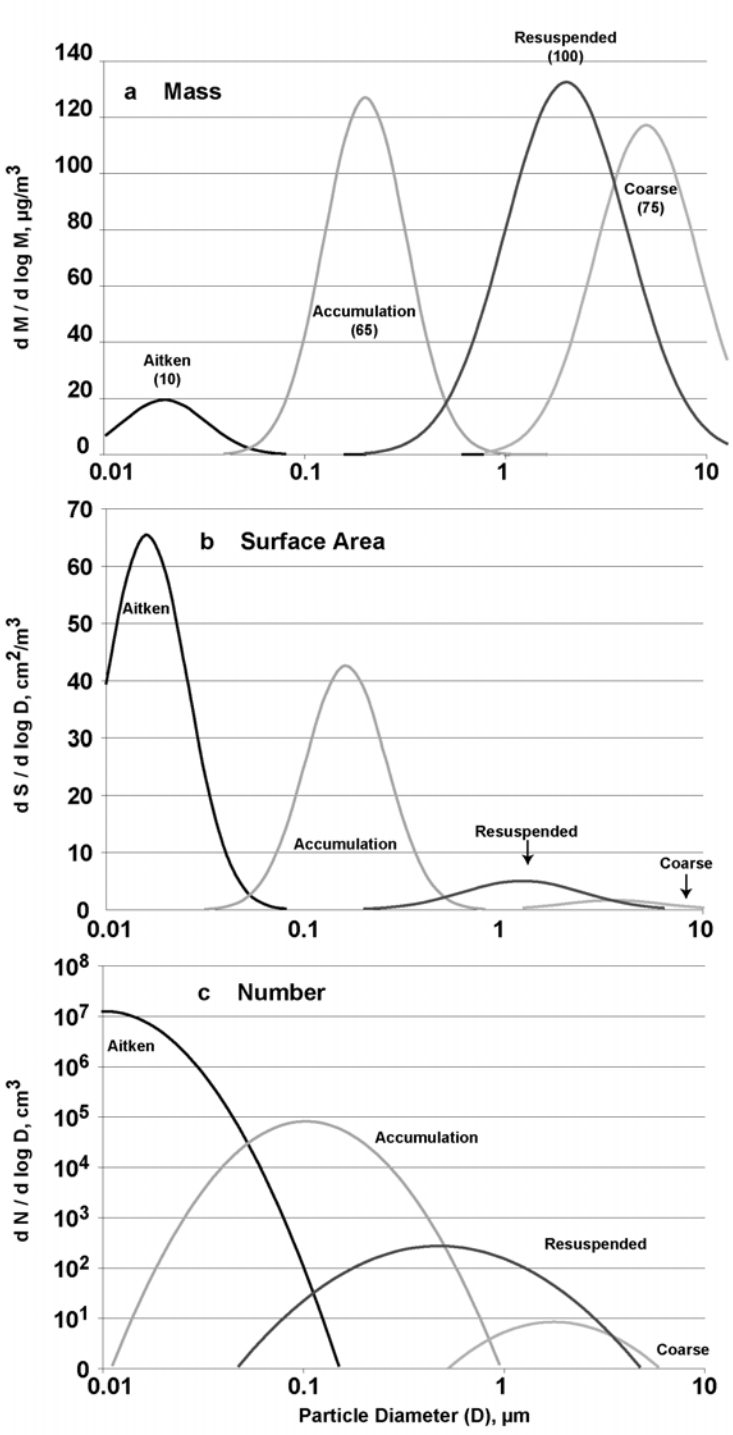

Figure 7A-1a,b,c. Size distributions of the Aitken, accumulation and coarse modes of the average urban aerosol (as reported by Whitby [1978]) and a resuspended PM mode: (a) mass distribution, (b) surface area distribution, and (c) number distribution. Concentrations, in µg/cm^3, are shown for each mode in (a).

used in subsequent dosimetric calculations and some examples of deposition fractions calculated with the MPPD model are given in Table 7A-2.

TABLE 7A-2. PARTICLE CHARACTERISTICS USED BY EPA IN MPPD MODEL CALCULATIONS AND SOME EXAMPLES OF REGIONAL DEPOSITION FRACTIONS

	Human			Rat
Size Distributions	**Aitken [a]**	**Accumulation [a]**	**Coarse [a]**	**Resuspended [b]**
Mass Mean Diameter, µm	0.031	0.31	5.7	2
Surface Mean Diameter, µm	0.023	0.19	3.3	1.2
Number Mean Diameter, µm	0.013	0.069	1.1	0.47
Geometric Standard Deviation, σ_g	1.7	2	2.1	2
Density, g/ml	1	1	1	1
% in Each Size Range	6.7	43.3	50	100
Fraction Deposited [c]				
TB Region	0.19	0.062	0.024	0.04
A Region	0.32	0.1	0.055	0.058
Thoracic Region	0.51	0.16	0.079	0.098

[a] Size distribution for human calculations from Whitby (1978).
[b] Size distribution for rats based on several reported resuspended PM size distributions.
[c] Calculated with the MPPD model for activity levels of light exertion for humans and rest for rats.

In many cases, it is difficult to find good quality and precise information on the size distribution of particles used in laboratory exposure studies. Accumulation mode CAPS might be expected to have a size distribution similar to the accumulation mode in the atmosphere. However, most concentrators have an upper cut of 2.5 µm and do not concentrate particles below about 0.1 to 0.15 µm. Hence, the lower tail of the accumulation mode will not be concentrated while the lower tail of the coarse mode will be. Thus, in atmospheres not influenced by fog or clouds, the size distribution the CAPs might be bimodal or otherwise non-log normal. Reports of σ_g of 1 or less (which is not possible) for CAPS (Gordon et al., 2000) suggest errors in the size

distribution measurements. Diesel exhaust, as generated for laboratory exposures, probably has a nucleation mode and an Aitken mode, with some particles possibly having grown by coagulation into the lower end of the accumulation mode. Thus, the size distribution of diesel particles cannot be adequately modeled as a uni-modal distribution. In addition, diesel exhaust contains particles below 0.01 μm in diameter. Since the lower limit of the MPPD model is 0.01 μm, it may underestimate the number of diesel exhaust particles depositing in the lung. The analysis presented here is limited to particles between 0.01 and 20 μm in diameter.

7A.4.3 Quantities Calculated by Dosimetric Models

7A.4.3.1 Deposition Fraction (DF)

The fraction of inhaled particles deposited in various regions of the respiratory tract depends on the particle size and the breathing pattern (breaths per minute, tidal volume, and whether breathing by nose or mouth). Examples of the ratio, DF_H/DF_R, for a resting rat and a human at various activity levels for nasal and oral breathing are given in Figures 7A-2 and 7A-3.

The ratio increases rapidly for particle diameters above about 5 μm diameter due to differences in inhalability as shown in Figure 7A-4. The DF_H/DF_R for the TB and A region differs only by a small factor in the accumulation size range. Due to the lower inhalability of coarse particles by the rat and differences in the nasal passages of the rat and human, the ratio is quite variable for coarse particles. The ratio is also variable for ultrafine particles due partially to differences in the removal of ultrafine particles in the extrathoracic region.

7A.4.3.2 Clearance

Poorly soluble fine and coarse particles deposited in the lung are cleared by a variety of mechanisms as discussed in Chapter 6. However, the clearance rates from both the TB and A regions are much higher for rats than for humans. Figures 7A-5a and 7A-5b show an example of clearance from the TB region for humans and rats. Note the different time scales for the two figures. Because of these species differences in clearance rates, retention half-times also vary by species. Retention half-times in the TB region are highly dependent on the site of deposition, but generally range from 1-2 hours in rats and 4-10 hours in healthy humans (Hoffmann and Asgharian, 2003).

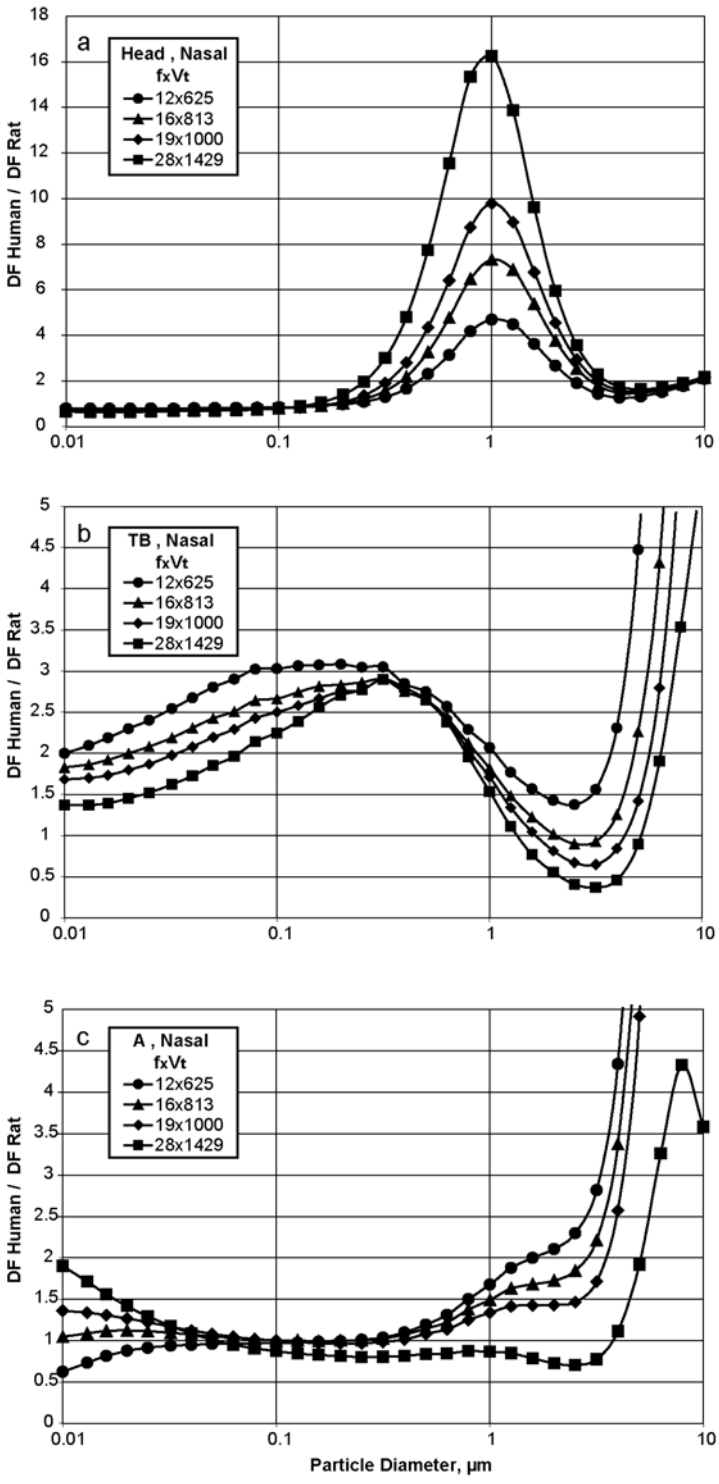

Figure 7A-2a,b,c. The ratio of the deposition fraction for human relative to rat at rest, DF_H/DF_R, (a) the head region, (b) the TB region, and (c) the A region for nasal breathing corrected for particle inhalability.

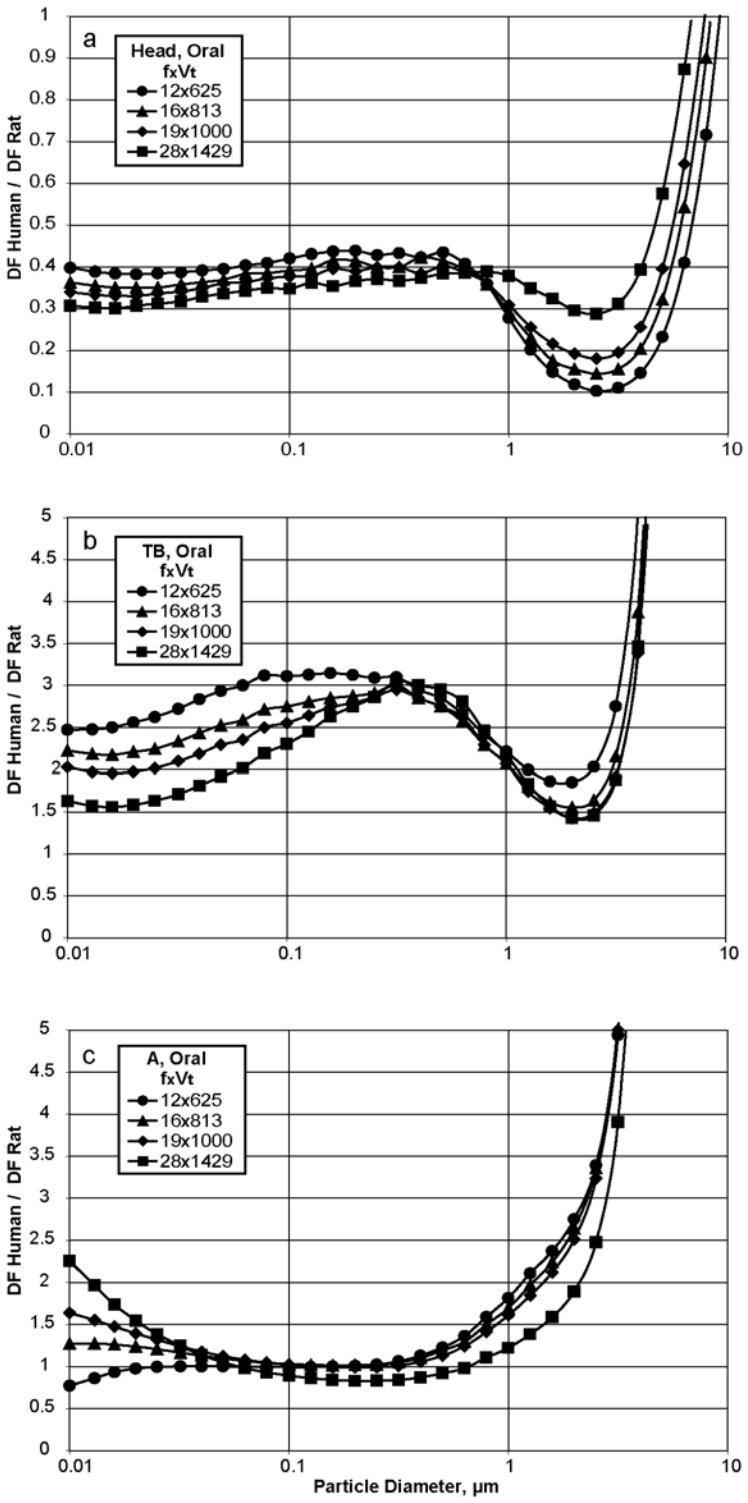

Figure 7A-3a,b,c. The ratio of the deposition fraction for human relative to rat at rest, DF_H/DF_R, (a) the head region, (b) the TB region, and (c) the A region for oral breathing corrected for particle inhalability.

