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Air Quality Criteria for Particulate Matter

Review Draft (Do Not Cite or Quote)

Volume II of III

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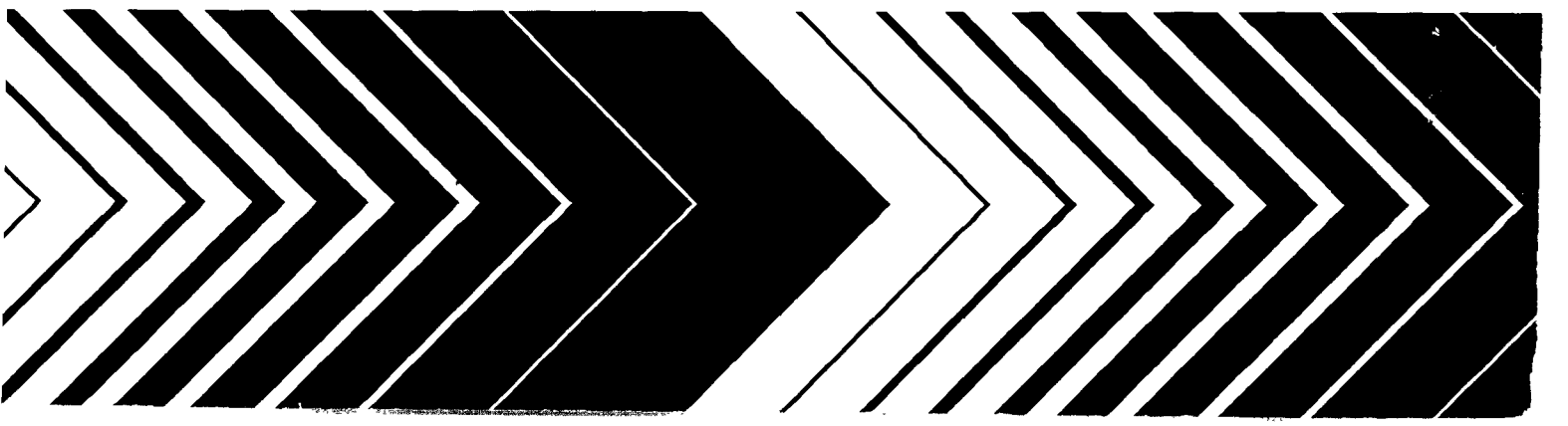

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Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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Air Quality Criteria for Particulate Matter

TABLE OF CONTENTS

Volume I

Volume II

Volume III

TABLE OF CONTENTS

Page

Page

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LIST OF TABLES

LIST OF TABLES (cont'd)

LIST OF TABLES

LIST OF TABLES (cont'd)

LIST OF TABLES (cont'd)

LIST OF TABLES (cont'd)

LIST OF TABLES (cont'd)

LIST OF TABLES (cont'd)

LIST OF FIGURES

LIST OF FIGURES

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8. EFFECTS ON VISIBILITY AND CLIMATE

8.1 INTRODUCTION

Visibility is defined as the relative ability to see objects under different conditions of distance, light, and atmosphere. It takes into account not only how far one can see but, also how well one can see nearby objects. The legislative mandate for visibility protection began with the Clean Air Act (CAA) of 1970. Additional protection for pristine areas - mainly Class I areas in National Parks and Wilderness areas, primarily in the western portion of the United States (U.S.), were mandated in the CAA Amendments of 1977 (Baedecker, 1991).

There are may complex physical (rain, dust, and snow) and chemical atmospheric processes that affect our ability to see distant objects or to distinguish nearby objects clearly. There are also atmospheric constituents that interfere with our visual range. These atmospheric constituents include fine particulate matter which individually have no effect on the visual range; however, collectively can significantly impair the visual range. Airborne particles can reduce visibility through both light scattering and absorption. Some questions about the relationship between particulate matter and visibility are still unanswered, but many have been resolved. Scientists have made progress in evaluating the optical changes and perceptual consequences from increased particulate matter, but it is more difficult to determine the effect of increased particulate pollution on the aesthetic appeal. It is, however, known that reduced aesthetic appeal carries significant social and economic costs.

The effects of particle induced light scattering and absorption may effect climate by reducing solar radiation at ground level, making less energy available for photosynthesis. Reduced solar radiation may alter local or regional temperatures. Also, increased cloud formation may alter precipitation patterns.

This chapter briefly discusses factors affecting visibility, ways to measure it, historical trends, and methods to determine its value. Particulate matter effects on climate will also be discussed. Much of the information contained in the section on visibility is a summarization of information from the previous criteria document on particulate matter and sulfur oxides. For a more detailed discussion of the information on visibility, see Air Quality Criteria for Particulate Matter and Sulfur Oxides (U. S. Environmental Protection Agency, 1982), Air

Quality Criteria for Oxides of Nitrogen (U. S. Environmental Protection Agency, 1993), and the National Acid Precipitation Assessment Program (Baedecker, 1991).

8.2 FUNDAMENTALS OF ATMOSPHERIC VISIBILITY

8.2.1 Physics of Light Extinction

Light, electromagnetic radiation, is altered by the interaction of its electric and magnetic fields with all matter through which and near which it passes. The altering may be by scattering (redirection) or by absorption. There are two theories that address the physics of light extinction in the atmosphere. The first theory was proposed by Lord Rayleigh in the late 1800's. The Raleigh theory (Raleigh scattering) refers to the scattering of light by the gaseous molecules comprising the atmosphere (Middleton, 1952; Kerker, 1969). Rayleigh scattering is directly proportional to the molecular number density and decreases as elevation increases. Rayleigh scattering represents the cleanest possible condition of the atmosphere and almost all cases of visibility impairment are caused by the presence of particles, the sole exception being discoloration caused by the pollutant gas NO_2.

The second theory, commonly referred to as the Mie theory, is the attenuation of light in the atmosphere by scattering due to particles of a size comparable to the wavelength of the incident light. It is this phenomenon that is largely responsible for the reduction of atmospheric visibility. The Mie theory allows the computation of light scattering in any or all directions and the absorption of light by a single spherical particle. For visible light, the size range requiring use of Mie theory extends from 0.05 to 10 μm (and larger if the particles are spherical), the sizes at which most long-lived atmospheric particles accumulate. Visible solar radiation falls into the range form 0.4 to 0.8 μm, with a maximum intensity of around 0.52 μm (U.S. National Acid Precipitation Assessment Program (Baedecker, 1991). The wavelength of light, particle size, and complex refractive index must be specified. For absorbing particles, the imaginary part of the refractive index is nonzero. For a monodisperse aerosol of number concentration N, the extinction coefficient (the proportionality constant determined by the scattering and absorption of light by particles and gases) becomes:

$$\sigma_{ext} = N\ Q_{ext}\ \pi r^2 \qquad (8\text{-}1)$$

where r is the particle radius and Q_{ext} is the extinction efficiency factor calculated from Mie theory. If the particles are of differing composition (and thus differing complex refractive index), the number size distribution of each species must be known. Extinction coefficients for the various species are then summed. The precise calculation of extinction by spherical particles allowed by Mie theory requires detailed knowledge of the composition and size distribution of the particles.

Mie theory is strictly applicable only to spherical particles. Fortunately, a majority of scattering particles in the optically important size range of 0.1- to 2-μm diameter are spherical (many being droplets), or nearly spherical (Allen et al., 1979; Pueschel and Wollman, 1978; Pueschel and Allee, 1980). Electromagnetic solutions have been achieved for several nonspherical shapes, such as spheroids (Latimer, 1980); disks (Weil and Chu, 1980); cylinders; and for the important case of layered or coated spheres (Kerker, 1969; Schuerman, 1980; Pinnick et al., 1976; Fowler and Sung, 1979; Mugnai and Wiscombe, 1980). These exact solutions can be applied if circumstances warrant. Absorbing particles are usually distinctly nonspherical. Many are chain-aggregates such as flame soot. Janzen (1980) empirically showed that Mie theory predicts measured absorption quite well for carbon black particles by assuming the aggregates to be spheres of equal volume.

8.2.2 Measurement Methods

8.2.2.1 Total Extinction

Human Observer

Human observation has by far been the most often used measure for determining visual range (Middleton, 1952). In practice, a set of targets at known distances is selected and an observer then records whether or not they are able see each target. The "prevailing visibility" is then defined as the greatest distance attained or surpassed around at least half of the horizon circle, but not necessarily in continuous sectors (National Weather Service, 1979). The human observer also can make qualitative statements about overall visual air quality, unusual coloration, and the presence of plumes. However, different days or studies

are difficult to compare because even minute changes of scenes from day to day may affect human perception. This limitation may be partially remedied by the use of photography. Visual range is affected not only by the optical properties of the atmosphere, but also by target characteristics, illumination conditions, and the observer (Duntley, 1964).

Photography

Photographs are typically used to document scenes for later qualitative analysis by humans or for later analysis of a target's apparent contrast by film densitometry (Steffans, 1949; Veress, 1972). Photographs provide a more accurate long-term retention of a scene than does the human mind and enables large numbers of people to evaluate a given scene for perception studies. Significant errors are possible, however, with the use of photography because of varying film characteristics, the use of filters, exposure and processing, aging, storage conditions, and reproducibility of the image. If the reproduced image of a scene is to accurately portray what a human eye sees, it is necessary that the overall response of the photographic process be photopic (i.e., match the wavelength response of the human eye); otherwise, the rendition may not be true, and both densitometry and qualitative applications may be seriously affected.

Telephotometry

A telephotometer, a photometer designed to measure the radiant energy arriving for a scene weighted in accordance with the response of the human eye brain system to spectral light, can measure the apparent brightness of a faraway object (Middleton, 1952; Ellestad and Speer, 1981). By measuring the brightness of an object at a predetermined distance, distance x, and the horizon sky around it, the object's apparent contrast can be computed.

$$\sigma_{ext} = \frac{-1}{x} \log_e \frac{C}{C_0} \qquad (8\text{-}2)$$

Telephotometry is useful for several reasons. It is a path measurement; thus, atmospheric nonuniformities are averaged. The instrument's absolute calibration is unimportant; only its linearity and short-term stability matter. It requires no sample aspiration, and therefore,

avoids large particle losses and sample heating or cooling. Finally, it is perhaps the closest instrumental approximation to human observation. The method is, however, limited when the target's intrinsic contrast is unknown or assumed, when measuring dark objects at close range (due to internal stray light errors), and when clouds cause uneven illumination.

Long-path Extinction

Long-path extinction measures σ_{ext} by measuring the decrease in intensity of a light beam over a known distance x,

$$\sigma_{ext} = \frac{-1}{x} \log_e \frac{I}{I_o} \qquad (8\text{-}3)$$

where I and I_o are the final and initial intensities, respectively. This method does not require the use of assumptions, it measures average extinction over the path, and it requires no sample aspiration. The method is limited because for values of σ_{ext} about 0.2 km^{-1}, the decrease over short paths (1 m) is small (0.02%) and cannot be measured accurately. An alternative is to increase the path length, but source intensity fluctuation, mirror reflectivity changes for single-ended systems, detector sensitivity drift, alinement, thermally induced scintillation, and the large background light of daytime again make the measurement difficult.

8.2.2.2 Light Scattering

Nephelometer

The integrating nephelometer, an instrument used to measure the light scattering component of σ_{ext}, measures only the scattering coefficient of an aerosol (Beuttell and Brewer, 1949; Crosby and Koerber, 1963; Ruppersberg, 1964; and Charlson et al., 1967). Using this instrument, Rayleigh scattering, σ_{sg}, can be excluded or included. The instrument consists of an enclosed volume painted black, a sensitive light detector looking through the volume, and a light source at one side of the volume. The only light reaching the detector is that scattered by gas molecules and particles within the volume. The nephelometer is sensitive, easily calibrated and automated, enables one to modify the sample if desired, and provides a point measurement for correlation analysis with point measurements of mass concentration and chemical composition. There are two sources of inherent errors using the

nephelometer when significant large particle concentrations occur. The first of these potential errors is angular truncation, resulting in underestimation of scattering (Ensor and Waggoner, 1970; Rabinoff and Herman, 1973), and secondly, sample aspiration (Heintzenberg and Quenzel, 1973), resulting in the loss of large particles through impaction on the ductwork. These inherent errors may result in depressed correlations between scattering and total mass concentration when significant large particle concentrations occur. Despite these limitations, nephelometry remains one of the most widely used visibility measurement methods.

8.2.2.3 Light Absorption Coefficient

Elemental carbon (soot, graphitic C, free C) is a prominent species in cities and industrial regions. Even a few percent of the submicrometer mass as soot produces a significant effect on σ_{ap} or σ_{ext}. No single method for evaluating σ_{ap} is widely accepted; however, the following particle absorption methods are commonly used:

1. Determining the difference between σ_{ext} and σ_{sp} by using long-path transmissometry and nephelometry (Weiss et al., 1979);

2. Determining change of transmission of Nuclepore ® filters with scattered light collected by an integrating plate of opal glass (Lin et al, 1973; Weiss et al., 1979);

3. Determining change of transmission of Millipore ® filters (Rosen et al., 1980);

4. Determining the reflectivity of a white powder with aerosol mixed into it, called the Kubelka-Monk method (Lindberg and Laude, 1974);

5. Determining absorption of light by a sample of particles inside a white sphere (integrating sphere) (Elterman, 1970);

6. Estimating an imaginary refractive index from regular scattering or polarization and size distribution (Eiden, 1971; Grams et al., 1974);

7. Measuring the amount of graphitic C and its size distribution and then calculating σ_{ap};

8. Detecting the acoustical pulse produced when energy is absorbed by particles as light and is transformed to heat (spectrophone) (Truex and Anderson, 1979).

8.2.3 Role of Particulate Matter in Visibility Impairment

As noted earlier, the extinction coefficient comprises contributions from gas and particle scattering and absorption:

$$\sigma_{ext} = \sigma_{sg} + \sigma_{ag} + \sigma_{sp} + \sigma_{ap} \quad (8\text{-}4)$$

This section discusses the relative magnitudes of these contributions.

8.2.3.1 Rayleigh Scattering

Rayleigh scattering is a definable and measurable background level of extinction with which other extinction components can be compared. Rayleigh scattering decreases with the fourth power of wavelength, and contributes a strongly wavelength-dependent component to extinction. When Rayleigh scattering dominates, dark objects viewed at distances over several kilometers appear behind a blue haze of scattered light, and bright objects on the horizon (such as snow, clouds, or the sun) appear reddened at distances greater than about 30 km. Scattering by gaseous pollutant molecules is negligible because of their low concentrations compared to N_2 and O_2; thus, variations in pollutant gas concentrations have no effect on Rayleigh scattering.

8.2.3.2 Nitrogen Dioxide Absorption

Of all common gaseous air pollutants, only NO_2 has a significant absorption band in the visible spectrum. Nitrogen dioxide strongly absorbs blue light and can color plumes or urban atmospheres red, brown, or yellow if significant concentrations and path lengths are involved. The effects of NO_2 on visibility are generally minor and are discussed more fully in the document Air Quality Criteria for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993).

8.2.3.3 Particle Scattering

In general, scattering by particles accounts for 50 to 95% of extinction, depending on location, with urban sites in the 50- to 80% range and nonurban sites in the 80- to 95% range (Waggoner et al., 1981; Weiss et al., 1979; Wolff et al., 1980).

Fine particles (i.e., those particles of diameter less than 1 to 3 μm) usually dominate light scattering. Particles smaller than 0.1 μm, though sometimes present in high numbers, are individually very inefficient at scattering light and thus contribute very little to visibility loss; particles larger than about 1 to 3 μm, though individually efficient at scattering light, usually exist in relatively small numbers and contribute only a small fraction of visibility loss.

In areas where fine-particle concentrations are low, coarse particles may contribute significantly to light extinction. However, coarse dust particles are much less efficient scatterers per unit mass (Figure 8-1), so that much higher mass concentrations are required to produce a given optical effect. In windblown dust, for example, Patterson and Gillette (1977) reported values of the ratio of light scattering to mass concentration that were more than an order of magnitude lower than those noted above for fine particles.

Atmospheric particles are made up of a number of chemical compounds (see Chapter 3). All these compounds exhibit a peak scattering efficiency in the same diameter range (0.1 to 1.0 μm) calculated to be optically important (Figure 8-2). Because of differences in refractive index, however, the values of the peak efficiency and the exact particle size at which it occurs vary considerably among the compounds (Figure 8-1; Faxvog, 1975).

Figure 8-1 demonstrates the high extinction efficiencies of carbon and water. As discussed later in chapter, these compounds are often significant fine mass components and are therefore, often responsible for significant amounts of extinction. Figure 8-1 should not, however, be taken to present invariable, precise extinction efficiencies of the various species. It was produced with best estimates of the refractive indexes and for monodisperse particles. In reality, the species do not exist as monodispersions or in equal concentrations and their relative roles in causing extinction may vary considerably.

Measured particle size distributions can be used in conjunction with Mie theory calculations to determine the contribution of different size classes to extinction. The results of this kind of calculation are shown in Figure 8-3. The peak in scattering per unit volume concentration is at 0.3 μm, so that the fine particles dominate extinction in most cases.

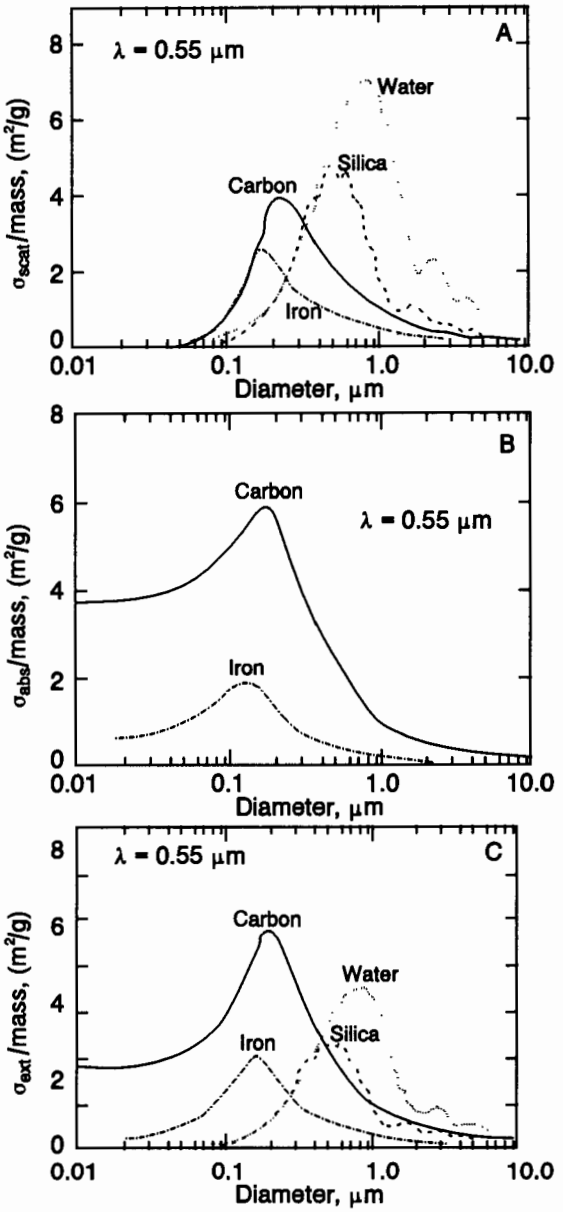

Figure 8-1. (A) Calculated scattering coefficient per unit mass concentration at a wavelength of 0.55 μm for absorbing and non-absorbing materials is shown as a function of diameter for single-sized particles. The following refractive indices and densities (g/cm^3) were used: carbon (m = 1.96-0.66i, d = 2.0), iron (m = 3.51-3.95i, d = 7.86), silica (m = 1.55, d = 2.66), and water (m = 1.33, d = 1.0). (B) Calculated absorption coefficient per unit mass concentration at 0.55 μm for single-sized particles of carbon and iron. (C) Calculated extinction coefficient per unit mass concentration at 0.55 μm for single-sized particles of carbon, iron, silica, and water.

Source: (a) Faxvog (1975); (b and c) Faxvog and Roessier (1978).

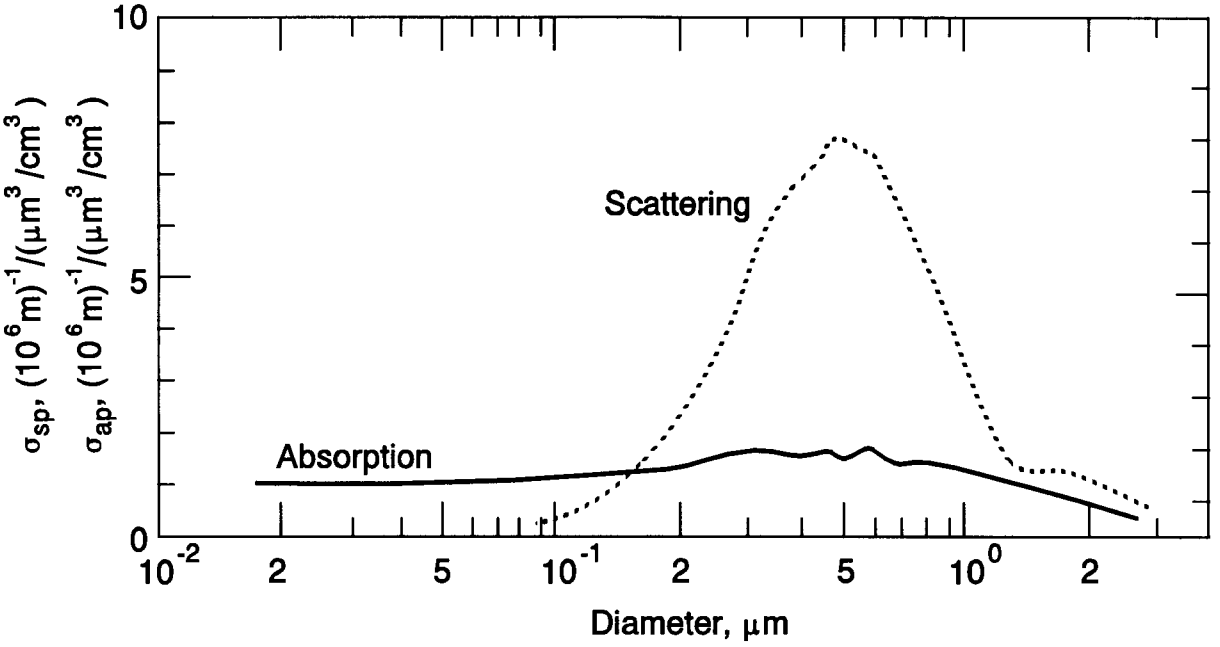

Figure 8-2. For a light-scattering and absorbing particle, the scattering per volume concentration has a strong peak at particle diameter of 0.5 μm (m = 1.5-0.05i; wavelength = 0.55 μm). However, the absorption per aerosol volume is only weakly dependent on particle size. Thus, the light extinction by particles with diameter less than 0.1 μm is primarily due to absorption. Scattering for such particles is very low. A black plume of soot from an oil burner is a practical example.

Source: Charlson et al. (1978a).

8.2.3.4 Particle Absorption

Particle absorption appears to be on the order of 5 to 10% of particle extinction in remote areas (Weiss et al., 1979). Its contribution may rise to 50% of σ_{ext} in urban areas, with values of 10 to 25% typical for suburban and rural sites (Weiss et al., 1979; Waggoner et al., 1981; Groblicki et al., 1981).

Estimates show the extinction per unit mass concentration for absorbing aerosols to be significantly higher than for scattering-only aerosols. Figure 8-1(c) shows the theoretical value for carbon particles to be higher than for any other species considered (Faxvog and Roessler, 1978). Jennings and Pinnick (1980), relying on the small size of combustion particles (diameters generally less than 0.3 μm) and the approximate linearity of

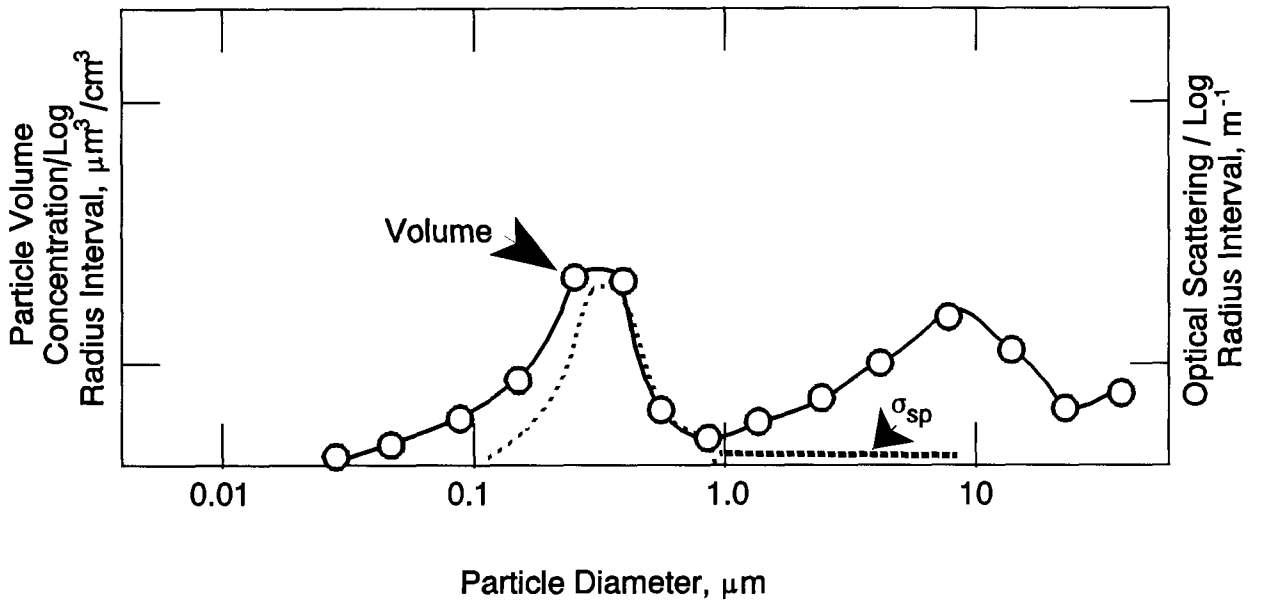

Figure 8-3. For a typical aerosol volume (mass) distribution, the calculated light-scattering coefficient is contributed almost entirely by the size range 0.1 to 1.0 μm. The total and total aerosol volume concentration are proportional to the area under the respective curves.

Source: Charlson et al. (1978a).

the extinction efficiency factor in this region, predicted a linear and size distribution-independent relation between extinction coefficient and mass concentration of carbon particles, with a ratio of 9.5 m^2/g at 0.55 μm. Laboratory studies by Roessler and Faxvog (1980) showed values of 9.8 m^2/g for acetylene smoke and 10.8 m^2/g for diesel exhaust. They also summarized results from other investigators on various aerosols that showed values of 6.1 to 9.5 m^2/g. In developing a spectrophone, Truex and Anderson (1979) measured an absorption of mass concentration ratio 17 m^2/g (at 0.417 μm wavelength) for aerosol from a propane-oxygen flame. As methods for measuring elemental carbon have improved, Groblicki et al. (1981) have performed atmospheric measurements of fine absorption/fine elemental carbon mass concentration in Denver and found an average of 11.8 m^2/g. While the amount of absorption per unit mass concentration depends on chemical composition and particle size distribution (Waggoner et al., 1973; Bergstrom 1973), the pattern emerging from these empirical and theoretical studies is that absorbing particles have a more significant

visibility impact than their mass would indicate, probably by a factor of 3 to 4, compared to scattering-only particles.

Weiss and Waggoner (1981) calculated that, for constant mass concentration, changing 20% of each particle of a nonabsorbing aerosol to an equal volume of absorbing soot reduces visual range (or increases σ_{ext}) by about 35%. They pointed out the importance of this concept as fuel conservation practices (e.g., use of diesel engines, wood burning) lead to greater emissions of light-absorbing aerosol.

8.2.4 Chemical Composition of Atmospheric Particles

This section briefly discusses the most commonly observed particulate species in the context of visibility impairment. For actual concentrations and a more detailed evaluation of the aerosol components see Chapters 4 and 6 of this document.

Current knowledge indicates that fine aerosol is composed of varying amounts of sulfate, ammonium, and nitrate ions; elemental carbon and organic carbon compounds; water; and smaller amounts of soil dust, lead compounds, and trace species. The components may also coexist within the same particle. Table 8-1 gives the average natural background levels of aerosols and light extinction.

Sulfate occurs predominantly in the fine mass (Stevens et al., 1978; Tanner et al., 1979; Lewis and Macias, 1980; Ellestad, 1980). The sulfate ion has been reported to compose 30 to 50% of the fine mass at a wide variety of sites (Stevens et al., 1978; Pierson et al., 1980; Stevens et al., 1980; Lewis and Macias, 1980; Ellestad, 1980; Macias et al., 1981), although some urban sites have values of 10 to 20% (Countess et al., 1980b; Cooper and Watson, 1979). Sulfate usually occurs in combination with hydrogen and ammonium ions (Stevens, 1978; Pierson et al., 1980; Charlson et al., 1978b; Stevens et al., 1980; Tanner et al., 1979) and to a lesser extent calcium and magnesium. Ammonium ion is typically found to account for 5 to 15% of the fine mass (Lewis and Macias, 1980; Patterson and Wagman, 1977; Countess et al., 1980b) and often correlates well with sulfate levels (Tanner et al., 1979). Because of the possible reaction of ammonia with previously collected acidic particles, reported ammonium ion values may be higher than those actually existing in the atmosphere.

TABLE 8-1. AVERAGE NATURAL BACKGROUND LEVELS OF AEROSOLS AND LIGHT EXTINCTION

	Average Concentration		Error Factor	Extinction Efficiencies[a]	Extinction Contributions	
	East $\mu g/m^3$	West $\mu g/m^3$		m^2/g	East Mm^{-1}	West Mm^{-1}
Fine Particles ($\leq$2.5 μm)						
Sulfates (as NH_4 HSO_4)	0.2	0.1	2	2.5	0.5	0.2
Organics	1.5	0.5	2	3.75	5.6	1.9
Elemental Carbon	0.02	0.02	2-3	10.5	0.2	0.2
Ammonium Nitrate	0.1	0.1	2	2.5	0.2	0.2
Soil Dust	0.5	0.5	1.5-2	1.25	0.6	0.6
Water	1.0	0.25	2	5	5.0	1.2
Coarse Particles (2.5-10 μm)						
	3.0	3.0	1.5-2	0.6	1.8	1.8
				Rayleigh Scatter	12	11
				Total	26$\pm$7	17$\pm$2.5

[a]The extinction efficiencies are based on the literature review by Trijonis et al. (1986, 1988). All the extinction efficiencies represent particle scattering, except for elemental carbon where the 10.5 m^2/g value is assumed to consist of 9 m^2/g absorption and 1.5 m^2/g scattering. Note that the 0.6 m^2/g value for coarse particles is a "pseudo-coarse scattering efficiency" representing the total scattering by all ambient coarse particles ($\leq$2.5 μm) divided by the coarse particle mass between 2.5 and 10 μm.

Source: Baedecker (1991).

Earlier particulate nitrate measurements had significant positive or negative biases. More recent measurement techniques provide a more accurate representation of ambient particulate nitrate concentrations.

Appel el al. (1983, 1985) reported that mean nitrate concentrations represented 17 to 37% of the total fine particle mass in 3 California cities. Watson et al. (1991) reported that ammonium nitrate represented 19% of the fine particle mass in the morning in Phoenix, AZ and 31% of the fine particle mass in the afternoon. Ammonium nitrate represented 6.4 to 10.4% of the fine particle mass at 3 locations in the Grand Canyon during January through March 1990 (Richards et al., 1991).

Several investigators have concluded that elemental carbon is the only significant light-absorbing species. Figure 8-1(c) shows the extinction mass concentration for carbon to be higher than for any other species.

Soil particles significantly impair visibility mostly in arid or semiarid areas (Patterson, 1977) (in the United States, the Southwestern states). This is likely due to the relatively low fine-particle concentrations there, than to high concentrations of soil particles. What fraction of coarse particles is derived from natural sources has not been established. However, it is likely that more dust is entrained over anthropogenically disturbed soil surfaces (e.g., unpaved roads, off-road-vehicle trails) than over undisturbed soils. Minor contributions to fine mass also are made by soil-related elements, lead compounds (especially in urban areas), and trace species (Stevens et al., 1978).

8.2.4.1 Role of Water in Visibility Impairment

Water affects visibility only when in the liquid or solid phase. Direct measurement of liquid water's contribution to mass is difficult due to its rapid phase change and the fact that, except in fogs, typically less than 0.01% of all water in a given volume exists in the liquid phase.

Relative humidities (RHs) above about 70% will often greatly reduce visibility due to the size growth of common aerosol species such as ammonium sulfate and sea salt (Orr et al., 1958). Natural fluctuations of RH can greatly influence the extinction of light by an aerosol. Since RH generally increases following sunset due to declining temperature (assuming a constant dew point), particles usually grow after sunset. After sunrise RH usually declines as temperature rises, causing particles to shrink as they release water to the vapor phase.

Particles of certain inorganic salts commonly observed in the atmosphere (e.g., ammonium sulfate and sodium chloride) exhibit the phenomenon of deliquescence (i.e., an abrupt transformation from solid particle to liquid droplet, and growth at a RH specific to each compound). Above the deliquescent RH, the droplets absorb water and grow smoothly as RH increases (Orr et al., 1958; Charlson et al., 1978b; Tang, 1980). As RH decreases, salt particles that have already deliquesced do not crystallize until a RH well below the deliquescent RH is achieved (Tang, 1980; Orr et al., 1958), a phenomenon generally referred

to as hysteresis. Until crystallization occurs, droplets become supersaturated, lose water gradually, and shrink gradually as RH declines. If crystallization has not occurred and RH increases, the growth of droplets will follow the smoothly hygroscopic curve along which it just fell. Figure 8-4 depicts the behavior of an ammonium sulfate particle.

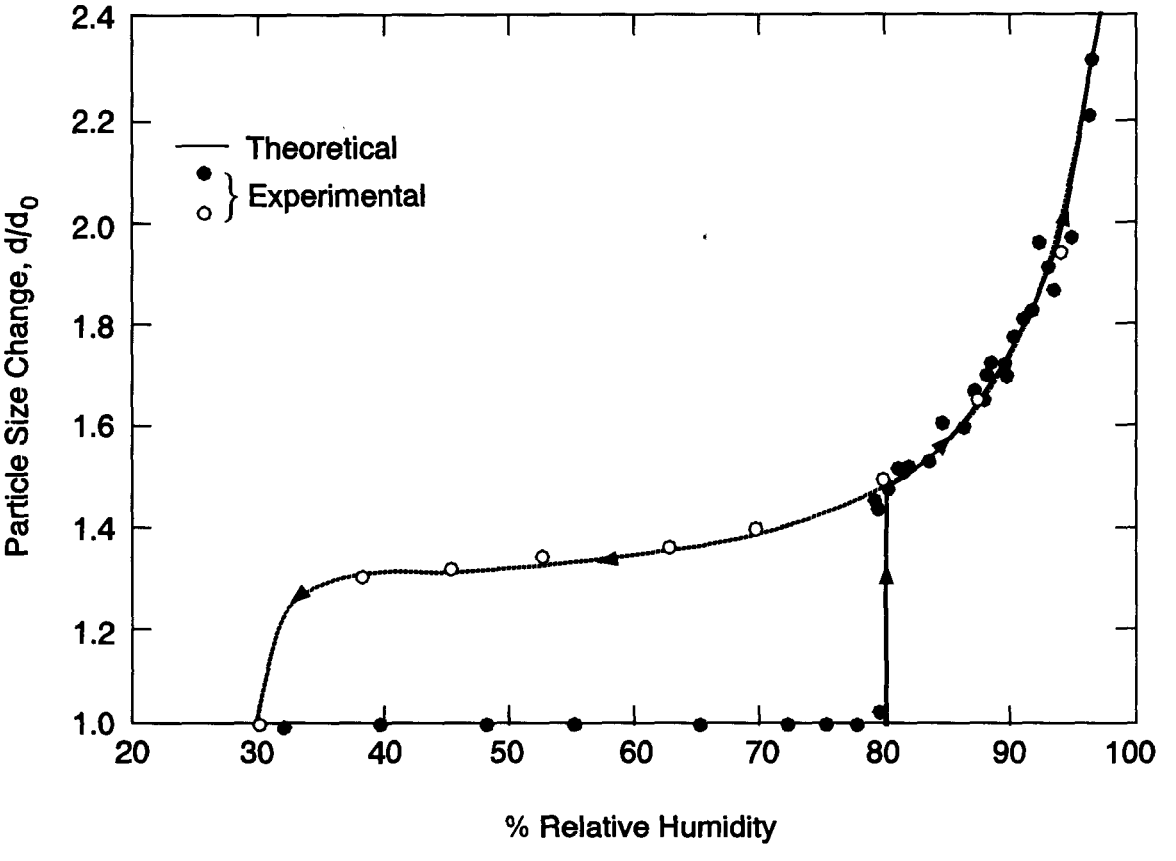

Figure 8-4. Relative size growth is shown as a function of RH for an ammonium sulfate particle at 25° C.

Source: Tang (1980).

Hysteresis explains the persistence of some hazes at RHs below that at which they formed (Orr et al., 1958). The RH of crystallization depends on the size of insoluble nuclei present in each droplet. The dissipation of a water-enhanced haze may not occur abruptly as RH falls (even though it may have formed abruptly) because the sizes of nuclei within the droplets may vary, causing the droplets to crystallize at different RHs.

8.2.4.2 Light Extinction Budgets

Light extinction budgets (LEBs) attempt to assign a percentage of the total extinction to each chemical species using the size distribution and refractive index. The great usefulness of LEB's is to exonerate or implicate emission sources as primary causes of visibility impairment.

Two approaches have been used to arrive at light extinction budgets: (1) measurement of each species' size distribution and calculation of σ_{ext} by Mie theory and (2) statistical analysis, usually multiple linear regression. The first method requires detailed size distributions for each species. This can result in a small error in the size distribution measurement. Many significant species have MMD's at the steepest part of the extinction efficiency curve, that may later cause a large error in the calculated extinction. Further, detection limits, artifact formation, volatilization, unknown particle density, or imperfect instrument performance often lead to substantial uncertainties in the size distribution. Still this approach is not affected by interdependencies among pollutant concentrations and allows an independent estimation of σ_{ext}, which can then be compared to the observed σ_{ext}.

The second approach, multiple linear regression, requires calculation of a coefficient for each species that is then multiplied by that species' concentration to yield its contribution. Calculation of the coefficients requires use of the observed σ_{ext}, so this method does not allow an independent check of the results. Only the fine particles of the species can be included in the species' concentration measurement; otherwise the coarse portion (relatively unimportant in visibility) will degrade the accuracy of the LEB.

No matter how accurately they may eventually be assessed, light extinction budgets are predictions only for the present conditions of sources, meteorology, etc. Because of the physical/chemical interactions among fine particles in the atmosphere, a good LEB may prove untenable as conditions change.

8.3 VISIBILITY AND PERCEPTION

The term "visibility" is used colloquially to refer to various characteristics of the optical environment, i.e., the clarity with which distant details can be resolved and the fidelity of their apparent coloration. Traditionally, visibility has been defined in terms of visual range: the distance from an object that corresponds to a minimum or threshold contrast between that

object and some appropriate background. Threshold contrast refers to the smallest brightness difference between two stimuli that the human eye can distinguish.

Visibility defined by visual range is a reasonably precise definition; however, visibility is more than being able to see a target at a distance for which the contrast is reduced to the threshold value. Visibility also includes seeing vistas at shorter distances and being able to appreciate the details of line, texture, color, and form.

Visibility may be impaired by layered haze or uniform haze (Malm et al., 1980a,b,c). Layered haze produces a visible spectral discontinuity between itself and background (sky or landscape). Uniform haze reduces overall air clarity. Because changes in uniform haze take place over hours or days, an evaluation of visual air quality change resulting from a change in uniform haze requires remembering what the scene looked like before the change in air pollution took place. An example of a layered haze is a tight, vertically constrained, coherent plume. As the atmosphere changes from a stable to an unstable condition and the plume mixes with the surrounding atmosphere, the diffused plume, may reduce overall air clarity. Whether the pollution occurs as layered or uniform haze, judgments of visual air quality as a function of air pollution might be altered by variations in sun angle, cloud cover, and/or landscape features.

Human visual perception and changes in the optical characteristics of the atmosphere must be considered when assessing visibility impairment produced by air pollution. The perception of brightness, contrast, and color is not determined simply by the pattern and intensity of incoming radiation; rather, it is a dynamic searching for the best interpretation of the visible scene. The relative brightness of an object may vary as a function of its background, even though its absolute brightness remains constant.

Malm et al. (1981) investigated the relationship of contrast and color, and of changes in these variables, to the perception of visual air quality. They determined that the various demographic backgrounds of visitors to a national park did not influence perception, but that changes in color contrast did influence the accuracy and consistency of perception of visual air quality. In photographic slides of a mountain scene used as the test vehicle, color contrast was determined by variables such as weather condition, time of day, and ground cover, as well as by the amount of air pollution. Although an incremental color contrast change was perceived to be the same across air pollution levels, clean air environments

appeared to be more sensitive to contrast changes. The evidence indicates that a change in air pollution level produces a larger contrast change in clean air than in relatively dirty air and is, therefore, more perceptible.

For small objects, the size of the visual image on the retina of the eye also plays an important role in the perception of contrast. As an object recedes from us and apparently becomes smaller, details with low contrast become difficult to perceive. The reason for this loss of contrast perception is not only that the relative brightness of adjacent areas changes, but also that the visual system is less sensitive to contrast when the spacing of contrasting areas decreases. If the contrast spacing is a regular pattern of light and dark bands, (e.g., a picket fence), a "spatial frequency" can be readily described by the number of pattern repetitions or "cycles" per degree of viewing angle.

Fine particle aerosols may change the perceived color of objects and sky. Because it is difficult to specify perceived color, only a qualitative description is possible. In general, as distance from the observer increase, the apparent color of a target fades toward the hue of the horizon sky. Without particles, scattered air light is blue, and dark objects appear increasingly blue with distance. The addition of small amounts (1 to 5 $\mu g/m^3$) of fine particles throughout the viewing distance tends to whiten the horizon sky, making distant dark objects and the intervening air light (haze), normally blue, appear more gray. According to Charlson et al. (1978a), even though the visual range may be decreased only slightly from the limit imposed by Rayleigh scattering, the change from blue to gray is an easily perceived discoloration. The apparent color of white objects is less sensitive to incremental fine particle loadings.

Aerosol haze may also degrade the view of the night sky by diminishing star brightness. The perception of stars is also reduced by an increase in the brightness of the night sky caused by scattering of available light. In or near urban areas, night sky brightness is significantly increased by particle scattering of artificial light. Leonard et al. (1977) reported that the combination of extinction of starlight and increased sky brightness markedly decreased the number of stars visible in the night sky at fine particle concentrations of 10 to 30 $\mu g/m^3$.

8.4 SOURCES OF VISIBILITY IMPAIRMENT

Although natural sources of light scattering and light absorbing aerosols are important in producing geographical and seasonal patterns of visibility impairment, analysis of visibility trends and other information suggests that manmade air pollution has a significant impact on visibility.

This section will briefly discuss both the natural and anthropogenic sources of visibility impairing particles and aerosols. This section will also summarize the recently published visibility trends data as reported in the Interim Findings on the Status of Visibility Research (U.S. Environmental Protection Agency, 1995). For a detailed discussion of previously published visibility trends data see the Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982) and National Acid Precipitation Assessment Program (Baedecker, 1991).

8.4.1 Natural Sources

The important sources of natural particles and aerosols include water (fog, rain, snow), windblown dust, forest fires, volcanoes, sea spray, vegetative emissions, and decomposition processes. The particle-free atmosphere scatters light and limits visual range to about 320 km (200 miles) at sea level. The natural contribution of fog, thunderstorms, snow, and other forms of precipitation can cause severe degradation of visual air quality. However, rarely do these intense events dominate the average visual range within the Continental U.S.; typically, only a small percentage of the hours involve storms or fog.

The frequency of fog in the continental U.S. is quite variable. Fogs tend to be local events and are rare during the summer months. According to Conway (1963) on an hourly basis, fogs exist less than 1% of the time.

Snow is an important factor in reduced visibility in the North and in some mountainous areas, occurring from 1 to 12% of the winter hours (Conway, 1963). Other forms of precipitation may affect visibility as well. Areas east of Nevada experience from 30 to 50 days of thunderstorm activity per year. Since thunderstorm activity is generally brief, their contribution to visibility reduction is less than 1% a year.

In the arid West, the contribution of windblown dust to degradation of visual air quality is an important problem. Because human activities that disturb natural soil surfaces add significantly to windblown dust, dust storms are only partially natural phenomena.

8.4.2 Anthropogenic Sources

The Clean Air Act established a goal to prevent further impairment of visibility in the Class I areas (those areas designated as national parks, large wildness areas, and some national monuments), and to correct existing visibility impairment in those areas. Monitoring of visibility and particulate pollution is necessary to establish existing visibility impairment, identify sources of particulate pollution, and evaluate long term progress. Several monitoring networks have been developed to address the Congressional mandate. These networks include, but are not limited to the Interagency Monitoring of Protected Visual Environments (IMPROVE), Subregional Cooperative Electric Utility, and the National Park Service, Environmental Protection Agency Study (SCENES). The IMPROVE monitoring program is managed by the National Park Service, the Forest Service, the Fish and Wildlife Service, the Bureau of Land Management and the Environmental Protection Agency. The main objective is to monitor visibility and particulate components in Class I areas. Tables 8-2 and 8-3 lists several visibility and aerosol data bases.

Records of visual range can be used to gain insight into the effects of changing emission patterns on visibility. One of the best examples of effects on visibility produced by atmospheric pollution was a strike that shut down the copper industry in the southwestern U.S. for more than 9 mo in 1967 to 1968. Copper production accounted for over 90% of the SO_x emissions, less than 1% of the NO_x emissions, and less than 10% of the conventional particulate emissions (Marians and Trijonis, 1979). Substantial decreases in sulfate occurred at 5 locations (Tucson, Phoenix, Maricopa County, White Pine, and Salt Lake City) within 19 to 113 km (12 to 70 miles) of copper smelters. Sulfates dropped by about 60% at Grand Canyon and Mesa Verde, 325 to 500 km (201 to 310 miles) from the main smelter area in southeast Arizona. Comparing measurements taken during the strike with those taken during the surrounding 4 or 6 years, Trijonis and Yuan (1978) found a large decrease in Phoenix sulfate loadings, accompanied by a substantial improvement in visibility. In fact, visibility improved at almost all locations during the strike, with the largest

TABLE 8-2. LONG-TERM VISIBILITY AND AEROSOL DATA BASES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
National and Regional Networks					
National Weather Service Airport Visibility Data	Rural and urban airports all over the nation.	1918 to present	Human estimates of prevailing visibility mainly in support of aircraft operations	To assess visibility trends; Assessment of the role of meterology on visibility impairment.	Quality varies from site to site; natural causes of visibility impairment (rain, snow, fog) included in data.
Interagency Monitoring of Protected Visual Environments (Improve)	Twenty remote locations nationwide, though primarily in the West.	1987 to present	Aerosol and visibility; PM_{10} and fine particle mass. Fine particle elements, ions, organic and light absorbing carbon. σ_{ext}, σ_{ap} , and σ_{sp} and photography.	To establish baseline values and identify existing impairment in visibility protected federal Class I areas.	Employs "state-of-art" methods for long term routine monitoring. Operated jointly by EPA four federal land managers.
Eastern Fine Particle Visibility Network	Five eastern rural locations.	1988-89 Five sites after 1989 two sites	Aerosol and visibility; fine particle elements organic and soot carbon. σ_{ext}, σ_{ap}, and σ_{ag}, and photography.	A research monitoring program to provide information needed to quality support development of a secondary fine particle standard.	An EPA operated network. Sites are collocated with other air monitoring programs.
National Park Service Network (NPS)	About 37 remote locations nationwide, though primarily in the west.	1987 to present Seventeen sites started in 1987.	Aerosol & visibility; 17 sites operated with IMPROVE measurements. Other have some subset of the IMPROVE measurements.	To document visibility and aerosol levels and to identify sources of visibility impairment measurements in NPS.	Represents the longes period of record for visibility and aerosol monitoring at remote locations.
SCENES	Eleven rural and remote southwestern locations.	1984-1989	Aerosol and visibility; PM_{15} and fine particle mass, elements, organic and light carbon at most sites. σ_{ext} or σ_{sp} and σ_{sg}, and photography at most sites.	To document levels and causes of visibility impairment in northern Arizona and southern Utah.	This cooperative research program included several intensive and special studies. An ambitious quality assurance protocol identified many monitoring method difficulties which new techniques ultimately solved.

TABLE 8-2 (cont'd). LONG-TERM VISIBILITY AND AEROSOL DATA BASES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
Western Regional Air Quality Study (WRAQS)	Eleven nonurban locations in the western U.S.	1981-1982	Aerosol and visibility; PM_{15} and fine particle mass, elements, ion.	To document bacground levels of visibility and related aerosols, organic and elemental carbon. σ_{sg} and σ_{sp}, observed visual range and photography.	Represents the highest times resolution for routinely collected filter samples (two four-hour samples each day).
National Air Surveillance Network (NASH)	Urban & rural areas of U.S.	1975 to present	Aerosol only; TSP ions, and some elements.	Air quality monitoring.	No size-fractioned data; collected only once every six days; artifact on filter possible.
Inhalable Particle Network (IP Network)	Urban and rural areas of U.S. Evans (84) Rodes and Evans (85)	June 1979 to present	Aerosol only; fine and coarse aerosol mass, PM_{15} mass, elements, and ions (every fourth sample).	Characterize inhalable particles	Discrepancy exists between PM_{15} and IP mass (sum of fine and coarse). Screening of the data required to remove invalid data points (~25%).
Sulfate Regional Experiment (SURE)	Nonurban areas of eastern U.S. (9 Class I sites and 45 Class II sites)	1977-1978	Aerosol only; TSP, fine and coarse aerosol mass, ions and elements.	Sulfacte characterization pollutant source characterization	Class I sites operated for 18 months continuously; Class II sites operated for one month every season for a total of six.
Eastern Regional Air Quality Studies (ERAQS)	Nine nonurban areas in northeastern U.S. SURE Class I sites.	Aerosol and visibility; TSP, fine and coarse aerosol mass, ions, elements, σ_{sg} and σ_{sp}, σ_{ext}, and photography.	To characterize visibility (at two sites only) and air quality in the northeastern U.S. region.	To characterize visibility (at two sites only) and air quality in the northeastern U.S. region.	The only long-term instrumental visibility data set generated in the eastern U.S. Visibility monitored only at 2 sites; intercomparison of visibility measurement methods made.
Ohio River Valley Study	Three rural sites in Ohio River Valley.	May 1980-August 1981	Aerosol only; fine and coarse aerosol mass and elements.	Characterization of fine and coarse aerosols in the region.	Portion of aerosol composition was not accounted for due to limitations in XRF analysis used. A long-term daily monitoring of aerosol in rural areas of the Ohio River Valley.

TABLE 8-2 (cont'd). LONG-TERM VISIBILITY AND AEROSOL DATA BASES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
Harvard School of Public Health's Six Cities Study	Portage, WI Topeka, KS Kingston, TN Watertown, MA St. Louis, MO Steubenville, OH	Spring 1979	Aerosol and visibility; fine and coarse aerosol mass, elements, $SO_4^=$, σ_{sg} and σ_{sp}.	Mass and elemental characterization of aerosol and their temporal variations to assess health effects of air pollution.	Portion of aerosol composition was not accounted for due to limitations in XRF analysis used.
RESOLVE	Seven remote sites in the California Mojave Desert	1983-1985	Aerosol and visibility; PM_{10} and fine particle mass, elements, organic and elemental carbon, σ_{ext}, σ_{sp} and σ_{sg}, σ_{ap} and σ_{ag}, and photography.	To document levels and identify causes of visibility impairment in the R-2508 military air space.	DOD sponsored study to provide information needed to limit future additional degradation of military testing by visibility impairment.
Single Air Shed Studies					
Great Smoky Mountain National Park Visibility and Air Quality Study (TVA)	Great Smoky Mountain National Park	1980-1983	Aerosol and visibility; fine and coarse aerosol mass and elements; σ_{sp} and σ_{sg} and σ_{ext}; photography.	Characterize visibility and aerosol.	Because of instrument problems, teleradio-meter data were lost. Total particulate matter mass only estimated in some cases. PIXE analysis could not provide some major elemental data.
Regional Air Pollution Study (RAPS)	100 km region around St. Louis, MO	1974-1977	Aerosol only; fine and coarse mass, $SO_4^=$, elements.	Develop and evaluate regional air quality models.	Comparison of Hi-Vol and dichotomous samplers.
Portland Aerosol Characterization Study (PACS)	Two rural and four urban areas in Portland, OR	July 1977-April 1978	Visibility and aerosol; fine and coarse mass, TSP, ions, elements, σ_{sp} and σ_{sg}.	Aerosol characterization source apportionment.	Significant role of carbonaceous aerosols recorded.

[a]Visibility data include light scattering and light extinction measurements using integrating nephelometer, teleradiometers, cameras, and human observers.

Source: Baedecker (1991).

TABLE 8-3. SHORT-TERM INTENSIVE VISIBILITY AND AEROSOL STUDIES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
			Rural Studies		
Allegheny Mountain Studies	Rural Allegheny Mountain site	24 July-11 Aug 1977 and Aug 1993	Visibility and aerosol; TSP, fine and coarse aerosol mass, ions, elements, σ_{sp} and σ_{sg}.	Characterization of visibility and $SO_4^=$ in the region.	Filter artifact investigated; no size fractionated data in 1977.
Shenandoah Valley Studies	Rural Shenandoah Valley	15 July - 15 Au 1980	Visibility and aerosol; fine and coarse aerosol mass, ions, elements, σ_{ext}, human estimates of visibility.	To characterize visibility and aerosol in the rural eastern U.S.	Since three different groups performed the study, intercomparability of data possible.
Great Smoky Mountain Study (EPA)	Great Smoky Mountain National Park	20-26 Sept 1978	Aerosol and gaseous pollutants; fine and coarse aerosol mass and elements.	Characterize aerosol in a rural area.	Comparison of day and night aerosol data made.
Research Triangle Park Visibility Study	Rural Research Triangle Park, NC	8 June - 3 Aug 1979	Visibility and aerosol; fine and coarse aerosol mass, elements, σ_{ext}, and σ_{sp} and σ_{sg}.	Characterize visibility and aerosol in the region.	Comparison of different visibility measurement methods studies.
Louisiana Gulf Coast Study	Gulf Coast	8 Aug - 7 Sept 1979	Visibility and aerosol; fine and coarse aerosol mass, ions, elements, σ_{sp} and σ_{sg}.	Investigation of sources of O_3 and haze.	Calibration errors of MRI 1550 integrating nephelometer applied to data.
Atlantic Coastal Study	Lewes, DE	1-31 Aug 82, 25 Jan - 28 Feb 1983	Visibility and aerosol; fine and coarse aerosol mass and chemistry, σ_{sp} and σ_{sg}.	Air quality and sources of haze.	
Pacific Northwest Regional Aerosol Mass Apportionment (PANORAMAS)	Twenty-six rural and remote locations in Washington, Oregon, and Idaho	May - Nov 1984	Visibility and aerosol; fine particle mass, elements, and ions. σ_{ext}, σ_{ap}, σ_{ag}, and photography.	To document the levels and sources of summer visibility impairment in the Northwest.	This cooperative monitoring program identified smoke as a major contributor to visibility impairment.

TABLE 8-3 (cont'd). SHORT-TERM INTENSIVE VISIBILITY AND AEROSOL STUDIES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
			Rural Studies		
California Aerosol Characterization Study (ACHEX)	Fourteen southern California cities	July- Nov 72, July - Oct 73	Aerosol and visibility TSP, fine and coarse aerosol mass, ions, elements, σ_{sg} and σ_{sp}.	Characterization of urban aerosols in California.	The most complete classic aerosol experiment. New methods sampling and analysis tested.
Denver Winter Haze Study I	Denver, CO	Nov - Dec 78	Visibility and aerosol; fine and coarse aerosol mass, ions, elements, σ_{sg} and σ_{sp}, and σ_{ext}.	Investigation of sources of Denver haze.	Role of local sources and the significant role of carbon in the air documented.
Denver Winter Haze Study II	Denver, CO	Jan 1982	Visibility and aerosol; fine and coarse aerosol mass, ions, elements, σ_{sp} and σ_{sg}.	Investigation of sources of Denver haze.	Role of local sources and the significant role of carbon in the air documented.
Metro Denver Brown Cloud Study	Denver, CO	Nov 1987 - Jan 1988	Visibility and aerosol; fine particle elements ions, organic and light absorbing carbon, σ_{ext}, σ_{sp} and σ_{sg}, σ_{ap} and σ_{ag}, and photography.	Investigate the sources of Denver haze.	Comprehensive spatial and temporal measurements included fuel switching to see effects of source modulation.
Detroit Visibility Study	Urban Detroit, MI	15-21 July 1981	Aerosol and visibility; fine and coarse aerosol, ions, elements, σ_{sp} and σ_{sg}.	Identification of chemical components of TSP.	Data from a major industrial and urban areas.
Houston Visibility Study	Houston, TX	11-19 Sept 1980	Visibility and aerosol; fine and coarse aerosol, ions, elements, σ_{sp} and σ_{sg}, and σ_{ext}.	Characterization of visibility and aerosol.	Comparison of day and night aerosols and different visibility measurement devices made.
CARB Los Angeles Basin Study	Los Angeles Basin	Aug 1992	Visibility and aerosol; fine and coarse aerosol mass, ions, and σ_{sp} and σ_{sg}.	Characterize visibility and aerosol in the basin.	Significant roles of NO_3^- and organics shown; the importance of filter artifacts reported.

TABLE 8-3 (cont'd). SHORT-TERM INTENSIVE VISIBILITY AND AEROSOL STUDIES

Study/Data Base	Air Sheds	Period	Type of Data[a]	Purpose of Study	Comments
Northern New Jersey Air Pollution Study	Newark, NJ Elizabeth, NJ Camden, NJ Ringwood, NJ	Winter 1982-1983	Aerosol only.	Inhalation toxicology studies.	Urban contributions of carbonaceous particles to air pollution episodes.
Willamette Valley Field and Slash Burning Study	Willamette Valley, OR	Summer 1978	Aerosol; fine and coarse mass, TSP, elements (carbon), ions	Assessment of field and slash burning on air quality.	Significant role of carbonaceous particles in fine aerosol demonstrated.
San Joaquin Valley Aerosol Study	San Joaquin Valley, CA	Nov-Dec 78, Jul and Sept. 79	Aerosol only; fine and coarse mass, ions.	Characterize ambient aerosols termittent data sets.	

[a]Visibility data include light scattering and light extinction measurements using integrating nephelometer, teleradiometers, cameras, and human observers.

Sourc: Baedecker (1991).

improvements occurring near and downwind (north) of the copper smelters in southeast Arizona and near the copper smelters in Nevada and Utah.

More recently, improvements in visibility have been reported in the east during the summer months from 1978 to 1982 and from 1988 to 1992. Using data from 1948 to 1983, Husar and Wilson (1993) reported that extinction coefficients calculated from visual range data showed a direct correlation with sulfur emissions in the northeastern U.S.

Hofmann (1993), using balloon measurements from 1971 to 1990 over Laramie, WY, showed a decrease of 1.6 to 1.8% per year of optically active tropospheric aerosols. Similar results were reported by Pennick et al. (1993) in New Mexico from the mid 1970s to 1990. Pennick et al. (1993) reported a slight decrease in optically active tropospheric aerosols but no change in elemental black carbon. Hofmann (1993) suggested that the decrease in the tropospheric aerosols was due to the reduction in SO_2 emissions in the U.S. during that time.

Eldred and Cahill (1994) reported that sulfate concentrations in the west decreased or remained unchanged except for during the winter months, when the sulfate concentrations increased. An increase in sulfate concentrations was noted for areas in the east except for during the winter months when a decrease was noted. Summer increases of sulfate in the Shenandoah National Park were more dramatic. Eldred and Cahill (1994) based these findings on monitoring data taken from 12 monitoring sites in remote Class I visibility areas from June 1982 to August 1992.

Hildemann et al. (1994) found seasonal trends in ambient organic aerosol concentrations in Los Angeles, CA. Strong peaks were noted in the fall and winter months. Husar and Poirot (1992) found that particles of less than 10 μm had different weekly patterns in different parts of the U.S. El Paso, TX had lower concentrations during the weekends, the highest concentrations for San Bernadino were reported on Mondays, and the highest concentrations for Yosemite National Park and Oceanside were on Sundays.

White et al. (1994) examined back-trajectories for air arriving at the Grand Canyon using the four quadrants (NE, NW, SE, and SW) as source zones. Back-trajectories were calculated for air parcels arriving in the Grand Canyon during the hours of 11:00 am to 5:00 pm. Methylchloroform was used as a regional tracer for air from the Los Angeles basin. White et al. (1994) concluded that the best visibility occurred at the Grand Canyon when the air is from the north. They found high methylchloroform at the mouth of the

Canyon from April to October. The back-trajectories on the days of high methylchloroform indicated that the air had been in the southwest quadrant several day prior. High levels of sulfate were observed on days when the back-trajectory of the air parcel spent three quarters of the time exclusively in one quadrant, but no specific quadrant could be identified as the primary quadrant of concern. Each quadrant was determined to have at least one high concentration day except the northwest quadrant. High RH and low visual range are associated with air from the southwest.

8.5 ECONOMIC VALUATION OF EFFECTS OF PARTICULATE MATTER ON VISIBILITY

The effects of particulate matter on visibility were described in previous sections of this chapter and are hazes and reductions in visual range in all of the U.S. This section discusses the available economic evidence concerning the value of preventing or reducing these types of effects on visibility. The following brief summary of economic estimation methods and available results is derived from the document. Air Quality Criteria for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993).

8.5.1 Basic Concepts of Economic Valuation

Visibility has value to individual economic agents primarily through its impact upon activities of consumers and producers. Studies of the economic impact of visibility degradation by air pollution have focused on consumer activities. Most economic studies of the effects of air pollution on visibility have focused specifically on the aesthetic effects to the individual. Some commercial activities, such as airport operations, may be affected by visibility degradation by air pollution, but available evidence suggests that the economic magnitude of the effects of haze on commercial operations probably is very small. In a 1985 report, the U.S. Enviromental Protection Agency concluded that some percentage of the visibility impairment incidents sufficient to affect air traffic activity might be attributable, at least in part, to manmade air pollutants (possibly 2% to 12% in summer in the eastern U.S.).

It is well established that people notice those changes in visibility conditions that are significant enough to be perceptible to the human observer, and that visibility conditions

affect the well-being of individuals. This has been verified in scenic and visual air quality rating studies (Middleton et al., 1983; Latimer et al., 1981; Daniel and Hill, 1987), through the observation that individuals spend less time at scenic vistas on days with lower visibility (MacFarland et al., 1983), and through use of attitudinal surveys (Ross et al., 1987). The intent of visibility-related economic studies has been to put a dollar value on changes in well-being associated with visibility degradation.

Welfare economics defines a dollar measure of the change in individual well-being (referred to as utility) that results from a change in the quality of any public good, such as visibility, as the change in income that would cause the same change in well-being as that caused by the change in the quality of the public good. One way of defining this measure of value is to determine the maximum amount the individual would be willing to pay to obtain improvements or prevent degradation in the public good (see Freeman [1979] for more detail). For most goods and services traded in markets, this measure can be derived from analysis of market transactions. For non-market goods, such as visibility, this economic measure of value must be derived some other way.

For purposes of this discussion, consumer values for changes in visibility can be divided into use and non-use values (there are slight variations in the way these are defined by different economists). Use values are related to the direct influence of visibility on the current and expected future activities of an individual at a site. Non-use values are the values an individual places on protecting visibility for use by others (bequest value) and on knowing that it is being protected regardless of current or future use (existence value). Total value, combining use and non-use, is sometimes called preservation value.

8.5.2 Economic Valuation Methods for Visibility

Two main economic valuation methods have been used to estimate dollar values for changes in visibility conditions in various settings: (1) the contingent valuation method (CVM), and (2) the hedonic property value method. Both methods have important limitations, and uncertainties surround the accuracy of available results for visibility. Ongoing research continues to address important methodological issues, but at this time some fundamental questions remain unresolved (Chestnut and Rowe, 1990a; Mitchell and Carson, 1989; Fischhoff and Furby, 1988; Cummings et al., 1986). Recognizing these uncertainties

is important, but the body of evidence as a whole suggests that economic values for changes in visibility conditions are probably substantial in many cases and that a sense of the likely magnitude of these values can be derived in some instances from the available results (Chestnut and Rowe, 1990a).

8.5.2.1 Contingent Valuation Method

The CVM involves the use of surveys to elicit values that respondents place on changes in visibility conditions (see Rowe and Chestnut [1982], Mitchell and Carson [1989], and Cummings et al. [1986] for more details on this method). The most common variation of the CVM relies on questions that directly ask respondents to estimate their maximum willingness to pay (WTP) to obtain or prevent various changes in visibility conditions. The potential changes in visibility conditions are usually presented to the respondents by means of photographs and verbal descriptions, and some hypothetical payment mechanism, such as a general price increase or a utility bill increase, is posed.

The CVM offers economists the greatest flexibility and potential for estimating use and non-use values for visibility. There are many types of changes in visibility for which total values cannot be derived from market data. As a result, most recent visibility value applications use the CVM. This approach continues to be controversial, however, and there are those who question whether the results are useful for policy analysis (Fischhoff and Furby, 1988; Kahneman and Knetsch, 1992). Smith (1992) has responded to some of the questions raised about the CVM, but a consensus on its usefulness and reliability has not been reached in the economics community. Cummings et al. (1986) and Mitchell and Carson (1989) have conducted the most comprehensive reviews of the CVM approach to date and have concluded that there is sufficient evidence to support the careful use of results from well-designed CVM studies in certain applications.

Among the fundamental issues concerning the application of CVM for estimating visibility values are (1) the ability of researchers to present visibility conditions in a manner relevant to respondents and to design instruments that can elicit unbiased values; and (2) the ability of respondents to formulate and report values with acceptable accuracy. As with any survey instrument, it is important that the presentation be credible, realistic, and as simple as possible. The optimal level of detail and the most critical pieces of information necessary in

the presentation to respondents to obtain useful CVM responses continue to be topics of research and discussion. Another important issue in CVM visibility research concerns the ability of respondents to isolate values related to visibility aesthetics from other potential benefits of air pollution control such as protection of human health. Preliminary results (Irwin et al., 1990; Carson et al., 1990) suggest that simply telling respondents before asking the WTP questions to include only visibility is not adequate and may cause some upward bias in the responses.

8.5.2.2 Hedonic Property Value Method

The hedonic property value method uses relationships between property values and air quality conditions to infer values for differences in air quality (see Rowe and Chestnut [1982] and Trijonis et al. [1984] for more detail on this method). The approach is used to determine the implicit, or "hedonic," price for air quality in a residential housing market, based on the theoretical expectation that differences in property values that are associated with differences in air quality will reveal how much households are willing to pay for different levels of air quality in the areas where they live. The major strength of this approach is that it uses real market data that reflect what people actually pay to obtain improvements in air quality in association with the purchase of their homes. The method can provide estimates of use value, but non-use values cannot be estimated with this method.

There are many theoretical and empirical difficulties in applying the hedonic property value method for estimating values for changes in visibility, but the most important limitation is the difficulty in isolating values for visibility from other effects of air pollution at the residence. Hedonic property value studies to date provide estimates of total value for all perceived impacts resulting from air pollution at the residence, including health, visibility, soiling, and damage to materials and vegetation. The potential for estimating separate values for visibility with this method is limited for two reasons. First, the actual effects of air pollution often are highly correlated, making it difficult to separate them statistically using objective measures. Second, individuals are likely to perceive a correlation between these effects and to act accordingly in their housing decisions, even if the effects are actually separable using objective measures.

8.5.3 Studies of Economic Valuation of Visibility

Economic studies have estimated values for two types of visibility effects potentially related to particulate matter and NO_x: (1) use and non-use values for preventing the types of plumes caused by power plant emissions, visible from recreation areas in the southwestern United States; and (2) use values of local residents for reducing or preventing increases in urban hazes in several different locations.

8.5.3.1 Economic Valuation Studies for Air Pollution Plumes

Three CVM studies have estimated on-site use values for preventing an air pollution plume visible from recreation areas in the southwestern U.S. (Table 8-4). One of these studies (Schulze et al., 1983) also estimated total preservation (use and non-use) values held by visitors and non-visitors for preventing a plume at the Grand Canyon. A fourth study concerning a plume at Mesa Verde National Park (Rae, 1983) was not included because of methodological problems with the contingent ranking approach used (Ruud, 1987). The plumes in all three studies were illustrated with actual or simulated photographs showing a dark, thin plume across the sky above scenic landscape features, but specific measures such as contrast and thickness of the plume were not reported. Respondents were told that the source of the plume was a power plant or an unspecified air pollution source. In one study (Brookshire et al., 1976), a power plant was visible in the photographs.

The estimated on-site use values for the prevention or elimination of the plume ranged from about $3 to $6 (1989 dollars) per day per visitor-party at the park. These value estimates are comparable to values obtained in these and other studies for preventing fairly significant reductions in visual range caused by haze at parks and recreation areas in the Southwest. A potential problem common to all of these studies is the use of daily entrance fees as a payment vehicle. Respondents may have anchored on the then-typical $2 per day fee and stated an acceptable proportional increase in entrance fees rather than reporting a maximum willingness to pay. This may have caused some downward bias in the responses, but empirical exploration of this question is needed. An alternative payment vehicle to consider might be total expenditures for the trip to the park.

The results of the Schulze et al. (1983) study suggest that on-site use values may be easily dwarfed by total preservation values held by the entire population. For example, with

TABLE 8-4. ECONOMIC VALUATION STUDIES FOR AIR POLLUTION PLUMES

Study	Location of Plume	Study Subjects	Year of Interviews	Type of Value	Valuation Method	Payment Vehicle	Mean Results ($ 1989)
Schulze et al. (1983)	Grand Canyon National Park	Urban residents who have visited or plan to visit Grand Canyon	1980	Daily use value at park per household	Contingent valuation, direct WTP[a] question	Daily park entrance fee	$6.17 per day at park per household
		Urban residents in Denver, Los Angeles, Chicago, Albuquerque; visitors and non-visitors	1980	Monthly preservation value per household	Contingent valuation, direct WTP[a] question	Monthly utility bill increase	$5.31 per month per household
MacFarland et al. (1983)	Grand Canyon National Park	Park visitors	1980	Daily use value at park per visitor-party (household)	Contingent valuation, direct WTP[a] question	Daily park entrance fee	$2.84 per day at park per visitor-party (household)
Brookshire et al. (1976)	Glen Canyon National Recreation Area (Lake Powell)	Nearby residents and lake visitors	1974	Daily use value at recreation area per visitor-party (household)	Contingent valuation, direct WTP[a] question	Daily entrance fee	Visitors: $3.32 per day additional to prevent visible plume Residents: $2.21 per day additional to prevent visible plume

[a]WTP = Willingness to pay.

average annual visitation at the Grand Canyon of about 1.3 million visitor-parties (about three people per party), annual on-site use values for preventing a visible plume every day would be about $8 million based on the Schulze et al. results, whereas the implied preservation value for preventing a visible plume most days (the exact frequency was not specified) at the Grand Canyon would be about $5.7 billion each year when applied to the total United States population. There is, however, considerable uncertainty in the preservation value estimates from this study. Chestnut and Rowe (1990b) found that the Schulze et al. (1983) preservation value estimates for haze at national parks in the Southwest are probably overstated by a factor of two or three and the same probably applies to the preservation value estimates for plumes.

8.5.3.2 Economic Valuation Studies for Urban Haze

Six economic studies concerning urban haze caused by air pollution are summarized in Table 8-5. Five of these are CVM studies and one is a hedonic property value study. Although many other hedonic property value studies concerning air quality have been conducted (see Trijonis et al. [1984] and Rowe and Chestnut [1982] for reviews), the study by Trijonis et al. (1984) is the only one that has used visibility as the measure of air quality.

The magnitudes of the changes in visual range considered in each study vary, making direct comparisons of the results difficult. In Table 8-5 implicit values obtained for a 10% change in visual range are reported to allow a comparison of results across the studies. Values for a 10% change are shown to illustrate the range of results across the different studies. These estimates are based on a model developed for comparison purposes that assumes economic values are proportional to the percentage change in visual range. Values for a 20% change, for example, would be about twice as large as those shown for a 10% change, given the underlying comparison model. Each of these studies relied on a reasonably representative sample of residents in the study area, such that a range of socioeconomic characteristics and of neighborhood pollution levels was included in each sample.

The first five studies in Table 8-5 all focused on changes in urban hazes with fairly uniform features that can be described as changes in visual range. The sixth study (Irwin et al., 1990) focused on visual air quality in Denver, where a distinct edge to the haze is

TABLE 8-5. ECONOMIC VALUATION STUDIES ON URBAN HAZE

Study	Location	Year	Valuation Method[a]	Payment Vehicle	Presentation/Definition of Change in Visibility	Implied Mean Annual WTP[a] for a 10% Change in Visual Range ($ 1989)
PART I. UNIFORM URBAN HAZE						
Western Cities						
Loehman et al. (1981)	San Francisco	1980	Contingent valuation, direct WTP question	Monthly utility bill increases	Change in frequency distribution illustrated with local photos for 3 levels of air quality	$106 per household
Brookshire et al. (1982)	Los Angeles	1978	Contingent valuation, direct WTP question	Monthly utility bill increases	Change in average visibility illustrated with local photos for 3 levels of air quality	$10 per household
Trijonis et al. (1984)	San Francisco	1978-79	Hedonic property value		Light extinction based on airport visibility data	$208-231 per household
	Los Angeles	1978-79	Hedonic property value		Light extinction based on airport visibility data	$112-226 per household
Eastern Cities						
Tolley et al. (1986)	Chicago; Atlanta; Boston; Mobile; Washington, D.C.; Miami; Cincinnati	1982	Contingent valuation, direct WTP question	Monthly payment for visibility improvement program	Change in average visibility illustrated with Chicago photos for levels of air quality	$8-51 per household

TABLE 8-5 (cont'd). ECONOMIC VALUATION STUDIES ON URBAN HAZE

Study	Location	Year	Valuation Method[a]	Payment Vehicle	Presentation/Definition of Change in Visibility	Implied Mean Annual WTP[a] for a 10% Change in Visual Range ($ 1989)
PART I (cont'd). UNIFORM URBAN HAZE						
Rae (1984)	Cincinnati	1982	Contingent valuation, direct WTP question	Monthly payment for visibility improvement program	Change in average visibility illustrated with Chicago photos for 3 levels of air quality	$48 per household
PART II. URBAN HAZE WITH BORDER						
Irwin et al. (1990)	Denver	1989	Contingent valuation, direct WTP question	General higher prices each year	1-step change in 7-point air quality scale, illustrated with photos	Preliminary results indicate mean annual WTP of about $100 per household for a 1-step change in the 7-point scale, with about one-third of the value attributed to visibility alone

[a]WTP = Willingness to pay.

often noticeable, making visual range a less useful descriptive measure because it would vary depending on the viewpoint of the individual and whether the target was in or above the haze layer. The studies conducted in Denver and in the California cities are likely to have a higher NO_x component than in the eastern cities.

Both of the CVM studies in California asked respondents to consider health and visual effects but used different techniques to have respondents partition the total values. They found that, on average, respondents attributed about one-third to one-half of their total values to aesthetic visual effects. In spite of many similarities in the approaches used, the CVM results for San Francisco are notably higher than for Los Angeles when adjusted to a comparable percentage change in visual range. One potentially important difference in the presentations was that Loehman et al. (1981) defined the change in visibility as a change in a frequency distribution rather than simply a change in average conditions. This type of presentation is more realistic but more complex; and it is unclear how it may affect responses relative to presentation of a change in the average. It is possible that the distribution presentation might elicit higher WTP responses because it may focus respondents' attention on the reduction in the number of relatively bad days (and on the increase in the number of relatively good days), whereas the associated change in the average may not appear as significant. The implied change in average conditions in the Loehman et al. (1981) San Francisco study was considerably smaller than that presented in the Brookshire et al. (1982) Los Angeles study, which may have also resulted in a higher value when adjusted to a comparable size change in average visual range because of diminishing marginal utility (i.e., the first incremental improvement is expected to be worth more than the second).

The California studies in Los Angeles and San Francisco provide some interesting comparisons because two different estimation techniques were applied for the same locations. Property value results for changes in air quality for both cities were found to be higher than comparable values (for changes in total air quality) obtained in the CVM studies. This is as expected given the theoretical underpinnings of each estimation method, although Graves et al. (1988) have reported that subsequent analysis of the property value data revealed that the estimates are more variable than the original results suggest. These property value results are not reported here because they are for changes in air pollution indices that are not tied to visual air quality.

The property value study results reported in Table 8-5 from Trijonis et al. (1984) were estimated using light extinction as the measure of air quality. However, as discussed in the previous section on the hedonic property value method, these estimates are still likely to include perceived benefits to human health for reductions in air pollution as well as values for visual aesthetics. Consistent with this expectation, the results for a 10% change in light extinction are higher than the CVM results for visual range changes for the same cities. Respondents in several CVM studies have reported that, on average, they would attribute to visibility aesthetics about one-fourth to one-half of their total WTP for improvements in air quality. This would imply that the Trijonis et al. results may reflect $25 to $100 for a change in visibility alone.

The results for the uniform urban haze studies in cities in the eastern U.S. fall between the respective CVM results for the California cities. The changes in visual range presented in these studies were similar to those presented in the Los Angeles study. In all of the eastern studies respondents were simply asked to consider only the visual effects when answering the WTP questions. This approach is now considered to be inadequate (Irwin et al., 1990; Carson et al., 1990).

A recent study that has not as yet completed the peer-review process has applied the approach recommended in recent methodological explorations to estimate values for changes in visibility. McClelland et al. (1991) conducted a mail survey in 1990 in Chicago and Atlanta. Residents were asked what they would be willing to pay to have an improvement in air quality, which amounted to about a 14% improvement in annual average visual range. Respondents were then asked to say what percentage of their response was attributable to concern about health effects, soiling, visibility, or other air quality impact. Respondents, on average, attributed about 20% of their total WTP to visibility. The authors conducted two analyses and adjustments on the responses. One was to estimate and eliminate the potential selection bias resulting from non-response to the WTP questions (including what has been called protest responses). The other was to account for the potential skewed distribution of errors caused by the skewed distribution of responses (the long tail at the high end). Both of these adjustments caused the mean value to decrease. The annual average household WTP for the designated visibility improvement was $39 before the adjustments and $18 after the adjustments. This adjusted mean value implies about $13 per household for a 10%

improvement in visual range. This is at the low end of the range of estimates shown in Table 8-5. If peer-review of this research effort confirms the appropriateness of the study design and analysis, the results suggest that greater confidence should be placed in the lower end of the range of results shown in Table 8-5 because this study represents an improvement in approach over the other eastern-cities studies.