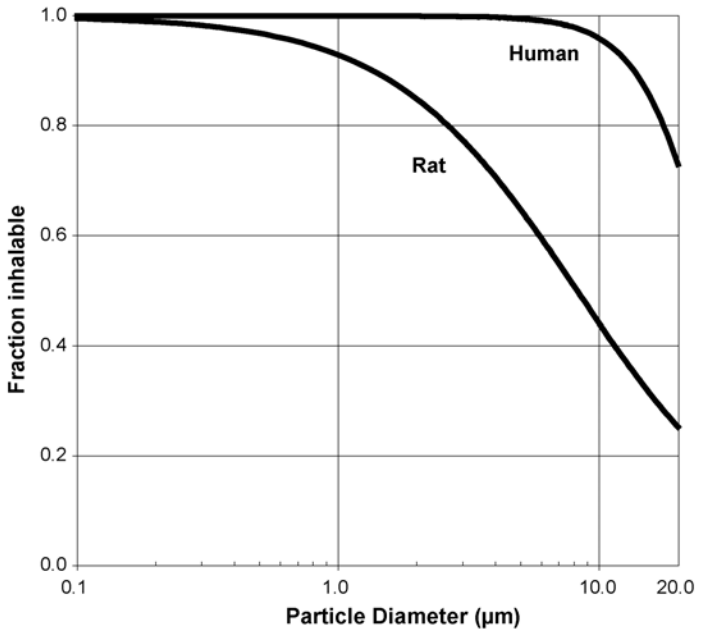

Figure 7A-4. Inhalability curves for human and rat showing the fraction of PM which enters the nose (Ménache et al., 1995).

Figure 7A-6 compares the longer term clearance of particles initially deposited in the A region for several species (Oberdörster, 1988). Clearance from the A region is much slower than clearance from the TB region for both species, while particles deposited in the A region are cleared more rapidly from the rat than the human. For the A region, retention half-times are 60 to 80 days in rats but up to 2 years in humans.

7A.4.3.3 Retention

Figures 7A-5 and 7A-6 show the clearance of particles after exposure had ceased as a fraction of the particles present in the lung at the time exposure ceased. For chronic exposures, however, it is necessary to consider the retained dose. The PM dose retained in a region of the lung is determined by the balance between the rate of input (deposition) and the rate of removal (clearance) as described by Equation 3. In comparing retention for rats and humans, how much of the deposited PM remains in the lung after exposures of various magnitudes and durations is of interest. Figure 7A-7a shows how the retained dose builds up over time in the TB regions of rats and humans as a function of time for an incremental exposure scenario of 6-hour exposure

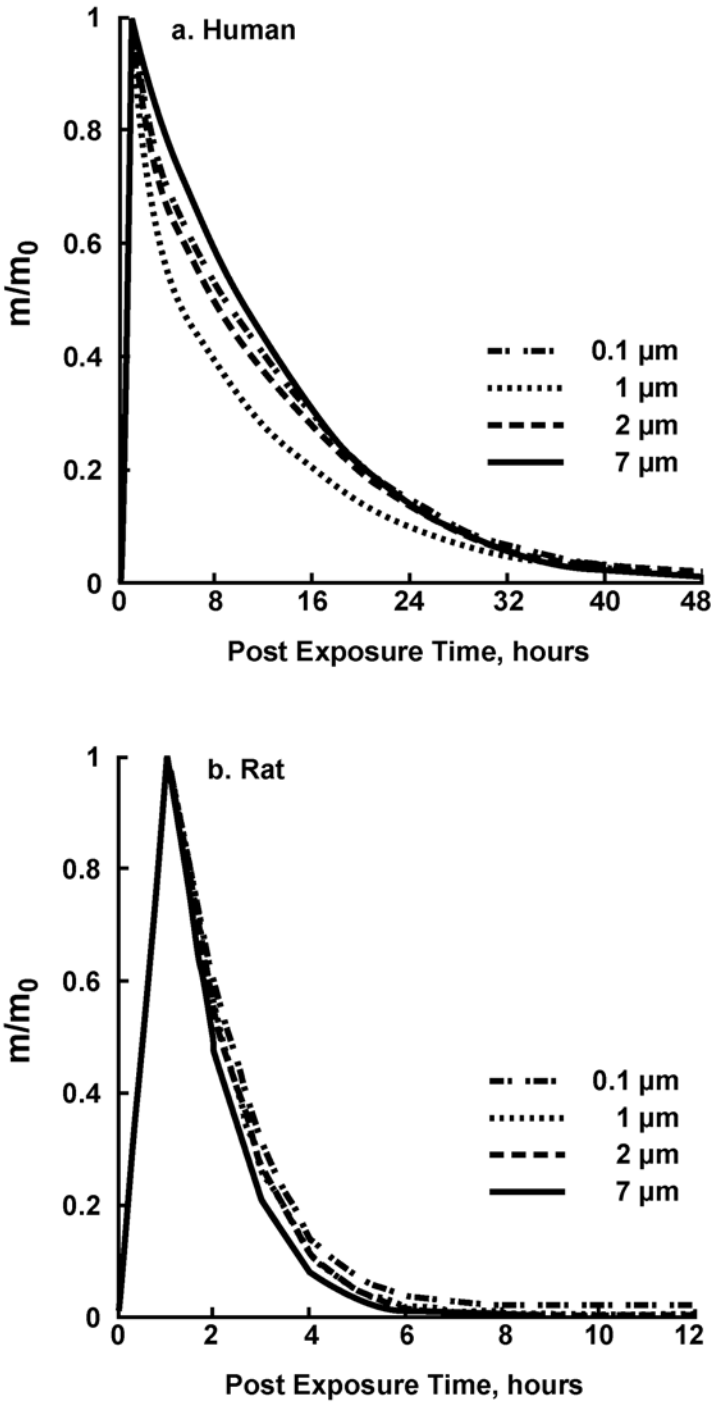

Figure 7A-5. Clearance curves for the TB region for highly insoluble particles for (a) human and (b) rat. Note different time scales. The rat clears PM from the TB region much faster than a human. Fraction of mass retained in the TB region after 1 hour of exposure to unit density particles of diameter shown. Adapted from Hofmann and Asgharian (2003).

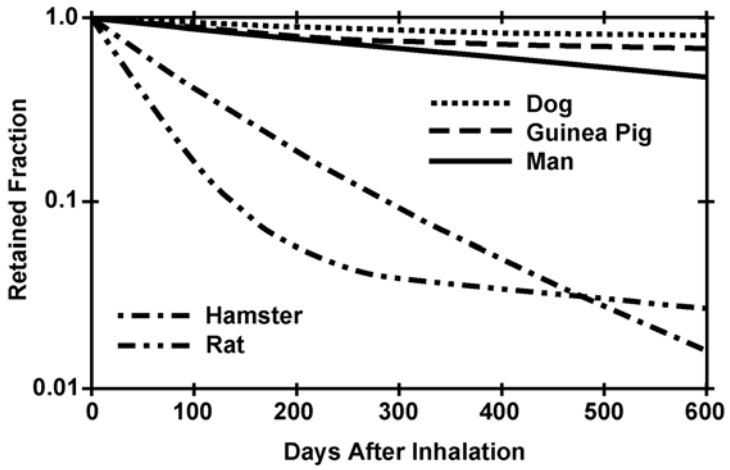

Figure 7A-6. A region clearance curves for highly insoluble particles for several different species. Note much higher clearance rate for rat compared to human. From Oberdörster (1988).

for 3 days to 100 μg/m^3 of 2-μm diameter particles with a σ_g of 2.0. The y-axis is the fraction of total PM mass (i.e., the total mass that would be deposited in the TB region over the 3-day exposure period) that is retained in the TB region. Because of the more rapid clearance of the rat, the fraction of deposited mass retained in the TB region is much smaller for the rat than the human. The maximum retained dose in the rat TB region is never greater than 0.07 of the total deposited dose; whereas, in the case of the human, the maximum retained TB dose reaches as high as 0.28 of the total deposited dose. Figure 7A-7b shows a similar plot for the A region. As shown in Figure 7A-7b, clearance is slower, and retention is greater, in the A region than the TB region for both rats and humans. However, retention in the rat is less than in the human due to the faster clearance in the rat.

7A.4.3.4 Long-Term Burden from Chronic Exposure

PM contains components with various degrees of solubility. Some components of PM deposited in the lung dissolve in seconds to minutes, and others within hours to days. However, there are some PM components that are sufficiently insoluble that they remain in the lung for months to years. If the exposure concentration, breathing rate, tidal volume, and any other dosimetric variables remained constant, then the processes of clearance and removal would

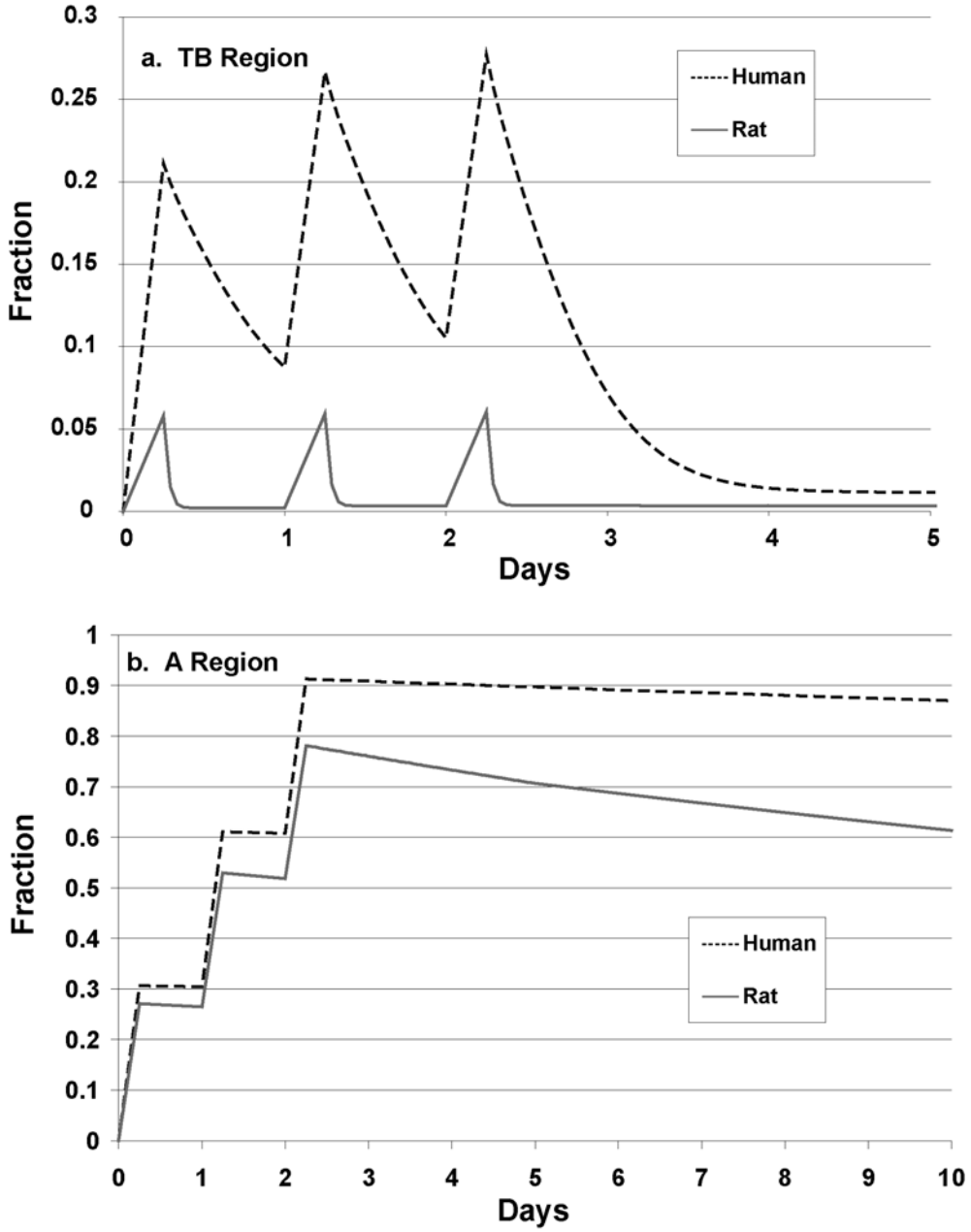

Figure 7A-7a,b. Fraction of total deposited PM retained in the lung after a 6-hour exposure in each of 3 days: (a) TB region, (b) A region. The deposition and clearance calculations used MPPD default values of 12 breaths/min at a tidal volume of 625 mL with tracheal mucus velocity of 5.5 mm/min for humans and 102 breaths/min at a tidal volume of 2.1 mL with tracheal mucus velocity of 1.9 mm/min for the rat. For both rats and humans the size distribution was MMAD = 2, σ_g = 2, and density = 1 g/cm^3. Note different time scales.

eventually approach an equilibrium; and the amount of insoluble PM in the lung would approach a steady-state value. In reality, the exposure concentration and dosimetric parameters will vary with time; but after a sufficient length of time, a near steady-state value with small excursions will be achieved. Furthermore, the available model does not allow long-term calculations with variable exposures and dosimetric parameters. Therefore, an average breathing pattern was used in the model.

Rats are usually kept in a laboratory setting and breathe air that has been filtered and conditioned and are, therefore, exposed to relatively clean air for the months prior to their experimental exposure. In addition, rat exposures usually have a daily schedule of 6 h exposure to an experimental atmosphere followed by 18 h exposure to relatively clean air for 5 days a week. On the other hand, people are exposed to ambient and nonambient PM all their lives. Because of its more rapid clearance rate, a rat will reach a near steady state retained dose of highly insoluble particles in the A region in a few months; it will take more than 10 years for a human to do so. Figure 7A-8 shows the accumulation of PM in the lung for chronic exposures for a rat and a human. Exposure parameters and particle sizes used in the MPPD model calculations and the calculated alveolar deposition fractions are given in Table 7A-3.

7A.4.4 Dose Metrics

For inhalation toxicology, several parameters are required to define a dose metric: a PM indicator, a respiratory region, the time over which the dose is integrated, whether the dose is deposited or retained, and whether the dose is incremental or accumulated. Thus, there are many possible dose metrics. It is not clear which dose metric is most appropriate and it may be that different health effects will be associated with different dose metrics. For example, for health effects associated with soluble PM components, mass may be the most appropriate PM indicator and deposited mass more appropriate than retained mass. For health effects associated with insoluble PM, the particle number or particle surface area might be the more appropriate PM indicator and the retained mass more appropriate than the deposited mass. For acute effects, the maximum deposited incremental dose may be the appropriate type of dose metric. For chronic effects, the total, retained, long-term burden may be more appropriate. For health effects associated with the rupture or inactivation of macrophages, the volume of particles might be an

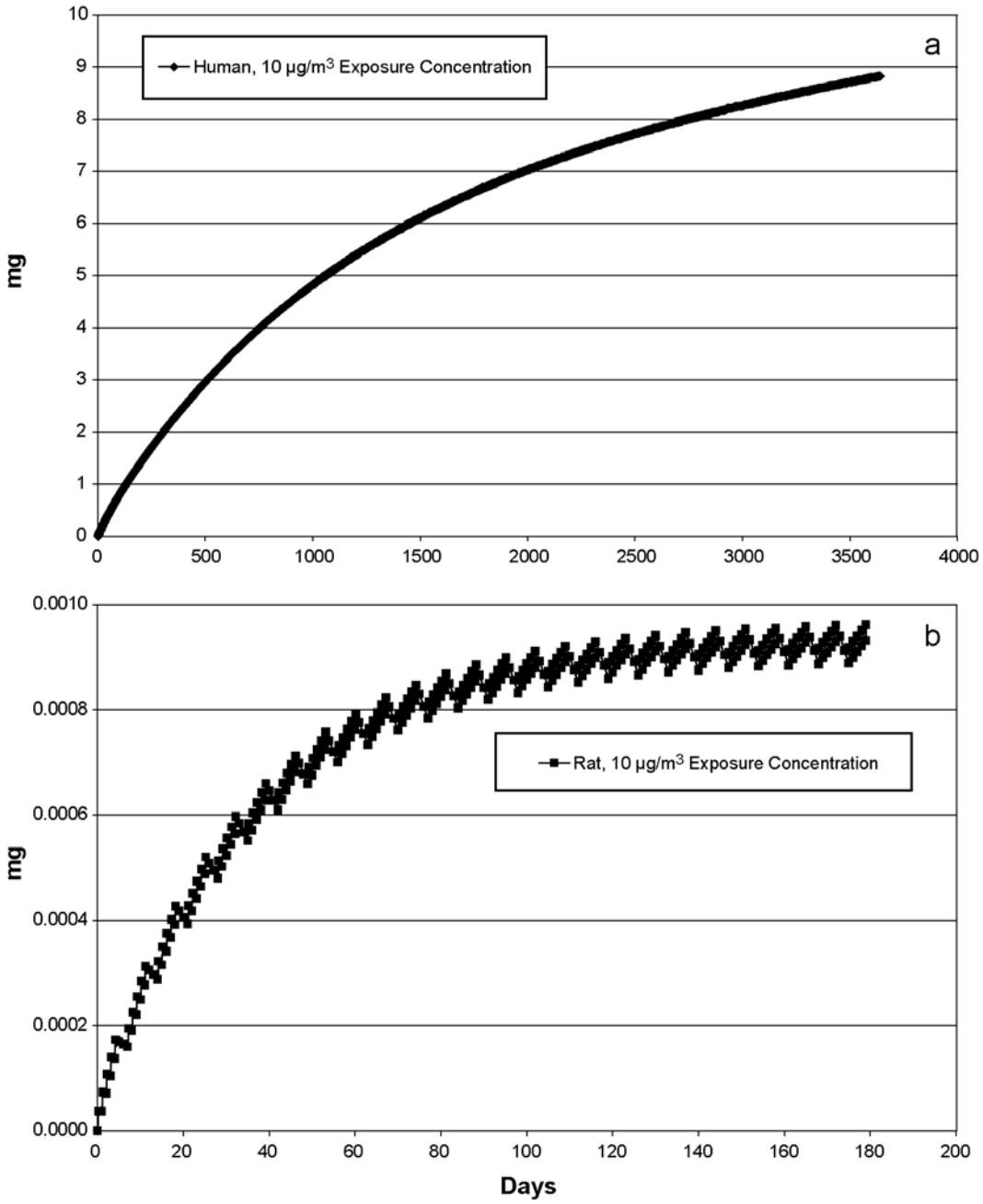

Figure 7A-8. Highly insoluble PM retained in the A region of (a) human and (b) rat. Human receives 10 µg/m^3 exposure to highly insoluble PM for 24 hours a day; rat receives 10 µg/m^3 exposure to highly insoluble PM for 6 hours a day, 5 days a week. The rat reaches a near steady-state burden in 6 months. After 10 years the human is approaching a steady-state burden that is a 1,000 times larger (or approximately 5 times as large for a lung area or body mass normalization). Note different time of scales.

TABLE 7A-3. EXPOSURE SCENARIOS FOR ACCUMULATION OF LONG-TERM BURDEN USED BY EPA IN MPPD MODEL CALCULATIONS

Exposure	**Human**	**Rat**
Hours a day	24	6
Days a week	7	5
Total time	10 years	6 months
Concentration of insoluble PM	10 μg/m^3	10 μg/m^3
Particle Size (MMAD)	1 μm	1 μm
Geometric Standard Deviation (σ_g)	1	1
Density, g/mL	1	1
Breathing pattern	Resting	Resting
Breaths per min	12	102
Tidal volume, mL	625	2.1
Alveolar Deposition Fraction [a]	0.0993	0.0593

[a] Calculated with MPPD model.

appropriate PM indicator and either total retained incremental dose or long-term burden the appropriate type of dose. Some possible parameters are listed in Table 7A-4.

TABLE 7A-4. PARAMETERS USED TO DEFINE A DOSE METRIC [a]

PM Indicator	1	Number, surface area, mass, or volume; total PM or of a specific PM component
Respiratory Region	2	Nasal, tracheobronchial (TB), alveolar (A), thoracic (total lower respiratory tract, TB + A), specific TB generation, alveolus, macrophage or other target cells
Type of Dose	3	Total, average, or maximum
	4	Deposited or retained
	5	Incremental dose (over and above long-term burden) or incremental dose plus accumulated, long-term burden

[a] One parameter is chosen from each of the five rows to form a dose metric.

7A.4.5 Normalizing Factors

The human and rat doses may be scaled by a normalizing parameter to better quantify dose to specific target sites of the respiratory tract. If epithelial cells are the target, the tracheobronchial or alveolar surface area would be the most likely normalizing parameter. If the interstitium is the target, then the lung mass or weight may be better parameters. If activation of macrophages is a causal process, then the number of macrophages would be an appropriate normalizing parameter. Respiratory parameters for the human and rat that may be used as normalizing factors are shown in Table 7A-5.

TABLE 7A-5. CHARACTERISTICS OF HUMAN AND RAT LUNGS

	Human	Rat	Human/Rat
Functional Residual Capacity, FRC, ml	3300 [a]	4.0 [a]	825
Body Mass, g	73000	330	221
Lung Mass, g	1100 [b]	1.65 [c]	667
TB Area, m^2	0.4419 [d]	0.002346 [e]	188
A Area, m^2	57.22 [d]	0.2972 [e]	193

[a] De Winter-Sorkina and Cassee (2002), [b] U.S. EPA (1996), [c] Takezawa (1980) for a 330g rat, [d] Yeh and Schum (1980) scaled to FRC, [e] Yeh et al. (1979) scaled to FRC.

7A.4.6 Summary of Dosimetric Differences between Humans and Rats

The various parameters discussed above are summarized in Table 7A-6.

TABLE 7A-6. DOSIMETRIC DIFFERENCES BETWEEN RATS AND HUMANS

Differences In:	Rats (Experimental Exposures)	Humans (Ambient Exposure)
Anatomy	Nasal breathers Monopodial branching lung structure	Oronasal breathers Dichotomous branching lung structure
Exertion Level	Usually resting during exposure	Exposure occurs over a range from sleep to heavy exercise or work
Clearance	Fast [a]	Slow
Prior Exposure	Usually kept in clean or relatively clean air in laboratory setting; only a few months of low exposure prior to test exposure	Mature or elderly humans likely will have accumulated larger burdens of PM from prior exposures than will have laboratory rats, on a normalized basis
PM Burden	Retained dose approaches steady state after several months, and at a lower fraction of deposited dose than for a human	On the order of 10 years required for the retained dose to approach steady state
PM Size Distribution	Experimental challenge exposures mostly to particles of limited size distribution. Representative size distributions: Resuspended PM: MMD = 1.2 - 2.5 µm, σ_g = 1.5 -2.5 Diesel exhaust: < 0.2 µm CAPS: usually only the 0.1 to 2.5 µm size range is concentrated	Exposed to all three atmospheric modes: Aitken (.01-.1 µm), σ_g = 1.6-1.7 Accumulation (.1-1 µm), σ_g = 1.6-2.2 Coarse (1-100 µm), σ_g = 1.8-2.4

[a] Alveolar clearance rates may be a function of retained dose.

7A.5 DOSIMETRIC CALCULATION FOR EXTRAPOLATION MODELING: COMPARING RATS TO HUMANS

7A.5.1 General Exposure Scenarios

7A.5.1.1 Acute Exposures

For the first series of extrapolation modeling, an acute exposure of 6-hours in duration for humans and rats is examined. Only an incremental dose is considered, ignoring the burden of PM preexisting in the lung at the time of exposure. For activity levels for the rat, the typical experimental exposure condition of resting is used; for the human, three levels of activity: resting, light exertion, and moderate exertion are used. For the latter, oronasal (normal augmentor) and oral breathing are considered. Breathing parameters are given in Table 7A-1. For the human exposure, a near-roadway situation with exposure to all three atmospheric modes is used. For the rat, exposure is considered to each of the three atmospheric modes separately. For the rat, exposures to resuspended collected particles, e.g., residual oil fly ash also (ROFA) or ambient particles collected on a filter, impactor, or electronic-air-cleaner plate are considered.

The size distribution and the fraction of particles in each mode used in the model simulations are given in Table 7A-2. Doses were calculated with the MPPD model (described in Section 7A.3). Normalized doses were calculated using several normalizing factors with the values given in Table 7A-5.

The equivalent concept of an exposure ratio, EqER, was discussed in 7A.2. If exposure times are the same, the rat exposure concentration that will give a dose equivalent to that received by a human at a specified concentration can be determined by multiplying the specified human concentration by EqER, i.e.,

$$EqC_R = EqER \times SpC_H \quad (11b)$$

In Tables 7A-7a to 7A-9b, values of EqER are reported for some of the variety of dose metrics listed in Table 7A-4. For example, EqER × 100 will yield the rat exposure concentration necessary to produce a dose equivalent to that received by a human at an exposure concentration of 100 μg/m^3. For clarity, if EqER is greater than 1, the rat must be exposed to a higher concentration than the human for effectively equivalent doses.

7A.5.1.2 Rat and Human Each Exposed to One Mode of the Atmospheric Particle Size Distribution

Tables 7A-7a and 7A-7b give results, in terms of EqER, for a series of simulations in which the rat normalized dose due to exposure to a mode of the atmospheric particle distribution was compared to a human normalized dose due to exposure to the same single mode. The specific particle size and breathing parameters are given in Tables 7A-1 and 7A-2. The rat was assumed to be resting, the usual condition for experimental exposures. Simulations were run for three human breathing patterns: resting, light exertion, and moderate exertion. Normalized doses to a specific mode (Aitken [At], accumulation [Ac], and coarse [C] mode particles) were compared over one 6-hour exposure period for a variety of dose metrics based on particle mass, surface area, and number for several normalizing parameters. Values of EqER for deposited dose per lung mass, body mass, or lung area range from 0.09 to 5.5. This means that to provide a normalized dose to a rat equivalent to that a human would receive at an exposure of 100 μg/m^3, depending on the dose metric chosen, the EqC_R would range from 9 μg/m^3 (TH deposition per lung mass for a resting human for Aitken particles) to 550 μg/m^3 (TB deposition per unit TB

TABLE 7A-7a. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. HUMAN AND RAT EACH EXPOSED TO ONE ATMOSPHERIC MODE. PARTICLE MASS DOSE METRICS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
Deposited Mass	At	Ac	C	At	Ac	C	At	Ac	C	At	Ac	C
TH per Lung Mass, µg/g	0.088	0.1	0.18	0.23	0.23	0.24	0.49	0.44	1.2	0.47	0.42	1.7
TH per Body Mass, µg/g	0.21	0.23	0.42	0.55	0.53	0.56	1.1	1.0	2.9	1.1	0.98	4.1
TH per Lung Area, µg/m^2	0.24	0.26	0.48	0.63	0.61	0.64	1.3	1.2	3.3	1.3	1.1	4.7
TB per TB Area, µg/m^2	0.45	0.53	0.42	0.90	1.2	0.42	1.6	2.6	4.1	1.6	2.4	5.5
A per A Area, µg/m^2	0.17	0.20	0.54	0.54	0.47	0.83	1.2	0.86	2.8	1.2	0.82	4.0
µg per Macrophage	0.16	0.19	0.52	0.52	0.46	0.81	1.2	0.83	2.7	1.2	0.79	3.9
Retained Mass in TB												
6-h Avg per lung mass, µg/g	0.7	0.7	0.6	1.3	1.4	0.5	2.4	2.7	2.3	2.3	2.6	3.4
24-h Avg per lung mass, µg/g	12	1.8	1.9	3.8	3.5	1.6	6.7	6.3	5.3	6.5	6.0	7.7
6-h Avg per body mass, µg/g	1.6	1.6	1.5	3.1	3.4	1.3	5.6	6.4	5.5	5.4	6.1	7.9
24-h Avg per body mass, µg/g	28	4.2	4.5	9.0	8.1	3.8	16	15	13	15	14	18
6-h Avg per TB area, µg/m^2	1.8	1.9	1.8	3.7	4.0	1.5	6.5	7.5	6.5	6.4	7.1	9.3
24-h Avg per TB area, µg/m^2	33	4.9	5.3	11	9.5	4.4	19	17	15	18	16	21
Retained Mass in A												
Maximum per A Area	0.16	0.19	0.54	0.54	0.46	0.83	1.2	0.84	2.7	1.2	0.80	4.0
6-h Avg per lung mass, µg/g	0.060	0.071	0.20	0.20	0.17	0.31	0.45	0.31	1.0	0.44	0.30	1.5
24-h Avg per lung mass, µg/g	0.061	0.072	0.20	0.20	0.17	0.31	0.45	0.32	1.0	0.44	0.30	1.5
6-h Avg per body mass, µg/g	0.14	0.17	0.47	0.47	0.40	0.72	1.0	0.73	2.4	1.0	0.69	3.5
24-h Avg per body mass, µg/g	0.14	0.17	0.48	0.47	0.41	0.74	1.1	0.74	2.4	1.0	0.70	3.5
6-h Avg per A area, µg/m^2	0.16	0.19	0.54	0.54	0.46	0.83	1.2	0.84	2.7	1.2	0.80	4.0
24-h Avg per A area, µg/m^2	0.16	0.19	0.55	0.54	0.47	0.84	1.2	0.85	2.8	1.2	0.81	4