Irwin et al. (1990) have reported preliminary results for the Denver study (Part II, Table 8-5). Comparison of these preliminary results with results from other studies is difficult because the photographs used to illustrate different levels of air quality were not tied to visual range levels. Instead, they were rated on a seven-point air quality scale by the respondents, who were then asked their maximum WTP for a one-step improvement in the scale. This study reports some important methodological findings. One of these is confirmation that simply asking respondents to think only about visibility results in higher WTP responses for visibility changes than when respondents are asked to give WTP for the change in air quality and then to say what portion of that total they would attribute to visibility only. The latter approach produced a mean WTP estimate for a one-step change in visibility that was about one-half the size of the mean WTP estimate given when respondents were simply asked to think only about visibility. This may result from the effect of budget constraints on marginal values (the respondent has less to spend on visibility when he also is buying health); however, the authors express the concern that some, but not all, of the value for health may be included in the response when respondents are told to think only about visibility. They recommend that respondents be asked to give total values for changes in urban air quality and then be asked to say what portion is for visibility.

8.6 CLIMATIC EFFECTS

8.6.1 Introduction

Particulate matter of submicrometer size in the earth's atmosphere perturbs the radiation field sufficiently to warrant its consideration in any discussion of processes that maintain the current climate. Perturbation of the radiation field generally is expressed as a *radiative forcing*, which is the change in average net radiation at the top of the troposphere because of a change in solar (shortwave) or terrestrial (longwave) radiation (Intergovernmental Panel on

Climate Change, 1990). Note that it is the net effect at the top of the troposphere (i.e., the tropopause) that forces climate, and not the change at the surface, because the surface and troposphere are intimately coupled through atmospheric energy exchange processes such as dry and moist convection (Ramanathan et al., 1987). The radiative forcing due to aerosols is negative (i.e., aerosols have a cooling effect through the enhanced reflection of solar energy). This is in contrast to radiatively active trace ("greenhouse") gases associated with industrial and agricultural activities, which produce a positive longwave radiative forcing (i.e., "greenhouse" gases cause a warming of the earth-troposphere system). A large fraction of atmospheric particulate matter is of anthropogenic origin, the chief sources being the emission of sulfur-containing aerosols by industry and the large-scale burning of biomass.

There is now little doubt that long-lived, optically thick, aerosol layers may have modified the earth's climate in the past. Geologic evidence suggests that there have been episodic injections of massive amounts of material into the earth's atmosphere as a result of the impact of large asteroids or comets. The diminution of solar radiation reaching the surface has been cited as the most likely cause of mass extinctions of species at the Cretaceous-Tertiary boundary (Alvarez et al., 1980) and also in the Late Devonian (Claeys et al., 1992). The possibility of a similar climatic catastrophe following a nuclear war has also been raised (Turco et al., 1983, 1990). However, these are examples of massive injections of particulate matter that result in extremely large radiative forcings. Current interest is focused on much more modest injections of materials that form thin aerosol layers in the troposphere. Although the radiative effects are smaller and have been generally ignored in climate model simulations (Hansen and Lacis, 1990), recent studies have estimated that they are not negligible and that their radiative forcing may be comparable (but opposite in sign) to the radiative effects of increased greenhouse gas emissions (Wigley, 1991; Charlson et al., 1992; Penner et al., 1992). Because there is so much concern regarding greenhouse gas-induced climate change, the study of this potential opposite effect of industrial emissions is expected to be quite intense in the near future (Penner et al., 1994).

8.6.2 Radiative Forcing

To appreciate what is at issue here, it is necessary to understand the concept of radiative forcing. Averaged globally and annually, about 240 watts per meter squared

(W m^{-2}) of solar energy is absorbed by the earth-atmosphere system (Hartmann, 1994). This must be balanced by an equal emission of thermal energy back to space for equilibrium. A *change* in average net radiation at the tropopause, because of a change in either solar or terrestrial radiation, perturbs the system and this perturbation is defined as the *radiative forcing*. In response to this perturbation, the climate system will try and reach a new equilibrium state. For example, the increase in longwave opacity of the atmosphere resulting from enhanced concentrations of greenhouse gases such as carbon dioxide (CO_2) and methane (CH_4) is a positive radiative forcing because it leads to a reduction in outgoing thermal radiation. For equilibrium, given that there is no change in solar input, the temperature of the surface-troposphere system must increase. The individual contributions to this positive forcing, since pre-industrial times, is shown in Figure 8-5 (Intergovernmental Panel on Climate Change, 1990). Carbon dioxide is the single most important contributor with a radiative forcing of 1.50 W m^{-2} for the period 1765 to 1990. The total for all greenhouse gases attributable to anthropogenic sources is 2.45 W m^{-2}.

Human activity has also led to an increase in the abundance of tropospheric aerosols, primarily as a result of enhanced sulfur dioxide emission, but also from biomass burning. This aerosol layer produces a radiative forcing by perturbing the amount of solar energy that is absorbed by the earth-atmosphere system. By increasing the amount of solar energy reflected by the planet, aerosols produce a direct radiative forcing. They can also force the climate system indirectly by modifying the microphysical properties of clouds, primarily by reducing the effective drop size of water clouds. Both the direct and indirect radiative forcing of aerosols are negative (i.e., in response to this perturbation, the planet will cool).

The succeeding sections of this chapter are devoted to the estimation of aerosol radiative forcing. Translating this forcing into a climate response requires the incorporation of the forcing into a climate model. The model simulations, of course, are only as reliable as the models, which typically incorporate numerous feedbacks in the climate system that are only represented to some degree of approximation. There are certainly many feedbacks missing from current climate models, and it is quite possible that some feedbacks have been modeled quite incorrectly. Moreover, the radiative forcing due to anthropogenic aerosols needs to be estimated separately from that due to naturally occurring aerosols in order to

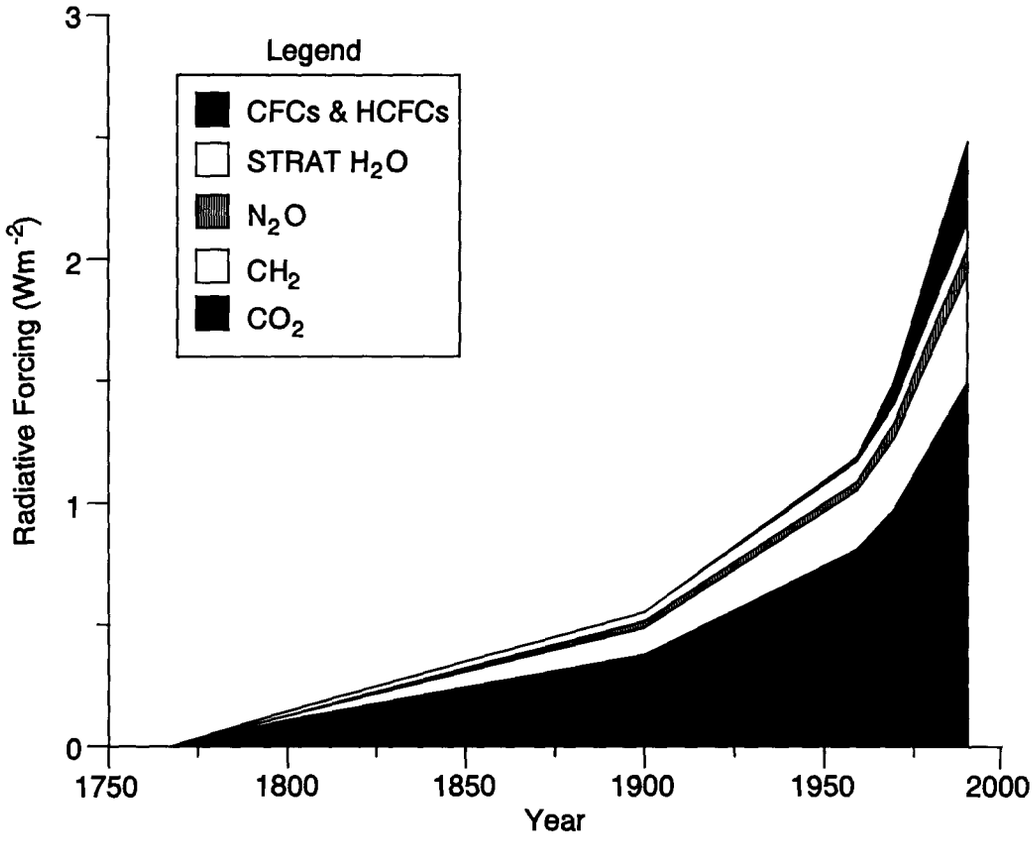

Figure 8-5. Changes in radiative forcing (W m^{-2}) due to increases in greenhouse gas concentrations between 1765 and 1990. Values are changes in forcing from 1765 concentrations.

Source: Intergovernmental Panel on Climate Change (1990).

evaluate the impact of human activity. The relationship between these aspects of the problem is shown in Figure 8-6 (Harshvardhan, 1993).

As has been mentioned, the radiative forcing due to aerosols is opposite in sign to that due to greenhouse gases, but the degree of offset in forcing may not translate into offsetting climatic consequences. We can only judge these by studying model simulations. Also, it must be kept in mind that climate variations occur in the absence of radiative forcing as a result of interactions between the atmosphere, oceans, and the various elements of the land surface such as snow cover and vegetation.

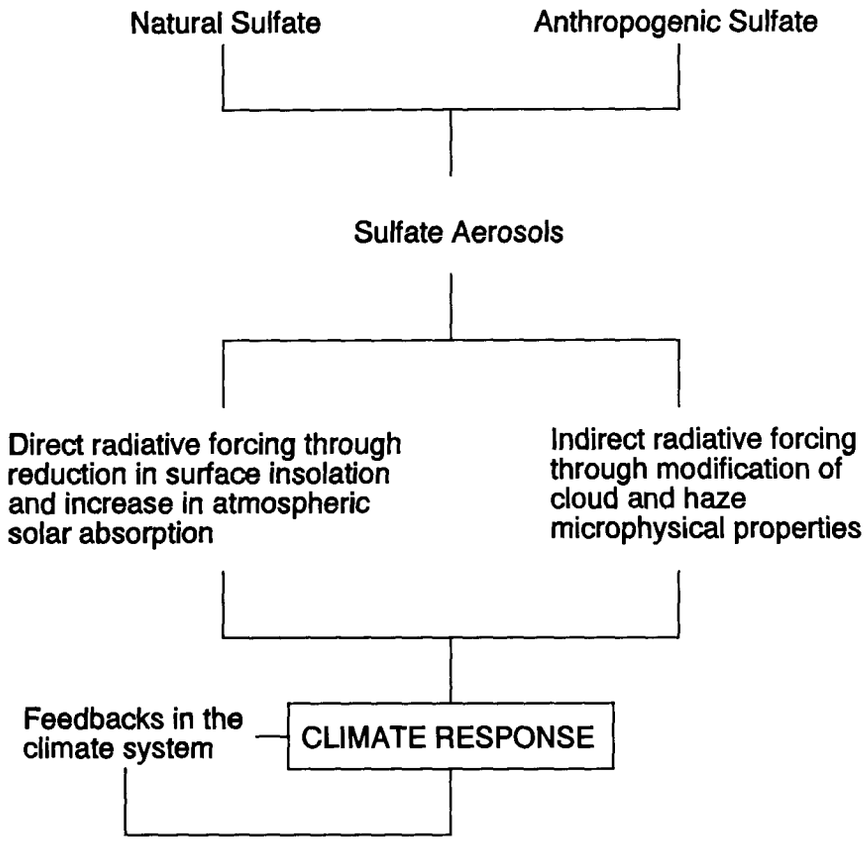

Figure 8-6. A schematic diagram showing the relationship between the radiative forcing of sulfate aerosols and climate response.

Source: Harshvardhan (1993).

8.6.3 Solar Radiative Forcing by Aerosols

Aerosol radiative forcing results from enhanced reflection of solar energy which enters the top of the earth's atmosphere as a collimated beam of infinite width, but is subsequently scattered and absorbed to some degree even on the clearest day. Figure 8-7 shows this process schematically. Throughout the troposphere molecules, constituting the atmosphere, scatter sunlight by the process of Rayleigh scattering, which is highly wavelength dependent. In the lower troposphere, sunlight is scattered by aerosols or haze and absorbed by aerosols and water vapor. Because the aerosol loading is quite variable, this component of aerosol scattered solar radiation is also very variable.

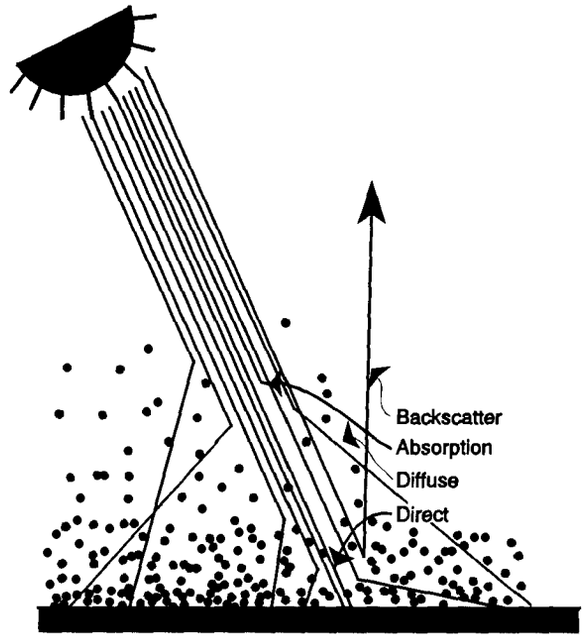

Figure 8-7. Extinction of direct solar radiation by aerosols showing the diffusely transmitted and reflected, as well as the absorbed components.

The degree to which a layer of particles scatters solar radiation is primarily determined by the nondimensional parameter referred to as the scattering optical depth of the layer, τ_s, which in turn is the column integrated volume scattering coefficient, σ_s (units are km^{-1}, see sections on visibility for details). Because σ_s depends on wavelength, the attenuation of the direct beam of sunlight is also wavelength dependent. This spectral behavior is usually expressed by the proportionality

$$\sigma_s \propto \lambda^{-\alpha} \tag{8-5}$$

where λ is the wavelength in micrometers (μm). The exponent, α, is the turbidity parameter introduced by Ångström (1964) and varies between 0.5 and 1.5 for aerosols (Twomey, 1977). For particles that are very small compared to the wavelength (Rayleigh scattering), $\alpha = 4$, and for relatively larger particles, such as cloud drops, $\alpha = 0$.

The downwelling portion of the radiation scattered by molecules and aerosols forms diffuse skylight whereas the unattenuated beam of solar radiation is said to be the directly

transmitted or beam radiation. The upwelling portion of scattered radiation, together with energy reflected by the surface, is the diffuse reflection of the earth-atmosphere system. It is the perturbation in this component of radiant energy by enhanced aerosol loadings that constitutes the radiative forcing to the system by aerosols. The sum of directly and diffusely transmitted solar energy is the global solar radiation incident on a surface.

Figure 8-8, from Iqbal (1983), shows computations of the spectral distribution of a solar energy incident on a horizontal surface for a solar zenith angle of 60° (air mass = 2) and standard clear conditions. The atmosphere contains 350 Dobson units of ozone (O_3), 2 ppt/cm of water vapor, and a nonabsorbing aerosol layer corresponding to a surface visibility of 28 km. The ground reflectance is 0.2. Some features of Figure 8-8 are worth noting. Virtually all solar radiation at wavelengths less than 0.29 μm is removed by O_3 absorption. Rayleigh scattering by molecules is the predominant source of the diffuse radiation at shorter wavelengths, but the contribution falls off very dramatically with increasing wavelength because of the inverse fourth power dependence. Aerosol scattering contributes to the diffuse component at visible and near-infrared wavelengths. Absorption by the strong water vapor bands is quite evident in the near-infrared.

An increase in the optical depth of aerosols results in a decrease in the direct beam radiation, which could be substantial, but the downwelling portion of the enhanced scattered radiation compensates for this to a large extent. This is illustrated in Figure 8-9, which shows surface measurements of direct, diffuse, and global solar radiation, made using a multifilter rotating shadowband radiometer (Harrison and Michalsky, 1994; Harrison et al., 1994) at Albany, NY, on two clear days in August of 1992 and 1993. The total atmospheric optical depth in 1992 was influenced by the eruption of Mt. Pinatubo in June 1991. Although the volcanic aerosols were in the stratosphere, their effect on direct and diffuse transmitted radiation is similar to that due to tropospheric aerosols. The quantity plotted is the spectral irradiance convolved with the average human eye response that peaks at 550 nm and falls to zero at 400 and 700 nm. The main feature of the plot is the substantial difference in direct and diffuse radiation, but quite similar global irradiances. Close inspection shows that on the hazier day (in 1992), the global transmitted radiation was somewhat less (i.e., the volcanic aerosol caused a negative radiative forcing to the earth-atmosphere system by increasing the planetary albedo). Locally, tropospheric aerosol optical

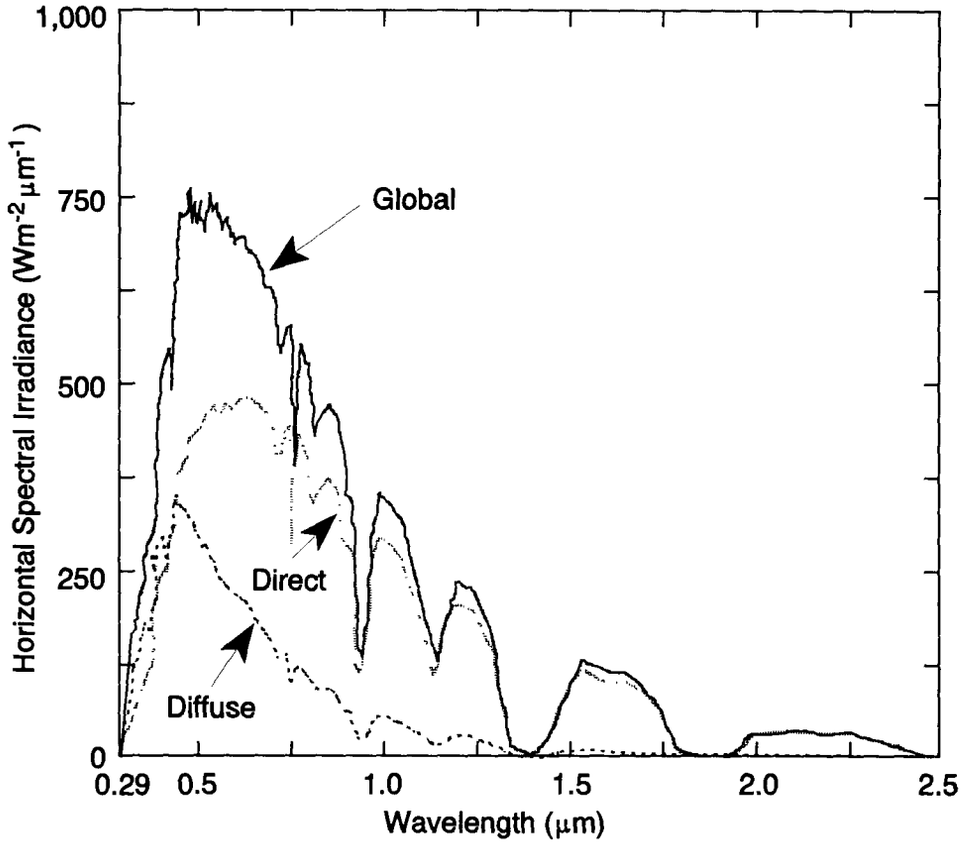

Figure 8-8. Global, direct, and diffuse spectral solar irradiance on a horizontal surface for a solar zenith angle of 60° and ground reflectance of 0.2. Atmospheric conditions are visibility, 28 km; water vapor, 2 ppt/cm.; ozone, 350 Dobson units.

Source: Iqbal (1983).

depths are much larger than the stratospheric optical depth and one would expect a more obvious diminution of global transmitted radiation than is shown here.

8.6.3.1 Modeling Aerosol Direct Solar Radiative Forcing

Some basic aspects of scattering and absorption by small particles typically present in aerosol layers govern the sign and magnitude of the direct radiative forcing by aerosols. The reflectance of an aerosol layer is chiefly determined by the optical depth, single scattering albedo $\tilde{\omega}$, and some measure of the scattering phase function. The $\tilde{\omega}$, is the ratio of the

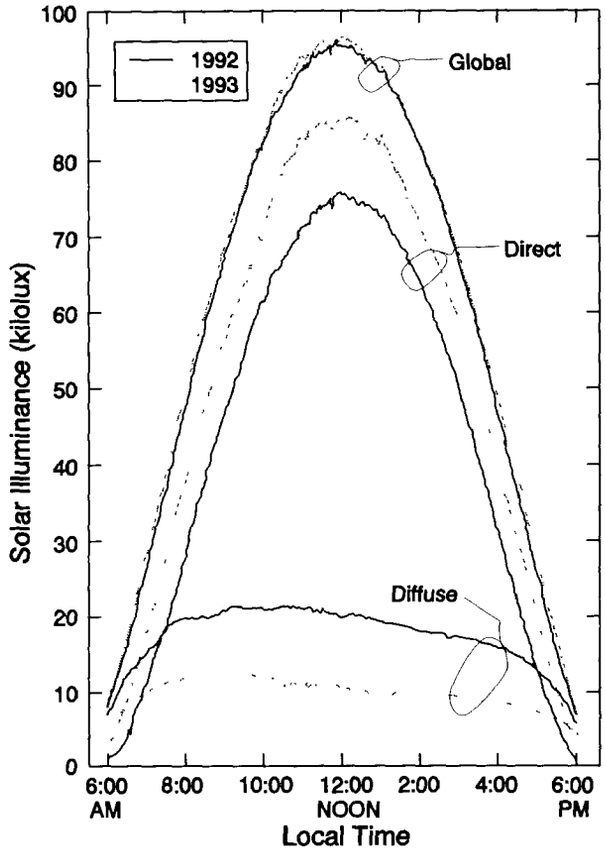

Figure 8-9. Surface measurements of direct, diffuse, and global solar radiation expressed as illuminance, at Albany, NY, on August 23, 1992, and August 26, 1993.

Source: Harrison and Michalsky (1994).

volume scattering coefficient, σ_s, to the volume extinction coefficient, σ_e, and is a measure of the absorptance of the aerosol layer. Related quantities are the specific extinction and scattering coefficients, ψ_e and ψ_s, which are defined as the coefficients per unit mass in units of m^2g^{-1}. The scattering phase function, $P(\Theta)$, determines the probability that incident radiation will scatter into a particular direction given by the scattering angle Θ measured from the forward direction of the incident radiation.

At visible wavelengths, the optical depth of tropospheric aerosols ranges from less than 0.05 in remote, pristine environments to about 1.0 near the source of copious emissions (Weller and Leiterer, 1988). The optical depth decreases quite rapidly with increasing wavelength if the layer is composed of fine particles as can be seen from Equation 8-1.

Aerosol layers, therefore, tend to be fairly transparent at thermal wavelengths and their radiative forcing is confined to solar wavelengths. Because there are strong water vapor absorption bands in the solar near-infrared (see Figure 8-8), the dominant effect of tropospheric aerosols is in the visible wavelengths. Harshvardhan (1993) has shown that, to first order, the change in the albedo with the addition of a thin aerosol layer over a surface of reflectance, R_s, is

$$\Delta R \approx R_a(1 - R_s)^2 - 2A_aR_s \qquad (8\text{-}6)$$

where R_a and A_a are the reflectance and absorptance, respectively, of the aerosol layer. The perturbation, ΔR, will be positive when

$$(1 - \tilde{\omega})/\tilde{\omega}\beta < (1 - R_s)^2/2R_s \qquad (8\text{-}7)$$

where β is the average backscatter fraction and can be computed from the scattering phase function. A positive value of ΔR implies a negative solar radiative forcing because the planetary albedo increases and less solar energy is absorbed by the earth-atmosphere system.

From Equation 8-7, it is obvious that the sign of the forcing will be determined to a large extent by $\tilde{\omega}$. At visible wavelengths, most constituents of tropospheric aerosols, with the exception of elemental carbon, are nonabsorbing and $\tilde{\omega} = 1.0$ (Bohren and Huffman, 1983) so that ΔR will be positive. Aerosols with absorbing components can be modeled as equivalent scatterers of refractive index, $m = n - ik$, with the imaginary index being a measure of particle absorption. Figure 8-10, from Harshvardhan (1993), shows the computed values of $\tilde{\omega}$ at a wavelength of 0.63 μm for single particles of varying radius. The three separate curves are for aerosols composed of carbon ($m = 2.0 - 0.64i$) and two models of sulfate aerosols containing absorptive components. Given the properties of an aerosol layer, ΔR can be computed from Equation 8-6. To calculate the radiative forcing, one must also include the effects of other atmospheric constituents such as molecular scattering, stratospheric O_3, water vapor absorption, and, most importantly, cloud cover.

8.6.3.2 Global Annual Mean Radiative Forcing

Charlson et al. (1991) calculated the global mean radiative forcing due to anthropogenic aerosols by making the following assumptions. They assumed that the perturbation would be exceedingly small over cloudy areas because cloud optical depths are one to two orders of magnitude greater than aerosol optical depths (Rossow and Schiffer, 1991). For nonabsorbing aerosols, they found that the change in planetary albedo could be expressed as

$$\Delta R_p \approx T^2_{atm} (1 - N_c) (1 - R_s^2) (2\beta\tau) \quad (8\text{-}8)$$

where T_{atm} is the transmittance of the atmosphere above the aerosol layer and N_c is the global mean cloud fraction. The planetary mean radiative forcing is then

$$\Delta F_R = \Delta R_p S_o/4 \quad (8\text{-}9)$$

where $S_o/4$ is the annual global mean insolation of the earth-atmosphere system (Hartmann, 1994) with S_o being the solar constant, which equal to 1,370 W m^{-2}. For generally accepted values of $T_{atm} = 0.71$, $N_c = 0.6$, $R_s = 0.15$ and $\beta = 0.3$, Charlson et al. (1991) obtained

$$\Delta F_R \approx 30.0\tau \quad (8\text{-}10)$$

such that for τ, the optical depth at visible wavelengths, ranging from 0.05 to 0.10, the direct solar radiative forcing is 1.5 to 3.0 W m^{-2}, a value comparable to the combined long-wave radiative forcing of several minor greenhouse gases (Section 8.6.2).

The above estimate was refined by Charlson et al. (1992) in which the anthropogenic sulfate aerosol burden was actually related to the source strength of anthropogenic sulfur dioxide (SO_2), the fractional yield of emitted SO_2 that reacts to produce sulfate aerosol and the sulfate lifetime in the atmosphere. The scattering properties of the sulfate aerosol were also modeled in terms of a relative humidity factor that accounts for the increase in particle size associated with deliquescent or hygroscopic accretion of water with increasing RH. The

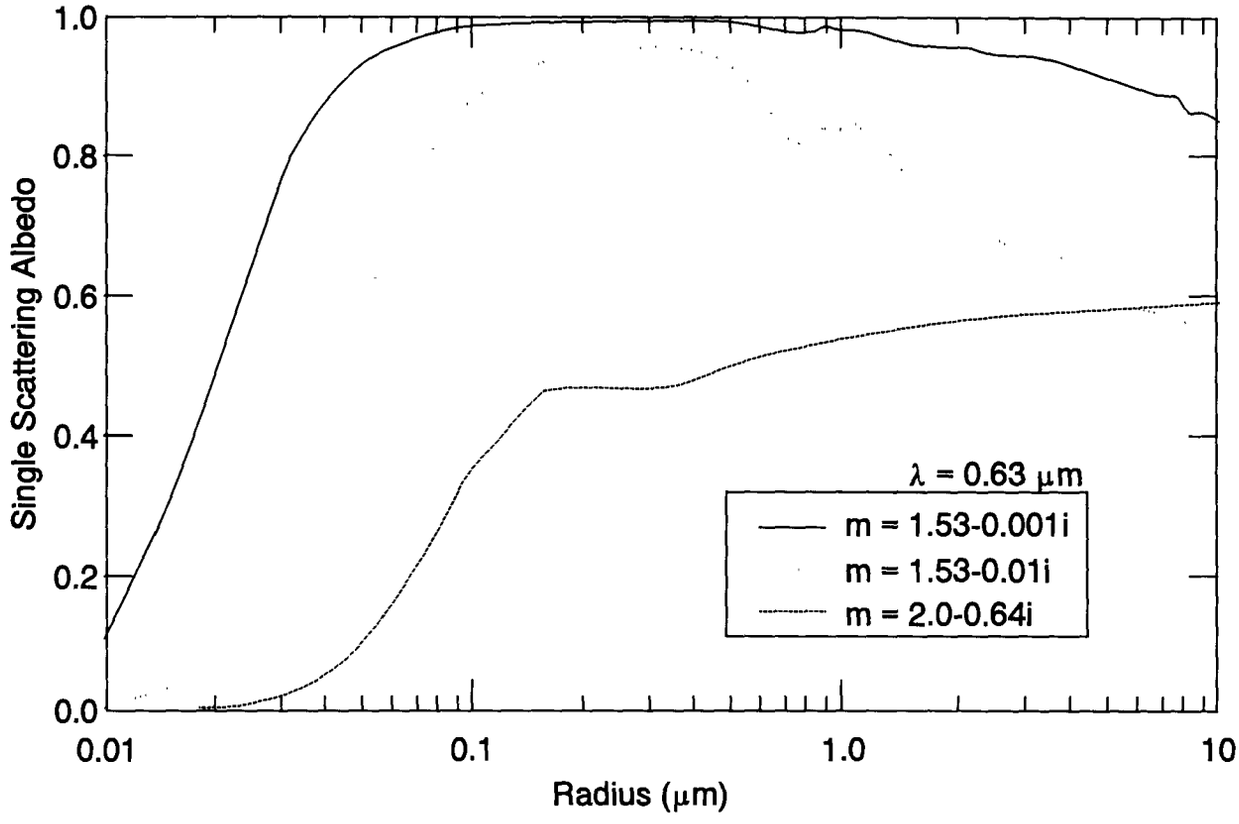

Figure 8-10. Single scattering albedo of monodispersed spherical aerosols of varying radius and three different refractive indices at a wavelength of 0.63 μm.

Source: Harshvardhan (1993).

relationship between optical depth and the areal mean column burden of anthropogenic sulfate aerosol, $B_{sulfate}$, is

$$\tau = \chi_{sulfate}\, f(RH)\, B_{sulfate} \qquad (8\text{-}11)$$

where $\chi_{sulfate}$ is the molar scattering cross section of sulfate at a reference low RH (30%) and f(RH) is the relative humidity factor. The sulfate burden, $B_{sulfate}$, is related to SO_2 emissions and sulfate lifetime. For an emission rate of 90×10^{12} g of sulfur per year, a yield fraction of 0.4, a sulfate lifetime of 0.02 years (7 days) and $\chi_{sulfate}$ of 500 $m^2 mol^{-1}$ (corresponding to a specific extinction coefficient, ψ_e, of 5 $m^2 g^{-1}$), Charlson et al. (1992) estimated that ΔF_R =

1.0 W m^{-2}, uncertain to a factor of 2 which perhaps should be more considering that the uncertainty in ψ_e alone is more than that (Hegg et al., 1993, 1994; Anderson et al., 1994).

The above is an estimate for the forcing due to industrial emissions. Another anthropogenic source of aerosols is biomass burning. Penner et al. (1992) have estimated that the radiative forcing due to this activity could be as much as 0.9 W m^{-2}, which is comparable to the sulfate forcing. One difference is that the smoke produced is somewhat absorbing and the atmosphere would experience a positive forcing of 0.5 W m^{-2}. Estimates of the global forcing due to biomass burning are even more uncertain than those for sulfate because of the sparsity of data on the relevant radiative properties of biomass aerosols.

8.6.4 Climate Response

8.6.4.1 Early Studies

Global Background Aerosols

The role of aerosols in modifying the earth's climate through solar radiative forcing has been a topic of discussion for many decades. Modeling studies assumed a climatological background distribution of aerosols such as that of Toon and Pollack (1976). Two simple types of climate models were used to calculate the effects of aerosols on climate: (1) the radiative-convective model, which resolves radiative perturbations in an atmospheric column, and (2) the energy balance model, which allows for latitudinal dependence, but parameterizes all processes in terms of the surface temperature. A typical study was that of Charlock and Sellers (1980) who used an enhanced one-dimensional radiative-convective model that included the effects of meridional heat transport and heat storage. The model was run with and without a prescribed aerosol layer of visible optical depth equal to 0.125 for conditions representative of 40° and 50° N latitude. The annual mean surface temperature with aerosols was 1.6 °C lower than that for the aerosol-free run.

Coakley et al. (1993) were the first to use an energy balance model to compute the latitudinally dependent radiative forcing for the Toon and Pollack (1976) aerosol distribution, including the effects of absorbing components. Even for moderately absorbing aerosols ($m = 1.5 - 0.01i$), the solar radiative forcing was negative, except in the 80° to 90° N latitude belt, which has a very high surface albedo. Here the criterion given by Equation 8-7 is not satisfied and the change in albedo, ΔR, is negative (i.e., the solar radiative forcing is

positive). The model results showed global mean surface temperature decreases ranging from 3.3 °C for nonabsorbing aerosols to 2.0 °C for the absorbing model. The maximum temperature drop was at polar latitudes even for the absorbing layer because advective processes responded to the aerosol-induced cooling at low- and middle-latitudes. Other two-dimensional model studies have confirmed this basic picture (Jung and Bach, 1987).

Regional and Seasonal Effects

Apart from global studies, there have been several programs devoted to ascertaining the effects of aerosols on regional and seasonal scales. An example is the radiative effect of aerosols in the Arctic (Rosen et al., 1981). A field experiment, the Arctic Gas and Aerosol Sampling Program, was conducted in 1983 (Schnell, 1984). It was determined that aerosols had a substantial absorbing component. The study by MacCracken et al. (1986) used both one- and two-dimensional climate models to evaluate the climatic effects. They found that the initial forcing of the surface-atmosphere system is positive for surface albedos greater than 0.17, and the equilibrium response of the one-dimensional radiative-convective model showed surface temperature increases of 8 °C. Infrared emission from the warmer atmosphere was found to be an important forcing agent of the surface. The two-dimensional model was run through the seasonal cycle and had an interactive cryosphere. Peak warming occurred in May, a month later than the peak radiative forcing, as a result of earlier snow melt.

Massive Aerosol Loads

In the 1980s, there were several studies related to what became known as the "nuclear winter" phenomenon (Turco et al., 1983) (i.e., the climatic consequences of widespread nuclear war). Modeling efforts ranged from radiative-convective models (Cess et al., 1985) to three-dimensional general circulation models (Thompson et al., 1987; Ghan et al., 1988), and mesoscale models (Giorgi and Visconti, 1989) with interactive smoke generation and removal processes and fairly detailed smoke optics. A review of modeling efforts has been made by Schneider and Thompson (1988) and Turco et al. (1990). The latter study summarized the best estimates of possible reduction in surface temperature from the smoke lofted into the atmosphere during the initial acute phase.

General Circulation Model (GCM) studies (Thompson et al., 1987; Ghan et al., 1988) indicate that for a July smoke injection, the average land temperatures over the latitude zone from 30° to 70° N, over a 5-day period, would decrease by 5 °C for smoke of optical depth equal to 0.3, but could decrease by 22 °C for large loadings of optical depth equal to 3. However, the temperature in the interior of land masses could drop by as much as 30 °C. The temperature perturbations for smoke injections in other seasons are smaller. At lower latitudes, the cooling is moderated by the delay in smoke transport (assuming initial injection in high northern latitudes), and the more humid climate. Model studies also indicate a dramatic decrease in rainfall over land and a failure of the Asian monsoon (Ghan et al., 1988).

8.6.4.2 Recent Regional Studies

There have been more recent studies of possible climatic effects resulting from severe aerosol loading on regional scales. The Arctic haze problem has been investigated extensively. Blanchet (1989, 1991), using a GCM, studied the effects of increasing aerosol loads north of 60° N. Although the solar heating rate in the troposphere increased quite dramatically, the temperature did not rise substantially. The positive forcing of 0.1 to 0.3 $Kday^{-1}$ resulted in a decrease in the meridional heat flux. Quite importantly, the simulated cloud cover in the experiment was altered sufficiently to produce that the changes of an order of magnitude greater in net radiative fluxes at the top were locally an order of magnitude greater than the initial forcing. This implies that it may be very difficult to identify climate change effects due to aerosols alone. Another effect of aerosols at high latitudes that has the potential for affecting climate is the change in surface albedo due to deposition of soot. This was studied with respect to the nuclear winter problem by Vogelmann et al. (1988). They found that the cooling due to smoke aerosol could be moderated somewhat by the "dirty" snow at very high latitudes.

Several studies have examined the effect of smoke from forest fires on climate. Since these are natural phenomena, it is important to understand their effects in order to place anthropogenic effects in context. Evidence of substantial climatic effects is present only when the smoke loading is substantial. For example, Robock (1988) examined the situation in northern California where a subsidence inversion trapped smoke in mountain valleys for

several days in September 1987. One station recorded an anomaly in the maximum temperature of −20 °C. Veltischev et al. (1988) analyzed data covering the period of major historical fires in Siberia, Europe, and Canada. They estimated that the optical depth of smoke following fires in Siberia in 1915 was about 3.0 and surface temperature dropped by 5 °C.

Other studies have also shown a relationship between smoke and surface temperature. Robock (1991) studied the smoke from Canadian fires in July 1982. He compared forecasted temperatures with observations and found that regions of negative anomaly were well correlated with the smoke layer. Westphal and Toon (1991) used a mesoscale model with interactive smoke physics and optics to simulate the smoke plume and its meteorological effects. They calculated the albedo of the smoke-covered area to be 35%, and the resulting surface cooling was 5 °C.

Perhaps the most extensive recent investigation of the possible climatic effects of heavy aerosol burdens was the study of the Kuwait oil fires in 1991. Several modeling studies were undertaken. Browning et al. (1991) simulated the smoke plume with a long-range dispersion model and concluded that the smoke would remain in the troposphere and not be lofted into the stratosphere where the residence time would be much longer. They estimated a maximum temperature drop of 10 °C beneath the plume, within about 200 km (i.e., only a regional, not global climatic effect). Bakan et al. (1991) used a GCM with an interactive tracer model to simulate the plume dispersion and climatic effects. The maximum temperature drop was estimated to be about 4 °C near the source. The local and regional nature of the effect was confirmed during a field experiment undertaken in May/June, 1991. The smoke from the oil fires had insignificant global effects because (1) particle emissions were less than expected, (2) the smoke was not as black as expected, (3) the smoke was not carried high in the atmosphere, and (4) the smoke had a short atmospheric residence time (Hobbs and Radke, 1992).

The study of severe events such as those described above is useful for investigating model response since such strong forcings usually provide unambiguous climate response signals. The simulated climate response to the more modest radiative forcing due to the distribution of natural and usual anthropogenic sulfate or smoke aerosols is well within the internal model variability. However, an estimate of the magnitude of possible effects can be

obtained by model simulations that integrate the chemistry, optics, and meteorology of anthropogenic aerosols.

8.6.4.3 Integrated Global Studies

Ideally, one should study the problem in an integrated manner, in which the emissions of sulfate precursors are tracked globally and the radiative forcing of the resulting aerosols computed locally in space and time. A further step would be to let the radiative response impact climate interactively. This latter step could be carried out by a GCM coupled to an oceanic model. Recent studies have accomplished various elements in this scenario.

Global three-dimensional models of the tropospheric sulfur cycle treat emission, transport, chemistry and removal processes for natural and anthropogenic sources. The primary natural source is dimethylsulfide (DMS), which is released by oceanic phytoplankton (Nguyen et al., 1983; Shaw, 1983; Charlson et al., 1987). The DMS reacts in air to form sulfate aerosols. Anthropogenic emissions are over land, especially in the heavily industrialized areas of the Northern Hemisphere. Examples of such sulfur cycle models are the Lagrangian model of Walton et al. (1988) and Erickson et al. (1991), known as the GRANTOUR model, and the Eulerian transport model of Langner and Rodhe (1991) and Langner et al. (1992), known as the MOGUNTIA model. Both models use prescribed mean winds, typically obtained from GCM simulations, to provide monthly mean concentrations of sulfate aerosols.

With such detailed input, it is possible to construct global maps of the radiative forcing due to sulfate and compare the magnitude with that due to greenhouse gases. Kiehl and Briegleb (1993) carried out such a study using the monthly mean sulfate abundances from the MOGUNTIA model. For meteorological parameters, they used monthly mean 1989 analyzed temperature and moisture fields from the European Center for Medium Range Weather Forecasting. Vertical distributions of clouds were taken from a GCM simulation using the National Center for Atmospheric Research Community Climate Model (CCM2) since such detailed observations are lacking. However, attempts were made to adjust the total cloud cover to correspond to observations.

The radiative forcing was calculated by Kiehl and Briegleb using an 18-band δ-Eddington model in the shortwave and a 100 cm^{-1} resolution band model in the longwave,

which includes the contributions due to trace gases such as CH_4, nitrogen dioxide (NO_2), and chlorofluorocarbons. The optical properties of sulfate aerosol were calculated spectrally using the refractive indices for 75% sulfuric acid (H_2SO_4) and 25% water (H_2O) and an assumed log-normal size distribution that has a geometric mean diameter by volume of 0.42 μm. The specific extinction, ψ_e, of the dry particles was found to be a very strong function of wavelength, decreasing from 10 m^2g^{-1} at 0.3 μm to less than 2.0 m^2g^{-1} at 1.0 μm. This is significant in interpreting the computed forcing when comparisons are made with earlier studies that used a constant value of ψ_e.

The direct radiative forcing is calculated by adding the sulfate burden to the model and computing the change in absorbed solar radiation. Figures 8-11a and 8-11b, from Kiehl and Briegleb (1993) show the annual mean direct solar radiative forcing resulting from anthropogenic sulfate aerosols (global mean = -0.28 W m^{-2}) and anthropogenic plus natural sulfate (global mean = -0.54 W m^{-2}). The patterns are similar to those obtained earlier by Charlson et al. (1991), but the magnitude is roughly half. Most of the difference is due to the assumption of a constant value of 5.0 m^2g^{-1} for ψ_e in the earlier study, but there was also a difference in the scattering phase function used. Therefore, assumptions regarding radiative properties were able to account for all the differences. Points to note in the figure are the local concentrations of anthropogenic forcing and particularly the hemispheric asymmetry in the forcing, even when natural sulfate is included. Although the southern hemisphere is largely ocean, the direct forcing due to natural sulfate is substantial only in the clear oceanic areas since, in the presence of clouds, the additional sulfate effect is minimal.

To place the role of anthropogenic sulfate in perspective, Kiehl and Briegleb (1993) compared the direct radiative forcing with that of increasing greenhouse gases from preindustrial times to the present. The greenhouse gas forcing is calculated by computing the spatial distribution of the change in the net longwave flux at the tropopause for the trace gas increases from the preindustrial period to the present. The annual averaged results for greenhouse gases alone and in combination with anthropogenic sulfate are shown in Figure 8-12a and 8-12b, respectively. The greenhouse gas forcing is, of course, positive and is the greatest in the clear regions over the land and oceanic deserts. The global annual mean is 2.1 Wm^{-2}. When the negative forcing of aerosols is added, the global annual mean direct

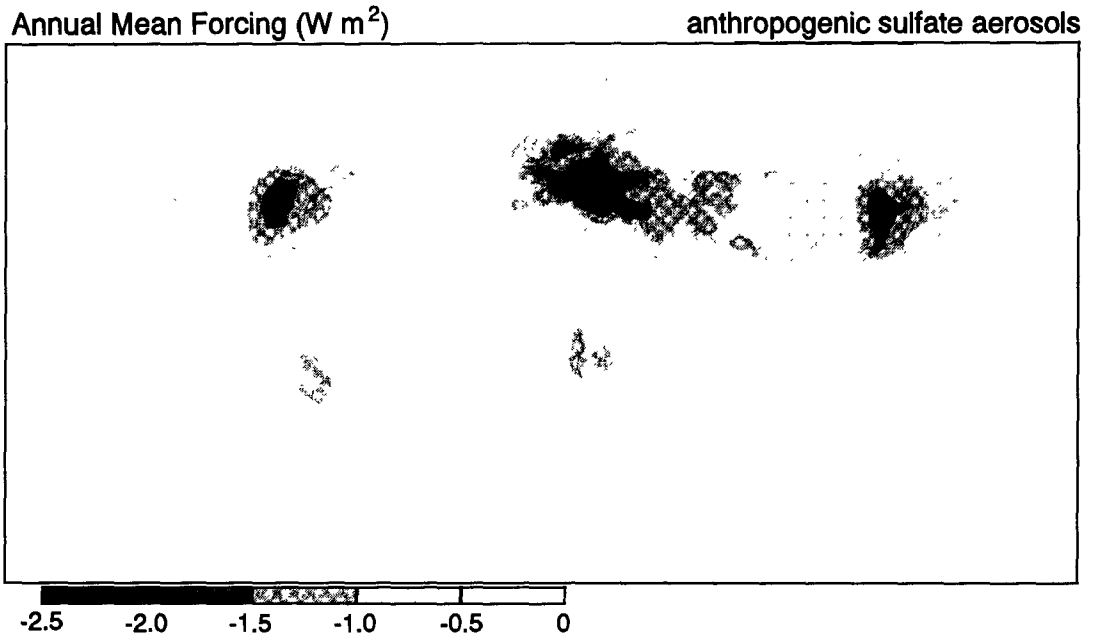

Figure 8-11a. Annual mean direct radiative forcing (W m^{-2}) resulting from anthropogenic sulfate aerosols.

Source: Kiehl and Briegleb (1993).

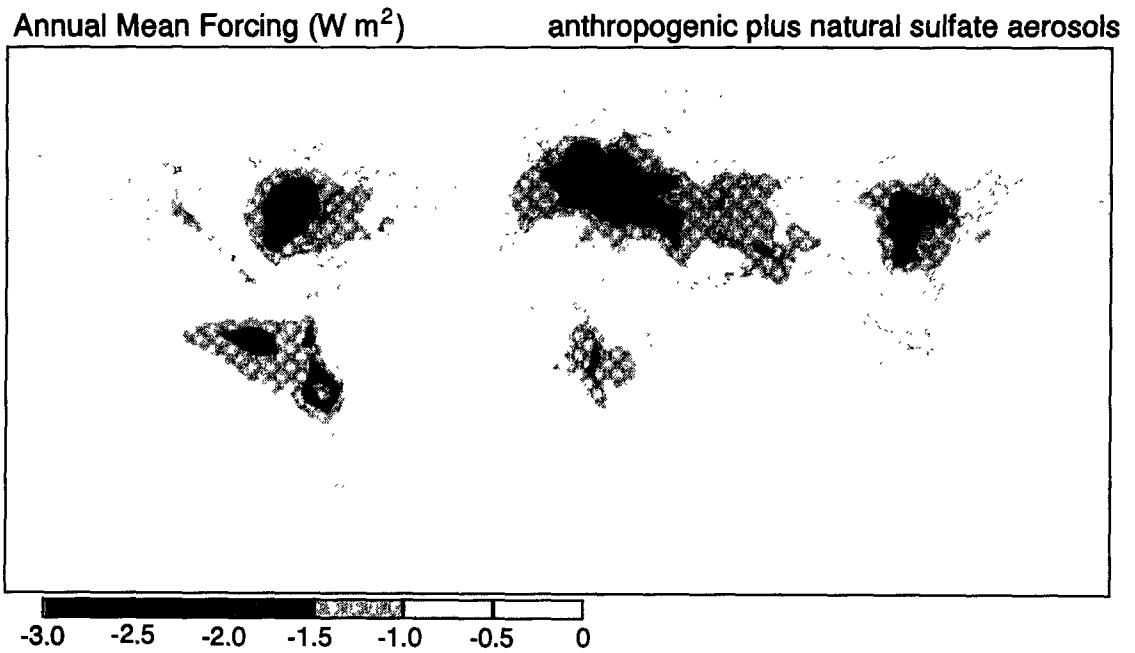

Figure 8-11b. Annual mean direct radiative forcing (W m^{-2}) resulting from anthropogenic and natural sulfate aerosols.

Source: Kiehl and Briegleb (1993).

radiative forcing due to anthropogenic activities is 1.8 W m^{-2}. However, locally, there are regions where the anthropogenic sulfate forcing cancels the greenhouse forcing.

The forcing is simply an initial perturbation. One is actually interested in the climate response. Because the sulfate forcing is in the shortwave and felt primarily at the surface (for nonabsorbing aerosols), a coupled atmospheric-oceanic climate model is required. Taylor and Penner (1994) have used the GRANTOUR model to provide the sulfate input to a GCM (CCM1), which was coupled to a 50 m mixed-layer ocean model with sea ice and specified meridional oceanic heat flux.

To assess the anticipated patterns of climate response to anthropogenic emissions of both SO_2 and CO_2, Taylor and Penner performed four 20-simulated-year integrations in which the atmospheric CO_2 concentration was fixed at either the preindustrial level (275 ppm) or the present day concentration (345 ppm). Anthropogenic sulfur emissions, corresponding to 1980, were either included or excluded. Table 8-6 summarizes their annual average results. The global average anthropogenic sulfate forcing was found to be -0.95 W m^{-2}; more than three times larger than calculated by Kiehl and Briegleb (1993). The differences in the annual anthropogenic sulfate forcing value in the two studies is due partially to the sulfate chemistry in the model used by Taylor and Penner, (1994). For example, there is a stronger seasonal cycle with enhanced northern hemisphere concentrations in summer. The remainder may be contributed to the use of a constant specific scattering coefficient (8.5 m^2g^{-1} at 0.55 μm) instead of the RH dependent model used by Kiehl and Briegleb, (1993). As noted earlier, the value of ψ_s chosen could be a gross overestimate and, therefore the values of the sulfate forcing shown in Table 8-6 are probably much too high.

Some noteworthy features of Table 8-1 are that the combined CO_2 and sulfate forcing is not linearly additive and there is a pronounced asymmetry in the climate response in the two hemispheres. What is clear is that the anthropogenic sulfate is expected to reduce somewhat the anticipated warming resulting from the increased emission of greenhouse gases, especially in the northern hemisphere. On a regional scale, Taylor and Penner (1994) found that the strongest response was in the polar regions associated with an increase in sea ice. Note that the change in sea ice coverage (ΔSI), in the northern hemisphere is essentially zero as the

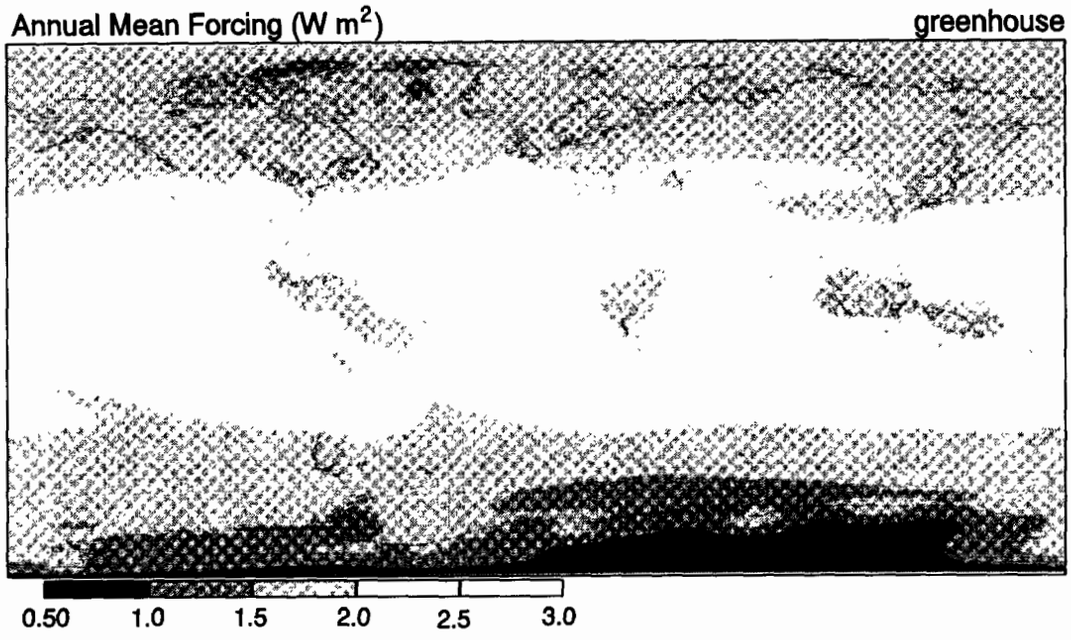

Figure 8-12a. Annual averaged greenhouse gas radiative forcing (W m^{-2}) from increases in CO_2, CH_4, N_2O, CFC-11, and CFC-12 from preindustrial time to the present.

Source: Kiehl and Briegleb (1993).

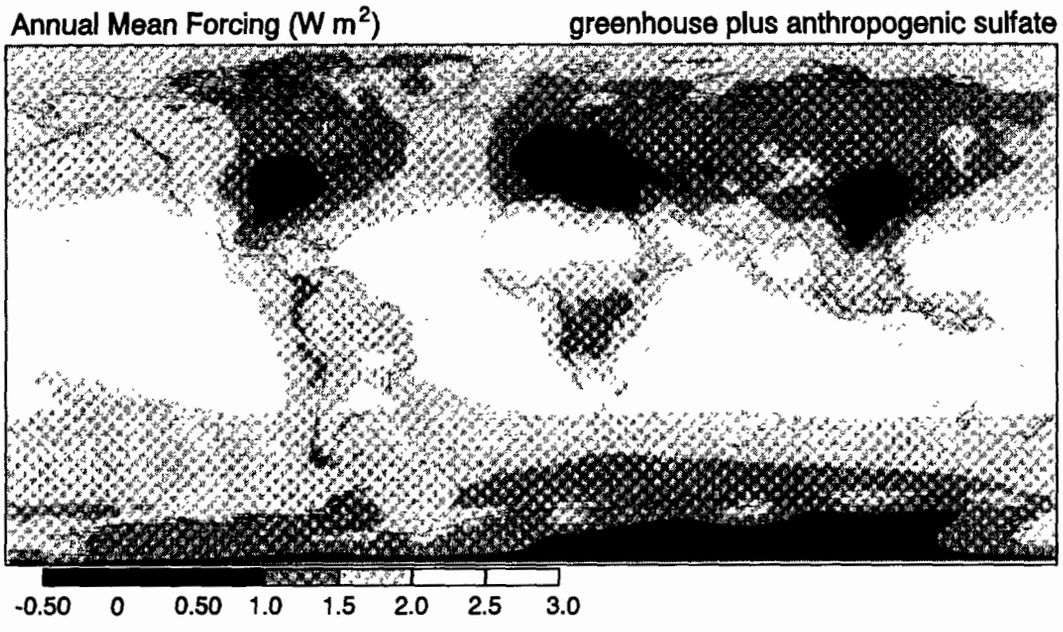

Figure 8-12b. Annual averaged greenhouse gas forcing plus anthropogenic sulfate aerosol forcing (W m^{-2}).

Source: Kiehl and Briegleb (1993).

TABLE 8-6. RADIATIVE FORCING AND CLIMATE STATISTICS

Case	ΔF (W m^{-2})	T_s (°C)	ΔT_s (°C)	P (mm d^{-1})	ΔP (mm d^{-1})	C (%)	ΔC (%)	SI (%)	ΔSI (%)
Northern Hemisphere									
Preindustrial		12.5		3.40		56.6		4.87	
Present-day CO_2	1.26	14.5	1.9	3.48	0.09	55.0	-1.7	4.13	-0.74
Present-day sulfate	-1.60	11.3	-1.2	3.36	-0.04	56.9	0.3	5.54	0.67
Combined CO_2 and sulfate	-0.34	13.0	0.5	3.43	0.03	55.8	-0.9	4.85	-0.02
Observed climate statistics		14.9		2.6		58.9		4.4	
Southern Hemisphere									
Preindustrial		12.5		3.54		62.4		6.64	
Present-day CO_2	1.25	14.8	2.3	3.61	0.08	61.1	-1.3	4.39	-2.26
Present-day sulfate	-0.30	11.7	-0.8	3.48	-0.06	63.1	0.7	7.24	0.59
Combined CO_2 and sulfate	0.95	13.6	1.1	3.56	0.02	62.1	-0.3	5.40	-1.24
Observed climate statistics		13.5		2.7		65.6		4.5	
Global average									
Preindustrial		12.5		3.47		59.5		5.76	
Present-day CO_2	1.26	14.6	2.1	3.55	0.08	58.0	-1.5	4.26	-1.50
Present-day sulfate	-0.95	11.5	-1.0	3.42	-0.05	60.0	0.5	6.39	0.63
Combined CO_2 and sulfate	0.31	13.3	0.8	3.49	0.02	58.9	-0.6	5.13	-0.63
Observed climate statistics		14.2		2.7		62.2		4.5	

ΔF = radiative forcing; T_s = surface temperature; P = precipitation; C = cloud cover; SI = sea ice coverage.

Source: Taylor and Penner (1994).

sulfate completely cancels the CO_2 effect. Also, the greatest cooling is found over broad regions of the northern hemisphere continents where all the sulfur emission is occurring. However, the maximum cooling is not over Europe where the maximum radiative forcing occurs, but further north, and associated with changes in sea ice.

Comparative Lifetimes of the Forcing

One extremely important aspect in comparing the effects of CO_2 and sulfur emissions is the disparate lifetimes of the forcing mechanisms. The residence times of trace gases that result in a positive longwave forcing of the climate system is from decades to a century or more (Intergovernmental Panel on Climate Change, 1990). On the other hand, the cycling time for sulfate in the troposphere is only about a week (Langner and Rodhe, 1991), which is dependent on the frequency precipitation removal (Charlson et al., 1992). Therefore, any changes in industrial emission patterns will be reflected immediately in the sulfate forcing, but the concentration of CO_2 and the accompanying forcing will continue to rise for more than century even if emissions were kept constant at present levels. See Figure 8-13.

One could infer from the above discussion that sulfate emissions are providing some amelioration of greenhouse warming, and that a curtailment of such emissions might result in enhanced global warming. However, given the uncertainties in present estimates of the effects of aerosols, especially the fact that many feedbacks are not fully included, it would bepremature to base any decisions on these current discussions of the possible effects of aerosols on climate. The detrimentalhealth effects of aerosols (and trace gases) covered elsewhere in this report are far more definite and should certainly take precedence in formulating regulatory policy.

8.6.5 Aerosol Effects on Clouds and Precipitation

8.6.5.1Indirect Solar Radiative Forcing

Cloud Microphysical Properties

A substantial portion of the solar energy reflected back to space by the earth system is due to clouds. The albedo (i.e., reflectivity) of clouds, in turn, depends to a large extent on the optical thickness, which is the column integrated extinction coefficient (see Section 8.6.3) The extinction coefficient is related to the size distribution and number concentration

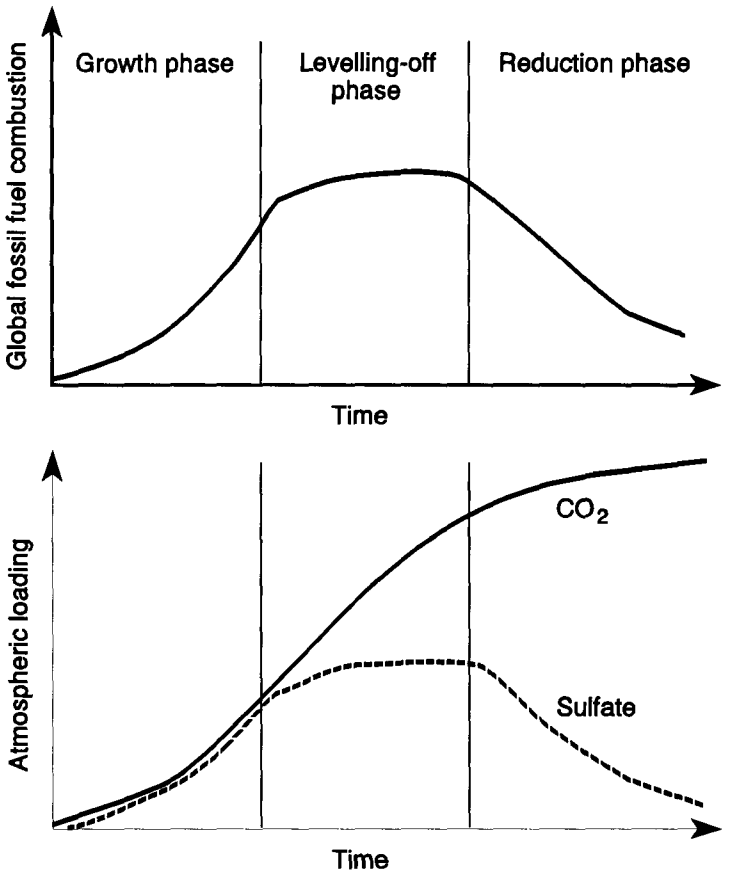

Figure 8-13. Schematic illustration of the difference between response times of climate forcing due to CO_2 (heating) and sulfate (cooling) during different patterns of global fossil fuel consumption.

Source: Charlson et al. (1991)

of cloud droplets. Because these cloud droplets nucleate on aerosols, it is to be expected that changes in aerosol loading could affect cloud albedo, particularly that marine stratiform clouds. Because of their effect on the earth's radiative energy budget, marine status and stratocumulus cloud systems are likely to influence climate and climate change. Their high albedo compared with ocean background provide a large negative shortwave forcing which is not compensated in thermal wavelengths because of their low altitude (Randall et al., 1984).

Stephens (1994) gave the volume extinction coefficient of a cloud of spherical polydispersed drops ranging in size as:

$$\sigma_e = \pi \int_{r_{min}}^{r_{max}} n(r) Q_{ext}\,(r) r^2 dr \qquad (8\text{-}12)$$

where n(r) represents the size distribution and is the number concentration per unit volume per unit radius increment and Q_{ext} is the extinction efficiency which approaches the value of 2.0 for drops that are large relative to the wavelength. At visible wavelengths, this limit for Q_{ext} is satisfied by cloud drops that are typically 10 μm in radius. Therefore,

$$\sigma_e \propto \int_{r_{min}}^{r_{max}} n(r) r^2 dr \qquad (8\text{-}13)$$

The mass (m) concentration of water in clouds, called the liquid water content, M (in kg^{-3}), is proportional to the total volume of liquid water in a unit volume of air. This may be written as

$$M \propto \int_{r_{min}}^{r_{max}} n(r) r^3 dr \qquad (8\text{-}14)$$

because the volume of each cloud drop is (4/3) π r^3. Comparing Equations 8-13 and 8-14, one can see that

$$\sigma_e \propto M/r_e \qquad (8\text{-}15)$$

where r_e is the effective radius, defined as the ratio

$$r_e = \frac{\int_{r_{min}}^{r_{max}} n(r) r^3 dr}{\int_{r_{min}}^{r_{max}} n(r) r^2 dr} \qquad (8\text{-}16)$$

For identical meteorological conditions, the liquid water content will be the same in two cloud layers that are composed of droplets of different effective radius. If other paramters remain the same, σ_e will increase as r_e decreases (Equation 8-15). Therefore, if the

geometric depth of two cloud layers is the same and the column amount of liquid water is the same, the cloud with more numerous, but smaller drops, will have a larger optical depth and a higher albedo. This sets the stage for a potentially important indirect effect of anthropogenic aerosols on the Earth's radiation balance. As suggested by Twomey (1974), the addition of cloud nuclei by pollution can lead to an increase in the solar radiation reflected by clouds, a negative radiative forcing that is in addition to the direct radiative forcing discussed in Section 8.6.3.

Another radiative consequence of pollution is the emission of elemental carbon, which can be incorporated into clouds and increase the absorptance at visible wavelengths at which pure water is nonabsorbing. This mechanism decreases the single scattering albedo of the cloud material (see Figure 8-10), causing a decrease in the reflectance of the layer. There are, therefore, two competing mechanisms, but Twomey et al. (1984) assessed the relative magnitudes of the two effects based on observations of clean and polluted air in Arizona, and concluded that increases in albedo from increases in cloud droplet concentration would dominate over the absorption effect.

Cloud Lifetimes

Another possible indirect effect of increased cloud condensation nuclei (CCN) is the inhibition of precipitation (Albrecht, 1989; Twomey, 1991). With more droplets, coagulative growth, which is the mechanism of water removal in liquid water clouds, will be hindered. This will result in longer residence times for clouds and a higher mean albedo time, which, again, is an indirect negative solar radiative forcing.

Cloud Chemistry

Novakov and Penner (1993) pointed out that anthropogenic activity could modify the nucleating properties of anthropogenic sulfate. It has already been mentioned that carbon black influences the direct radiative forcing. The presence of carbon black and other organics can also alter the hygroscopic properties of sulfate aerosol. For instance, the condensation of hydrophobic organics onto preexisting sulfate particles may render these inactive as CCN. On the other hand, the condensation of sulfuric acid vapor on a hydrophobic organic aerosol may convert it to a hydrophilic particle. Because the indirect

radiative forcing depends on the ability of sulfate to nucleate, organics may enhance or diminish the potential indirect radiative forcing.

8.6.5.2 Observational Evidence

The relationship between the availability of (CCN) and cloud droplet size distribution has been a subject of research in cloud physics for decades. It has been known, for instance, that continental clouds are composed of far more numerous, but smaller drops than maritime clouds (Wallace and Hobbs, 1977). The more difficult question is whether the additional contribution to CCN by anthropogenic activities has increased the reflectance of clouds over large areas of the Earth. If so, this would be an additional indirect radiative forcing attributable to sulfate emissions.

The most dramatic evidence of such an indirect effect (albeit on a small scale) is the observation of "ship tracks" in marine stratocumulus (Conover, 1966; Coakley et al., 1987). These are visible in satellite images as white lines against a gray background and follow the path of ships that have been emitting effluents. King et al. (1993) reported the first radiation and microphysics measurements on ship tracks obtained from a research aircraft as it flew within marine stratocumulus clouds off California. Comparing the flight track with satellite images, they were able to locate two distinct ship tracks in which they measured enhanced droplet concentration, and liquid water contents, greater than in the surrounding clouds. They also derived the effective radius of the cloud drops and found that there was a significant decrease within the ship tracks. The radiation measurements were consistent with increased optical depths in the ship tracks. The increased liquid water content is compatible with the suppression of drizzle as a result of slower coagulative growth (Albrecht, 1989), an indirect aerosol effect.

Twomey (1991) estimated that the visible reflectance of clouds, R, is affected by cloud droplet concentration, N, according to the following relationship for a fixed liquid water content, M.

$$\left[\frac{dR}{dN}\right]_M = \frac{R(1-R)}{3N} \qquad (8\text{-}17)$$

The parameter, *dR/dN*, the susceptibility, is a measure of the sensitivity of cloud reflectance to changes in microphysics (Platnick and Twomey, 1994). It has a maximum value at $R = 0.5$ and is inversely proportional to N such that when N is low as in marine clouds, the susceptibility is high. It is, therefore, not surprising that emissions from ships can influence cloud albedo.

To determine whether the indirect effect of aerosols on clouds is detectable on a global scale, Schwartz (1988) compared cloud albedos in the two hemispheres and also historic changes in surface temperature from preindustrial times. The sulfate signal is expected in both: cloud albedos in the Northern Hemisphere should be higher, and the rate of greenhouse warming should be slower. The results of his study were inconclusive in that no inter-hemispheric differences were found.

However, more recent studies suggest some influence of sulfate emissions. Falkowski et al. (1992) showed that cloud albedos in the central North Atlantic Ocean, far from continental emission sources, were well correlated with chlorophyll in surface waters. These correspond to higher ocean productivity and DMS emissions, indicating that natural sources of sulfate emission can influence cloud albedo. More substantial evidence of the effect of sulfate aerosol has been presented by Han et al. (1994) who made a near-global survey of the effective droplet radii in liquid water clouds by inverting satellite visible radiances obtained from advanced very-high-resolution radiometer (AVHRR) measurements. Han et al. (1994) found systematic differences between the effective radius of continental clouds (global mean $r_e = 8.5$ μm) and maritime clouds (global mean $r_e = 11.8$ μm), which is the expected result based on differences in CCN concentrations. In addition, they found inter-hemispheric differences in r_e over both land and ocean. Northern Hemisphere clouds had smaller effective radii, the difference being 0.4 μm for ocean and 0.8 μm for land. However, Southern Hemisphere clouds tended to be optically thicker, which explains why Schwartz (1988) was unable to detect inter-hemispheric albedo differences.

8.6.5.3 Modeling Indirect Aerosol Forcing

If the appropriate radiative properties of aerosols are known, it is fairly straightforward to model the direct solar radiative forcing of aerosols (Section 8.6.3) and estimate possible climatic responses (Section 8.6.4). Calculations of the indirect forcing of aerosols, on the

other hand, is much more difficult since several steps are involved and the uncertainty at each level is high. Charlson et al. (1992) proposed that enhancements in albedo would occur only for marine stratocumulus clouds and for a uniform global increase of droplet concentration of 15% in only these clouds, the global mean solar radiative forcing would be -1.0 W m^{-2}, which is comparable to the direct forcing (Section 8.6.4) and of the same sign. The greatest uncertainty in this estimate is the degree that cloud droplet number concentration is enhanced by increasing emissions. The uncertainty has been estimated by Kaufman et al. (1991) to be at least a factor of 2. Leaitch and Isaac (1994) have addressed this issue based on their observations of the relationship between cloud droplet concentrations and cloud water sulfate concentrations. They find that the assumptions in Kaufman et al. (1991) are within reasonable bounds. The Scientific Steering Committee for the International Global Aerosol Program concluded that the uncertainties involved in determining the indirect effects of aerosols on the Earth's radiation balance are so great that no formal value can be given at this time (Hobbs, 1994).

The indirect forcing has been included in climate model simulations by Kaufman and Chou (1993) who used a zonally averaged multilayer energy balance model and by Jones et al. (1994) who used a GCM. Kaufman and Chou (1993) modeled the competing effects of enhanced anthropogenic emissions of CO_2 and SO_2 since preindustrial times. They concluded that SO_2 has the potential of offsetting CO_2-induced warming by 60% for present conditions and 25% by the year 2060 given the Intergovernmental Panel on Climate Change BAU (business as usual) scenario of industrial growth (Intergovernmental Panel on Climate Change, 1990). They also found a small inter-hemispheric difference in climate response, with the Northern Hemisphere cooler than Southern Hemisphere by about -0.2 °C.

Jones et al. (1994) used a GCM with a prognostic cloud scheme and a parameterization of the effective radius of cloud water droplets that links effective radius to cloud type, aerosol concentration and liquid water content. The parameterization is based on extensive aircraft measurements. The distribution of column sulfate mass loading was obtained from the model of Langner and Rodhe (1991) separately for natural and anthropogenic sources. Simulated effective radius, r_e, distributions of low-level clouds showed land-ocean contrasts and also inter-hemispheric differences as observed by Han et al. (1994). The indirect forcing due to anthropogenic sulfate was estimated by performing a series of single-timestep

calculations with the GCM. For present conditions, the mean Northern Hemisphere forcing was calculated to be -1.54 W m^{-2} and the southern Hemisphere forcing was -0.97 W m^{-2}. This is comparable to the estimates of Charlson et al. (1992) and Kaufman and Chou (1993) and substantially larger than the direct forcing estimates of Kiehl and Briegleb (1993). The combined direct and indirect forcing is more than half the total positive forcing of greenhouse gas emissions. It should be noted that the indirect effect is greatest when the atmosphere is very clean and so, in principle, could saturate with time. The direct effect is linear with emissions and may dominate in the future. In any case, the negative forcing of sulfate aerosol must be considered in any overall estimate of the total anthropogenic effect on climate.

8.7 SUMMARY

Traditionally, visibility has been defined in terms of the distance from an object that is necessary to produce a minimum detectable contrast between that object and its background. Although visibility is often defined by this "visual range," it includes not only being able to see or not see a target, but also seeing targets at shorter distances and appreciating the details of the target, including its colors. Visibility impairment can manifest itself in two ways: (1) as a layer of haze (or a plume), which is visible because it has a visual discontinuity between itself and its background, or (2) as a uniform haze which reduces atmospheric clarity. The type and degree of impairment are determined by the distribution, concentrations, and characteristics of atmospheric particles and gases, which scatter and absorb light traveling through the atmosphere. Scattering and absorption determine light extinction.

On a regional scale, the extinction of light is generally dominated by particle scattering. In urban areas, absorption by particles becomes important and occasionally dominant. Extinction by particles is usually dominated by particles of diameter 0.1 to 2 μm (fine particles). In general, scattering by particles accounts for 50 to 95% of extinction, depending on location, with urban sites in the 50 to 80% range and nonurban sites in the 80 to 95% range.

The currently available visibility monitoring methods measure different aspects of visibility impairment. Generally, contrast-type measurements (such as photography, telephoto-

metry, and human eye observations) relate well to the perception of visual air quality, while extinction or scattering measurements (such as transmissometry and nephelometry) relate to the cause of visibility degradation. Each of the above measurement methods can be used to approximate visual range.

Current knowledge indicates that fine particulate matter is composed of varying amounts of sulfate, ammonium, and nitrate ions, elemental carbon, organic carbon compounds, water, and smaller amounts of soil dust, lead compounds, and trace species. Sulfate often dominates the fine mass and light scattering, while elemental carbon is sometimes the primary visibility-reducing species. Ammonium ion is typically found to account for 5 to 15% of the fine mass and often correlates well with sulfate levels. Data indicate that mean nitrate concentrations can represent up to 37% of the total fine particle mass in urban cities.

Visibility has value to individual economic agents primarily through its impact upon activities of consumers and producers. Most economic studies of the effects of air pollution on visibility have focused on the aesthetic effects to the individual, which are, at this time, believed to be the most significant economic impacts of visibility degradation caused by air pollution in the U.S. It is well established that people notice those changes in visibility conditions that are significant enough to be perceptible to the human observer, and that visibility conditions affect the well-being of individuals.

Welfare economics defines a dollar measure of the change in individual well-being (referred to as utility) that results from the change in the quality of any public good, such as visibility, as the change in income that would cause the same change in well-being as that caused by the change in the quality of the public good. One way of defining this measure of value is to determine the maximum amount the individual would be willing to pay to obtain improvements or prevent degradation in the public good. Two economic valuation techniques have been used to estimate willingness to pay for changes in visibility: (1) the contingent valuation method, and (2) the hedonic property value method. Both methods have important limitations, and uncertainties exist in the available results. Recognizing these uncertainties is important, but the body of evidence as a whole suggests that economic values for changes in visibility conditions are probably substantial in some cases, and that a sense of the likely magnitude of these values can be derived from available results in some instances.

Economic studies have estimated values for two types of visibility effects potentially related to particulate air pollution: (1) use and non-use values for preventing the types of plumes caused by power plant emissions, visible from recreation areas in the southwestern U.S.; and (2) use values of local residents for reducing or preventing increases in urban hazes in several different locations.

Available evidence suggests that visitors to major recreation areas in the southwestern U.S. value the prevention of manmade plumes visible from the recreation area. The results of two studies suggest values per visitor-party per day in the range of $3 to $6 (1989 dollars) in additional park entrance fees to ensure that a thin, dark plume is not visible from a popular observation point at Grand Canyon National Park. A similar study at Lake Powell found somewhat smaller values, in the range of $2 to $3 per day.

The best economic information available for visibility effects is for on-site use values related to changes in visual range in urban areas caused by uniform haze. These values fall roughly between $10 and $100 per year per local household for a 10% change in visual range in major urban areas in California and throughout the eastern U.S..

Very little work has been done regarding layered hazes in recreation or residential settings. However, available evidence suggest annual residential household values of about $30 for a noticeable improvement in visibility conditions in the Denver area, where layered hazes are common. More information is needed about the specific visual characteristics of such hazes that are most important to viewers, as well as about the value people may place on reducing or preventing them.

Particulate matter of submicron size in the earth's atmosphere perturbs the radiation field. There is no doubt that anthropogenic aerosol emissions primarily sulfur oxides, have the potential to affect climate; the question is by how much. There are two chief avenues through which aerosols impact the radiation budget of the earth. The direct effect is that of enhanced solar reflection by the cloud-free atmosphere. Since aerosols, even those containing some absorptive component, are primarily reflective, their impact is felt as a negative radiative forcing (i.e., a cooling) on the climate system. Although there is some uncertainty in the global distribution of such aerosols and in the chemical and radiative properties of the aerosols, the radiative effects can still be modeled within certain bounds.

Estimates of this forcing range from -0.3 W m^{-2} to about twice that value for current conditions over pre-industrial times.

The indirect forcing results from the way in which aerosols affect cloud microphysical properties. The most important is the effective radius of cloud droplets, which decrease in the presence of higher concentrations of CCN. This effect is most pronounced when the concentration, N, is very low, and clouds are moderately reflective. Other effects are the enhancement of cloud lifetimes and also changes in the nucleating ability of CCN through chemical changes. Although estimates of the indirect effect are uncertain by at least a factor of 2, but perhaps much more, it appears to be potentially more important than the direct effect. Taken together, on a global mean basis, anthropogenic emissions of anthropogenic aerosols could have offset substantially the positive radiative forcing due to greenhouse gas emissions. High priority should be given to acquiring the measurements needed to quantifying these effects with greater accuracy.

The one crucial difference between aerosol forcing and greenhouse (gas) forcing is the atmospheric lifetime of aerosols and gases and hence, forcing. The aerosol forcing is fairly localized, whereas the greenhouse forcing is global. One should, therefore, expect inter-hemispheric differences in the forcing and perhaps climate response. However, climate models are not currently at the level of sophistication needed to determine climate response unambiguously. Global observations of surface temperature can not yet separate natural and anthropogenic causal mechanisms with few exceptions.

A relevant question for policy planning is whether reducing fossil-fuel emissions could cause global warming by the reduction of negative radiative forcing. Given the uncertainties in the database and in climate models, it would be premature to base such economic decisions solely on the radiative forcing of aerosols. There is ample reason to believe that some of the greenhouse warming expected since pre-industrial times has been masked by the aerosol forcing. However, the suggestion that efforts to reduce aerosol emissions could prove harmful by exacerbating greenhouse warming should not be considered when there are other deleterious effects of these emissions.

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9. EFFECTS ON MATERIALS

The deposition of airborne particulate matter on surfaces of building materials and culturally important articles (e.g., statuary) can cause soiling, thus reducing the aesthetic appeal of such structures (National Research Council, 1979; Baedecker, 1991). Furthermore, the presence of particulate matter on surfaces may also increase the physical and chemical degradation of materials that occurs normally when these materials are exposed to environmental factors such as wind, sun, temperature fluctuations, and moisture. Beyond these effects, particulate, whether suspended in the atmosphere, or already deposited on a surface, adsorbs or absorb acidic gases from other pollutants like sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) thus serving as nucleation sites for these gases. The deposition of "acidified" particles on a susceptible material surface is capable of accelerating chemical degradation of them aerial. Therefore, the concerns about the effect of particulate matter on materials are for both the aesthetic appeal and the physical damage to the surface, both of which may have serious economics consequences.

This chapter will briefly discuss the effects of particulate matter exposure on the aesthetic appeal and physical damage to different types of building materials, and economic consequences, including background information on the physics and chemistry of atmospheric corrosion. For a more detailed discussion of the physics and chemistry of atmospheric corrosion, see U.S. National Acid Precipitation Assessment Program (Baedecker, 1991). Where possible, the chapter will discuss only those effects associated with particle exposure; however, most of the available data are on the effects of particles in combination with SO_2.

9.1 CORROSION AND EROSION

9.1.1 Metals

Only limited information is available on the effects of particulate matter alone on metals. Goodwin et al. (1969) reported damage to steel, protected with a nylon screen, exposed to quartz particles. The damage did not, however, become substantial until the particle size exceeded 5 μm. Barton (1958) found that dust contributed to the early stages of metal corrosion. The effect of dust was lessened as the rust layer formed. Still other early

studies indicate that suspended particles can play a significant role in metal corrosion. Sanyal and Singhania (1956) wrote that particulate matter, along with other cofactors and SO_2 promoted the corrosion of metals in India. Yocom and Grappone (1976) and Johnson et al. (1977) reported that moist air containing both particulate matter and SO_2 resulted in a more rapid corrosion rate than air polluted with SO_2 alone. Russell (1976) stated that particles serve as points for the concentration of active ionic species on electrical contact surfaces, thereby, increasing the corrosion rate of sulfur dioxides (SO_x). Other studies have not established a conclusive statistical correlation between total suspended particulates (TSP) and corrosion, possibly due to data limitations (Mansfeld, 1980; Haynie and Upham, 1974; and Upham, 1967; Yocom and Upham 1977).

Edney et al. (1989) reported on the effects of SO_2, nitrogen oxides (NO_x), ozone (O_3), and particulates on galvanized steel panels exposed under actual field conditions in Research Triangle Park, NC and Steubenville, OH between April 25 and December 28, 1987. The panels were exposed under the following conditions: (1) dry deposition only; (2) dry plus ambient wet deposition; and (3) dry deposition plus deionized water. The average concentrations for SO_2 and particulate matter was 22 ppb and 70 $\mu g/m^3$ and <1 ppb and 32 $\mu g/m^3$ for Steubenville and Research Triangle Park, respectively. By analyzing the runoff from the steel panel the authors concluded that the dissolution of the steel corrosion products for both sites was likely the result of deposited gas phase SO_2 on the metal surface and not particulate sulfate.

Walton et al. (1982) performed a laboratory study of the direct and synergistic effects of different types of particulate matter and SO_x on the corrosion of aluminum, iron, and zinc. The four most aggressive species were salt and salt/sand from marine or deiced locations, ash from iron smelters, ash from municipal incinerators, and coal mine dusts. Fly ashes of various types were less aggressive. Coal ash with SO_x did promote corrosion but oil fly ash was relatively noncorrosive. This suggests that catalytic species in the ash promote the oxidation of SO_x and the presence of SO_x alone is not sufficient to accelerate corrosion. Other laboratory studies of metal corrosion provide considerable evidence that the catalytic effect is not significant and that atmospheric corrosion rates are dependent on the conductance of the thin-film surface electrolyte and that the first-order effect of contaminant

particles is to increase solution conductance, and, hence corrosion rates (Skerry et al., 1988a,b; Askey et al., 1993).

9.1.2 Paints

Paints, opaque film coatings, are by far the dominant class of manmade materials exposed to air pollutants in both indoor and outdoor environments. Paints are used as decorative coverings and protective coatings against environmental elements on a variety of finishes including woods, metals, cement, asphalt, etc.

Paints primarily consists of two components: the filming forming component and the pigments. Paints undergo natural weathering processes from exposure to environmental factors such as sunlight (ultraviolet light), moisture, fungi, and varying temperatures. In addition to the natural environmental factors, evidence exists that demonstrates the particulate matter exposure alters the appearance of paint, giving it a dirty appearance (see Section 9.2.1.2) (National Research Council, 1979; U.S. Environmental Protection Agency, 1993). Several studies also suggest that particles serve as carriers of other more corrosive pollutants, allowing the pollutants to reach the underlying surface or serve as concentration sites for other pollutants (Cowling and Roberts, 1954).

Finishes on automobiles have also been damaged by particulate matter. In an early study, staining and pitting of automobile finishes was reported in industrial areas. The damage was traced to iron particles emitted for nearby plants (Fochtman and Langer, 1957). General Motors conducted a field test to determine the effect of various meteorological events, the chemical composition of rain and dew, and the ambient air composition during the event, on automotive paint finishes. The study was conducted in Jacksonville, Florida. Painted (basecoat/clearcoat technology) steel panels were exposed for varying time periods, under protected and unprotected conditions. Damage to paint finishes appeared as circular, elliptical, or irregular spots, that remained after washing. Using scanning electron microscopy (high magnification) the spot appeared as crater-like deformities in the paint finish. Chemical analyses of the deposit determined calcium sulfate to be the predominant species. The researches concluded that calcium sulfate was formed on the paints surface by the reaction of calcium from dust and sulfuric acid contained in rain or dew. The damage to the paint finish increased with increasing days of exposure (Wolff et al., 1990).

The formulation of the paint will affect the paint's durability under exposure to varying environmental factors and pollution; however, failure of the paint system results in the need for more frequent repainting and addition cost.

9.1.3 Stone

Air pollutants are known to damage various building stones. Some of the more susceptible stones are the calcareous stones, such as limestone, marble and carbonated cemented stone. Baedecker et al. (1991) reviewed the published literature on calcareous stones and concluded that the most significant damage to these stones resulted from the exposure to natural constituents of nonpolluted rain water; carbonic acid from the reaction of carbon dioxide with rain reacts with the calcium in the stone. Based on the work conducted by the National Acid Precipitation Assessment Program, the largest percentage (20%) of chemical weathering of marble and limestone was caused by wet deposition of hydrogen ions from all acid species (Baedecker et al., 1991). Luckat (1972) suggested that dusts containing heavy metals may accelerate stone erosion by converting ambient SO_2 to sulfuric acid. Under high wind conditions, particulates have been reported to result in slow erosion of the surfaces, similar to sandblasting (Yocom and Upham, 1977).

Mansfeld (1980), after performing statistical analysis of damage to marble samples exposed for 30 mo at nine air quality monitoring sites in St. Louis, MO, concluded that TSP and nitrates were best correlated with stone degradation. However, there is some concern over the statistical techniques used.

Generally, black and white areas can be observed on the exposed surfaces of any building. The black areas, found in zones protected from direct rainfall and from surface runs, are covered by an irregular, dendrite-like, hard crust composed of crystals of gypsum mixed with dust, aerosols and particulate matter of atmospheric origin. Among these the most abundant are black carbonaceous particles originating from oil and coal combustion. On the other hand, surfaces directly exposed to rainfall show a white color, since the deterioration products formed on the stone surface are continuously washed out.

Del Monte et al. (1981) reported evidence of a major role for carbonaceous particles in marble deterioration, using scanning electron microscopy. The majority of the carbonaceous particles were identified as products of oil fired boiler/combustion. Particle median diameter

was ≈ 10 μm. Sabbioni and Zappia (1992) analyzed samples of damaged layers on marble and limestone monuments and historical buildings from eight urban sites in Northern and Central Italy. Samples of black crust were taken from various locations at each site to be representative of the entire site. The predominant species in the black crust matrix was calcium sulphate dihydrate (gypsum). The evaluation of enrichment factors with respect to the stone and to the soil dust show the main components of the atmospheric deposition to be from the combustion of fuels and incineration. Saiz-Jimenez (1992) also found, after analyzing the organic compounds extracted for black crusts removed for building surfaces in polluted areas, that the main components were composed of molecular markers characteristic of petroleum derivatives. The composition of each crust; however, is governed by the composition of the particular airborne pollutants in the area.

9.1.4 Electronics

Exposure to ionic dust particles can contribute significantly to the corrosion rate of electronic devices, ultimately leading to failure of that device. Natural and anthropogenically derived particles ranging in size from tens of angstroms to 1 μm cause corrosion of electronics because many are sufficiently hygroscopic and corrosive at normal relative humidities to react directly with non-noble metals and passive oxides, or to form sufficiently conductive moisture films on insulating surfaces to cause electrical leakage. The effects of particulates on electronic components were first reported by telephone companies, when particulates high in nitrates caused stress corrosion cracking and ultimate failure of the wire spring relays (Hermance, 1966; McKinney and Hermance, 1967). More recently, attention has been directed to the effects of particles on electronic components, primarily in the indoor environment.

Sinclair (1992) has discussed the relevance of particle contamination to corrosion of electronics. Data collected during the eighties show that the indoor mass concentrations of anthropogenically derived airborne particles and their arrival rates at surfaces are comparable to the concentrations and arrival rates of corrosive gases for many urban environments.

Frankenthal et al. (1993) examined the effects of ionic dust particles, ranging from 0.01 to 1 μm in size, on copper coupons under laboratory conditions. The copper coupons, after being polished with diamond paste, were inoculated with ammonium sulfate

[$(NH_4)_2SO_4$)] particles and exposed to air at 100 °C at relative humidities ranging from 65 to 100% for up to 600 h. The particles were deposited on the metal surface by thermophoretic deposition and cascade impaction.

Exposure of the copper coupons to $(NH_4)_2SO_4$ at 65% relative humidity had little effect on the corrosion rate. However, when the relative humidity was increased to 75%, the critical relative humidity for $(NH_4)_2SO_4$ at 100 °C, localized areas of corrosion were noted on the metal surface. The corrosion product, determined to be brochantite, was only found in areas where the $(NH_4)_2SO_4$ was deposited on the metal surface. When the relative humidity was increased to 100%, the corrosion became widespread (Frankenthal et al., 1993).

9.2 SOILING AND DISCOLORATION

A significant detrimental effect of particulate matter pollution is the soiling of manmade surfaces. Soiling may be defined as a degradation mechanism that can be remedied by cleaning or washing, and depending on the soiled material, repainting. Faith (1976) described soiling as the deposition of particles of less than 10 μm on surfaces by impingement. Carey (1959) observed when particles descended continuously onto paper in a room with dusty air, the paper appeared to remain clean for a period of time and then suddenly appeared dirty. Increased frequency of cleaning, washing, or repainting over soiled surfaces becomes an economic burden and can reduce the life usefulness of the material soiled. In addition to the aesthetic effect, soiling produces a change in reflectance from opaque materials and reduces light transmission through transparent materials (Beloin and Haynie, 1975; National Research Council, 1979). For dark surfaces, light colored particulate matter can increase reflectance (Beloin and Haynie, 1975).

Determining at what accumulated level particulate matter leads to increased cleaning is difficult. For instance, in the study by Carey (1959), Carey found that the appearance of soiling only occurred when the surface of the paper was covered with dust specks spaced 10 to 20 diameters apart. When the contrast was strong, e.g., black on white, it was possible to distinguish a clean surface from a surrounding dirty surface when only 0.2% of the areas was covered with specks, while 0.4% of the surface had to be covered with specks

with a weaker color contrast. Still, the effect is subjective and not easy to judge between coverages.

Support for Carey's (Carey, 1959) work was reported by Hancock et al. (1976). These authors also found that with maximum contrast, a 0.2% surface coverage (effective area coverage; EAC) by dust can be perceived against a clean background. A dust deposition level of 0.7% EAC was needed before the object was considered unfit for use. The minimum perceivable difference between varying gradations of shading was a change of about 0.45% EAC. Using the information on visually perceived dust accumulation and a telephone survey, Hancock et al. (1976) concluded that a dustfall rate of less than 0.17% EAC/day would be tolerable to the general public.

Some materials that are soiled are indoors. In general, particulate matter pollution levels indoors may be affected by outdoor ambient levels; however, other factors generally have greater effects on concentration and composition (Yocom, 1982). For that reason, discussion of indoor soiling will be limited primarily to works of art.

9.2.1 Building Materials

Dose-response relationships for particulate matter soiling were developed by Beloin and Haynie (1975) using a comparison of the rates of soiling and TSP concentrations on different building materials (painted cedar siding, concrete block, brick, limestone, asphalt singles, and window glass) at five different study sites over a 2-year period. Particulate matter concentrations ranged from 60 to 250 mg/m^3 for a rural residential location and an industrial residential location, respectively. The results were expressed as regression functions of reflectance loss (soiling) directly proportional to the square root of the dose. With TSP expressed in mg/m^3 and time in months, the regression coefficients ranged from -0.11 for yellow brick to $+0.08$ for a coated limestone depending on the substrate color and original reflectance. For dark surfaces, light colored particulate matter can increase reflectance. Not all of the coefficients were significantly different from zero.

A theoretical model of soiling of surfaces by airborne particles has been developed and reported by Haynie (1986). This model provides an explanation of how ambient concentrations of particulate matter are related to the accumulation of particles on surfaces and ultimately the effect of soiling by changing reflectance. Soiling is assumed to be the

contrast in reflectance of the particles on the substrate to the reflectance of the bare substrate. Thus, the average reflectance from the substrate (R) equals the reflectance from the substrate not covered by particles [Ro(1-X)] plus the reflectance from the particles (RpX) where X is the fraction of surface covered by particles.

Under constant conditions, the rate of change in fraction of surface covered is directly proportional to the fraction of surface yet to be covered. Therefore, after integration: $X = 1-\exp(-kt)$ where k is a function of particle size distribution and dynamics and t is time.

Lanting (1986) evaluated similar models with respect to soiling by particulate elemental carbon (PEC) in the Netherlands. He determined that the models were good predictors of soiling of building materials by fine mode black smoke. Based on the existing levels of PEC, he concluded that the cleaning frequency would be doubled.

An important particle dynamic is deposition velocity which is defined as flux divided by concentration and is a function of particle diameter, surface orientation, and surface roughness, as well as other factors such as wind speed, atmospheric stability, and particle density. Thus, soiling is expected to vary with the size distribution of particles within an ambient concentration, whether a surface is facing skyward (horizontal or is vertical), and whether a surface is rough or smooth.

Van Aalst (1986) reviewed particle deposition models existing at that time and pointed out both their benefits and their faults. The lack of significant experimental verification was a major fault. Since then, Hamilton and Mansfeld (1991, 1993) have applied the model reported by Haynie (1986) and Haynie and Lemmons (1990) to soiling experiments with relatively good predictive success.

Tarrat and Joumard (1990) found that the simple plate method (a measurement of the number of particles deposited on a flat inert plate of material), as well as the measurement of reflectance and transmission of the light really showed the amount of soiling deposit in a town. The simple plates are more suitable for a high particles pollution and the optical methods are more suitable for a low pollution. This study also gave evidence that the main responsibility in soiling the facades along roads was motor vehicles.

9.2.1.1 Fabrics

No recent information on the effects of particulate matter on fabrics was located in the published literature. Earlier studies indicate particles are only damaging to fabrics when they are abrasive. Yocom and Upham (1977) reported that curtains hanging in an open window often split in parallel lines along the fold after being weakened by particle exposure. The appearance and life usefulness also may be lessened from increased frequencies of washing as a result of particulate matter 'soiling'. Rees (1958) described the mechanisms (mechanical, thermal, and electrostatic) by which cloth is soiled. Tightly woven cloth exposed to moving air containing fine carbon particles was found to be the most resistant to soiling. Soiling by thermal precipitation was related to the surface temperature of the cloth versus that of the air. When the surface temperature of the cloth was greater than that of the air, the cloth resisted soiling. When cloth samples were exposed to air at both positive and negative pressure, the samples exposed to positive pressure showed greater soiling than those exposed to equivalent negative pressure.

9.2.1.2 Household and Industrial Paints

As indicated earlier, research suggest that particles can serve as carriers of more corrosive pollutants, allowing the pollutants to reach the underlying surface or serve as concentration sites for other pollutants on painted surfaces (Cowling and Roberts, 1954). Paints may also be soiled by liquids and solid particles composed of soot, tarry acids, and various other constituents.

Haynie and Lemmons (1990) conducted a soiling study at an air monitoring site in a relatively rural environment in Research Triangle Park, NC. The study was designed to determine how various environmental factors contribute to the rate of soiling of white painted surfaces. White painted surfaces are highly sensitive to soiling by dark particles and represent a large fraction of all manmade surfaces exposed to the environment. Hourly rainfall and wind speed, and weekly data for dichotomous sampler measurements and TSP concentrations were monitored. Gloss and flat white paints were applied to hardboard house siding surfaces and exposed vertically and horizontally for 16 weeks, either shielded from or exposed to rainfall. Measurements of exposed samples were taken at 2, 4, 8, and 16 weeks. Reflectance was measured at 2, 4, 8, and 16 weeks. The scanning electron microscopy

stubs, that had been flush-mounted on the hardboard house siding prior to painting, were also removed at these intervals.

The unsheltered panels were initially more soiled by ambient pollutants that the sheltered panels; however, washing from rain reduced the effect. The vertically exposed panels soiled at a slower rate than the horizontally exposed panels. This was attributed to additional contribution to particle flux from gravity. The reflectivity was found to decrease faster on glossy paint than on the flat paint (Haynie and Lemmons, 1990).

Least squares fits through zero of the amounts on the surfaces with respect to exposure doses provided the deposition velocities. There was no statistical difference between the horizontal and vertical surfaces for the fine mode and the combined data given a deposition velocity of 0.00074 + 0.000048 cm/s (which is lower than some reported values). The coarse mode deposition velocity to the horizontal surfaces at 1.55 cm/s is around five times greater than to vertical surfaces at 0.355 cm/s. By applying assumptions these deposition velocities can be used to calculate rates of soiling for sheltered surfaces. The empirical prediction equation for gloss paint to a vertical surface based on a theoretical model (Haynie, 1986) is:

$$R = R_0 \exp\left(-0.0003\,[0.0363C_f + 0.29C_c]t\right)$$

where R and R_0 are reflectance and original reflectance respectively, C_f and C_c are coarse and fine mode particulate matter concentrations in mg/m^3, respectively, and t is time in weeks of exposure.

The fine mode did not appear to be washed away by rain, but most of the coarse mode was either dissolved to form a stain or was washed away. Therefore, for the surfaces exposed to rain, the 0.0363 coefficient for the fine mode should remain the same as it is for sheltered surfaces but there should be a time-dependent difference in the coefficient for the coarse mode.

Based on the results of this study, the authors concluded that: (1) coarse mode particles initially contribute more to soiling of both horizontal and vertical surfaces than fine mode particles; (2) coarse mode particles, however, are more easily removed by rain than are fine mode particles; (3) for sheltered surfaces reflectance changes is proportional to surface

coverage by particles, and particle accumulation is consistent with deposition theory; (4) rain interacts with particles to contribute to soiling by dissolving or desegregating particles and leaving stains; and (5) very long-term remedial actions are probably taken because of the accumulation of fine rather than coarse particles (Haynie and Lemmons, 1990).

Similar results were also reported by Creighton et al. (1990). They found that horizontal surfaces, under the test conditions, soiled faster than did the vertical surfaces, and that large particles were primarily responsible for the soiling of horizontal surfaces not exposed to rainfall. Soiling was related to the accumulated mass of particles from both the fine and coarse fractions. Exposed horizontal panels stain because of dissolved chemical constituents in the deposited particles. The size distribution of deposited particles was bimodal, and the area of coverage by deposited particles was also bimodal with a minimum at approximately 5 μm. The deposition velocities for each of the size ranges onto the horizontal, sheltered panel was in general agreement with both the theoretical settling velocity of density 2.54 g/cm^3 spheres and the reported results of laboratory tests. An exponential model (Haynie, 1986) was applied to the data set and gave a good fit.

Beloin and Haynie (1975) determined by reflectance measurements that the degree of soiling of painted surfaces was directly proportional to the square root of the particulate matter dose, accounting for 74 to 90% of the measured variability.

Spence and Haynie (1974) reported on the published data on the effects of particulate matter on the painted exterior surfaces of homes in Steubenville and Uniontown, Ohio, Suitland and Rockville, Maryland, and Fairfax, Virginia. There was a direct correlation between the ambient concentration of particulate matter in the city and the number of years between repainting. The average repainting time for homes in Steubenville, where particulate matter concentrations reached 235 μg/m^3, was approximately one year. In the less pollutant city, Fairfax, the time between repainting was 4 years. Parker (1955) reported the occurrence of black specks on the freshly paint surface of a building in an industrial area. The black specks were not only aesthetically unappealing, but also physically damaged the painted surface. Depending on the concentration of particulate matter, the building required repainting every 2 to 3 years.

9.2.1.3 Soiling of Works of Art

Ligocki et al. (1993) studied potential soiling of works of art. The concentrations and chemical composition of suspended particulate matter were measured in both the fine and total size modes inside and outside five Southern California museums during summer and winter months. The seasonally averaged indoor/outdoor ratios for particulate matter mass concentrations ranged from 0.16 to 0.96 for fine particles and from 0.06 to 0.53 for coarse particles, with lower values observed for buildings with sophisticated ventilation systems that include filters for particulate matter removal. Museums with deliberate particle filtration systems showed indoor fine particle concentrations generally averaging less than 10 $\mu g/m^3$. One museum with no environmental control system showed indoor fine particles concentrations averaging nearly 60 $\mu g/m^3$. Analysis of indoor versus outdoor concentrations of major chemical species indicated that indoor sources of organic matter may exist at all sites, but that none of the other measured species appear to have major indoor sources at the museums studied. The authors concluded that a significant fractions of the dark-colored fine elemental carbon and soil dust particles present in outdoor had penetrated to the indoor atmosphere of the museums studied and may constitute a soiling hazard to displayed works of art.

Methods for reducing the soiling rate in museums that included reducing the building ventilation rate, increasing the effectiveness of particle filtration, reducing the particle deposition velocity onto surfaces of concern, placing objects within display cases or glass frames, managing a site to achieve lower outdoor aerosol concentrations, and eliminating indoor particle sources were proposed by Nazaroff and Cass (1991). According to model results the soiling rate can be reduced by at least two orders of magnitude through practical application of these control measures. Combining improved filtration with either a reduced ventilation rate for the entire building or low-air-exchange display cases is a very effective approach to reducing the soiling hazard in museums.

9.3 ECONOMIC ESTIMATES

Several types of financial losses result from damage and soiling. These losses include the reduction in service life of a material, decreased utility, substitution of a more expensive

material, losses due to an inferior substitute, protection of susceptible materials, and additional required maintenance, including cleaning. The major losses of amenity, as defined by Mäler and Wyzga (1976), are associated with enduring and suffering soiled, damaged, or inferior products and materials because of particulate pollution and any corrosive pollutant that may be absorbed on or adsorbed to particles. In addition, amenity losses are suffered when pollution damage repair or maintenance procedures result in inconvenience or other delays in normal operations. Some of these losses, such as effects on monuments and works of art, are especially difficult to specify (Mäler and Wyzga, 1976).

Like the effects of other pollutants, the reduced value and attractiveness of property and the costs of cleaning and maintenance resulting from particulate matter pollution must be considered when evaluating monetary losses. In calculating monetary damage, the approach selected depends on whether financial losses or losses of amenity are emphasized, the type of damage being considered, and the availability of cost information. Generally, damage estimates are based on physical damage approaches (willingness-to-pay approaches: physical damage function, nonmarket, and indirect market approaches); however, one may proceed directly from ambient pollutant levels to economic damage estimates. Willingness-to-pay approaches try to estimate a monetary value to damage caused by changes in pollutant concentrations that all affected parties assign to the effect.

The damage function approach, the most widely used method for evaluating economic loss or cost, uses the relationship of pollutant exposure to physical damage. The physical damage is then linked to a dollar estimate of willingness-to-pay. The nonmarket approach generally uses surveys that attempt to determine the monetary value assigned to the pollutant related effect. The willingness-to-pay for nonmarketed environmental attributes that are closely related to marketed goods is used by the indirect market approach (Freeman, 1979a).

In the damage function approach, physical damage (any undesirable change in the function of specific materials, including appearance, leading to failure of specific components) is determined before economic cost is estimated. Physical damage is estimated from ambient pollutant concentrations over a specified period of time. Depending on the material damaged, both short-term and long-term exposure data may be needed. The damage function is expressed in terms appropriate to the interaction of the pollutant and material. For example, the corrosion of metal may be expressed in units of thickness lost, while the

deterioration of paint from soiling may be expressed in units of reflectance lost. It is, however, difficult to estimate financial loss because reliable information on physical damage is not available for all economically important materials, and on the spatial and temporal distribution of the materials being used. Further, techniques do not reflect the use of more resistant and reduced maintenance materials, and loss estimates may assume that substitute materials cost more than the original materials, and that the cost differential is attributable solely to pollution, in this case, particulate matter.

A critical damage level, the level at which the service life or functional utility of the material has ended or is severely impaired, must be established before an economic loss estimate is place on the material damaged by pollution. The damage from a specified pollutant exposure is calculated by comparing the amount of material damage in a polluted area with that from a clean area.

A major problem in developing reliable damage functions is the inability to separate pollutant effects from natural weathering processes due to various meteorological parameters (temperature, relative humidity, wind speed, and surface wetness). Since weathering in a natural phenomenon, proceeding at an finite rate irrespective of anthropogenic pollution, materials damage estimates must represent only that damage directly produced by anthropogenic pollutant exposure. Also, this approach cannot account for irreplaceable items such as works of art or national monuments.

In the studies where estimations of monetary damage associated with soiling are not dominated by the physical damage approach, the loss of amenity has been considered as well as direct financial loss (no market and indirect market approaches). These approaches have been used to relate changes in the amount of money to reduce air pollution. A major source of error using these approaches is the requirement that all factors that affect cost other than air quality have to be accounted for. In general, however, all approaches to estimating costs of air pollution effects on materials are limited by the difficulty in quantifying the human response to damage based upon the ability and the incentive to pay additional costs (Yocom and Grappone, 1976).

Only limited new information was located in the published literature on the economic cost of soiling and corrosion by particulate matter. The following sections will, therefore, be primarily a summarization of some of the more important earlier studies. A more detailed

discussion of these studies can be found in the 1982 criteria document, Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982).

9.3.1 Economic Loss Associated with Materials Damage and Soiling

To be able to accurately estimate the economic costs of damage to construction materials from pollution, information on the geographic distribution of various types of exposed materials is needed. Lipfert and Daum (1992) analyzed the efforts done in this area. They focused on the identification, evaluation and interpretation of data describing the distribution of exterior construction materials, primarily in the United States. Materials distribution surveys for 16 cities in the United States and Canada and five related data bases from government agencies and trade organizations were examined. Data on residential buildings were more available than non-residential buildings; little geographically resolved information on distributions on materials in infrastructure was found.

Lipfert and Daum (1992) observed several important factors relating pollution to distribution of materials. In the United States, buildings constitute the largest category of surface areas potentially at risk to pollution damage. Within this category, residential buildings are the most important. On average, commercial and industrial buildings tend to be larger than residential buildings and to use more durable materials. However, because they are more numerous (and use less durable materials) more surface area for residential buildings is exposed to potentially damaging pollutants. For residential buildings in general, painted surfaces are preferred over masonry in the Northeastern United States (with the exception of large inner cities), brick is popular in the South and Midwest) and stucco in the West. The use of brick appears to be declining, painted wood increasing, and the use of vinyl siding is gaining over aluminum. One of the factors underlying the present regional distribution of materials is their durability under the environmental conditions which exist when they were installed. Thus, changing pollution levels have possibly affected materials selection and is expected to do so.

9.3.1.1 Metals and Other Material Damage

In an early study, Bennett et al. (1978) examined the cost of corrosion in the United States in 1975. The report estimated the total annual metallic corrosion cost at $82 billion;

however, the damage costs were not pollutant-specific. Fink et al. (1971) also estimated the economic loss from pollutant-induced damage of external metal structures. The estimated annual cost of metallic corrosion was $1.45 billion; however, like the Bennett et al. (1978) study, this study was not pollutant-specific, nor were the damage costs associated directly with ambient pollutant concentrations.

9.3.1.2 Soiling of Paint and Other Materials

One of the earliest studies on national estimates of soiling costs was the Beaver report (1954). This study suggested an annual total fast of 152 million pounds sterling for damage by all forms of air pollution in Great Britain.

Michelson and Tourin (1966) compared cleaning and maintenance costs in Steubenville, Ohio with Uniontown, Pennsylvania. The average TSP levels were 383 and 115 $\mu g/m^3$, respectively. These researchers, reported that per capita costs for cleaning and maintenance were $84 higher in Steubenville, based on 30% response to a questionnaire mailed to 2 to 6% of the population of these communities. In a second study (Suitland and Rockville, Maryland and Fairfax, Virginia), Michelson and Tourin (1967) also showed an increase in cleaning frequency with increased TSP. However, there were errors with the measurement techniques, averaging over a community, and the influence of socioeconomic factors was not considered.

In 1968, the National Air Pollution Control Administration (NAPCA), the forerunner of the U.S. EPA, commissioned the Booz, Allen and Hamilton, Inc. (1970) (BAH) study to determine residential soiling costs of particulate air pollution for the 11-county Philadelphia area, including areas in Delaware and New Jersey. The primary purpose of the study was to determine the residential soiling costs in the 11 county area. It was also to provide methods of estimating residential soiling costs under various abatement strategies and develop a sampling methodology that could be applied in other metropolitan areas. The finding of this study was that there were no measurable effects on cleaning cost based on the annual particulate levels ($\approx$ 50 to 150 mg/m^3) in the Philadelphia area. However, the study did not consider the value of the direct personal labor or time of a "do-it-yourself" as a cost. Further, the reason why exterior soiling costs were not statistically different may have been associated with the use of more soil resistant materials and the pollution levels. All but five

of the houses surveyed in the region of highest pollution were brick (80% of the structures in Philadelphia were brick or masonry).

Salmon (1970) calculated the economic loss for materials (stainless steel, zinc, building stone, leather and paper, cotton, and paint) by first determining the value of the materials and then multiplying that figure by the estimated difference in useful lifetime between clean rural and polluted urban areas. The purpose of the study was to rank potential pollutant/materials damage problems. Soiling costs attributed to particulate matter were estimated to be $99 billion. The study estimated the economic loss for stainless steel, zinc, building stone, leather and paper, cotton, and paint. According to the author, the cost estimation represented susceptibility to economic loss or potential loss, and not actual incurred loss. However, the study has been used quantitatively in many of the national estimates for materials damage attributed to air pollution.

Spence and Haynie (1972) reported an estimated total annual economic loss of $540 million in 1968 dollars for increased exterior household painting. The calculation was based on the assumption that exterior household paint service life is reduced by half in an (urban) area averaging 110 mg/m^3 TSP compared to a service life of 6 years in a (rural) area averaging 40 mg/m^3 TSP.

Narayanan and Lancaster (1973), using a questionnaire survey, reported that the cost of maintaining a house in the Mayfield area (a polluted area in New South Wales, Australia) was about $90/year higher than in the relatively unpolluted Rotar area. The cost differential was attributed to higher levels of air pollution and airborne particulate matter in Mayfield. This study did not consider socioeconomic factors, including respondents' attitude and how these factors could bias the estimates.

Waddell (1974), using Salmon's (1970) list of economically important materials significantly affected by air pollution and other published studies to date on material effects, concluded that particulate matter had no significant economic effect in terms of household maintenance and cleaning. However, when he examined published reports on property value differentials to air pollution, he postulated the property value estimate for loss in aesthetic appeal and soiling cost $2.9 billion, a total of $5.8 billion for particulate matter and SO_2 combined.

Liu and Yu (1976) designed a study to generate physical and economic damage functions, by receptor, for both TSP and SO_2, to establish a cost/benefit relationship. The study used the BAH results (Booz, Allen and Hamilton Inc., 1970) on cleaning frequency and related those results to TSP levels in 148 standard metropolitan statistical areas (SMSAs). The study included effects of TSP exposure on health, materials, vegetation, and household soiling. The technique, using Monte Carlo technique, created a sample of data pairs for each cleaning tasks. The study concluded soiling from TSP exposure cost $5 billion nationwide. The authors did not, however, take into consideration the socioeconomic factors in the BAH data base and the insensitivity of high-cost cleaning and maintenance tasks to TSP levels.

Watson and Jaksch (1978), building on the results reported by Booz, Allen and Hamilton, Inc., (1970), introduce the benefits of pollution control; the psychological and other advantages of living in a cleaner environment. The value of these psychological and health benefits were estimated by applying the standard measure of net contribution to consumer welfare. In estimating the cost of achieving a given level of cleanliness, the authors relied on a formula derived by Beloin and Haynie (1975). This formula estimated the cost of maintaining a given level of reflectance, which is not the same thing as the perceived level of cleanliness. "Cleanliness," as posed by Watson and Jaksch (1978), is the reciprocal of the difference between the actual reflectance of a surface and its maximum reflectance, raised to a power that depends on the rate at which reflectance decreases over time. Based on this definition, the marginal cost (or price to the consumer) of maintaining a given average level of cleanliness, may be expressed as

$$MC = aP^nQ,$$

where a and n are empirical constants, P denotes the ambient concentration of particulate matter, and Q represents the given average level of cleanliness. Of importance is that this formula depends on both the empirical studies of reflectance and the assumed relationship between reflectance and perceived cleanliness.

Watson and Jaksch (1978), using the data from the Booz, Allen and Hamilton, Inc. (1970) study, concluded that out-of-pocket costs of home maintenance are not affected by

particulate matter; however, psychological satisfication is. They suggested that consumers can be expected to choose the level of cleanliness at which the cost of further improvement is equal to the amount they are willing to pay. People will tolerate lower levels of cleanliness in heavily polluted areas than in less polluted areas because of the maintenance costs.

Watson and Jaksch (1982) compared the changes in consumer welfare with changes in particulate matter concentrations (using supply and demand functions) by calculating the level of cleanliness the would be chosen as a function of the ambient particulate matter concentration. A demand curve for cleanliness was estimated based on the assumption that households prefer more cleanliness to less. The estimates were made for households in the BAH study survey and extrapolated to cover the entire Philadelphia metropolitan area, and later extended to cover 123 SMSAs in the United States. Allowances were made for the differing particulate matter concentrations in the different SMSAs. Watson and Jaksch (1982) estimated that the nationwide gains to consumers, in 1978 dollars, from attaining the primary TSP standard in all SMSAs ranged from $1.4 to $5.1 billion dollars. An estimated $2.4 to $9.1 billion dollars would be saved from attaining the secondary standard.

Using the framework developed by Watson and Jaksch (1982), Hamilton (1979) estimated benefits from reduced TSP in six SMSAs (Fresno, Los Angeles-Long Beach, Sacramento, San Bernadino-Riverside-Ontario, San Diego, and San Francisco-Oakland) in California. Benefits were estimated to be $40 per household (1978 dollars) based on a 25% reduction in TSP levels. The total estimated benefit was $223 million.

Haynie (1989) performed a risk assessment of particulate matter soiling of exterior house paints. Much of the data that was used is from the same data sets analyzed and discussed by Lipfert and Daum (1992). County-wide census of housing data for 1970 and 1980 were linearly extrapolated to 1990. From reported survey data, the average exterior wall surface for single-family houses was taken as 325 m^2. For multi-family units the value was 100 m^2. About 10% of survey respondents painted because of dirt. Using national average painting costs and frequencies, $1.74 billion of annual national residential repainting costs could be attributed to soiling.

The geographic distribution of fine and coarse mode particles were calculated from the 1987 EPA AIRS data base for PM_{10}, and TSP. A regression coefficient was obtained for the relationship between PM_{10} and TSP from data at co-located sites. This value was used to

estimate missing data. Since most counties do not have monitoring sites, a geographic linear extrapolation scheme was developed to obtain those estimates as county-wide averages. Dichotomous sampler data was used to determine the fractions of PM_{10} in the fine and coarse modes.

Haynie (1990) used the methodology developed in a risk assessment of soiling of painted exterior residential walls (Haynie, 1989) to calculate potential effects of PM_{10} nonattainment. The data base was updated with 1988 and 1989 AIRS data. An extreme value statistical model was used to adjust every sixth day monitoring to 365 days for counting violation days (one violation in 60 does not translate to 6 violations in 360). The resulting paint cost due to soiling was subjected to a sensitivity analysis using various assumed values. When the model is restricted to only a national average of 10% of households repainting because of soiling, the effects of other assumptions become inversely related and tend to cancel out each other (possibly associated with individual cost minimization choices).

The top twenty counties were ranked by estimated soiling costs. Fourteen of the counties with actual violation days in 1989 were in this group. All but three were west of the Mississippi. A total of 29 counties with measured violations are in the set of 123 counties for which PM_{10} nonattainment soiling costs were calculated. When the given set of behavior assumptions was used, there were no costs calculated for 19 counties that actually measured violations in 1989. The distribution of a national estimated $1 billion in painted exterior residential wall soiling costs is shown in Figure 9-1.

Haynie and Lemmons (1990) experimentally determined soiling function for unsheltered, vertically exposed house paint was used to determine painting frequency. An equation was set up to express paint life in integer years because when exterior painting is done is usually controlled by seasonal weather. Different values for normal paint life without soiling and levels of unacceptable soiling could be used in the equation. If four was taken as the most likely average paint life for other than soiling reasons, then painting because of soiling would likely be done at 1, 2, or 3 year intervals.

Soiling costs by county were calculated and ranked by decreasing amounts and the logarithm of costs plotted by rank. The plot consisted of three distinct straight lines with intersections at ranks 4 and 45. The calculated cost values provide a reasonable ranking of

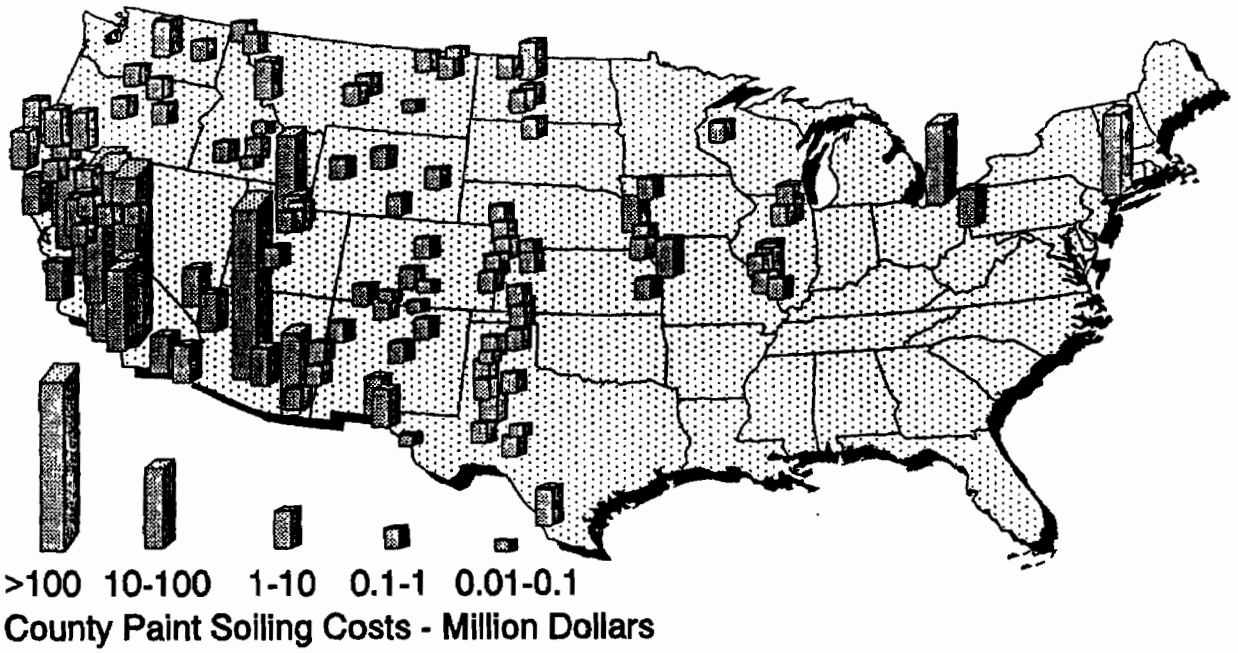

Figure 9-1. Geographic distribution of paint soiling costs.

Source: Haynie (1990).

the soiling problem by county, but do not necessarily reflect actual painting cost associated with extreme concentrations of particulate matter. Households exposed to extremes are not expected to respond with average behavior. Several alternatives can be selected that will lower painting costs. First, individuals can learn to live with higher particulate matter levels, accepting greater reductions in reflectance before painting. Second, they may wash painted surfaces rather than paint as often. Third, they may select other materials or paint colors that do not tend to show dirt. An example of the latter is the predominant use of beige colored stucco in the desert southwest where wind blown soil is a problem.

Extrapolating the middle distribution of costs to the top four ranked counties reduces their estimated costs considerably. For example Maricopa County, AR, was calculated to rank first at $70.2 million if all households painted each year as predicted, but was calculated to be only $29.7 million based on the distribution extrapolation.

Based on these calculations and error analysis, the national soiling costs associated with repainting the exterior walls of houses probably were within the range of $400 to $800 million a year in 1990. This sector represents about 70% of the exterior paint market, so that extrapolating to all exterior paint surfaces gives a range of from $570 to $1,140 million (Haynie and Lemmons, 1990).

9.4 SUMMARY OF ECONOMIC DAMAGE OF PARTICULATE MATTER TO MATERIALS

A significant detrimental effect of particulate matter pollution is the soiling of painted surfaces and other building materials. Soiling is defined as a degradation mechanism that can be remedied by cleaning or washing, and depending on the soiled surface, repainting. Available data on pollution exposure indicates that particulate matter can result in increased cleaning frequency of the exposed surface, and may reduce the life usefulness of the material soiled. Data on the effects of particulate matter on other surfaces are even less well understood. Some evidence also shows damage to fabrics, electronics, and works of art composed of one or more materials, but this evidence is largely qualitative and sketchy.

The damaging and soiling of materials by airborne pollutants have an economic impact, but this impact is difficult to measure. The accuracy of economic damage functions is limited by several factors. One of the problems has been to separate costs related to particulate matter-related materials from other pollutants, as well as from those related to normal maintenance. Cost studies typically involve broad assumptions about the kinds of materials that are exposed in a given area and then require complex statistical analysis to account for a selected number of variables. Attitudes regarding maintenance may vary culturally, further confounding the problem of quantifying economic impact.

The nature and extent of damage to materials by particulate matter have been investigated by field and laboratory studies. Both physical and economic damage functions have been developed for specific damage/effect parameters associated with exposure to particulate matter. To date, only a few of these functions are relatively reliable in determining damage, while none has been generally accepted for estimating costs.

In recent years fairly reliable damage functions for soiling of exterior wall paints have been developed. The available damage functions are few in number but represent a major fraction of the total surface that is exposed and sensitive to pollution damage.

Although their still remains a lack of sensitive materials distribution data, the geographic resolution of available data is about as good as that of environmental monitoring data. These limitations may hinder accurate estimates of total material damage and soiling, but they do not prevent estimates within ranges of error. Studies have used various approaches to determine pollutant-related costs for extra cleaning, early replacement, more frequent painting, and protective coating of susceptible materials, as well as other indicators of the adverse economic effects of pollutants. No study has produced completely satisfactory results, and estimates of cost vary widely. In 1978 dollars, the estimated economic loss for 1970 TSP exterior soiling of residential structures was $2 billion. Damage functions indicate that reductions in pollutants will decrease physical and, therefore, economic damage. Approaches to cost estimation with data requirements different from those necessary for the physical damage function approach have been attempted. These, however, do not directly relate cause to effect.

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10. DOSIMETRY OF INHALED PARTICLES IN THE RESPIRATORY TRACT

10.1 INTRODUCTION

Almost all studies of the health effects of particulate matter (PM) investigate exposure-response' relationships or associations. In controlled studies, an animal or human volunteer breathes a measured concentration of PM for a specified duration (i.e., the exposure), and responses, such as pulmonary function or clearance rates, are measured. In epidemiological studies, an index of exposure from personal or stationary monitors of selected pollutants is analyzed for associations with health outcomes, such as morbidity or mortality. However, it is a basic tenet of toxicology that the dose delivered to the target site, not the external exposure, is the proximal cause of a response. Therefore, there is increased emphasis on understanding the exposure-dose-response relationship. Exposure is what gets measured (or estimated) in the typical study and what gets regulated; dose is the causative factor. Dose is quite important to intra and interspecies extrapolations. For example, a healthy individual and a person with emphysema will not get identical doses to specific lung regions even if their external exposure is identical. Knowledge of how and to what extent disease factors affect dose can assist in characterizing susceptible subpopulations. If a rat and a human are identically exposed, they will receive different doses to regions of the respiratory tract. Insofar as this is quantitatively understood, laboratory animal data can be more useful in assessing human health risks.

The exposure-dose-response relationship is quite complex, beginning with definitions. Although dose is a common generic term, for PM it can and has been defined as delivered dose or retained dose; as a net dose over a unit time or a dose-rate; as a particulate mass, number or surface area; and as a compound (e.g., sulfuric acid) or a component of that compound (e.g., hydrogen ion). Even if dose could be easily defined, it fits within a complex continuum. For example, as illustrated in Figure 10-1, it is ultimately desirable to have a comprehensive biologically-based dose-response model that incorporates the mechanistic determinants of chemical disposition, toxicant-target interactions, and tissue response integrated into an overall model of pathogenesis. Mathematical dosimetry models

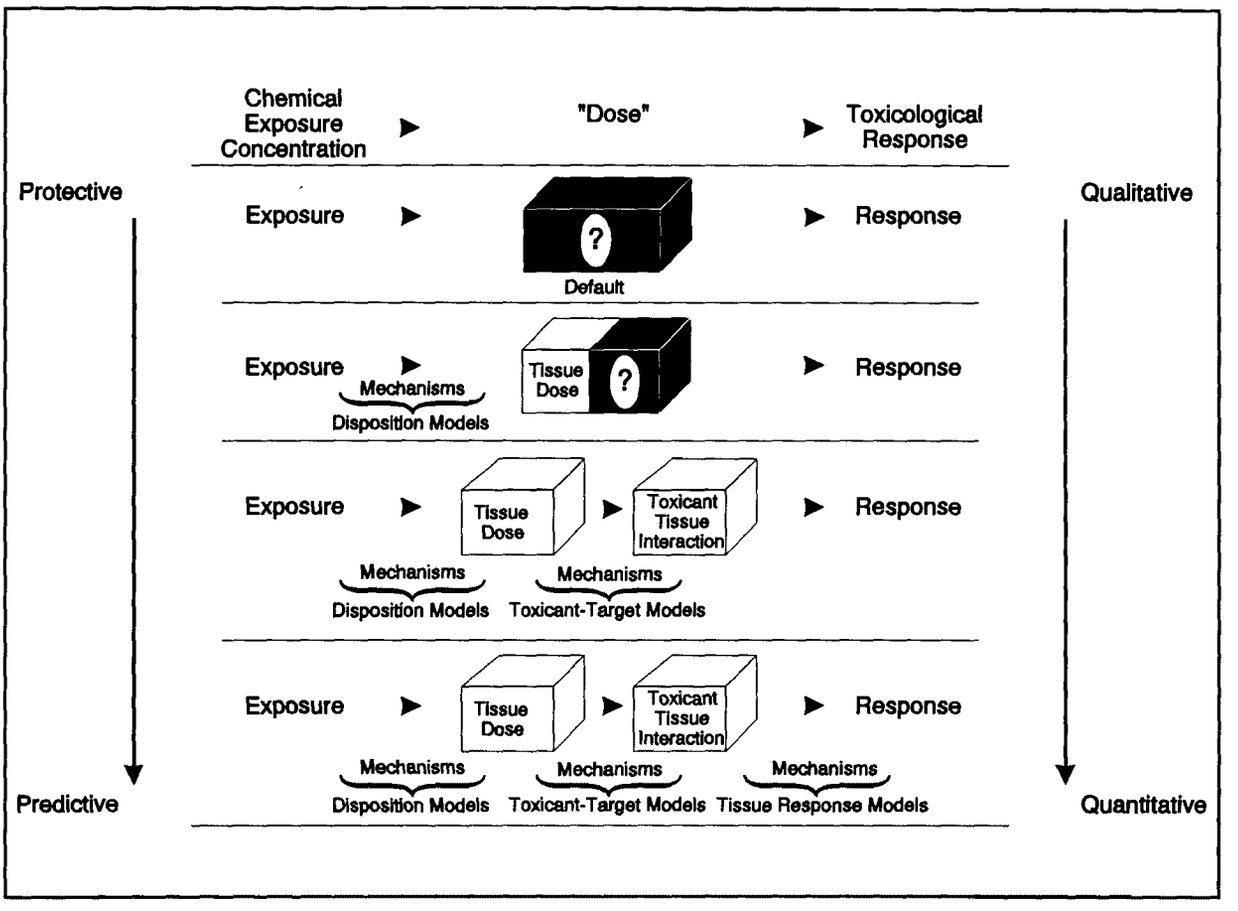

Figure 10-1. Schematic characterization of comprehensive exposure-dose-response continuum and the evolution of protective to predictive dose-response estimates.

Adapted from Conolly (1990) and Andersen et al. (1992).

that incorporate mechanistic determinants of disposition (deposition, absorption, distribution, metabolism, and elimination) of chemicals have been useful in describing relationships along this continuum (e.g., between exposure concentration and target tissue dose), particularly as applied to describing these relationships for the exposure-dose-response[1] component of risk assessment. With each progressive level, incorporation and integration of mechanistic determinants allow elucidation of the exposure-dose-response continuum and, depending on the knowledge of model parameters and fidelity to the biological system, a more accurate

[1]"Response" is an indication of an alteration influence regardless of whether the data were measured as quantal, count, continuous, or ordered categorical; response and effect are used interchangeably.

characterization of the pathogenetic process. Due to the increase in accuracy of the characterization with each progressive level, exposure-dose-response estimates also progress from more protective to predictive, although there will always be some degree of uncertainty.

This chapter addresses exposure-dose relationships, primarily discussing the mechanistic determinants of inhaled dose and the available mathematical dosimetry models for humans and laboratory animals in order to provide background on the potential extrapolations that may be applied to the observed response data in both Chapter 11 (human and animal toxicity data) and Chapter 12 (epidemiologic data). The chapter deals exclusively and generically with aerosols (i.e., both airborne droplets and solid particles, including the hygroscopic, acidic variety). It briefly reviews selected studies that have been reported in the literature on particle deposition and retention since the publication of the 1982 Air Quality Criteria Documents on Particulate Matter and Sulfur Oxides and the 1989 Acid Aerosols Issue Paper (U.S. Environmental Protection Agency; 1982, 1989), but the focus is on newer information. After an overview of general considerations for extrapolation modeling, the chapter proceeds to describe important particle characteristics and the basic mechanisms of particle deposition and clearance in the respiratory tract. After the available deposition and clearance data are reviewed, various models are described. Because dosimetry models may provide insight on what the appropriate dose metric may be for characterizing the exposure-dose-response relationships for PM, human and laboratory animal dosimetry models were chosen to extrapolate data for various exposures and endpoints. A later section discusses the choice of the extrapolation model and illustrates calculations to determine plausible dose metrics for different endpoints. This information should be useful to the interpretation of health effects data in Chapters 11 and 12.

10.1.1 General Considerations for Extrapolation Modeling

Major factors that affect the disposition (deposition, uptake, distribution, metabolism, and elimination) of inhaled particles include the physicochemical properties of the particles (e.g., particle diameter, distribution, hygroscopicity) and anatomic (e.g., upper respiratory tract architecture, regional surface areas, airway diameters, airway lengths, branching patterns) and physiologic (e.g., ventilation rates, clearance mechanisms) parameters of

individual mammalian species. The relative contribution of each of these factors is a dynamic relationship. Further, the relative contribution of these determinants is also influenced by exposure conditions such as concentration and duration. A comprehensive description of the exposure-dose-response continuum is desired for accurate extrapolation. Therefore, a dosimetry model should incorporate all of the various deterministic factors into a computational structure. Clearly, many advances in the understanding and quantification of the mechanistic determinants of particle disposition, toxicant-target interactions, and tissue responses (including species sensitivity) are required before an overall model of pathogenesis can be developed for a specific aerosol. Such data do exist to varying degrees, however, and may be incorporated into less comprehensive models that nevertheless are useful in describing delivered doses or in some cases, target tissue interactions.

10.1.1.1 Model Structure and Parameterization

Data on the mechanistic determinants of particle disposition, toxicant-target interactions, and tissue responses to incorporate into a model vary in degree of availability for chemicals and species. A theoretical mathematical model to describe particle deposition would require detailed information on all of the influential parameters (e.g., respiratory rates, exact airflow patterns, complete measurement of the branching structure of the respiratory tract, pulmonary region mechanics) across different humans or across various laboratory species of interest. An empirical model (i.e., a system of equations fit to experimental data) is an alternative approach. Depending on the relative importance of these various mechanistic determinants, models with less detail may be used as a default to adequately describe differences in dosimetry for the purposes of extrapolation.

An understanding of the basis for model structures also allows development of a framework for the evaluation of whether one available model structure may be considered optimal relative to the another. A model structure might be considered more appropriate than another for extrapolation when default assumptions or parameters are replaced by more detailed, biologically-motivated descriptions or actual data, respectively. For example, a model could be preferred if it incorporates more chemical or species-specific information or if it accounts for more mechanistic determinants. Empirical models may differ in the quality

or appropriateness of the data used to estimate equations. These considerations are summarized in Table 10-1.

TABLE 10-1. HIERARCHY OF MODEL STRUCTURES FOR DOSIMETRY AND EXTRAPOLATION

Optimal model structure
Structure describes all significant mechanistic determinants of particle disposition, toxicant-target interaction, and tissue response
Uses chemical-specific and species-specific parameters
Dose metric described at level of detail commensurate to epidemiologic or toxicity data
Default model structure
Limited or default description of mechanistic determinants of particle disposition, toxicant-target interaction, and tissue response
Uses categorical or default values for chemical and species parameters
Dose metric at generic level of detail

Adapted from U.S. Environmental Protection Agency (1994); Jarabek (1994).

The sensitivity of the model to differences in structure may be gauged by their relative importance in describing the response function for a given chemical. For example, a model which incorporates many parameters may not be any better at describing ("fitting") limited response data than a simpler model.

Woodruff et al. (1992) used Monte Carlo analyses to assess the impact that structure and parameterization of physiologically-based pharamcokinetic (PBPK) models has on output predictions and variability. Nonphysiologically based (NPB) models of three or two compartments were compared with PBPK models that either used five compartments (PBPK5) to describe the body (well-perfused, poorly-perfused, fat, bone marrow, and liver tissue compartments) or that "lumped" the body into three (fat, bone marrow, and central) compartments (PBPK3). Comparisons were run for different data sets from inhalation to benzene. The two main influences on variability of model output predictions were (1) the quantity and type of data used to calibrate the model and (2) the number of parameters in the model. While some differences existed between the models' average predictions when

calibrated to the same experimental data, these differences were smaller than the differences between the predictions made by the same model fitted to different data sets. An excessive number of parameters was shown to lead to overparameterization and cause large variability in the output. The similarities in the average predictions of the NPB and PBPK models supported the use of NPB models in some cases. The NPB models have fewer parameters and are potentially easier to fit. The PBPK models did show greater reliability for extrapolation, but NPB models provided reliable results with less effort needed in fitting data when the objective was to interpolate from the current data. Issues addressed in the review by Woodruff et al. (1992) and others (Hattis et al., 1989; Farrar et al., 1989; Portier and Kaplan, 1989; Bois et al., 1990) regarding evaluation of the uncertainty in input parameters and the variability of predictions due to alternate structures and data sets, should be considered when evaluating different available model structures.

10.1.1.2 Intraspecies Variability

There are essentially three areas of concern in assessing the quality of epidemiologic or toxicity data. These involve the design and methodological approaches for (1) exposure measures, (2) effect measures, and (3) the control of covariables and confounding variables. Although these topics are discussed in detail in other chapters, it is important to also consider these concerns when evaluating potential dosimetry models for extrapolation of such data. For example, although the epidemiologic investigations attempt to relate an exposure to a given health effect, the way the exposure is characterized may influence the choice of an appropriate dosimetry model. Characterization of a particular health effect in a human population may include pre-existing pathologic conditions (e.g., lung disease) that may alter inhalation dosimetry and have implications for model choice. The broad genetic variation of the human population in processes related to chemical disposition and tissue response (e.g., age, gender, disease status) may cause individual differences in sensitivity to inhaled aerosols. Dosimetry models could be exercised as a means of analyzing the sensitivity of model outputs to ranges for various parameters (e.g., range in ventilation due to gender).

10.1.1.3 Extrapolation of Laboratory Animal Data to Humans

Both qualitative and quantitative extrapolation of laboratory animal data to humans are of interest. Qualitative extrapolation refers to the "class" of the effects. For example, if the function of rabbit alveolar macrophages is depressed by sulfuric acid, will it also be depressed in humans, albeit at an unknown exposure? This type of extrapolation is limited to known homologous effects. For example, given the similarities in of human and laboratory animal alveolar macrophages, and likely toxicity mechanisms, the qualitative extrapolation is reasonable. However, in some cases, the homology is not understood adequately. For example, what is the laboratory animal model comparison to the mortality observed in the epidemiological studies? Several hypotheses exist, but at present, there is inadequate evidence for concensus. Once a qualitative extrapolation has been performed, a quantitative extrapolation can be initiated. In order for the laboratory animal data to be useful to the risk assessment of particulate matter, interspecies extrapolation should account for differences in dosimetry and species sensitivity. Dosimetry, here, is used broadly to represent the effective dose to target site which may be some complex combination of delivered dose and retained dose. Given the identical exposure, this dose will be different in different species. Even if knowledge on dose were complete, there still needs to be an understanding of species differences in sensitivity to that dose. For example, perhaps one species has more efficient repair or chemical defense mechanisms than another, making that one species more sensitive to a given dose.

10.2 CHARACTERISTICS OF INHALED PARTICLES

Information about particle size distribution aids in the evaluation of the effective inhaled dose. Because the characteristics of inhaled particles interact with the other major factors controlling comparative inhaled dose, this section discusses aerosol attributes requiring characterization and provides general definitions.

An aerosol is a suspension of particulate matter in air. It is intrinsically unstable, and hence, tends to deposit both continuously and inelastically onto exposed surfaces. From the perspective of health-related actions of aerosols, interest is limited to particles that can penetrate, at least, into the nose or mouth and that deposit on respiratory tract surfaces. For

humans, this constraint ordinarily eliminates very coarse particles, viz, greater than about 100 μm diameter. Particles between 1 μm and 20 μm diameter are commonly encountered in the work place and the ambient air. Still smaller, i.e., submicron diameter particles, especially between 0.1 to 1.0 μm diameter, are perhaps the most numerous in the environmental air. Even particles down to the nanometer (nm) size domain are found in the atmosphere and are of interest, although until recently, these "ultrafine" particles were of greater interest to atmospheric scientists than to biomedical scientists. Typically, "ultrafine" aerosols are produced by highly energetic reactions (e.g., high temperature sublimation and combustion, or by gas phase reactions involving atmospheric pollutants). Note that 10 nm = 100 Ångstroms = 0.01 μm or 1×10^{-6} cm diameter.

Because aerosols can consist of almost any material, descriptions of aerosols in simple geometric terms can be misleading unless important factors relating to size, shape, and density are considered. Aerosols are usually described in terms of geometric or aerodynamic sizes. Additionally, aerosols may be defined in terms of particle surface area. It is important to note that aerosols present in natural and work environments all have polydisperse size distributions. This means that the particles comprising the aerosols have a range of geometric size, aerodynamic size, and surface area and are more appropriately described in terms of size distribution parameters. Aerosol sampling devices can be used to collect bulk or size fractions of aerosols to allow defining the size distribution parameters. In this procedure, the fraction of particles in defined size parameter groups (number, mass, or surface area) is divided by the total number, mass, or surface of all particles collected and divided also by the size interval for each group. Data from the sampling device are then expressed in terms of the fraction of particles per unit size interval. The next step is to use this information to define an appropriate particle size distribution.

The lognormal distribution has been widely used for describing size distributions of radioactive aerosols (Raabe, 1971) and is also generally used as a function to describe other kinds of aerosols. For many aerosols, their size distributions may be described by a lognormal distribution, meaning that the distribution will resemble the bell-shaped Gaussian error curve, if the frequency distribution is based on the logarithms of the particle size. The lognormal distribution is a skewed distribution characterized by the fact that the logarithms of particle diameter are normally distributed. In linear form, the logarithmic mean is the

median of the distribution. The standard deviation, σ, of this logarithmic normal distribution is a logarithm, so that addition and subtraction of this logarithm to and from the logarithmic mean is equivalent to multiplying and dividing the median by the factor σ_g, with $\ln \sigma_g = \sigma$. The factor σ_g is defined as the geometric standard deviation. When any aerosol distribution is "normalized", it acquires parameters and properties equivalent to those of the Gaussian distribution. Accordingly, the only two parameters needed to describe the log normal distribution are the median diameter and the geometric standard deviation, σ_g, (ratio of the log 84%/log 50% size cut or log 50%/log 16% size cut, where the 50% size cut is the median). While there may be occasions when the number of the particles is of the greatest interest, the distribution of mass in an aerosol according to particle size is of interest if particle mass determines the dose of interest. This is essentially a matter of converting a diameter distribution to a diameter-cubed distribution since the volume of a sphere with diameter d is $\pi d^3/6$ and mass is simply the product of particle volume and physical density. For a distribution formed by counting particles, the median is called the count median diameter (CMD).

The cumulative distribution of a lognormally distributed size distribution is conveniently evaluated using log-probability graph paper on which the cumulative distribution forms a straight line (Figure 10-2). This distribution can be used for all the three lognormally distributed particle size parameters discussed above, which are related as indicated in Figure 10-2. The characteristic parameters of this distribution are the size and σ_g. The CMD is characterized by the fact that half of the particles in the size distribution are larger than the CMD and half of the particles are smaller. Multiplying and dividing the CMD by σ_g yields the particle size interval for the distribution that contains about 68% of the particles by number.

When particles are not spherical, equivalent diameters can be used in place of the physical diameters of particles. A calculated parameter, the projected area diameter (diameter of a circle having a cross sectional area equivalent to the particles in the distribution of interest) is used as the equivalent diameter.

The mass median diameter (MMD) and surface median diameter (SMD), also shown in Figure 10-2, are additional ways to describe size distributions of lognormally distributed aerosols. In these distributions, half of the mass or surface area of particles is associated

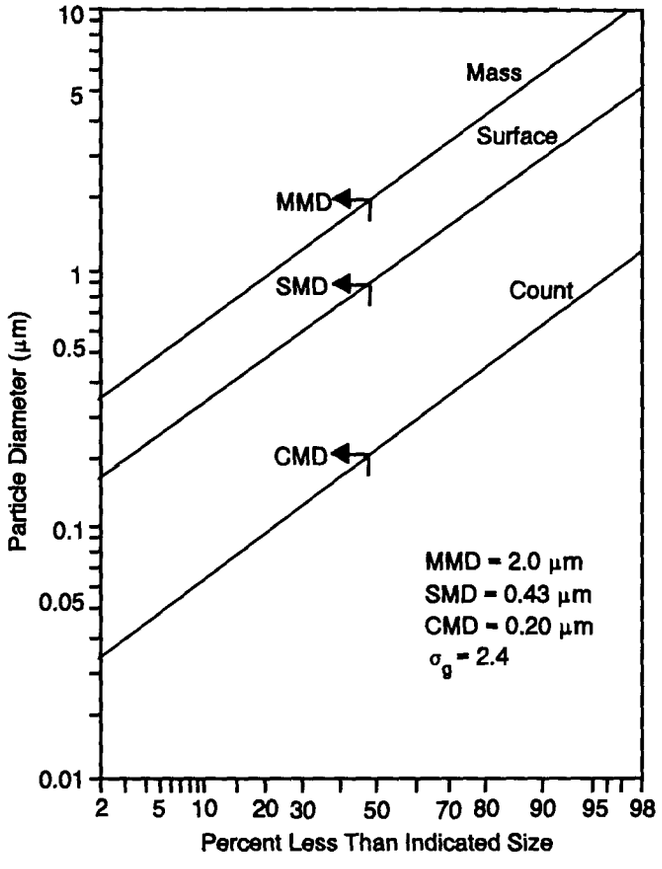

Figure 10-2. Lognormal particle size distribution for a hypothetical aerosol.

with particles smaller than the MMD or SMD; the other half of the particles is associated with particles larger than the MMD or SMD, respectively.

The relationship of the various lognormal distribution parameters based on geometric diameter of particles is unique, since the CMD, SMD, and MMD are all lognormal with the same σ_g, but with different means that can be calculated. The CMD and σ_g can be determined and extrapolated to MMD, and SMD using the following relationships

$$\ln(\text{MMD}) = \ln(\text{CMD}) + 3(\ln\sigma_g)^2, \qquad (10\text{-}1)$$

and

$$\ln(\text{SMD}) = \ln(\text{CMD}) + 2(\ln\sigma_g)^2. \qquad (10\text{-}2)$$

For most aerosols, it is useful to define particle size in terms of its aerodynamic size wherein particles of differing geometric size, shape and density are compared aerodynamically with the instability behavior of particles that are unit density (1 gm/cm^3) spheres. The aerodynamic behavior of unit density spherical particles can be determined, both experimentally and theoretically, consequently, they constitute a useful standard by which all particles can be compared in matters of inertial impaction and gravitational settling. Thus, if the terminal settling velocity of a unit density sphere of 10 μm diameter is measured in tranquil air, the velocity induced by gravity would be $\sim 3 \times 10^{-1}$ cm/s. If the gravitational settling of an irregularly shaped particle of unknown density was measured and the same terminal velocity was obtained, the particle would have a 10 μm aerodynamic diameter (d_{ae}). Its tendency to deposit by inertial processes on environmental surfaces or onto the surfaces of the human respiratory tract will be the same as for the 10 μm unit density sphere.

A term that is frequently encountered is mass median aerodynamic diameter (MMAD), which refers to the mass median of the distribution of mass with respect to aerodynamic diameter. With commonly-encountered aerosols having low to moderate polydispersity, $\sigma_g \leq 2.5$, the Task Group on Lung Dynamics (TGLD) (1966) showed that mass deposition in the human respiratory tract could be approximated by the deposition behavior of the particle of median aerodynamic size in the mass distribution, the so-called MMAD. This is successful because the particles which dominate control of the mass distribution are those which deposit mainly by settling and inertial impaction.

In many urban environments, the aerosol frequency and mass distributions have been found to be bimodal or trimodal (Figure 10-3), usually indicating a composite of several log normal distributions where each aerosol mode was presumably derived from different formation mechanisms or emission sources (John et al., 1986). Conversely, in the laboratory, experimentalists often create aerosol distributions which are lognormal, and very frequently, they generate monodisperse aerosols consisting of particles of nearly one size. The use of monodisperse aerosols of nearly uniform, unit density, spherical particles greatly simplifies experimental deposition and retention measurements and also instrument calibrations. With uniform particles, the mass, surface area and frequency distributions are nearly identical, another important simplification.

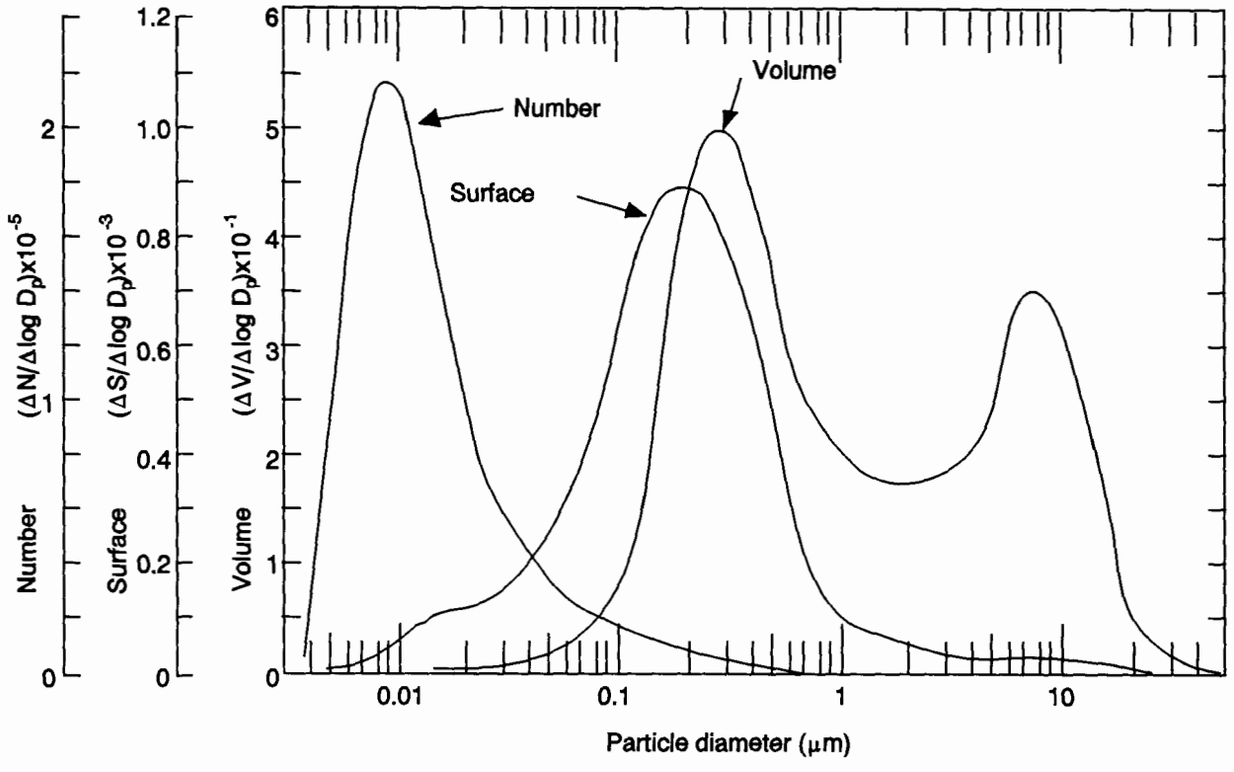

Figure 10-3. These normalized plots of number, surface and volume (mass) distributions from Whitby (1975) show a bimodal mass distribution in a smog aerosol. Historically, such particle size plots were described as consisting of a coarse mode (2.5 to 15 μm), a fine mode (0.1 to 2.5 μm), and a nuclei mode (< 0.05μm). The nuclei mode would currently fall within the ultrafine particle range (0.005 to 0.1 μm).

The terms count median aerodynamic diameter (CMAD) and surface median aerodynamic diameter (SMAD) might be encountered. These distributions are useful in that they include consideration of aerodynamic properties of the particles. If the particle aerodynamic or diffusive diameter is determined when sizing is done, then the median of the particle size distribution is the CMAD, or count median diffusive (or thermodynamic) diameter (CMDD or CMTD), respectively. If the mass of particles is of concern, then the median that is derived is the MMAD or mass median diffusive (or thermodynamic) diameter (MMDD or MMTD). Generally, MMDs or MMADs are generally used to evaluate particle deposition patterns in the respiratory tract because deposition of inhaled aerosol particles, as discussed in detail later in this chapter, is determined primarily by particle diffusive and

aerodynamic properties of the particles rather than simply particle physical size, surface area, volume, or mass. Activity median aerodynamic diameter (AMAD) is the median of the distribution of radioactivity or toxicological or biological activity with respect to size. Both MMAD and AMAD are determined using aerosol sampling devices such as multistage impactors. When particles become smaller than about 0.1 μm diameter, their instability as an aerosol depends mainly on their interaction with air molecules. Like particles in Brownian motion, they are caused to "diffuse". For these small particles and especially for ultrafine particles, this interaction is independent of the particle density and varies only with geometric particle diameter. Very small particles are not expressed in aerodynamic equivalency, but instead to a thermodynamic-equivalent size. The thermodynamic particle diameter (d_{TH}) is the diameter of a spherical particle that has the same diffusion coefficient in air as the particle of interest. The activity median thermodynamic diameter (AMTD) is the diameter associated with 50 percent of the activity for particles classified thermodynamically.

The selection of the particle size distribution to associate with health effects depends on decisions about the importance of number of particles, mass of particles, or surface area of particles in producing the effects. In some situations, numbers of particles or mass of particles phagocytized by alveolar macrophages may be important; in other cases, especially for particles that contain toxic constituents, surface area may be the most important parameter that associates exposures with biological responses or pathology. These particle distributions should all be considered during the course of evaluating relationships between inhalation exposures to particles and effects resulting from the exposures.

Most of the discussion in the remainder of this chapter will focus on MMAD because it is the most commonly used measure of aerosol distributions. If MMAD is not measured directly, an alternative is to determine MMAD from one of the particle size distributions that is based on physical size of the particles (CMD, MMD, and SMD), which can all be readily converted to MMAD. The approximate conversion of MMD to MMAD is made using the following relationship (neglecting slip)

$$\text{MMAD} = \text{MMD} \cdot (\text{particle density})^{0.5}. \qquad (10\text{-}3)$$

By definition, MMDD = CMDT or MMDD, because behavior of particles in this size category does not depend on aerodynamic properties.

Because aerosols of small particles contain such a large surface area, they acquire greater reactivity. For example, tantalum is a very stable, unreactive metal, whereas aerosols of tantalum particles can be caused to explode by a spark. The rates of oxidation and solubility are proportional to surface area as are the processes of gas adsorption and desorption, and vapor condensation and evaporation. Accordingly, special concerns arise from gas-particle mixtures and from "coated" particles. For a general review of atmospheric aerosols, their characteristics and behavior, the publication Airborne Particles prepared under the aegis of the National Research Council (1979) is recommended.

10.3 ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY TRACT

The respiratory systems of humans and various experimental animals differ in anatomy and physiology in many quantitative and qualitative ways. These differences affect air flow patterns in the respiratory tract, and in turn, the deposition of an inhaled aerosol. Particle deposition connotes the removal of particles from their airborne state due to their inherent instabilities in air and to their induced-instabilities in air when additional external forces are applied. For example, in tranquil air, a 10 μm diameter, unit density particle only undergoes sedimentation due to the force of gravity. If a 10 μm particle is transported in a fast moving air stream, it acquires an inertial force which can cause it to deposit on a surface projecting into the air stream without significant regard to gravitational settling. For health-related issues, interest in particle deposition is limited to that which occurs in the respiratory tract of humans and laboratory animals during the respiration of dust-laden air.

Once particles have deposited onto the surfaces of the respiratory tract, some will undergo transformation, others will not, but subsequently, all will be subjected either to absorptive or non-absorptive particulate removal processes, e.g., mucociliary transport, or a combination thereof. This will result in their removal from the respiratory tract surfaces. Following this, they will undergo further transport which will remove them, to a greater or less degree, from the respiratory tract. Such particulate matter is said to have undergone clearance. To the extent particulate matter is not cleared, it is retained. The temporal

persistence of uncleared (retained) particles within the structure of the respiratory tract is termed retention.

Thus, either the deposited or retained dose of inhaled particles in each region is governed by the exposure concentration, by the individual species anatomy (e.g., airway size and branching pattern) and physiology (e.g., breathing rate, cell types, and clearance mechanisms), and by the physicochemical properties (e.g., particle size, distribution, hygroscopicity, solubility) of the aerosol. The anatomic and physiologic factors are discussed in this section. The physicochemical properties of particles were discussed in Section 10.2. Deposition and clearance mechanisms will be discussed in Section 10.4.6.

The respiratory tract in both humans and various experimental mammals can be divided into three regions on the basis of structure, size, and function: the extrathoracic (ET) region or upper respiratory tract (URT) that extends from just posterior to the external nares to the larynx, i.e., just anterior to the trachea; the tracheobronchial region (TB) defined as the trachea to the terminal bronchioles where proximal mucociliary transport begins; and the alveolar (A) or pulmonary region including the respiratory bronchioles and alveolar sacs. The thoracic (TH) region is defined as the TB and A regions combined. The anatomic structures included in each of these respiratory tract regions are listed in Table 10-2, and Figure 10-4 provides a diagrammatic representation of these regions as described in the International Commision on Radiological Protection (ICRP) Human Respiratory Tract Model (ICRP66, 1994).

Figure 10-5 depicts how the architecture of the respiratory tract influences the airflow in each region and thereby the dominant deposition mechanisms. The 5 major mechanisms (gravitational settling, inertial impaction, Brownian diffusion, interception and electrostatic attraction) responsible for particle deposition are schematically portrayed in Figure 10-5 and will be discussed in detail in Section 10.4.1.

The nasal hairs, anterior nares, turbinates of the nose and glottic aperture in the larynx are areas of especially high air velocities, abrupt directional changes, and turbulence, hence, the predominant deposition mechanism in the ET region is inertial impaction. In this process, changes in the inhaled airstream direction or magnitude of air velocity streamlines or eddy components are not followed by airborne particles because of their inertia. Large

TABLE 10-2. RESPIRATORY TRACT REGIONS

Region	Anatomic Structure	Other Terminology
Extrathoracic (ET)	Nose Mouth Nasopharynx Oropharynx Laryngopharynx Larynx	Head airways region Nasopharynx (NP) Upper respiratory tract (URT)
Tracheobronchial (TB)	Trachea Bronchi Bronchioles (including terminal bronchioles)	Lower conducting airways
Alveolar (A)	Respiratory bronchioles Alveolar ducts Alveolar sacs Alveoli	Gas exchange region Pulmonary region

Adapted from: Phalen et al. (1988a).

particles (>5 μm in humans) are more efficiently removed from the airstream in this region. The respiratory surfaces of the nasal turbinates are in very close proximity to and designed to warm and humidify the incoming air, consequently they can also function effectively as a diffusion deposition site for very small particles and an effective absorption site for water-soluble gases. The turbinates and nasal sinuses are lined with cilia which propel the overlying mucous layer posteriorly via the nasopharynx to the laryngeal region. Thus, the airways of the human head are major deposition sites for the largest inhalable particles (>10 μm aerodynamic diameter) as well as the smallest particles (<0.1 micrometers diameter). For the most part, the ET structures are lined with a squamous, non-ciliated mucous membrane. Collectively, the movement of upper airway mucus, whether transported by cilia or gravity, is mainly into the gastrointestinal tract.