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-7b. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. HUMAN AND RAT EACH EXPOSED TO ONE ATMOSPHERIC MODE. PARTICLE SURFACE AND NUMBER DOSE METRICS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
Surface Area of Particles Deposited	At	Ac	C	At	Ac	C	At	Ac	C	At	Ac	C
TH per Lung Mass, SA /g	0.09	0.09	0.17	0.24	0.22	0.26	0.52	0.42	1.1	0.55	0.43	1.5
TH per Body Mass, SA /g	0.21	0.21	0.41	0.56	0.52	0.60	1.2	0.99	2.5	1.3	.1.0	3.5
TH per Lung Area, SA /m^2	0.24	0.25	0.47	0.65	0.59	0.69	1.4	1.1	2.9	1.5	1.2	4.0
TB per TB Area, SA /m^2	0.43	0.55	0.45	0.86	1.20	0.53	1.5	2.4	3.3	1.6	2.5	4.6
A per A Area, SA /m^2	0.16	0.18	0.49	0.56	0.46	0.82	1.3	0.87	2.6	1.4	0.88	3.7
SA per Macrophage	0.15	0.18	0.47	0.54	0.45	0.79	0.87	0.56	1.7	1.4	0.85	3.6
Surface Area of Particles Retained in TB												
6-h Avg per TB area, SA /m^2	1.7	2.3	2.2	3.6	5.1	2.4	4.3	4.9	5.2	7.0	9.8	16
24-h Avg per TB area, SA /m^2	4.9	8.0	8.8	11	16	8.7	13	12	13	20	29	47
Surface Area of Particles Retained in A												
6-h Avg per A area, SA /m^2	0.16	0.18	0.48	0.55	0.46	0.82	0.88	0.57	1.7	1.4	0.87	3.6
24-h Avg A per A area, SA /m^2	0.16	0.18	0.49	0.56	0.46	0.82	0.89	0.58	1.8	1.4	0.88	3.7
Number of Particles Deposited												
TH per Lung Mass, # /g	0.09	0.09	0.12	0.25	0.22	0.23	0.63	0.43	0.53	0.63	0.44	0.64
TH per Body Mass, # /g	0.21	0.20	0.29	0.60	0.51	0.53	1.5	1.0	1.2	1.5	1.0	1.5
TH per Lung Area, # /m^2	0.24	0.23	0.33	0.69	0.59	0.61	1.7	1.2	1.4	1.7	1.2	1.7
TB per TB Area, # /m^2	0.39	0.49	0.36	0.80	1.00	0.65	0.9	1.8	1.8	1.6	1.9	2.1
A per A Area, # /m^2	0.14	0.17	0.32	0.61	0.49	0.60	2.3	1.0	1.3	1.8	1.0	1.6
# per Macrophage	0.13	0.17	0.31	0.59	0.48	0.58	1.1	0.65	0.82	1.8	1.0	1.5
Number of Particles Retained in TB												
6-h Avg per TB area, # /m^2	1.6	2.0	1.4	3.6	3.8	2.1	4.3	4.3	3.3	6.9	6.7	5.8
24-h Avg per TB area, # /m^2	4.7	5.2	3.8	10.7	10.3	5.6	13	12	8.1	21	18	15
Number of Particles Retained in A												
6-h Avg per A area, # /m^2	0.14	0.17	0.31	0.62	0.49	0.59	1.1	0.66	0.84	1.8	1.0	1.5
24-h Avg per A area, # /m^2	0.14	0.17	0.31	0.62	0.49	0.60	1.1	0.67	0.84	1.8	1.0	1.5

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

area for a human undergoing moderate exertion for coarse particles). For short-term retention in the TB region, EqER values are higher, 0.67 to 33, because of the more rapid clearance of PM from the rat TB region. For short-term retention in the A region, EqER values are lower, 0.06 to 4.05.

Dose metrics based on surface area or number are somewhat different from those based on mass due to changes in DF since the median diameter decreases in going from mass to surface area to number. For surface area dose metrics, EqER values range from 0.09 to 4.6 for deposited dose metrics; 1.7 to 47 for short-term (6- or 24-hr) retention in TB regions; and 0.16 to 3.7 for short term retention in the A region. For particle number dose metrics, the EqER range is 0.09 to 2.1 for deposited dose metrics, 1.4 to 15 for short term retention in the TB region, and 0.14 to 1.8 for short term retention in the A region. The MPPD model has a lower particle size limit of 0.01 µm. Hence, it could not calculate the DF for the count distribution of the Aitken mode with a σ_g of 1.7, because 29% of the particles are below 0.01. Therefore, the EqER for number distribution of the Aitken mode is based on monodisperse particle of 0.013 diameter, the number mean diameter of the Aitken mode.

7A.5.1.3 Exposure to Resuspended Combustion Particles

Experimental studies with rats have typically used only one particle size range, either Aitken mode particles (exposure to diesel or auto exhaust), accumulation mode particles (CAPs or some acid aerosol exposure studies), or resuspended PM. Resuspended PM, regardless of its initial size distribution, if passed through a 2.5 µm cyclone or impactor, will have a MMAD between 1 and 2 µm and a σ_g between 1.5 and 2.5. One can ask if it is appropriate to compare the rat dose, from only one of the PM size ranges, to the human dose from only that size range when the human is exposed to the entire atmospheric aerosol. The answer to this question may be brought into focus by asking what size particle should be used to calculate the human dose to compare with rat exposures to resuspended combustion particles such as the stationary source combustion particles (e.g., ROFA) used in many EPA studies. It would not be appropriate to use as a basis for the human dose, or for the equivalent human exposure, an exposure to resuspended particles. People do not typically breath resuspended particles with a MMAD of 2 µm and a σ_g of 2. As shown in Figure 7A-1, resuspended particles have minimal surface area or particle number compared to the PM that a human would be exposed to in an urban atmosphere. Thus, if

the health effect of interest were related to particle surface area or particle number, it would require very high doses of a typical resuspended PM to achieve surface area or number doses equivalent to those received by a human. Tables 7A-8a and 7A-8b report calculated values EqER for the comparison of a rat exposed to resuspended PM (MMAD = 2 μm, σ_g = 2) relative to a human exposed to all three modes of the atmospheric size distribution for four human exposure scenarios.

For a comparison of a rat exposed to resuspended PM for 6 hours to a human exposed to ambient PM near a roadway for 6 hours, the EqER for mass-based metrics have a smaller range than for the comparison of individual modes: 0.13 to 2.7 for deposited mass, 0.54 to 16 for mass retained in the TB region, and 0.12 to 2.0 for mass retained in the A region. However, for dose metrics based on surface area or number, EqER values are very high because resuspended PM is lacking in smaller particles. Thus, for particle surface area-based dose metrics, EqER values range from 1.3 to 380 and for particle number-based dose metrics from 1,100 to 1,100,000.

7A.5.1.4 Rat Exposed to One Fraction, Human Exposed to All Three Modes of the Atmospheric Particle Size Distribution

As suggested in 7A.5.1.2, it may not be appropriate to compare a rat dose from one particle size fraction to a human dose from the same size fraction (as was reported in Tables 7A-7a and 7A-7b) because humans are exposed to the full range of particle sizes. Tables 7A-9a and 7A-9b show EqER values derived from normalized doses calculated from the combined exposure to all three particles size fractions for humans whereas rats were considered to be exposed to only one of the three size fractions in a given individual study. Again, a wide range of EqER values is found: from 0.03 to 4.1 for deposited mass, from 0.19 to 24 for retained mass in the TB region, and from 0.03 to 3.9 for retained mass in the A region. For particle surface area- and particle number-based dose metrics the range in EqER values are very high, 0.008 to 1,300 for surface area and 0.01 to 1.3×10^7 for number.

7A.5.1.5 Rat-to-Human Extrapolation of Long-Term PM Burden in the Alveolar Region

As discussed in 7A.4.3.4, differences in clearance, and resulting differences in the long-term burden of insoluble PM retained in the lungs of humans and rats, must be considered in extrapolation of chronic exposures. The alveolar clearance rate of the human is thought to be independent of PM load for expected exposures, but the clearance rate for a rat depends on the

TABLE 7A-8a. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. RAT EXPOSED TO RESUSPENDED PM (e.g., ROFA), HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES. PARTICLE MASS DOSE METRICS.*

Deposited Mass	Resting	Light	Moderate Normal Augmentor	Moderate Oral Breathing
TH per Lung Mass, µg/g	0.13	0.25	0.72	0.84
TH per Body Mass, µg/g	0.29	0.59	1.7	2.0
TH per Lung Area, µg/m^2	0.34	0.67	1.9	2.3
TB per TB Area, µg/m^2	0.35	0.61	2.3	2.7
A per A Area, µg/m^2	0.33	0.73	1.7	2.0
µg per Macrophage	0.32	0.70	1.7	1.9
Retained Mass in TB				
6-h Avg per lung mass, µg/g	0.54	0.84	2.0	2.3
24-h Avg per lung mass, µg/g	3.6	2.4	5.1	5.7
6-h Avg per body mass, µg/g	1.3	2.0	4.7	5.4
24-h Avg per body mass, µg/g	8.4	5.6	12	13
6-h Avg per TB area, µg/m^2	1.5	2.3	5.5	6.3
24-h Avg per TB area, µg/m^2	9.9	6.6	14	16
Retained Mass in A				
Maximum per A Area	0.33	0.72	1.7	2.0
6-h Avg per lung mass, µg/g	0.12	0.27	0.63	0.73
24-h Avg per lung mass, µg/g	0.12	0.27	0.64	0.74
6-h Avg per body mass, µg/g	0.29	0.62	1.5	1.7
24-h Avg per body mass, µg/g	0.29	0.63	1.5	1.7
6-h Avg per A area, µg/m^2	0.33	0.72	1.7	2.0
24-h Avg per A area, µg/m^2	0.33	0.73	1.7	2.0

* At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-8b. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. RAT EXPOSED TO RESUSPENDED PM (e.g., ROFA), HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES. PARTICLE SURFACE AND NUMBER DOSE METRICS.*

Surface Area of Particles Deposited	Resting	Light	Moderate, Normal Augmentor	Moderate, Oral Breathing
TH per Lung Mass, SA /g	1.7	4.4	9.4	9.9
TH per Body Mass, SA /g	4.0	10	22	23
TH per Lung Area, SA /m^2	4.6	12	25	27
TB per TB Area, SA /m^2	6.7	14	26	27
A per A, SA /m^2	3.5	11	25	27
SA per Macrophage	27	87	132	208
Surface Area of Particles Retained in TB				
6-h Avg per TB area, SA /m^2	31	65	74	125
24-h Avg per TB area, SA /m^2	94	198	218	381
Surface Area of Particles Retained in A				
6-h Avg per A area, SA /m^2	3.4	11	17	26
24-h Avg A per A area, SA /m^2	3.4	11	17	27
Number of Particles Deposited				
TH per Lung Mass, # /g	2.6E + 03	7.3E + 03	1.8E + 04	1.8E + 04
TH per Body Mass, # /g	6.1E + 03	1.7E + 04	4.2E + 04	4.2E + 04
TH per Lung Area, # /m^2	7.0E + 03	2.0E + 04	4.8E + 04	4.9E + 04
TB per TB Area, # /m^2	2.0E + 04	4.1E + 04	4.5E + 04	8.0E + 04
A per A Area, # /m^2	3.0E + 03	1.3E + 04	5.0E + 04	3.9E + 04
# per Macrophage	2.9E + 03	1.3E + 04	2.4E + 04	3.8E + 04
Number of Particles Retained in TB				
6-h Avg per TB area, # /m^2	9.0E + 04	2.0E + 05	2.3E + 05	3.8E + 05
24-h Avg per TB area, # /m^2	2.3E + 05	5.3E + 05	6.4E + 05	1.1E + 06
Number of Particles Retained in A				
6-h Avg per A area, # /m^2	2.9E + 03	1.3E + 04	2.4E + 04	3.9E + 04
24-h Avg per A area, # /m^2	2.9E + 03	1.3E + 04	2.3E + 04	3.9E + 04

* At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-9a. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. RAT EXPOSED TO ONE MODE AT A TIME, HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES. PARTICLE MASS DOSE METRICS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
Deposited Mass	At	Ac	C	At	Ac	C	At	Ac	C	At	Ac	C
TH per Lung Mass, µg/g	0.033	0.10	0.22	0.07	0.20	0.43	0.19	0.58	1.2	0.22	0.68	1.5
TH per Body Mass, µg/g	0.078	0.24	0.51	0.15	0.47	1.0	0.44	1.4	2.9	0.52	1.6	3.4
TH per Lung Area, µg/m^2	0.089	0.27	0.59	0.18	0.54	1.2	0.51	1.6	3.4	0.60	1.8	3.9
TB per TB Area, µg/m^2	0.14	0.57	0.54	0.25	0.98	0.92	0.93	3.7	3.5	1.1	4.4	4.1
A per A Area, µg/m^2	0.071	0.20	0.64	0.16	0.44	1.4	0.37	1.0	3.3	0.43	1.2	3.9
µg Mass per Macrophage	0.069	0.19	0.62	0.15	0.42	1.4	0.36	1.0	3.2	0.42	1.2	3.7
Retained Mass in TB												
6-h Avg per lung mass, µg/g	0.19	0.82	0.81	0.30	1.3	1.3	0.71	3.0	3.0	0.8	3.5	3.5
24-h Avg per lung mass, µg/g	1.2	4.8	5.6	0.80	3.2	3.7	1.70	6.8	7.9	1.9	7.7	8.9
6-h Avg per body mass, µg/g	0.45	1.9	1.9	0.70	3.0	3.0	1.66	7.1	7.1	1.9	8.2	8.1
24-h Avg per body mass, µg/g	2.8	11	13	1.9	7.6	8.7	4.00	16	19	4.5	18	21
6-h Avg per TB area, µg/m^2	0.52	2.2	2.2	0.82	3.5	3.5	1.95	8.4	8.4	2.2	9.6	9.5
24-h Avg per TB area, µg/m^2	3.3	13	15	2.2	8.9	10	4.69	19	22	5.3	21	24
Retained Mass in A												
Maximum per A Area	0.071	0.20	0.64	0.15	0.43	1.4	0.36	1.0	3.3	0.42	1.2	3.8
6-h Avg per lung mass, µg/g	0.026	0.073	0.24	0.057	0.16	0.51	0.13	0.37	1.2	0.16	0.44	1.4
24-h Avg per lung mass, µg/g	0.026	0.074	0.24	0.057	0.16	0.52	0.14	0.38	1.2	0.16	0.44	1.4
6-h Avg per body mass, µg/g	0.062	0.17	0.56	0.13	0.37	1.2	0.32	0.88	2.9	0.37	1.0	3.3
24-h Avg per body mass, µg/g	0.062	0.17	0.56	0.13	0.38	1.2	0.32	0.89	2.9	0.37	1.0	3.4
6-h Avg per A area, µg/m^2	0.071	0.20	0.64	0.15	0.43	1.4	0.36	1.01	3.3	0.42	1.2	3.8
24-h Avg per A area, µg/m^2	0.071	0.20	0.65	0.16	0.43	1.4	0.37	1.02	3.3	0.43	1.2	3.9