As air is conducted into the airways of the head and neck during inspiration, it first passes through either the nasal passages or mouth. Whereas nasal breathing is normal with most people most of the time, this option usually depends upon the work load. Work loads which tend to treble or quadruple minute ventilation i.e., go from 10 L/m to 30 to 40 L/m,

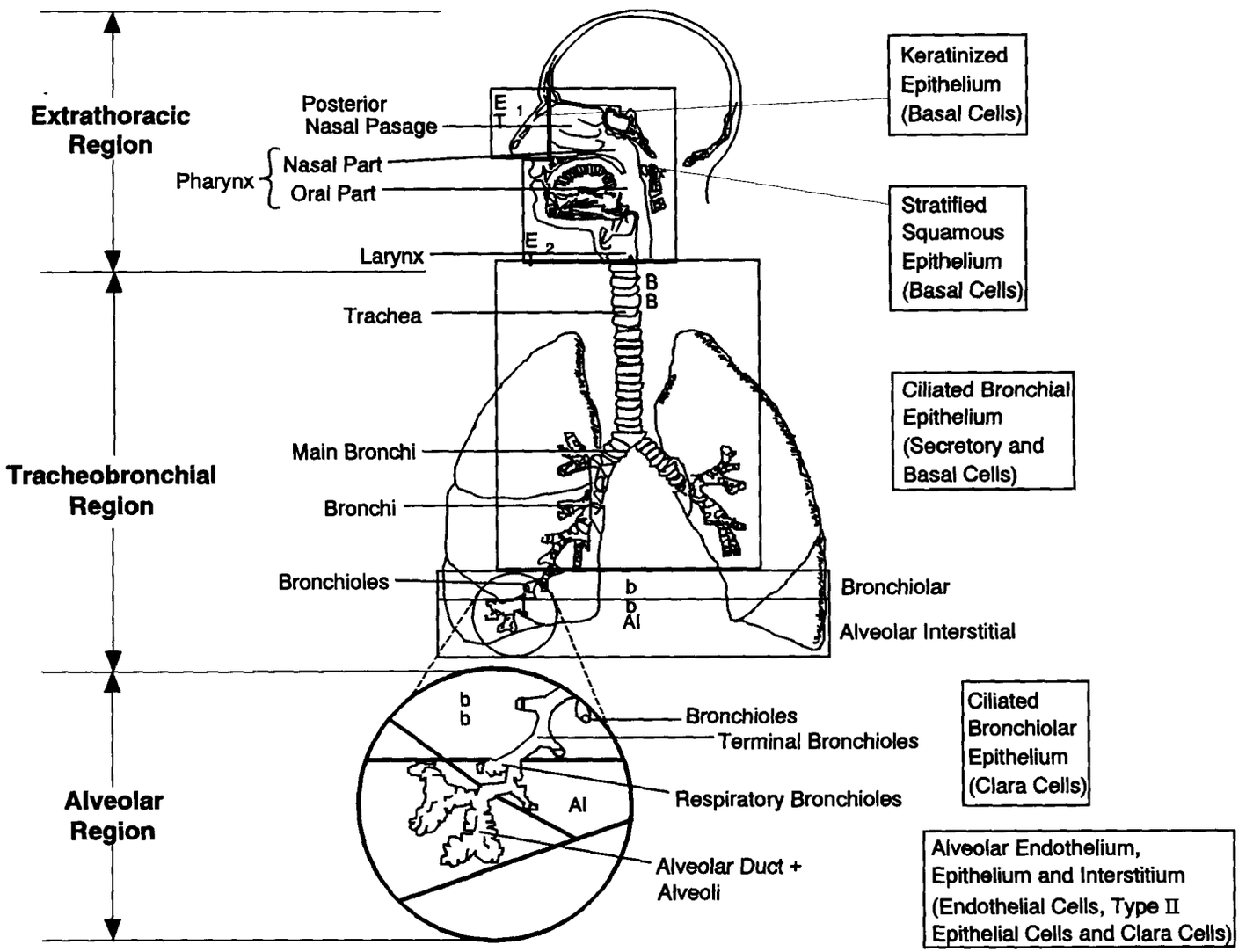

Figure 10-4. Diagrammatic representation of respiratory tract regions in humans.

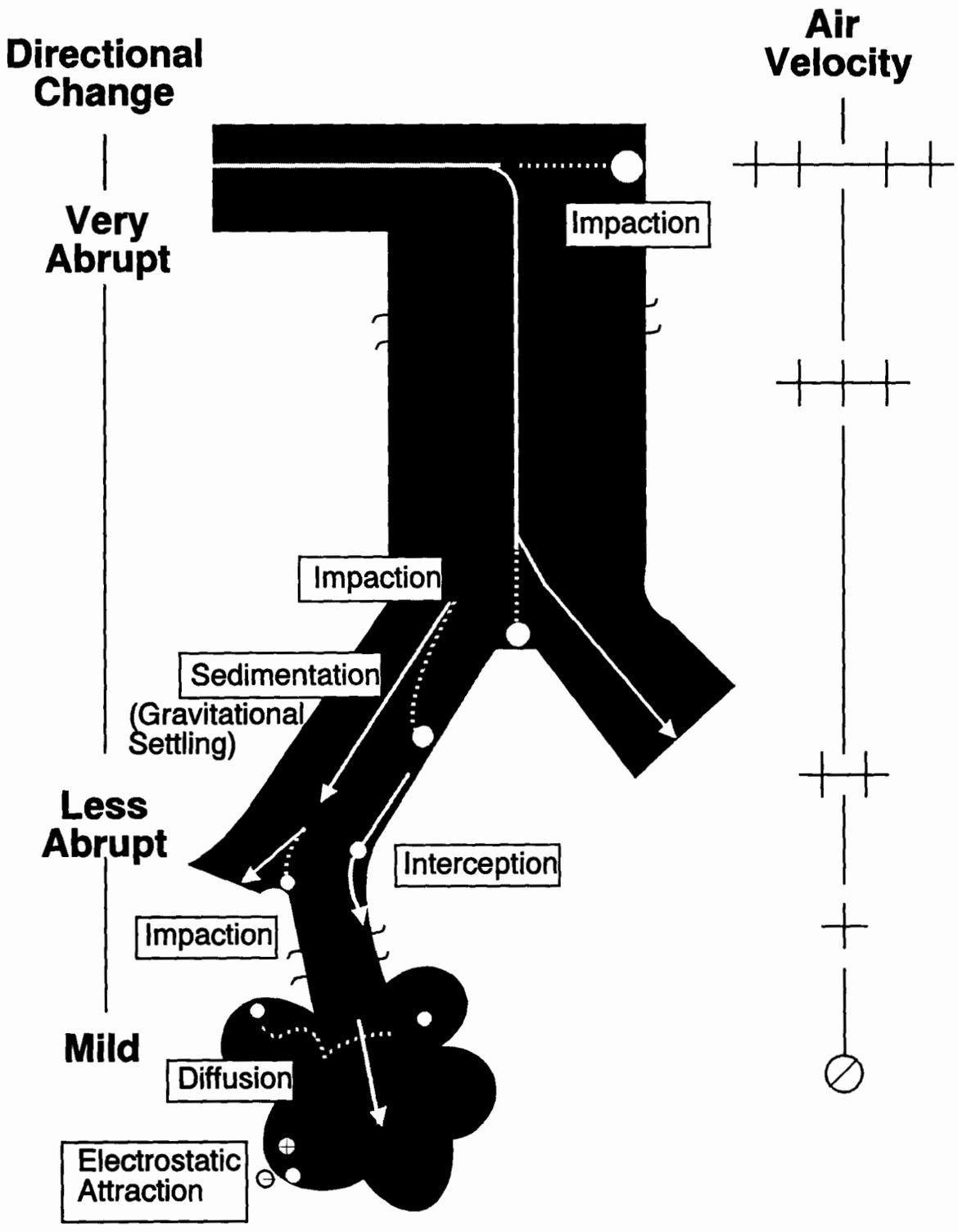

Figure 10-5. Schematic representation of five major mechanisms causing particle deposition where airflow is signified by the arrows and particle trajectories by the dashed line.

Source: Adapted from Casarett (1975); Raabe (1979); Lippmann and Schlesinger (1984).

cause most subjects to change from nasal to oronasal breathing. In either case, the inspired air then passes through the pharyngeal region into the larynx.

From the larynx, the inspired air passes into the trachea, a cylindrical, muscular-cartilaginous tube. The trachea measures approximately 1.8 cm diameter × 12 cm long in humans. The trachea, like other conducting airways of the lungs, is ciliated and richly endowed with secretory glands and mucus-producing goblet cells. The major or main stem bronchi are the first of approximately 16 generations of branching that occur in the human bronchial "tree". For modeling purposes, Weibel (1963;1980) described bronchial branching as regular and dichotomous, i.e., where the branching parent tube gives rise, symmetrically, to two smaller (by $\sqrt[3]{2}$) tubes of the same diameter. While this pattern provides a simplification for modeling, the human bronchial tree actually has irregular dichotomous branching, wherein the parent bronchi gives rise to two smaller tubes of differing diameter and length. The number of generations of branching occurring before the inspired air reaches the first alveolated structures varies from about 8 to 18 (Raabe et al. 1976, Weibel 1980).

Impaction remains a significant deposition mechanism for particles larger than 2.5 μm aerodynamic equivalent diameter (d_{ae}) in the larger airways of the TB region in humans and competes with sedimentation, with each mechanism being influenced by mean flow rate and residence time, respectively. As the airways successively bifurcate, the total cross-sectional area increases. This increases airway volume in the region, and the air velocity is decreased. With decreases in velocity and more gradual changes in air flow direction as the branching continues, there is more time for gravitational forces (sedimentation) to deposit the particle. Sedimentation occurs because of the influence of the earth's gravity on airborne particles. Deposition by this mechanism can occur in all airways except those very few that are vertical. For particles $\approx$4 μm d_{ae}, a transition zone between the two mechanisms, from impaction to predominantly sedimentation, has been observed (U.S. Environmental Protection Agency, 1982). This transition zone shifts toward smaller particles for nose breathing.

The surface area of the human TB region is estimated to be about 200 cm^2 and its volume is about 150 to 180 mL, the so-called anatomical dead space. At the level of the terminal bronchiole, the most peripheral of the distal conducting airways, the mean airway diameter is about 0.3 to 0.4 mm and their number is estimated at about 6×10^4. As to the

variability of bronchial airways of a given size, Weibel's (1963) considered a 0.2 cm diameter airways and noted that such airways occur from the 4th to 14th generations of branching, peaking in frequency around the 8th generation. An insight into the variabilities in various lung models was provided by Forrest (1993) who indicated that the number of terminal bronchioles incorporated in Weibel's model was about 66,000, whereas, Findeisen (1935) used 54,000 and Horsfield and Cummings (1968) estimated only 28,000 (op cit). The transitional airways of the human lung, the respiratory bronchioles and alveolar ducts, undergo another 6 generations of branching according to Weibel (1980) before they become alveolar sacs. On this basis, the dichotomous lung model indicates there should be about 8.4×10^6 branches (2^{23}), serving 3×10^8 alveoli. The recent "typical path" model of Yen and Schum (1980), adopted by the National Council on Radiation Protection (NCRP) (Cuddihy et al., 1988), cites $\approx$33,000 terminal bronchioles. The International Commission on Radiological Protection (ICRP) utilized the dimensions from three sources in its human respiratory tract model (ICRP66, 1994).

The parenchymal tissue of the lungs surrounds all of the distal conducting airways except the trachea and portions of the mainstem bronchi. This major branch point area is termed the mediastinum; it is where the lungs are suspended in the thorax by a band of pleura called the pulmonary ligament, where the major blood vessels enter and leave the hilus of each lung, and the site of the mediastinal pleura which envelopes the heart and essentially subdivides the thoracic cavity.

Humans lungs are demarcated into 3 right lobes and 2 left lobes by the pleural lining. The suspension of the lungs in an upright human gives rise to a gradient of compliance increasing from apex to base. Subdivisions of the lobes, segments, are not symmetrical due to a fusion of 2 (middle left lung) of the 10 lobar segments of the lung and occasionally an underdeveloped segment in the lower left lobe. Lobar segments can be related to specific segmental bronchi and are useful anatomical delineators for bronchoalveolar lavage.

The lung parenchyma is composed primarily of alveolated structures of the A region and the associated blood vessels and lymphatics. The parenchyma is organized into functional units called acini which consist of the dependent structures of the first order respiratory bronchioles. The alveoli are polyhedral, thin-walled structures numbering approximately 3×10^8 in the adult human lung. Schreider and Raabe (1981) provided a range

of values, viz, 2×10^8 to 5.7×10^8. The parenchymal lung tissue can be likened to a thin sheet of pneumocytes (0.5 to 1.0 μm thickness) that envelopes the pulmonary capillary bed and is supported by a lattice of connective tissue fibers: these fibers enclose the alveolar ducts (entrance rings), support the alveolar septa, and anchor the parenchymal structures axially (e.g. from pulmonary veins) and peripherally (from the pleural surface).

The alveolar walls or septa are constructed of a network of meandering capillaries consisting mainly of endothelial cells, an epithelium made of membranous Type I pneumocytes (97% of the surface) with a few Type II pneumocytes (3% of the surface), and an interstitium which contains interstitial histiocytes and fibroblasts. For about one-half of the alveolar surface, the Type I pneumocytes and the capillary endothelia share a fused basement membrane. Otherwise, there is an interstitial space within the septa which communicates along the capillaries to the connective tissue cuffs around the airways and blood vessels. The connective tissue spaces or basal lamina of these structures are served by pulmonary lymphatic vessels whose lymph drainage, mainly perivascular and peribronchial, is toward the hilar region where it is processed en route by islets of lymphoid tissue and filtered principally by the TB lymph nodes before being returned to the circulation via the subclavian veins. From the subpleural connective tissue, lymphatic vessels also arise whose drainage is along the lobar surfaces to the hilar region (Morrow, 1972).

The epithelial surface of the A region is covered with a complex lipo-proteinaceous liquid called pulmonary surfactant. This is a misnomer as this complex liquid contains a number of surface-active materials, primarily phospholipids, with a predominance of dipalmitoyl lecithin. This surfactant materials exists on the respiratory epithelium non-uniformly as a thin film (<0.01 μm thick) on a hypophase approximately 10 times thicker. This lining layer stabilizes alveoli of differing dimensions from collapsing spontaneously and helps to prevent the normal capillary effusate from diffusing from the interstitium into the alveolar spaces. The role of the lining layer as an environmental interface is barely understood, especially in terms of how the layer may modify the physicochemical state of deposited particles and vice versa.

The epithelial surface of the A region, which can exceed 100 m^2 in humans, maintains a population of mobile phagocytic cells, the alveolar macrophage (AM), that have many important functions, e.g. removing cellular debris, eliminating bacteria and elaborating many

cytologic factors. The AM is also considered to play a major role in non-viable particle clearance. The resident AM population varies, inter alia, according to conditions of particle intake, as do their state of activation. An estimate of the normal AM population in the lungs of non-smokers is about 7×10^9 (Crapo et al. 1982) while in the Fischer 344 rat, estimates are about 2.2×10^7 AM (Lehnert et al. 1985). According to prevailing views, the importance of AM-mediated particle clearance via the bronchial airways in the rat and human lungs may be different (refer to Section 10.4.2.).

The respiratory tract is a dynamic structure. During respiration, the caliber and length of the airways changes as do the angles of branching at each bifurcation. The structural changes that occur during inspiration and expiration differ. Since respiration, itself, is a constantly changing volumetric flow, the combined effect produces a complex pattern of airflows during the respiratory cycle within the conducting airways and volumetric variations within the A region. Even if the conducting airways were rigid structures and a constant airflow was passed through the diverging bronchial tree, the behavior of air flow within these structures would differ from that produced by the identical constant flow passed in the reverse or converging direction. Consequently, important distinctions exist between inspiratory and expiratory airflows through the airways, especially those associated with the glottic aperture and nasal turbinates. Distinctions occurring in particle deposition during inspiration and expiration are not as marked as those in airflow. This is because the particles with the greatest tendency to deposit, will deposit during inspiration and will mostly be absent from the expired air.

At rest, the amount of air that is inspired, the tidal volume (TV), is normally about 500 mL. If a maximum inspiration is attempted, about 3300 mL of air can be added; this constitutes the Inspiratory Reserve Volume. During breathing at rest, the average expired TV is essentially unchanged from the average inspired TV. At the end of a normal expiration, there still remains in the lungs about 2200 ml, the FRC. When a maximum expiration is made at the end of a normal tidal volume, approximately 1000 mL of additional air will move out of the lung: this constitutes the Expiratory Reserve Volume. Remaining in the lungs after a maximal expiration is the Residual Volume (RV) of approximately 1200 mL. These volumes and capacities are illustrated in Figure 10-6. From the perspective of air volumes within the respiratory tract, estimates are based on both anatomic and

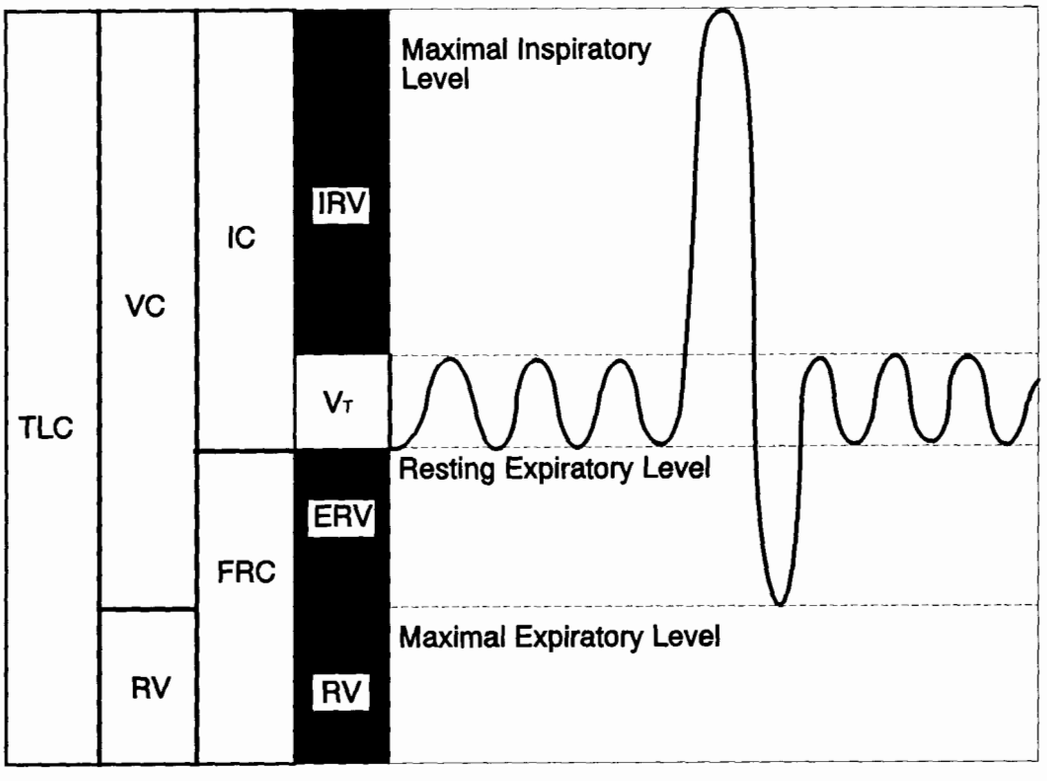

Figure 10-6. Lung volumes and capacities. Diagrammatic representation of various lung compartments, based on a typical spirogram. TLC, total lung capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; V_T, tidal volume; IRV, inspiratory reserve volume; ERV, expiratory reserve volume. Shaded areas indicate relationships between the subdivisions and relative sizes as compared to the TLC. The resting expiratory level should be noted, since the remains more stable than other identifiable points during repeated spirograms, hence is used as a starting point for FRC determinations, etc.

Source: Ruppel (1979).

physiologic measurements. The ET airways have a volume in the average adult of about 80 mL, whereas the composite volume of the transitional airways is about 440 mL. At rest, the total gas-exchange volume in the lungs is usually around 2200 ml and is called the Functional Residual Capacity (FRC). This gas exchange volume is in contact with between 60 and 100 m^2 of alveolar epithelium depending on the state of lung inflation, viz, $Alv_{sa} = 22\ (V_L)^{2/3}$ where the surface area (Alv_{sa}) is in m^2 and the lung volume (V_L) in liters. The alveolar

volume is juxtaposed with a variably estimated (70 to 230 mL) pulmonary capillary blood volume which contacts an endothelial surface area of comparable size to the alveolar.

The average respiratory frequency of an adult human at rest is about 12 to 15 cycles per min. This indicates a cycle length of 5 s: about 2 s for inspiration and 3 s for expiration. With a 500 mL TV, this results in a Minute Ventilation (MV) of about 6 to 7.5 L/min: about 60 to 70% of the MV is considered alveolar ventilation due to the dead space volume constituting about 30 to 40% of the TV. With the foregoing assumptions, the mean inspiratory and expiratory air flows will be about 250 mL/s and 166 mL/s, respectively. During moderate to heavy exercise, the MV will often quadruple and this can be assumed to be accomplished by a doubling of both TV and RF, although there is considerable individual variability. One impact of such an assumed change in MV is that the duration of the respiratory phases become shorter and more similar, consequently, the mean inspired and expired air flows will both likely increase to about 800 mL/s. With nose breathing, an inspiratory airflow of 800 ml/sec would be expected to produce linear velocities in the anterior nares greater than 10 m/sec.

Because of the irregular anatomic architecture of the nasal passages, the incoming air induces many eddies and turbulence in the ET airways. This is also true in the upper portions of the TB region largely due to the turbulence created by the glottic aperture. As the collective volume and cross sectional area of the bronchial airways increases, the mean airflow rates fall, but "parabolic airflow", a characteristic of laminar airflow does not develop because of the renewed development of secondary flows due to the repetitive airway branching. Conditions of true laminar flow probably do not occur until the inspired air reaches the transitional airways. Whether air flow in a straight circular tube is laminar or turbulent is determined by a dimensionless parameter known as the Reynolds number (Re) which is defined by the ratio $\rho_a D_a U/\mu$ where ρ_a is the air density, D_a is the tube diameter, U the air velocity, and μ is the viscosity of air. As a general rule, when Re is below 2000, the flow is expected to be laminar (Owen, 1969). See Table 10-3.

Pattle (1961) was the first investigator to demonstrate that the nasal deposition of particles was proportional to the product of the aerodynamic diameter dae squared and the mean inspiratory flow rate ($d_{ae}^2 Q$); where the aerodynamic diameter is the diameter of a unit density sphere having the same terminal settling velocity (see Section 10.2) as the particle of

TABLE 10-3. ARCHITECTURE OF THE HUMAN LUNG ACCORDING TO WEIBEL'S (1963) MODEL A, WITH REGULARIZED DICHOTOMY

Region	Generation	Number	Diameter (mm)	Length (mm)	Cum.[b] Length (mm)	Area[a] (cm)	Volume (ml)	Cum.[b] Volume (mL)	At flow of 1 L/sec	
									Speed (cm/s)	Reynolds Number
Trachea[c]	0	1	18	120.0	120	2.6	31	31	393	4,350
Main bronchus	1	2	12.2	47.6	167	2.3	11	42	427	3,210
Lobar bronchus	2	4	8.3	19.0	186	2.2	4	46	462	2,390
	3	8	5.6	7.6	194	2.0	2	47	507	1,720
Segmental bronchus	4	16	4.5	12.7	206	2.6	3	51	392	1,110
	5	32	3.5	10.7	217	3.1	3	54	325	690
Bronchi with	6	64	2.8	9.0	226	4.0	4	57	254	434
cartilage	7	128	2.3	7.6	234	5.1	4	61	188	277
in wall	8	256	1.86	6.4	240	7.0	4	66	144	164
	9	512	1.54	5.4	246	9.6	5	71	105	99
	10	1,020	1.30	4.6	250	13	6	77	73.6	60
Terminal bronchus	11	2,050	1.09	3.9	254	19	7	85	52.3	34
	12	4,100	0.95	3.3	257	29	10	95	34.4	20
Bronchioles with	13	8,190	0.82	2.7	260	44	12	106	23.1	11
muscle in wall	14	16,400	0.74	2.3	262	70	16	123	14.1	6.5
	15	32,800	0.66	2.0	264	113	22	145	8.92	3.6
Terminal bronchiole	16	65,500	0.60	1.65	266	180	30	175	5.40	2.0
Resp. bronchiole	17	131×10^3	0.54	1.41	267	300	42	217	3.33	1.1
Resp. bronchiole	18	262×10^3	0.50	1.17	269	534	61	278	1.94	0.57
Resp. bronchiole	19	524×10^3	0.47	0.99	270	944	93	370	1.10	0.31
Alveolar duct	20	1.05×10^6	0.45	0.83	271	1,600	139	510	0.60	0.17
Alveolar duct	21	2.10×10^6	0.43	0.70	271	3,200	224	734	0.32	0.08
Alveolar duct	22	4.19×10^6	0.41	0.59	272	5,900	350	1,085	0.18	0.04
Alveolar sac	23	8.39×10^6	0.41	0.50	273	12,000	591	1,675	0.09	—
Alveoli, 21 per duct		300×10^6	0.28	0.23	273		3,200	4,800		

[a]Area = total cross sectional area.
[b]cum. = cumulative.
[c]Dead space, approx. 175 mL + 40 mL for mouth.

Source: Y.C. Fung (1990).

concern. Albert et al. (1967) and Lippmann and Albert (1969) were among the earliest to report experimentally that the same general relationship governed inertial deposition of different uniformly-sized particles in the conducting airways of the TB region. Recent papers by Martonen (1994a,b) have considered the influence of both the cartilaginous rings and the carinal ridges of the upper TB airways on the dynamics of airflow. As in the case of the glottic aperture, these structures appear to contribute to the non-uniformity of particulate deposition sites within these airways. Concomitantly, Martonen et al. have pointed to the limitations incurred by assuming smooth tubes in modeling the aerodynamics of the upper TB airways.

Smaller particles, i.e. those with an aerodynamic size of between 0.1 and 0.5 μm, are the particles with the greatest airborne stability. They are too small to gravitate appreciably, they are too large to diffuse, hence they tend to persist the inspired air as a gas would, but in matters of alveolar mixing, they behave as "non-diffusible" gas. The study of these particles have provided very useful information on the distribution of tidal air under different physiologic conditions (Heyder et al., 1985). A recent analysis of airflow dynamics in human airways, conducted by Chang and Menon (1993), concluded that the measurement of flow dynamics aids in the understanding of particle transport and the development of enhanced areas of particle deposition.

Sedimentation becomes insignificant relative to diffusion as the particles become smaller. Deposition by diffusion results from the random (Brownian) motion of very small particles caused by the collision of gas molecules in air. The terminal settling velocity of a particle approaches 0.001 cm/s for a unit density sphere with a physical diameter of 0.5 μm, so that gravitational forces become negligible at smaller diameters. The main deposition mechanism is diffusion for a particle whose physical (geometric) size is <0.5 μm. Impaction and sedimentation are the main deposition mechanisms for a particle whose size is greater than 0.5 μm. Hence, $d_{ae} = 0.5$ μm is convenient for use as the boundary between the diffusion and aerodynamic regimes. Although this convention may lead to confusion in the case of very dense particles, most environmental aerosols have densities below 3 g/cm^3 (U.S. Environmental Protection Agency, 1982). Diffusional deposition is important in the small airways and in the A region where distances between the particles and airway

epithelium are small. Diffusion has also been shown to be an important deposition mechanism in the ET region for small particles (Cheng et al., 1988, 1990).

With mouth-only breathing, the regional deposition pattern changes dramatically compared to nasal breathing, with ET deposition being reduced and both TB and A deposition enhanced. Oronasal breathing (partly via the mouth and partly nasally), however, typically occurs in healthy adults while undergoing moderate to heavy exercise. Therefore, the appropriate activity pattern of subjects for risk assessment estimation remains an important issue. Miller et al. (1988) examined ET and thoracic deposition as a function of particle size for ventilation rates ranging from normal respiration to heavy exercise. A family of estimated deposition curves were generated as a function of breathing pattern. Anatomical and functional differences between adults and children are likely to yield complex interactions with the major mechanisms affecting respiratory tract deposition, again with implications for risk assessment.

Humidification and warming of the inspired air begins in the nasal passages and continues into the deep lung. This conditioning of the ambient air is not significant to particle deposition unless the particulate material is intrinsically hygroscopic, in which case, it is very important. For both droplet and particulate aerosols that are hygroscopic, there are physical laws that control both particle growth and deposition and these have been modeled extensively. In a recent review of this general subject (Morrow, 1986), many experimental measurements of the humidity (RH) and temperature of the air within the respiratory tract have been reported, but because of the technical problems involved, uncertainties remain. Two major problems prevail: the accurate measurement of temperature requires a sensor with a very rapid response time; hygrometric measurements of conditions of near saturation (>99% RH) are the most difficult to make. The latter technicality is of special significance, because the growth of hygroscopic aerosols are greatest near saturation. For example, distinguishing the difference between 99.0% and 99.9% is more important than measuring the difference between 20 and 80% RH. A more complete discussion of models and experimental determinations of the deposition of hygroscopic aerosols are given in Section 10.4.

The differences in respiratory tract anatomy summarized briefly in this section are the structural basis for the species differences in particle deposition. In addition to the structure

of the respiratory tract, the regional thickness and composition of the airway epithelium (a function of cell types and distributions) is an important factor in clearance (Section 10.4). Characteristic values and ranges for many respiratory parameters have been published for "Reference Man" by the International Commission on Radiological Protection (ICRP) (1975) and they are also available from many reference sources (Altose, 1993; Collett et al., 1988; Cotes, 1979). A typical description of respiratory tract morphology, cytology, histology, structure, and function is given in Table 10-4. This description of the respiratory tract is used in the human dosimetry model applied in Section 10.7 (ICRP66, 1994). For additional information on human respiratory tract structure, the papers of Weibel (1963,1980), Hatch and Gross (1964); Proctor (1977), Forrest (1993), and Gehr (1994) are recommended.

10.4 FACTORS CONTROLLING COMPARATIVE INHALED DOSE

As discussed in Section 10.1, comprehensive characterization of the exposure-dose-response continuum is the fundamental objective of any dose-response assessment. Within human and species differences in anatomical and physiological characteristics, the physicochemical properties of the inhaled aerosol, the diversity of cell types that may be affected, and a myriad of mechanistic and metabolic differences combine to make the characterization particularly complex for the respiratory tract as the portal of entry. This section attempts to discuss these factors within the exposure-dose-response context in order to present unifying concepts. These concepts are used to construct a framework by which to evaluate the different available dosimetry models; appreciate why they are constructed differently, and determine which are the most appropriate for extrapolation of the available toxicity data. The section discusses the major factors controlling the disposition of inhaled particles. Note that disposition is defined as encompassing the processes of deposition, absorption, distribution, metabolism, and elimination.

It must be emphasized that dissection of the factors that control inhaled dose into discrete topic discussions is deceptive and masks the dynamic and interdependent nature of the intact respiratory system. For example, although deposition in a particular respiratory region will be discussed separately from the clearance mechanisms for that region, retention

TABLE 10-4. MORPHOLOGY, CYTOLOGY, HISTOLOGY, FUNCTION, AND STRUCTURE OF THE RESPIRATORY TRACT AND REGIONS USED IN THE ICRP (1994) HUMAN DOSIMETRY MODEL.

Functions	Cytology (Epithelium)	Histology (Walls)	Generation Number	Anatomy	Regions used in Model: New	Regions used in Model: New	Regions used in Model: Old [d]	Zones (Air)	Zones (Air)	Location	Location	Airway Surface[a]	Number of Airways
Air Conditioning; Temperature and Humidity, and Cleaning; Fast Particle Clearance; Air Conduction	Respiratory Epithelium with Goblet Cells: Cell Types: -Ciliated Cells -Nonciliated Cells: • Goblet Cells • Mucous (Secretory) Cells • Serous Cells • Brush Cells • Endocrine Cells • Basal Cells • Intermediate Cells	Mucous Membrane, Respiratory Epithelium (Pseudostratified, Ciliated, Mucous), Glands Mucous Membrane, Respiratory or Stratified Epithelium, Glands		Anterior Nasal Passages	ET_1		(N-P)	Conditioning		Extrathoracic		2×10^{-3} m^2	——
				Nose, Mouth, Pharynx, Posterior, Larynx, Esophagus	ET_2	LN_{ET}					Extrapulmonary	4.5×10^{-2} m^2	——
		Mucous Membrane, Respiratory Epithelium, Cartilage Rings, Glands	0	Trachea	BB	LN_{TH}[e]	(T-B)			Thoracic		2.9×10^{-2} m^2 (a)	511 (a)
			1	Main Bronchi									
		Mucous Membrane, Respiratory Epithelium, Cartilage plates, Smooth Muscle Layer, Glands	2-8	Bronchi									
	Respiratory Epithelium with Clara Cells (No Goblet Cells) Cell Types: - Ciliated Cells - Nonciliated Cells • Clara (Secretory) Cells	Mucous Membrane, Respiratory Epithelium, No Cartilage, No Glands, Smooth Muscle Layer	9-14	Bronchioles	bb			Conduction	0.175×10^{-3} m^3 (Anatomical Dead Space)		Pulmonary	2.4×10^{-1}m^2 (a)	6.5×10^4 (a)
		Mucous Membrane, Single-Layer Respiratory Epithelium, Less Ciliated, Smooth Muscle Layer	15	Terminal Bronchioles									
Air Conduction; Gas Exchange; Slow Particle Clearance	Respiratory Epithelium Consisting Mainly of Clara Cells (Secretory) and Few Ciliated Cells	Mucous Membrane, Single-Layer Respiratory Epithelium of Cuboidal Cells, Smooth Muscle Layers	16-18	Respiratory Bronchioles	AI		P	Gas-Exchange Transitory	0.2×10^{-3} m^3			7.5 m^2	4.6×10^5 (a)
Gas Exchange; Very Slow Particle Clearance	Squamous Alveolar Epithelial Cells (Type I), Covering 93% of Alveolar Surface Areas Cuboidal Alveolar Epithelial Cells (Type II, Surfactant-Producing), Covering 7% of Alveolar Surface Area Alveolar Macrophages	Wall Consists of Alveolar Entrance Rings, Squamous Epithelial Layer, Surfactant	(c)	Alveolar Ducts					4.5×10^{-3} m^3			140 m^2	4.5×10^7 (b)
		Interalveolar Septa Covered by Squamous Epithelium, Containing Capillaries, Surfactant	(c)	Alveolar Sacs									
				Lymphatics			L						

[a]Dimensions from three sources (James, 1988; adapted from Weibul, 1963; Yeh and Schum, 1980; and Phalen et al., 1985) were averaged after all were adjusted to a funtional residual capacity (FRC) of 3.3×10^{-3}m^3 (Yu and Diu, 1982; James, 1988).

[b]Calculated from Hansen and Ampaya (1975) and scaled to a funtional residual capacity (FRC) of 3.3×10^{-3}m^3.

[c]Unnumbered because of imprecise information.

[d]Previous ICRP Model.

[e]As described in the text, lymph nodes are located only in BB region but drain the broncholar and alveolar-interstitial regions as well as the bronchial region.

(the actual amount of inhaled agent found in the respiratory tract at any time) is determined by the relative rates of deposition and clearance. Retention and the toxicologic properties of the inhaled agent are related to the magnitude of the pharmacologic, physiologic, or pathologic response. Therefore, although the deposition mechanisms, clearance mechanisms, and physicochemical characteristics of particles are described in distinct sections, assessment of the overall dosimetry and toxic response requires integration of the various factors.

Inasmuch as particles occur in the environmental air which are too massive to be inhaled, the description "inhalability" has been used to denote the overall spectrum of particle sizes which are potentially capable of entering the respiratory tract of humans and depositing therein. Except under conditions of microgravity (spaceflight) and possibly some other rare circumstances, unit density particles >100 μm diameter have a negligible probability of entering the mouth or nose. Nevertheless, there is no sharp cutoff to zero probability because the settling velocity of >100 μm particles can become comparable to air velocities into the nose or mouth during heavy breathing and be inhaled, provided such particles are in close proximity to the subject's breathing zone. Since particles of this size settle at terminal velocities >25 cm/s, the presence of such particles in the breathing zone air would require the subject to be close to the point of the aerosol generation. Inhalability can be defined as the ratio of the number concentration of particles of a certain aerodynamic diameter, d_{ae}, that are inspired through the nose or mouth to the number concentration of the same d_{ae} present in the inspired volume of ambient air (ICRP66, 1994). The concept of aerodynamic diameter is discussed in Section 10.2. In studies with head and torso models, inhalability has been considered generally under conditions of different wind velocities and horizontal head orientations.

Description of a "respirable dust fraction" was first suggested by the British Medical Research Council and implemented by C.N. Davies (1952) using the experimentally-estimated pulmonary deposition curve of Brown et al. (1950). This curve described the respirable dust fraction as that which would be available to deposit in the alveolated lung structures including the respiratory bronchioles, thereby making "respirable dusts" applicable to pneumoconiosis-producing dusts. The horizontal elutriator was chosen as a particle size selector, and respirable dust was defined as that dust passing an ideal horizontal elutriator. The elutriator cutoff was chosen to result in the best agreement with experimental lung

deposition data. The Johannesburg International Conference on Pneumoconiosis in 1959 adopted the same standard (Orenstein, 1960). Later, an Atomic Energy Commission working group defined "respirable dust" by a deposition curve which indicated 0% deposition at 10 μm d_{ae}; and 100% deposition for particles $\leq$2.0 μm d_{ae}. "Respirable dust" was defined as that portion of the inhaled dust which penetrates to the nonciliated portions of the lung (Hatch and Gross, 1964). The AEC respirable size deposition curve was pragmatically adjusted to 100% deposition for $\leq$2 μm d_{ae} particles so that the "respirable" curve could be approximated by a two-stage selective sampler and because comparatively little dust mass was represented by these small particles (Mercer 1973a). This definition was not intended to be applicable to dusts that are readily soluble in body fluids or are primarily chemical intoxicants, but rather only for "insoluble" particles that exhibit prolonged retention in the lung.

Other groups, such as the American Conference of Governmental Industrial Hygienists (ACGIH), incorporated respirable dust sampling concepts in setting acceptable exposure levels for other toxic dusts. Such applications are more complicated, since laboratory animal and human exposure data, rather than predictive calculations, from the data base for standards. The size-selector characteristic specified in the ACGIH standard for respirable dust (Threshold Limits Committee, 1968) was almost identical to that of the AEC, differing only at 2 μm D_{ae}, where it allowed for 90% passing the first-stage collector instead of 100 percent. The difference between them appeared to be a recognition of the properties of real particle separators, so that, for practical purposes, the two standards could be considered equivalent (Lippmann, 1978).

The cutoff characteristics of the precollectors preceding respirable dust samplers are defined by these criteria. The two sampler acceptance curves have similar, but not identical, characteristics, due mainly to the use of different types of collectors. The BMRC curve was chosen to give the best fit between the calculated characteristics of an ideal horizontal elutriator and available lung deposition data; on the other hand, the design for the AEC curve was based primarily on the upper respiratory tract deposition data of Brown et al. (1950). The separation characteristics of cyclone type collectors simulate the AEC curve. Whenever the particle size distribution has a $\sigma_g > 2$, samples collected with instruments meeting either criterion will be comparable (Lippmann, 1978). Various comparisons of samples collected

on the basis of the two criteria are available (Knight and Lichti, 1970; Breuer, 1971; Maquire and Barker, 1969; Lynch, 1970; Coenen, 1971; Moss and Ettinger, 1970).

The various definitions of repsirable dust were somewhat arbitrary, with the BMRC and AEC definitions being based on the "insoluble" particles that reach the A region. Since part of the aerosol that penetrates to the alveoli remains suspended in the exhaled air, respirable dust samples are not intended to be a measure of A deposition but only a measure of aerosol concentration for those particles that are the primary candidates for A deposition. Given that the "respirable" dust standards were intended for "insoluble dusts", most of the samplers developed to satisfy their criteria have been relatively simple two-stage instruments. In addition to an overall size-mass distribution curve, multistage aerosol sampler data can provide estimates of the "respirable" fraction and deposition in other functional regions. Field application of these samplers has been limited because of the increased number and cost of sample analyses and the lack of suitable instrumentation. Many of the various samplers, along with their limitations and deficiencies, were reviewed by Lippman (1978).

PM_{10} dust is based on the PM10 sampler efficiency curve promulgated by the U.S. Environmental Protection Agency. This sample is equivalent to the thoracic dust sample defined by the American Conference of Governmental Industrial Hygienists (Raabe, 1984).

The American Conference of Governmental Industrial Hygienists (1985) has expressed inhalability in terms of an intake efficiency of a hypothetical sampler. This expression was replaced in 1989 by international definitions for inspirable (also called inhalable) thoracic and respirable fractions of airborne particle (Solderholm, 1989). Each definition is expressed as a sampling efficiency (S) which is a function of particle aerodynamic diameter (d_{ae}) and specifies the fraction of the ambient concentration of airborne particles collected by an ideal sampler. For the inspirable fraction,

$$SI(d_{ae}) = 0.5(1 + e^{-0.06d_{ae}}). \quad (10\text{-}4)$$

For the thoracic fraction,

$$ST(d_{ae}) = SI(d_{ae})\,[1 - F(x)], \quad (10\text{-}5)$$

where

$$x = \frac{\ln(d_{ae}/\Gamma)}{\ln(\Sigma)}, \ \Gamma = 11.64\,\mu m, \ \Sigma = 1.5. \qquad (10\text{-}6)$$

F(x) is the cumulative probability function of a standardized normal random variable. For the respirable fraction,

$$SR(d_{ae}) = SI(d_{ae})\,[1 - F(x)], \qquad (10\text{-}7)$$

where

$$\Gamma = 4.25\,\mu m, \ \Sigma = 1.5. \qquad (10\text{-}8)$$

Swift (1976) estimated the deposition of particles by impaction in the nose, based on a nasal entrance velocity of 2.3 m/s and a nasal entrance width of 0.5 cm, and deduced that particles >61 μm d_{ae} have a negligible probability of entering the nasal passages due to the high impaction efficiency of the external nares. Experiments by Breysse and Swift (1990) in tranquil air estimated a practical upper limit for inhalability to be $\sim$ 40 μm d_{ae} for individuals breathing at 15 breaths per min at rest. No information on tidal volumes was provided. Studies reported by Vincent (1990) of inhalability made use of a mannequin with mouth and nasal orifices that could be placed in a wind tunnel and rotated 360 degrees horizontally. At low wind speeds, the intake efficiency approached 0.5 for particle sizes between 20 μm and 100 μm d_{ae}. The empirical relationship derived from these studies of Vincent led to its adoption by the ICRP for its new lung model (ICRP66, 1994), viz

$$\eta_1 \text{ (sampler)} = 0.5\,[1 + \exp(-0.06\,d_{ae}) = 1 \times 10^{-5}\,U^{2.75} \exp(0.055\,d_{ae}), \qquad (10\text{-}9)$$

where n_1 is the intake efficiency of the sampler, d_{ae} is the aerodynamic diameter, and U is the wind speed. The filtration efficiency of the respiratory tract is the complement of the term "inhalability" or intake efficiency, i.e., η_1. Particle inhalability is assumed to depend on d_{ae} and generally to decrease with increasing d_{ae}. However, for large particles, the

inhalability is assumed to increase with windspeed. For particles with $d_{ae} < 10$ μm, the expression was modified to increase accuracy

$$\eta_1 = 1 - 0.5\,((1 - [7.6 \times 10^{-4}\,(d_{ae})^{2.8} + 1]^{-1})) + 1 \times 10^{-5}\,U^{2.75}\,(0.055\,d_{ae}), \quad (10\text{-}10)$$

where d_{ae} is in μm and U is the windspeed in (m s-1) (for $D \leq U \leq 10$ ms^{-7}).

While there is some contention about the practical upper size limit of inhalable particles in humans, there is no lower limit to inhalability as long as the particle exceeds a critical (Kelvin) size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties, in distinction to those of free ions or gas molecules. *Inter alia,* particles are considered to experience inelastic collisions with surfaces and with each other. The lower limit for the existence of aerosol particles is assumed to be around 1 nanometers for some materials (refer to Section 10.2.). If the particulate material has an appreciable vapor pressure, particles of a certain size may "evaporate" as fast as they are formed. For example, pure water droplets as large as 1 μm diameter will evaporate in less than 1 second even when they are in water-saturated air at 20° Celsius (Greene and Lane, 1957).

10.4.1 Deposition Mechanisms

This section will review briefly the aerosol physics that both explains how and why particle deposition occurs and provides the theoretician a capability to develop predictive deposition models. Some of these models will be described in Section 10.5, together with recent experimental results on particle deposition. The ability of the experimentalist to measure deposition quantitatively has continued to advance, but theoretical models remain the only practical way for predicting the impact of aerosol exposures and for delineating the patterns of intra-regional deposition.

The motion of an airborne particle between 1 and 100 μm d_{ae} is primarily related to its mass, and the resulting resistive force of air is proportional to

$$\mu v d, \quad (10\text{-}11)$$

where μ is the viscosity of air, v is the velocity of the particle relative to the air, and d is the particle diameter. This is a statement of Stokes law for viscous resistance which is appropriate to sphere moving in air at low particle Reynolds numbers, i.e., less than 1. The particle Reynolds number (Re_p) is defined as

$$\rho_a dv/\mu, \qquad (10\text{-}12)$$

where ρ_a is the density of air. When the particle velocity relative to air is sufficiently slow that the airflow pattern around the sphere is symmetrical and only viscous stresses resist the sphere's motion, Stokes law applies. As the value of Re_p increases, asymmetrical flow about the moving sphere and a pressure drop across the sphere, both progressively develop. These changes in flow signify the condition of inertial resistance prevails and Stokes law does not pertain (Mercer, 1973b).

For the range of particle sizes just discussed (1 to 100 μm), the motion of airborne particles is characterized by a rapid attainment of a constant velocity whereby the viscous resistance of air matches the force(s) on the sphere responsible for its motion. This constant velocity is termed the terminal velocity of the particle. For the size region below 1 μm diameter, particle motion is also based on the viscous resistance of air and described by its terminal velocity. In this region of particle size, the viscous resistance of air on the particle, using Stokes law, begins to be overestimated and the particle's terminal velocity, underestimated. This general phenomenon is termed "slip"; consequently, Slip Correction Factors have been developed. These slip corrections become more important as the particle diameter nears, or is less than, the mean free path of air molecules ($\approx$ 0.068 μm at 25 °C and 760 mm Hg air pressure).

10.4.1.1 Gravitational Settling or Sedimentation

All aerosol particles are continuously influenced by gravity, but for practical purposes, particles with an $d_{ae} > 0.5$ μm are mainly involved. Within the respiratory tract, an d_{ae} of 100 μm will be considered as an upper cut-off. A spherical, compact particle within these arbitrary limits will acquire a terminal settling velocity when a balance is achieved between

the acceleration of gravity, g, acting on the particle of density, ρ, (g/cm^3) and the viscous resistance of the air according to Stokes law

$$(\pi/6)\rho d^3 g = 3\pi\mu d v_t. \quad (10\text{-}13)$$

The left hand side of Equation 10-13 is the force of gravity on the particle, neglecting the effect of the density of air. Solving for the terminal velocity, v_t, gives

$$v_t = d_{ae}^2 \rho g K_s / 18\mu. \quad (10\text{-}14)$$

In Equation 10-14 a slip correction factor, K_s is added to account for the slip effect on particles with diameters about or below 1 μm. For particles as small as 0.02 μm, the K_s used by Knudsen and Weber increases v_t six fold (cited by Mercer, 1973c).

The relationship for the terminal settling velocity, just described, is not restricted to measurements in tranquil air. For example, moving air in a horizontal airway will tend to carry the particle at right angles to gravity at an average velocity, U. The action of gravity on the particle will nonetheless result in a terminal settling velocity, v_t; consequently the particle will follow, vectorially, the two velocities and provided the airway is sufficiently long or the settling velocity is relatively high, the particle will sediment in the airway. For every orientation of the airways with respect to gravity, it is possible to calculate the particle's settling behavior using Stokes law.

10.4.1.2 Inertial impaction

Sudden changes in airstream direction and velocity, cause particles to fail to follow the streamlines of airflow as depicted in Figure 10-5. As a consequence, the relatively massive particles impact on the walls or branch points of the conducting airways. The ET and upper TB airways have been described as the dominant sites of high air velocities and sharp directional changes, hence, they dominate as sites of inertial impaction. Because the air (and particle) velocities are affected by the breathing pattern, it is easy to imagine that even small

particles also experience some inertial impaction. Moreover, as nasal breathing shifts to oral breathing during work or exercise, the particle that would normally be expected to impact in the ET region will pass into the TB region greatly increasing TB deposition. That all impaction sites become lower down in the TB region when such a shift occurs, is also expected.

The probability that a particle with a diameter, d, moving in an air stream with an average velocity, U, will impact at a bifurcation is related to a parameter called the Stokes number, Stk; defined as:

$$\rho d^2 \, U/9\mu \, D_a \, , \tag{10-15}$$

or

$$\rho d^{2_{ae}} \, U/9\mu \, D_a . \tag{10-16}$$

As far as particulate properties are concerned, the aerodynamic diameter (d_{ae}) is again the significant parameter (see Section 10.2). In Landahl's lung deposition model (1950a) of impaction in the TB region, impaction efficiency was proportional to

$$\rho d^2 U_i \sin \theta_i \, / \, D_{ai} \, S_{i-1} , \tag{10-17}$$

where U_i is the air velocity in the airway generation i, θ_i is the branching angle between generations i and i-1, D_{ai} is diameter of the airway of generation i, and S_{i-1} is the total cross sectional area of airway generation i-1.

Prevailing TB models have simplistically targeted the airways as smooth, bifurcating tubes. Martonen et al. (1993,1994) have predicted that the cartilaginous rings and carinal ridges perturb the dynamics of airflow and help to explain the non-uniformity of particle deposition.

It should be evident that both gravitational settling and inertial impaction cause the deposition of many particles within the same size range. These deposition forces are always

acting together in the ET and TB regions, with inertial impaction dominating in the upper airways and gravitational settling becoming increasingly dominant in the lower conducting airways, and especially for the largest of the particles which can penetrate into the transitional airways and alveolar spaces.

For sedimenting particles with diameters between 0.1 μm to 1.0 μm, their Slip Correction Factor will be greater than 1.0, although the magnitude of their respective v_t will only range from about 1 μm/s to 35 μm/s. Concurrently, 0.1 μm diameter particles are affected by diffusion such that the root mean displacement they experience in one second is about 0.3 μm. The size region, 1.0 μm down to about 0.1 μm, is frequently described as consisting of particles which are too small to settle and too large to diffuse. Indeed, it is this circumstance that makes them the most persistent and stable particles in aerosols and those which undergo the least deposition in the respiratory tract. As any aerosol ages and continuously undergoes deposition without particle replenishment, the ultimate aerosol will exist largely within this same size range, i.e., have a median size of about 0.5 μm diameter.

10.4.1.3 Brownian diffusion

Particles < 1 μm diameter are increasingly subjected to diffusive deposition as their size decreases. Even particles in the nanometer diameter range are large compared to individual air molecules, hence, the collisions resulting between air molecules, undergoing random thermal motion, and the surface of a particle produce numerous very small changes in the particle's spatial position. These frequent, minute excursions are each made at a constant or terminal velocity due to the viscous resistance of air. The root mean square (r.m.s.) displacement that the particle experiences in a unit of time along a given cartesian coordinate, x, y or z is a measure of its diffusivity. For instance, a 0.1 μm diameter particle has a r.m.s. displacement of about 37 μm during one s. This 1 μm displacement in one s does not describe a velocity of particle motion because the displacement resulted from numerous relatively high velocity excursions.

The diffusion of particles by Brownian motion is described by the Einstein-Stokes' equation

$$\Delta_x = \sqrt{2Dt}\,, \qquad (10\text{-}19)$$

where Δ_x is the root-mean-square displacement in one second along coordinate x, D is the diffusion coefficient for the particle expressed in cm^2/s, t is time in seconds. The diffusion coefficient of a particle of diameter, d, is

$$D = \kappa T K_s / 3\pi\mu d, \qquad (10\text{-}20)$$

where κ is the Boltzmann constant, and T the absolute temperature, collectively describing the average kinetic energy of the gas molecules.

It is apparent that the density of the particle is ordinarily unimportant in determining particle diffusivity which increases as K_s increases and d decreases. Instead of having an aerodynamic equivalent size, diffusive particles of different shapes can be related to the diffusivity of a thermodynamic equivalent size based on spherical particles (Heyder and Scheuch, 1983). In terms of the architecture of the respiratory tract, diffusive deposition of particles, is favored by proximate surfaces and by relatively long residence times for particles, both conditions occurring in the alveolated structures of the lungs, the PU region. Experimental studies with diffusive particles (<0.5 μm) in replicate casts of the human nose and theoretical predictions, both indicate a rising deposition efficiency for the nasal airways as d becomes very small (Cheng et al., 1988).

10.4.1.4 Interception

The interception potential of any particle depends on its physical size. As a practical matter, particles that approach airway sizes $>$ 150 μm in more than one dimension, will be too massive to be inhaled. Airborne fibers, on the otherhand, frequently exceed 150 μm in length and appear to be relatively stable in air. This is because their aerodynamic size is determined predominantly by their diameter, not their length. Fibers, therefore, are the chief concern in the interception process, especially as their length approaches the diameters of peripheral airways (>150 μm).

The theoretical model of Asgharian and Yu (1988, 1989) for the deposition of fibrous particles in the respiratory tract is complex. While the model includes interception as an important process for long fibers, it also depends on a combination of inertial, gravitational

and diffusional forces to explain fiber deposition. The deposition efficiencies of the three deposition mechanisms cited have been developed for spherical particles, but these can be extended to fibrous particles by considering orientation effects which are strongly related to the direction of airflow. The orientation of fibers depends upon the velocity shear of the airflow and Brownian motion.

For their analysis of orientational effects throughout the respiratory tract, Asgharian and Yu (1988, 1989) defined the equivalent mass diameter, d_{em}, of fibers as

$$d_{em} = d_f \beta^{1/3}, \tag{10-21}$$

where d_f is the fiber diameter and β is its aspect ratio (length/diameter). For example, a fiber 100 μm long and 3 μm diameter has a d_{em} of 10 μm diameter. In Figure 10-7, two sets of TB deposition predictions for the rat are reproduced from Asgharian and Yu (1989) that clearly show an example of the relative importance of particle interception.

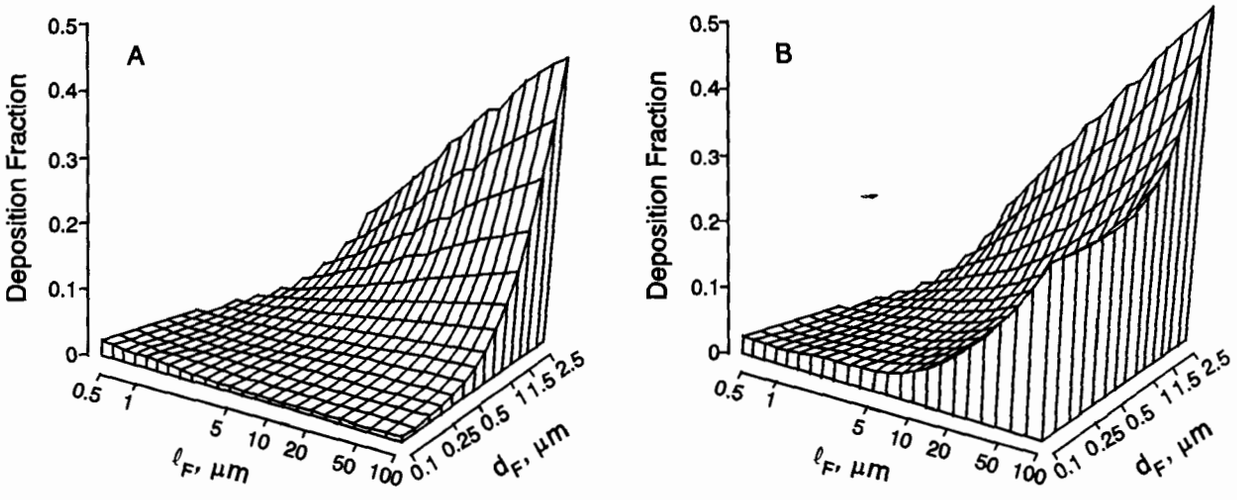

Figure 10-7. Estimated TB deposition in the rat lung, via the trachea, with no interceptional deposition, Graph A, is shown in relation to total TB deposition, via the trachea, Graph B, for the same fibrous aerosol under identical respiratory conditions.

Source: Asgharian and Yu (1989).

Several general reviews of particle deposition mechanisms in the human respiratory tract have been published, e.g, Stuart (1973), Lippmann (1977), and Brain and Blanchard (1993), and are recommended to the reader, as is the excellent review of particle deposition mechanisms prepared by Phalen (1984).

10.4.1.5 Electrostatic Precipitation

The minimum charge an aerosol particle can have is zero, which is when it is electrically neutral. This condition is rarely achieved because of the random charging of aerosol particles by the omnipresent air ions. Every cubic centimeter of air contains about 10^3 ions in approximately equal numbers of positive and negative ions. Aerosol particles that are initially neutral will acquire charges from these ions by collisions with them due to their random thermal motion. Aerosols that are initially charged will lose their charge slowly as the charged particles attract oppositely charged ions. An equilibrium state of these competing processes is eventually achieved. The Boltzmann equilibrium represents the charge distribution of an aerosol in charge equilibrium with bipolar ions. The minimum amount of charge is very small, with a statistical probability that some particles will have no charge and others will have one or more charges.

The electrical charge on some particles may result in an enhanced deposition over what would be expected from size alone. This is due to image charges induced on the surface of the airway by these particles or to space-charge effects whereby repulsion of particles containing like charges results in increased migration toward the airway wall. The effect of charge is inversely proportional to particle size and airflow rate. This deposition is probably small compared to the effects of turbulence and other deposition mechanisms and is generally a minor contributor to overall particle deposition, but it may be important in some laboratory studies. This deposition is also negligible for particles below 0.01 μm because so few of these particles carry any charge at Boltzmann equilibrium.

10.4.1.6 Comparative Aspects of Deposition

The various species used in inhalation toxicology studies that serve as the basis for dose-response assessment do not receive identical doses in a comparable respiratory tract region (ET, TB, or A) when exposed to the same aerosol or gas (Brain and Mensah, 1983).

Such interspecies differences are important because the adverse toxic effect is likely more related to the quantitative pattern of deposition within the respiratory tract than to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose but also the specific pathways by which the inhaled material is cleared and redistributed (Schlesinger, 1985). Differences in ventilation rates and in the URT structure and size and branching pattern of the lower respiratory tract between species result in significantly different patterns of airflow and particle deposition. Disposition varies across species and with the respiratory tract region. For example, interspecies variations in cell morphology, numbers, types, distributions, and functional capabilities contribute to variations in clearance of initially deposited dose. Tables 10-5, 10-6, and 10-7 summarize some of these differences for the ET, TB, and A regions, respectively. This section only briefly summarizes these considerations. Comprehensive and detailed reviews of species differences are recommended (Phalen and Oldham, 1983; Patra, 1986; Crapo, 1987; Gross and Morgan, 1991; Mercer and Crapo, 1991; Parent, 1991).

The geometry of the upper respiratory tract exhibits major interspecies differences (Gross and Morgan, 1992). In general, laboratory animals have much more convoluted nasal turbinate systems than do humans, and the length of the nasopharynx in relation to the entire length of the nasal passage also differs between species. This greater complexity of the nasal passages, coupled with the obligate nasal breathing of rodents, is generally thought to result in greater deposition in the upper respiratory tract (or ET region) of rodents than in humans breathing orally or even nasally (Dahl et al., 1991), although limited data are available. Species differences in gross anatomy, nasal airway epithelia (e.g., cell types and location) and the distribution and composition of mucous secretory products have been noted (Harkema, 1991; Guilmette, 1989). The extent of upper respiratory tract removal affects the amount of particles or gas available to the distal respiratory tract.

Airway size (length and diameter) and branching pattern affect the aerodynamics of the respiratory system in the following ways:

- The airway diameter affects the aerodynamics of the air flow and the distance from the particle to the airway surface.

- The cross-sectional area of the airway determines the airflow velocity for a given volumetric flow.

TABLE 10-5. INTERSPECIES COMPARISON OF NASAL CAVITY CHARACTERISTICS

	Sprague-Dawley Rat	Guinea Pig	Beagle Dog	Rhesus Monkey	Human[a]
Body weight	250 g	600 g	10 kg	7 kg	≈70 kg
Naris cross-section	0.7 mm^2	2.5 mm^2	16.7 mm^2	22.9 mm^2	140 mm^2
Bend in naris	40°	40°	30°	30°	
Length	23 cm	3.4 cm	10 cm	5.3 cm	7-8 cm
Greatest vertical diameter	9.6 mm	12.8 mm	23 mm	27 mm	40-45 mm
Surface area (both sides of nasal cavity)	10.4 cm^2	27.4 cm^2	220.7 cm^2	61.6 cm^2	181 cm^2
Volume (both sides)	0.4 cm^3	0.9 cm^3	20 cm^3	8 cm^3	16-19 cm^3 (does not include sinuses)
Bend in nasopharynx	15°	30°	30°	80°	≈90°
Turbinate complexity	Complex scroll	Complex scroll	Very complex membranous	Simple scroll	Simple scroll

[a]Adult male.

Source: Schneider (1983); Gross and Morgan (1991).

TABLE 10-6. COMPARATIVE LOWER AIRWAY ANATOMY AS REVEALED ON CASTS

Mammal/ Body Mass	Gross Structure: Left Lung Lobes	Gross Structure: Right Lung Lobes	Gross Structure: Airway Branching	Gross Structure: Trachea length/diameter (cm)	Gross Structure: Major Airway Bifurcations	Typical Structure (Generation 6): Average Airway L/D (ratio)	Typical Structure (Generation 6): Branch Angles (Major Daughter/ Minor Daughter) (degrees)	Typical Number of Branches to Terminal Bronchiole	Respiratory Bronchioles
Human/70 kg	Upper and lower	Upper, middle, and lower	Relatively symmetric	12/2	Sharp for about the first 10 generations, relatively blunt thereafter	2.2	11/33	14-17	About 3-5 orders
Rhesus monkey/2 kg	Superior, middle, and inferior	Superior, middle, and inferior, azygous	Monopodial	3/0.3	Mixed blunt and sharp	2.6	20/62	10-18	About 4 orders
Beagle dog/ 10 kg	Apical, intermediate, and basal	Apical, intermediate, and basal	Strongly monopodial	17/1.6	Blunt tracheal bifurcation, others sharp	1.3	8/62	15-22	About 3-5 orders
Ferret/ 0.61 kg	NR[a]	NR	strongly monopodial	10/0.5	Sharp	2.0	16/57	12-20	About 3-4 orders
Guinea pig/ 1 kg	Superior and inferior	Superior, middle, and inferior	Monopodial	5.7/0.4	Very sharp and high	1.7	7/76	12-20	About 1 order
Rabbit/ 4.5 kg	Superior and inferior	Cranial, middle, caudal, and postcaval	Strongly monopodial	6/0.5	Sharp	1.9	15/75	12-20	About 1-2 orders
Rat/0.3 kg	One lobe	Cranial, middle, caudal, and postcaval	Strongly monopodial	2.3/0.26	Very sharp and very high throughout lung	1.5	13/60	12-20	Rudimentary
Golden hamster/ 0.14 kg	Superior and inferior	Cranial, middle, caudal, and postcaval	Strongly monopodial	2.4/0.26	Very sharp	1.2	15/63	10-18	About 1 order

[a]NR = Not reported.

Source: Phalen and Oldham (1983); Patra (1986); Crapo (1987).

TABLE 10-7. ACINAR MORPHOMETRY

Species	Fixation[1]	Number/Lung	V (mm^3)	D or L (mm)[2]	Number Alveoli/Acinus	Alveolar Duct Generations	References
Human			1.33-30.9		15,000		Pump (1964)
		27,992			10,714	6	Horsfield and Cuming (1968); Parker et al. (1971)
	75% TLC	23,000	160.8	7.04 (L)	14,000-20,000	9	Hansen and Ampaga (1975); Hansen et al. (1975)
		80,000	15.6			2-5	Boyden (1971)
				5.1 (L)	7,100	8-12	Schreider and Raabe (1981)
	TLC	26,000-32,000	187.0	8.8 (L)	10,344	9	Haefeli-Bleuer and Weibel (1988)
	FRC	43,000	51.0	6.0 (D)	8,000	9	Mercer, personal communication
Rabbit		17,900	2.54				Kliment (1973)
	55% TLC	18,000	3.46	1.95 (L)		6	Rodriguez et al. (1971)
Guinea pig		5,100	1.25				Kliment (1973)
	FRC	4,097	1.09	1.56 (D)	6,890	9-12	Mercer, personal communication
Rat		2,500	1.0				Kliment (1973)
		2,487	5.06				Yeh et al. (1979)
	FRC	2,020	1.9	1.5 (D)	5,243	10-12	Mercer and Crapo, (1987)
	70% TLC	5,993	1.46	1.5 (L)		6	Rodriguez et al. (1988)

[1]Volume of lung at fixation (TLC, total lung capacity; FRC, function residual capacity).
[2]Acinar size (D, diameter; L, length)

Source: Mercer and Crapo (1991).

- Airway length, airway diameter, and branching pattern variations affect the mixing between tidal and reserve air.

The airways show a considerable degree of within species variability (e.g., size and branching pattern) and this is most likely the primary factor responsible for the deposition variability seen within single species (Schlesinger, 1985a).

Larger airway diameter results in greater turbulence for the same relative flow velocity (e.g., between a particle and air). Therefore, flow may be turbulent in the large airways of humans, whereas for an identical flow velocity, it would be laminar in the smaller experimental animal. Relative to humans, experimental animals also tend to have tracheas that are much longer in relation to their diameter. This could result in increased relative deposition in humans because of the increased likelihood of laryngeal jet flow extending into the bronchi. Human airways are characterized by a more symmetrical dichotomous branching than that found in most laboratory mammals, which have highly asymmetrical airway branching (monopodial). The more symmetrical dichotomous pattern in humans is susceptible to deposition at the carina because of its exposure to high air flow velocities toward the center of the air flow profile.

Alveolar size also differs between species, which may affect deposition efficiency due to variations on the distance between the airborne particle and alveolar walls (Dahl et al., 1991).

Addressing species differences in ventilation, which affects the tidal volume and ventilation to perfusion ratios, is also critical to estimating initial absorbed dose. Due to the expected variations in airflows within the respiratory tract, the variabilities among lungs in the human or animal population, and the variations in respiratory performance that members of the population experience during their normal activities, e.g. sleep and exercise, must be considered in order to gain some insight into the variability that might be expected in particle deposition, total and regional, of particles in the urban atmosphere. The experimentalist must try to keep respiratory parameters relatively constant to obtain reasonably consistent deposition data.

10.4.1.7 Additional Factors Modifying Deposition

The available deposition data in humans are commonly for healthy adult Caucasian males using stable, monodisperse, low electrostatic charge particles. When these conditions

do not hold, changes in deposition are expected to occur. In the following, the effects of different factors on deposition are summarized based upon the information reported from various studies.

Gender

Average females have a smaller thoracic size than males. The diameter of the female trachea is approximately 75% that of the male (Warwick and Williams, 1973) and the size of the bronchi is approximately linearly dependent on the size of the trachea (Weibel, 1963). In addition, the minute ventilation and inspiratory flow rate are smaller for females. It is therefore expected that deposition will be different in females than males. Using radioactive-labeled polystyrene particles in the 2.5 to 7.5 μm size range, Pritchard et al. (1986) measured total and regional deposition in 13 healthy nonsmoking female adults at mouth breathing through a tube. Because deposition of particles in this particle size range in the ET region is controlled by impaction, they reported the data as a function of d_{ae}^2 Q to accommodate the difference in flow rate between male and female. Their data are shown in Table 10-8. At a comparative value of d_{ae}^2 Q, females were found to have higher ET and TB deposition and smaller A deposition. The ratio of A deposition to total thoracic deposition in females was also found to be smaller. The differences in depositions were attributed by Pritchard et al. (1986) to the differences in the airway size between males and females.

TABLE 10-8. DEPOSITION DATA FOR MEN AND WOMEN

		Deposition as a Fraction of Inhaled Material (%) ± Standard Error			
Sex	$d_{ae}^2 Q$ (μm^2 $Lmin^{-1}$)	Total	ET	TB	A
Female	405 ± 47	75.9 ± 1.7	21.2 ± 2.4	16.9 ± 1.5	37.5 ± 2.5
Male	430 ± 41	81.5 ± 1.8	19.9 ± 2.5	14.7 ± 1.7	46.9 ± 2.7

Age

As a human grows from birth to adulthood, both airway structure and respiratory conditions vary with age. These variations are likely to alter the deposition pattern of inhaled particles. Total deposition data for particles of 1 to 3.1 μm size range were reported by Becquemin et al. (1987, 1991) for a group of 41 children at 5 to 15 years of age and by Schiller-Scotland et al. (1992) for 29 children at two age groups (6.7 and 10.9 years). Although Bequemin et al. (1987, 1991) did not find a clear dependence of total deposition on age, slightly higher deposition was found by Schiller-Slotland et al. (1992) for each diameter when children breathed at their normal rates (see Figure 10-8), than found in adults.

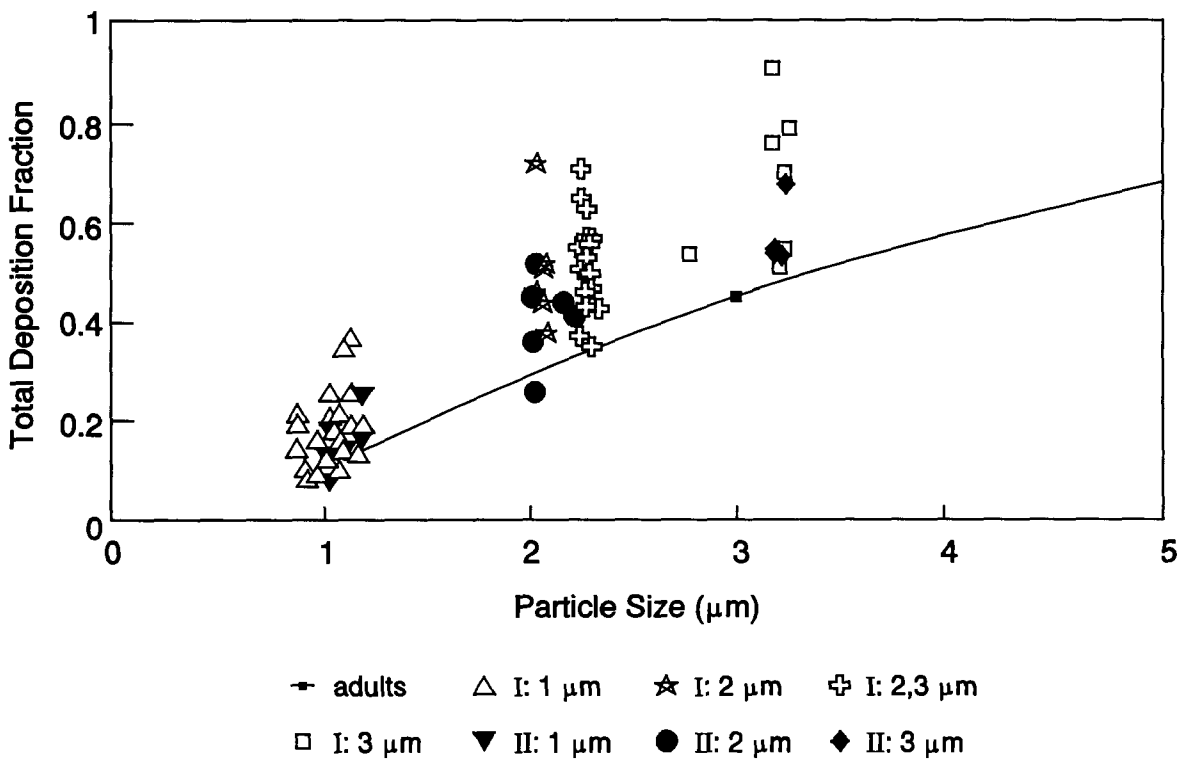

Figure 10-8. Total deposition data in children with/during spontaneous breathing as a function of particle diameter (unit density). Group I (10.6 ± 2.0 yrs); Group II (5.3 ± 1.5 yrs). The adult curve represents the mean valve of deposition from the data of Stahlhofen et al. (1989).

Source: Schiller-Scotland et al. (1992).

Mathematical models for children have been developed by many workers (Hofmann, 1982; Crawford, 1982; Xu and Yu, 1986; Yu and Xu, 1987;Phalen et al., 1988b; Hofmann et al., 1989; Yu et al., 1992; Martenon and Zhang, 1993). Phalen et al. (1988b) reported morphometric data of twenty TB airway casts of children from 21 days to 21 years. With the use of these data, they calculated a higher TB deposition in children during inhalation for particle diameters between 0.01 and 10 μm. If the entire respiratory tract and a complete breathing cycle at normal rate are considered in the modeling, the results show that ET deposition in children is higher than adults, but that TB and A deposition in children may be either higher or lower than the adult depending upon the particle size (Xu and Yu, 1986).

Respiratory Tract Disease

Effect of airway diseases on deposition have been studied extensively. In 8 healthy nonsmokers, Svartengren et al. (1986, 1989) found that A deposition at different flow rates were lower (26% versus 48% of thoracic deposition) in subjects after induced bronchoconstriction. The degree of bronchoconstriction was quantified by measurements of airway resistance using a whole-body plethysmograph. A close relation between airway resistance and A deposition was formed with a decrease of A deposition with an increase of airway resistance. The data from the same laboratory (Svartengren et al., 1990, 1991) using 2.6 μm d_{ae} particles with maximally deep inhalations at 0.5 L/min showed no significant changes in mouth and throat deposition in asthmatics but thoracic deposition was higher than healthy subjects (83% versus 73% of total deposition). TB deposition was also found higher in asthmatics. The results are similar to those found in subjects with obstructive lung disease (e.g., Dolovich et al., 1976; Itoh et al., 1981; Anderson et al., 1990).

Another extensive study of the relationship between deposition and lung abnormality was made by Kim et al. (1988). One-hundred human subjects with various lung conditions (normal, asymptomatic smoker, smoker with small airway disease, chronic simple bronchitis and chronic obstructive bronchitis) breathed 1 μm test particles from a bag at a rate of 30 breaths/min. The number of rebreathing breaths resulting in 90% aerosol loss from the bag was determined. From these data, they estimated total deposition and found that total deposition increased with increasing level of airway obstruction.

Particle charge

Many of the freshly generated particles are electrostatically charged. Experimental studies in a lung cast (Chan et al., 1978) and measurements in rats and humans (Melandri et al., 1977, 1983; Tarroni et al., 1980; Jones et al., 1988; Scheuch et al., 1990) all showed that particle charge increased deposition. For low particle number concentration ($< 10^5$ cm^{-3}), the deposition increase is due to the presence of electrostatic image force acting on the particle by particle-wall interaction (Yu, 1985). Figure 10-9 shows the experimental data on human deposition of Melandri et al. (1983) and Tarroni et al. (1980) for three particle sizes and the modeling results by Yu (1985). The vertical axis in Figure 10-9 is the deposition increment, defined as

$$\Delta T = (DE - DE_0)/(1 - DE_0), \qquad (10\text{-}22)$$

where DE is total deposition at particle charge level, q, and DE_0 is the total deposition of particles at Boltzmann charge equilibrium. It is seen for each particle size, deposition increments increase linearly with q. Figure 10-9 also shows that there exists a threshold charge level above which the increase in deposition becomes significant. For 1 μm particles, the threshold charge was found to be about 54 elementary charges (Yu, 1985).

Particle Polydispersity

Aerosol particles are often generated polydisperse and can be approximated by a lognormal distribution (Section 10.2). The mass deposition of spherical particles in the respiratory tract depends upon mass median diameter (MMD), geometric standard deviation, σ_g, and physical density (Diu and Yu, 1983; Rudolf et al., 1988). For large particle (d_{ae} > 1 μm) deposition governed by impaction and sedimentation, the dependence on MMD and mass density can be combined with the use of mass medium aerodynamic diameter (MMAD), as suggested by TGLD (1966). However, this method is not valid for particles in the size range where diffusion deposition becomes important. Figure 10-10 shows the calculated total and regional mass deposition results by Yeh et al. (1993) for polydisperse aerosols of unit density with various σ_g as function of MMD at quiet mouth breathing. The

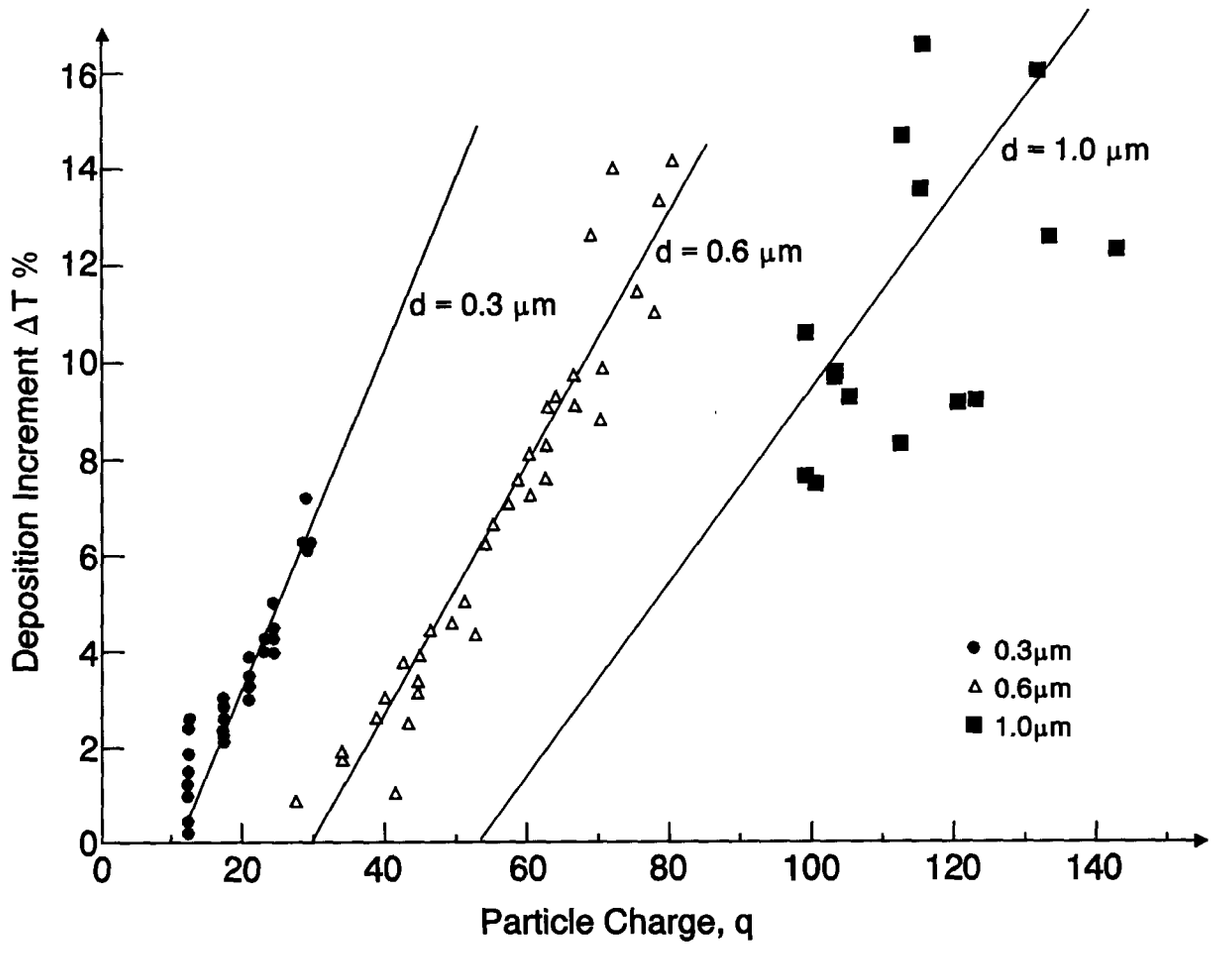

Figure 10-9. Deposition increment data versus particle electronic charge q for three particle diameters at 0.3, 0.6, and 1.0 μm (unit density). The solid lines represent the theoretical predictions.

Source: Yu (1985).

dependence of deposition on σ_g depends strongly on the MMD of the aerosol. Whereas at certain MMD's variability with σ_g is zero, variations at other MMD's can be very large. One of the main effects of polydisperse deposition is the flattening of the deposition curves as a function of particle size, as shown in Figure 10-10.

Particle Hygroscopicity

Another important particle factor which affects deposition is the hygroscopicity of the particle. Many atmospheric particles such as acid particles are water soluble. As these

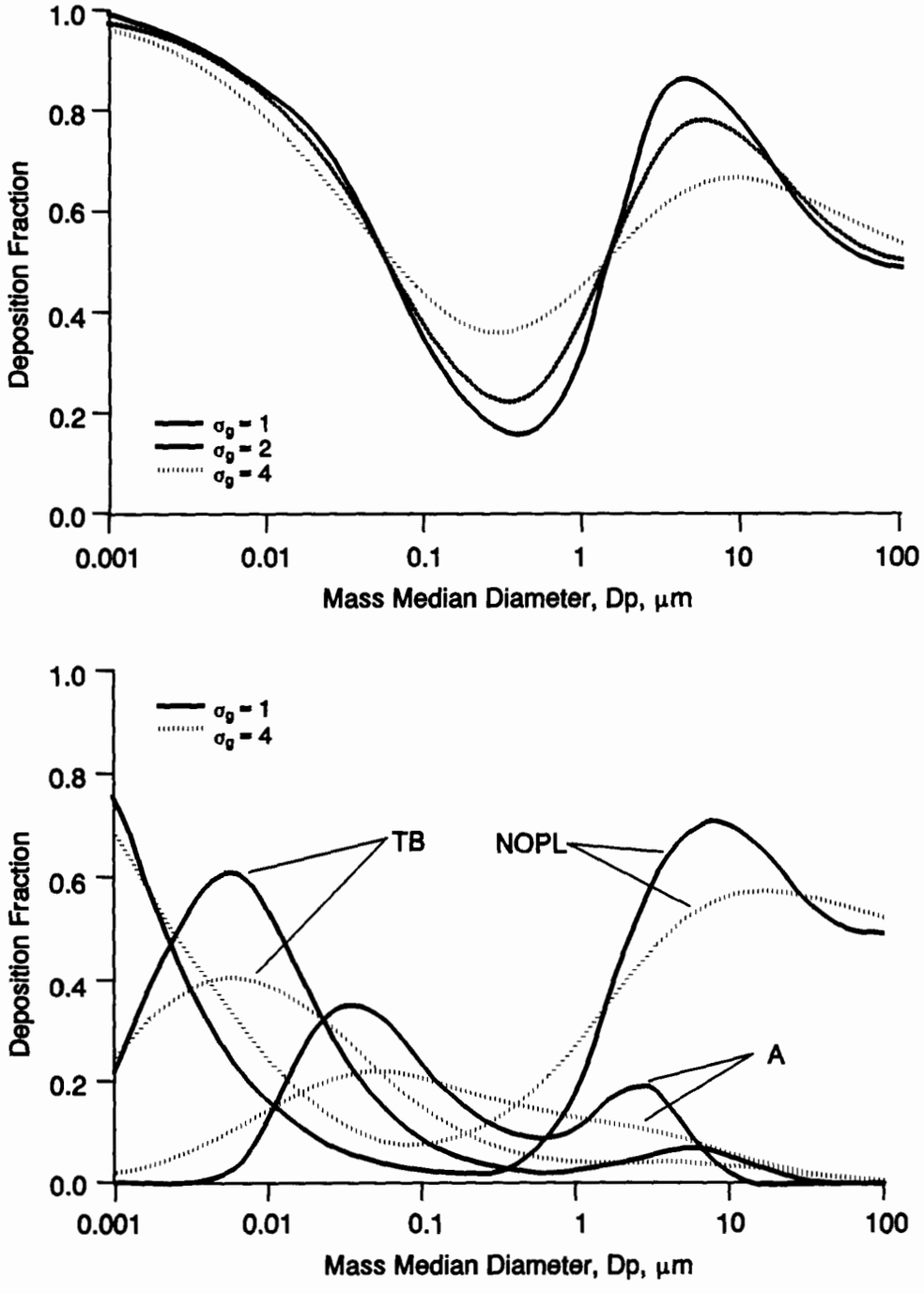

Figure 10-10. Calculated mass deposition from polydisperse aerosols of unit density with various geometric standard deviations (σ_g) as a function of MMD for quiet breathing (tidal volume = 750 mL, breathing frequency = 15 min^{-1}). The upper panel is total deposition and the lower panel is regional deposition (NOPL = Naso-oro-pharyngo-laryngeal, TB = Tracheobronchial, A = Alveolar).

Source: Yeh et al. (1993).

particles travel along the humid respiratory tract, they grow in size and, as a result, the deposition pattern is altered. A discussion on deposition of hygroscopic particles follows in Section 10.4.3.1.

Fibrous Particles

For elongated particles such as fibers, deposition depends upon both diameter and length although the dependence on the diameter is stronger (Yu and Asgharian, 1993). Because of the difficulty encountered in generating monodisperse fibers, size-selective but polydisperse fibers have been normally used in animal deposition studies (e.g., Evans et al., 1973; Morgan et al. 1975, 1978, 1980). At present, no deposition data is available for humans although there have been several attempts to measure local deposition of fibers in human airway casts (Sussman et al., 1991a,b; Myojo, 1987, 1990). Regional deposition in the human respiratory tract can be estimated from mathematical models (Asgharian and Yu, 1988; Yu and Asgharian, 1993). Figure 10-11 presents the regional deposition results in humans calculated by Yu and Asgharian (1993). A complete discussion of fiber deposition in the lung is beyond the scope of this document.

10.4.2 Clearance and Translocation Mechanisms

Particles which deposit upon airway surfaces may be cleared from the respiratory tract completely, or may be translocated to other sites within this system, by various regionally distinct processes. These clearance mechanisms, which are outlined in Table 10-9, can be categorized as either absorptive, i.e., dissolution, or nonabsorptive, i.e., transport of intact particles, and may occur simultaneously or with temporal variations. It should be mentioned that particle solubility in terms of clearance refers to solubility *in vivo* within the respiratory tract fluids and cells. Thus, an "insoluble" particle is considered to be one whose rate of clearance by dissolution is insignificant compared to its rate of clearance as an intact particle. For the most part, all deposited particles are subject to clearance by the same mechanisms, with their ultimate fate a function of deposition site, physicochemical properties (including any toxicity), and sometimes deposited mass or number concentration. Clearance routes

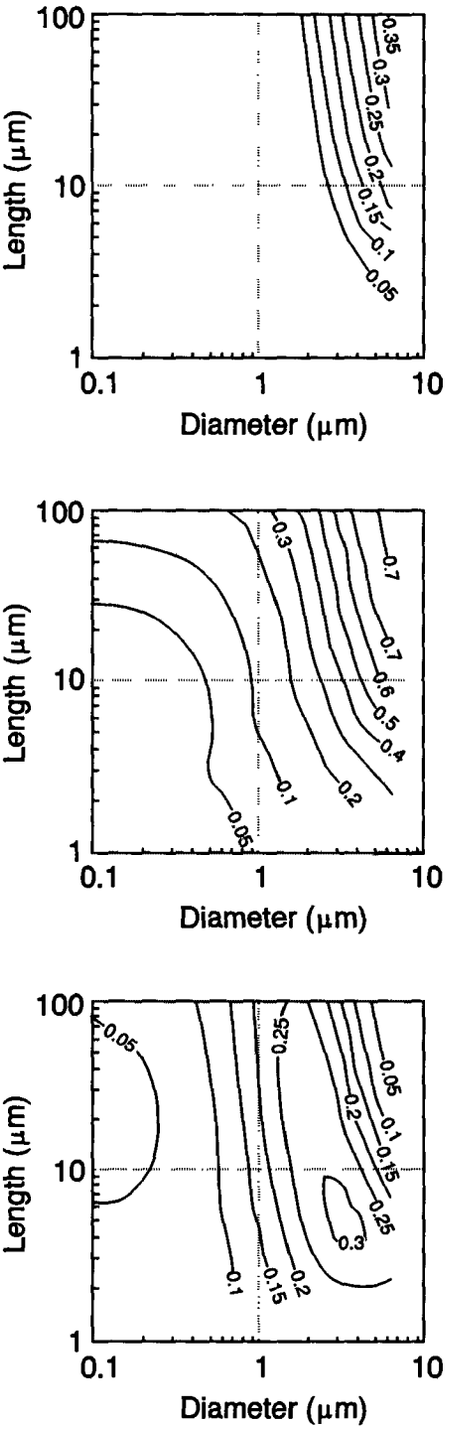

Figure 10-11. Calculated regional deposition fraction of unit-density fibers in humans at quiet mouth breathing.

Source: Yu and Asgharian (1993).

TABLE 10-9. OVERVIEW OF RESPIRATORY TRACT PARTICLE CLEARANCE AND TRANSLOCATION MECHANISMS

Extrathoracic region
Mucociliary transport
Sneezing
Nose wiping and blowing
Dissolution (for "soluble" particles) and absorption into blood
Tracheobronchial region
Mucociliary transport
Endocytosis by macrophages/epithelial cells
Coughing
Dissolution (for "soluble" particles) and absorption into blood
Alveolar region
Macrophages, epithelial cells
Interstitial
Dissolution for "soluble" and "insoluble" particles (intra-and extracellular)

Source: Schlesinger (1995)

from the various regions of the respiratory tract are schematically outlined in Figures 10-12 and 10-13. Furthermore, clearance is a continuous process and all mechanisms operate simultaneously for deposited particles.

10.4.2.1 Extrathoracic Region

The clearance of insoluble particles deposited in the nonolfactory portion of nasal passages occurs via mucociliary transport, and the general flow of mucus is backwards, i.e., towards the nasopharynx (Figure 10-12). However, the epithelium of the most anterior portion of the nasal passages is not ciliated, and mucus flow just distal to this is forward, clearing deposited particles to a site (vestibular region) where removal is by sneezing (a reflex response), wiping, or blowing (mechanisms known as extrinsic clearance).

Soluble material deposited on the nasal epithelium will be accessible to underlying cells if it can diffuse to them through the mucus prior to removal via mucociliary transport. Dissolved substances may be subsequently translocated into the bloodstream following

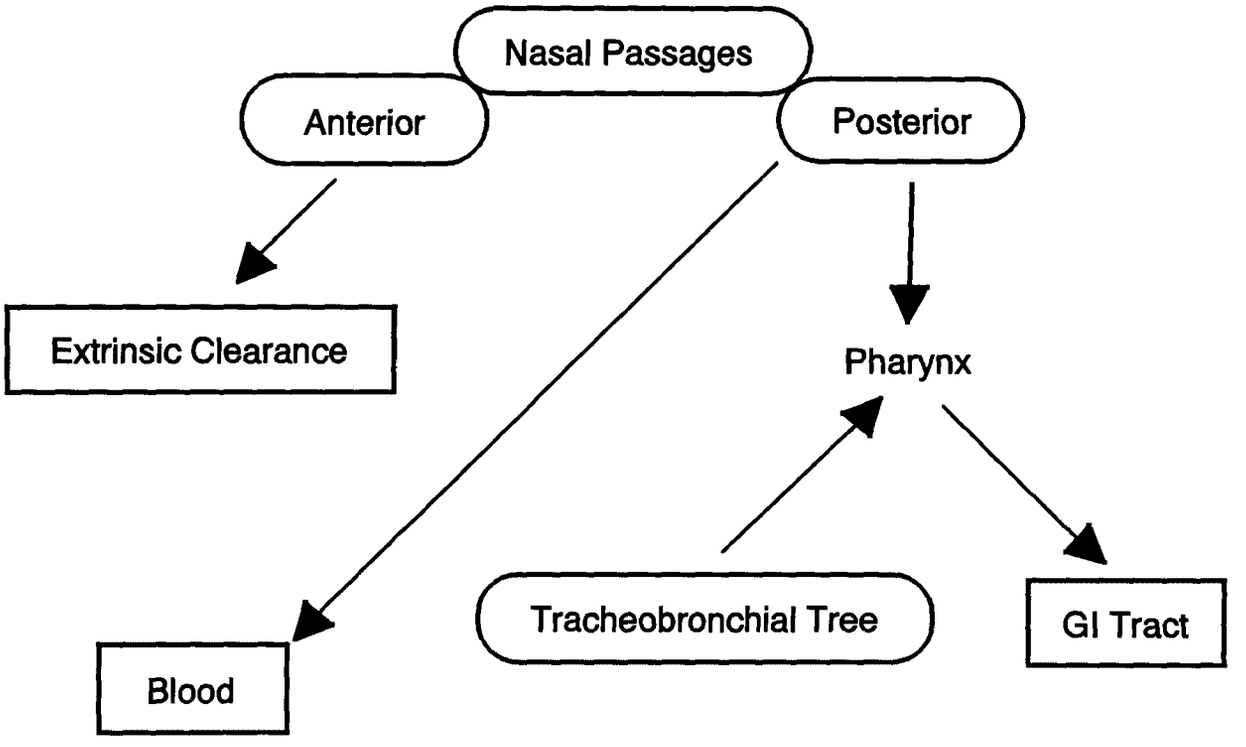

Figure 10-12. Major clearance pathways from the extrathoracic region and tracheobronchial tree.

movement within intercellular pathways between epithelial cell tight junctions or by active or passive transcellular transport mechanisms. The nasal passages have a rich vasculature, and uptake into the blood from this region may occur rapidly.

Clearance of insoluble particles deposited in the oral passages is by swallowing into the gastrointestinal tract. Soluble particles are likely rapidly absorbed after deposition (Swift and Proctor, 1988).

10.4.2.2 Tracheobronchial Region

Insoluble particles deposited within the tracheobronchial tree are cleared primarily by mucociliary transport, with the net movement of fluid towards the oropharynx, followed by swallowing. Some insoluble particles may traverse the epithelium by endocytotic processes,

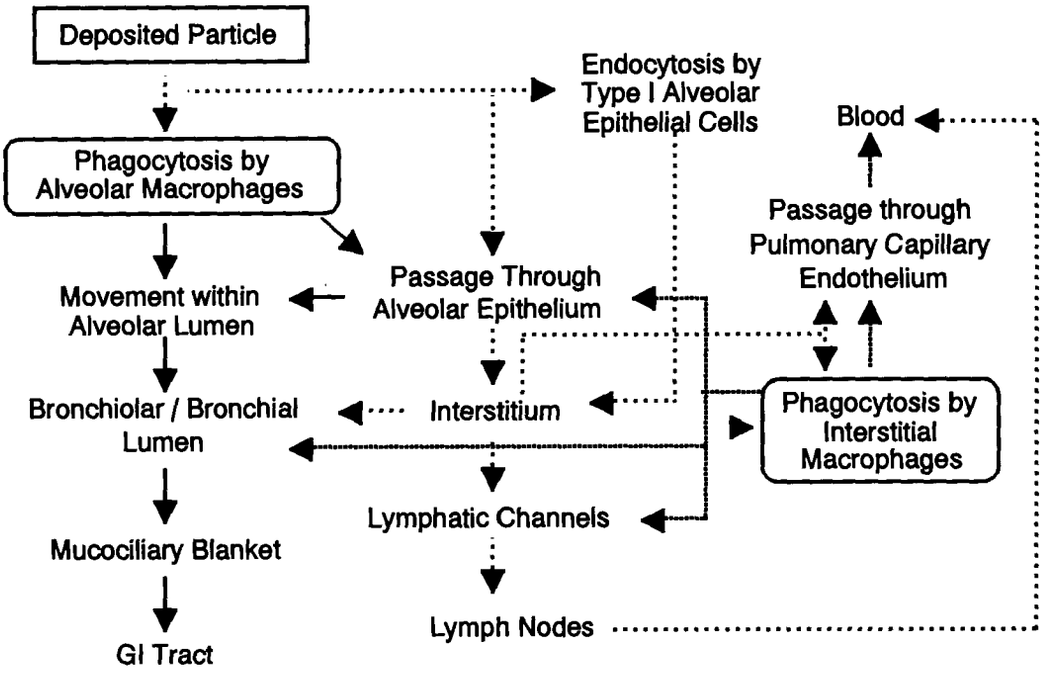

Figure 10-13. Diagram of known and suspected clearance pathways for insoluble particles depositing in the alveolar region. (?) = speculated routes.

Source: Schlesinger (1995).

entering the peribronchial region (Masse et al., 1974; Sorokin and Brain, 1975). Clearance may also occur following phagocytosis by airway macrophages, located on or beneath the mucus lining throughout the bronchial tree, which then move cephalad on the mucociliary blanket, or via macrophages which enter the airway lumen from the bronchial or bronchiolar mucosa (Robertson, 1980).

As in the nasal passages, soluble particles may be absorbed through the mucus layer of the tracheobronchial airways and into the blood, via intercellular pathways between epithelial cell tight junctions or by active or passive transcellular transport mechanisms.

The bronchial surfaces are not homogeneous; there are openings of daughter bronchi and islands of non-ciliated cells at bifurcation regions. In the latter, the usual progress of mucus movement is interrupted, and bifurcations may be sites of relatively retarded

clearance. The efficiency with which such non-ciliated regions are traversed is dependent upon the traction of the mucus layer.

Another method of clearance from the tracheobronchial region, under some circumstances, is cough, which can be triggered by receptors located in the area from the trachea through the first few bronchial branching levels. While cough is generally a reaction to some inhaled stimulus, in some cases, especially respiratory disease, it can also serve to clear the upper bronchial airways of deposited substances by dislodging mucus from the airway surface.

10.4.2.3 Alveolar Region

Clearance from the A region occurs via a number of mechanisms and pathways, but the relative importance of each is not always certain and may vary between species.

Particle removal by macrophages comprises the main nonabsorptive clearance process in the A region. Alveolar macrophages reside on the epithelium, where they phagocytize and transport deposited material that they contact by random motion, or more likely via directed migration under the influence of local chemotactic factors (Warheit et al, 1988). Contact may be facilitated as some deposited particles are translocated, due to pressure gradients or via capillary action within the alveolar surfactant lining, to sites where macrophages congregate (Schurch et al., 1990; Parra et al., 1986).

Alveolar macrophages normally comprise ≈ 3 - 5% of the total alveolar cells in healthy (non-smoking) humans and other mammals, and represent the largest subpopulation of nonvascular macrophages in the respiratory tract (Gehr, 1984; Lehnert, 1992). However, the actual cell count may be altered by particle loading. While a low number of deposited particles may not result in an increase in cell number, above some level macrophage numbers will increase proportionally to particle number until a saturation point is reached (Adamson and Bowden, 1981; Brain, 1971). Since the magnitude of this increase is related more to the number of deposited particles than to total deposition by weight, equivalent masses of an identical deposited substance may not produce the same response if particle sizes differ; thus, smaller particles would tend to result in a greater elevation in cell number than would larger ones.

Particle-laden macrophages may be cleared from the A region along a number of pathways (Figure 10-13). One route is cephalad transport via the mucociliary system after the cells reach the distal terminus of the mucus blanket. However, the manner by which macrophages actually attain this is not certain. The possibilities are chance encounter; passive movement along the alveolar surface due to surface tension gradients between the alveoli and conducting airways; directed locomotion along a gradient produced by chemotactic factors released by macrophages ingesting deposited material; or passage through the alveolar epithelium and the interstitium, perhaps through aggregates of lymphoid tissue (bronchus associated lymphoid tissues, BALT) located at bronchioalveolar junctions (Sorokin and Brain, 1975; Kilburn, 1968; Brundelet, 1965; Green, 1973; Corry et al., 1984; Harmsen et al., 1985).

Some of the cells which follow interstitial clearance pathways are likely resident interstitial macrophages which have ingested particles that were transported through the alveolar epithelium, probably via endocytosis by Type I pneumocytes (Brody et al., 1981; Bowden and Adamson, 1984). Particle-laden interstitial macrophages can also migrate across the alveolar epithelium, becoming part of the alveolar macrophage cell population (Adamson and Bowden, 1978).

Macrophages which are not cleared via the bronchial tree may actively migrate within the interstitium to a nearby lymphatic channel or, along with uningested particles, be carried in the flow of interstitial fluid towards and into the lymphatic system (Harmsen et al., 1985). Passive entry into lymphatic vessels is fairly easy, since the vessels have loosely connected endothelial cells with wide intercellular junctions (Lauweryns and Baert, 1974). Lymphatic endothelium may also actively engulf particles from the surrounding interstitium (Leak, 1980). Particles within the lymphatic system may be translocated to tracheobronchial lymph nodes, which often become reservoirs of retained material. Particles penetrating the nodes and subsequently reaching the post-nodal lymphatic circulation may enter the blood.

Uningested particles or macrophages in the interstitium may traverse the alveolar-capillary endothelium, directly entering the blood (Raabe, 1982; Holt, 1981); endocytosis by endothelial cells followed by exocytosis into the vessel lumen seems, however, to be restricted to particles <0.1 μm diameter, and may increase with increasing lung burden (Lee et al., 1989; Oberdörster, 1988). Once in the systemic circulation,

transmigrated macrophages, as well as uningested particles, can travel to extrapulmonary organs. Some mammalian species have pulmonary intravascular macrophages, which can remove particles from circulating blood and which may play some role in the clearance of material deposited in the alveoli (Warner and Brain, 1990) .

Uningested particles and macrophages within the interstitium may travel to perivenous, peribronchiolar or subpleural sites, where they become trapped, increasing particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the redistribution of initially diffuse deposits into focal aggregates (Heppleston, 1953). Some particles can be found in the pleural space, often within macrophages which have migrated across the visceral pleura (Sebastien et al., 1977; Hagerstrand and Siefert, 1973). Resident pleural macrophages do occur, but their role in clearance, if any, is not certain.

During clearance, particles can be redistributed within the alveolar macrophage population (Lehnert, 1992). One mechanism is by death of the macrophage, and release of free particles to the epithelium followed by uptake by other macrophages. Some of these newly freed particles may, however, translocate to other clearance routes.

Clearance by the absorptive mechanism involves dissolution in the alveolar surface fluid, followed by transport through the epithelium and into the interstitium, and diffusion into the lymph or blood. Some soluble particles translocated to and trapped in interstitial sites may be absorbed there. Although the factors affecting the dissolution of deposited particles are poorly understood, it is influenced by the particle's surface to volume ratio and other surface properties (Morrow, 1973; Mercer, 1967). Thus, materials generally considered to be relatively insoluble may have high dissolution rates and short dissolution half-times if the particle size is small.

Some deposited particles may undergo dissolution in the acidic milieu of the phagolysosomes after ingestion by macrophages, and such intracellular dissolution may be the initial step in translocation from the lungs for these particles (Kreyling, 1992; Lundborg et al, 1985). Following dissolution, the material can be absorbed into the blood. Dissolved particles may then leave the lungs at rates which are more rapid than would be expected based upon their normal dissolution rate in lung fluid. Because of this, the clearance rate of such a material can vary with the form in which it is inhaled and where the particle resides. For example, while insoluble (in lung fluid) MnO_2 dissolves in the macrophage, soluble

manganese chloride ($MnCl_2$) likely dissolves extracellularly and is not ingested, resulting in manganese clearing at different initial rates depending upon the form in which it was initially inhaled (Camner et al, 1985). Differences in rates of clearance may also occur for particles whose rate of dissolution is pH dependent (Marafante et al., 1987).

Finally, some particles can bind to epithelial cell membranes or macromolecules, or other cell components, delaying clearance from the lungs.

10.4.2.4 Clearance Kinetics

Although deposited particles may be cleared completely from the respiratory tract, the actual time frame over which this occurs affects dose delivered to the respiratory tract, as well as to extrapulmonary organs. Particle-tissue contact and retained dose in the extrathoracic region and tracheobronchial tree are often limited by rapid clearance from these regions and are, thus, approximately proportional to toxicant concentration and exposure duration, dependent on particle size and distribution. On the other hand, the dose from material deposited in the A region is highly dependent upon the characteristics of the particles.

Various experimental techniques have been used to assess clearance rates in both humans and experimental animals (Schlesinger, 1985b). Because of technical differences and the fact that measured rates are strongly influenced by the specific methodology, comparisons between studies are often difficult to perform. However, regional clearance rates, i.e., the fraction of the deposit which is cleared per unit time, are well defined functional characteristics of an individual human or experimental animal when repeated tests are performed under the same conditions; but, as with deposition, there is a substantial degree of inter-individual variability.

Extrathoracic Region

Mucus flow rates in the posterior nasal passages are highly nonuniform. Regional velocities in the healthy adult human may range from < 2 to > 20 mm/min (Proctor, 1980), with the fastest flow occurring in the midportion of the nasal passages. The median rate in a healthy adult human is about 5 mm/min, the net result being a mean transport time of about 10-20 min for insoluble particles deposited within the nasal passages (Stanley et al., 1985;

Rutland and Cole, 1981). However, particles deposited in the anterior portion of the nasal passages are cleared more slowly, at a rate of 1-2 mm/h (Hilding, 1963). Since clearance at this rate may take upwards of 12 h, such deposits are usually more effectively removed by sneezing, wiping, or nose blowing, in which case clearance may occur in 0.5 h (Morrow, 1977; Fry and Black, 1973).

Tracheobronchial Region

Mucus transport in the tracheobronchial tree occurs at different rates in different local regions; the velocity of movement is fastest in the trachea, and it becomes progressively slower in more distal airways. In healthy non-smoking humans, and using non-invasive procedures and no anesthesia, average tracheal mucus transport rates have been measured at 4.3 to 5.7 mm/min (Leikauf et al., 1981, 1984; Yeates et al., 1975, 1981b; Foster et al., 1980), while that in the main bronchi has been measured at $\approx$2.4 mm/min (Foster et al., 1980). While rates of movement in smaller airways have not been directly determined, estimates for human medium bronchi range between 0.2-1.3 mm/min, while those in the most distal ciliated airways range down to 0.001 mm/min (Yeates and Aspin, 1978; Morrow et al., 1967b; Cuddihy and Yeh, 1988).

It is not certain whether the transport rate for deposited insoluble particles is independent of their nature, i.e., shape, size, composition. While particles of different materials and sizes have been shown to clear at the same rate in the trachea in some studies (Man et al., 1980; Patrick, 1983; Connolly et al., 1978), other studies (using instillation) have indicated that the rate of mucociliary clearance may be greater for smaller particles ($\leq 2\mu$m) than for larger ones (Takahashi et al, 1992). Reasons for such differences between these studies are not known. There may, however, be more than one phase of clearance within individual tracheobronchial airways. For example, the rat trachea shows a biphasic clearance pattern, consisting a rapid phase within the first 2-4 h after deposition clearing up to 90% of deposited particles with a half time of $<$ 0.5 h, followed by a second, slower phase clearing most of the remaining particles with a half-time of 8-19 h (Takahashi et al, 1992). But in any case, most of the particles deposited in the trachea are cleared very rapidly, within about 2 to 4 h after deposition.

The total duration of bronchial clearance, or some other time parameter, is often used as an index of mucociliary kinetics yet the temporal clearance pattern is not certain. In healthy adult non-smoking humans, 90% of insoluble particles depositing within the tracheobronchial tree were found to be cleared from 2.5 to 20 h after deposition, depending upon the individual subject and the size of the particles (Albert et al., 1973); while this latter does not affect surface transport, it does affect the depth of particle penetration and deposition and the subsequent pathway length for clearance. Due to differences in regional transport rates, clearance times from different regions of the bronchial tree will differ. While removal of a TB deposit is generally 99% completed by 48 h after exposure (Bailey et al., 1985a), there is the possibility of longer-term retention under certain circumstances.

Studies with rodents, rabbits, and humans have indicated that a small fraction ($\approx$1%) of insoluble material may be retained for a prolonged period of time within the upper respiratory tract (nasal passages) or tracheobronchial tree (Patrick and Stirling, 1977; Gore and Patrick, 1982; Watson and Brain, 1979; Radford and Martell, 1977; Svartengren et al., 1981). The mechanism(s) underlying this long-term retention is unknown, but may involve endocytosis by epithelial cells with subsequent translocation into deeper (submucosal) tissue, or merely passive movement into this tissue. In addition, uptake by the epithelium may depend upon the nature, or size, of the deposited particle (Watson and Brain, 1980). The retained particles may eventually be cleared to regional lymph nodes, but with a long half time that may be $>$ 80 days (Patrick, 1989; Oghiso and Matsuoka, 1979).

There is some suggestion of a greater extent of long term retention in the bronchial tree. Stahlhofen et al. (1986), using a specialized inhalation procedure, noted that a significant fraction, up to 40%, of particles which were likely deposited in the conducting airways were not cleared up to six days post-deposition. They also noted that the size of the particles influenced this retention, with smaller ones being retained to a greater extent than were larger ones (Stahlhofen et al., 1987, 1990). Although the reason for this is not certain, the suggested presence of a surfactant film on the muccous lining of the airways (Gehr et al., 1990) may result in a reduced surface tension which, in turn, influences the displacement of particles into the gel layer and subsequently into the sol layer towards the epithelial cells. Particles which reach the latter may then be phagocytized, increasing retention time in the

lungs. However, the issue of retention of large fractions of tracheobronchial deposit is not resolved.

Long-term TB retention patterns are not uniform. There is an enhancement at bifurcation regions (Cohen et al., 1988; Radford and Martell, 1977; Henshaw and Fews, 1984), the likely result of both greater deposition and less effective mucus clearance within these areas. Thus, doses calculated based upon uniform surface retention density may be misleading, especially if the material is, toxicologically, slow acting. Solubilized material may also undergo long-term retention in ciliated airways due to binding to cells or macromolecules.

Alveolar Region

Clearance kinetics in the A region are not definitively understood, although particles deposited there generally remain longer than do those deposited in airways cleared by mucociliary transport. There are limited data on rates in humans, while within any species rates vary widely due to different properties of the particles used in the various studies. Furthermore, some of these studies employed high concentrations of insoluble particles, which may of itself have interfered with normal clearance mechanisms, producing rates different from those which would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle "overload." This is discussed in greater detail in Section 10.4.2.7.

There are numerous pathways of A region clearance, and these may depend upon the nature of the particles being cleared. Thus, kinetic generalizations are difficult to make, especially since the manner in which particle characteristics affect kinetics is not resolved. Nevertheless, A region clearance can be described as a multiphasic process, each component considered to represent removal by a different mechanism or pathway, and often characterized by increasing retention half-times with time post-exposure.

Clearance of inert, insoluble particles in healthy, nonsmoking humans has been generally observed to consist of two phases, with the first having a half-time measured in days, and the second in hundreds of days. Table 10-10 presents some observed times for the longer, second phase of clearance as reported in a number of studies. Although wide variations in retention reflect a dependence upon the nature of the deposited material (e.g.,

particle size) once dissolution is accounted for, mechanical removal to the gastrointestinal tract and/or lymphatic system appears to be independent of size, especially for particles < 5 μm (Snipes et al., 1983). Although not evident from Table 10-10, there is considerable intersubject variability in the clearance rates of identical particles, which appears to increase with time post-exposure (Philipson et al, 1985; Bailey et al, 1985a). The large differences in clearance kinetics among different individuals suggests that equivalent chronic exposures to insoluble particles may result in large variations in respiratory tract burdens.

TABLE 10-10. LONG-TERM RETENTION OF INSOLUBLE PARTICLES FROM THE ALVEOLAR REGION IN NON-SMOKING HUMANS

Particle		Retention half-time[a]	
Material	Size (μm)	(days)	Reference
Polystyrene latex	5	150 to 300	Booker et al. (1967)
Polystyrene latex	5	144 to 340	Newton et al. (1978)
Polystyrene latex	0.5	33 to 602	Jammett et al. (1978)
Polystyrene latex	3.6	296	Bohning et al. (1982)
Teflon	4	100 to 2,500	Philipson et al. (1985)
Aluminosilicate	1.2	330	Bailey et al. (1982)
Aluminosilicate	3.9	420	Bailey et al. (1982)
Iron oxide (Fe_2O_3)	0.8	62	Morrow et al. (1967a,b)
Iron oxide (Fe_2O_3)	0.1	270	Waite and Ramsden (1971)
Iron oxide (Fe_3O_4)	2.8	70	Cohen et al. (1979)

[a]Represent the half-time for the slowest clearance phase observed.

While the kinetics of overall clearance from the A region have been assessed to some extent, much less is known concerning relative rates along specific pathways and available information is generally from studies with laboratory animals. The usual initial step in clearance, i.e., uptake of deposited particles by alveolar macrophages, is very rapid. Unless the particles are cytotoxic or very large, ingestion by macrophages occurs within 24 h of a single inhalation (Naumann and Schlesinger, 1986; Lehnert and Morrow, 1985). But the actual rate of subsequent macrophage clearance is not certain; perhaps 5% or less of their total number is translocated from the lungs each day for rodents (Lehnert and Morrow, 1985; Masse et al., 1974).

The rate and amount of particle uptake by macrophages is likely governed by particle size and surface properties (Tabata and Ikada, 1988). For example, the effect of particle size was examined by incubating mouse peritoneal macrophages with polymer microspheres (0.5 to 5 μm). Both the number of particles ingested per cell and the volume of these particles per cell reached a maximum for particle diameters of 1-2 μm, declining on either side of this range. In terms of particle surface, those with hydrophobic surfaces were ingested to a greater extent than were those with hydrophilic surfaces. Phagocytosis also increased as the surface charge density of a particle increased, but for the same charge density there was no difference in uptake between positively or negatively charged particles.

The time for clearance of particle-laden alveolar macrophages via the mucociliary system depends upon the site of uptake relative to the distal terminus of the mucus blanket at the bronchiolar level. Furthermore, clearance pathways, and subsequent kinetics, may depend to some extent upon particle size. For example, some smaller ultrafine particles (perhaps < 0.02 μm) may be less effectively phagocytosed than are larger ones (Oberdörster, 1993). But once ingestion occurs, alveolar macrophage-mediated kinetics are independent of the particle involved, as long as solubility and cytotoxicity are low.

In terms of other clearance pathways, uningested particles may penetrate into the interstitium, largely by Type I cell endocytosis, within a few hours following deposition (Ferin and Feldstein, 1978; Sorokin and Brain, 1975; Brody et al., 1981). This transepithelial passage seems to increase as particle loading increases, especially to a level above the saturation point for increasing macrophage number (Adamson and Bowden, 1981; Ferin, 1977). It may also be particle size dependent, since insoluble ultrafine particles (<0.1 μm diameter) of low toxicity show increased access to and greater lymphatic uptake than do larger ones of the same material (Oberdörster et al., 1992). However, ultrafine particles of different materials may not enter the interstitium to the same extent. Similarly, a depression of phagocytosis by toxic particles or the deposition of large numbers of smaller ultrafine particles may increase the number of free particles in the alveoli, enhancing removal by other routes. In any case, free particles and alveolar macrophages may reach the lymph nodes, perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985), although this route is not certain and may be species dependent.

The extent of lymphatic uptake of particles may depend upon the effectiveness of other clearance pathways. For example, lymphatic translocation likely increases when phagocytic activity of alveolar macrophages is decreased (Greenspan, et al., 1988). This may be a factor in lung overload, as discussed in Section 10.4.2.7. However, it seems that the deposited mass or number of particles must reach some threshold below which increases in loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle and Brieger, 1961).

The rate of translocation to the lymphatic system may be somewhat particle size dependent. Although no human data are available, translocation of latex particles to the lymph nodes of rats was greater for 0.5 to 2 μm particles than for 5 and 9 μm particles (Takahashi et al, 1992), and smaller particles within the 3-15 μm size range were found to be translocated at faster rates than were larger sizes (Snipes and Clem, 1981). On the other hand, translocation to the lymph nodes was similar for both 0.4 μm barium sulfate or 0.02 μm gold colloid particles (Takahashi et al, 1987). It seems that particles $\leq$ 2 μm clear to the lymphatic system at a rate independent of size, and it is particles of this size, rather than those $\geq$ 5 μm, that would have significant deposition within the pulmonary region following inhalation.

In any case, and regardless of any particle size dependence, the normal rate of translocation to the lymphatic system is quite slow, on the order of 0.02-0.003%/day (Snipes, 1989), and elimination from the lymph nodes is even slower, with half-times measured in tens of years (Roy, 1989).

Soluble particles depositing in the A region may be rapidly cleared via absorption through the epithelial surface into the blood, but there are few data on dissolution and transfer rates to blood in humans. Actual rates depend upon the size of the particle (i.e., solute size), with smaller ones clearing faster than larger ones. Chemistry also plays a role, since water soluble compounds generally clear at a slower rate than do lipid soluble materials.

Absorption may be considered as a two stage process, with the first stage dissociation of the deposited particles into material that can be absorbed into the circulation (dissolution) and the second stage the uptake of this material. Each of these stages may be time dependent. The rate of dissolution depends upon a number of factors, including particle

surface area and chemical structure. Uptake into the circulation is generally considered as instantaneous, although a portion of the dissolved material may be absorbed more slowly due to binding to respiratory tract components. Accordingly, there is a very wide range for absorption rates depending upon the physicochemical properties of the material deposited. For example, a highly soluble particle may be absorbed at a rate faster than the particle transport rate and significant uptake may occur in the conducting airways. On the other hand, a particle that is less soluble and remains in the lungs for years would have a much lower rate, perhaps $< 0.0001\%$/day.

10.4.2.5 Factors Modifying Clearance

A number of host and environmental factors may modify normal clearance patterns, affecting the dose delivered by exposure to inhaled particles. These include aging, gender, workload, disease and irritant inhalation. However, in many cases, the exact role of these factors is not resolved.

Age

The evidence for aging-related effects on mucociliary function in healthy individuals is equivocal, with studies showing either no changes or some slowing in mucous clearance function with age after maturity (Goodman et al., 1978; Yeates et al., 1981a; Puchelle et al, 1979). However, it is often difficult to determine whether any observed functional decrement was due to aging alone, or to long-term, low level ambient pollutant exposure (Wanner, 1977). In any case, the change in mucous velocity between approximately age 20 and 70 in humans is about a factor of two (Wolff, 1992) and would likely not significantly affect overall kinetics.

There are few data to allow assessment of aging-relating changes in clearance from the pulmonary region. Although functional differences have been found between alveolar macrophages of mature and senescent mice (Esposito and Pennington, 1983), no age-related decline in macrophage function has been seen in humans (Gardner et al., 1981).

There are also insufficient data to assess changes in clearance in the growing lung. Nasal mucociliary clearance time in a group of children (average age = 7 yrs) was found to be ≈ 10 min (Passali and Ciampoli, 1985); this is within the range for adults. There is one

report of bronchial clearance in children (12 yrs old), but this was performed in patients hospitalized for renal disease (Huhnerbein et al., 1984).

Gender

No gender related differences were found in nasal mucociliary clearance rates in children (Passali and Ciampoli, 1985) nor in tracheal transport rates in adults (Yeates et al., 1975). Slower bronchial clearance has been noted in male compared to female adults, but this was attributed to differences in lung size (and resultant clearance pathway length) rather than to inherent gender related differences in transport velocities (Garrard et al., 1986).

Physical Activity

The effect of increased physical activity upon mucociliary clearance is unresolved, with the available data indicating no change to a speeding with exercise (Wolff et al., 1977; Pavia, 1984). There are no data concerning changes in pulmonary region clearance with increased activity levels, but CO_2-stimulated hyperpnea (rapid, deep breathing) was found to have no effect on early pulmonary clearance and redistribution of particles (Valberg et al., 1985). Increased tidal volume breathing was noted to increase the rate of particle clearance from the pulmonary region, and this was suggested to be due to distension related evacuation of surfactant into proximal airways, resulting in a facilitated movement of particle-laden macrophages or uningested particles due to the accelerated motion of the alveolar fluid film (John et al., 1994).

Respiratory Tract Disease

Various respiratory tract diseases are associated with clearance alterations. The examination of clearance in individuals with lung disease requires careful interpretation of results, since differences in deposition of tracer particles used to assess clearance function may occur between normal individuals and those with respiratory disease, and this would directly impact upon the measured clearance rates, especially in the tracheobronchial tree. In any case, nasal mucociliary clearance is prolonged in humans with chronic sinusitis, bronchiectasis, or rhinitis (Majima et al., 1983; Stanley et al., 1985), and in cystic fibrosis (Rutland and Cole, 1981). Bronchial mucus transport may be impaired in people with

bronchial carcinoma (Matthys et al., 1983), chronic bronchitis (Vastag et al., 1986), asthma (Pavia et al., 1985), and in association with various acute infections (Lourenco et al., 1971; Camner et al., 1979; Puchelle et al., 1980). In certain of these cases, coughing may enhance mucus clearance, but it generally is effective only if excess secretions are present.

Normal mucociliary function is essential to respiratory tract health. Studies of individuals with a syndrome characterized by impaired clearance, i.e., primary ciliary dyskinesia (PCD), may be used to assess the importance of mucociliary transport and the effect of its dysfunction upon respiratory disease, and to provide information on the role of clearance in maintaining the integrity of the lungs. The lack of mucolciliary function in PCD is directly responsible for the early development of recurrent respiratory tract infections and, eventually, chronic bronchitis and bronchiectasis (Rossman et al., 1984; Wanner, 1980). It is, however, not certain whether partial impairment of the mucociliary system will increase the risk of lung disease.

Rates of pulmonary region particle clearance appear to be reduced in humans with chronic obstructive lung disease (Bohning et al., 1982) and in experimental animals with viral infections (Creasia et al., 1973). The viability and functional activity of macrophages was found to be impaired in human asthmatics (Godard et al., 1982).

Studies with experimental animals have also found disease related clearance changes. Hamsters with interstitial fibrosis showed an increased degree of pulmonary clearance (Tryka et al., 1985). Rats with emphysema showed no clearance difference from control (Damon et al., 1983), although the co-presence of inflammation resulted in prolonged retention (Hahn and Hobbs, 1979). On the other hand, inflammation may enhance particle and macrophage penetration through the alveolar epithelium into the interstitium, by increasing the permeability of the epithelium and the lymphatic endothelium (Corry et al., 1984). Neutrophils, which are phagocytic cells present in alveoli during inflammation, may contribute to the clearance of particles via the mucociliary system (Bice et al., 1990).

Macrophages have specific functional properties, namely phagocytic activity and mobility, which allow them to adequately perform their role in clearance. Alveolar macrophages from calves with an induced interstitial inflammation (pneumonitis) were found to have enhanced phagocytic activity compared to normal animals (Slauson et al, 1989). On the other hand, depressed phagocytosis was found with virus-induced acute bronchiolitis and

alveolitis (Slauson et al, 1987). How such alterations affect clearance from the pulmonary region is not certain, since the relationship between macrophage functional characteristics and overall clearance is not always straightforward. While changes in macrophage function do impact upon clearance, the manner by which they do so may not always be easily predictable. In any case, the modification of functional properties of macrophages appear to be injury specific, in that they reflect the nature and anatomic pattern of disease.

Inhaled Irritants

Inhaled irritants have been shown to have an effect upon mucociliary clearance function in both humans and experimental animals (Schlesinger, 1990; Wolff, 1986). Single exposures to a particular material may increase or decrease the overall rate of tracheobronchial clearance, often depending upon the exposure concentration (Schlesinger, 1986). Alterations in clearance rate following single exposures to moderate concentrations of irritants are generally transient, lasting < 24 h. However, repeated exposures may result in an increase in intra-individual variability of clearance rate and persistently retarded clearance. The effects of irritant exposure may be enhanced by exercise, or by coexposure to other materials.

Acute and chronic exposures to inhaled irritants may also alter PU region clearance (Cohen et al., 1979; Ferin and Leach, 1977; Schlesinger et al., 1986; Phalen et al., 1994), which may be accelerated or depressed, depending upon the specific material and/or length of exposure. While the clearance of insoluble particles from conducting airways is due largely to only one mechanism, i.e., mucociliary transport, clearance from the respiratory region involves a complex of multiple pathways and processes. Because transit times along these different pathways vary widely, a toxicant-induced change in clearance rate could be due to a change in the time for removal along a particular pathway and/or to a change in the actual route taken. Thus, it is often quite difficult to delineate specific mechanisms of action for toxicants which alter overall clearance from respiratory airways. Alterations in alveolar macrophages likely underlay some of the observed changes, since numerous irritants have been shown to impair the numbers and functional properties of these cells (Gardner, 1984).

Since a great number of people are exposed to cigarette, it is of interest to summarize effects of this irritant upon clearance processes. Smoke exposed animals and humans show

increased number of macrophages recoverable by bronchopulmonary lavage (Brody and Davis, 1982; Warr and Martin, 1978; Matulionis, 1984; Zwicker et al., 1978). However, the rate of particle clearance from the pulmonary region of the lungs appears to be reduced in cigarette smokers (Bohning et al., 1982; Cohen et al., 1979).

While cigarette smoking has been shown to affect tracheobronchial mucociliary clearance function, the effects range from acceleration to slowing. Some of the apparent discrepancies in different studies is related to differences in the effects of short-term versus long-term effects of cigarette smoke. Long term smokers appear to have mucolciliary clearance which is slower than that in nonsmokers (Lourenco et al., 1971; Albert et al., 1971) and which also show certain anomalies, such as periods of intermittent clearance stasis. On the other hand, the short term effects of cigarette smoke range from acceleration to retardation depending upon the number of cigarettes smoked (Albert et al, 1971; Lippmann et al., 1977; Albert et al., 1974).

10.4.2.6 Comparative Aspects of Clearance

As with deposition analyses, the inability to study the retention of certain materials in humans for direct risk assessment requires use of experimental animals. Since dosimetry depends upon clearance rates and routes, adequate toxicologic assessment necessitates that kinetics in these animals be related to that occurring in humans. The basic mechanisms and overall patterns of clearance from the respiratory tract appear to be similar in humans and most other mammals. However, regional clearance rates can show substantial variation between species, even for similar particles deposited under comparable exposure conditions (Snipes, 1989).

Dissolution rates and rates of transfer of dissolved substances into the blood may or may not be species independent, depending upon certain chemical properties of the deposited material (Griffith et al., 1983; Bailey et al., 1985b; Roy, 1989). For example, lipophilic compounds of comparable molecular weight are cleared from the lungs of various species at the same rate (dependent solely upon solute molecular weight and the lipid/water partition coefficient), but hydrophilic compounds do show species differences.

On the other hand, there are distinct interspecies differences in rates of mechanical transport in the conducting and A airways. While mucous transport rates in the nasal

passages seem to be similar in humans and the limited other species examined (Morgan et al, 1986; Whaley, 1987), tracheal mucous velocities vary among species as a function of body weight (Felicetti et al., 1981; Wolff, 1992).

In the A region, macrophage-mediated clearance of insoluble particles is species dependent, with small mammalian species generally exhibiting faster clearance than larger species, with the exception of the Guinea pig which clears slower than rodents. This may result from interspecies differences in macrophage-mediated clearance of insoluble particles (Valberg and Blanchard, 1992; Bailey et al., 1985b); transport of particles from the A region to pulmonary lymph nodes (Snipes et al., 1983; Mueller et al., 1990); phagocytic rates and chemotactic responses of alveolar macrophages (Warheit and Hartsky, 1994); or the prevalence of BALT (Murray and Driscoll, 1992). These likely result in species-dependent rate constants for these clearance pathways, and differences in regional (and perhaps total) clearance rates between some species are a reflection of these differences in mechanical processes. For example, the relative proportion of particles cleared from the PU region in the short and longer term phases of clearance differs between rodents and larger mammals, with a greater percentage cleared in the faster first phase in rodents. The end result of interspecies differences in deposition and clearance is that the retention of deposited particles can differ between species, and this may result in differences in response for similar inhaled particulate atmospheres.

10.4.2.7 Lung Overload

Some experimental studies using rodents employed high exposure concentrations of relatively nontoxic, insoluble particles, which interfered with normal clearance mechanisms, producing clearance rates different from those which would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle "overload." This is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of insoluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in PU region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of particles into the interstitium (Muhle et al., 1990; Lehnert, 1990; Morrow, 1994). While overload induced effects are reversible, the extent of such reversibility

decreases as the degree of overloading increases. Furthermore, it appears that once some critical particle burden is reached, particles of all sizes (those studies ranged from ultrafine to 4 μm) show increased interstitialization (Oberdörster et al, 1992). This phenomenon involves macrophage-mediated clearance, and has been suggested to be due to the inhibition of alveolar macrophage mobility.

While the exact amount of deposition needed to induce overload is not certain, it has been hypothesized that it will likely begin, at least in the rat, when deposition approaches 1 mg particles/g lung tissue (Morrow, 1988). When the concentration reaches 10 mg particles/g lung tissue, macrophage-mediated clearance of the particles would effectively cease. However, overload may be related more to the volume of particles ingested than to the total mass (Morrow, 1988; Oberdörster et al, 1992b). Furthermore, tumors and fibrosis may develop following the overloading and retardation of lung clearance in rats, subsequent accumulation of particles, inflammation, and the interaction of inflammatory mediators with cell proliferative processes and DNA (Mauderly, 1994).

Lung overload may result from two types of exposure scenarios. One is repeated exposures to relatively insoluble materials until some critical lung burden is reached. Until this occurs, clearance is normal, but above this threshold level, clearance becomes progressively retarded and associated other changes occur. The other scenario is that overload is a function of the amount of such particles which deposit daily, i.e., deposition rate (Muhle, 1988). Clearance retardation was suggested to occur if exposure reached levels of 3 mg/m^3 or higher. Thus, some critical deposition rate over a sufficient exposure duration would result in retardation of clearance (Yu et al, 1989).

The relevance of lung overload to humans, and even to nonrodent animal species, is not clear. While it is, however, likely to be of little relevance for most "real world" ambient exposures of humans, it is of concern in interpreting some long-term experimental exposure data. It may, however, be of some concern to humans occupationally exposed to some particle types (Mauderly, 1994), since overload may involve all insoluble materials and affect all species if the particles are deposited at a sufficient rate (Pritchard, 1989), (i.e., if the deposition rate exceeds the clearance rate). In addition, the relevance to humans is also clouded by the suggestion that macrophage-mediated clearance is normally slower and

perhaps less important in humans than in rats (Morrow, 1994), and that there will be significant differences in macrophage loading between the two species.

10.4.3 Acidic Aerosols

An Issue Paper on Acid Aerosols was published by the Environmental Protection Agency in 1989. Section 3 of that document was devoted to the deposition and fate of acid aerosols. Moreover, that Section provided an update of particle deposition data from both human and experimental animal studies, described hygroscopic aerosol studies reported between 1977 and 1987, and presented a thorough discussion of the neutralization of acid aerosols by airway secretions and absorbed ammonia.

This section consists of two subsections: the first concerns the phenomenon of hygroscopicity; and the second presents current information on acidic aerosol neutralization. Deposition data and models appropriate to acidic aerosols are reviewed in Section 10.6.3.

10.4.3.1 Hygroscopicity of Acidic Aerosols

Hygroscopicity can be defined as the propensity of a material for taking up and retaining moisture under certain conditions of humidity and temperature. It is well known that action of ocean waves continuously disperses tons of hygroscopic saline particles into the atmosphere and these contribute to the worldwide meteorologic phenomena. As the growth of industrialization has expanded, the evolution of gaseous pollutants, especially the oxides of sulfur and nitrogen, has caused a greatly increased atmospheric burden of aerosols mainly derived from gas-phase reactions. These aerosols are predominantly both acidic and hygroscopic, consisting of mixtures of partially neutralized nitric, sulfuric and hydrochloric acids: i.e., inorganic salts, such as nitrites, bisulfates, sulfates and chlorides. In addition, small amounts of organic acid salts, e.g., formate and acetate, are present as are a variety of trace elements, e.g., cadmium, carbon, vanadium, chromium and phosphorus, whose oxides and other chemical forms tend also to be acid forming (Aerosols, 1986).

Two reviews on hygroscopic aerosols (Morrow, 1986; Hiller, 1991) have been published which consider the implications of hygroscopic particle growth on deposition in the human respiratory tract. Much of the treatment of hygroscopic particle growth is based on theoretical models (e.g., Xu and Yu, 1985; Ferron et al., 1988; Martonen and Zhang, 1993)

which will be reviewed in Section 10.5. Suffice it to say, particulate sodium chloride has been commonly utilized in these models and to a lesser extent, sulfuric acid droplets, and ammonium sulfate and ammonium bisulfate particles. There are no major distinctions in the growth of these several hygroscopic materials except that sulfuric acid does not manifest a deliquescent point (when the particle becomes an aqueous droplet). It can be seen in Figure 10-14 that the growth rate of hygroscopic particles is controlled by the relative humidity (RH): the closer to saturation (100% RH), the faster the growth rate.

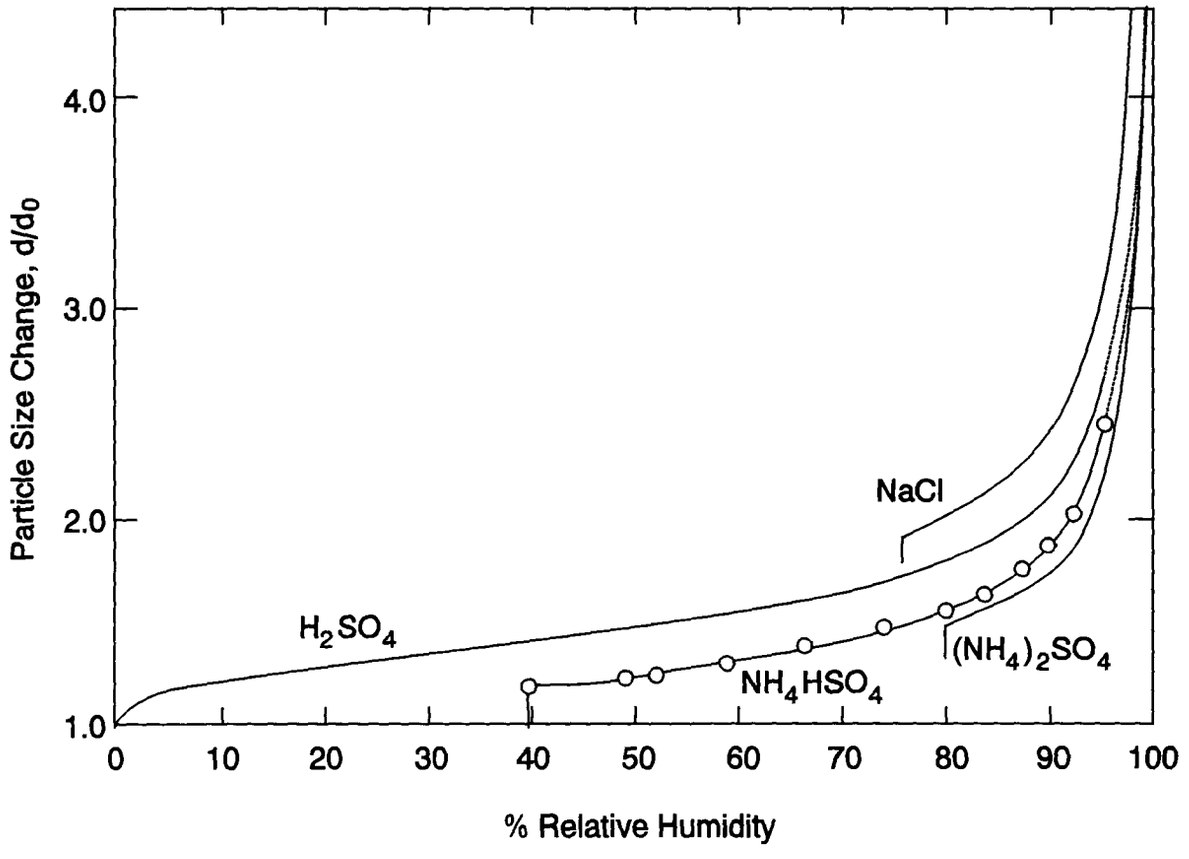

Figure 10-14. Theoretical growth curves for sodium chloride, sulfuric acid, ammonium bisulfate and ammonium sulfate aerosols in terms of the initial (d_0) and final (d) size of the particle. Note that the H_2SO_4 curve, unlike those for the three salts, has no deliquescence point.

Source: Tang and Munkelwitz (1977).

Hygroscopic particles or droplets of different initial size will experience different growth rates: the smallest particles being the fastest to reach an equilibrium size. For example, a 0.5 μm diameter particle will require approximately 1 s, whereas a 2.0 μm particle will require close to 10 s. It is immediately evident that many inhaled hygroscopic particles will not reach their equilibrium size (maximum growth) during the duration of a single respiratory cycle (ca 4 s). Conversely, the growth of ultrafine particles does not resemble that for particles >0.1 μm and thereby represents a special case. Moreover, the hygroscopic growth characteristics of aqueous droplets, containing one or more solutes, depend not only on their initial size, but their initial composition. The study of Cocks and Fernando (1982), using the condensation model of Fukata and Walter (1970), with ammonium sulfate droplets illustrate both of these last points (Figure 10-15).

The direct measurement of the RH of alveolar air and the temperature of air at the alveolar surface have been attempted, but because of technical limitations, the direct experimental determinations of these and other values at different levels of the respiratory tract have only been considered reliable for conditions in the conducting airways (Morrow 1986). Fortunately, indirect methods for these determinations have been successful. For deep-lung temperature, Edwards et al. (1963) used solubility of a helium-argon mixture in arterial blood. By this approach they found the mean pulmonary capillary temperature in five normal subjects to be 37.52 °C. Because of individual variability, they also provided an equation for estimating the deep lung temperature in an individual from a measurement of rectal temperature.

Ferron and co-workers (1983, 1985) made the logical assumption that the RH of the alveolar air was determined by an equilibrium with the vapor pressure of blood serum at the capillary level. The osmolarity of serum at 37 °C (287 $\pm$ 4 mmol/kg) provided these investigators a sound basis for selecting 99.5% RH as the value to use in all of the modeling estimations. In Figure 10-16 (from Xu and Yu, 1985) the calculated equilibrium diameters for sodium chloride particles on the basis of their initial size (d_0) is depicted. The equilibrium diameters (d_{oo}) that can be achieved theoretically for each particle size is shown as a function of three different RH values. For an RH of 99.5%, the growth of salt particles with an initial size greater than 0.5 μm, yields about a 6-fold increase in diameter.

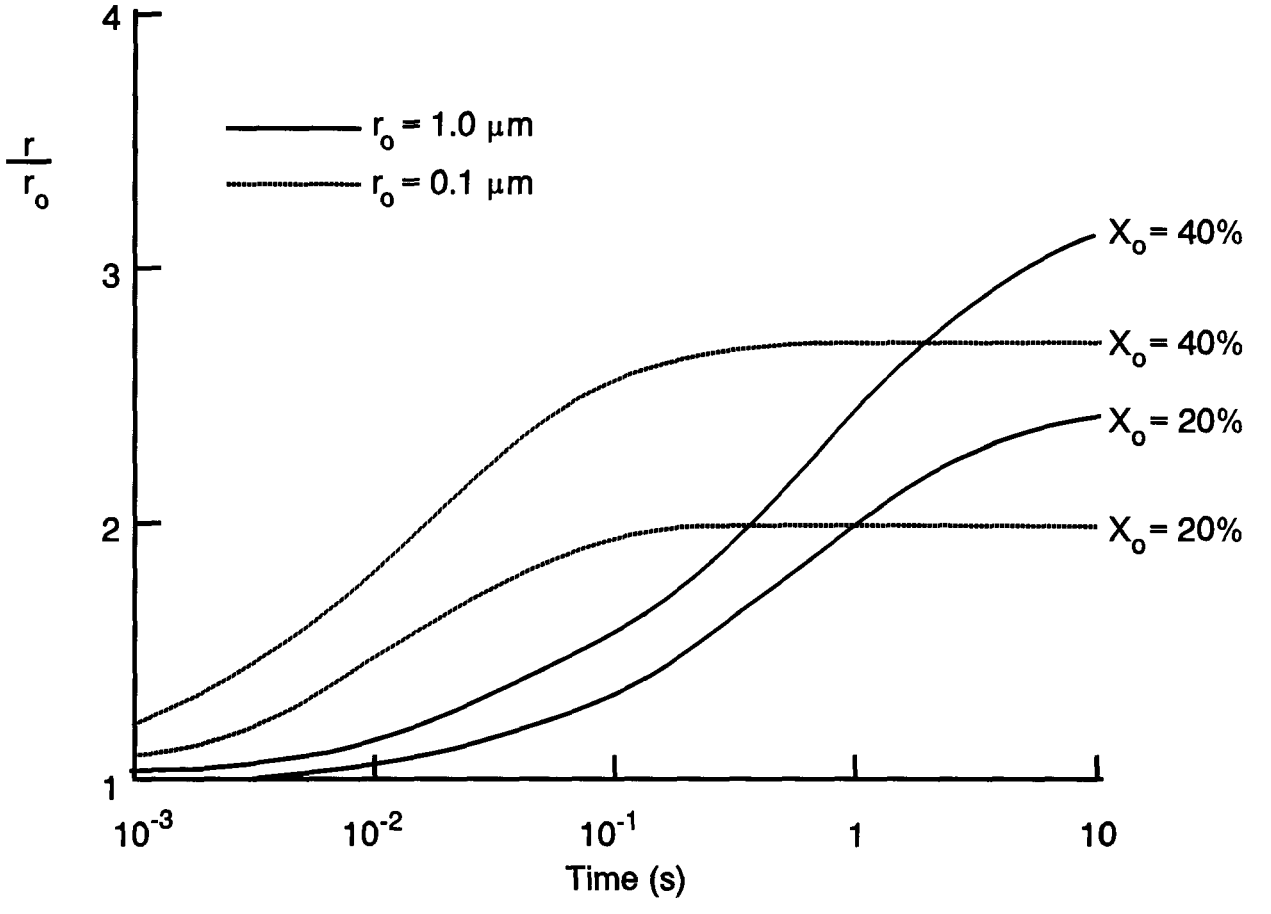

Figure 10-15. Distinctions in growth (r/r_0) of aqueous $(NH_4)_2SO_4$ droplets of 0.1 and 1.0 μm initial size are depicted as a function of their initial solute concentrations (X_0).

Source: Cocks and Fernando (1983).

Ferron et al. (1988) calculated the RH in the human airways by employing a transport theory for heat and water vapor using cylindrical coordinates. Several parameters of the theory were chosen to best fit the available experimental data. These authors also used the transport theory to model the growth and deposition of three salts, viz., NaCl, $CoCl_{2.6}H_2O$, and $ZnSO_{4.7}H_2O$, which were selected because these differentially hydrated particles have large, moderate and small hygroscopic growth potentials, respectively. Figure 10-17 depicts the growth of these three salts when their initial dry particle size is 1.0 μm diameter, the average inspired airflow is 250 cc/s, and the inhalation is by mouth. In this depiction, the

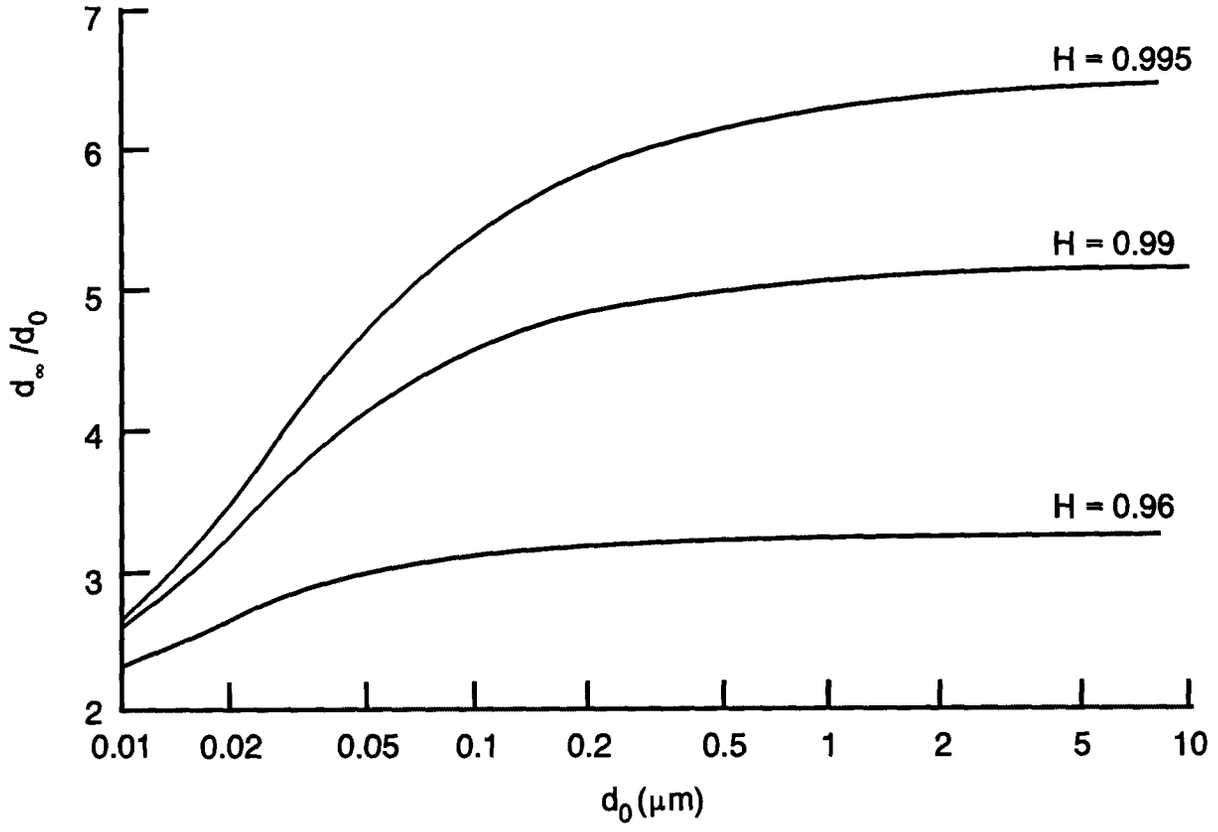

Figure 10-16. The initial diameter of dry NACl particles (d_0) and equilibrium diameter achieved (d) are shown for three relative humidity assumptions.

Source: Xu and Yu (1985).

particle growth is expressed as the ratio of the achieved aerodynamic diameter to the initial aerodynamic size.

A recent experimental study by Anselm et al. (1990) used an indirect method, similar to that employed earlier by Tu and Knudsen (1984), to validate the 99.5% RH assumption for alveolar air. In this instance, monodisperse NaCl particles between 0.2 and 0.5 μm were made by vibrating orifice generator and administered, by mouth, as boli during a constant inspiratory airflow. During expiration, the particles suspended in the same volume element were size classified. To determine equilibrium particle sizes, 600 cc of aerosol was inspired followed by 400 cc of clean air. Expiration was initiated after different periods of breath holding and the behavior of NaCl particles (loss and settling velocities) was compared to that

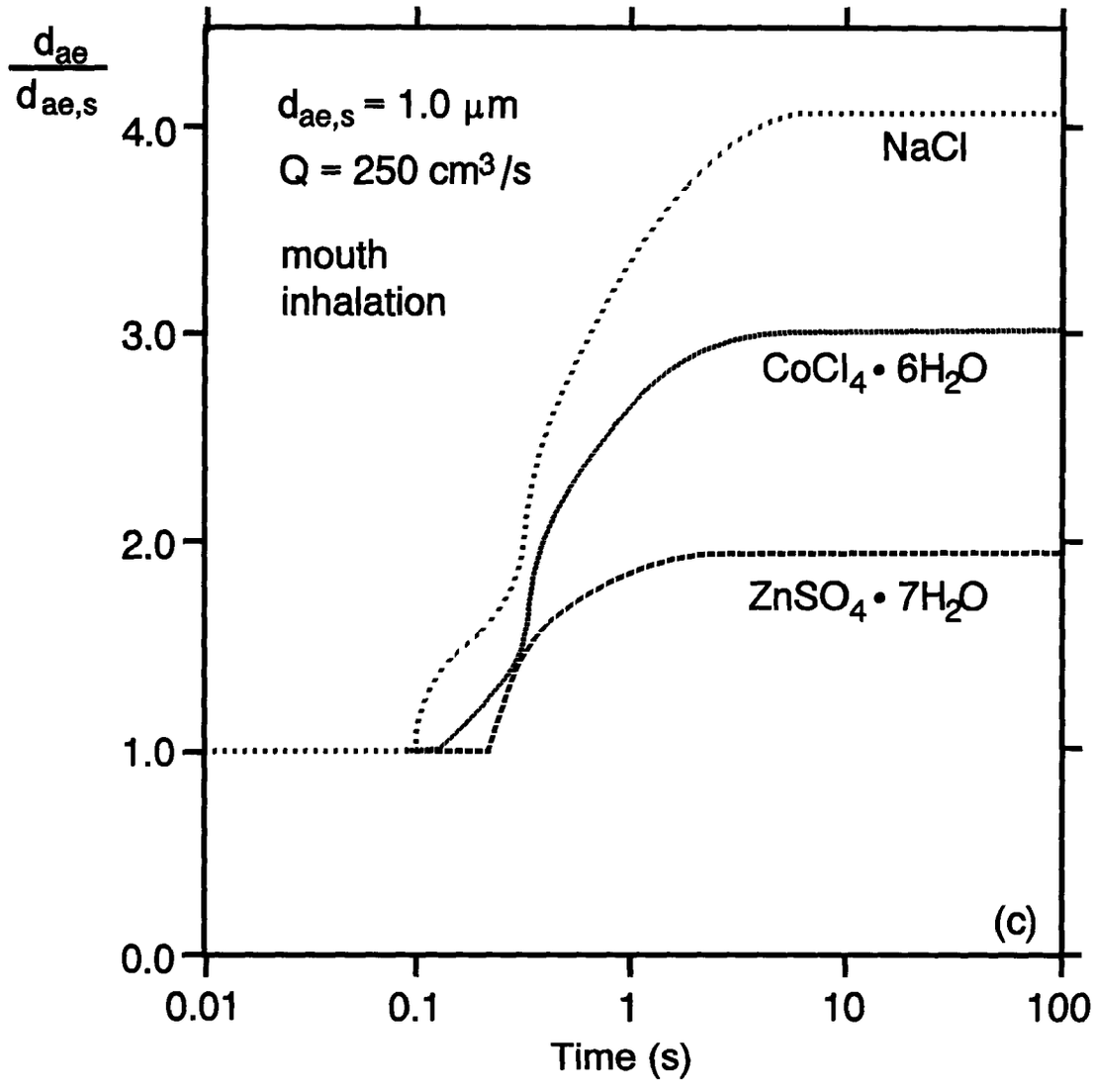

Figure 10-17. The initial dry diameter ($d_{ae,s}$) of three different salts is assumed to be 1.0 μm. Their subsequent growth to an equilibrium diameter at 99.5%RH is shown by the ratio ($d_{ae}/d_{ae,s}$). The highly hydrated salts of cobalt chloride and zinc sulfate exhibits a reduced growth potential compared to sodium chloride.

Source: Ferron et al. (1988).

of a stable (nonhygroscopic) aerosol. Through this approach, the investigators found that the diameters of the NaCl particles initially 0.2 μm and 0.25 μm, increased 5.55 and 5.79-fold, respectively. These values were found to be consistent with a 99.5% RH.

To make the transport theory model estimations more pragmatic, Ferron and coworkers (1992, 1993) made estimations for heterodisperse aerosols of salts with the range of growth potentials used in their 1988 study. Also, deposition estimates for H_2SO_4 aerosols, incorporating variabilities in age-related airway morphometry and in physical activity levels, have been reported by Martonen and Zhang (1993) using some unique modeling assumptions.

In his excellent review of hygroscopic particle growth and deposition and their implications to human health, Hiller (1991) concluded that despite the importance of models, there remains insufficient experimental data on total and regional deposition of hygroscopic aerosols in humans to confirm these models adequately.

10.4.3.2 Neutralization and Buffering of Acidic Particles

The toxicity of acidic particles may be modulated following their inhalation. This may occur within the inhaled air, by neutralization reaction with endogenous respiratory tract ammonia, or following deposition, due to buffering within the fluid lining of the airways.

Reaction of Acidic Particles with Respiratory Tract Ammonia

Ammonia (NH_3) is present in the air within the respiratory tract. Measurements of taken in exhaled air have found that the NH_3 concentration varies depending upon the site of measurement, with levels obtained via oral breathing greater than those measured in the nose or trachea (Larson et al, 1977; Vollmuth and Schlesinger, 1984). Because of these concentration differences between the oral and nasal passages, the route of acidic particle inhalation likely plays a significant role in determining the hydrogen ion (H^+) available for deposition in the lower respiratory tract. Thus, for the same mass concentration of acidic particles, inhalation via the mouth will result in more neutralization compared to inhalation via the nose, and less H^+ available for deposition in the lungs (Larson et al, 1982). The toxicity of acidic particles may be due to the H^+, as discussed in Chapter 11 (human and animal toxicity data).

The possibility that endogenous ammonia could chemically neutralize inhaled acidic particles to their ammonium salts prior to deposition on airway surfaces, thereby reducing toxicity, was originally proposed by Larson et al (1977) in relation to acidic sulfate aerosols. Since, stoichiometrically, 1 μg of NH_3 can convert 5.8 μg of H_2SO_4 to ammonium bisulfate

(NH_4HSO_4), or 2.9 μg of H_2SO_4 to ammonium sulfate $[(NH_4)_2SO_4]$, they determined, based upon the range of NH_3 levels measured in the exhaled air of humans, that up to 1,500 $\mu g/m^3$ of inhaled H_2SO_4 could be converted to $(NH_4)_2SO_4$. For a given sulfate content in an exposure atmosphere, both ammonium bisulfate and ammonium sulfate are less potent irritants than is sulfuric acid, as discussed in Chapter 11.

Complete neutralization of inhaled sulfuric acid or ammonium bisulfate would produce ammonium sulfate. However, partial neutralization of sulfuric acid would reduce to varying extends the amount of H^+ available for deposition, thereby modulating toxicity. The extent of neutralization has been shown to play a role in measured toxicity from inhaled sulfuric acid. Utell et al (1986) exposed asthmatic subjects to sulfuric acid under conditions of high or low levels of expired ammonia. The response to inhaled acid exposure was greater when exposure was conducted under conditions of low oral ammonia levels.

The extent of reaction of ammonia with acid sulfates depends upon a number of factors. These include residence time within the airway, which is a function of ventilation rate, and inhaled particle size. In terms of the latter, for a given amount of ammonia, the extent of neutralization is inversely proportional to particle size, at least within the range of 0.1-10 μm (Larson et al, 1993). In addition, for any given ammonia concentration, the extent of neutralization of sulfuric acid increases as mass concentration of the acid aerosol decreases (Schlesinger and Chen, 1994).

Cocks and McElroy (1984) presented a model analysis for neutralization of sulfuric acid particles in human airways. Particle acidity was a function of both dilution by particle growth and neutralization by ammonia. As an example of their results, neutralization would be complete in 3 sec for H_2SO_4 (3M) having a particle size of 0.5 μm and a mass concentration of 100 $\mu g/m^3$, with the ammonia level at 500 $\mu g/m^3$. If the NH_3 level is reduced to 50 $\mu g/m^3$, neutralization would take longer.

Larson (1989) presented another model for neutralization of inhaled acidic sulfate aerosols in humans. It was concluded that significant deposition of acid in the lower respiratory tract would occur in the presence of typical respiratory tract NH_3 levels, for both oral or nasal inhalation of H_2SO_4 particles at 0.3μm. However, particles at 0.03μm should be completely neutralized in the upper respiratory tract. While this latter seems to contradict findings of significant biological responses in guinea pigs following exposure to ultrafine acid

particles (Chapter 11), this could reflect differences in residence times and ammonia levels between different species. On the other hand, response to ultrafine acid particles has not been examined in humans, so the model predictions have not been tested as yet. Furthermore, it is likely that under most circumstances, only partial neutralization of inhaled sulfuric acid occurs prior to deposition (Larson et al, 1977). In any case, these conclusions support toxicological findings of biological effects following inhalation of sulfuric acid concentrations that should, based solely upon stoichiometric considerations, be completely neutralized, and highlights the complexity of neutralization processes in the respiratory tract.

Larson et al (1993) examined the role of ammonia and ventilation rate on response to inhaled (oral) sulfuric acid, by estimating, using the model of Larson (1989), the acid concentrations to which the lungs would be exposed during oral inhalation. They concluded that combinations of high ammonia and low ventilation rate or low ammonia and high ventilation rate produce smaller or larger amounts of acid deposition, respectively, even if the acid concentration at the point of inhalation remained constant. The former condition resulted in greater neutralization than did the latter.

Buffering by Airway Surface Fluid (Mucus)

Mucus lining the conducting airways has the ability to buffer acid particles which deposit within it. The pH of mammalian tracheobronchial mucus has been reported to be within a range of about 6.5 to 8.2 (Boat et al, 1994; Gatto, 1981; Holma et al, 1977). This variability may be due to differences in the methods used and species examined, as well as the likelihood that the acid-base equilibrium differs at different levels of the tracheobronchial tree, but may also reflect variations in secretion rate and the occurrence of inflammation. The influence on pH of various other endogenous factors, such as secretion of hydrogen or bicarbonate ions, and the role of specific mucus constituents, such as secreted acidic glycoproteins and basic macromolecules, have not been extensively examined.

The buffering capacity of human sputum, a mixture of saliva and mucus, was examined by Holma (1985), by titrating sputum equilibrated with 5% carbon dioxide at 37 °C and 100% relative humidity (RH) with sulfuric acid. While the buffering capacity was variable, depending upon the sputum sample examined, depression of pH from 7.25 to 6.5 required the addition of approximately 6 μmol of hydrogen ion (H^+) per ml of sputum. Assuming a

tracheobronchial mucus volume of 2.1 mL, between 8 and 16 μmol of H^+, if evenly distributed through the airways, would be required to depress mucus pH from 7.4 to 6.5. Since 1 μg H^+ is obtained from 49 μg of sulfuric acid, between 390 and 780 μg of sulfuric acid would be required to cause this change in pH. With an inhalation exposure duration of 0.5 h, ventilation at 20 L/min and 50% deposition (in the total respiratory tract) of 100 $\mu g/m^3$ sulfuric acid (at 1M), 0.6 μmol of H^+ would be deposited in the lungs. However, the distribution of submicrometer acid particles in the respiratory tract is not uniform and, therefore, greater changes in pH may be anticipated on a regional basis in those areas having higher than average deposition. If, for example, 30 μg of acid deposited in 0.2 ml of mucus, a greater change in pH would likely occur.

The above example may apply to healthy individuals. However, the buffering capacity of mucus may be altered in individuals with compromised lungs. For example, sputum from asthmatics had a lower pH than that from healthy subjects, and a reduced buffering capacity (Holma, 1985). This group may, therefore, represent a portion of the population which is especially sensitive to inhaled acidic particles. The potential sensitivity of asthmatics to acid particles is discussed in greater detail in Chapter 11.

While biological responses following the inhalation of acidic aerosols are likely due to the H^+ component of these particles (as discussed in Chapter 11), it has been suggested that pH may not be the sole determinant of response to acid particles, but that response may actually depend upon total available hydrogen ion, or titratable acidity, depositing upon airway surfaces. Fine et al (1987) hypothesized that buffered acid aerosols (with a greater H^+ pool) would cause a greater biological response than would unbuffered acid aerosols having the same pH. Since airway surface fluids have a considerable capacity to buffer acid, it was suggested that the buffered acid would cause a more persistent decrease in airway surface fluid pH. Thus, it appears that the specific metric of acidity used, i.e., pH or titratable acid, would, therefore, be reflected in the relationship between amount of deposited acidity and resultant biological response.