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-9b. EQUIVALENT EXPOSURE RATIO, EqER, FOR A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS. RAT EXPOSED TO ONE MODE AT A TIME, HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES. PARTICLE SURFACE AND NUMBER DOSE METRICS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
Surface Area of Particles Deposited	At	Ac	C	At	Ac	C	At	Ac	C	At	Ac	C
TH per Lung Mass, SA /g	0.008	0.17	7	0.021	0.44	18	0.04	0.93	37	0.05	1.0	40
TH per Body Mass, SA /g	0.019	0.40	16	0.048	1.04	42	0.10	2.2	88	0.11	2.3	93
TH per Lung Area, SA /m^2	0.021	0.46	18	0.056	1.2	48	0.12	2.5	100	0.12	2.7	110
TB per TB Area, SA /m^2	0.035	1.30	23	0.072	2.7	47	0.13	4.9	87	0.14	5.2	92
A per A Area, SA/ m^2	0.015	0.28	15	0.049	0.88	49	0.11	2.0	110	0.12	2.1	120
SA per Macrophage	0.12	2.2	120	0.38	6.9	390	0.58	11	590	0.91	17	920
Surface Area of Particles Retained in TB												
6-h Avg per TB area, SA /m^2	0.052	2	38	0.11	4.1	81	0.13	4.7	92	0.21	8.0	160
24-h Avg per TB area, SA /m^2	0.16	5.3	120	0.33	11	250	0.37	12	280	0.64	21.4	490
Surface Area of Particles Retained in A												
6-h Avg per A area, SA /m^2	0.015	0.27	15	0.048	0.87	49	0.07	1.3	74	0.12	2.1	120
24-h Avg A per A area, SA /m^2	0.015	0.27	15	0.049	0.88	50	0.07	1.3	75	0.12	2.1	120
Number of Particles Deposited												
TH per Lung Mass, # /g	0.006	3.2	4.4E + 04	0.017	9.0	1.2E + 05	0.042	22	3.0E + 05	0.043	22	3.1E + 05
(TH per Body Mass, # /g	0.014	7.5	1.0E + 05	0.040	21	2.9E + 05	0.099	52	7.1E + 05	0.10	52	7.2E + 05
TH per Lung Area, # /m^2	0.016	8.6	1.2E + 05	0.046	24	3.3E + 05	0.11	60	8.2E + 05	0.11	60	8.2E + 05
TB per TB Area, # /m^2	0.026	29	2.5E + 05	0.054	60	5.0E + 05	0.06	66	5.5E + 05	0.10	115	9.7E + 05
A per A Area, # /m^2	0.009	3.5	5.7E + 04	0.041	15	2.5E + 05	0.16	59	9.6E + 05	0.12	46	7.6E + 05
per Macrophage	0.009	3	5.5E + 04	0.040	15	2.5E + 05	0.07	28	4.6E + 05	0.12	45	7.4E + 05
Number of Particles Retained in TB												
6-h Avg per TB area, # /m^2	0.040	42	4.0E + 05	0.086	91	8.7E + 05	0.10	110	1.0E + 06	0.17	180	1.7E + 06
24-h Avg per TB area, # /m^2	0.12	107	1.1E + 06	0.26	240	2.5E + 06	0.32	290	3.1E + 06	0.52	480	5.0E + 06
Number of Particles Retained in A												
6-h Avg per A area, # /m^2	0.009	3.4	5.6E + 04	0.042	16	2.5E + 05	0.076	28	4.6E + 05	0.12	46	7.5E + 05
24-h Avg per A area, # /m^2	0.009	3.5	5.7E + 04	0.042	16	2.6E + 05	0.073	27	4.4E + 05	0.12	46	7.6E + 05

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

amount of particles in the alveolar region. As a result, the fraction of deposited PM mass retained in the alveolar region of a human, as estimated by the MPPD model, does not depend on the amount of PM deposited. However, the modeled fraction of deposited PM retained in the rat alveolar region will increase as the exposure concentration increases. This phenomenon of the rate of clearance decreasing with increased loading is illustrated in Figure 7A-9 for the exposure parameters and particle size given in Table 7A-3.

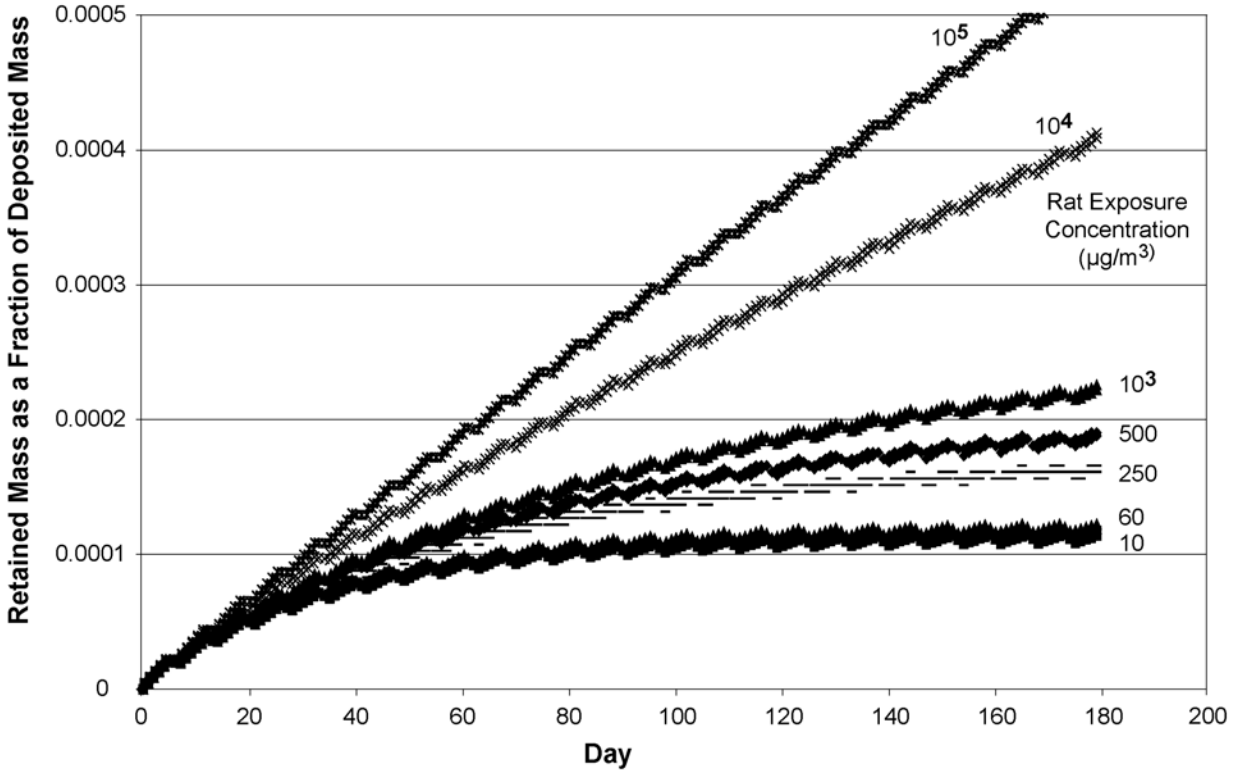

Figure 7A-9. Highly insoluble PM mass retained in the A region of the rat as a fraction of deposited mass in the A region for several exposure concentrations. Same exposure conditions as given in Table 7A-3.

For rat to human extrapolation of chronic exposure, we have chosen the dose metric of retained mass of highly insoluble PM per unit lung surface area. Dosimetric modeling enables us to estimate the exposure scenario to yield a retained dose in the rat equivalent to a retained

dose in a human. As illustrated in Figure 7A-10, a rat would require an exposure of 60 µg/m^3 versus a human exposure of only 10 µg/m^3 to have the same retained PM mass per unit alveolar area after 6-months exposure. For shorter exposure times, the rat equivalent dose would be less than 60 µg/m^3.

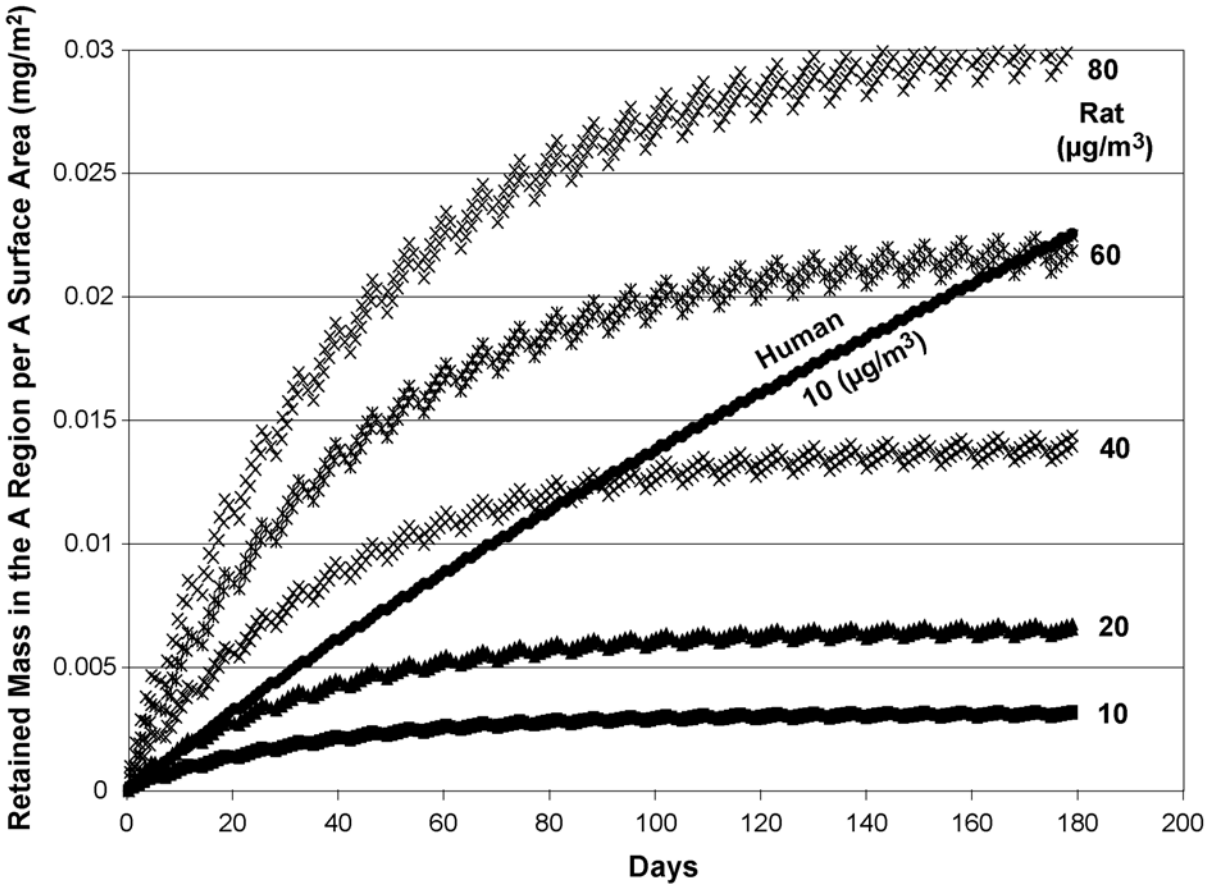

Figure 7A-10. Highly insoluble PM mass retained in the A region per A surface area (mg/m^2) for several exposure concentrations for the rat and 10 µg/m^3 for the human. Exposure conditions given in Table 7A-3.

Suppose that it is necessary to give a rat an exposure such that after 6 months the rat dose (in mass of PM retained per unit alveolar surface area) is the same as a human's steady state dose (0.15 mg/m^2) reached only after about 10-years exposure. Figure 7A-11 shows the

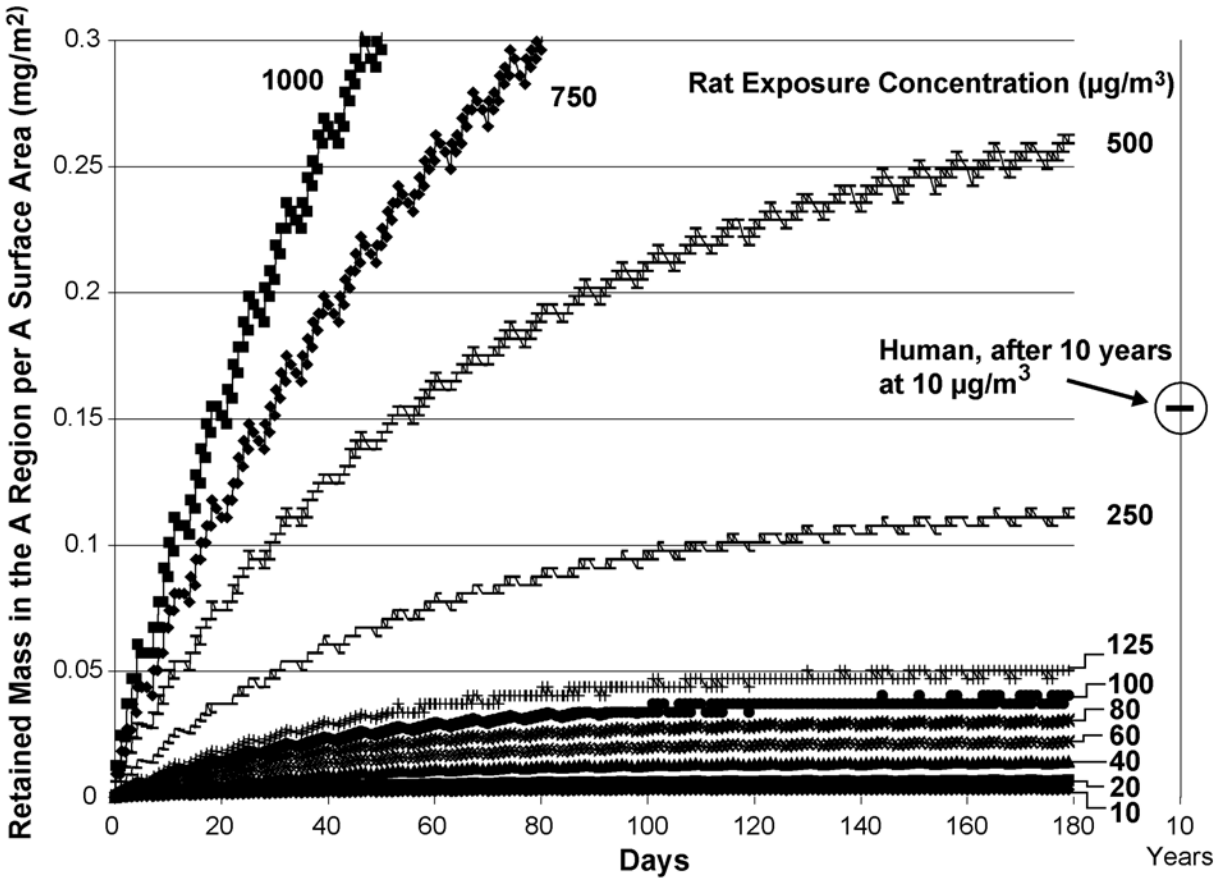

Figure 7A-11. Highly insoluble PM mass retained in the A region per A surface area (mg/m^2). As shown, a human would reach about 0.15 after a 10-year exposure to 10 $\mu g/m^3$. Exposure conditions given in Table 7A-3.

accumulation of PM burden per unit area in a rat for various exposure concentrations. In order to better interpolate the rat 6-month exposure concentration needed to yield the burden in a human at steady state, Figure 7A-12 shows a log log plot of burden versus exposure concentration and the equation for the regression line. This equation can be used to calculate the rat-equivalent exposure concentration. The equivalent rat exposure concentration is 300 $\mu g/m^3$. If one assumes a human exposure to 50 $\mu g/m^3$ total PM of which 20% is insoluble, the rat would have to be exposed to the same PM at a concentration of 1,500 $\mu g/m^3$ for 6 months (6 hours a day, 5 days a week) in order to receive a dose or burden equivalent to the near steady-state dose or burden of a human after exposure to 50 $\mu g/m^3$ 24 hours a day, 7 days a week, for 10 years.

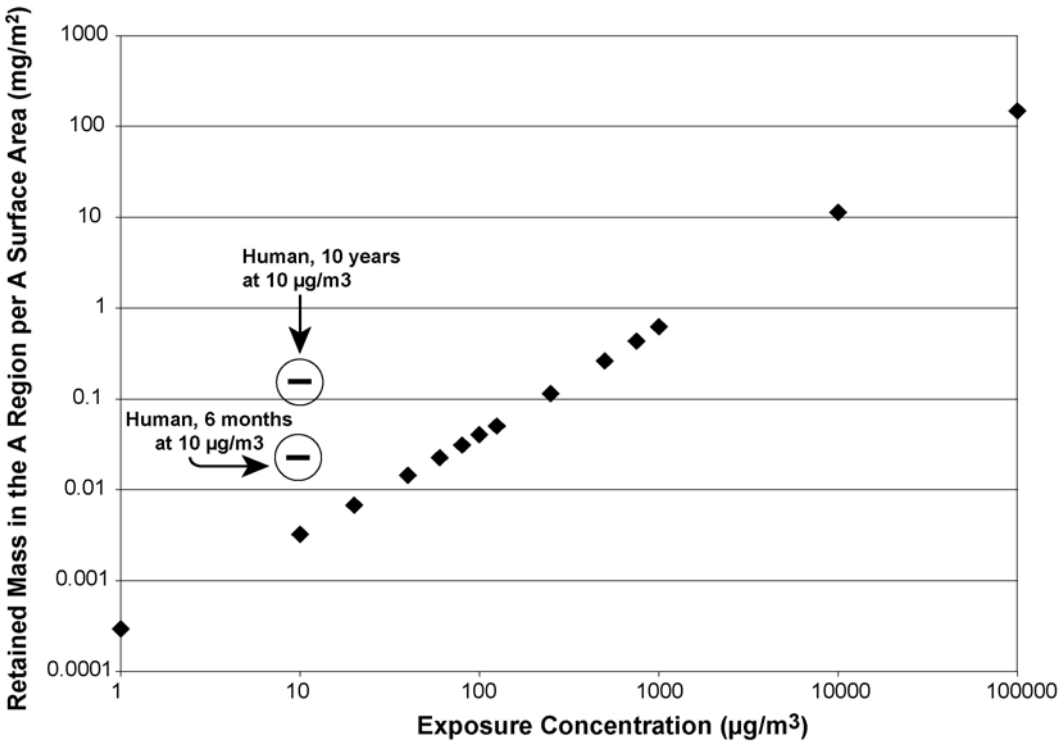

Figure 7A-12. Highly insoluble PM mass retained in the A region per A surface area (mg/m^2) for a rat after 6-months exposure for various exposure concentrations. On a log-log plot, particle retention per alveolar surface area in a rat is nearly linear (R^2= 0.9994) with exposure concentration (Retention [mg/m^2] = 0.0015 × Concentration [$\mu g/m^3$] − 0.4836). Human retentions after 6 months and 10 years of exposure to 10 $\mu g/m^3$ are also shown. Particle size and breathing patterns are given in Table 7A-3.

7A.5.1.6 Long-Term Burden Plus Acute Dose

It may also be useful to compare rat and human exposures in terms of both the incremental dose due to a 6-hour exposure plus the total retained burden built up over the time it takes to reach an equilibrium dose, about 10 years for a human but less than 6 months for a rat. Table 7A-10 shows results of a simulation in which the human burden was based on a 6-hour acute exposure to 100 $\mu g/m^3$ PM_{10} while working near a roadway (6.7 Aitken, 43.3 accumulation, and 50 coarse; normal augmentor, moderate exertion as shown in Table 7A-1) plus the accumulated burden resulting from a 10-year exposure (24 hour/day, 7 day/week) to an average of 64 $\mu g/m^3$ PM_{10} (4 Aitken, 30 accumulation, and 30 coarse) at an average breathing pattern with a tidal volume of 900 mL and a nasal breathing rate of 17 breaths per minute

TABLE 7A-10. RAT EXPOSURE CONCENTRATION TO GIVE TOTAL PM BURDEN EQUIVALENT TO HUMAN (STEADY-STATE BURDEN PLUS INCREMENT DUE TO 6-HOUR EXPOSURE) [a]

Mass Burden in the TB Region	
TB burden per body mass	2.7 mg/m^3
TB burden per TB area	3.1 mg/m^3
Mass Burden in the A Region	
A burden per body mass	116 mg/m^3
A burden per A area	134 mg/m^3

[a] Steady-state retained PM burden (based on 24-hours a day, 7 days a week exposure to average concentration, reached in rat in 6 months, in humans in 10 years) plus additional PM mass retained due to 6-hour exposure (rat to resuspended PM while resting, human to ambient PM near busy road while working).

(minute ventilation of 15.3 L/min). The rat burden was based on a 6-hour acute exposure to resuspended dust plus the retained burden resulting from a 6-month exposure (24 hour/day, 7 day/week) to 40 $\mu g/m^3$ PM_{10} (20 accumulation and 20 coarse) at the resting breathing parameters. The additional 6-hour rat exposure concentration to give an accumulated dose or PM burden equivalent to the corresponding human dose following a 6-hour work exposure was estimated using the MPPD model. It was assumed that 25% of the PM from the long-term exposure could be considered highly insoluble and therefore would contribute to the long-term burden. This simulation is only a rough estimate since breathing patterns vary over time and the fraction of PM that would remain insoluble for 10 years is uncertain. The results indicate that rat exposure concentrations of the order of 3 mg/m^3 (TB burden per body mass) and 5 mg/m^3 (TB burden per TB surface area) can give a PM mass burden in the TB region equivalent to that for a human. However, for dose metrics based on burden in the A region, extremely high rat exposure concentrations of approximately 43 times larger would be required. While the concentrations are only rough approximations, this simulation indicates the complexity of using a rat model to simulate the effects of PM in the human lung.

7A.5.1.7 Caveats

The simulations are based on a model, and while the model uses similar deposition calculations for humans and rats, the results of the simulations are only considered to be estimates. The particles were assumed to have a density of 1 g/cm^3, making the physical and aerodynamic diameters the same. The calculations for the number dose of At particles used a single size, 0.013 µm, rather than a distribution since the MPPD model does not go below 0.01 µm diameter in particle size. No consideration was given to the difference between human PM exposures and ambient PM concentrations nor to exposures to indoor-generated or occupational PM. Thus, while the results may not be quantitatively accurate, the general relationships between human and rat exposure may provide useful information in the attempt to understand rat to human PM dose extrapolation.

7A.6 HEALTH STATUS: A NON-DOSIMETRIC CONSIDERATION

Clearly, many host factors may come into play when considering response to PM. While the mechanistic reasons for enhanced responsiveness are poorly understood, some specific host attributes or health conditions seem to be contributory. Chronic conditions such as diabetes, chronic heart or vascular disease, or chronic lung disease generally have been shown to lead to increased susceptibility. It appears that existent lung conditions which may increase or alter the deposition or retention of PM provide one means (i.e., dose) by which risk is augmented. The very old and the very young may also be more susceptible due to underlying disease, impaired or immature defenses, perhaps exacerbated or associated with other factors such as poor nutrition. Rats normally have higher concentrations of some of the major endogenous antioxidants than people (e.g., ascorbate), and, thereby, may be better able to resist the effects of reactive oxygen species thought to be generated by or in response to PM. However, rats also are subject to "overload," a condition in which sufficiently high doses of PM overwhelm both their clearance and antioxidant defenses. Under these conditions the rat lung is highly sensitive to PM, and fibrosis and tumor formation can occur.

7A.7 COMPARATIVE DOSIMETRY FOR SPECIFIC PUBLISHED STUDY EXAMPLES

This section describes specific human and rat PM exposure studies. The section is divided into three main parts: one examining exposures by intratracheal instillation, a second exposure by inhalation, and a third discussing overload in rats. The MPPD model served as the primary means of estimating regional deposition fractions and retained doses for comparisons. The first part of this section considers ***Utah Valley Dust*** (UVD) instillation studies conducted in humans by Ghio and Devlin (2001) and in rats by Dye et al. (2001). Under the premise that equal tissue doses might produce similar across-species responses, instilled doses are compared across species and inhalation exposure scenarios leading to comparable tissue doses are presented. The second part examines ***Concentrated Ambient Air Particle (CAPs)*** inhalation studies conducted in humans by Ghio et al. (2000) and in rats by Kodavanti et al. (2000) and Clarke et al. (1999). Across-species dose comparisons are made for the same exposure durations and concentrations used in each of the studies. The final part of this section discusses ***Clearance Overload in Rats*** and derives exposure concentrations predicted to achieve varied levels of alveolar loading in sub-chronically and chronically exposed rats.

7A.7.1 Utah Valley Dust

Table 7A-11a provides assumed exposure scenarios and alveolar doses based on the Utah Valley epidemiology study by Pope (1989) in the context of instillation studies conducted in humans by Ghio and Devlin (2001) and in rats by Dye et al. (2001). The hypothetical exposure scenarios are for humans and rats in the Utah Valley during an "Open-Plant" period (December 1985 - January 1986). On 13 occasions during those 2 months, the 24-hr average PM_{10} values exceeded 300 $\mu g/m^3$. The 2-month average PM_{10} was 120 $\mu g/m^3$ (Pope, 1989). In order to compare instilled doses with a dose received by inhalation, it is necessary to assume a size distribution of the UVD. For this region of the U.S., PM_{10} might typically be expected to be about 50% $PM_{2.5}$ by mass (Chapter 3). However, because the steel mill accounted for the majority of PM_{10}, it was assumed that $PM_{2.5}$ was likely closer to 80% of the mass, such as in a highly polluted industrial area (Pinto et al., 1998).

The activity patterns of the exposed humans and rats are also provided in Table 7A-11a. People were presumed generally sedentary, spending 50% of their time at rest and 50% of their

TABLE 7A-11a. UTAH VALLEY DUST: EXPOSURE SCENARIO

Utah Valley Dust, ambient exposures (December 1985-January 1986)	
– 120 μg/m^3 PM_{10} (2-month average)	
Assumed characteristics of Utah Valley Dust	
– 80% Fine mode (MMAD = 0.31 μm; σ_g = 2.03)	
– 20% Coarse mode (MMAD = 5.7 μm; σ_g = 2.1)	
Activity level and route of breathing	
Human	Rat
– 12 hr rest, 12 hr slow walk [a]	– 24 hr rest
– nasal and oral breathing	– nasal breathing
Predicted Daily Mass Depositing in A region	
Human	Rat
– 176 μg (nasal breathing)	– 2.0 μg
– 222 μg (oral breathing)	

[a] These values represent the presumed average amount of time over the course a day that a person might spend either at rest (sitting or sleeping) or engaged in an activity similar in exertion to a slow walk.

time in an activity similar to a slow walk. Rats were assumed always at rest. Tidal volumes and breathing frequencies associated with these activity levels were provided earlier in Table 7A-1. Based on these exposure conditions, people are predicted to deposit between 176 μg (nasal breather) and 222 μg (oral breather) in the A region of the lung on a daily basis, whereas rats are predicted to deposit 2 μg. Only the alveolar region of the lung was considered for comparison to the instilled doses, because most material depositing in the tracheobronchial airways is rapidly cleared.

Ghio and Devlin (2001) tested the hypothesis that the soluble components of UVD might differ between years when the Geneva Steel Mill was open (1986 and 1988) versus when it was closed (1987) and that these differences might affect biological response. In their study of 24 healthy adults, UVD extracts (500 μg) from either 1986 (n = 8), 1987 (n = 8), or 1988 (n = 8) were instilled into the lingula of the lung. As a control, saline was instilled into a subsegment of the right middle lobe of each study participant. Extracts of UVD were prepared by agitating

filter samples in deionized water for 24 hours. Following centrifugation, supernatants were removed and lyophilized. The desired amounts of the resulting dry but soluble extracts for each year were then placed in sterile saline for instillations. The estimated surface dose of the instilled material is ~170 µg per m^2 of alveolar surface area (see Table 7A-11b). At 24-hours post-instillation and relative to a saline control, lavage fluid from subjects instilled with the 1986 and 1988 extracts contained significantly increased total cells, neutrophils, protein, fibronectin, albumin, and cytokines. The extracts of UVD from 1987 (the year the steel mill was closed) did not elicit a response different from the saline control. Considering the inflammatory response, neutrophil levels were increased 3.5- and 2.9-fold by the 1986 and 1988 UVD extracts, respectively, but only 1.2-fold by the 1987 UVD extract.

TABLE 7A-11b. UTAH VALLEY DUST: HUMAN INSTILLATION STUDY

Instilled Mass and Surface Dose	
Human	Rat {Equivalent}
– 500 µg to lingula[a] (Ghio and Devlin, 2001)	– 50 µg to entire lung
– 170 µg/m^2 (lingular surface dose)	– 170 µg/m^2 (whole lung surface dose)
Predicted Time to Achieve Instilled Surface Dose by Inhalation (assuming no A clearance)[b]	
Human	Rat {Equivalent}
– 55 days (nasal breathing)	– 25 days
– 44 days (oral breathing)	
Predicted Time to Achieve Instilled Surface Dose by Inhalation (adjusted for A clearance)[b]	
Human	Rat {Equivalent}
– 65 days (nasal breathing)	– 32 days
– 50 days (oral breathing)	

[a] The lingula is the lower anterior portion of the left upper lobe and is the left lung's homologue of the right middle lobe. The volume of lobes relative to total lung capacity is 15.4% for the left upper lobe, 15.4% for the right upper lobe, and 7.7% for the right middle lobe (Yeh and Schum, 1980). Based on the ratio of right middle lobe to right upper lobe volume, the lingula was assumed one-third the volume of the left upper lobe or 5.1% of total lung volume and lung surface area.

[b] Exposure scenario provided in Table 7A-11a.

Ghio and Devlin (2001) provided an estimate of the time it might take for their instilled dose to occur by inhalation. They assumed a hypothetical ambient UVD exposure level of PM_{10} (100 µg/m^3). The computations described in their discussion were based on a total lung DF of 0.42. They concluded that the dose instilled (500 µg) into the lingula of human volunteers was roughly comparable to the PM deposited as the result of living about 5 days in the Utah Valley. Strictly speaking, the Ghio and Devlin (2001) analysis is flawed in that they only instilled the soluble fraction of UVD (~20% of particle mass on average for 1986-1988 UVD), whereas their estimates of dose by inhalation are based on total PM_{10}, which contains both soluble and insoluble components. For simplicity, the analysis presented here also considered PM_{10} as insoluble. The results of this analysis are provided in Table 7A-11b. It was estimated that between 44 and 65 days would be required for a person to deposit the instilled dose on the basis of mass per surface area. A comparable surface dose would occur in a rat after a month of exposure.