10.5 DEPOSITION DATA AND MODELS

The background information in Sections 10.4 demonstrates that a knowledge of where particles of different sizes deposit in the respiratory tract and the amount of their deposition is necessary for understanding and interpreting the health effects associated with exposure to particles. As was seen, the respiratory tract can be divided into the ET, TB and A regions on the basis of structure, size and function. Particles deposited in the various regions have large differences in clearance pathways and consequently retention times. This section discusses the available data on particle deposition in humans and laboratory animals. Different approaches for modeling these data are also discussed. Theoretical models must assume average values and simplifying conditions of respiratory performance in order to make reasonable estimates. This latter approach was initiated by the meteorologist Findeisen (1935), over fifty years ago when he developed a simplified anatomic model of the respiratory tract and assumed steady inspiratory and expiratory air flows in order to estimate the interactions between the anatomy of the respiratory tract and particle deposition based on physical laws. Despite much progress in respiratory modeling, there are not major distinctions in total particle deposition predictions among models and experimental verifications have been generally satisfactory.

10.5.1 Humans

The deposition of particles within the human respiratory tract have been assessed using a number of techniques (Valberg, 1985). Unfortunately, the use of different experimental methods and assumptions results in considerable variations in reported values. This section discusses the available particle deposition data in humans for either total or regions of the respiratory tract.

10.5.1.1 Total Deposition

If the quantity of aerosol particles deposited in the entire respiratory tract is divided by that inhaled, the result is called total deposition fraction or total deposition. Thus, total deposition can be measured by comparing particle concentrations of the inhaled and exhaled, but the regional involvement cannot be distinguished. By the use of test aerosol particles with radiolabels, investigators have been able to separate deposition by region, beginning

from the ET region with either nasal and nasopharyngeal deposition for nose breathing or oral and pharyngeal deposition for mouth breathing. The measurement of clearance of the radiolabeled particles from the thorax can be used to separate fast clearance, usually assumed to be an indicator of TB deposition, from the more slowly cleared A deposition (see below for more discussion).

Total human deposition data, as a function of particle size with nose and mouth breathing compiled by Schlesinger (1988), are depicted in Figure 10-18. These data were obtained by various investigators using different sizes of test spherical particles in healthy male adults under different ventilation conditions. Deposition with nose breathing is generally higher than that with mouth breathing because mouth breathing bypasses the filtration capabilities of the ET region. For large particles with aerodynamic diameters d_{ae} greater than 1 μm, deposition is governed by impaction and sedimentation and it increases with increasing d_{ae}. When $d_{ae} > 10$ μm, almost all inhaled particles are deposited. As the particle size decreases from 0.1 μm, diffusional deposition becomes dominant and total deposition depends more upon the physical diameter d of the particle. Decreasing particle diameter leads to an increase in total deposition in this particle size range. Total deposition shows a minimum for particle diameters in the range of 0.1 μm to 0.5 μm where both sedimentation and diffusion deposition are about equally important. The particle diameter at which the minimum deposition occurs is different for nose breathing and mouth breathing and it depends upon flow rate and airway dimensions. For all particle sizes, mixing of the tidal air and functional residual air can also contribute to deposition. This factor is more significant for particle sizes for which deposition is low. Good deposition experiments therefore should account for mixing into the residual volume by requiring subjects fully exhale.

Although various studies in Figure 10-18 all appear to show the same trend, there is a significant amount of scatter in the data. Some of this scatter can be explained by the use of different test particles and methods in the experimental studies, as well as different breathing modes and ventilation conditions employed by the subjects. However, a good portion of the scatter is caused by the differences in airway morphology and breathing pattern among subjects (Heyder et al., 1982, 1988; Yu et al., 1979; Yu and Diu, 1982a,b; Bennett and

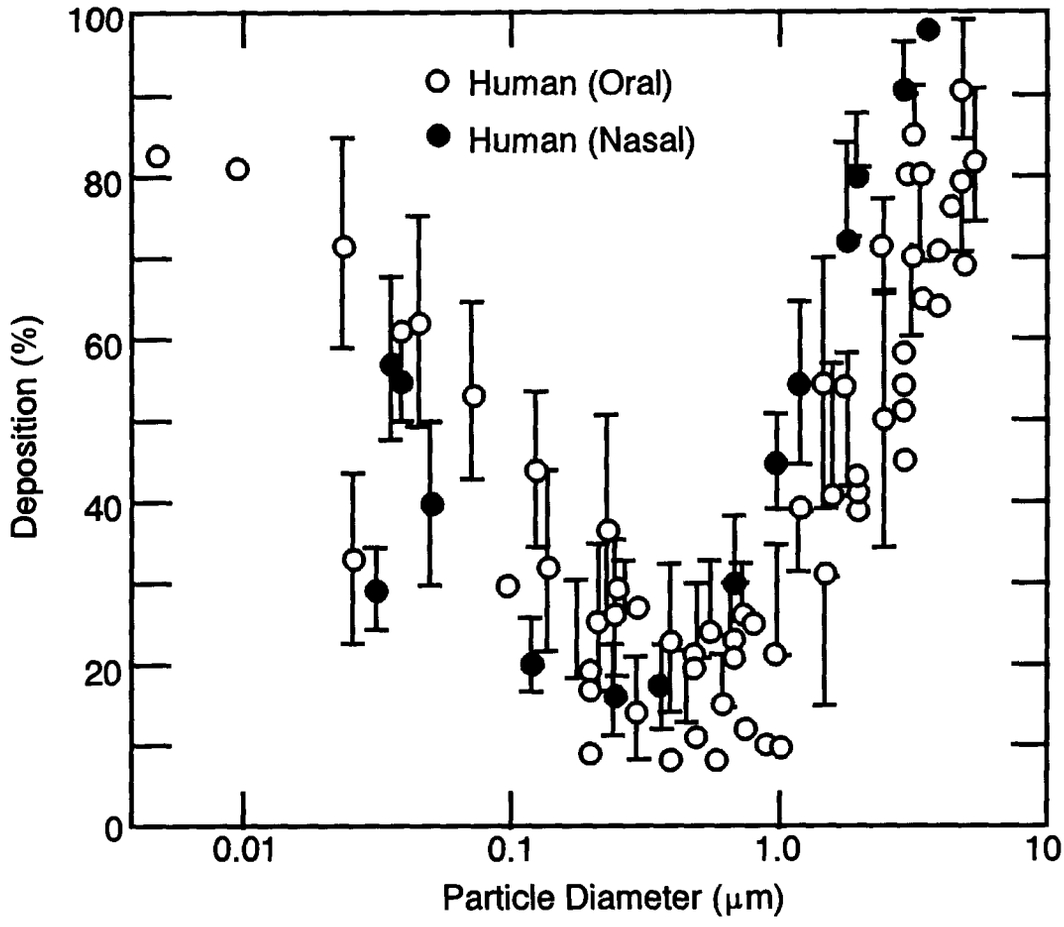

Figure 10-18. Total deposition data (percentage deposition of amount inhaled) in humans as a function of particle size. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 μm.

Source: Schlesinger (1988).

Smaldone, 1987; Bennett, 1988). In addressing the health-related issues of inhaled particles, this intersubject variability is an important factor which must be taken into consideration.

Indeed, for well controlled experiments and controlled breathing patterns (constant inspiratory flow in half a cycle and constant expiratory flow in another half cycle and no pause), total deposition data do not have the amount of scatter shown in Figure 10-18. Figure 10-19 shows the data by Heyder et al. (1986) and Schiller et al. (1986, 1988) reported by Stahlhofen et al. (1989) at controlled mouth breathing for particle size ranging from 0.005 μm to 15 μm and three different ventilation conditions. Total deposition was

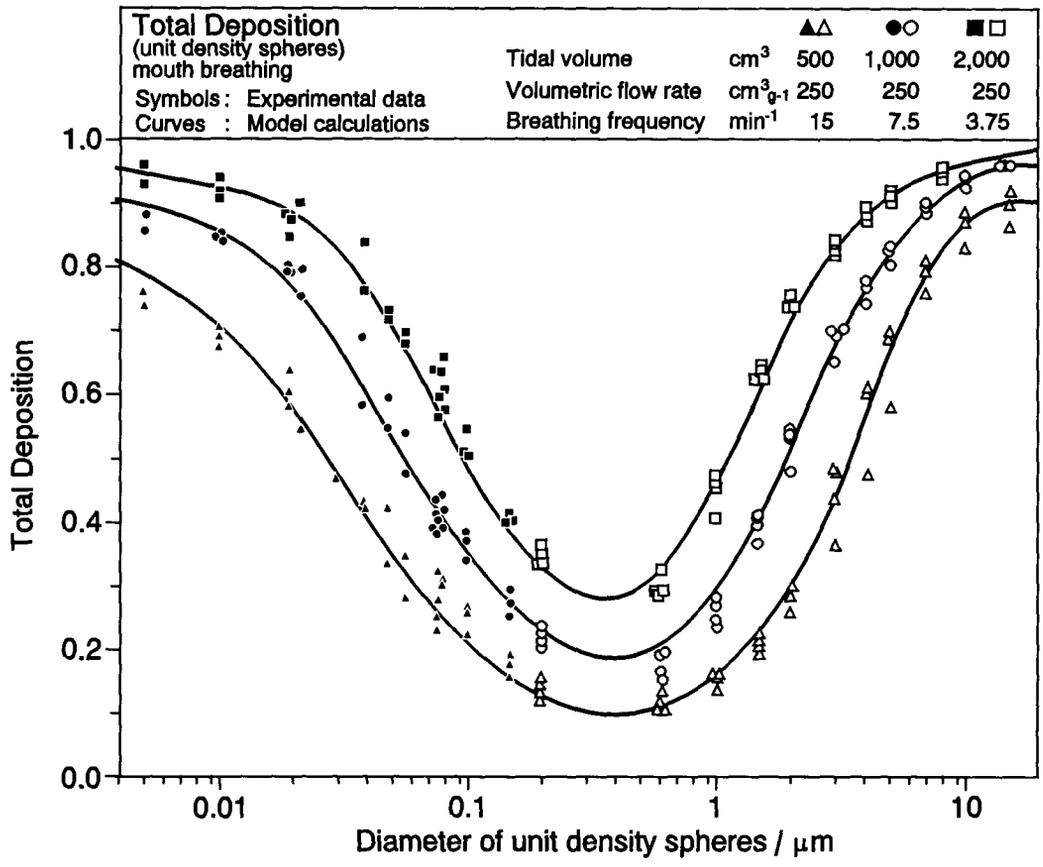

Figure 10-19. Total deposition as a function of the diameter of unit density spheres in humans for variable tidal volume and breathing frequency. Experimental data are by Heyder et al. (1986) and Schiller et al. (1988). The curves represent empirical fitting.

Source: Stahlhofen et al. (1988).

found higher for larger tidal volume while the minimum deposition occurred at about 0.4 μm for all three ventilation conditions.

10.5.1.2 Extrathoracic Deposition

The fraction of inhaled particles depositing in the ET region can be quite variable, depending on particle size, flow rate, breathing frequency and whether the breathing is through the nose or through the mouth. During exertion, the flow resistance of the nasal passages cause a shift to mouth breathing in almost all individuals, thereby bypassing much of the filtration capabilities of the head and leading to increased deposition in the lung (TB

and A regions). For nose breathing, the usual technique for measuring inspiratory deposition is to draw the aerosol through the nose and out of the mouth while the subject holds his mouth open (Pattle, 1961; Lippmann, 1970; Hounam et al., 1969, 1971). The aerosol concentration is measured before it enters the nose and after it leaves the mouth. Neglecting mouth deposition during expiration, inspiratory nasal deposition can be calculated from the concentration difference. Another method to measure the nasal deposition is to use the lung as a part of the experimental system (Giacomelli-Maltoni et al., 1972; Martens and Jacobi, 1973; Rudolph, 1975). The deposition of particles in the nose is calculated from total deposition of particles in the entire respiratory tract for mouth, nose, mouth-nose and nose-mouth breathing. Because mouth deposition is not significant under the experimental conditions, this method allows the determination of nasal deposition for both inspiration and expiration.

Deposition in the mouth for expiration is normally assumed to be negligible. For inspiration, the deposition in mouth has been measured using radioactive aerosol particles (Rudolph, 1975; Lippmann, 1977; Foord et al., 1978; Stahlhofen et al., 1980; Chan and Lippmann, 1980; Stahlhofen et al., 1981, 1983). The amount of deposition is obtained from the difference of activity measurements, one immediately after exposure and the other after the deposited particles are removed with mouthwash or other means. Because the subjects in these experiments breathe through a large bore tube, the deposition via the mouth occurs predominantly in the larynx. Rudolf et al. (1984, 1986) have suggested to name this laryngeal deposition. Mouth deposition by natural mouth breathing without using a mouthpiece was measured in an earlier study by Dennis (1961) and recently by Bowes and Swift (1989) during natural oronasal breathing at moderate and heavy exercise conditions. The data showed a much greater deposition than breathing through a mouth-piece.

For $d_{ae} > 0.2$ μm, ET deposition is usually expressed as a function of d_{ae}^2 Q where Q is the flow rate since this is the appropriate parameter for normalizing impaction-dominated deposition when the actual flow rates in the experimental studies are not identical. Even with this normalization, deposition data in the extrathoracic region by various workers exhibit a very large amount of scatter as shown in Figures 10-20 and 10-21, respectively, for inspiratory nasal and mouth deposition. Besides uncertainty in measurement techniques, one major source of this scatter, similar to the case of total deposition comes from intersubject

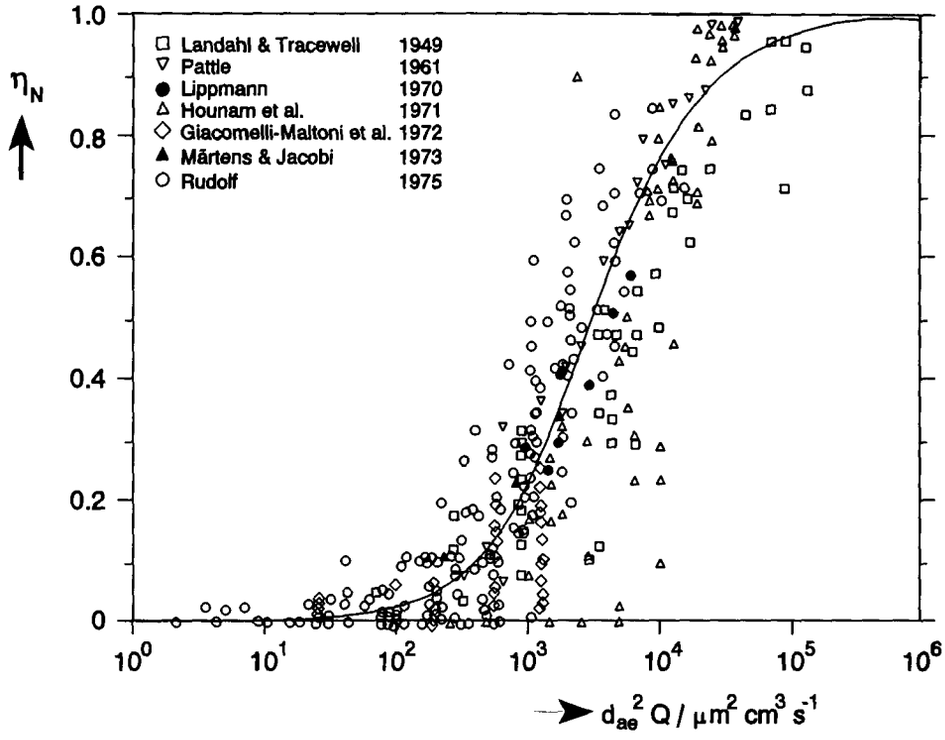

Figure 10-20. Inspiratory deposition A of the human nose as a function of $d_{ae}^2 Q$. The curve represents equation (10-23).

Source: Stahlhofen et al. (1988).

and intrasubject variabilities. The intersubject variability may arise from the difference in anatomical structure and dimensions, number of nasal hairs, breathing pattern, etc., while the intrasubject variability may be caused by the degree of mouth opening and by the nasal resistance cycle in which airflow may be redistributed from one side to the other side, by as much as 20-80%.

Mathematical model studies on the deposition in the nose and mouth are very limited. There have been only two attempts to determine nasal deposition during inspiration (Landahl, 1950b; Scott et al., 1978). At present, formulas useful for predicting ET deposition are derived empirically from experimental data (Pattle, 1961; Yu et al., 1981; Rudolf et al., 1983, 1984, 1986; Miller et al., 1988; Zhang and Yu, 1993). The formulas by Rudolf et al. (1983, 1984, 1986) given below with a minor modification, have been adopted by the International Commission on Radiological Protection (ICRP, 1994) in their dosimetry model.

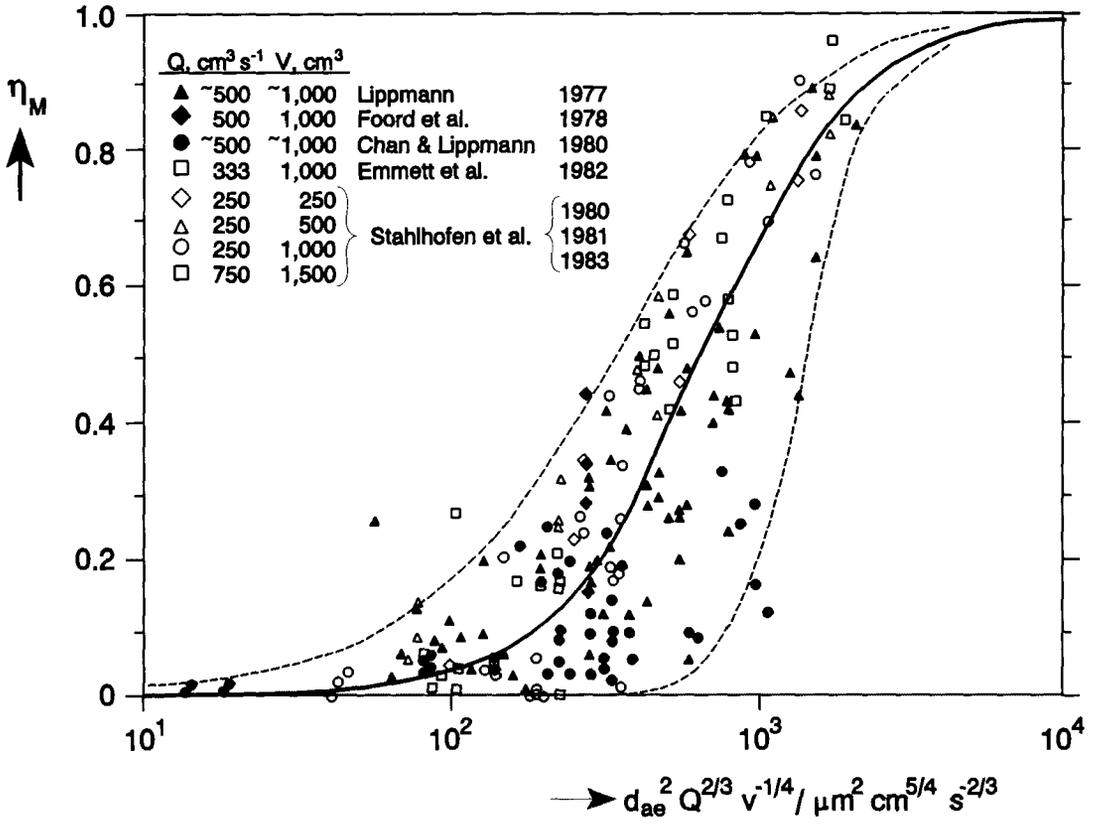

Figure 10-21. Inspiratory extrathoracic deposition data in humans during mouth breathing as a function of $d_{ae}^2 Q^{2/3} V_T^{1/4}$. The curve represents equation (10-24).

Source: Stahlhofen et al. (1988).

Deposition efficiency of the nose on inhalation (η_N) is expressed in terms of an impaction parameter as

$$\eta_N = 1 - [3.0\times10^{-4}(d_{ae}^2 Q) + 1]^{-1} , \qquad (10\text{-}23)$$

where d_{ae} is in the unit of μm, Q in cm^3/s, and V_T is the tidal volume in cm^3.

An equal amount of deposition is assumed to occur in the posterior nasal passages (compartment ET2 in Table 10-4).

$$\eta_M = 1 - [5.5\times10^{-5}(d_{ae}^2 Q^{2/3} V_T^{-1/4})^{1.7} + 1]^{-1} . \quad (10\text{-}24)$$

Equation 10-23 applies to both inspiration and expiration since the data by Heyder and Rudolf (1977) do not show a systematic difference between the two efficiencies. The inclusion of V_T in Equation 10-24 is caused by the fact that the size of the ET region during mouth breathing increases with increasing flow rate and with increasing tidal volume.

For ultrafine particles ($d < 0.1$ μm), deposition in the ET region is controlled by the mechanism of diffusion which depends only on the particle geometric diameter, d. At this time, ET deposition for this particle size range has not been studied extensively in humans. George and Breslin (1969) measured nasal deposition of radon progeny in three subjects but the diffusion coefficient of the progeny was uncertain. Schiller et al. (1986, 1988) later obtained inspiratory nasal deposition from total deposition measurements using a nose in - mouth out and mouth in-nose out maneuver. However, their data cannot be considered reliable because mouth deposition is not negligible compared to nose deposition.

The only data available to date for ET deposition of ultrafine particles are from cast measurements (Cheng et al., 1988, 1990, 1993; Yamada et al., 1988; Gradon and Yu, 1989; Swift et al, 1992). Figure 10-22 shows these data on inspiratory nasal deposition from several laboratories reported by Swift et al. (1992) as a function of the diffusion parameter $D^{1/2}Q^{-1/8}$ where D is the particle diffusion coefficient in cm^2/sec and Q is the flow rate in L/min. Swift et al. (1992) also proposed an equation to fit the data in the form

$$\eta_N = 1 - \exp[-12.65 D^{1/2} Q^{-1/8}], \quad (10\text{-}25)$$

which was adopted by ICRP (1994) in the dosimetry model. Expiratory nasal deposition for particles between 0.005 μm to 0.2 μm was found to have the same trend as Figure 10-22 but was approximately 10% higher than the inspiratory nasal deposition (Yamada et al., 1988). Cheng et al. (1993) derived the following empirical equations to fit the data

$$\eta_{N,ex} = 1 - \exp[-15.0 D^{1/2} Q^{-1/8}] , \text{ and} \quad (10\text{-}26)$$

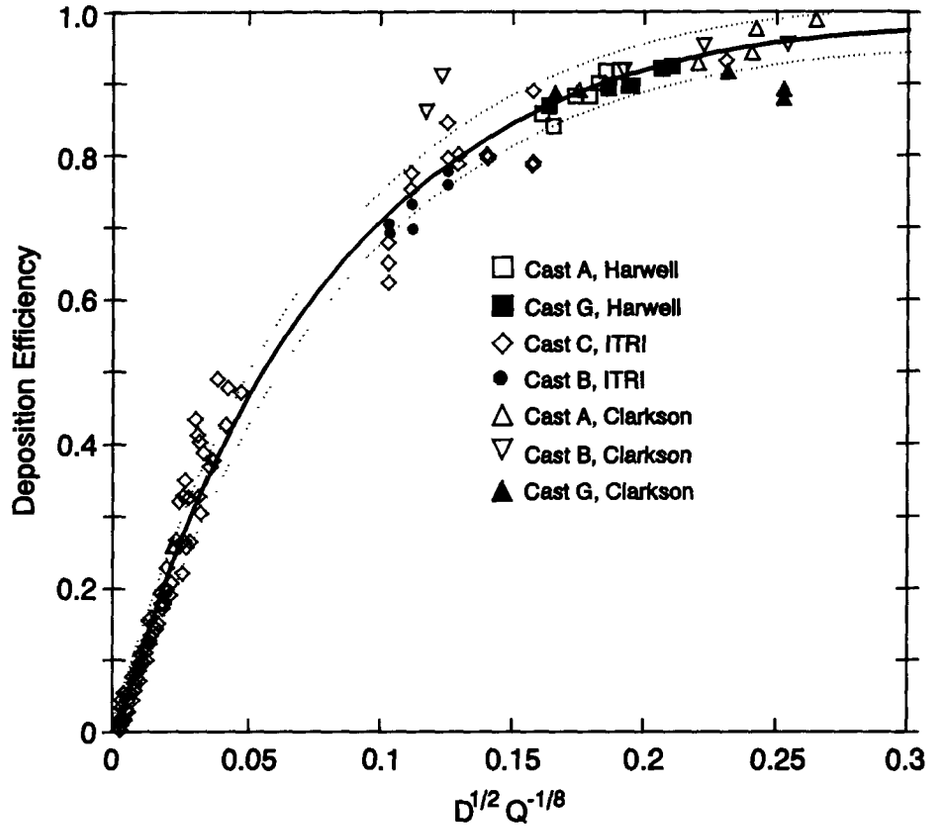

Figure 10-22. Inspiratory deposition efficiency data and fitted curve for human nasal casts plotted versus $Q^{-1/8}D^{1/2}$ $(Lmin^{-1})^{-1/8}(cm^2s^{-1})^{1/2}$. Dotted lines are 95% confidence limits.

Source: Swift et al. (1992).

$$\eta_M = 1 - \exp(-10.3D^{1/2}Q^{-1/8}), \quad (10\text{-}27)$$

for inspiration, and

$$\eta_M = 1 - \exp(-8.51D^{1/2}Q^{-1/8}), \quad (10\text{-}28)$$

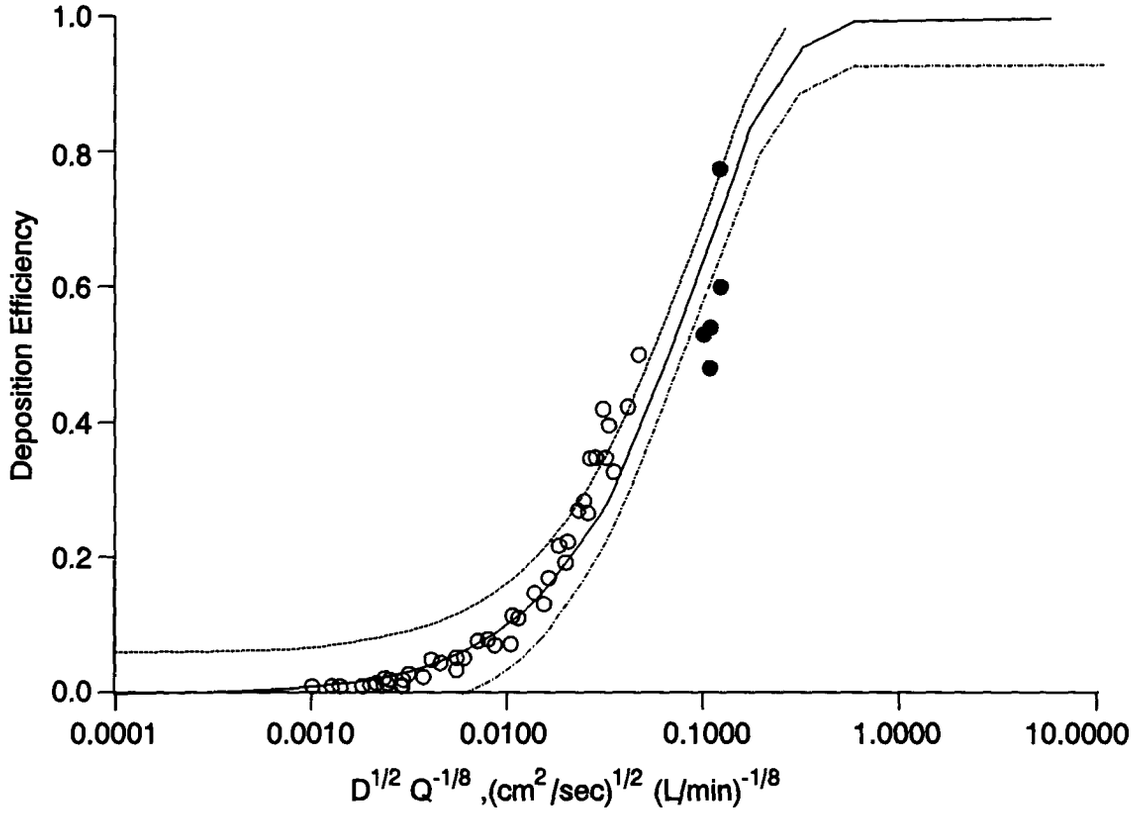

Figure 10-23. Inspiratory deposition efficiency data in human oral casts plotted versus $Q^{-1/8}D^{1/2}$ $(Lmin^{-1})^{-1/8}(cm^2s^{-1})^{1/2}$. The solid curve represents equation (10-27) and the broken curves are the 95% confidence limits.

Source: Cheng et al. (1993).

for expiration. The inspiratory deposition efficiency function fit to the data is shown in Figure 10-23. Contrary to nasal deposition, deposition in the mouth is slightly higher for inspiration than for expiration.

10.5.1.3 Tracheobronchial (TB) Deposition

Particles escaping from deposition in the ET region enter the lung, but their regional deposition in the lung cannot be precisely measured. All the available regional deposition data have been obtained from experiments with radioactive labeled insoluble particles above 0.1 μm in diameter. The amount of activity retained in the lung as a function of time normally exhibits a fast and slow decay component which have been identified as mucociliary

and macrophage clearance. Since the tracheobronchial airways are ciliated, the rapidly cleared fraction of initial activity can be considered as a measure of the amount of material deposited in the TB region, whereas the slowly cleared fraction corresponds to the material deposited in the A region. However, there is experimental evidence that a significant fraction of material deposited in the TB region is retained much longer than 24 h (Stahlhofen et al., 1986a,b; Scheuch and Stahlhofen, 1988; Smaldone et al., 1988). This may be caused by the fact that the TB airway surface is lined with ciliated epithelium, but not all of the ciliated epithelium is covered with mucus all the time (Stahlhofen et al., 1989). Other mechanisms for prolonged TB clearance include phagocytosis by airway macrophages and deposition of particles further down into the A region due to mixing of flow during inspiration. Thus, tracheobronchial and pulmonary deposition measured based upon the clearance of radioactive labeled particles have been suggested as the "fast-cleared" and "slow-cleared" thoracic deposition (Stahlhofen et al., 1989).

Figure 10-24 shows the data from various investigators (Lippmann, 1977; Foord et al., 1978; Chan and Lippmann, 1980; Emmett et al., 1982; and Stahlhofen et al., 1980, 1981, 1983) on TB deposition or fast-cleared thoracic deposition for mouth breathing as a function of d_{ae} reported by Stahlhofen et al. (1989). Again, the data are quite scattered due to differences in experimental technique and intersubject and intrasubject variabilities that have been cited previously. Another cause for the scatter is from the difference in the flow rate employed by various studies. For $d_{ae} > 0.5$ μm, deposition in the TB region is contributed by both impaction and sedimentation. Whereas the impaction deposition is governed by the parameter d_{ae}^2Q, sedimentation deposition is controlled by the parameter d_{ae}^2/Q. It is therefore not possible to have a single relationship between deposition and d_{ae} for different flow rates.

Data in Figure 10-24 show that TB deposition does not increase monotonically with d_{ae}. A higher d_{ae} leads to a greater ET deposition and consequently a lower TB deposition. For the range of flow rates employed in various studies, the maximum TB deposition occurs at about 4 μm d_{ae}. It is also seen that the data by Stahlhofen et al. (1980, 1981, 1983) in Figure 10-24 are considerably lower than those from other investigators. Chan and Lippmann (1980) cited two possible reasons for this difference. One was that Stahlhofen and coworkers used constant respiratory flow rates in their studies as opposed to the variable

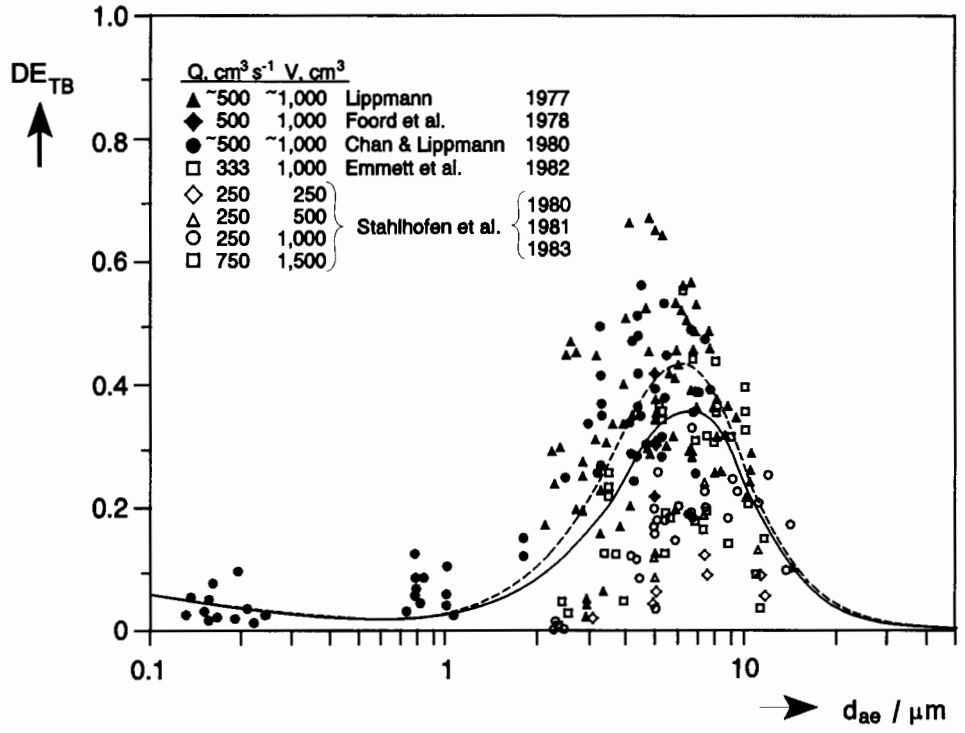

Figure 10-24. TB deposition data in humans at mouth breathing as a function of d_{ae}. The solid curve represents the approximate mean of all the experimental data; the broken curve represents the mean excluding the data of Stahlhofen et al.

Source: Stahlhofen et al. (1988).

flow rates used by others. The second reason was that different methods of separating the initial thoracic burden into TB and A regions were used. Stahlhofen et al. (1980) extrapolated the thoracic retention values during the week after the end of fast clearance back to the time of inhalation; they considered A deposition to be the intercept at that time, with the remainder of the thoracic burden considered as TB deposition. This approach yields results similar to, but not identical with, those obtained by treating TB deposition as equivalent to the particles cleared within 24 h. Another possibility for the differences is that Fe_2O_3 particles used in experiment by Chan and Lippman (1980) are hygroslopic, resulting in higher TB deposition.

10.5.1.4 Alveolar Deposition

The A deposition data as a function of d_{ae} for mouth breathing are shown in Figure 10-25. These data are from the same studies which reported TB deposition in Figure 10-24 but there is a better agreement between different studies than with the TB data. Alveolar deposition is favored by slow and deep breathing. The data of Stahlhofen et al. (1980, 1981, 1983) at 1000 cm^3 tidal volume and 250 cm^3/sec flow rate thus are higher than other data. Figure 10-25 also shows that A deposition reaches the maximum at about 3.5 μm d_{ae} and that for d_{ae} between 0.2 μm and 1.0 μm, A deposition does not show significant change although a minimum deposition may occur near 0.5 μm.

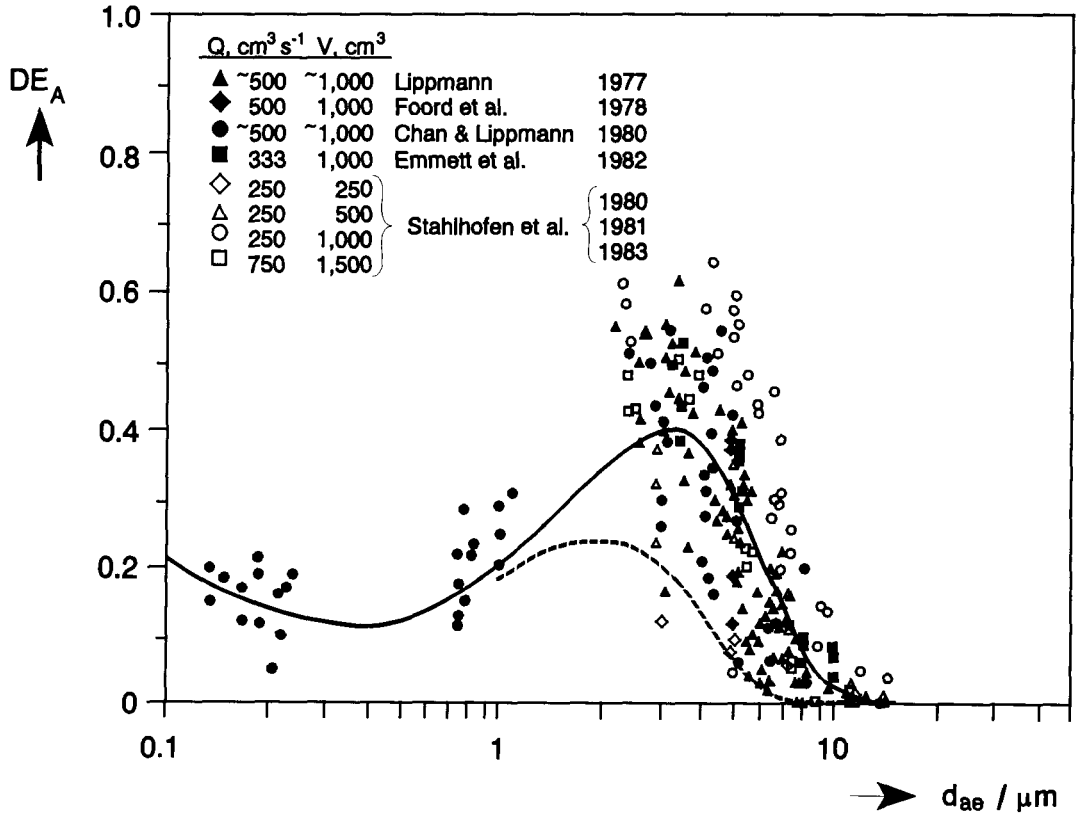

Figure 10-25. Slow-cleared or alveolar deposition data in humans as a function of d_{ae}. The solid curve represents the mean of all the data; the broken curve is an estimate of deposition for nose breathing by Lippmann (1977).

Source: Stahlhofen et al. (1988).

By switching from mouth breathing to nose breathing, alveolar deposition will decrease. Lippmann (1977) made an estimate by analysis of the difference in the ET deposition for nose and mouth breathing. The nose breathing result is also shown in Figure 10-25. For d_{ae} greater than 7 μm, practically no particles deposit in the A region in this breathing mode.

During exercise, most subjects switch from nose breathing to breathing partly through the mouth (Niinimaa et al., 1981). The amount of inhaled material that deposits in the lungs is affected because mouth and nose have different filtration efficiencies. Niinimaa et al. (1981) found that in thirty subjects, twenty switched to oro-nasal breathing (normal augmenters), typically at a ventilation rate of about 35 L/min, five continued to breathe through the nose, the rest who were habitual mouth breathers breathed oro-nasally at all levels of exercise. These data were reviewed by Miller et al. (1988) and used to estimate thoracic deposition (TB and A deposition) at different ventilation rates. At higher ventilation rate, Miller et al. (1988) predicted little difference in thoracic deposition between normal augmenters and mouth breathers, but for ventilation rate less than 35 L/min they predicted substantially lower deposition in normal argumenters compared to mouth breathers. Based upon this finding, ICRP (1994) recommended a different breathing pattern for normal augmenters and mouth breathers that typifies the breathing habits of adult males as a function of ventilation rate. The split in airflow for the recommended breathing patterns by ICRP (1994) is shown in Figure 10-26. Table 10-11 provides the same information on the percentages of total ventilatory airflow passing through the nose versus mouth at reference levels of physical exertion for a normal augmenter and a mouth breather adult male. These are the same levels of exercise and values for fraction of nasal ventilatory airflow used to construct the activity patterns in Section 10.7. In the absence of specific data, it must be assumed that a similar breathing pattern applies to young healthy subjects at equivalent levels of exercise. Alveolar deposition at different ventilation rates can be estimated from Figure 10-26 or Table 10-11. For example, a mouth breather doing light exercise (V_E = 1.5 m^3/h) has about 40% ventilatory air-flow passing through the nasal route. At a particle size of 2 μm $d_{ae,}$ Figure 10-26 gives, respectively, 0.24 and 0.36 A deposition for mouth and nose breathing. Thus, the resultant A deposition at this ventilation rate is $0.4 \times 0.36 + 0.6 \times 0.24 = 0.288$.

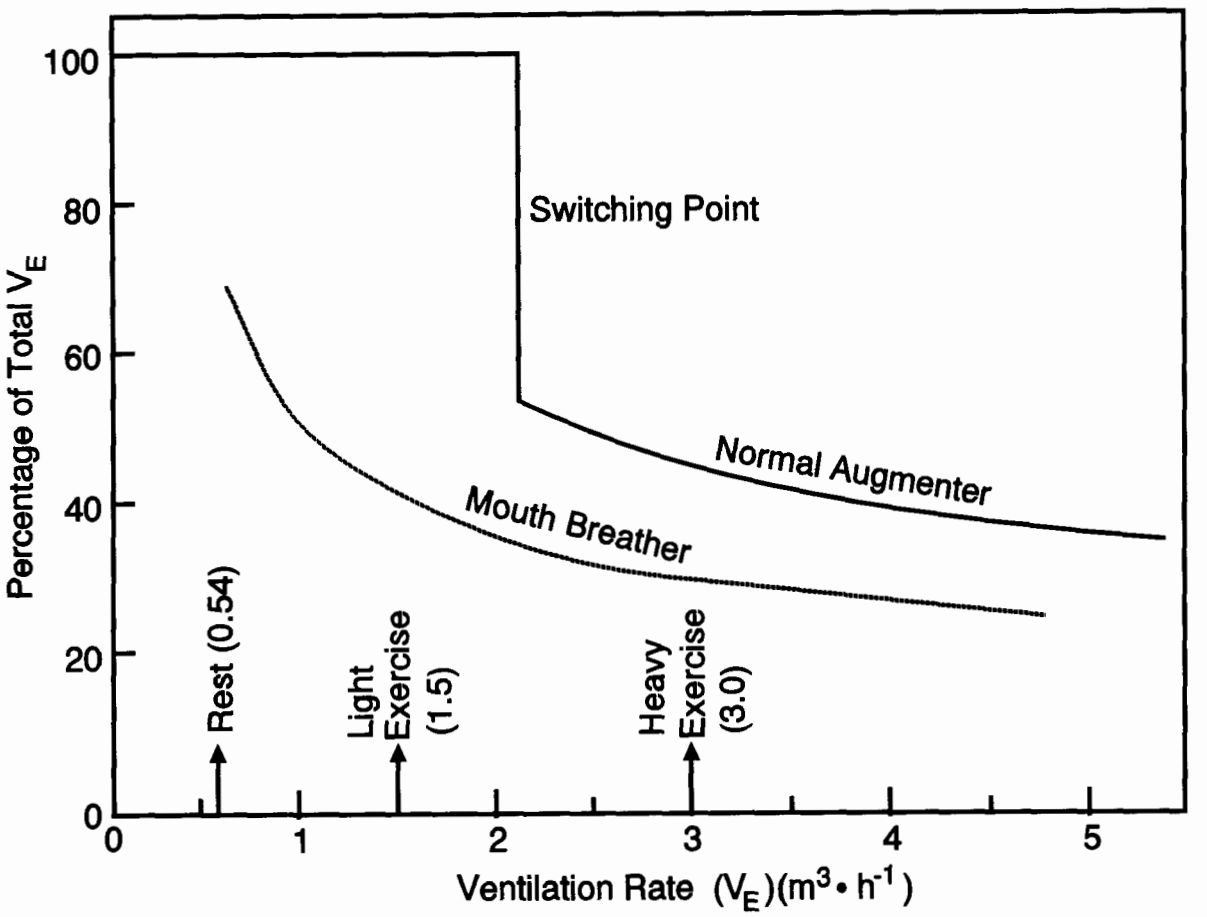

Figure 10-26. Percentage of total ventilatory airflow passing through the nasal route in human "normal augmenter" (solid curve) and in habitual "mouth breather" (broken curve).

Source: International Commission on Radiological Protection (ICRP66, 1994).

TABLE 10-11. FRACTION OF "NORMAL" VENTILATORY AIRFLOW PASSING THROUGH THE NOSE IN HUMAN AUGMENTER" AND "MOUTH BREATHER"[a]

	F_n	
Level of excertion	Nasal augmenter	Mouth breather
Sleep	1.0	0.7
Rest	1.0	0.7
Light exercise	1.0	0.4
Heavy exercise	0.5	0.3

[a](ICRP66, 1994) as derived from Miller et al. (1988a).

10.5.1.5 Nonuniform Distribution of Deposition and Local Deposition Hot Spots

The deposition data in different regions of the respiratory tract presented above do not provide information on deposition nonuniformity in each region and local deposition intensity at a specific site. Such information may be of great importance from a toxicology perspective. Because airway structure and its associated air flow patterns are exceedingly complex (Change and Menon, 1993), and ventilation distribution of air in different parts of the lung is uneven (Milic-Emili et al., 1966), it is expected that particle deposition patterns in ET, TB and A regions are highly nonuniform. Fry and Black (1973) measured regional deposition in the human nose using radiolabelled particles and found that most of deposition occurred in the anterior region of the nose. Sclesinger and Lippmann (1978) found nonuniform deposition in the trachea by the airflow disturbance of the larynx. In a single airway bifurcation model, measurements show that deposition occurs principally around the carinal ridge (e.g., Bell and Friedlander; Lee and Wang, 1977) Martonen and Lowe, 1983; Kim and Iglesias, 1989 a,b). Similar result was observed in the alveolar duct bifurcations in rats and mice (Brody and Roe, 1983). Figure 10-27 shows the data on local deposition pattern obtained by Kim and Iglesias (1989a,b) in a bifurcating tube for both inspiration and expiration. The peak deposition occurs in the daughter tube during inspiration and the parent tube during expiration, but always near the carinal ridge. In addition, airways are not smooth tubes. More recently, Martonen et al. (1994 a,b,c) have called attention to the existence of cartilaginous rings on the wall of airways in the tracheobronchial region. Using a numerical analysis, they showed that such surface structure can lead to a considerable alteration of the flow pattern and enhancement of deposition.

Deposition measurements in small rodents (Raabe et al., 1977) also showed differences in lobar distribution with up to 60 percent higher than the average in the right apical lobe (corresponding to the human upper lobe). The difference was greater for large particles than for small particles. Raabe et al. (1977) further showed that these differences in relative lobar deposition were related to geometric mean number of airway bifurcations between trachea and terminal bronchioles in each lobe for rats and hamsters. Since similar morphologic differences occur in the human lungs, nonuniform lob distribution should also occur.

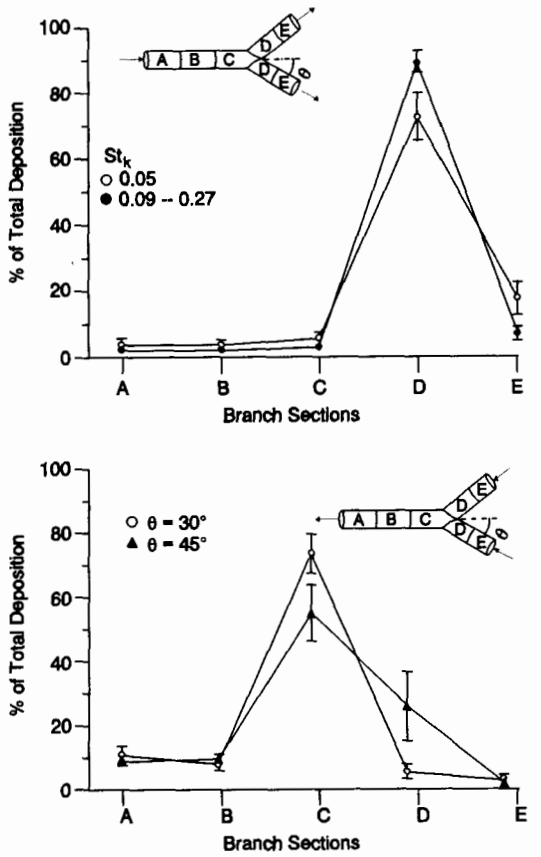

Figure 10-27. Local deposition pattern in a bifurcating tube for inhalation (top panel) and exhalation (bottom panel).

Source: Kim and Iglesias (1989a,b).

10.5.1.6 Summary

Mathematical models of lung deposition have been developed in recent years to help interpret experimental data and to make predictions of deposition for cases where data are not available. A review of various mathematical models was given by Morrow and Yu (1993). There are three major elements involved in mathematical modeling. First, a model of airways simulating the real structure must be specified. Secondly, deposition efficiency in each airway due to various mechanisms must be derived. Finally, a computational procedure must be developed to account for the transport and deposition of the particles in the airways.

Three different approaches have been used in the mathematical modeling. The first approach is a compartmental model first formulated by Findeisen (1935). Starting with the trachea, Findeisen divided the airways into nine compartments based upon the anatomical

structure. Particles which did not deposit in one compartment remained airborne and transported to the next compartment for deposition. Findeisen's lung model and analysis were later modified by Landahl (1950a, 1963) and Beeckmans (1965). Detailed calculations of regional deposition with additional consideration of nasal deposition based upon the Findeisen-Landahl-Beeckmans theory were later published in a report by the Task Group on Lung Dynamics (TGLD) in 1966.

Because of advancement in measuring techniques, refined airway models have become available (as discussed in Section 10.2). Several new models based upon the compartmental analysis have been proposed (e.g., Gerrity et al., 1979; Yeh and Schum, 1980; Martonen and Graham, 1987). The expressions used for deposition efficiency of each compartment differed somewhat in these models. In the absence of any careful comparison with the experimental data, it is difficult to assess the applicability of these models to deposition prediction. However, one difficulty often encountered in the compartmental model is the derivation of deposition efficiency in each airway for combined mechanisms of impaction, sedimentation and diffusion. A commonly used assumption is that each deposition mechanism is independent, thus the joint efficiency can be written in the form

$$\eta = 1-(1-\eta_I)(1-\eta_S)(1-\eta_D)\,, \qquad (10\text{-}29)$$

where η_I, η_S, and η_D are, respectively, deposition efficiency in an airway or compartment by the individual mechanisms of impaction, sedimentation and diffusion, and η is th joint efficiency. Yu et al., (1977) have shown, in a detailed mathematical analysis of a combined sedimentation and diffusion problem, that the above equation is an inaccurate expression of deposition when η_S and η_D are not small and have about the same magnitude. Another difficulty in the compartmental model is that air-mixing effect (mixing of tidal air and lung air) on deposition cannot be easily accounted for. Such effect is important for transient exposure. However, the compartmental model is easy to formulate and to understand conceptually.

The second approach to deposition modeling was put forward by Yu and coworkers (Taulbee and Yu, 1975; Yu, 1978; Yu and Diu, 1983) and later by Egan et al. (1985, 1989).

In this approach, the many generations of airways are viewed as a chamber shaped like a trumpet. The cross-sectional area of the chamber varies with airway depth measured from the beginning of the trachea according to the anatomical data. The concentration of inhaled particles in the chamber as a function of airway depth and time during breathing is described by a convective diffusion equation with a loss-term accounting for airway deposition. This equation can be solved either exactly (without longitudinal diffusion) or numerically with appropriate initial and boundary conditions. Deposition at different sites in the airways in then calculated once the concentration is known.

The deposition model formulated in this manner has some advantages over the compartmental model. First, the use of differential airway length in the model allows the joint deposition efficiency per unit airway length to be the superposition of efficiencies by each individual mechanism. Secondly, the variation of airway dimensions during breathing is accounted for in the model. Thirdly, the model is time-dependent, thus can be applied to any breathing pattern and transient exposure condition. Fourthly, air-mixing and uneven airway path lengths can be accounted for with the use of an equivalent longitudinal diffusion term in the convective-diffusion equation. Finally, in the case of no longitudinal diffusion, the exact solution of the convective-diffusion is obtainable, thus reducing the time required for deposition calculation.

The airway geometry of the human lungs is not identical over a population. In a given lung, the dimension of the airways in a specified generation is also not uniform and the bifurcation is not symmetric (Weibel, 1963). The above two approaches of modeling have been extended to account for the randomness of the airway geometry (Yu et al., 1979; Yu and Diu, 1982a,b; Koblinger and Hofmann, 1990; Hofmann and Koblinger, 1990). Yu and Diu (1982b) compared their modeling results with total and regional deposition data of Stahlhofen et al. (1981) and Heyder et al. (1982) at controlled breathing and found that the difference in lung morphology was probably the principal cause for intersubject variability observed in deposition.

Another approach to deposition modeling is an empirical one proposed by Rudolf et al. (1983, 1984, 1986, 1990) similar to that developed for ET deposition. This model considers the lung as a series of two filters representing the TB and A regions of the lung. The model requires no assumptions on airway geometry, airflow pattern and distribution, nor on particle

deposition efficiency in each airway. However, the construction of the model relies heavily on experimental data of regional deposition for a wide range of particle sizes (monodisperse) and breathing conditions. These data are not always available. Additional difficulty in the empirical modeling is the development of deposition equations in each region for combined deposition mechanisms. As discussed earlier, impaction, sedimentation and diffusion deposition depend, respectively, on the parameters d_{ae}^2Q, D_{ae}^2/Q and D/Q, where D is a function of particle geometrical diameter. It is a very difficult task to come up with an equation for deposition in terms of these parameters which can match all experimental data. Furthermore, because only a few compartments are used in the empirical model, more detailed deposition information such as deposition at a specific air-way generation cannot be predicted. However, as mentioned, with an empirical model the geometry and relative importance of mechanisms and airflow splits are all "correct" in the subjects tested and are reflected in the measured deposition. This may be an advantage over theoretical models that must rely on extremely limited information on geometry. An empirical model is simple mathematically and a semi-emperical model has been adopted by the International Commission on Radiological Protection (ICRP66, 1994) for deposition predictions with a theoretical component for scaling size between gender and different ages.

10.5.2 Laboratory Animals

Since much information concerning inhalation toxicology is collected with canines or rodents, the comparative regional deposition in these experimental animals must be considered to help interpret, from a dosimetric viewpoint, the possible implications of animal toxicological results to humans. In evaluating deposition studies in terms of interspecies extrapolation, it is not adequate to express the amount of deposition merely as a percentage of the total inhaled. For some particle sizes, regional deposition in humans and experimental animals may be quite similar and appears to be species independent (McMahan et al., 1977; Brain and Mensah, 1983). However, different species exposed to identical particles at the same exposure concentration will not receive the same particle mass per unit exposure time because of their differences in tidal volume and breathing rate. In addition, because of differences in the lung weight and airway surface area, the amount of deposition normalized to these quantities are also very different between species.

However, it is difficult to systematically compare interspecies deposition patterns obtained from various reported studies, because of variations in experimental protocols, measurement techniques, definitions of specific respiratory tract regions, and so on. For example, tests with humans are generally conducted under protocols that standardize the breathing pattern, whereas those using experimental animals involve a wider variation in respiratory exposure conditions (for example, spontaneous breathing versus controlled breathing as well as various degrees of sedation). Much of the variability in the reported data for individual species is due to the lack of normalization for specific respiratory parameters during exposure. In addition, the various studies have used different exposure techniques, such as nasal mask, oral mask, oral tube, or tracheal intubation. Regional deposition may be affected by the exposure route and delivery technique employed.

Figure 10-28 shows the regional deposition data versus particle diameter in commonly used experimental animals obtained by various investigators and compiled by Schlesinger (1988). Although there is much variability in the data, it is possible to make some generalizations concerning comparative deposition patterns. The relationship between total respiratory tract deposition and particle size is approximately the same in humans and most of these animals; deposition increases on both sides of a minimum, which occurs for particles of 0.2 to 0.9 μm. Interspecies differences in regional deposition occur due to anatomical and physiological factors. In most experimental animal species, deposition in the ET region is near 100 percent for d_{ae} greater than 2 μm, indicating greater efficiency than that seen in humans. In the TB region, there is a relatively constant, but lower, deposition fraction for d_{ae} greater than 1 μm in all species compared to humans. Finally, in the A region, deposition fraction peaks at a lower particle size (d_{ae} about 1 μm) in experimental animals, than in humans.

Asgharian et al. (1995) developed an empirical model of particle deposition in the A region based on the published data of Schlesinger (1985). Although restricted to the A region, the approach could be applied to other regions. A deposition function (η) was described using a polynomial regression of the form

$$\eta = \sum_{i=0}^{N} a_i(\log_{10}d)^i \text{ for } d \leq d_{cut\text{-}off}, \text{ and} \qquad (10\text{-}30)$$

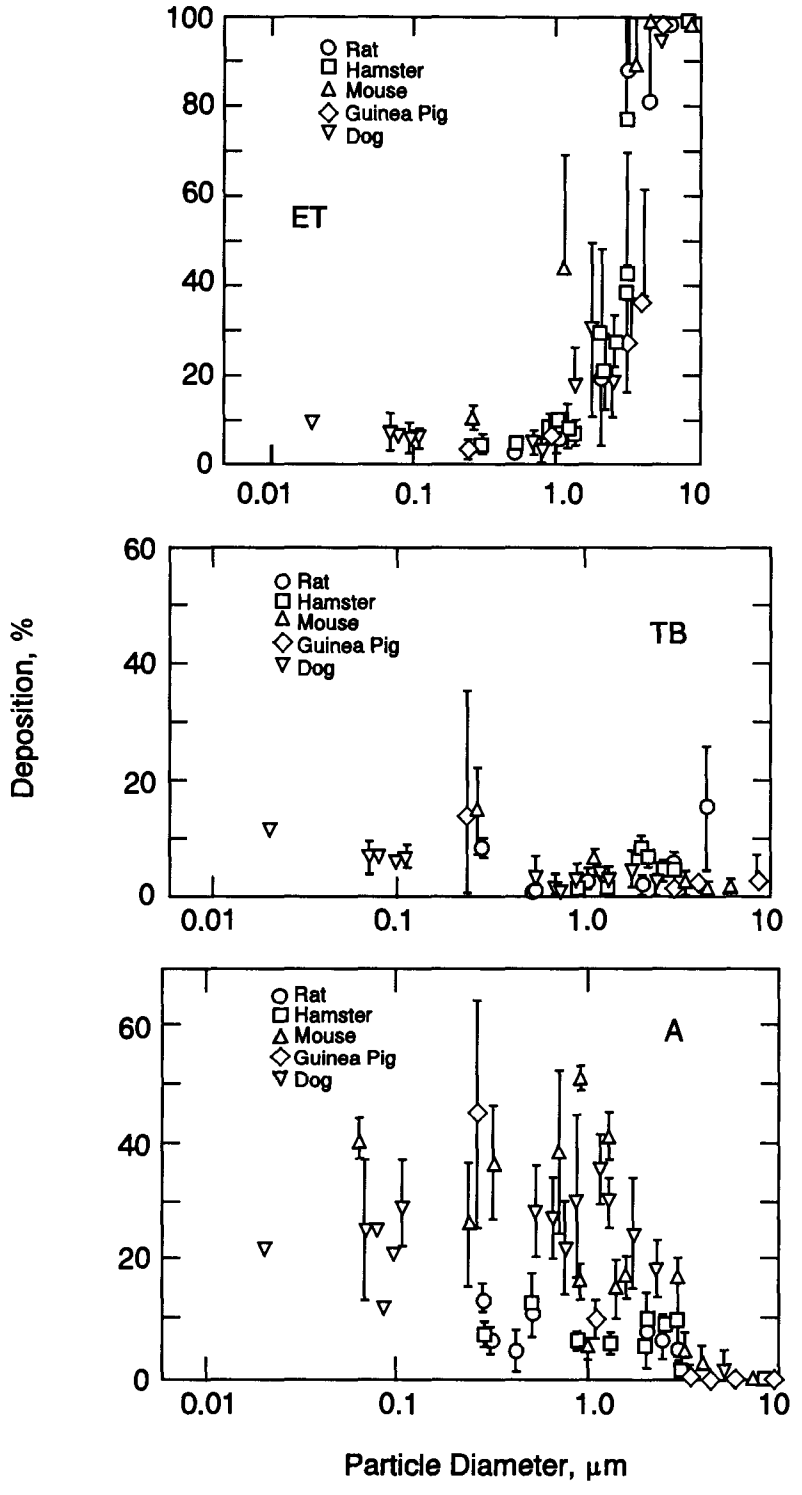

Figure 10-28. Regional deposition efficiency in experimental animals as a function of particle size. Particle diameters are aerodynamic (MMAD) for those > 0.5 μm and geometric (or diffusion equivalent) for those < 0.5 μm.

Source: Schlesinger (1988).

$$\eta(d)=0 \text{ for } d \geq d_{cut\text{-}off}. \quad (10\text{-}31)$$

where N is the degree of the polynomial, d is the particle diameter in micrometers, and $d_{cut\text{-}off}$ is the diameter at which the deposition efficiency becomes zero. Since Equation 10-30 is a 4^{th}-degree polynomial, it will give a non-zero value for $d_{cut\text{-}off}$. For this reason, Equation 10-31 was added to be consistent with the deposition data and $d_{cut\text{-}off}$ was determined by setting Equation 10-30 to zero. Newton's method was employed to find $d_{cut\text{-}off}$ for different cases. Particle deposition was then integrated with particle distributions differing in median particle and σ_g to calculate deposition mass fraction. The approach is similar to that employed by Ménache et al. (1995) but inhalability was not addressed. Also, the deposition data set included both monodisperse and polydisperse particles which may have contributed to scatter in the particle size versus deposition efficiency data.

Mathematical deposition models in rats, hamsters, and guinea pigs have been developed by several investigators (e.g., Schum and Yeh, 1980; Xu and Yu, 1987; Martonen et al., 1992) in a similar manner as the human models without including diffusion deposition in the ET region. Although the modeling results are generally in agreement with experimental data, there is a considerable uncertainty in the respiratory parameters of the laboratory animals used in the modeling studies. In addition, the airway branching patterns in the animals are commonly monopodial as compared to the dichotomous branching in the human lung. The deposition efficiency of an airway (the amount of deposition in an airway divided by the amount entered) developed in the human model may not be applicable to laboratory animal species. Despite some of these difficulties, modeling studies in laboratory animals remain to be a useful step to extrapolate exposure-dose-response relationships from experimental animals to the human (Yu et al., 1991).

Ménache et al. (1995a) developed a revised empirical model to estimate fractional regional deposition efficiency for dosimetric adjustment factors used in the U.S. EPA's methodology for derivation of inhalation dose-response estimates or inhalation reference concentrations (U.S. Environmental Protection Agency, 1994). This approach will be described more fully in Section 10.7. This revised model represents significant refinement of previously published models used for dosimetric interspecies extrapolation in the 1990

interim RfC methods (Jarabek et al., 1989, 1990; Miller et al., 1988). For example, rather than linear interpolation between the published (Raabe et al., 1988) means for deposition measured at discrete particle diameters, as previously done for the laboratory animal deposition modeling, equations have now been fit to an expanded set of raw data.

The equations describing fractional deposition were fit using data on particle deposition in CF_1 mice, Syrian golden hamsters, Fischer 344 rats, Hartley guinea pigs, and New Zealand rabbits. A description of the complete study including details of the exposure may be found elsewhere (Raabe et al., 1988). Briefly, the animals were exposed to radiolabelled ytterbium (^{169}Yb) fused aluminosilicate spheres in a nose-only exposure apparatus. Twenty unanesthetized rodents or eight rabbits were exposed simultaneously to particles of aerodynamic diameters (d_{ae}) about 1, 3, 5, or 10 μm. Half the animals were sacrificed immediately post exposure; the remaining half were held 20 h post exposure. One-half of the animals at each time point were male and the other half were female. The animals were dissected into 15 tissue compartments, and radioactivity was counted in each compartment. The compartments included the head, larynx, GI tract, trachea, and the five lung lobes. This information was used directly in the calculation of the deposition fractions. Radioactivity was also measured in other tissues including heart, liver, kidneys, and carcass; and additionally in the urine and feces of a group of animals held 20 h. In the animals sacrificed immediately post exposure, these data were used to ensure that there was no contamination of other tissue while the data from the animals held 20 h were used in the calculation of a fraction used to partition thoracic deposition between the TB and A regions. This partition is discussed below briefly and described in detail elsewhere (Raabe et al., 1977). Finally, radioactivity was measured in the pelt, paws, tail, and headskin as a control on the exposure.

Although there are some other studies of particle deposition in laboratory animals (see review by Schlesinger, 1985), no other data have the level of detail or the experimental design (i.e., freely breathing, unanesthetized, nose-only exposure) required to provide deposition equations representative of the animal exposures used in many inhalation toxicology studies. However, many inhalation toxicology studies are not nose-only exposures. While this is a necessary exposure condition to determine fractional particle deposition, adjustments for particle inhalability and ingestion can be made to estimate deposition fractions under whole-body exposure conditions.

The advantages of using the data of Raabe et al. (1988) to develop the deposition equations include:

- the detailed measurements were made in all tissues in the animal, providing mass balance information and indicating that there was no contamination of nonrespiratory tract tissue with radioactivity immediately post exposure,
- the use of five species of laboratory animals under the same exposure conditions,
- the use of unanesthetized, freely breathing animals, and
- the use of an exposure protocol that makes it virtually impossible for the animals to ingest any particles as a result of preening.

Regional fractional deposition, F_r, was calculated as activity counted in a region normalized by total inhaled activity (Table 10-12). The proportionality factor, f_L, in Equations 10-33 and 10-34 is used to partition thoracic deposition between the TB and A regions. It was calculated using the 0 and 20-h data and is described in detail by Raabe and co-workers (1977).

TABLE 10-12. REGIONAL FRACTIONAL DEPOSITION

$$F_r = \frac{\text{Activity Counted in a Region}}{\text{Total Inhaled Activity}}$$

Extrathoracic (ET): $$F_{ET} = \frac{[\text{head} + \text{GI tract} + \text{larynx}]_{0\ h}}{\text{Total Inhaled Activity}} \qquad 10\text{-}32$$

Tracheobronchial (TB): $$F_{TB} = \frac{\text{trachea}_{0\ h} + f_L \times \sum_{i=1}^{5} \text{lobe}_{i,0\ h}}{\text{Total Inhaled Activity}} \qquad 10\text{-}33$$

Pulmonary (PU): $$F_{PU} = \frac{(1 - f_L) \times \sum_{i=1}^{5} \text{lobe}_{i,0\ h}}{\text{Total Inhaled Activity}} \qquad 10\text{-}34$$

Source: U.S. Environmental Protection Agency (1994).

These regional deposition fractions, F_r, however, are affected not only by the minute volume ($\dot{V}_E$), MMAD and σ_g, but also by deposition in regions through which the particles have already passed. Deposition efficiency, η_r, on the other hand, is affected only by $\dot{V}_E$, MMAD, and σ_g. The differences between deposition fraction and efficiency are calculated as provided below and are described in more detail elsewhere (Ménache et al., 1994a). In the aerodynamic domain, that is for particles with diameters >0.5 μm, efficiencies increase monotonically and are bounded below by 0 and above by 1. The logistic function has mathematical properties that are consistent with the shape of the efficiency function (Miller et al., 1988)

$$E(\eta_r) = \frac{1}{1 + e^{\alpha + \beta \log_{10} x}}, \tag{10-35}$$

where $E(\eta_r)$ is the expected value of deposition efficiency (η_r) for region r, and x is expressed as an impaction parameter, $d_{ae}^2 Q$, for extrathoracic deposition efficiency and as aerodynamic particle size, d_{ae}, for TB and PU deposition efficiencies. The flow rate, Q, in the impaction parameter may be approximated by $\dot{V}_E/30$. The parameters α and β are estimated using nonlinear regression techniques.

To fit this model, efficiencies must be derived from the deposition fractions that were calculated as described in Table 10-12. Efficiency may be defined as activity counted in a region divided by activity entering that region. Then, considering the region as a sequence of filters in steady state, efficiencies may be calculated as follows

$$\eta_{ET} = F_{ET} \tag{10-36}$$

$$\eta_{TB} = \frac{\text{trachea}_{0\ h} + f_L \times \sum_{i=1}^{5} \text{lobe}_{i,0\ h}}{(1 - \eta_{ET})} \tag{10-37}$$

$$\eta_{PU} = \frac{(1 - f_L) \times \sum_{i=1}^{5} \text{lobe}_{i,0\ h}}{(1 - \eta_{ET})\,(1 - \eta_{TB})}. \tag{10-38}$$

Using these calculated regional efficiencies in the individual animals, the logistic function was fit for the ET, TB, and A regions for the five animal species and humans. The parameter estimates from these fits are listed in Table 10-13. Curves produced by these equations have been compared where applicable to the data reported in Schlesinger (1985), and the results are not inconsistent. As discussed by Schlesinger (1985), there are many sources of variability that could explain differences in predicted deposition using this model and the observed deposition data in the studies reported by Schlesinger (1985).

TABLE 10-13. DEPOSITION EFFICIENCY EQUATION ESTIMATED PARAMETERS

	ET (Nasal)		TB		PU	
Species	α	β	α	β	α	β
Human	7.129[a]	-1.957[a]	3.298	-4.588	0.523	-1.389
Rat	6.559	-5.524	1.873	-2.085	2.240	-9.464
Mouse	0.666	-2.171	1.632	-2.928	1.122	-3.196
Hamster	1.969	-3.503	1.870	-2.864	1.147	-7.223
Guinea Pig	2.253	-1.282	2.522	-0.865	0.754	0.556
Rabbit	4.305	-1.628	2.819	-2.281	2.575	-1.988

[a]Source: Miller et al., 1988.

The fitted equations are then used to generate predicted efficiencies ($\hat{\eta}$) as a function of impaction in the ET region and of aerodynamic particle size in the TB and A regions. Finally, the predicted efficiencies are multiplied together and adjusted for inhalability, I, as shown in Equations 10-39 through 10-41 to produce predicted deposition fractions (F_r) for monodisperse and near monodisperse ($\sigma_g < 1.3$) particles

$$\hat{F}_{ET} = I \times \hat{\eta}_{ET} \quad (10\text{-}39)$$

$$\hat{F}_{TB} = I \times (1 - \hat{\eta}_{ET}) \times \hat{\eta}_{TB} \quad (10\text{-}40)$$

$$\hat{F}_{PU} = I \times (1 - \hat{\eta}_{ET}) \times (1 - \hat{\eta}_{TB}) \times \hat{\eta}_{PU}. \quad (10\text{-}41)$$

Inhalability, I, is an adjustment for the particles in an ambient exposure concentration that are not inhaled at all. For humans, an equation has been fit using the logistic function (Ménache et al., 1995b). Using the experimental data of Breysse and Swift (1990):

$$I = 1 - \frac{1}{1 + e^{10.32 - 7.17 \log_{10} d_{ae}}} . \qquad (10\text{-}42)$$

The logistic function was also fit to the data of Raabe et al. (1988) for laboratory animals (Ménache et al., 1995b):

$$I = 1 - \frac{1}{1 + e^{2.57 - 2.81 \log_{10} d_{ae}}} . \qquad (10\text{-}43)$$

Figure 10-29 illustrates the relationship between the predicted efficiencies and predicted depositions using this model for the mice. A qualitatively similar set of curves could be produced for any of the other four species. The particles were assumed to be monodisperse. A default body weight (BW) for the mice of 0.0261 kg was used to calculate a default $\dot{V}_E$ using allometric scaling (U.S. Environmental Protection Agency, 1994). Regional deposition efficiencies and fractions were calculated for particles with d_{ae} ranging from 0.5 to 10 μm. These calculated points were connected to produce the smooth curves shown in Figure 10-29. The three panels on the left of Figure 10-29 are plots of the predicted regional deposition efficiencies; the three panels on the right show the predicted regional deposition fractions derived from the estimated efficiencies and adjusted for inhalability. The vertical axis for the predicted deposition efficiency panels range from 0 to 1. Although the deposition fraction is also bounded by 0 and 1, the vertical axes in the figure are less than 1 in the TB and A regions. The top two panels of Figure 10-29 are the predicted deposition efficiency and fraction, respectively, for the ET region. These two curves are plotted as a function of the impaction parameter described for Equation 10-35. The middle two and lower two panels show the predicted deposition efficiencies and fractions for the TB and A regions, respectively. These four curves are plotted as a function of d_{ae}. When a particle is from a monodisperse size distribution, the d_{ae} and the MMAD are the same. If, however, the

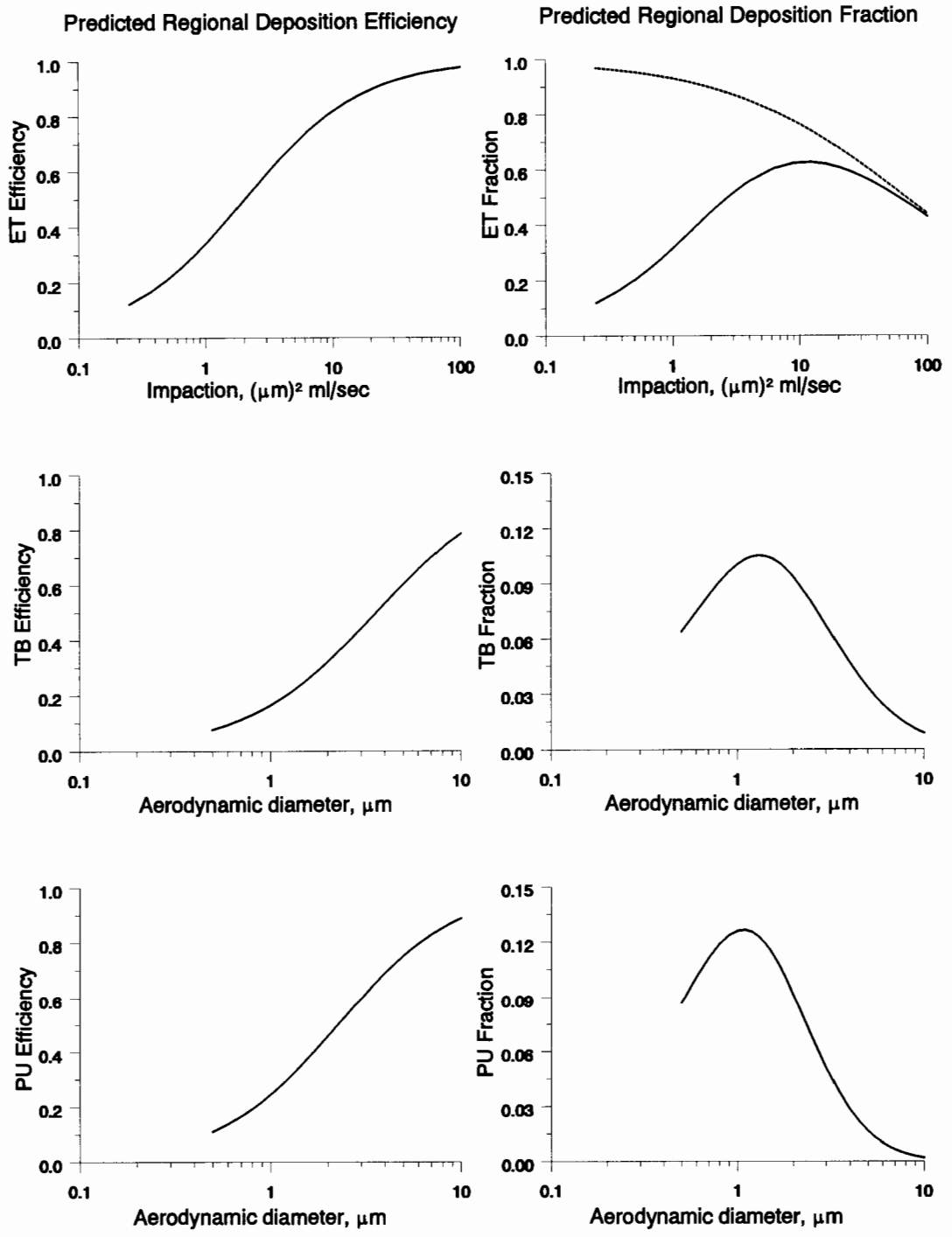

Figure 10-29. Comparison of regional deposition efficiencies and fractions for the mouse. A default body weight of 0.0261 kg (U.S. Environmental Protection Agency, 1994) was used in these calculations. The fractional deposition (solid line) and inhalability (dashed line) are shown in the upper right panel.

particle is from a polydisperse size distribution, the particle can not be described by a single d_{ae}; the average value of the distribution, the MMAD, must be used. In the aerodynamic particle size range, the deposition efficiency curves all increase monotonically as a function of the independent variable (i.e., either the impaction parameter or d_{ae}) and have both lower and upper asymptotes. The curves describing the deposition fractions, however, have different shapes that are dependent on the respiratory tract region. Deposition fractions in all three regions are nonmonotonic—initially increasing as a function of particle size but decreasing as particle sizes become larger. This is because particles that have been deposited in proximal regions are no longer available for deposition in distal regions. As an extreme example, if all particles are deposited in the ET region, no particles are available for deposition in either the TB or A regions. In the ET region, the nonmonotonic shape for fractional deposition is due to the fact that not all particles in an ambient concentration are inhalable.

As discussed in Section 10.2, particles in an experimental or ambient exposure are rarely all a single size but rather have some distribution in size around an average value. As this distribution becomes greater, the particle is said to be polydisperse. Panel A of Figure 10-30 illustrates the range of particle sizes from a distribution that is approximately monodisperse (σ_g = 1.1) and particles that come from a lognormal highly polydisperse distribution (σ_g = 3.0), although both distributions have the same MMAD of 4.0 μm. Also drawn in Panel A of Figure 10-30 is a vertical line through the MMAD that represents the extreme case of σ_g = 1.0, that is, an exact monodisperse particle distribution in which all particles are a single size, which is also the MMAD.

The empirical model of Ménache et al. (1995a) was developed from exposures using essentially monodisperse particles (which are treated as though they are exactly monodisperse). It is therefore possible to multiply the particle size distribution function (which is customarily considered to be the lognormal distribution) by the predicted depositions (calculated as described in Equations 10-39 through 10-41) and integrate over the entire particle size range (0 to ∞). Mathematically, this calculation is performed as described by Equation 10-34, and is illustrated for the mouse and human ET regions in panels B and C respectively, of Figure 10-30.