The human dose estimate provided in Table 7A-11b differs from that of Ghio and Devlin (2001) for a number of reasons. First, their DF included the nasal, TB, and A regions of the lung. In contrast, the estimate provided here considered only the A region and had an average DF of only 0.1. Second, the lingula is only about 5% of total lung volume, whereas the authors assumed the lingula represented 10% of lung volume. This difference effectively doubled the estimated surface dose from the instillation. Based on the present analysis, it is clearly possible to achieve the instilled surface dose at the relatively high ambient PM_{10} concentrations. However, this instilled dose would be achieved only from a subchronic exposure and not in the acute manner in which it was delivered by instillation. Considered from the perspective of a *single exposure day*, the corresponding estimated *24-hour average* PM exposure would need to be between 5.2 mg/m^3 (oral breather) and 6.6 mg/m^3 (nasal breather) for humans and 3.0 mg/m^3 for rats.

In the study by Dye et al. (2001), rats received intratracheal instillations of soluble extracts from UVD collected in 1986, 1987, and 1988. UVD extracts were prepared by agitating filter samples in deionized water for 96 hours. Following centrifugation, supernatants were removed and lyophilized. The desired amounts of the resulting dry but soluble extracts for each year were then placed in sterile saline for instillations. The 1986 UVD extracts were instilled at the doses of 250, 1000, and 2500 µg. Largely driven by an influx of neutrophils, the BAL fluid collected

at 24 hours post-instillation showed a dose dependent increase in total cell counts (see Figure 4 in Dye et al., 2001). Neutrophil cell counts (BAL fluid cell counts × 10^3/mL) were 105, 245, and 370 for the 250-, 1000-, and 2500-µg doses, respectively. These increases in neutrophils are 10-, 22-, and 34-fold [for the doses of 250, 1000, and 2500 µg, respectively] relative to an average neutrophil level of 11 (BAL fluid cell counts × 10^3/mL) in the saline controls (n = 22). The 1987 UVD (collected the year the Geneva Steel Mill was closed) extract instilled at the dose of 5000 µg only increased neutrophil levels to 61 (BAL fluid cell counts × 10^3/mL). These findings are generally consistent with Ghio and Devlin (2001) in the 1987 dust extracts were far less potent producers of an inflammatory response relative to 1986 and 1988 extracts.

Considering the 250-µg dose instilled by Dye et al. (2001), the surface dose to the entire rat lung was computed to be 840 µg per m^2 alveolar surface area and used as the dose-equivalent parameter for comparison to humans. These data appear in Table 7A-11c(1). By inhalation and ignoring particle clearance, an 840 µg per m^2 alveolar surface area dose of PM could occur in 124 days for rats and between 215 and 272 days for humans at an ambient PM concentration of 120 µg/m^3 (see Table 7A-11a for exposure scenarios). When clearance is considered, however, a lung burden equal the instilled dose is not achievable in rats by inhalation given the exposure conditions provided in Table 7A-11a. Other exposure conditions in which the rat would receive the instilled dose are provided in Table 7A-11c(2). One finds that the rat instillation of 250 µg corresponded to a *single 24-hour* exposure by inhalation to a concentration of 15 mg/m^3 in the rats or roughly double this concentration for humans. A 30-day (24 hours per day) exposure would still require PM concentrations of 0.6 mg/m^3 in the rats or about 1 mg/m^3 in humans.

7A.7.2 Concentrated Ambient Air Particle (CAPs)

In this section, tissue doses predicted to occur in a human and a rat CAPs exposure study are determined. Ghio et al. (2000) exposed healthy young adult human subjects (n = 38) to an average 120 µg/m^3 CAPs for 2 h. Table 7A-12a provides the predicted tissue doses to the subjects that participated in this study as well as the doses that would be predicted to occur in rats for similar exposure conditions (time and concentration). For this particle size and exposure conditions, the dose to the A region of the lung is quite similar between species. This dose elicited a mild inflammatory response but did not affect the pulmonary function of the exposed subjects.

TABLE 7A-11c(1). UTAH VALLEY DUST: RAT INSTILLATION STUDY

Rat	Human {Equivalent}
Instilled Mass and Surface Dose	
– 250 μg to whole lung (Dye et al., 2001)	– 48,000 μg to whole lung
– 840 $\mu g/m^2$ (whole lung surface dose)	– 840 $\mu g/m^2$ (whole lung surface dose)
Predicted Time to Achieve Instilled Surface Dose by Inhalation (assuming no A clearance)[b]	
Rat	Human {Equivalent}
– 124 days	– 272 days (nasal breathing)
	– 215 days (oral breathing)
Predicted Time to Achieve Instilled Surface Dose by Inhalation (adjusted for A clearance)[b]	
Rat	Human {Equivalent}
– indefinite time[a]	– 3.0 years (nasal breathing)
	– 2.0 years (oral breathing)

[a] The equilibrium lung burden for the exposure conditions is only 160 μg. After one year of exposure, the burden is within 2.5% of this equilibrium.
[b] Exposure scenario provided in Table 7A-11a.

TABLE 7A-11c(2). UTAH VALLEY DUST: RAT INSTILLATION STUDY EXPOSURE SCENARIOS ACHIEVING INSTILLED DOSE

Rat	Human {Equivalent}
Predicted 24-hr Exposure Concentration to Achieve Instilled Surface Dose by Inhalation[a]	
Rat	Human {Equivalent}
– 15,000 $\mu g/m^3$	– 32,500 $\mu g/m^3$ (nasal breathing)
	– 26,000 $\mu g/m^3$ (oral breathing)
Predicted 30-day Exposure Concentration to Achieve Instilled Surface Dose by Inhalation[a]	
Rat	Human {Equivalent}
– 590 $\mu g/m^3$	– 1,200 $\mu g/m^3$ (nasal breathing)
	– 950 $\mu g/m^3$ (oral breathing)

[a] With the exception of exposure concentrations, the exposure scenario is provided in Table 7A-11a.

TABLE 7A-12a. CAPS: HUMAN INHALATION STUDY

	Human CAPs Ghio et al. (2000) [a]	Rat {Equivalent} [b]
MMAD (σ_g)	0.65 (2.35)	0.65 (2.35)
Concentration ($\mu g/m^3$)	120	120
Deposited TB Dose per SA [c] ($\mu g/m^2$)	64	37
Deposited A Dose per SA ($\mu g/m^2$)	0.7	0.78

[a] Two-hour protocol with 15-minute periods of heavy exercise ($\dot{V}_E$ = 50 L/min) followed by 15-minutes of recovery ($\dot{V}_E$ = 13 L/min) repeated four times. Subjects were presumed to breathe as normal oronasal augmenters.
[b] Rats were presumed exposed at rest.
[c] Surface area of lung region.

Kodavanti et al. (2000) exposed healthy (n = 5) and bronchitic (n = 4) rats to 590 $\mu g/m^3$ CAPs, 6 hours per day, for 3 days. Table 7A-12b provides the predicted tissue doses in the rats and predicted doses for similarly exposed humans. As a control, healthy (n = 4) rats were exposed 6 hours per day for 3 days to filtered air. At 18 hours after the third exposure, the CAPs-exposed rats showed no significant inflammatory response despite the high delivered and retained doses relative to controls. For clarification, in two of four additional CAPs exposure protocols, Kodavanti et al. (2000) observed a significant neutrophil influx in bronchitic rats when lavaged within 3 hours post-exposure. However, data from the rats lavaged at 18 hours post-exposure are used here for comparison to the Ghio et al. (2000) and Clarke et al. (1999) studies where lavages were performed at 18 and 24 hours post-exposure, respectively.

Clarke et al. (1999) exposed healthy (n = 12) and bronchitic (n = 12) rats to 515 $\mu g/m^3$ of CAPs, 5 hours per day, for 3 days. Table 7A-12c provides the predicted tissue doses for rats in the Clarke et al. (1999) study and the predicted doses for similarly exposed humans. Note that due to differences in the inhaled particle size, the rats in the Clarke et al. (1999) study were predicted to receive a greater dose than the rats in the Kodavanti et al. (2000) study despite a shorter exposure time and lower CAPs concentration. The dose of CAPs per alveolar surface area was about 67 times greater in the rats (Clark et al., 1999) relative to the humans (Ghio et al., 2001). The inflammatory response observed in healthy rats by Clarke et al. (1999), however, was quantitatively similar to that observed by Ghio et al. (2000) in healthy humans.

TABLE 7A-12b. CAPS: RAT INHALATION STUDY

	Rat CAPs Kodavanti et al. (2000) [a]	Human {Equivalent} [a]
MMAD (σ_g)	0.98 (1.41) [b]	0.98 (1.41)
Concentration ($\mu g/m^3$)	590	590
Deposited TB Dose per SA [c] ($\mu g/m^2$)	1740	642
Deposited A Dose per SA ($\mu g/m^2$)	29	8.8
Retained TB Dose per SA ($\mu g/m^2$)	11 [d]	43 [d]
Retained A Dose per SA ($\mu g/m^2$)	28 [d]	8.6 [d]

[a] Exposure was for 6 hr/day for 3 days, both rats and humans were presumed exposed at rest.
[b] Personal communication by study authors.
[c] Surface area of lung region.
[d] Retained dose at 18 hours following the 3rd exposure.

TABLE 7A-12c. CAPS: RAT INHALATION STUDY

	Rat CAPs Clarke et al. (1999) [a]	Human {Equivalent} [a]
MMAD (σ_g)	0.18 (2.9) [b]	0.18 (2.9)
Concentration ($\mu g/m^3$)	515	515
Deposited TB Dose per SA [c] ($\mu g/m^2$)	1580	802
Deposited A Dose per SA ($\mu g/m^2$)	48	8.9
Retained TB Dose per SA ($\mu g/m^2$) [b]	16 [d]	36 [d]
Retained A Dose per SA ($\mu g/m^2$) [b]	47 [d]	8.8 [d]

[a] Exposure was for 5 hr/day for 3 days, both rats and humans were presumed exposed at rest.
[b] This is the size distribution of the ambient particles and may differ from the concentrated aerosol to which the rats were exposed.
[c] Surface area of lung region.
[d] Retained dose at 24 hours following the 3rd exposure.

7A.7.3 Clearance Overload in Rats

Unlike other laboratory animals and humans, rats appear susceptible to "overload"-related effects due to impaired macrophage-mediated alveolar clearance. Numerous reviews have discussed this phenomenon and the difficulties it poses for the extrapolation of chronic effects in rats to humans (ILSI, 2000; Miller, 2000; Oberdörster, 1995, 2002; Morrow, 1994). In brief, rats chronically exposed to high concentrations of insoluble particles, even those which may generally be considered as nuisance dusts or inert materials, experience a reduction in their alveolar clearance rates. With continued exposure, some rats eventually develop pulmonary fibrosis and both benign and malignant tumors. These high-dose effects are not observed at lower doses in rats. Oberdörster (2002) proposed that high-dose effects observed in rats may be associated with two thresholds. The first threshold is the pulmonary dose that results in a reduction in macrophage-mediated clearance. The second threshold, occurring at a higher dose than the first, is the dose at which antioxidant defenses are overwhelmed and pulmonary tumors develop. In chronic exposure studies, maintaining pulmonary doses below these thresholds should lessen the uncertainty in the extrapolation of effects observed in rats to those expected in humans. Here the focus will be on the lower threshold, i.e., the dose capable of overwhelming macrophage-mediated alveolar clearance in rats, and derive concentrations for chronic exposures below which overload might be avoided.

Overload has been loosely defined as the alveolar burden causing a 2- to 4-fold reduction in alveolar clearance rates relative to normal clearance rates (ILSI, 2000; Oberdörster, 1995). There is some discrepancy between whether overload is effected by deposited particle volume or surface area (Miller, 2000; Oberdörster, 2002). Here, only the relationship between volume loading and overload is considered. To be consistent with Morrow's (1988, 1994) analyses in this discussion of overload, the following values are assumed for rats: lung weight, 1.5 grams; displaced volume of an AM, 1000 μm^3; number of AM, 2.5×10^7. Morrow (1988) suggested a rat's macrophage-mediated clearance was impaired at a volumetric loading of 60 μm^3 per AM and that macrophage stasis occurred at a loading of 600 μm^3. These volumes represent 6 and 60% of the AM's displaced volume and correspond to the volumetric loadings of 1,000 and 10,000 nL/g-lung, respectively. Clearance rates do not differ from control at the volume loading of 100 nL/g-lung or 6 μm^3 per AM (Morrow, 1994). Morrow (1994) described the relationship between alveolar clearance rates (k, day^{-1}) in rats and the particle volume loading (V_a,

nL/g-lung) as $k = 0.021 - 0.0052 \times \log(V_a)$ for $100 < V_a < 10{,}000$ nL/g-lung. Based on this equation and consistent with Morrow (1988), the loading that would cause a doubling of the clearance half-time (a loose definition of overload) can be determined to occur at 1,000 nL/g-lung or 60 μm^3 per AM. For comparison, from Table 2 in Oberdörster (1995), a loading of 1,400 nL/g-lung can be inferred as doubling clearance half-times, fairly consistent with Morrow (1994).

Based on the work of Morrow (1988, 1994), estimates of the volumetric loadings associated with no effect on clearance (100 nL/g-lung), the onset of overload (1,000 nL/g-lung), and AM stasis (10,000 nL/g-lung) can be determined. The goal here was to derive concentrations for chronic exposures below which overload might be avoided. Miller (2000) estimated the amount of time that it would take for a rat (F344) exposed to 10 mg/m^3 for 24 hours per day to reach clearance stasis on the basis of volumetric loading. For monodisperse 1 µm particles (DF = 0.04, V_T = 2.1ml, f = 102 min^{-1}), Miller estimated it would take about 80 days (ignoring clearance) for the AM to become filled and reach stasis. Within the macrophage, particles were assumed to be tightly packed spheres occupying a volume of 1.43 times greater than the volume of the particles themselves, i.e., the porosity or void space between spheres is 0.3. Using the clearance kinetics from the MPPD model, an additional 10 days (90 days total) would be required to reach stasis. This approach can also be used to determine the amount of time required to reach lower levels of AM loading, or conversely, the exposure concentration achieving a level of loading in a given period of time.

In Table 7A-13, particle concentrations for rat exposures predicted to cause various levels of alveolar loading are shown. Alveolar loadings in this table refer to the volumes occupied by unit density spheres. However, particle density cannot be ignored, because for a constant MMAD, the physical size and volume of particles decreases with increasing density. Hence, despite having the same MMAD, dense particles would achieve a lower volumetric loading than unit density spheres for the same exposure concentration. The loading achieving stasis has been reduced from 10 µL/g-lung to 7 µL/g-lung as an adjustment for the void space between packed particles within macrophages. The onset of overload may also be considered as adjusted for void space based on a reduction from 1.4 µL/g-lung (Oberdörster, 1995) to1 µL/g-lung. Although, this difference (1 versus 1.4 µL/g-lung) may be due to variability between experiments.