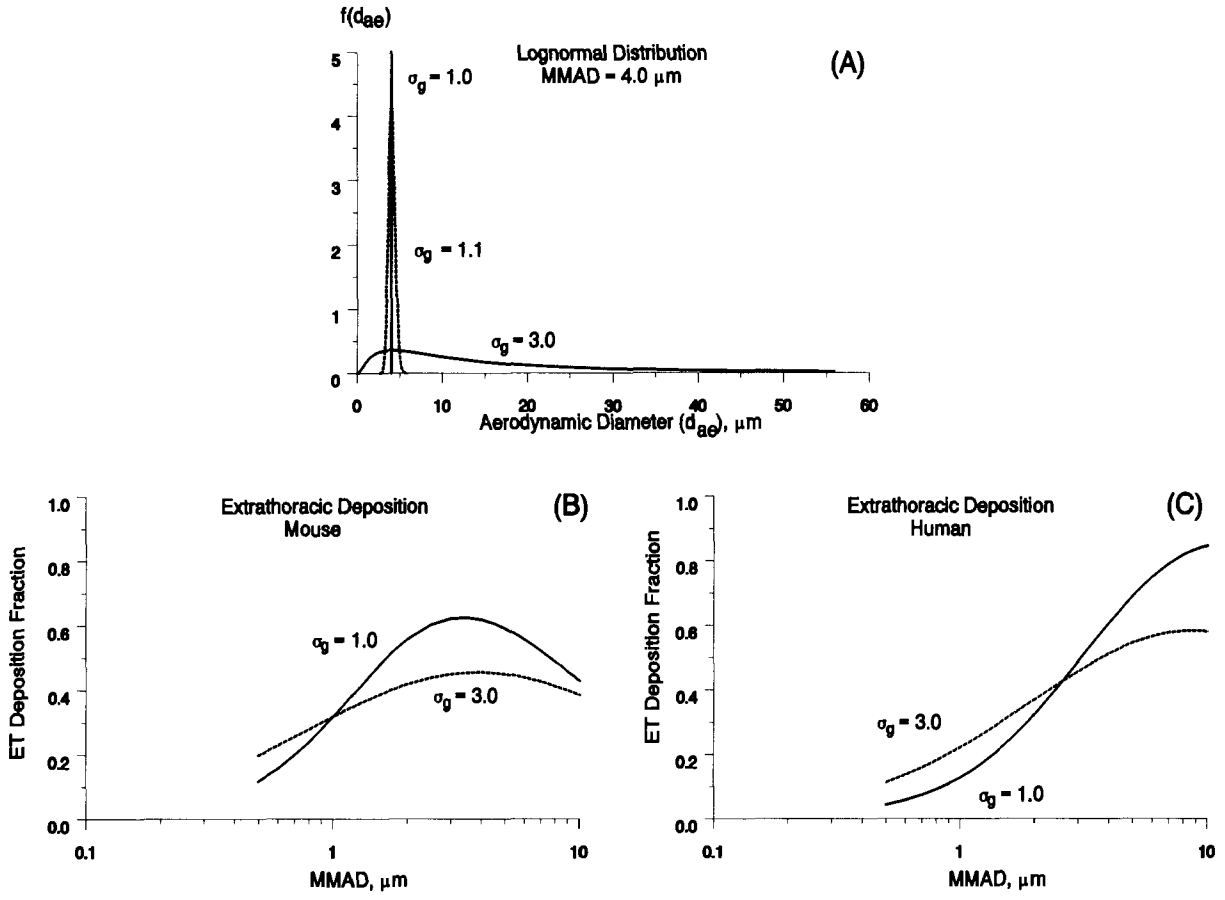

Figure 10-30. Range of particles for lognormal distributions with same MMAD but differing geometric standard deviations (A). Effect of polydisperse particles on predicted extrathoracic deposition fractions in mice (B) and humans (C).

$$[\hat{F}_r]_p = \int_0^{\infty} [\hat{F}_r]_m \times \frac{1}{d_{ae}(\log\sigma_g)\sqrt{2\pi}} \times \exp\left[-1/2\frac{(\log d_{ae} - \log MMAD)^2}{\log\sigma_g}\right] dd_{ae} \qquad (10\text{-}44)$$

where log refers to the natural logarithm, $[\hat{F}_r]_p$ is the predicted polydisperse fractional deposition for a given MMAD, and $[\hat{F}_r]_m$ is the predicted monodisperse fractional deposition for particles of size d_{ae}. The limits of integration are defined from 0 to ∞ but actually include only four standard deviations (99.95% of the complete distribution). For each particle size in the integration, $[\hat{F}_r]_m$ is calculated and then multiplied by the probability of observing a particle of that size in a particle size distribution with that MMAD and σ_g.

Panels B and C of Figure 10-30 illustrate one of the principal effects of polydisperse particle size distributions on predicted deposition fractions in the ET region, which is to flatten the deposition curve as a function of MMAD. This same effect is observed also in the TB and PU regions. (Note that the curves in panels B and C are expressed as a function of MMAD. They were generated as a function of the impaction parameter but are expressed as a function of MMAD for ease of comparison between species. A $\dot{V}_E$ of 37.5 mL/min was used for the mouse and of 13.8 L/min for the human.) Rudolf and colleagues (1988) have also investigated the effect of polydisperse particle size distributions on predicted regional uptake of aerosols in humans and present a more detailed discussion of these and related issues.

10.5.3 Acidic Aerosols

Experimental studies on deposition of acid aerosols are limited. There have been two studies in experimental animals using H_2SO_4 aerosols. Dahl and Griffith (1983) measured regional deposition of these aerosols in the size range from 0.4 to 1.2 μm MMAD generated at 20% and 80% relative humidities. Their data showed greater total and regional deposition of H_2SO_4 aerosols in rats compared to nonhygroscopic aerosols having the same MMAD's (Figure 10-31). Deposition of H_2SO_4 aerosols generated at 20% RH was also higher than those generated at 80% RH, indicating that the increase in deposition was caused by the growth of the particles in the highly humid environment of the respiratory tract.

However, a similar study by Dahl et al. (1983) found that deposition of H_2SO_4 aerosols in beagle dogs at these two relative humidities was similar to that of nonhygroscopic aerosols having the same size although deposition at 20% RH was again higher than that at 80% RH. The inconsistent results were explained by Dahl et al. (1985) to be caused by the large intersubject variability of deposition in dogs.

In humans, deposition of acid aerosols in the respiratory tract has only been obtained by model studies. In a recent study, Martonen and Zhang (1993) calculated deposition of H_2SO_4 aerosols in the human lung of various ages at three different activity levels. The H_2SO_4 aerosols was considered to be in equilibrium with atmospheric conditions outside the lung prior to being inhaled. The results of their calculation at rest breathing without considering extrathoracic deposition are shown in Figure 10-32. Comparing to

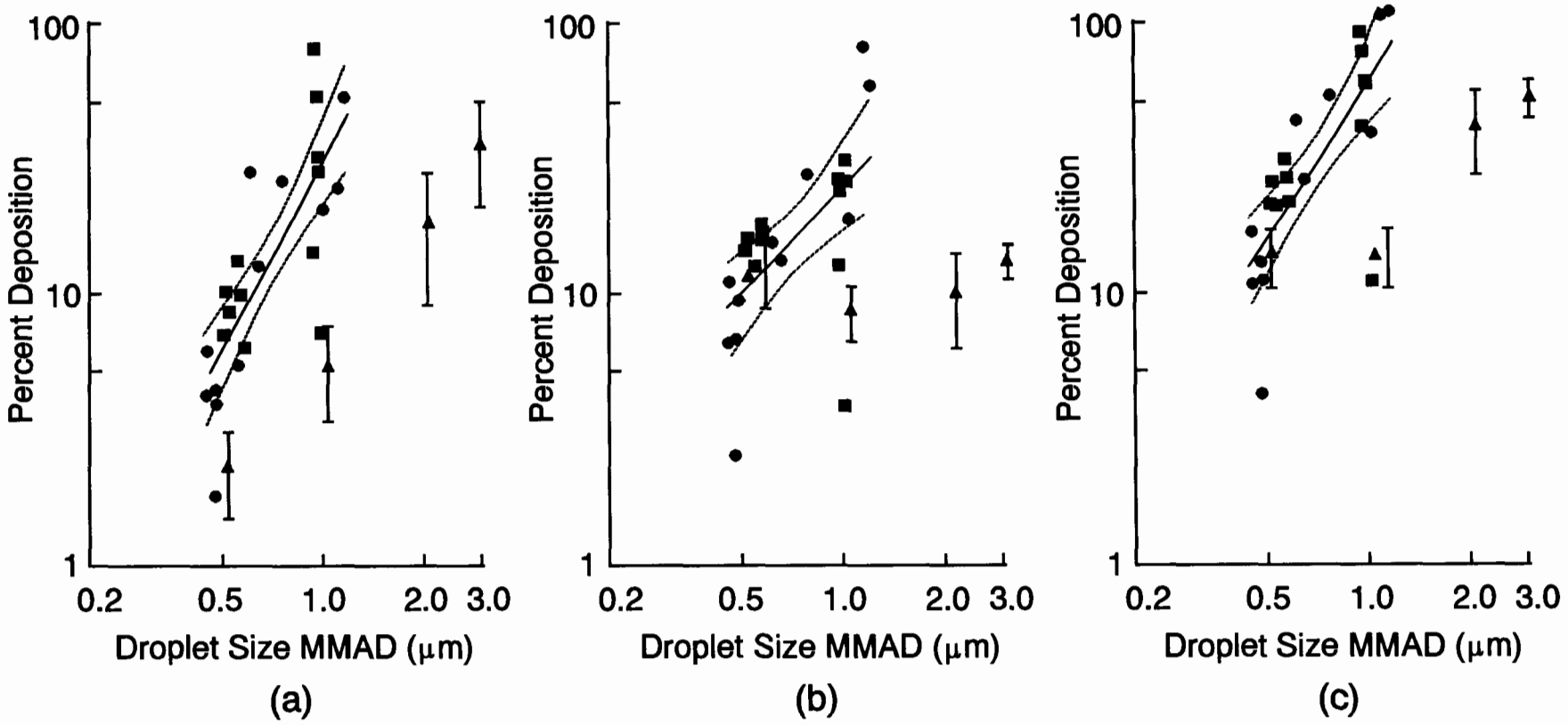

Figure 10-31. Regional deposition data in rats versus particle size for sulfuric acid mists and dry particles. Circles are 20% relative humidity; squares are 80% relative humidity; triangles are dry nonhygroscopic particles. Solid curves represent the mean of the data for sulfuric acid mists. Error bars and broken O curves represent 95% confidence limits.

Source: Dahl and Griffith (1983).

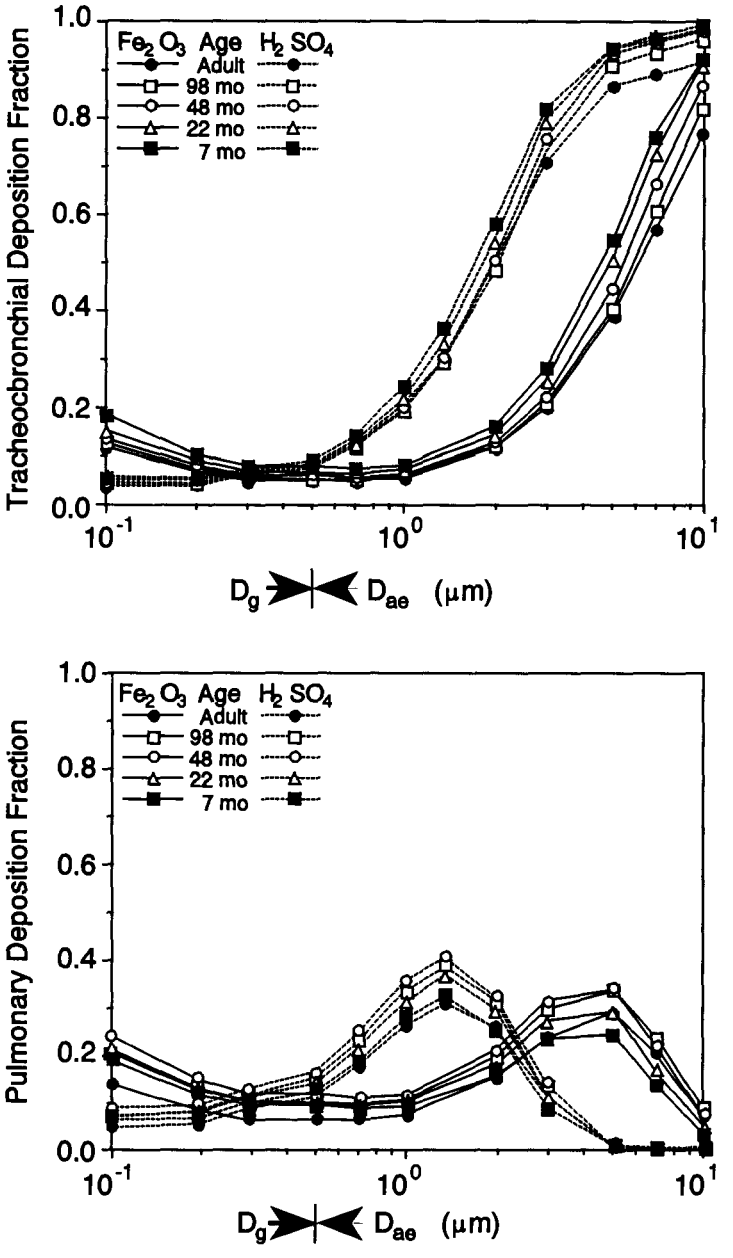

Figure 10-32. Regional deposition of hygroscopic H_2SO_4 and control Fe_2O_3 particles at quiet breathing in the human lung as a function of subject age.

Source: Martonen and Zhang (1993).

nonhygroscopic aerosols such as Fe_2SO_3, deposition of H_2SO_4 aerosols in different regions of the lung may be higher or lower depending upon the initial particle size. There is a critical initial size of H_2SO_4 in the 0.2 to 0.4 μm range. For larger particles the influence of

hygroscopicity of H_2SO_4 aerosols is to increase total lung deposition, whereas for smaller particles the opposite occurs.

10.6 CLEARANCE DATA AND MODELS

As discussed in previous sections, the biologic effects of inhaled particles are a function of their disposition. This, in turn, depends on their patterns of both deposition — i.e., the sites within which they initially come into contact with airway epithelial surfaces and the amount removed from the inhaled air at these sites, and clearance — i.e., the rates and routes by which deposited materials are physically removed from the respiratory tract. Deposition and clearance mechanisms were discussed in Sections 10.5 and 10.6, respectively.

Respiratory-tract clearance begins immediately upon deposition of inhaled particles. Given sufficient time, the deposited particles may be completely removed by these clearance processes. However, single inhalation exposures may be the exception rather than the rule. It is generally accepted that repeated or chronic exposures are common for environmental aerosols. As a result of such exposures, A accumulations of the particles may occur. Chronic exposures produce respiratory tract burdens of inhaled particles that continue to increase with time until the rate of deposition is balanced by the rate of clearance. This is defined as the "equilibrium respiratory tract burden". The accumulation patterns are unique to each laboratory animal species, and possibly unique to the inhaled material, especially if the inhaled material alters deposition and/or clearance patterns.

It is important to evaluate these accumulation patterns, especially when assessing ambient chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined as "species-dependent concentrations of airborne particles which, when chronically inhaled, produce equal lung deposits of inhaled particles per gram of lung during a specified exposure period". This section presents available data and approaches to evaluating exposure atmospheres to laboratory animals and humans that produce similar respiratory tract burdens.

10.6.1 Humans

Models for deposition, clearance, and dosimetry of the respiratory tract of humans have been available for the past four decades and continue to evolve. The International Commission on Radiological Protection (ICRP) has recommended three different mathematical models during this time period (ICRP 1959, 1979, 1994). The models changed substantially in structure, expanding from two compartments in the 1959 model (ICRP, 1959) to five compartments in the 1994 model (ICRP, 1994). These models have always represented an important aspect of radiation protection programs for inhaled radioactive materials. The models make it possible to calculate the absorbed radiation doses received by different parts of the respiratory tract and provide the necessary mathematical descriptions of the translocation of portions of the deposited radionuclides to other organs and tissues beyond the respiratory tract. The structure and complexity of the ICRP models increased with each version. These increases in complexity reflect both the expanded knowledge of the behavior and dosimetry of inhaled materials in the respiratory tract that has become available and an increased need for models that can be applied to a broader range of uses. Earlier uses of these models were primarily for general prospective health protection planning purposes and to support routine workplace monitoring. As the models have become more detailed and flexible in their application, increasing uses have been made of them for site-and process-specific applications, as well as retrospective analyses of individual exposures.

The 1959 model (ICRP, 1959) had a very simple structure in which the respiratory tract was divided into an upper respiratory tract (URT), and a lower respiratory tract (LRT). No information was given on the anatomical division between the URT and the LRT. In the 1959 model, 50% of inhaled particles deposited in the URT, 25% deposited in the LRT, and the remaining 25% was exhaled. No information on the effects of the sites or magnitude of particle deposition was given, and relationships between particle size, deposition, and clearance were not incorporated into the 1959 model. The URT was considered an air passage from which all deposited particles cleared quickly by mucociliary activity and swallowed. Particles deposited in the LRT were classified as soluble or insoluble. For soluble particles, chemical constituents of all 25% of the inhaled particles that reach the LRT were assumed to be rapidly absorbed into the systemic circulation. For insoluble particles, 12.5% were assumed to clear by mucociliary activity and swallowed during the first 24 h

following deposition. The remaining 12.5% was assumed to be retained with a biological half-time of 120 d. No clearance of particles to the regional lymph nodes was included in the 1959 model.

The 1979 model (ICRP, 1979) was based on the Task Group Lung Model (TGLM) report (Morrow et al., 1966) and was divided into three compartments (nasopharyngeal, NP; tracheobronchial, TB; and pulmonary, PU). The NP region including anatomical structures from the tip of the nose to the larynx; the TB region extended from the trachea to the end of the terminal bronchioles; and the PU region was the remaining, non-ciliated pulmonary parenchyma. Deposition probabilities were given for the NP, TB, and PU regions for activity median aerodynamic diameters (AMAD) of inhaled particles that covered about two orders of magnitude (0.2 - 10 μm). This incorporation of particle size considerations and the AMAD concept were major improvements in the health protection aspects of modeling related to inhaled radioactive particles. The 1979 ICRP model also incorporated consideration for clearance rates using three classes (D, W, Y). Class D particles cleared rapidly ($T_{1/2}$ = 0.5 d), class W particles cleared at an intermediate rate ($T_{1/2}$ = 50 d), and class Y particles cleared slowly ($T_{1/2}$ = 500 d). It was also recognized that the competing processes of dissolution-absorption and physical clearance operated on the deposited particles, but inadequate information was available to differentiate between the two mechanisms. This model also included a clearance pathway to the tracheobronchial lymph nodes. The long-term clearance of particles by either physical transport processes or by dissolution-absorption processes are described by the same clearance half-time.

A substantial increase in knowledge about the effects of particle size on the deposition of inhaled particles occurred since the publication of the TGLM report (Morrow et al., 1966). This new information is reflected in the latest ICRP model (IRCP66, 1994). This new ICRP model considers the respiratory tract as four anatomical regions. The extrathoracic (ET) region is divided into two sub-regions: the anterior nasal airways, which clear only by extrinsic processes such as nose blowing, defined as ET_1, and the posterior nasal passages, pharynx, mouth and larynx defined as ET_2, which clears to the gastrointestinal tract via a combination of mucociliary action and fluid flow. The airways within the lungs are comprised of the bronchial (BB) and bronchiolar (bb) regions, which combined are equivalent to the Tracheobronchial (TB) region described in Table 10-4. The TB region was divided in

the ICRP model to meet the need for calculating radiation doses to the bronchi and bronchiolar tissues separately because of possible great differences in doses to these tissues and apparent differences in radiation sensitivity. The gas-exchange tissues are defined as the alveolar-interstitial (AI) region, which is exactly comparable to the pulmonary region or A region (see Tables 10-2 and 10-4). There are two lymph node regions; LN_{ET} drains the extrathoracic region and LN_{TH} drains the BB, bb, and AI regions. Deposition in the four anatomical regions (ET, BB, bb, and AI) is given as a function of particle size covering five orders of magnitude, and two different types of particle size parameters are used. The activity median thermodynamic diameter (AMTD) is used to describe the deposition of particles ranging in size from 0.0005 to 1.0 micrometer; the AMAD is used to describe deposition for the size range of 0.1 to 100 micrometer. The model applies to hygroscopic particles by estimating particle growth in each region during inhalation. Reference values of regional deposition are provided, and guidance is given for extrapolating to specific individuals and populations under different levels of activity. Deposition is expressed as a fraction of the number or activity of particles of a given size that is present in a volume of ambient air before inspiration, and activity is assumed to be log-normally distributed as a function of particle size for a typical particle density of 3 g/cm^3 and dynamic shape factor of 1.5, although particle density and shape factor are included as variables in the deposition calculations. As discussed in Section 10.5, the 1994 ICRP model includes consideration of particle inhalability, which is a measure of the degree to which particles can enter the respiratory tract and be available for deposition. After deposition occurs in a given region, two different clearance processes act competitively on the deposited particles, except in the ET_1 region where the only clearance process is extrinsic. These two processes are: particle transport that includes mucociliary clearance from the respiratory tract and physical clearance of particles to the regional lymph nodes, and absorption which includes movement of material to blood regardless of process whether dissolution-absorption or transport of ultra fine particles. It is assumed that the rates of particle clearance are the same for all types of particles. Rates were derived from studies with human subjects. Particle clearance from the BB and bb regions includes two slow phases: (1) to account for observations of slow mucociliary clearance in humans and (2) to account for observations of long term retention of

small fractions of deposited material in the tracheobronchial tissues of both experimental animals and humans. The structure for the ICRP 1994 model is shown in Figure 10-33.

Absorption into blood is material specific, acts in all regions except ET_1, and is assumed to occur at the same rates for all regions. Absorption into blood is a two stage process. The first step (dissolution) involves dissociation of the particles into a form that can be absorbed into blood; the second step involves absorption of the subunits of the particles. Because these processes act independently on the regionally deposited particles, each can be specified separately and allowed to compete against the other processes involved in the model. This approach makes it possible to use time-dependent functions to describe processes such as dissolution-absorption. However, for ease of calculation it is assumed that time dependent dissolution can be approximated by dividing the material into two fractions with different dissolution rates: material in an initial state dissolves at a constant rate, simultaneously changing to a transformed state in which it dissolves at another rate. Uptake into blood is treated as instantaneous for the material immediately absorbed after dissolution. Another fraction of dissolved material may be absorbed more slowly as a result of binding with tissue components. The model can use observed rates of absorption for compounds for which there are reliable human or experimental animal data. The absorption of other compounds are specified as fast, moderate or slow. In the absence of specific information, compounds are assigned to types fast, moderate or slow according to their classification as D, W or Y, respectively, under the previous ICRP model. Greater attention to the transfer of particles to regional lymph nodes is given in this model than in the 1979 model by incorporating these clearance processes at each level in the respiratory tract, not just in the AI or pulmonary region in the 1979 model. Additionally, while the new ICRP model was developed primarily for use with airborne radioactive particles and gases, its use for non-radioactive substances is also desirable and should be encouraged.

An alternative new respiratory tract dosimetry model that developed concurrently with the new ICRP model is being proposed by the National Council on Radiation Protection (NCRP). This model is still being developed (Phalen et al., 1991), but might be available in 1995. As with the new ICRP model, the proposed NCRP model considers (1) inhalability of aerosols, (2) new sub-regions of the respiratory tract are considered,

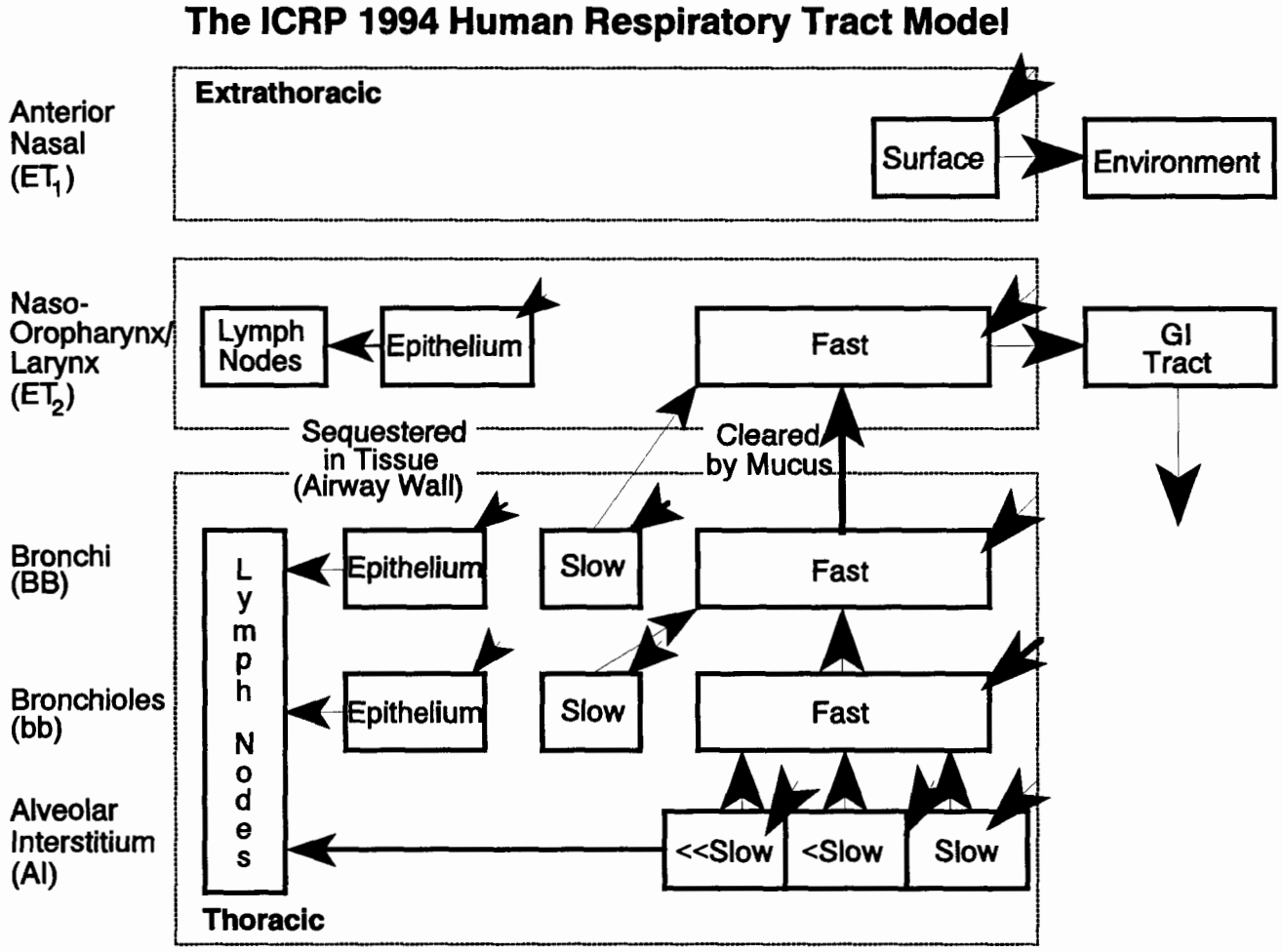

Figure 10-33. Schematic of the International Commission on Radiological Protection (ICRP66, 1994) model. Respiratory tract compartments in which inhaled particles may be deposited are illustrated. An explanation of clearance pathways, clearance rates, and subfractions of activity committed to different pathways is provided in the text.

Source: International Commission on Radiological Protection (ICRP66, 1994).

(3) dissolution-absorption is an important aspect of the model, and (4) body size (and age) are considered. The proposed NCRP model defines the respiratory tract in terms of a naso-oro-pharyngo-laryngeal (NOPL) region, a tracheobronchial (TB) region, a pulmonary (P) region, and the lung-associated lymph nodes (LN). As with the ICRP model, inhalability of aerosol particles is considered, and deposition in the various regions of the respiratory tract is modeled using methods that relate to mechanisms of inertial impaction, sedimentation, and diffusion. The rates of dissolution-absorption of particles and their constituents are derived from clearance data from humans and laboratory animals. The effect of body growth on particle deposition is also considered in the model, but particle clearance rates are assumed to be independent of age. The NCRP model does not consider the fate of inhaled materials after they leave the respiratory tract. Although the proposed NCRP model describes respiratory tract deposition, clearance, and dosimetry for radioactive substances inhaled by humans, the model can be used for evaluating inhalation exposures to all types of particles.

A considerable amount of information has accumulated relevant to the biokinetics of inhaled radioactive materials. The radiation associated with these materials allows relative ease of analysis to determine temporal patterns for retention, distribution, and excretion of inhaled radioactive particles and their constituents. Non-radioactive particles are difficult to study because the particles and their chemical constituents are generally difficult to detect in biological systems, tissues, and excreta. Some studies have shown that the physicochemical forms and sites of deposition of chemical toxicants influence clearance rates. Also, adsorption of chemicals onto particles can influence deposition patterns and alter rates of dissolution-absorption of the particles and their constituents. For example, vapors that would not normally reach the AI region will do so if they are adsorbed onto particles. Also, adsorption onto particles might slow the rates at which chemicals can be absorbed into lung tissue or the circulatory system. Amounts of inhaled material may markedly influence clearance as a consequence of lung overload. The cytotoxicity and shapes of particles (i.e.fibers) also influence clearance. Additionally, metabolic products of the inhaled materials may cause pathology and disease states that may result in nonpredictable retention and clearance patterns.

10.6.2 Laboratory Animals

Several animal models have been developed to help interpret results from specific studies that involved chronic inhalation exposures to non-radioactive particles (Wolff et al., 1987; Strom et al., 1988; Stöber et al., 1994). These models were adapted to data from studies involving high level chronic inhalation exposures in which massive lung burdens of low toxicity, poorly soluble particles were accumulated and the models have not been adapted to chronic exposures to low concentrations of aerosols in which lung overload does not occur.

Snipes et al. (1983) adapted a materials balance simulation model to evaluate repeated or chronic inhalation exposures. The model was described by Pritsker (1974) and uses a Fortran-based numerical integration of differential equations. The integration method is a fourth order, variable step-size Runge-Kutta-England routine for integrating systems of first order ordinary differential equations with initial values. The model was used to describe the retention and clearance of poorly soluble aerosol inhaled by mice, rats, and dogs (Snipes et al., 1983) and guinea pigs (Snipes et al., 1984). A distinct advantage of this kind of model is the requirement that dissolution-absorption rates are approximated as part of the modeling process. The simulation model was adapted to repeated or chronic exposures using the assumption that each individual exposure in a series of inhalation exposures is the same with regard to deposition and clearance kinetics. The model for repeated or chronic inhalation exposures therefore simply integrates the results of the individual exposures and predicts the lung (and other compartment) burdens of the exposure material during the course of the exposures. This model adequately accounted for the observed lung burdens of diesel exhaust particles (DEP) achieved in rats over the course of a 2-year chronic inhalation exposure to 0.35 mg DEP/m^3 (Snipes, 1989). The specific lung burdens of DEP achieved in the rats during the 2-year study were about 0.4 mg DEP/g lung, which is less that the amount that is generally predicted to cause lung overload. This model, and alternatives that are easily adapted to inhalation exposure scenarios, appears to be useful for predicting pulmonary clearance patterns for a variety of inhaled materials as long as exposure concentrations are reasonably low and lung overload is not incurred.

10.6.3 Species Similarities and Differences

Rates for particle translocation from the A region to tracheal lymph nodes (TLNs) appear to vary considerably among species. Rats and mice have particle translocation rates from the A region to TLNs that are quite different from those of guinea pigs, dogs, and possibly humans (Snipes et al., 1983; 1984). Translocation from the A region to TLNs begins soon after an acute inhalation exposure. However, after a few days the transport of particles from the A region to TLNs appears to be negligible in mice and rats (Snipes et al., 1983), but continues at a constant rate in guinea pigs and dogs (Snipes et al., 1983; 1984). No experimental information is available about the rates of translocation of particles from the A region to TLNs in humans. However, data for amounts of particles accumulated in the lungs of humans exposed repeatedly to dusty environments (Stöber et al., 1967; Carlberg et al., 1971; McInroy et al., 1976; Cottier et al., 1987) suggest that poorly soluble particles accumulate in TLNs of humans at rates that may be comparable to those observed for guinea pigs, dogs, and monkeys. However, the ICRP evaluated the translocation from lung to TLNs and concluded that the rate for humans could be represented as 2×10^{-5}/day, i.e., lower than the rate for dogs and monkey by approximately a factor of ten.

Physical movement of particles from the A region to the TLNs affords the opportunity to transport particles out of the lung, but the result is to sequester, or trap the particles in what is generally perceived to be a dead-end compartment. Because the TLNs represent traps for particles cleared from the lung, particles can accumulate to high concentrations in the TLNs. Thomas (1968, 1972) discussed the implications of particle translocation from the A region to TLNs when the particles contain specific radionuclides, but he presented information that is relevant to all types of particles. Translocation of particles from the A region to the TLNs results in concentrations of particles in the lymph nodes that can be more than 2 orders of magnitude higher than concentrations in the lung. The implications of this consequence of inhalation exposures has not been fully evaluated but may have important implications for immunological responses in humans exposed to specific kinds of aerosols.

Many measurements of alveolar retention and clearance have been conducted on humans and a variety of laboratory animal species. In some cases, at least two laboratory animal species were exposed to the same aerosolized material, so direct comparisons among species are possible. Few human inhalation exposures to the same materials as used for the

animal studies have occurred, so only a limited number of direct comparisons are possible between laboratory animals and humans.

Table 10-14 contains a summary of selected results for pulmonary retention of inhaled materials after single inhalation exposures to small masses of poorly soluble particles. Studies of less than about 3 mo duration were not included. The variability in these results was caused by several factors. In many cases, the reported results did not allow division of the pulmonary burden between short- and long-term clearance. Also, for most studies, dissolution-absorption of the exposure materials were not known or were not reported. The broad range of particle sizes would have influenced deposition patterns, and dissolution-absorption rates, but probably not physical clearance of particles from the A region.

The information shown in Table 10-14 was used to approximate biological clearance rates for particles inhaled by the species listed in Table 10-15. In addition, approximations are included for the fractions of pulmonary burdens initially deposited in the A region that were subjected to short- or long-term clearance. These trends clearly will not apply to all types of inhaled particles. For example, in some cases, deposition and clearance may be influenced by the physicochemical and/or biological characteristics of the inhaled material. Further, the generalizations that led to Table 10-15 allow comparisons for the consequences of chronic inhalation exposures among these animal species and humans that might not otherwise be possible.

The mathematical expressions for curve fits to data depend on the study duration. The values for percent initial alveolar burden (% IAB) versus time in the following table were obtained by simulating lung retention of poorly soluble particles in the rat using the physical clearance rates from Table 10-15. Two-component exponential curve fits were next made for % IAB versus time using the model results for days 1 to 150, 1 to 300, and 1 to 730. As indicated Table 10-16, the curve fit parameters for the data for days 1 to 150 agree well with the expectations of individuals who are familiar with the results of relatively short-term lung clearance studies.

Physical clearance patterns for alveolar burdens of particles are similar for guinea pigs, monkeys, dogs, and humans. For these species, about 20-30% of the initial burden of particles clears with a half-time on the order of 1 mo, the balance clears with a half-time of

TABLE 10-14. COMPARATIVE PULMONARY RETENTION PARAMETERS FOR POORLY SOLUBLE PARTICLES INHALED BY LABORATORY ANIMALS AND HUMANS

Species	Aerosol Matrix	Particle Size[a]		Alveolar Burden[b]				Study Duration (days)	References
		μm	Measure	P_1	T_1(d)	P_2	T_2(d)		
Mouse	FAP[c]	0.7	AMAD[d]	0.93	34	0.07	146	850	Snipes et al. (1983)
	FAP	1.5	AMAD	0.93	35	0.07	171	850	Snipes et al. (1983)
	FAP	2.8	AMAD	0.93	36	0.07	201	850	Snipes et al. (1983)
	Ru Oxide	0.38	CMD[e]	0.88	28	0.12	230	490	Bair (1961)
	Pu Oxide	0.2	CMD	0.86	20	0.14	460	525	Bair (1961)
Hamster	FAP	1.2	CMD	0.73	50	0.27	220	463	Bailey et al. (1985a)
Rat	Diesel soot	0.12	MMAD[f]	0.37	6	0.63	80	330	Lee et al. (1983)
	FAP	1.25	CMD	0.62	20	0.38	180	492	Bailey et al. (1985b)
	FAP	0.7	AMAD	0.91	34	0.09	173	850	Snipes et al. (1983)
	FAP	1.5	AMAD	0.91	35	0.09	210	850	Snipes et al. (1983)
	FAP	2.8	AMAD	0.91	36	0.09	258	850	Snipes et al. (1983)
	FAP	1.2	AMAD	0.83	33	0.17	310	365	Finch et al. (1994)
	FAP	1.4	AMAD	0.76	26	0.24	210	180	Finch et al. (1995)
	Fibers	1.2-2.3	AMAD			1.00	46-76	101-171	Morgan et al. (1977)
	Latex	3.0	CMD	0.39	18	0.61	63	190	Snipes et al. (1988)
	Pu Oxide	<1.0	CMD	0.20	20	0.80	180	350	Langham (1956)
	Pu Oxide	2.5	AMAD	0.75	30	0.25	250	800	Sanders et al. (1976)
	U_3O_8	≈1-2	CMD	0.67	20	0.33	500	768	Galibin and Parfenov (1971)
	Co_3O_4	2.69	MMAD	0.70	19	0.30	125	180	Kreyling et al. (1993)
Guinea Pig	FAP	2.0	AMAD	0.22	29	0.78	385	1100	Snipes et al. (1984)
	Diesel soot	0.12	MMAD			1.00	>2,000	432	Lee et al. (1983)
	Latex	3.0	CMD			1.00	83	190	Snipes et al. (1988)
Dog	Coal dust	2.4	MMAD			1.00	1,000	160	Gibb et al. (1975)
	Coal dust	1.9	MMAD			1.00	≈700	301-392	Morrow and Yuile (1982)
	Ce Oxide	0.09-1.4	MMD[g]			1.00	>570	140	Stuart et al. (1964)

TABLE 10-14 (cont'd). COMPARATIVE RETENTION RETENTION PARAMETERS FOR POORLY SOLUBLE PARTICLES INHALED BY LABORATORY ANIMALS AND HUMANS

Species	Aerosol Matrix	Particle Size		Alveolar Burden[b]				Study Duration (days)	References
		μm	Measure	P_1	T_1(d)	P_2	T_2(d)		
Dog, cont'd	FAP	2.1-2.3	AMAD	0.09	13	0.91	440	181	Boecker and McClellan, (1968)
	FAP	0.7	AMAD	0.15	20	0.85	257	850	Snipes et al. (1983)
	FAP	1.5	AMAD	0.15	21	0.85	341	850	Snipes et al. (1983)
	FAP	2.8	AMAD	0.15	21	0.85	485	850	Snipes et al. (1983)
	FAP	2.01	AMAD	0.05		0.95	910	1,000	Kreyling et al. (1988)
	Nb Oxide	1.6 -2.5	AMAD			1.00	>300	128	Cuddihy (1978)
	Pu Oxide	1-5	CMD			1.00	1,500	280	Bair (1961)
	Pu Oxide	4.3	MMD			1.00	300	300	Bair et al. (1962)
	Pu Oxide	1.1-4.9	MMAD		≈1		400	468	Morrow et al. (1967)
	Pu Oxide	0.1-0.65	CMD	0.10	200	0.90	1,000	≈4,000	Park et al. (1972)
	Pu Oxide	0.72	AMAD	0.10	3.9	0.90	680	730	Guilmette et al. (1984)
	Pu Oxide	1.4	AMAD	0.32	87	0.68	1,400	730	Guilmette et al. (1984)
	Pu Oxide	2.8	AMAD	0.22	32	0.78	1,800	730	Guilmette et al. (1984)
	Pu Oxide	4.3	MMD	0.50	20	0.50	1,600	270	Bair and McClanahan (1961)
	Tantalum	4.0	AMAD	0.40	1.9	0.60	860	155	Bianco et al. (1974)
	U_3O_8	0.3	CMD	0.47	4.5	0.53	120	127	Fish (1961)
	Zr Oxide	2.0	AMAD			1.0	340	128	Waligora (1971)
Monkey	Pu Oxide	2.06	CMAD			1.0	500-900	200	Nolibe et al. (1977)
	Pu Oxide	1.6	AMAD			1.0	770-1,100	990	LaBauve et al. (1980)
Human	FAP	1	CMD	0.14	40	0.86	350	372-533	Bailey et al. (1985a)
	FAP	4	CMD	0.27	50	0.73	670	372-533	Bailey et al. (1985a)
	Latex	3.6	CMD	0.27	30	0.73	296	≈480	Bohning et al. (1982)
	Latex	5	CMD	0.42	0.5	0.58	150-300	160	Booker et al. (1967)
	Pu Oxide	0.3	MMD			1.00	240	300	Johnson et al. (1972)
	Graphite & PuO_2	6	AMAD			1.00	240-290	566	Ramsden et al. (1970)
	Pu Oxide	<4-5	CMD			1.00	1,000	427	Newton (1968)

TABLE 10-14 (cont'd). COMPARATIVE ALVEOLAR RETENTION PARAMETERS FOR POORLY SOLUBLE PARTICLES INHALED BY LABORATORY ANIMALS AND HUMANS

Species	Aerosol Matrix	Particle Size		Alveolar Burden[b]				Study Durantion (days)	References
		μm	Measure	P_1	T_1(d)	P_2	T_2(d)		
Human, cont'd	Th Oxide	<4-5	CMD			1.00	300-400	427	Newton (1968)
	Teflon	4.1	CMD	0.30	4.5-45	0.70	200-2,500	300	Philipson et al. (1985)
	Zr Oxide	2.0	AMAD			1.00	224	261	Waligora (1971)

[a]Some aerosols were monodisperse, but most were polydisperse, with geometric standard deviations in the range of 1.5 to 4.

[b]Pulmonary burden = $P_1 \cdot e^{-(\ln 2)t/T_1} + P_2 \cdot e^{-(\ln 2)t/T_2}$, where P_1 and P_2 are fractions constrained to total 1.00, T_1 and T_2 equal retention half-times in (d), and t equals days after exposure. Retention half-times are approximations and are the net result of dissolution-absorption and physical clearance processes. In some examples, the original data were subjected to a computer curve-fit procedure to derive the values for P_1 and T_1 presented in this table.

[c]FAP = fused aluminosilicate particles.

[d]AMAD = activity median aerodynamic diameter.

[e]CMD = count median diameter.

[f]MMAD = mass median aerodynamic diameter.

[g]MMD = mass median diameter.

TABLE 10-15. AVERAGE PULMONARY RETENTION PARAMETERS FOR POORLY SOLUBLE PARTICLES INHALED BY SELECTED LABORATORY ANIMAL SPECIES AND HUMANS

	Alveolar Retention Parameters[a]			
Species	P_1	T_1	P_2	T_2
Mouse	0.9	30	0.1	240
Rat, Syrian Hamster	0.9	25	0.1	210
Guinea Pig	0.2	29	0.8	570
Monkey, Dog, Human	0.3	30	0.7	700

[a]Alveolar burden (fraction of initial deposition) =

$$P_1 \exp^{(-\ln 2)t/T_1} + P_2 \exp^{(-\ln 2)t/T_2},$$

where:
P_1 and P_2 = fractions of alveolar burden in fast and slow-clearing components;
T_1 and T_2 = retention half-times (days) for P_1 and P_2; and
t = time in days after an acute inhalation exposure.

several hundred days. Mice, Syrian hamsters, and rats clear about 90% of the deposited particles with a half-time of about 1 month and 10% with a half-time greater than 100 days. The relative division of the alveolar burden between short-term and long-term clearance represents a significant difference between most rodents and larger mammals and has considerable impact on long-term patterns for retention of material acutely inhaled, as well as for accumulation patterns for materials inhaled in repeated exposures.

10.6.4 Models to Estimate Retained Dose

Models have routinely been used to express retained dose in terms of temporal patterns for pulmonary retention of acutely inhaled materials. Available information for a variety of mammalian species and humans can be used to predict deposition patterns in the respiratory tract for inhalable aerosols with reasonable degrees of accuracy. Additionally, as indicated above, alveolar clearance data for mammalian species commonly used in inhalation studies are available from numerous experiments that involved small amounts of inhaled radioactive particles. The amounts of particles inhaled in those studies were small and can be presumed to result in clearance patterns characteristic of the species unless radiation damage was a

TABLE 10-16. PHYSICAL CLEARANCE RATES

Days	% IAB	P_1	T_1	P_2	T_2
1	96.96				
7	81.21				
14	66.89				
28	47.00				
35	40.03				
42	34.43				
49	29.87				
56	26.14				
63	23.06				
70	20.49				
100	13.26				
150	7.80	71.6	18.4	29.4	78.3
200	5.39				
250	4.10				
300	3.30	84.4	22.0	15.6	131
400	2.36				
500	1.78				
600	1.37				
730	0.99	91.0	25.6	9.0	221

confounding factor, which was probably not the case except where acute effects were an experimental objective.

A very important factor in using models to predict retention patterns in laboratory animals or humans is the dissolution-absorption rate of the inhaled material. Factors that affect the dissolution of materials or leaching of their constituents in physiological fluids, then absorption of their constituents are not fully understood. Solubility is known to be influenced by the surface-to-volume ratio and other surface properties of particles (Mercer, 1967; Morrow, 1973). The rates at which dissolution and absorption processes occur are influenced by factors that include chemical composition of the material. Temperature history of materials is an important consideration for some metal oxides. For example, in controlled laboratory environments, the solubility of oxides usually decreases when the oxides are produced at high temperatures, which generally results in compact particles having small surface-to-volume ratios. It is sometimes possible to accurately predict dissolution-absorption characteristics of materials based on physical/chemical considerations. However, predictions

for *in vivo* dissolution-absorption rates for most materials, especially if they contain multivalent cations or anions, should be confirmed experimentally.

Phagocytic cells, primarily macrophages, clearly play a role in dissolution-absorption of particles retained in the respiratory tract (Kreyling, 1992). Some particles dissolve within the phagosomes due to the acidic milieu in those organelles (Lundborg et al., 1984, 1985), but the dissolved material may remain associated with the phagosomes or other organelles in the macrophage rather than diffuse out of the macrophage to be absorbed and transported elsewhere (Cuddihy, 1984). Examples of delayed absorption of presumably soluble inorganic materials are beryllium (Reeves and Vorwald, 1967) and americium (Mewhinney and Griffith, 1983). This same phenomenon has been reported for organic materials. For example, covalent binding of benzo(a)pyrene or metabolites to cellular macromolecules resulted in an increased pulmonary retention time for that compound after inhalation exposures of rats (Medinsky and Kampcik, 1985). Certain chemical dyes are also retained in the lung (Medinsky et al., 1986), where they may dissolve and become associated with lipids or react with other constituents of lung tissue. Understanding these phenomena and recognizing species similarities and differences are important for evaluating alveolar retention and clearance processes and interpreting results of inhalation studies.

In one study related to the issue of species differences in dissolution-absorption, Oberdörster et al. (1987) evaluated clearance of ^{109}Cd from the lungs of rats and monkeys after inhalation of ^{109}Cd-labeled aerosols of $CdCl_2$ and CdO. The inhaled Cd was cleared 10 times faster from the lungs of the rats than from the lungs of monkeys. Cadmium in the lungs of mammalian species is probably bound to metallothionein, and these differences in rates of Cd clearance appear to be the result of species differences in metallothionein metabolism. Bailey et al. (1989) conducted a study that included an interspecies comparison of the translocation of ^{57}Co from the A region to blood after inhalation of $^{57}Co_3O_4$. The results of this multi-species study suggest that mammalian species demonstrate considerable variability with regard to rates of dissolution of particles retained in lung tissue, degree of binding of solubilized materials with constituents of lung tissue, and rates of absorption into the circulatory system.

Dissolution-absorption of fibers has been the subject of several studies (Morgan et al., 1982; Johnson et al., 1984; Le Bouffant et al., 1984, 1987; Hammad, 1984; Hammad et al.,

1988). Solubility of fibers in rat lungs, which was determined on the basis of changes in the size distributions of the fibers over time, was dependent on both fiber size and composition. Morgan et al. (1982) attributed the dependency of dissolution on fiber length to the differences in pH encountered by the fibers. The shorter fibers retained within macrophages were presumed to be exposed to a lower pH than nonphagocytized fibers in extracellular fluid. These results indicate that physical and chemical attributes of the fibers, as well as retention sites (intracellular versus extracellular) are important factors in processes that dissolve or etch them. Additionally, most fibers found in lymph nodes were less than 10 μm long and present in macrophages as single fibers (Le Bouffant et al., 1984, 1987). This was a clear demonstration that biological action *in vivo* reduced the more labile types of fibers to sizes which had biokinetics resembling moderately soluble particles and showed that the subunits of fibers could be physically translocated to TLNs.

Dissolution-absorption of materials in the respiratory tract is clearly dependent on the chemical and physical attributes of the material. While it is possible to predict rates of dissolution-absorption, it is prudent to experimentally determine this important clearance parameter to understand the importance of this clearance process for the lung, TLNs, and other body organs that might receive particles or fibers, or their constituents which enter the circulatory system from the lung.

10.6.4.1 Extrathoracic and Conducting Airways

Insufficient data are available to adequately model long-term retention of particles deposited in the conducting airways of any mammalian species. It is probable that some particles that deposit in the head airways and TB region during an inhalation exposure are retained for long times and may represent significant dosimetry concerns. Additionally, some of the particles that are cleared from the A region via the mucociliary transport pathway may become trapped in the TB epithelium during their transit through the airways. Additional research must be done to provide the information needed to properly evaluate retention of particles in conducting airways.

Based on the results of longitudinal scans of dogs that inhaled promethium oxide particles, Stuart (1966) concluded that particles were retained for relatively long times in the heads of the dogs. A study by Snipes et al. (1983) included mice, rats, and dogs exposed by

inhalation to monodisperse or polydisperse ^{134}Cs-labeled fused aluminosilicate particles. In all three species, 0.001 to 1% of the initial internally deposited burden of particles was retained in the head airways and was removed only by dissolution-absorption. Autoradiography revealed that retained particles were in close proximity to the basement membrane of nasal airway epithelium. In another study by Snipes et al. (1988), 3-, 9-, and 15-μm latex microspheres were inhaled by rats and guinea pigs. About 1 and 0.1% of all three sizes of microspheres were retained in the head airways of the rats and guinea pigs, respectively. For rats, the 9- and 15-μm microspheres cleared with half-times of 23 days; for guinea pigs, the same size microspheres cleared with half-times of about 9 days. The 3-μm microspheres were cleared from the head airways of the rats and guinea pigs with biological half-times of 173 and 346 days, respectively. The smaller particles are apparently more likely to penetrate the epithelium and reach long-term retention sites.

Whaley et al. (1986) studied retention and clearance of radiolabeled, 3-μm polystyrene latex particles instilled onto the epithelium of the maxillary and ethmoid turbinates of Beagle dogs. Retention of the particles at both sites after 30 days was about 0.1% of the amount initially deposited. Autoradiographs of turbinate tissue indicated that the particles were retained in the epithelial submucosa of both regions.

It is also generally concluded that most inhaled particles that deposit in the TB region clear within hours or days. However, results from a number of studies in recent years challenge this belief. These studies have demonstrated that small portions of the particles that deposit in, or are cleared through, the TB region are retained with half-times on the order of weeks or months. Patrick and Stirling (1977) noted that about 1% of barium sulfate particles instilled intratracheally into rats remained in the bronchial tissue for at least 30 days. In a followup study, Stirling and Patrick (1980) used autoradiography to demonstrate the temporal retention patterns for some of the retained $^{133}BaSO_4$ particles in TB airways. The particles were retained within macrophages in the tracheal wall for at least 7 days after intratracheal instillation of $^{133}BaSO_4$. By two h after instillation, some of the particles were buried in the tracheal wall. After 24 h, when most of the initial deposition of particles had cleared, 74% of $^{133}BaSO_4$ particles located by autoradiography were in macrophages proximate to the basement membrane. After 7 days, practically all of the remaining particles were incorporated into the walls of the airways. The authors did not determine the

mechanisms by which the particles were moved into the airway epithelium. It is possible that the particles were phagocytized by macrophages and transported into the airway epithelium. Another possibility is direct uptake by epithelial cells of the airways. It is also probable that intratracheal instillation procedures perturb airway epithelium and influence the results of these kinds of studies.

Gore and Thorne (1977) exposed rats by inhalation to polydisperse aerosols of UO_2. At 2, 4, 7, and 35 days after inhalation of the UO_2, autoradiography was used to determine the locations of particles retained in the TB and A regions. The authors did not report seeing particles of UO_2 retained in the airways, but did note two phases of clearance. The first phase was associated with a clearance half-time of 1.4 days, the second phase with a clearance half-time of about 16 days. The faster clearance was presumably associated with particles deposited on the conducting airways during the inhalation exposure; the longer-term clearance was associated with clearance of UO_2 particles from the A region. In a separate study, Gore and Patrick (1978) evaluated the distribution of UO_2 particles in the trachea and bronchi of rats for up to 14 days after inhalation of aerosols similar to those used by Gore and Thorne (1977). Retention of UO_2 at airway bifurcations was noted, as was retention of particles in the trachea.

In another study, Gore and Patrick (1982) also compared the retention sites of inhaled UO_2 particles and intratracheally instilled barium sulphate particles. Both types of particles were found in macrophages at sites near the basement membrane of the airways of the TB region. The macrophages appeared to have engulfed the particles in the airways, then passed through the airway epithelium and remained in the vicinity of the basement membrane. About 4% of the UO_2 in lungs of rats was associated with intrapulmonary airways (Gore, 1983; Patrick, 1983). Watson and Brain (1979) observed similar results with aerosols of gold colloid and iron oxide. Both types of particles were found in bronchial epithelium, but more of the iron oxide was observed, suggesting a possible particle size effect, or a relationship between the process of material uptake and chemical composition of the material. Both types of particles were found in bronchial epithelial cells, but neither gold nor iron oxide particles were seen in interstitial macrophages.

In a recent inhalation study, Briant and Sanders (1987) exposed rats to 0.7 μm AMAD chain-aggregate aerosols of U-Pu. These authors observed retained particles of U-Pu in the

larynx, trachea, carina, and bronchial airways throughout the course of their 84-day study. The amounts retained varied, but were at any time approximately 1% of the concurrent pulmonary burden. The pulmonary burden of U-Pu cleared with a biological half-time of 100 days, and the relative amounts of U-Pu in the airways suggested comparable particle clearance rates from the airways. Particles of U-Pu retained in the airways were located in epithelial cells.

Stahlhofen et al. (1981, 1986) conducted inhalation studies with humans to directly assess deposition and retention of poorly soluble particles that deposit in the TB region by inhalation. Human subjects inhaled small volumes of aerosols using procedures that theoretically allowed deposition to occur at specific depths in the TB region, but not in the A region. Results of those studies suggested that as much as 50% of the particles that deposited in the TB region clear slowly, presumably because they become incorporated into the airway epithelium. Smaldone et al. (1988) reported the results from gamma camera imaging analyses of aerosol retention in normal and diseased human subjects, and also suggested that particles deposited on central airways of the human lung do not completely clear within 24 h. There have also been a few reports indicating that poorly soluble particles associated with cigarette smoke are retained in the epithelium of the tracheobronchial tree of humans (Little et al., 1965; Radford and Martell, 1977; Cohen et al., 1988). The cumulative results of these studies strongly suggest that a portion of particles that deposit on the conducting airways can be retained for long periods of time, or indefinitely.

Long-term retention and clearance patterns for radioactive particles that deposit in the head airways and TB region must be thoroughly evaluated because of their implications for respiratory tract dosimetry and risk assessment (James et al., 1991; Johnson and Milencoff, 1989; Roy, 1989; ICRP, 1994). Similar concerns exist for non-radioactive particles that might be cytotoxic or elicit inflammatory, allergic, or immune responses at or near retention sites in conducting airways.

10.6.4.2 Alveolar Region

Model projections are possible for the A region using the cumulative information in the scientific literature relevant to deposition, retention, and clearance of inhaled particles. Table 10-17 summarizes reasonable approximations for physical pulmonary clearance

TABLE 10-17. PHYSICAL CLEARANCE RATES[a] FOR MODELING ALVEOLAR CLEARANCE OF PARTICLES INHALED BY HUMANS AND SELECTED MAMMALIAN SPECIES

Species	Clearance via Mucociliary Transport Pathway	Clearance to Thoracic Lymph Nodes
Mouse[b]	$0.023\ \exp^{-0.008t} + 0.0013$	$0.0007\ \exp^{-0.5t}$
Rat[b], Syrian Hamster[c]	$0.028\ \exp^{-0.01t} + 0.0018$	$0.0007\ \exp^{-0.5t}$
Guinea Pig[b]	$0.007\ \exp^{-0.03t} + 0.0004$	0.00004
Monkey[d], Dog[b]	$0.008\ \exp^{-0.022t} + 0.0001$	0.0002

[a]Fraction of existing alveolar burden physically cleared per day.
[b]Adapted from Snipes (1989)
[c]Clearance rates assumed to be the same as for rats.
[d]Clearance rates assumed to be the same as for dogs.

parameters for humans and six laboratory animal species. Alveolar clearance curves produced using the parameters in Table 10-17 agree with curves produced using the parameters in Table 10-15. An advantage to using the parameters in Table 10-17 is that they separate physical clearance from the A region into its two components, physical clearance via the mucociliary clearance pathway to the GI tract and clearance to TLNs. To model the pulmonary biokinetics of a specific type of particle, the physical clearance parameters in Table 10-17 are used in conjunction with a dissolution-absorption parameter to derive rates for effective clearance from the A region.

10.7 APPLICATION OF DOSIMETRY MODELS TO DOSE-RESPONSE ASSESSMENT

As discussed in the introduction of this chapter, objectives of dosimetry modeling for this effort included an attempt to ascertain whether or not such modeling can provide insight into the discrepancies between the epidemiologic and laboratory animal data, to identify plausible dose metrics of relevance to the available health endpoints, and to identify modifying factors that may enhance susceptibility to inhaled particles. In order to accomplish these objectives, this section presents an application of dosimetry modeling to data typically available from the epidemiologic and laboratory animal studies. Choice of a

dosimetry model for humans and laboratory animals, respectively, is discussed and these models are used to simulate deposition and retained doses of various exposures. Different dose metrics and their relevance to observed health endpoints are also discussed.

10.7.1 Dosimetry Model Selection

Available deposition models for humans and laboratory animals were presented in Section 10.5.1 and 10.5.2, respectively. Clearance models, required to calculate retained doses, were discussed in Section 10.6.

Human Model

The semi-empirical compartmental model of the International Commission on Radiological Protection (ICRP66, 1994) was chosen and used to model the dosimetry of inhaled particles in humans (Sections 10.7.4 and 10.7.5 below). A distinct advantage of this model is that it incorporates both deposition and clearance mechansisms so that both deposited and retained doses can be calculated. LUDEP® software version 1.1 was used to run the ICRP 1994 model simulations (National Radiological Protection Board, 1994).

Although the theoretical models described in Section 10.5 might allow prediction to more localized regions of the respiratory tract, information about the dimensions of the numerous gross and microscopic structures of the respiratory tract are extremely limited. Experimental data are still available only for the adult Caucasian male, and for a limited range of particle sizes (d_{ae} from about 1 μm to 10 μm), making validation of theoretical models also limited. For these reasons, the semi-empirical approach taken for development by the ICRP was viewed as advantageous. The parametric analysis of regional lung desposition, developed by Rudolf et al. (1986, 1990) and described in Section 10.5, was used to represent the results of complex theoretical modeling by relatively simple algebraic approximations. A theoretical model of gas transport and particle deposition (Egan et al., 1989) was applied to apportion the subdivision of particle deposition among the lower respiratory tract regions (BB, bb, AI — see Section 10.6), and to quantify the effects of a lung size and breathing rate. The structure of the respiratory tract is represented explicitly by a morphometric anatomical model as described in Table 10-4 and Figure 10-4. The ICRP model reasonably describes the experimental data relating total thoracic deposition to particle

size and breathing behavior. The model also succeeds in simulating the variation of regional deposition with particle size and breathing pattern that was inferred by Stahlhofen et al. (1980,1983) from their measurements of thoracic depostion and retention. In common with earlier theoretical models of Yeh and Schum (1980) and Yu and Diu (1982), the ICRP 1994 model predicts significantly less thoracic deposition for particles in the range of d_{ae} from 1 μm to 5 μm than the median values reported by Lippmann (1977) and Chan and Lippmann (1980). These data are crucial since they represent the largest group of experimental subjects studied to date. However, as described in detail elsewhere (ICRP66, 1994), when allowance is made for the hygroscopic growth within the lungs of the particulate matter used in the New York University studies, these key experimental measurements are also found to support the ICRP deposition model. The problem of time-dependent functions to describe clearance from the various regions in the respiratory tract was overcome by using a combination of compartments. Clearance from each region by three routes (absorption into blood, transport to GI tract, and transport to lymphatics) is accomplished by pathways with assigned rate constants.

Laboratory Animal Model

The particle dosimetry model of Ménache et al. (1995a) was chosen to calculate deposited dose estimates for laboratory animal species (U.S. EPA, 1994). Attributes of the model that were viewed as especially advantageous for this exercise included the detailed measurements made in all tissues that served as the source of deposition data (Raabe et al., 1988); that the deposition data were available in unanesthetized, freely breathing animals of five species under the same exposure conditions; and that inhalability was accounted for and used to adjust the logistic function to describe deposition efficiency. This model represents a revised version (Miller et al., 1988; Jarabek, et al., 1989, 1990) that has been useful to develop inhalation reference concentration (RfC) values for dose-response assessment of air toxics (U.S. EPA, 1994). The same approach will be used to calculate deposited doses as discussed following in greater detail Section 10.7.4. For calculation of retained doses, the simulation model based on Pritsker (1974) and described in Section 10.6 was used. This clearance model was applied to output of the Ménache et al. (1995a) deposition model in order to calculate retained dose as discussed following in Section 10.7.5.

10.7.2 Choice of Dose Metrics

As discussed in the preceding sections, inhaled dose, especially to different regions or locations within the respiratory tract, is not necessarily related linearly to the exposure concentration. For this reason, an internal dose to characterize the dose-response relationship of PM is desired. In general, the objective is to provide a metric that is mechanistically-motivated by the observed response. For example, alveolar effects could be characterized by deposited mass, mass per regional surface area, mass per alveolus, or mass per alveolar macrophage depending on the putative pathogenesis of the particles in question. As shown in Figures 10-2 and 10-3, the smaller size fractions of aerosols are associated with greater amounts of particles when characterized by surface area or by number rather than by mass. That is, concentrations in this region are very small by mass but extremely high by number. The need to consider this is accentuated when the high deposition of small particles in the lower respiratory tract is also factored. Miller et al., (1995) recently investigated differences in interspecies particle dosimetry. A summary table of this investigation is provided as Table 10-18 and supports the conclusion that dose metrics based on particle number per various anatomical normalizing factors indicate a need to examine the role of fine particles in eliciting morbidity and mortality, particularly in patients with compromised lung status (Miller et al., 1995). Anderson et al. (1990) have shown that the deposition of ultrafine particles in patients with COPD is greater than that in healthy people. For this external review draft, particle mass burdens have been selected as the dose metric. Application of modeling to calculated number and surface area metrics are under consideration.

The health effects data include effects that could be characterized as either "acute" (e.g., mortality) or "chronic" (e.g., morbidity or laboratory animal pathology after two-year biossays). Dose may be accurately described by particle deposition alone if the particles exert their primary action on the surface contacted (Dahl et al., 1991), i.e., deposited dose may be an appropriate metric for acute effects. An alternative to consider is dose rate (μg/min) per unit surface area because insoluble particles deposit and clear along the surface of the respiratory tract. Depending on the availability of morphometric information, other normalizing factors that could be explored include those listed in Table 10-18.

TABLE 10-18. SPECIES COMPARISONS BY MILLER ET AL. (1995) OF VARIOUS DOSE METRICS AS A FUNCTION OF PARTICLE SIZE FOR 24 H EXPOSURES TO 150 $\mu g/m^3$

Particle Size	Dose Metric	Rat[a]	Human Lung Status		Ratio: Human/Rat	
			Normal	Compromised	Normal	Compromised
	Mass/Unit Area	$3.74\text{-}3.76 \times 10^{-3}$	5.0×10^{-4}	NC[d]	0.13	NC[d]
0.1 μm	No.[b] Deposited	1.2×10^{10}	5.9×10^{11}	4.3×10^{11}	49	37
	No./Unit Surface Area	7.1×10^{6}	9.5×10^{5}	2.8×10^{6}	0.1	0.4
	No./Ventilatory Unit	4.9×10^{6}	1.8×10^{7}	5.3×10^{7}	4	11
	No./Alveolus[c]	303-598	1,190-1,930	3,570-5,790	2-5	6-15
	No./Macrophage[c]	262-399	100-61	298-482	0.3-0.6	0.8-1.8
1 μm	Mass/Unit Area	$1.1\text{-}1.2 \times 10^{-3}$	2.8×10^{-4}	NC[d]	0.23-0.25	NC[d]
	No. Deposited	3.5×10^{6}	3.3×10^{6}	2.4×10^{8}	92	69
	No./Unit Surface Area	2,130	532	1,590	0.3	0.8
	No./Ventilatory Unit	1,470	9,910	29,700	7	20
	No./Alveolus[c]	0.12-0.18	0.07-1.1	2.0-3.3	4-9	11-28
	No./Macrophage[c]	0.08-0.12	0.06-0.09	0.2-0.3	0.5-1.2	1.4 -3.5
5 μm	Mass/Unit Area	$2.8\text{-}4.4 \times 10^{-4}$	9.1×10^{4}	NC[d]	2.09-3.23	NC[d]
	No. Deposited	7.1×10^{3}	8.5×10^{6}	6.4×10^{6}	1,195	897
	No./Unit Surface Area	4	14	42	3.2	9.7
	No./Ventilatory Unit	3	260	780	88	263
	No./Alveolus[c]	0.0002	0.02-0.03	0.05-0.09	49-120	145-359
	No./Macrophage[c]	0.0002	0.001-0.002	0.004-0.007	6-15	18-45

[a]Rat data values adjusted for inhalability.
[b]No. = Number of particles.
[c]Intervals for these dose metrics and ratios reflect the range of values for the number of alveoli. Lower and upper interval values for the rat correspond to using the data of Yet et al. (1979) and Mercer et al. (1994) and for humans Mercer et al. (1994) and Weibel (1963), respectively. Lower dose ratios reflect using the data of Mercer et al. (1994).
[d]Not calculated.

Some of the human parameter values used in the ICRP model (ICRP66, 1994) and the LUDEP® software are provided in Table 10-19. Surface area values were derived by the ICRP based on the morphometry provided previously in Table 10-4. LUDEP® allows simulations of either normal augmenter or mouth breather adult male humans. The proportion of nasal airflow for these two types of breathing at different levels of activity were previously provided in Figure 10-26 and Table 10-11 in Section 10.5. The levels of activity to apportion nasal airflow are the same as those used to construct the three different activity patterns (general population; worker, light work; and worker, heavy work) shown in Table 10-19.

The broad spectrum of mammals used in inhalation toxicology research have body weights ranging upwards from a few grams to hundreds of kg; these mammals also exhibit a broad range of respiratory parameters. Table 10-20 lists body weights, lung weights, respiratory minute ventilation and respiratory tract region surface areas for six laboratory animal species. Lung weights and ventilation parameters are important variables for inhalation toxicology because these parameters dictate the amounts of inhaled materials potentially deposited in the lung, as well as the specific alveolar burdens (mass of particles/g lung) that will result from inhalation exposures. The inverse relationship between body size and metabolic rate is demonstrated by the values for respiratory minute ventilation and body weight or lung tissue volume. For example, liters of air inhaled per minute per gram of lung is about 20 times higher for resting mice than for resting humans, which is an important factor to consider relative to potential amounts of aerosol deposited in the respiratory tract per unit of time during inhalation exposures.

For deposited doses, a dose expression with normalizing factors can be calculated as the regional deposited dose (RDD_r) can be calculated as

$$RDD_r = 10^{-3} \times C_i \times \dot{V}_E \times F_r, \qquad (10\text{-}45)$$

where:

RDD_r = dose deposited in region r, $\mu g/min$,

C_i = concentration, $\mu g/m^3$,

$\dot{V}_E$ = minute ventilation (L/min),

F_r = fractional deposition in region r.

TABLE 10-19. HUMAN MODEL PARAMETER VALUES

TABLE 10-19(a). BODY WEIGHT AND RESPIRATORY TRACT REGION SURFACE AREAS

		Respiratory Tract Surface Areas		
Body Weight (kg)	Lung Weight (g)	ET (cm^2)	TB (cm^2)	A (m^2)
73.0	1,100	470	2,690	54.0

TABLE 10-19(b). HUMAN ACTIVITY PATTERNS AND ASSOCIATED RESPIRATORY MINUTE VENTILATION.

Activity Pattern	Sleeping (.45 m^3/h)		Sitting (.54 m^3/h)		Activity Light (1.5 m^3/h)		Activity Heavy (3.0 m^3/h)		Total/Day	
	Hours	Total	Hours	Total m^3	Hours	Total m^3	Hours	Total m^3	Hours	Total m^3
Adult male, general population	8	3.6	8	4.32	8	12	0	0	24	19.9
Adult male, light work	8	3.6	6.5	3.5	8.5	12.75	1	3	24	22.85
Adult male, heavy work	8	3.6	4	2.16	10	15	2	6	24	26.76

[a]International Commission on Radiological Protection (ICRP66, 1994).

TABLE 10-20. BODY WEIGHTS, LUNG WEIGHTS, RESPIRATORY MINUTE VENTILATION AND RESPIRATORY TRACT REGION SURFACE AREA FOR SELECTED LABORATORY ANIMAL SPECIES

Species	Body Weight (kg)	Lung Weight (g)	Minute Ventilation (L/min)	Respiratory Region Surface Area		
				ET (cm^2)	TB (cm^2)	A (m^2)
Mouse (B6C3F1)	0.037[a]	0.43[b]	0.044[a]	3[a]	3.5[a]	0.05[a]
Syrian Hamster	0.134[a]	1.54[b]	0.057[a]	14[a]	20.0[a]	0.30[a]
Rat (F344)	0.380[a]	4.34[b]	0.253[a]	15[a]	22.5[a]	0.34[a]
Guinea Pig	0.890[a]	10.1[b]	0.286[a]	30[a]	200[a]	0.90[a]
Monkey	2.45[c]	27.4[b]	0.776[b]	NA[d]	NA[d]	4.2[e]
Dog	12.6[c]	139[b]	2.88[b]	NA[d]	NA[d]	41[e]

[a]U.S. Environmental Protection Agency (1994; 1988a). Default values for males in chronic bioassays.
[b]Stahl, 1967: lung weight in g = $11.3 \cdot (\text{kg BW})^{0.99}$; minute ventilation = $379 \cdot (\text{kg BW})^{0.8}$.
[c]Phalen (1984).
[d]Not available.
[e]Scaled from results of dogs and baboons in Crapo et al. (1983).

If the RDD in animals is expressed relative to humans, the resultant ratio can be used as a multiplicative factor to adjust an inhalation particulate exposure in an experimental species to a predicted human equivalent concentration (HEC) that would be expected to be associated with the same dose delivered to the r^{th} region of the respiratory tract. This regional deposited dose ratio ($RDDR_r$) can be calculated as a series of ratios

$$RDDR_r = \frac{(10^{-3} \times C_i)_A}{(10^{-3} \times C_i)_H} \times \frac{(\text{Normalizing Factor})_H}{(\text{Normalizing Factor})_A} \times \frac{(\dot{V}_E)_A}{(\dot{V}_E)_H} \times \frac{(F_r)_A}{(F_r)_H}. \quad (10\text{-}46)$$

For the purposes of calculating the $RDDR_r$, the exposure concentration for the laboratory animal (A) and human (H) are assumed to be the same because it is assumed that the observed effect in the laboratory animal is relevant to human health risk. The $RDDR_r$ is used as a factor to adjust for interspecies differences in delivered dose under the same exposure scenario. The first term in Equation 10-46, therefore, equals one and will not be discussed further. The last term, the ratio of deposition fractions in a given respiratory region, (F_r), is calculated using the respective human and laboratory animal dosimetry models.

The dosimetric adjustment of laboratory animal exposures to an HEC by the application of the $RDDR_r$ has been used in derivation of inhalation RfC estimates. The inhalation RfC is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime (U.S. EPA, 1994). As such, it represents an estimate of dose-response used for assessment of chemicals known as air toxics. A similar approach to the data on PM is appropriate. An HEC would be calculated by

$$\text{HEC } (\mu g/m^3) = \text{NOAEL}_{[ADJ]} \ (\mu g/m^3) \times RDDR_r, \quad (10\text{-}47)$$

where the $NOAEL_{[ADJ]}$ is the no-observed-adverse-effect level (or other effect level) of the laboratory animal study; this level, if from an intermittent exposure regimen, is often

adjusted for the number of hours per day and days per week (#/24 x #/7) in order to a continuous exposure.

Because the ICRP model utilizes an activity pattern, however, Equation 10-46 must be modified to account for the fraction of time spent at each different ventilation rate corresponding to different activity levels

$$RDDR_{r_{[ACT]}} = \frac{a}{t_{[1]} \times \dot{V}_{E_{H[1]}} \times F_{r_{H[1]}} + t_{[2]} \times \dot{V}_{E_{H[2]}} \times F_{r_{H[2]}} + \ldots + t_{[n]} \times \dot{V}_{E_{H[n]}} \times F_{r_{H[n]}}} \quad (10\text{-}48)$$

where $t_{[i]}$ is the fractional time spent breathing minute volume [i],

$$t_{[1]} + t_{[2]} + \ldots + t_{[n]} = 1, \quad \text{and} \quad (10\text{-}49)$$

$$a = \frac{(\text{Normalizing Factor})_H}{(\text{Normalizing Factor})_A} \times \dot{V}D_{E_A} \times F_{r_A}, \quad (10\text{-}50)$$

where $\dot{V}D_{E_A}$ is a daily ventilation rate (L/min $\times$ 1440 min/day). It should be noted that the human denominator is the fractional deposition value output from the ICRP model simulations using the LUDEP® software using an activity pattern.

Although clearance is dependent on the site of initial deposition, calculation of retained dose is probably more appropriate for assessing chronic heatlh effects. Again, different normalizing factors such as retained mass per region, retained mass per surface area, or retained mass per other available morphometric information may be worthwhile to explore. The regional retained dose ratio $RRDR_r$ for interspecies dosimetric adjustment is calculated as a series of five ratios

$$RRDR_r = \frac{(10^{-3} \times Ci)_A}{(10^{-3} \times Ci)_H} \times \frac{(\text{Normalizing Factor})_H}{(\text{Normalizing Factor})_A} \times \frac{(\dot{V}_E)_A}{(\dot{V}_E)_H} \times \frac{(F_r)_A}{(F_r)_H)} \times \frac{(AI_t)_A}{(AI_t)_H} \quad (10\text{-}51)$$

where:

$RRDR_r$ = relative μg of particles retained in region, r;

Ci = exposure atmosphere concentration, $\mu g/m^3$;

Normalizing Factor = lung weight in grams;

$\dot{V}_E$ = minute ventilation (L/min);

Fr = fractional aerosol deposition in region r;

(AI_t) = relative accumulated alveolar interstitial burden of particles as a function of time from the start of a chronic exposure.

Again, since the ICRP model allows simulation of an activity pattern, Equation 10-51 must be adjusted to account for the fraction of time spent at each different ventilation rate corresponding to different activity levels.

$$RRDR_{r_{[ACT]}} = \frac{a}{t_{[1]} \times \dot{V}_{E_{H[1]}} \times F_{r_{H[1]}} \times (AI_t)_{H[1]} \times t_{[2]} \times \dot{V}_{E_{H[2]}} \times F_{r_{H[2]}} \times (AI_t)_{H[2]} + \ldots + t_{[n]} \times \dot{V}_{E_{H[n]}} \times (AI_t)_{H[n]}} \quad (10\text{-}52)$$

where $t_{[i]}$ is the fractional time spent breathing at minute ventilation [i],

$$t_{[1]} + t_{[2]} + \ldots + t_{[n]} = 1, \text{ and} \quad (10\text{-}53)$$

$$\alpha = \frac{(\text{NormalizingFactor}_r)_H}{(\text{NormalizingFactor})} \times (\dot{V}D_E)_A \times (Fr)_A \times (AI_t)_A , \quad (10\text{-}54)$$

and $\dot{V}D_{E_A}$ is a daily average ventilation rate (L/min × 1440 min/day).

The relative accumulated alveolar interstitial burden of particles as a function of time from the start of a chronic exposure must be calculated for specific exposure scenarios to account for species differences in clearance, as well as the dissolution-absorption characteristics of the inhaled particles. This ratio is not a constant and must be calculated for the chronic exposure time of interest. Physical clearance functions and dissolution-absorption rates for particles deposited in the A region are used to integrate daily deposition and clearance over the chronic exposure time period of interest. The equations for laboratory animals are derived using the information in Table 10-17. Physical clearance parameters for

humans are in the ICRP model (ICRP66, 1994) and the calculation of A burden for humans can be made using LUDEP®.

It should also be stated that calculating these ratios (either deposited or retained) depends on particle diameter (MMAD) and distribution (σ_g) but not on aerosol concentration, i.e., it assumes no altered deposition or clearance due to exposure concentration or chemical-specific toxicity.

10.7.3 Choice of Exposure Metrics

Human Exposure Data

Ambient exposure data provided elsewhere in the document were chosen to represent typical human exposures. Three different aerosols were chosen. Additional information on the characterization of each of these aerosols can be found in Chapter 3.

The first is the trimodal aerosol shown in Figure 10-34. Table 10-21 shows the cumulative distribution of particles, based on the count diameter (d_c), surface diameter (d_s), mass diameter (d), or aerodynamic diameter (d_{ae}). Recall from Section 10.2 that the 50% size cut for each of these diameters would be the respective median diameter of the distribution, i.e., the 50% size-cut diameter of the d_{ae} is the MMAD. Table 10-22 shows a distribution of the particles from Figure 10-34 and Table 10-21 into arbitrary size fractions (assuming the modes were distributed lognormally) and containing 1, 4, 5 or 10% of each mass median size distribution.

The two aerosols depicted in Figure 10-35, panels A and B, for Philadelphia and Phoenix respectively, were also chosen and treated similarly. Table 10-23 shows the cumulative distribution of particles, based on the count diameter (d_c), surface diameter (d_s), mass diameter (d), or aerodynamic diameter (d_{ae}). Recall from Section 10.2 that the 50% size cut for each of these diamters would be the respective median diamter of the distribution, e.g., the 50% size-cut diameter of the d_{ae} is the MMAD. Table 10-24 shows a distribution of the particles from Figure 10-35(a) and Table 10-23 into arbitrary size fractions (assuming the modes were distributed lognormally) and containing 1, 4, 5 or 10% of each mass median size distribution. Tables 10-25 and 10-26 are analogous to Tables 10-23 and 10-24 but show the data for Phoenix (Figure 10-35b).