TABLE 7A-13. EXPOSURE CONCENTRATIONS (mg/m^3) LEADING TO VARIED LEVELS OF ALVEOLAR LOADING AS A FUNCTION OF PARTICLE SIZE AND EXPOSURE DURATION

Exposure Time[1]	MMAD[2] (μm)	Alveolar Loading (uL / g-lung)				
		no effect		overload		stasis
		0.1	0.3	1	3	7
2 months	1	1.1	3	9.1	25	57
	2	1	2.7	8.1	22	50
	3	1.3	3.4	10	29	64
	4	1.8	4.8	15	40	90
3 months	1	0.8	2.2	6.2	16	36
	2	0.8	1.9	5.5	15	32
	3	1	2.5	7	19	41
	4	1.3	3.5	10	26	58
6 months	1	0.6	1.5	3.9	9.5	20
	2	0.6	1.4	3.5	8.4	18
	3	0.7	1.7	4.4	11	22
	4	1	2.4	6.2	15	32
1 year	1	0.6	1.3	2.8	6.1	12
	2	0.5	1.1	2.5	5.4	10
	3	0.7	1.4	3.2	6.9	13
	4	0.9	2	4.5	9.7	19
2 years	1	0.6	1.2	2.4	4.4	7.6
	2	0.5	1	2.1	3.9	6.8
	3	0.6	1.3	2.7	5	8.6
	4	0.9	1.9	3.8	7.1	12

[1] Rats presumed exposed at rest for 6 hours per day, 5 days per week.
[2] Geometric standard deviation of 1.5.

The volumetric loadings in the Table 7A-13 were estimated for an exposure scenario of 6 hours per days, 5 days per week. However, other exposure scenarios can easily be considered by maintaining a constant weekly exposure. For instance, in rats exposed 6 hours per days, 1 day per week for 1 year to an aerosol (MMAD = 2μm, σ_g = 1.5), a loading of 1 μL/g-lung is predicted for an exposure concentration of 12.5 mg/m^3. This exposure concentration of 12.5 mg/m^3 is calculated as 2.5 mg/m^3 (from table) × 30 hours (used for table estimates) ÷ 6 hours (the desired weekly exposure time).

The analysis of particle overload in rats presented here is somewhat simplistic in that it only considered the accumulated volumetric burden of particles in the lung. More sophisticated multi-compartment models of AM-mediated clearance, based on particle volume (Stöber, 1994) and particle surface area (Tran, 2000), exist. An important consideration addressed by Stöber et al. (1994) is that not all AM carry the same burden. Another important AM-related consideration is that particle uptake by AM depends on particle size. The efficiency of phagocytosis by AM appears to be greatest for particles between 1.5 and 3 μm in diameter (Oberdörster, 1988). Adamson and Bowden (1981) reported less phagocytic activity in rats following instillation of 0.1 μm versus 1.0 μm latex spheres. In addition, Adamson and Bowden (1981) identified 0.1 μm spheres in Type 1 epithelial cells, free in the interstitium, and in interstitial macrophages; all of which were rarely seen for the larger 1.0 μm spheres. Ferin et al. (1992) conducted an inhalation study using particle aggregates having mass median aerodynamic diameters of 0.78 and 0.71 μm, which were composed of smaller "primary" 0.021 and 0.25 μm TiO_2 particles, respectively. They found clearance rates were reduced for aggregates composed of ultrafine primary particles (0.021 μm diameter) relative to larger fine primary particles (0.25 μm diameter). Recognizing the importance of particle size on AM-mediated clearance, only values of MMAD between 1 and 4 μm were included in the analysis of overload discussed here.

7A.8 SUMMARY

The MPPD model was used to calculate concentrations of atmospheric and resuspended PM that would be necessary to achieve doses in the rat comparable to those in humans breathing ambient PM, as measured by a variety of dose metrics. The same model was then used to estimate the differences in doses in rats and humans exposed to comparable types of ambient or emission PM in salient published studies. Complementary approaches were used to analyze the relationship between PM doses resulting from inhalation exposures or intratracheal instillation in rats and PM doses in humans resulting from exposures during a variety of activities.

The MPPD model estimates in Table 7A-8a suggest that a rat may need to be exposed to between 33 and 200 $\mu g/m^3$ (depending on the activity of the person) resuspended PM over 6 hours to receive an incremental dose in the A region per surface area (measured as deposited or retained mass) comparable to that of a healthy human working for 6 hours near a busy road and exposed to 100 $\mu g/m^3$ ambient PM_{10}. To achieve an incremental dose retained in the rat TB region per TB surface area (averaged over 6 hours) comparable to that in the human, the rat would need to be exposed to between 150 and 630 $\mu g/m^3$ (dependent on human activity level) resuspended PM for 6 hours. However, because of the more rapid clearance in the rat, the higher exposure concentration of between 0.7 and 1.6 mg/m^3 would be required for the rat to achieve a retained TB dose per TB surface area (averaged over 24 hours) comparable to that in the human.

If one attempts to simulate not just the incremental dose from an acute single exposure, but the total cumulative burden of PM in the human lung after a decade of exposure, the 6-hour laboratory exposure concentrations required to produce a burden in the rat lung comparable to that in the human lung following exposure to 100 $\mu g/m^3$ of PM during 6 hours of work would be considerably greater. For an equivalent burden in the rat TB region an exposure concentration of about 3 mg/m^3 would be needed. Due to the more rapid clearance of particles from the A region of rats, much higher exposure concentrations, in excess of 100 mg/m^3 would be required to simulate the A dose in humans (see Table 7A-10).

The chronic retention of PM in the A region of the human cannot be simulated in the rat except under conditions in which the normal clearance process of the rat is inhibited. However, the "overload" situation in a rat may not yield effects representative of the effects on PM on humans. It is not clear whether or not rat doses in the "impaired clearance" condition are representative of comparable human doses. However, the overload or impaired clearance

situation might simulate the response of a human who is vulnerable to PM due to an impaired antioxidant or anti-inflammatory response. The high concentrations given to rats may also simulate high deposition at "hot spots" or in active portions of diseased human lungs. However, giving high doses of PM to healthy mature rats will likely not simulate the response of humans who are vulnerable because of heart or vasculature disease, infectious diseases of the lung, conditions such as diabetes, or acute or chronic stress. Therefore, development of rat models of human vulnerabilities would enhance the value of the rat in inhalation toxicology studies. Understanding the interplay of dose and responsiveness in animal models as well as in the human will substantially advance the ability to predict adverse health outcomes in the human population.

In daily life, humans are exposed to PM in the atmosphere and inhale a complex profile of Aitken, accumulation, and coarse mode particles covering a size range from below 0.1 to over 10 μm diameter. On the other hand, laboratory inhalation studies do not simulate the full size distribution to which humans are exposed and in some cases do not simulate the chemical composition or physical structure of atmospheric particles. Resuspended PM (e.g., ROFA-like material or other bulk material) has a particle size intermediate between coarse and accumulation modes but does not have the smaller sizes of the accumulation or of Aitken modes. CAPs give a better simulation of the chemical composition of atmospheric particles but typically concentrate only one mode. For ultrafine particles, the physical structure and possibly the chemical composition may be changed by going through growth and shrinkage during the concentration process. Fresh diesel exhaust particles, especially if more concentrated than in a roadway, will have a larger particle size than when diluted by vehicle turbulence. They will also differ in physical structure and chemical composition from aged diesel particles. Acid aerosol studies may also use particle sizes in the accumulation mode size range but usually do not contain the metals and organic components found in atmospheric aerosols. Laboratory exposures of rats to resuspended dust can simulate the dose of particle mass to the alveolar region but cannot simulate dose metrics based on particle surface area or number unless very high concentrations are used.

While the calculation of EqER for various dose metrics and normalizing factors is simple, the interpretation of the resulting EqERs can be somewhat more ambiguous. Optimally, the choice of dose metrics and normalizing factors should be based on the biological mechanisms

mediating an effect. For soluble compounds, the mass of PM depositing in a region of the lung may be the most appropriate dose metric. For highly insoluble particles depositing in the A region, particle surface area or particle volume may be more appropriate dose metrics. The appropriateness of a normalizing factor is, in part, determined by the site most effected by PM. For soluble compounds, an appropriate normalizing factor could be the surface area of the airways for irritants whereas body mass would be more logical when considering systemic effects. For insoluble compounds retained in the lung, normalizing factors can range from the number of macrophages in an alveolus to the mass of the lung. Due to the more rapid clearance in rats, larger rat exposure doses will be required to simulate retained doses in humans than would be the case for deposited doses. If dose metrics based on surface area or particle number are appropriate, rat exposure concentrations using resuspended PM must be very high because resuspended PM contains few accumulation mode or ultrafine particles.

It appears that no single dose metric nor normalizing factor is appropriate for all situations. As illustrated in Tables 7A-7a through 7A-9b, the parameters chosen can drastically affect the rat exposure concentration required to provide a normalized dose equivalent to that occurring in a human. A rat exposure which simulates a human dose for one specific dose metric or normalizing factor may provide a higher or lower dose as measured by a different dose metric or normalizing factor. In addition, regardless of the dose metric and normalizing factor chosen, the exposure concentration required for a rat to achieve an equivalent human dose increases with the level of activity of the human being considered. From a purely dosimetric standpoint, the complexity of interspecies extrapolation is obvious but not necessarily insurmountable. Conclusions regarding rat to human comparisons may require the use of a variety of dose metrics and normalizing factors depending on the degree to which biological mechanisms mediating an effect are understood.

Instillation studies in both animals and humans have been critiqued for lack of relevance related to dose and means of administration. Ghio and Devlin (2001) instilled 500 µg of Utah Valley Dust (UVD) extracts into the lingula of human volunteers (healthy young adults). This instilled dose (about 170 µg per m^2 alveolar surface area) elicited a robust inflammatory response for the 1986 and 1988 extracts, but not the 1987 extract, suggesting that extract composition is important. In a complementary animal study, the intratracheal instillation of rats with 250 µg (840 µg per m^2 alveolar surface area) of 1986 UVD extracts also caused an

inflammatory response (Dye et al., 2001). The neutrophilic response elicited by the 1986 UVD extract instillations was about 3 times greater in the rats (10-fold PMN increase) than in humans (3.5-fold PMN increase). On the basis of mass per alveolar surface area, however, the dose delivered to the rats was about 5 times greater than delivered to the humans. This disparity (3 times the response at 5 times the dose) is suggestive of a decreased susceptibility for an inflammatory response in the rats relative to humans.

For comparison to delivery by inhalation, it was estimated that 44-65 days of exposure in the Utah Valley during the winter 1985-1986 would be required for a person to receive an a PM dose per alveolar surface area equivalent to that of instillations in the study by Ghio and Devlin (2001) (see Table 7A-11b). However, it was estimated that a rat lung burden of 250 µg, the mass instilled by Dye et al. (2001), could not be achieved by inhalation at the assumed ambient exposure scenario due to the rapid clearance in the rat (Table 7A-11c[1]). Toxicologically, it is obvious that a different response might be expected between an instilled dose (delivered as a bolus) versus the a sub-chronic delivery by inhalation. For a more acute (24-hour period) delivery by inhalation, humans would need be exposed to ~6 mg/m^3 and rats to 15 mg/m^3 in order to reach the instilled doses used in the Ghio and Devlin (2001) and Dye et al. (2001) studies, respectively. Dosimetrically, the relevance of both the human and the rat instillation studies to exposure by inhalation are difficult to judge and it should again be noted that the extracts contained only the soluble fraction of the UVD. However, both rat and human instillation studies showed that the 1987 UVD (collected while the Gevena Steel Mill was closed) extract was relatively less potent comparted to the 1986 and 1988 extracts.

Several studies (one human and two rat) involving exposure by inhalation to CAPs provide a seemingly more useful basis for comparing dose and response. Tables 7A-12a, -12b, and -12c provided exposure conditions and estimated doses for the human study by Ghio et al. (2000), the rat study by Kodavanti et al. (2000), and the rat study by Clarke et al. (1999), respectively. Bronchial lavages were performed at 18 hours post-exposure in both the Ghio et al. (2000) and Kodavanti et al. (2000) studies and at 24 hours post-exposure in the Clarke et al. (1999) study. At the time of bronchial lavage, the estimated alveolar dose in the human study was 0.7 $\mu g/m^2$. This dose produced a mild inflammatory response in young healthy human subjects. In the Clarke et al. (1999) study, an increase in neutrophils in response to CAPs exposure was found in healthy rats (air, ~1%; CAPs, ~7%) that was very similar to that observed in healthy humans

(air, 2.7%; CAPs, 8.1%) by Ghio et al. (2000). However, the alveolar tissue doses (mass per surface area) are estimated to be 67 times greater in the rats than in the humans. The similarity in the response, but disparity in dose, suggests that healthy rats are less susceptible to CAPs effects than healthy humans. In the Kodavanti et al. (2000) study, rats were predicted to have 40 times the human dose in the Ghio et al. (2000) study but only 60% of the dose delivered to the rats in the Clarke et al. (1999) study. Interestingly, neither the healthy nor bronchitic rats in the Kodavanti et al. (2000) study showed a consistent inflammatory response, again suggesting that rats are less susceptible to CAPs effects than healthy humans.

A key premise for the dosimetric analysis presented here is that comparable tissue doses should cause comparable effects. From the preceding discussion of CAPs studies, however, it appears that rats (whether healthy or compromised) have a decreased response relative to healthy humans at comparable tissue doses. The decreased sensitivity of rats relative to humans may only occur in studies of several days duration. For longer sub-chronic and chronic studies, rats appear susceptible to an overload of their macrophage-mediated alveolar clearance. Under conditions of overload, rats may indeed be more susceptible than humans, having decreased rates of alveolar clearance and antioxidant defenses. Table 7A-13 provided exposure concentrations for chronic exposures below which overload might be avoided. Depending on the susceptibility of the human population to which one may wish to extrapolate the results of rat studies, there may be occasions where some extent of overload could be needed, e.g., to mimic decreased pulmonary defenses in compromised humans.

7A.9 CONCLUSIONS

- The dosimetric calculations indicate that PM concentration exposures in rats, somewhat higher than in humans, would be justified to achieve nominally similar acute doses per surface area relative to the humans undergoing moderate to high exertion.
- Given the MPPD model results which show that rats clear PM much faster than humans, much higher exposure concentrations in the rat are required to simulate the retained burden of highly insoluble particles which builds up over years of human exposure.
- Resuspended PM, used in some inhalation studies, does not contain the smaller particles found in the accumulation and Aitken modes of the atmospheric aerosol. Thus, for dose metrics based on particle surface area or number very high exposure concentrations of resuspended PM for rats would be required to provide a dose equivalent to that received by humans exposed to atmospheric aerosol.
- The biological mechanisms of PM toxicity are uncertain as are the dose metrics most appropriate for establishing human-rat equivalent doses. The concept of using dosimetric calculations to provide a quantitative rat to human extrapolation depends on the assumption that an equal dose to target cells or tissues will produce a similar response in each species. At sufficiently high doses, however, the rat is subject to an overload phenomenon. When this occurs in the rat, clearance slows and anti-inflammatory defenses become depleted. Under these conditions, rats are more sensitive to PM than humans and tumor formation and fibrosis may occur. At lower doses, rats clear PM faster than humans and appear less sensitive to PM than humans. Thus, it is essential for toxicological studies to characterize dose to the fullest extent possible and to carefully consider dose-response relationships in both rats and humans.

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