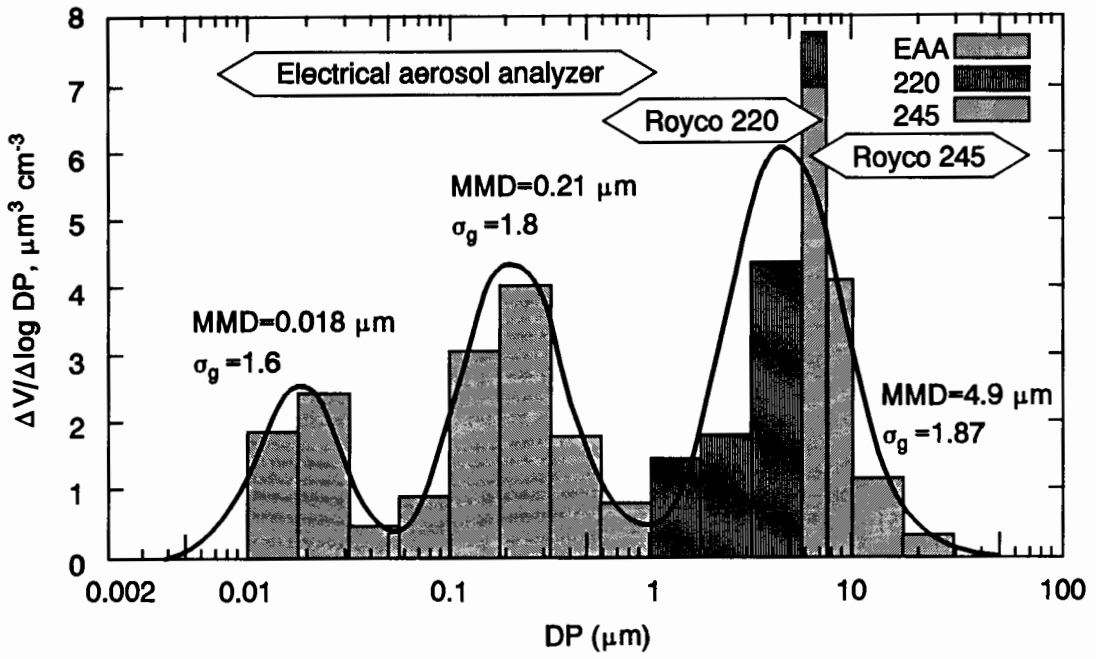

Figure 10-34. An example of histogram display and fitting to log-normal functions for particle-counting size distribution data. Instruments used and the range covered by each are shown. Counts are combined into reasonably-sized bins and displayed. Lognormal functions, fitted to the data, are shown with geometric mean sizes (MMD) of each mode and the width (σg) of each mode. Data taken from a study of fine sulfate and other particles generated by catalyst equipped cars as part of a cooperative study by EPA and General Motors Corporation. Note the clear separation of the nuclei mode (MMD = 0.018 μm), the accumulation mode (MMD = 0.21 μm) and coarse mode (MMD = 4.9 μm). Fine particles, as defined by Whitby (1988), include the nuclei and accumulation mode.

Source: Wilson et al., 1977.

The last aerosol chosen to represent ambient human exposures is that shown in Figure 10-36. Tables 10-27 and 10-28 show the cumulative distributions and recalculated distribution (using assignment into arbitrary size fractions and based on assuming that the mode was distributed lognormally) for these data.

TABLE 10-21. DISTRIBUTION OF PARTICLE SIZES IN A TRIMODAL POLYDISPERSE AEROSOL DEFINED IN FIGURE 10-34. THE TABULATED NUMBERS REPRESENT THE UPPER SIZE LIMIT FOR EACH PARTICLE SIZE INTERVAL BASED ON THE COUNT MEDIAN DISTRIBUTION (d_c), SURFACE MEDIAN DISTRIBUTION (d_g), MASS MEDIAN DISTRIBUTION (d), OR MASS MEDIAN AERODYNAMIC EQUIVALENT SIZE DISTRIBUTION (d_{ae})[a]

		Percent of Particles Smaller Than Size Cut												
Aerosol Mode	Particle Parameter, μm	1	5	10	20	30	40	50	60	70	80	90	95	99
Nuclei[b]	d_c	0.0031	0.0043	0.0051	0.0062	0.0072	0.0082	0.0093	0.010	0.012	0.014	0.017	0.020	0.028
	d_g	0.0048	0.0067	0.0079	0.0096	0.011	0.013	0.014	0.016	0.018	0.022	0.026	0.031	0.043
	d	0.0060	0.0083	0.010	0.012	0.014	0.016	0.018	0.020	0.023	0.027	0.033	0.039	0.054
	d_{ae}	0.044	0.051	0.056	0.062	0.067	0.072	0.076	0.081	0.087	0.095	0.106	0.116	0.139
Accumulation[c]	d_c	0.019	0.028	0.034	0.046	0.055	0.064	0.074	0.087	0.103	0.124	0.160	0.199	0.294
	d_g	0.038	0.057	0.069	0.091	0.109	0.127	0.149	0.173	0.205	0.248	0.319	0.396	0.588
	d	0.053	0.080	0.097	0.129	0.154	0.180	0.210	0.245	0.290	0.350	0.450	0.560	0.830
	d_{ae}	0.127	0.162	0.183	0.220	0.248	0.278	0.311	0.350	0.400	0.466	0.576	0.698	0.995
Coarse[d]	d_c	0.346	0.534	0.673	0.880	1.08	1.28	1.51	1.79	2.41	2.56	3.40	4.32	6.48
	d_g	0.757	1.17	1.47	1.93	2.37	2.80	3.31	3.92	5.27	5.61	7.43	9.46	14.2
	d	1.12	1.73	2.18	2.85	3.50	4.15	4.90	5.80	7.80	8.30	11.0	14.0	21.0
	d_{ae}	1.78	2.68	3.35	4.35	5.31	6.28	7.39	8.72	11.7	12.4	16.4	20.9	31.3

[a]Values for d_{ae} were calculated using Equations 5 and 7 of Raabe (1972), which include a slip correction factor and particle density to calculate d_{ae} from d: $d_{ae} = d(\rho[1 + \alpha + \beta e^{-(\gamma/2\lambda)})(2\lambda/d])^{0.5}$ where $\alpha \sim 1.26$, $\beta \sim 0.45$; $\gamma \sim 0.0650$ μm for air at 21 °C at sea level.
[b]Mass median diameter (MMD) = 0.018 μm; geometric standard deviation (σ_g) = 1.6; density, (ρ) = 1.4 g/cm^3.
[c]MMD = 0.21 μm; σ_g = 1.8; density, ρ = 1.2 g/cm^3.
[d]MMD = 4.9 μm; σ_g = 1.87; density, ρ = 2.2 g/cm^3.

TABLE 10-22. DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL DEFINED IN FIGURE 10-34. EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH MASS MEDIAN SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 15.6% OF THE TOTAL MASS WAS IN THE "NUCLEI MODE," 38.7% IN THE "ACCUMULATION MODE, " AND 45.7% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
Nuclei[a]	1	0.156	0.0031	0.0048	0.0060	0.044
	4	0.624	0.0043	0.0067	0.0083	0.051
	5	0.780	0.0051	0.0079	0.0099	0.056
	10	1.560	0.0062	0.0096	0.012	0.062
	10	1.560	0.0072	0.011	0.014	0.067
	10	1.560	0.0082	0.013	0.016	0.072
	10	1.560	0.0093	0.014	0.018	0.076
	10	1.560	0.010	0.016	0.020	0.081
	10	1.560	0.012	0.018	0.023	0.087
	10	1.560	0.014	0.022	0.027	0.095
	10	1.560	0.017	0.026	0.033	0.105
	5	0.780	0.020	0.031	0.039	0.116
	4	0.624	0.028	0.043	0.054	0.139
	1	0.156	0.103	0.160	0.200	0.324
Accumulation[b]	1	0.385	0.019	0.038	0.053	0.127
	4	1.544	0.028	0.057	0.080	0.162
	5	1.925	0.034	0.069	0.097	0.183
	10	3.850	0.046	0.091	0.129	0.220
	10	3.850	0.055	0.109	0.154	0.248
	10	3.850	0.064	0.127	0.180	0.278
	10	3.850	0.074	0.149	0.210	0.311
	10	3.850	0.087	0.173	0.245	0.350

TABLE 10-22 (cont'd). DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL DEFINED IN FIGURE 10-34. EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH MASS MEDIAN SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 15.6% OF THE TOTAL MASS WAS IN THE "NUCLEI MODE," 38.7% IN THE "ACCUMULATION MODE, " AND 45.7% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
	10	3.850	0.103	0.205	0.290	0.400
	10	3.850	0.124	0.248	0.350	0.466
	10	3.850	0.160	0.319	0.450	0.576
	5	1.925	0.199	0.396	0.560	0.698
	4	1.544	0.294	0.588	0.830	0.995
	1	0.385	1.06	2.12	3.00	3.37
Coarse[c]	1	0.457	0.346	0.757	1.12	1.78
	4	1.828	0.534	1.17	1.73	2.68
	5	2.285	0.673	1.47	2.18	3.35
	10	4.570	0.880	1.93	2.85	4.35
	10	4.570	1.08	2.37	3.50	5.31
	10	4.570	1.28	2.80	4.15	6.28
	10	4.570	1.51	3.31	4.90	7.39
	10	4.570	1.79	3.92	5.80	8.72
	10	4.570	2.41	5.27	7.80	11.7
	10	4.570	2.56	5.61	8.30	12.4
	10	4.570	3.40	7.43	11.0	16.4
	5	2.285	4.32	9.46	14.0	20.9
	4	1.828	6.48	14.2	21.0	31.3
	1	0.457	24.7	54.1	80.0	119

[a]Mass median diameter (MMD) = 0.018 μm; geometric standard deviation (σ_g) = 1.6; density, ρ = 1.4 g/cm^3.
[b]MMD = 0.21 μm; σ_g = 1.8; density, ρ = 1.2 g/cm^3.
[c]MMD = 4.9 μm; σ_g =1.87; density, ρ = 2.2 g/cm^3.

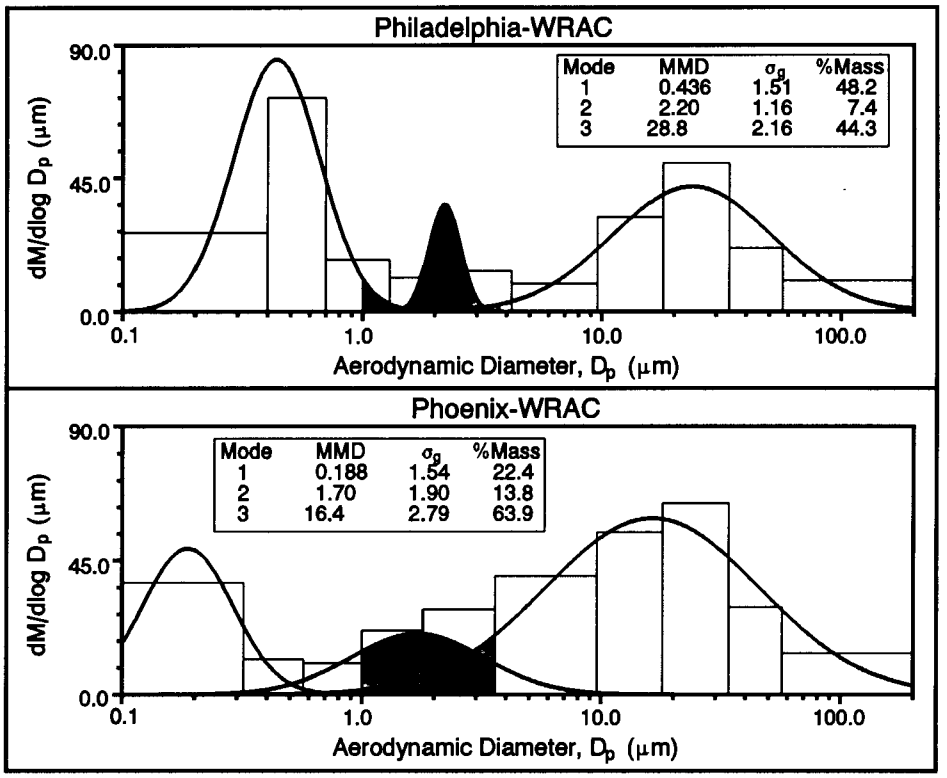

Figure 10-35. Impactor size distribution measurement generated by Lundgren et al. with the Wide Range Aerosol Classifier: (a) Philadelphia and (b) Phoenix. Note the much larger, small size tail to the coarse mode in the dryer environment of Phoenix.

Source: Lundgren et al., EPA Report.

Laboratory Animal Data

Because the particle diameters and distributions used in laboratory animal studies that are the basis of the toxicity data in Chapter 11 span a range, no one particular particle size or distribution was chosen. For calculation of deposited doses, fractional deposition was estimated for a range of particle diameters (d_{ae}) and distributions (σ_g). Deposited doses for two different particle diameters and distributions were then used to calculate retained doses (see Section 10.7.5).

10.7.4 Deposited Dose Estimations

The respective models discussed in Section 10.7.1 were used to estimate deposition in each of the respiratory tract regions. Note that the ICRP human model divides the ET

TABLE 10-23. DISTRIBUTION OF PARTICLE SIZES IN A TRIMODAL POLYDISPERSE AEROSOL FOR PHILADELPHIA DEFINED IN FIGURE 10-35(a). THE TABULATED NUMBERS REPRESENT THE UPPER SIZE LIMIT FOR EACH PARTICLE SIZE INTERVAL BASED ON THE COUNT MEDIAN DISTRIBUTION (d_c), SURFACE MEDIAN DISTRIBUTION (d_g), MASS MEDIAN DISTRIBUTION (d), OR MASS MEDIAN AERODYNAMIC EQUIVALENT SIZE DISTRIBUTION (d_{ae})[a]

		Percent of Particles Smaller Than Size Cut												
Aerosol Mode	Particle Parameter, μm	1	5	10	20	30	40	50	60	70	80	90	95	99
Accumulation[b]	d_c	0.100	0.132	0.153	0.183	0.207	0.231	0.262	0.287	0.320	0.362	0.434	0.503	0.667
	d_g	0.140	0.186	0.215	0.257	0.291	0.325	0.368	0.403	0.449	0.509	0.609	0.707	0.937
	d	0.166	0.220	0.255	0.305	0.345	0.385	0.436	0.478	0.532	0.603	0.722	0.838	1.11
	d_{ae}	0.273	0.335	0.376	0.433	0.479	0.525	0.584	0.632	0.694	0.776	0.912	1.04	1.36
Intermodal[c]	d_c	1.45	1.61	1.69	1.82	1.91	1.98	2.05	2.14	2.24	2.34	2.51	2.64	2.92
	d_g	1.52	1.68	1.77	1.90	2.00	2.07	2.15	2.24	2.34	2.45	2.62	2.76	3.05
	d	1.55	1.72	1.81	1.94	2.04	2.12	2.20	2.29	2.39	2.50	2.68	2.82	3.12
	d_{ae}	1.86	2.05	2.16	2.30	2.42	2.51	2.60	2.70	2.82	2.94	3.15	3.31	3.65
Coarse[d]	d_c	0.802	1.37	1.79	2.53	3.24	4.00	4.86	5.94	7.34	9.37	13.3	17.6	29.5
	d_g	2.62	4.48	5.86	8.29	10.6	13.1	15.9	19.5	24.0	30.7	43.7	57.5	96.7
	d	4.75	8.10	10.6	15.0	19.2	23.7	28.8	35.2	43.5	55.5	79.0	104	175
	d_{ae}	5.51	9.33	12.2	17.2	22.0	27.1	32.9	40.2	49.7	63.4	90.2	119	200

[a]Values for d_{ae} were calculated using Equations 5 and 7 of Raabe (1972), which include a slip correction factor and particle density to calculate d_{ae} from d: $d_{ae} = d(\rho[1 + \alpha + \beta e^{-(\gamma/2\lambda)})(2\lambda/d])^{0.5}$ where $\alpha \sim 1.26$, $\beta \sim 0.45$; $\gamma \sim 0.0650$ μm for air at 21 °C at sea level.
[b]Mass median diameter (MMD) = 0.436 μm; geometric standard deviation (σ_g) = 1.51; density, (ρ) = 1.3 g/cm^3.
[c]MMD = 2.20 μm; σ_g = 1.16; density, ρ = 1.3 g/cm^3.
[d]MMD = 28.8 μm; σ_g = 2.16; density, ρ = 1.3 g/cm^3.

TABLE 10-24. DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL FOR PHILADELPHIA DEFINED IN FIGURE 10-35(a). EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH MASS MEDIAN SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 48.2% OF THE TOTAL MASS WAS IN THE "ACCUMULATION MODE," 7.4% IN THE "INTERMODAL MODE," AND 44.3% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
Accumulation[a]	1	0.482	0.100	0.140	0.166	0.273
	4	1.928	0.132	0.185	0.220	0.335
	5	2.410	0.153	0.215	0.255	0.376
	10	4.820	0.183	0.257	0.305	0.433
	10	4.820	0.207	0.291	0.345	0.479
	10	4.820	0.231	0.325	0.385	0.525
	10	4.820	0.262	0.368	0.436	0.583
	10	4.820	0.287	0.403	0.478	0.632
	10	4.820	0.320	0.449	0.532	0.694
	10	4.820	0.362	0.509	0.603	0.776
	10	4.820	0.434	0.609	0.722	0.912
	5	2.410	0.503	0.707	0.838	1.04
	4	1.928	0.667	0.937	1.11	1.36
	1	0.482	1.80	2.53	3.00	3.51
Intermodal[b]	1	0.074	1.45	1.52	1.55	1.86
	4	0.296	1.61	1.68	1.72	2.05
	5	0.370	1.69	1.77	1.81	2.16
	10	0.740	1.82	1.90	1.94	2.30
	10	0.740	1.91	2.00	2.04	2.42
	10	0.740	1.98	2.07	2.12	2.51
	10	0.740	2.06	2.15	2.20	2.60
	10	0.740	2.14	2.24	2.29	2.70

TABLE 10-24 (cont'd). DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL FOR PHILADELPHIA DEFINED IN FIGURE 10-35(a). EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH MASS MEDIAN SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 48.2% OF THE TOTAL MASS WAS IN THE "ACCUMULATION MODE," 7.4% IN THE "INTERMODAL MODE," AND 44.3% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
	10	0.740	2.24	2.34	2.39	2.82
	10	0.740	2.34	2.45	2.50	2.94
	10	0.740	2.51	2.62	2.68	3.15
	5	0.370	2.64	2.76	2.82	3.31
	4	0.296	2.92	3.05	3.12	3.65
	1	0.074	4.21	4.40	4.50	5.22
Coarse[c]	1	0.443	0.802	2.62	4.75	5.51
	4	1.772	1.37	4.48	8.10	9.33
	5	2.215	1.79	5.86	10.6	12.2
	10	4.430	2.53	8.29	15.0	17.2
	10	4.430	3.24	10.6	19.2	22.0
	10	4.430	4.00	13.1	23.7	27.1
	10	4.430	4.86	15.9	28.8	32.9
	10	4.430	5.94	19.5	35.2	40.2
	10	4.430	7.34	24.0	43.5	49.7
	10	4.430	9.37	30.7	55.5	63.4
	10	4.430	13.3	43.7	79.0	90.2
	5	2.215	17.6	57.5	104	119
	4	1.772	29.5	96.7	175	200
	1	0.443	118	387	700	798

[a]Mass median diameter (MMD) = 0.436 μm; geometric standard deviation (σ_g) = 1.51; density, ρ = 1.3 g/cm^3.
[b]MMD = 2.20 μm; σ_g = 1.16; density, ρ = 1.3 g/cm^3.
[c]MMD = 28.8 μm; σ_g = 2.16; density, ρ = 1.3 g/cm^3.

TABLE 10-25. DISTRIBUTION OF PARTICLE SIZES IN A TRIMODAL POLYDISPERSE AEROSOL FOR PHOENIX DEFINED IN FIGURE 10-35(b). EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH SIZE DISTRIBUTION. THE TABULATED NUMBERS REPRESENT THE UPPER SIZE LIMIT FOR EACH PARTICLE SIZE INTERVAL BASED ON THE COUNT MEDIAN DISTRIBUTION (d_c), SURFACE MEDIAN DISTRIBUTION (d_g), MASS MEDIAN DISTRIBUTION (d), OR MASS MEDIAN AERODYNAMIC EQUIVALENT SIZE DISTRIBUTION (d_{ae})[a]

		Percent of Particles Smaller Than Size Cut												
Aerosol Mode	Particle Parameter, μm	1	5	10	20	30	40	50	60	70	80	90	95	99
Accumulation[b]	d_c	0.039	0.053	0.061	0.074	0.085	0.096	0.107	0.120	0.134	0.154	0.187	0.219	0.329
	d_g	0.057	0.076	0.089	0.107	0.124	0.139	0.156	0.174	0.195	0.224	0.272	0.318	0.477
	d	0.069	0.092	0.107	0.130	0.149	0.168	0.188	0.210	0.235	0.270	0.328	0.383	0.575
	d_{ae}	0.177	0.210	0.232	0.263	0.289	0.314	0.341	0.370	0.403	0.449	0.526	0.598	0.850
Intermodal[c]	d_c	0.108	0.169	0.215	0.288	0.352	0.418	0.494	0.581	0.694	0.851	1.13	1.44	2.24
	d_g	0.246	0.384	0.490	0.656	0.801	0.954	1.13	1.32	1.58	1.94	2.58	3.28	5.10
	d	0.372	0.580	0.740	0.990	1.21	1.44	1.70	2.00	2.39	2.93	3.90	4.95	7.70
	d_{ae}	0.584	0.857	1.07	1.39	1.68	1.98	2.32	2.71	3.22	3.93	5.19	6.56	10.1
Coarse[d]	d_c	0.063	0.127	0.186	0.295	0.408	0.540	0.697	0.914	1.21	1.69	2.68	3.44	7.86
	d_g	0.516	1.05	1.53	2.42	3.35	4.43	5.72	7.50	9.95	13.9	22.0	28.3	64.6
	d	1.48	3.00	4.38	6.95	9.60	12.7	16.4	21.5	28.5	39.8	63.0	81.0	185
	d_{ae}	2.03	4.02	5.82	9.17	12.6	16.7	21.5	28.1	37.3	52.0	82.2	106	241

[a]Values for d_{ae} were calculated using Equations 5 and 7 of Raabe (1972), which include a slip correction factor and particle density to calculate d_{ae} from d: $d_{ae} = d(\rho[1 + \alpha + \beta e^{-(\gamma/2\lambda)})(2\lambda/d])^{0.5}$ where $\alpha \sim 1.26$, $\beta \sim 0.45$; $\gamma \sim 0.0650$ μm for air at 21 °C at sea level.
[b]Mass median diameter (MMD) = 0.188 μm; geometric standard deviation (σ_g) = 1.54; density, (ρ) = 1.7 g/cm^3.
[c]MMD = 1.70 μm; σ_g = 1.90; density, ρ = 1.7 g/cm^3.
[d]MMD = 16.4 μm; σ_g = 2.79; density, ρ = 1.7 g/cm^3.

TABLE 10-26. DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL DEFINED FOR PHOENIX IN FIGURE 10-35(b). EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 22.4% OF THE TOTAL MASS WAS IN THE "ACCUMULATION MODE", 13.8% IN THE "INTERMODAL MODE," AND 63.9% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
Accumulation[a]	1	0.224	0.039	0.057	0.069	0.177
	4	0.896	0.053	0.076	0.092	0.210
	5	1.120	0.061	0.089	0.107	0.232
	10	2.240	0.074	0.108	0.130	0.263
	10	2.240	0.085	0.124	0.149	0.289
	10	2.240	0.096	0.139	0.168	0.314
	10	2.240	0.107	0.156	0.188	0.341
	10	2.240	0.120	0.174	0.210	0.370
	10	2.240	0.134	0.195	0.235	0.403
	10	2.240	0.154	0.224	0.270	0.449
	10	2.240	0.187	0.272	0.328	0.526
	5	1.120	0.219	0.318	0.383	0.598
	4	0.896	0.329	0.477	0.575	0.850
	1	0.224	0.857	1.24	1.50	2.06
Intermodal[b]	1	0.138	0.108	0.246	0.372	0.584
	4	0.552	0.169	0.384	0.580	0.857
	5	0.690	0.215	0.490	0.740	1.07
	10	1.380	0.288	0.656	0.990	1.39
	10	1.380	0.352	0.801	1.21	1.68
	10	1.380	0.418	0.954	1.44	1.98
	10	1.380	0.494	1.13	1.70	2.32
	10	1.380	0.581	1.32	2.00	2.71

TABLE 10-26 (cont'd). DISTRIBUTION OF PARTICLE MASS IN A TRIMODAL POLYDISPERSE AEROSOL DEFINED FOR PHOENIX IN FIGURE 10-35(b). EACH INDIVIDUAL MODE OF THE TRIMODAL AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF EACH SIZE DISTRIBUTION. THE PERCENT OF TOTAL AEROSOL MASS IN EACH SIZE FRACTION WAS CALCULATED BASED ON THE KNOWLEDGE THAT 22.4% OF THE TOTAL MASS WAS IN THE "ACCUMULATION MODE", 13.8% IN THE "INTERMODAL MODE," AND 63.9% IN THE "COARSE MODE"

Mode	Percent of Mode	Percent of Trimodal Aerosol	Particle Size Interval Cutoff			
			d_c	d_g	d	d_{ae}
	10	1.380	0.694	1.58	2.39	3.22
	10	1.380	0.851	1.94	2.93	3.93
	10	1.380	1.13	2.58	3.90	5.19
	5	0.690	1.44	3.28	4.95	6.56
	4	0.552	2.24	5.10	7.70	10.1
	1	0.138	8.72	19.9	30.0	39.2
Coarse[c]	1	0.639	0.063	0.516	1.48	2.03
	4	2.556	0.127	1.05	3.00	4.02
	5	3.195	0.186	1.53	4.38	5.82
	10	6.390	0.295	2.43	6.95	9.17
	10	6.390	0.408	3.35	9.60	12.6
	10	6.390	0.540	4.43	12.7	16.7
	10	6.390	0.697	5.72	16.4	21.5
	10	6.390	0.914	7.50	21.5	28.1
	10	6.390	1.21	9.95	28.5	37.3
	10	6.390	1.69	13.9	39.8	52.0
	10	6.390	2.68	22.0	63.0	82.2
	5	3.195	3.44	28.3	81.0	106
	4	2.556	7.86	64.6	185	241
	1	0.639	63.7	523	1500	1956

[a]Mass median diameter (MMD) = 0.188 μm; geometric standard deviation (σ_g) = 1.54; density, (ρ) = 1.7 g/cm^3.
[b]MMD = 1.70 μm; σ_g = 1.90; density, ρ = 1.7 g/cm^3.
[c]MMD = 16.4 μm; σ_g = 2.79; density, ρ = 1.7 g/cm^3.

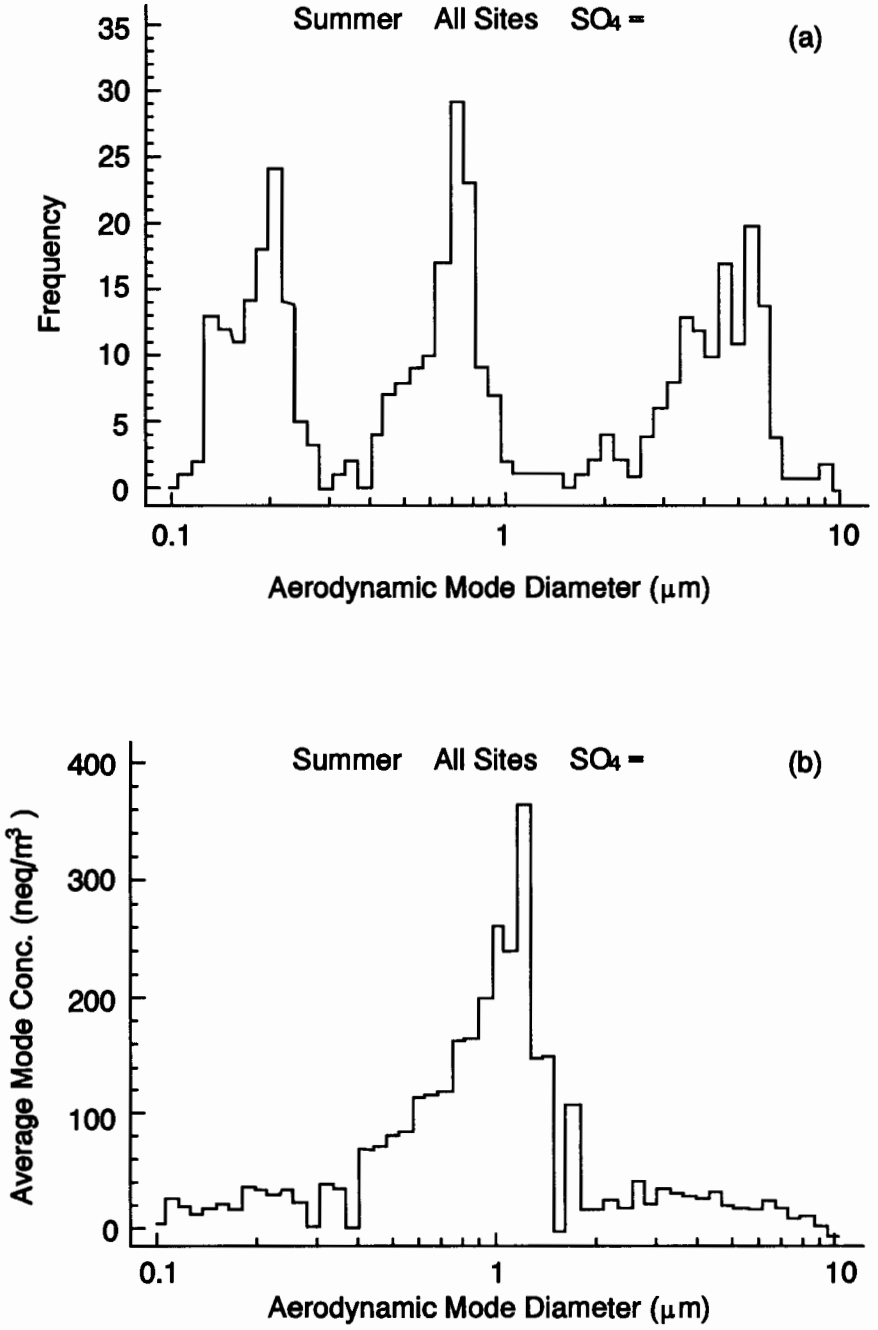

Figure 10-36. Data from the South Coast Air Quality Study (John et al., 1990). Plots show (a) frequency of sulfate modes of various sizes as a function of mode mass mean diameter (MMD) and (b) average sulfate mode concentration as a function of mode MMD. Note that although there are only a few instances when the MMD is near 1.0 μm diameter may be due to collection of fog droplets containing sulfate or reaction of SO_2 in liquid droplets of NaCl due to NaCl sea spray droplets in which SO_2 has dissolved and reacted to form sulfate and release HCl gas.

TABLE 10-27. DISTRIBUTION OF PARTICLE SIZES IN A POLYDISPERSE AEROSOL FOR LOS ANGELES IN FIGURE 10-36(b). THE TABULATED NUMBERS REPRESENT THE UPPER SIZE LIMIT FOR EACH PARTICLE SIZE INTERVAL BASED ON THE COUNT MEDIAN DISTRIBUTION (d_c), SURFACE MEDIAN DISTRIBUTION (d_g), MASS MEDIAN DISTRIBUTION (d), OR MASS MEDIAN AERODYNAMIC EQUIVALENT SIZE DISTRIBUTION (d_{ae})[a]

		Percent of Particles Smaller Than Size Cut												
Aerosol Mode	Particle Parameter, μm	1	5	10	20	30	40	50	60	70	80	90	95	99
Nuclei[b]	d_c	0.063	0.108	0.134	0.174	0.209	0.245	0.284	0.333	0.390	0.468	0.614	0.752	1.12
	d_g	0.125	0.215	0.268	0.347	0.418	0.488	0.566	0.664	0.779	0.934	1.22	1.50	2.23
	d	0.177	0.304	0.378	0.490	0.590	0.690	0.800	0.938	1.10	1.32	1.73	2.12	3.15
	d_{ae}	0.263	0.397	0.476	0.594	0.700	0.805	0.921	1.07	1.24	1.47	1.90	2.31	3.39

[a]Values for d_{ae} were calculated using Equations 5 and 7 of Raabe (1972), which include a slip correction factor and particle density to calculate d_{ae} from d: $d_{ae} = d(\rho[1 + \alpha + \beta e^{-(\gamma/2\lambda)})(2\lambda/d])^{0.5}$ where $\alpha \sim 1.26$, $\beta \sim 0.45$; $\gamma \sim 0.0650$ μm for air at 21 °C at sea level.
[b]Mass median diameter (MMD) = 0.8 μm; geometric standard deviation (σ_g) = 1.8; density, (ρ) = 1.1 g/cm^3.

TABLE 10-28. DISTRIBUTION OF PARTICLE MASS IN A POLYDISPERSE AEROSOL FOR LOS ANGELES DEFINED IN FIGURE 10-36(b). THE AEROSOL WAS SEPARATED INTO ARBITRARY SIZE FRACTIONS CONTAINING 1, 4, 5, OR 10% OF THE SIZE DISTRIBUTION

Aerosol	Percent of Aerosol	Particle Size Interval Cutoff			
		d_c	d_g	d	d_{ae}
LA-WET[a]	1	0.063	0.125	0.177	0.263
	4	0.108	0.215	0.304	0.397
	5	0.134	0.268	0.378	0.476
	10	0.174	0.347	0.490	0.594
	10	0.209	0.418	0.590	0.700
	10	0.245	0.488	0.690	0.805
	10	0.284	0.566	0.800	0.921
	10	0.333	0.664	0.938	1.07
	10	0.390	0.779	1.10	1.24
	10	0.468	0.934	1.32	1.47
	10	0.614	1.22	1.73	1.90
	5	0.752	1.50	2.12	2.31
	4	1.12	2.23	3.15	3.39
	1	3.55	7.08	10.0	10.6

[a]Mass median diameter (MMD) = 0.8 μm; geometric standard deviation (σ_g) = 1.8; density, ρ = 1.1 g/cm^3.

region into compartments, ET1 and ET2. The ICRP model also divides the TB region into two compartments, the bronchi (BB) and bronchiole (bb). The alveolar interstitial (AI) compartment is equivalent to the A region. When compared to the laboratory animal data, deposition fractions for ET1 and ET2 were summed to calculate ET deposition. Likewise, the BB and bb deposition fractions were summed to calculate the TB fraction.

Human Deposition Estimates

Tables 10-29 through 10-35 present the regional deposition fractions (% deposition) and regional deposited particle mass (ug) for each of the three ambient human exposure aerosols depicted in Figures 10-34, 10-35(a) (Philadelphia), 10-35(b) (Phoenix), and 10-36 (Los Angeles). Data are shown for normal augmenters (Tables 10-29, 10-31, 10-33, and 10-35) versus mouth breathers (Tables 10-30, 10-32, 10-34, and 10-35) for three different activity patterns.

TABLE 10-29. DAILY MASS DEPOSITION OF PARTICLES FROM AEROSOL IN FIGURE 10-34 IN THE RESPIRATORY TRACT OF "NORMAL AUGMENTER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m³

		Trimodal Aerosol Modes[a]					
		Nuclei Mode		Accumulation Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	2.27	3.53	3.19	12.30	36.20	164.77
	ET_2	2.34	3.64	3.13	12.06	41.19	187.48
	BB	0.86	1.34	0.48	1.85	1.71	7.78
	bb	5.64	8.76	2.26	8.71	1.26	5.74
	AI	21.96	34.12	9.91	38.20	3.95	17.98
	Total	33.06	51.39	18.97	73.12	84.31	383.75
Workers, light work[c]	ET_1	2.11	3.76	3.10	13.72	34.13	178.36
	ET_2	2.32	4.14	3.12	13.81	41.98	219.38
	BB	0.80	1.43	0.48	2.12	3.04	15.89
	bb	5.28	9.42	2.10	9.29	1.33	6.95
	AI	21.75	38.80	9.74	43.10	3.81	19.91
	Total	32.26	67.55	18.54	82.04	84.29	440.49
Workers, heavy work[d]	ET_1	2.00	4.17	3.11	16.10	32.89	201.11
	ET_2	2.29	4.78	3.19	16.52	42.68	260.97
	BB	0.74	1.54	0.48	2.49	3.96	24.21
	bb	4.94	10.31	1.96	10.15	1.31	8.01
	AI	21.56	45.00	9.55	49.45	3.56	21.77
	Total	31.53	65.80	18.29	94.71	84.40	516.07

[a]Nuclei mode MMAD = 0.076 μm, σ_g = 1.6, density = 1.4 g/cm³, 15.6% of the aerosol mass; accumulation mode MMAD = 0.311 μm, σ_g = 1.8, density = 1.2 g/cm³, 38.7% of the aerosol mass; coarse mode MMAD = 7.39 μm, σ_g = 1.87, density = 2.2 g/cm³, 45.7% of the aerosol mass (see Tables 10-21 and 10-22).
[b]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-30. DAILY MASS DEPOSITION OF PARTICLES FROM AEROSOL IN FIGURE 10-34 IN THE RESPIRATORY TRACT OF "MOUTH BREATHER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m³

		Trimodal Aerosol Modes[a]					
		Nuclei Mode		Accumulation Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	1.27	1.97	0.94	3.51	16.62	75.65
	ET_2	2.41	3.74	1.26	4.71	38.94	177.24
	BB	0.86	1.34	0.44	1.64	8.95	40.74
	bb	5.68	8.83	1.90	7.10	4.10	18.66
	AI	22.10	34.34	8.68	32.45	10.43	47.47
	Total	32.32	50.22	13.22	49.41	79.04	359.76
Workers, light work[c]	ET_1	1.17	2.09	0.92	4.07	15.58	81.57
	ET_2	2.38	4.25	1.28	5.66	40.22	210.58
	BB	0.80	1.43	0.44	1.95	10.13	53.04
	bb	5.30	9.45	1.76	7.79	3.90	20.42
	AI	21.89	39.05	8.51	37.66	9.66	50.58
	Total	31.54	56.27	12.91	57.13	79.49	416.19
Workers, heavy work[d]	ET_1	1.08	2.25	0.89	4.61	14.59	89.21
	ET_2	2.35	4.91	1.28	6.63	41.35	252.84
	BB	0.74	1.54	0.46	2.38	11.20	68.48
	bb	4.96	10.35	1.64	8.49	3.73	22.81
	AI	21.71	45.31	8.35	43.24	9.01	55.09
	Total	30.84	64.36	12.62	63.35	79.88	488.43

[a]Nuclei mode MMAD = 0.076 μm, σ_g = 1.6, density = 1.4 g/cm³, 15.6% of the aerosol mass; accumulation mode MMAD = 0.311 μm, σ_g = 1.8, density = 1.2 g/cm³, 38.7% of the aerosol mass; coarse mode MMAD = 7.39 μm, σ_g = 1.87, density = 2.2 g/cm³, 45.7% of the aerosol mass (see Tables 10-21 and 10-22).
[b]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-31. DAILY MASS DEPOSITION OF PARTICLES FROM PHILADELPHIA AEROSOL IN FIGURE 10-35(a) IN THE RESPIRATORY TRACT OF "NORMAL AUGMENTER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m^3

		Trimodal Aerosol Modes[a]					
		Accumulation Mode		Intermodal Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	4.05	19.44	25.34	18.68	29.34	129.46
	ET_2	3.94	18.91	35.64	26.27	30.24	133.43
	BB	0.38	1.82	2.07	1.53	0.40	1.76
	bb	1.44	6.91	2.51	1.85	0.15	0.66
	AI	7.73	37.11	15.37	11.33	0.26	1.15
	Total	17.54	84.19	80.93	59.66	60.39	266.46
Workers, light work[c]	ET_1	3.97	21.88	24.36	20.61	27.45	139.05
	ET_2	3.94	21.72	34.99	29.61	31.94	161.80
	BB	0.42	2.31	3.16	2.67	0.62	3.14
	bb	1.34	7.39	2.54	2.15	0.14	0.71
	AI	7.57	41.72	15.17	12.84	0.24	1.22
	Total	17.24	95.02	80.22	67.88	60.39	305.92
Workers, heavy work[d]	ET_1	4.02	25.93	24.09	23.85	26.18	155.18
	ET_2	4.05	26.12	35.22	34.87	33.12	196.31
	BB	0.44	2.84	3.96	3.92	0.76	4.50
	bb	1.24	8.00	2.50	2.48	0.13	0.77
	AI	7.40	47.72	14.64	14.50	0.22	1.30
	Total	17.15	110.61	80.41	79.62	60.41	358.06

[a]Accumulation mode MMAD = 0.436 μm, σ_g = 1.51, density = 1.3 g/cm^3, 48.2% of the aerosol mass; intermodal mode MMAD = 2.20 μm, σ_g = 1.16, density = 1.3 g/cm^3, 7.4% of the aerosol mass; coarse mode MMAD = 28.8 μm, σ_g = 1.3, density = 1.3 g/cm^3, 44.4% of the aerosol mass (see Tables 10-23 and 10-24).
[b]Average for 24 h, as derived from ICRP-66, (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-32. DAILY MASS DEPOSITION OF PARTICLES FROM PHILADELPHIA AEROSOL IN FIGURE 10-35(a) IN THE RESPIRATORY TRACT OF "MOUTH BREATHER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m³

		Trimodal Aerosol Modes[a]					
		Accumulation Mode		Intermodal Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	1.07	5.14	8.95	6.60	14.87	65.61
	ET_2	1.26	6.05	14.12	10.41	41.19	181.74
	BB	0.40	1.92	4.17	3.07	2.49	10.99
	bb	1.48	7.11	4.10	3.02	0.56	2.47
	AI	8.04	38.60	25.31	18.65	0.85	3.75
	Total	12.25	58.82	56.65	41.75	59.96	264.56
Workers, light work[c]	ET_1	1.06	5.84	8.66	7.33	13.78	69.31
	ET_2	1.29	7.11	14.46	12.24	42.39	214.74
	BB	0.44	2.43	5.42	4.59	2.59	13.12
	bb	1.38	7.61	4.08	3.45	0.51	2.58
	AI	7.86	43.32	24.59	20.81	0.76	3.85
	Total	12.03	66.31	57.21	48.42	60.03	304.10
Workers, heavy work[d]	ET_1	1.05	6.77	8.38	8.30	12.74	75.51
	ET_2	1.31	8.45	14.72	14.57	43.52	257.96
	BB	0.46	2.97	6.42	6.36	2.69	15.94
	bb	1.28	8.25	4.03	3.99	0.45	2.67
	AI	7.70	49.66	23.99	23.76	0.68	4.03
	Total	11.80	76.10	57.54	56.98	60.08	356.11

[a]Accumulation mode MMAD = 0.436 μm, σ_g = 1.51, density = 1.3 g/cm³, 48.2% of the aerosol mass; intermodal mode MMAD = 2.2 μm, σ_g = 1.16, density = 1 g/cm³, 7.4% of the aerosol mass; coarse mode MMAD = 28.8 μm, σ_g = 2.16, density = 1.3 g/cm³, 44.3% of the aerosol mass. (See Tables 10-23 and 10-24).
[b]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-33. DAILY MASS DEPOSITION OF PARTICLES FROM PHOENIX AEROSOL IN FIGURE 10-35(b) IN THE RESPIRATORY TRACT OF "NORMAL AUGMENTER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m³

		Trimodal Aerosol Modes[a]					
		Accumulation Mode		Intermodal Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	1.76	3.93	21.09	28.99	31.77	202.20
	ET_2	1.62	3.61	27.60	37.94	34.28	218.17
	BB	0.54	1.20	1.56	2.14	0.91	5.79
	bb	3.08	6.87	1.97	2.71	0.58	3.69
	AI	11.87	26.48	12.54	17.24	1.87	11.90
	Total	18.87	42.09	64.76	89.02	69.41	441.75
Workers, light work[c]	ET_1	1.66	4.25	20.29	32.02	29.83	217.97
	ET_2	1.61	4.12	27.25	43.00	35.62	260.27
	BB	0.50	1.28	2.44	3.85	1.53	11.18
	bb	2.86	7.33	1.98	3.12	0.60	4.38
	AI	11.68	29.92	12.33	19.46	1.80	13.15
	Total	18.31	46.90	64.29	101.45	69.38	506.95
Workers, heavy work[d]	ET_1	1.62	4.86	20.07	37.06	28.59	244.44
	ET_2	1.61	4.83	27.51	50.80	36.62	313.09
	BB	0.46	1.38	3.08	5.69	1.96	16.76
	bb	2.66	7.97	1.92	3.55	0.58	4.96
	AI	11.50	34.47	11.91	21.99	1.69	14.45
	Total	17.85	53.51	64.49	119.09	69.44	593.70

[a]Accumulation mode MMAD = 0.188 μm, σ_g = 1.54, density = 1.7 g/cm³, 22.4% of the aerosol mass; intermodal mode MMAD = 1.70 μm, σ_g = 1.9, density = 1.7 g/cm³, 13.8% of the aerosol mass; coarse mode MMAD = 16.4 μm, σ_g = 2.79, density = 1.7 g/cm³, 63.9% of the aerosol mass. (See Tables 10-25 and 10-26).
[b]Average for 24 h, as derived from ICRP-66, (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-34. DAILY MASS DEPOSITION OF PARTICLES FROM PHOENIX AEROSOL IN FIGURE 10-35(b) IN THE RESPIRATORY TRACT OF "MOUTH BREATHER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m^3.

		Trimodal Aerosol Modes[a]					
		Accumulation Mode		Intermodal Mode		Coarse Mode	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[b]	ET_1	0.81	1.81	7.45	10.24	15.41	98.08
	ET_2	1.41	3.15	12.21	16.78	39.98	254.45
	BB	0.54	1.20	3.73	5.13	4.88	31.06
	bb	3.08	6.87	3.39	4.66	1.87	11.90
	AI	11.94	26.64	19.43	26.71	4.65	29.59
	Total	17.78	39.67	46.21	63.72	66.79	425.08
Workers, light work[c]	ET_1	0.75	1.92	7.19	11.35	14.35	104.85
	ET_2	1.39	3.56	12.55	19.80	41.20	301.05
	BB	0.50	1.28	4.69	7.40	5.37	39.24
	bb	2.88	7.38	3.32	5.24	1.76	12.86
	AI	11.74	30.07	18.80	29.67	4.31	31.49
	Total	17.26	44.21	46.55	73.46	66.99	489.49
Workers, heavy work[d]	ET_1	0.70	2.10	6.94	12.81	13.34	114.05
	ET_2	1.38	4.14	12.81	23.65	42.32	361.83
	BB	0.46	1.38	5.49	10.14	5.82	49.76
	bb	2.68	8.03	3.25	6.00	1.65	14.11
	AI	11.56	34.65	18.27	33.73	4.02	34.37
	Total	16.78	50.30	46.76	86.33	67.15	574.12

[a]Accumulation mode MMAD = 0.188 μm, σ_g = 1.54, density = 1.7 g/cm^3, 22.4% of the aerosol mass; intermodal mode MMAD = 1.70 μm, σ_g = 1.9, density = 1.7 g/cm^3, 13.8% of the aerosol mass; coarse mode MMAD = 16.4 μm, σ_g = 2.79, density = 1.7 g/cm^3, 63.9% of the aerosol mass. (See Tables 10-25 and 10-26).
[b]Average for 24 h, as derived from ICRP-66, (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[d]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-35. DAILY MASS DEPOSITION OF PARTICLES FROM LOS ANGELES AEROSOL IN FIGURE 10-36(b) IN THE RESPIRATORY TRACT OF "NORMAL AUGMENTER" AND "MOUTH BREATHER" ADULT MALE HUMANS EXPOSED AT 50 μg PARTICLES/m^3

		Breathing Modes			
		Normal Augmenter		Mouth Breather	
Activity Pattern	Region of Respiratory Tract	Percent Deposition	Mass of Particles (μg)	Percent Deposition	Mass of Particles (μg)
General population[a]	ET_1	10.44	103.98	3.07	30.58
	ET_2	12.77	127.19	3.96	39.44
	BB	0.76	7.57	1.11	11.06
	bb	1.42	14.14	1.70	16.93
	AI	10.43	103.88	12.57	125.20
	Total	35.82	356.76	22.41	223.21
Workers, light work[b]	ET_1	10.17	116.29	3.02	34.53
	ET_2	12.65	144.65	4.09	46.77
	BB	1.04	11.89	1.42	16.24
	bb	1.34	15.32	1.61	18.41
	AI	10.21	116.75	12.27	140.31
	Total	35.41	404.90	22.41	256.26
Workers, heavy work[c]	ET_1	10.22	136.74	2.97	39.74
	ET_2	12.91	172.74	4.18	55.93
	BB	1.24	16.59	1.66	22.21
	bb	1.25	16.73	1.53	20.47
	AI	9.94	133.00	11.99	160.43
	Total	35.56	475.80	22.33	298.78

[a]Average for 24 h, as derived from ICRP-66, (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[b]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

As expected from experimental studies, these simulations predict different deposition fractions for mouth breathing versus nasal breathing. This is most noticeable for deposition of the intermodal and coarse modes of the Philadelphia and Phoenix aerosols (depicted in Figures 10-35a and 10-35b), which showed significant increases in BB and AI deposition fractions. The MMAD for the intermodal and coarse modes were 2.6 and 27.1, respectively for the Philadelphia aerosol and 2.32 and 21.5 for the Phoenix aerosol. The accumulation mode was less effected by mouth breathing as would be anticipated for these smaller MMADs.

Activity pattern influenced the deposition fractions greatly. Again the influence was more significant for the intermodal and coarse modes. A noticeable increase in both BB and AI deposition occurred with percent changes of increased deposition ranging from 60 to 500%. Differences were also apparent in the nuclei and accumulation modes. For the aerosol depicted in Figure 10-34, the nuclei mode (MMAD = .076 μm) deposition fractions decreased in the BB, bb, and AI regions with the heavy work activity pattern compared to that for the general population. For the Philadelphia aerosol, deposition of the accumulation mode (MMAD = .584 μm) increased in the BB region but decreased in the bb and AI regions with the heavy work activity pattern. For the Phoenix aerosol, deposition of the accumulation mode (MMAD = .341 μm) decreased for all three lower respiratory compartments (BB, bb, and AI) with the heavy work activity pattern.

Differences among the aerosols were also apparent and reflected the differences in the MMAD values and percent mass of each mode. Table 10-36 presents summary data for each of the three chosen ambient aerosols. To better understand the deposition differences for each mode, however, the previous Tables 10-29 through 10-35 should also be consulted.

Laboratory Animal Deposition Estimates

Tables 10-37 through 10-42 provide the deposition fractions of various particle sizes (MMAD) for either a relatively monodisperse (σ_g = 1.3) versus a more polydisperse (σ_g = 2.4) distribution in four different laboratory animal species. Deposition fractions of these aerosols for an adult male human normal augmenter and mouth breather with a general population activity pattern were calculated using the ICRP model. Deposition fraction for each respiratory tract region are presented: ET in Tables 10-37 and 10-38; TB in

TABLE 10-36. DAILY MASS DEPOSITION OF AEROSOL PARTICLES IN THE RESPIRATORY TRACTS OF "NORMAL AUGMENTER" AND "MOUTH BREATHER" ADULT MALE HUMANS EXPOSED TO 50 μg PARTICLES/m³

Aerosol Figure		10-34		10-35(a) (Philadelphia)		10-35(b) (Phoenix)		10-36 (Los Angeles)	
Activity Pattern	Region of Respiratory Tract	Normal Augmenter	Mouth Breather	Normal Augmenter	Mouth Breather	Normal Augmenter	Mouth Breather	Normal Augmenter	Mouth Breather
		Deposition Fraction (μg particles)							
General population[a]	ET_1	180.6	81.1	167.6	77.4	235.1	110.1	104.0	30.6
	ET_2	203.2	185.7	178.6	198.2	259.7	274.4	127.2	39.4
	BB	11.0	43.7	5.1	16.0	9.1	37.4	7.6	11.1
	bb	23.2	34.6	9.4	12.6	13.3	23.4	14.1	16.9
	AI	90.3	114.3	49.6	61.0	55.6	82.9	103.9	125.2
	Total	508.3	459.4	410.3	365.1	572.9	528.3	356.8	223.2
Workers, light work[b]	ET_1	195.8	87.7	181.5	83.0	254.2	118.1	116.3	34.5
	ET_2	237.3	220.5	213.1	234.1	307.4	324.4	144.7	46.8
	BB	19.4	56.4	8.1	20.1	16.3	47.9	11.9	16.2
	bb	25.7	37.7	10.3	13.6	14.8	25.5	15.3	18.4
	AI	101.8	127.3	55.8	68.0	62.5	91.2	116.8	140.3
	Total	580.1	529.6	468.8	418.8	655.3	607.2	404.9	256.3
Workers, heavy work[c]	ET_1	221.4	96.1	205.0	90.6	286.4	129.0	136.7	39.7
	ET_2	282.3	264.4	257.3	281.0	368.7	389.6	172.7	55.9
	BB	28.2	72.4	11.3	25.3	23.8	61.3	16.6	22.2
	bb	28.5	41.7	11.3	14.9	16.5	28.1	16.7	20.5
	AI	116.2	143.6	63.5	77.5	70.9	102.8	133.0	160.4
	Total	676.6	616.1	548.3	489.2	766.3	710.8	475.8	298.8

[a]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 33.3% sitting, and 33.3% light exercise. (See Table 10-19).
[b]Average for 24 h, as derived from ICRP-66 (1974): for 33.3% sleep, 27.1% sitting, 35.4% light exercise, 4.2% heavy exercise. (See Table 10-19).
[c]Average for 24 h, as derived from ICRP-66 (1994): for 33.3% sleep, 16.7% sitting, 41.7% light exercise, 8.3% heavy exercise. (See Table 10-19).

TABLE 10-37. EXTRATHORACIC DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS (σ_g=1.3) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.0868	0.0236	0.008	0.161	0.042	0.141
0.6	0.1203	0.0307	0.019	0.211	0.07	0.166
0.7	0.1569	0.0397	0.039	0.26	0.106	0.189
0.8	0.1953	0.05	0.071	0.308	0.149	0.211
0.9	0.2343	0.0614	0.117	0.353	0.198	0.231
1	0.2728	0.0736	0.178	0.394	0.251	0.25
1.5	0.4431	0.141	0.554	0.544	0.497	0.326
2	0.5661	0.2085	0.737	0.621	0.639	0.377
2.5	0.6511	0.2704	0.77	0.653	0.695	0.41
3	0.711	0.3259	0.757	0.661	0.706	0.43
3.5	0.7541	0.3754	0.731	0.655	0.697	0.442
4	0.7854	0.4201	0.702	0.642	0.679	0.447
4.5	0.8079	0.4601	0.673	0.626	0.657	0.448
5	0.8235	0.4958	0.645	0.607	0.634	0.445
5.5	0.8337	0.5274	0.619	0.587	0.61	0.44
6	0.8392	0.5551	0.594	0.568	0.587	0.434
6.5	0.8411	0.5789	0.57	0.548	0.565	0.426
7	0.84	0.5989	0.548	0.53	0.544	0.418
7.5	0.8364	0.6156	0.527	0.511	0.524	0.409
8	0.8304	0.6291	0.507	0.494	0.505	0.4
8.5	0.8237	0.6397	0.489	0.477	0.487	0.391
9	0.8153	0.6478	0.471	0.461	0.47	0.382
9.5	0.8062	0.6536	0.455	0.446	0.453	0.372
10	0.7963	0.6575	0.439	0.432	0.438	0.363

Tables 10-39 and 10-40; and A in Tables 10-41 and 10-42. These regional deposition fractions are shown plotted in Figures 10-37, 10-38, and 10-39, respectively. The top panel in each figure represents the deposition fractions for the relatively monodisperse aerosol (σ_g = 1.3) and the bottom panel represents the more polysdisperse aerosol (σ_g = 2.4). Note that the y-axis scale changes from one panel to the other and from figure to figure.

TABLE 10-38. EXTRATHORACIC DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS (σ_g=2.4) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.1638	0.0566	0.127	0.224	0.144	0.166
0.6	0.1997	0.0698	0.166	0.263	0.182	0.188
0.7	0.234	0.0837	0.204	0.297	0.218	0.207
0.8	0.2666	0.0978	0.24	0.328	0.251	0.225
0.9	0.2971	0.112	0.274	0.354	0.281	0.24
1	0.3257	0.1261	0.304	0.378	0.309	0.254
1.5	0.4419	0.1925	0.421	0.459	0.412	0.305
2	0.5238	0.2499	0.489	0.501	0.472	0.336
2.5	0.5822	0.2985	0.528	0.523	0.506	0.354
3	0.6244	0.3395	0.547	0.532	0.524	0.365
3.5	0.6551	0.3741	0.555	0.533	0.532	0.371
4	0.6775	0.4035	0.555	0.529	0.533	0.373
4.5	0.6937	0.4284	0.551	0.523	0.529	0.374
5	0.7053	0.4496	0.543	0.515	0.523	0.372
5.5	0.7133	0.4678	0.534	0.505	0.515	0.369
6	0.7187	0.4833	0.524	0.495	0.506	0.365
6.5	0.722	0.4966	0.513	0.485	0.496	0.361
7	0.7237	0.5081	0.501	0.475	0.486	0.356
7.5	0.7241	0.5179	0.49	0.464	0.475	0.352
8	0.7235	0.5263	0.478	0.454	0.465	0.346
8.5	0.7221	0.5337	0.467	0.444	0.455	0.341
9	0.7202	0.5399	0.456	0.434	0.445	0.336
9.5	0.7177	0.5453	0.445	0.424	0.435	0.33
10	0.7148	0.5499	0.435	0.415	0.425	0.325

As discussed in Section 10.5, polydisperity tends to blund or smear the regional deposition across the range of particles. The interspecies differences in fractional deposition are readily apparent from these figures. The data in Tables 10-37 through 10-42 or from Figures 10-37 through 10-39 can be used to calculate the fractional deposition term, i.e., $F_r(A)/F_r(H)$ in Equation 10-51 in order to calculate an $RDDR_r$.

TABLE 10-39. TRACHEOBRONCHIAL DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS (σ_g=1.3) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.017	0.0176	0.073	0.061	0.057	0.048
0.6	0.0164	0.0172	0.083	0.07	0.067	0.049
0.7	0.0168	0.0182	0.092	0.077	0.076	0.05
0.8	0.018	0.0198	0.098	0.082	0.083	0.05
0.9	0.02	0.0226	0.101	0.085	0.088	0.051
1	0.0216	0.0258	0.1	0.088	0.091	0.05
1.5	0.0328	0.0478	0.061	0.085	0.08	0.048
2	0.042	0.0744	0.025	0.073	0.056	0.045
2.5	0.0475	0.1008	0.01	0.061	0.038	0.041
3	0.0498	0.1246	0.005	0.05	0.025	0.037
3.5	0.0499	0.1443	0.002	0.041	0.018	0.034
4	0.0487	0.1594	0.001	0.034	0.013	0.031
4.5	0.0466	0.1702	0.001	0.028	0.009	0.028
5	0.044	0.1766	0	0.024	0.007	0.026
5.5	0.0412	0.1792	0	0.02	0.005	0.024
6	0.0385	0.1785	0	0.017	0.004	0.022
6.5	0.0356	0.1753	0	0.015	0.003	0.02
7	0.033	0.1703	0	0.013	0.002	0.019
7.5	0.0306	0.1636	0	0.011	0.002	0.017
8	0.0281	0.1559	0	0.01	0.001	0.016
8.5	0.0259	0.1476	0	0.009	0.001	0.015
9	0.0238	0.139	0	0.008	0.001	0.014
9.5	0.0221	0.1305	0	0.007	0.001	0.013
10	0.0202	0.1219	0	0.006	0.001	0.012

In the TB region, Figure 10-38 illustrates that at the smaller particle diameters (MMAD < 2 μm) the laboratory animal species have higher deposition fractions than humans. As expected, these differences are more pronounced for the smaller diameter and more monodisperse aerosol (0.5 μm MMAD and σ_g = 1.3). At the larger particle diameters (MMAD > 2.5 μm for σ_g = 1.3), the laboratory animal species have very litte deposition

TABLE 10-40. TRACHEOBRONCHIAL DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS (σ_g=2.4) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.026	0.0319	0.06	0.055	0.051	0.045
0.6	0.0258	0.0342	0.062	0.059	0.055	0.045
0.7	0.0263	0.0374	0.062	0.061	0.057	0.045
0.8	0.0268	0.0409	0.061	0.063	0.058	0.045
0.9	0.0276	0.0448	0.06	0.064	0.058	0.045
1	0.0284	0.0488	0.058	0.065	0.058	0.045
1.5	0.0322	0.0681	0.048	0.063	0.054	0.042
2	0.0348	0.0838	0.039	0.058	0.047	0.04
2.5	0.036	0.0957	0.031	0.053	0.041	0.037
3	0.0363	0.1042	0.025	0.048	0.035	0.034
3.5	0.036	0.1099	0.021	0.043	0.031	0.032
4	0.0352	0.1137	0.017	0.039	0.027	0.03
4.5	0.0345	0.1156	0.014	0.036	0.023	0.028
5	0.0333	0.1165	0.012	0.032	0.02	0.026
5.5	0.0322	0.1163	0.01	0.03	0.018	0.025
6	0.0311	0.1155	0.008	0.027	0.016	0.023
6.5	0.03	0.114	0.007	0.025	0.014	0.021
7	0.0288	0.1123	0.006	0.023	0.013	0.02
7.5	0.0276	0.1103	0.005	0.021	0.011	0.019
8	0.0266	0.1079	0.005	0.02	0.01	0.018
8.5	0.0255	0.1055	0.004	0.018	0.009	0.017
9	0.0244	0.1029	0.004	0.017	0.008	0.016
9.5	0.0235	0.1003	0.003	0.016	0.008	0.016
10	0.0225	0.0977	0.003	0.015	0.007	

due to the lack of inhalability of these particle diameters. This may help to explain why larger exposure concentrations have exhibited little effect in some bioassays.

The information in Tables 10-37 through 10-42 and depicted in Figures 10-37 through 10-39, can be used to calculate the deposition fraction term in Equation 10-48. The average ventilation rates and parameters such as surface area to use for normalizing factors for laboratory animals are found in Table 10-20. Respiratory tract region surface areas for

TABLE 10-41. ALVEOLAR DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS (σ_g=1.3) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.0769	0.0799	0.005	0.083	0.03	0.279
0.6	0.0842	0.0892	0.011	0.094	0.05	0.259
0.7	0.093	0.1008	0.02	0.102	0.072	0.242
0.8	0.1023	0.1135	0.032	0.107	0.097	0.227
0.9	0.1112	0.1267	0.046	0.11	0.121	0.213
1	0.1194	0.1398	0.063	0.11	0.142	0.201
1.5	0.1459	0.198	0.099	0.094	0.166	0.154
2	0.1504	0.2368	0.056	0.071	0.113	0.122
2.5	0.1415	0.2556	0.024	0.052	0.066	0.099
3	0.1262	0.2576	0.011	0.038	0.038	0.081
3.5	0.1089	0.2475	0.005	0.028	0.023	0.068
4	0.092	0.2295	0.002	0.021	0.014	0.058
4.5	0.0767	0.2071	0.001	0.016	0.009	0.049
5	0.0634	0.183	0.001	0.012	0.006	0.042
5.5	0.052	0.159	0	0.009	0.004	0.037
6	0.0425	0.1364	0	0.007	0.003	0.032
6.5	0.0347	0.1158	0	0.006	0.002	0.029
7	0.0283	0.0975	0	0.005	0.001	0.025
7.5	0.023	0.0815	0	0.004	0.001	0.023
8	0.0187	0.0679	0	0.003	0.001	0.02
8.5	0.0153	0.0563	0	0.002	0.001	0.018
9	0.0124	0.0466	0	0.002	0	0.016
9.5	0.0102	0.0384	0	0.002	0	0.015
10	0.0083	0.0317	0	0.001	0	0.014

humans are found in Table 10-19. The human male adult general population activity pattern in Table 10-20 corresponds to 19.9 m^3/day. This is the average ventilation rate that was used to run the LUDEP® simulations and would be used in the denominator of Equation 10-48. The normal augmenter or mouth breather deposition fractions found in Tables 10-37 through 10-42 represents the sum of the Fr_H factors in the denominator of the

TABLE 10-42. ALVEOLAR DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS (σ_g=2.4) IN VARIOUS LABORATORY SPECIES AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"

MMAD	Normal Augmenter	Mouth Breather	Rat	Mouse	Hamster	Guinea Pig
0.5	0.1041	0.1195	0.022	0.07	0.054	0.273
0.6	0.1047	0.1252	0.026	0.073	0.062	0.254
0.7	0.1061	0.1317	0.3	0.075	0.069	0.238
0.8	0.1078	0.1384	0.033	0.076	0.074	0.224
0.9	0.1093	0.1447	0.035	0.077	0.078	0.212
1	0.1105	0.1506	0.036	0.076	0.08	0.201
1.5	0.1124	0.1709	0.038	0.07	0.082	0.16
2	0.1089	0.179	0.035	0.061	0.075	0.133
2.5	0.1028	0.1794	0.031	0.053	0.067	0.113
3	0.0957	0.1753	0.027	0.046	0.058	0.097
3.5	0.0885	0.1687	0.023	0.04	0.051	0.085
4	0.0815	0.1608	0.02	0.035	0.044	0.076
4.5	0.0749	0.1523	0.017	0.031	0.039	0.068
5	0.0689	0.1438	0.015	0.027	0.034	0.061
5.5	0.0634	0.1354	0.013	0.024	0.03	0.055
6	0.0583	0.1273	0.011	0.022	0.026	0.05
6.5	0.0538	0.1196	0.01	0.02	0.023	0.046
7	0.0496	0.1123	0.009	0.018	0.021	0.042
7.5	0.0459	0.1055	0.008	0.016	0.018	0.039
8	0.0424	0.0991	0.007	0.014	0.016	0.036
8.5	0.0393	0.0932	0.006	0.013	0.015	0.034
9	0.0365	0.0876	0.005	0.012	0.013	0.032
9.5	0.034	0.0824	0.005	0.011	0.012	0.03
10	0.0316	0.0776	0.004	0.01	0.011	0.028

expression found in Equation 10-48. Likewise, the deposition fractions for the various species represent the Fr_A factor.

If Equation 10-48 is used to calculate deposited dose with the tracheobronchial surface area as the normalizing factor, a $RDDR_{TB[ACT]}$ of 9.39 is calculated for a rat exposed to an aerosol with a 0.5 μm MMAD and σ_g of 1.3. The $RDDR_{TB[ACT]}$ calculated for the guinea pig exposed to the same aerosol is 0.79. This factor could be used to adjust an exposure

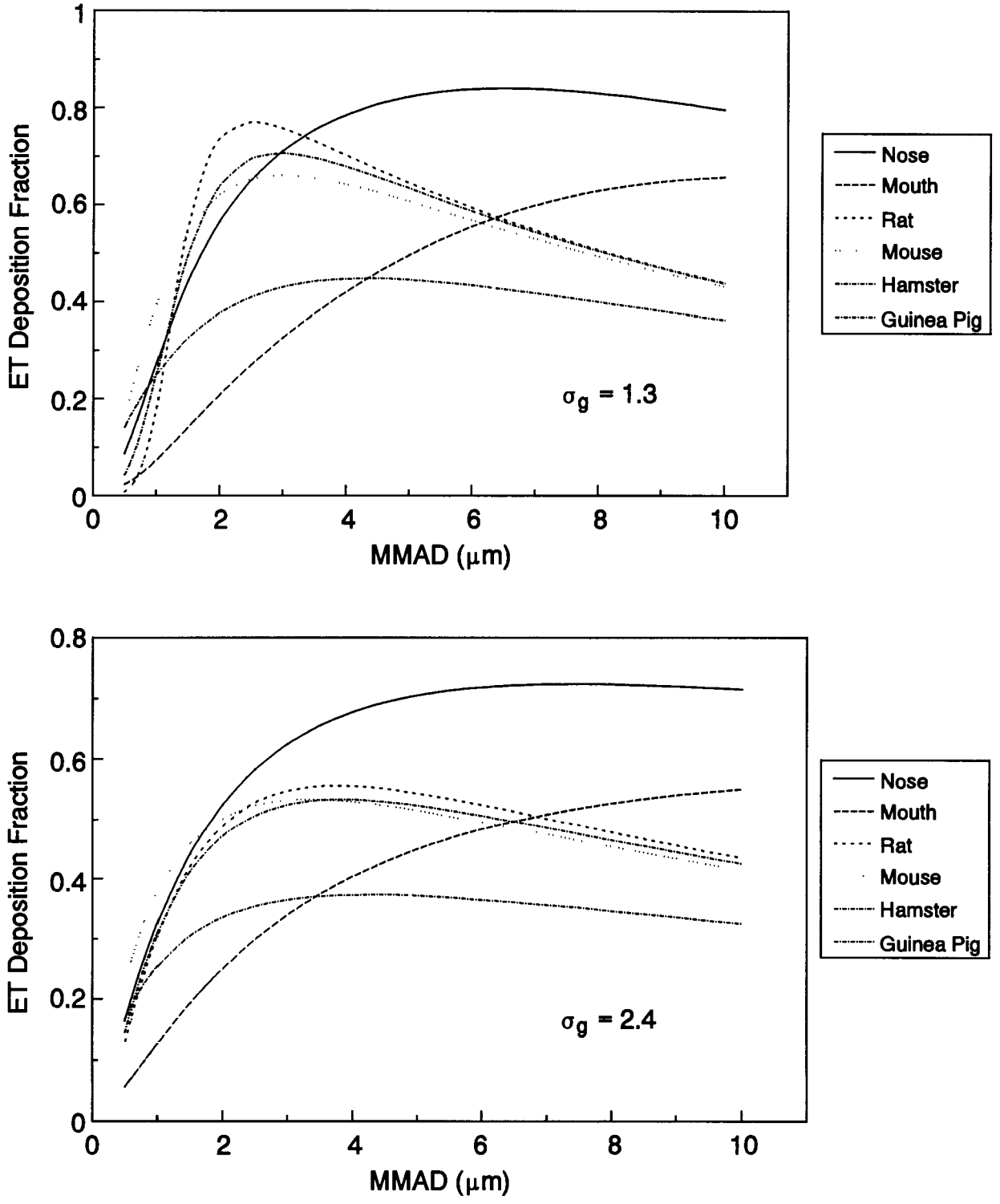

Figure 10-37. Predicted extrathoracic deposition fractions versus MMAD of inhaled monodisperse (σ_g = 1.3) aerosols shown in top panel or polydisperse (σ_g = 2.4) aerosols shown in bottom panel.

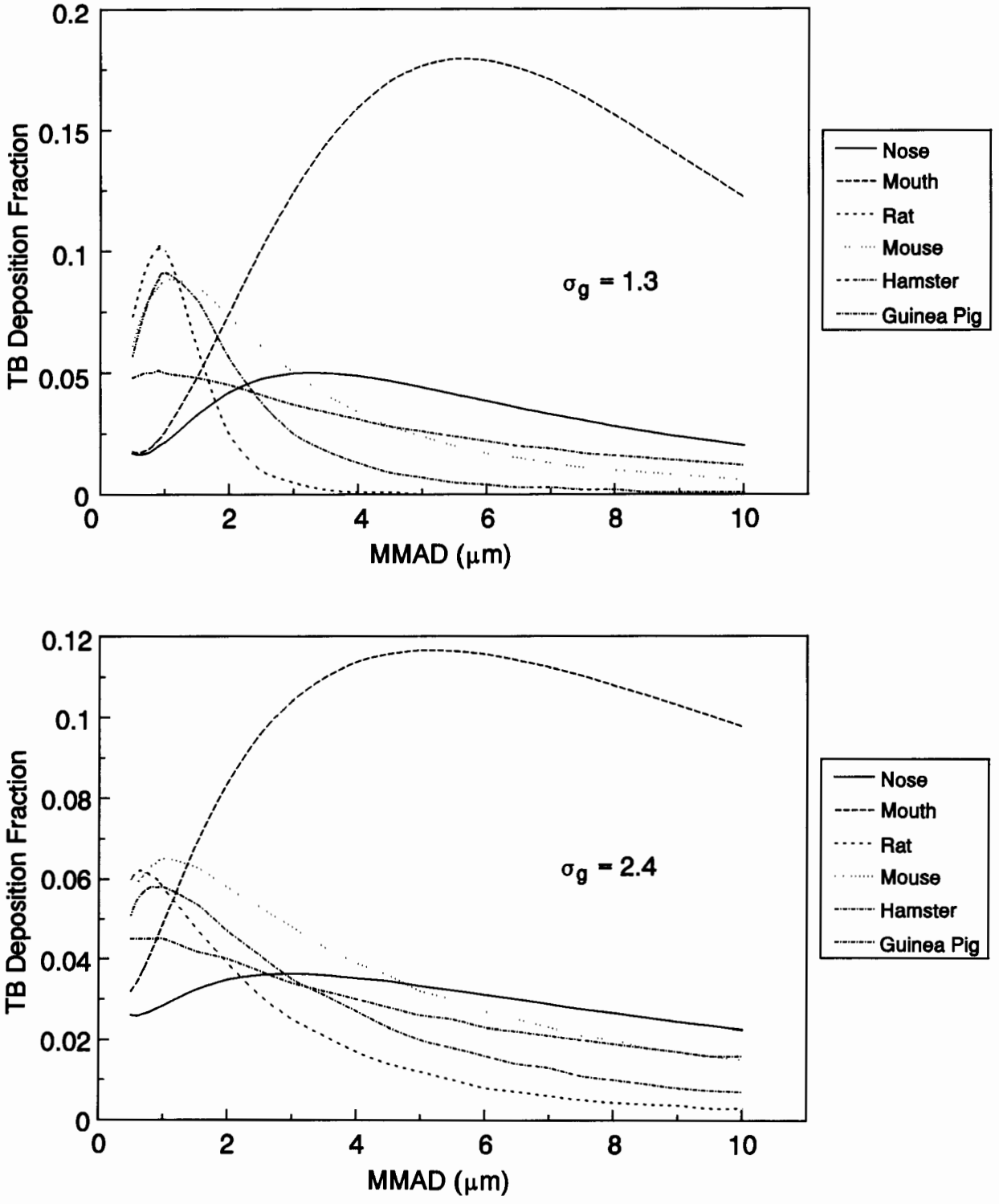

Figure 10-38. Predicted tracheobronchial deposition fractions versus MMAD of inhaled monodisperse (σ_g = 1.3) aerosols shown in top panel or polydisperse (σ_g = 2.4) aerosols shown in bottom panel.

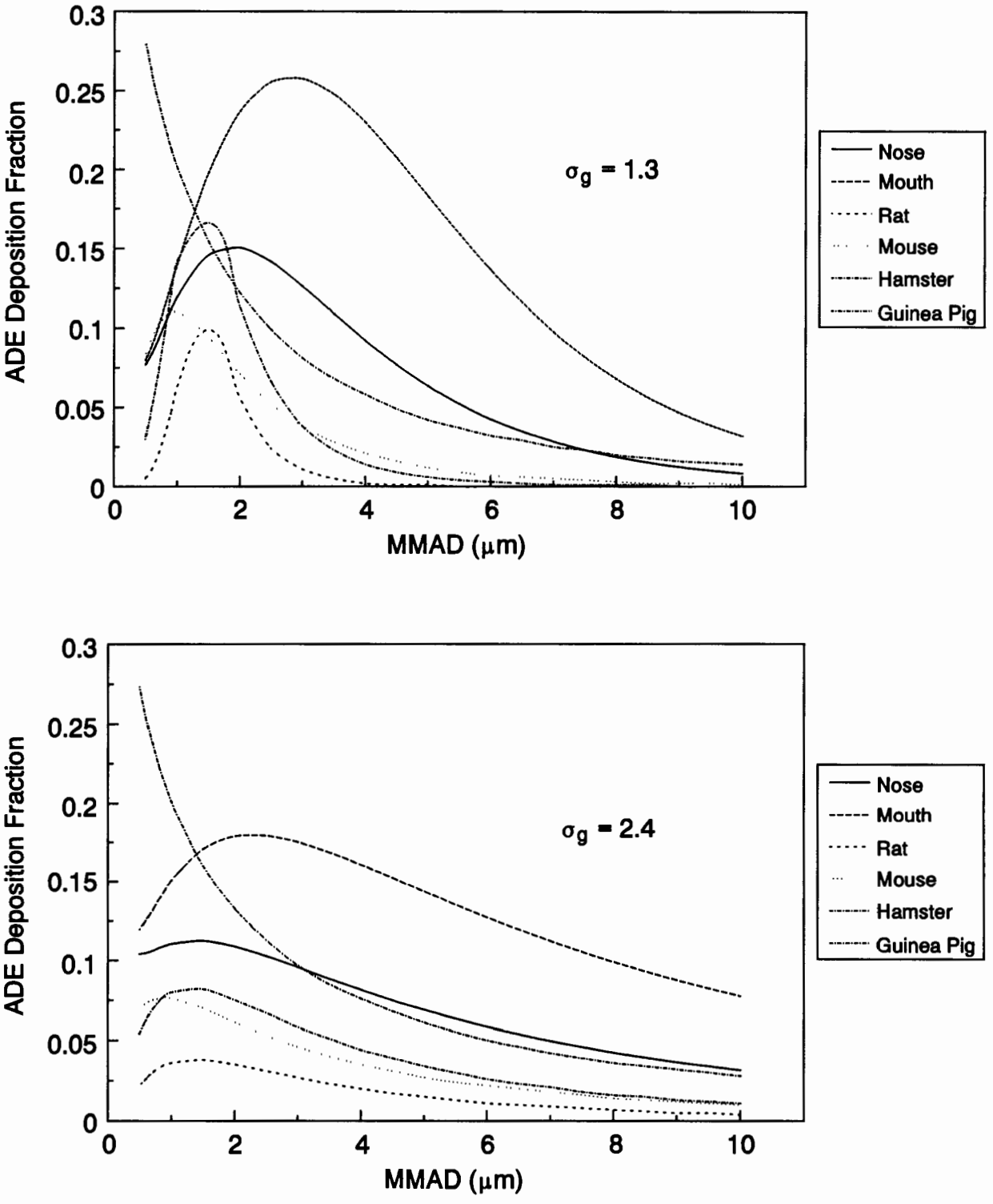

Figure 10-39. Predicted alveolar deposition fractions versus MMAD of inhaled monodisperse (σ_g = 1.3) aerosols shown in top panel or polydisperse (σ_g = 2.4) aerosols shown in bottom panel.

concentration to a human equivalent concentration using Equation 10-47. To illustrate, if a rat exhibited tracheobronchial effects when exposed to this aerosol at 100 $\mu g/m^3$, the predicted HEC would be 939 $\mu g/m^3$. This HEC would result in a similar tracheobronchial deposited dose and thereby a similar effect in humans, assuming species sensitivity to a given dose is equal. The HEC calculated from the guinea pig would be 79 $\mu g/m^3$. For an alveolar effect, the $RDDR_{A[ACT]}$ would be calculated. The $RDDR_{A[ACT]}$ for rat and guinea pigs is 0.19 and 4.5, respectively. Thus, although the two laboratory species were exposed to the same aerosol and same concentration, each received a very different deposited dose and when normalized for differences in surface areas, results in very different HEC values. Thus, taking into account species differences in dosimetry is necessary before comparing effective concentrations when interpreting toxicity data.

The impact of particle diameter and distribution as illustrated in Figures 10-37 through 10-39 is also reflected in calculated $RDDR_{r[ACT]}$ values. For an aerosol with a 2.55 μm MMAD and σ_g of 2.4, the $RDDR_{TB[ACT]}$ is 1.88 and 0.29 for the rat and guinea pig, respectively. The $RDDR_{A[ACT]}$ for this aerosol is 0.88 and 1.36 for rat and guinea pig, respectively.

10.7.5 Retained Dose Estimations

An important issue in inhalation toxicology is the relationship between repeated or chronic inhalation exposures and the resulting alveolar burdens of exposure material achieved in the human lung versus the lungs of laboratory animal species. It is generally assumed that the magnitude of the alveolar burden of particles produced during an inhalation exposure is an important determinant of biological responses to the inhaled particles. Therefore, understanding the basis for differences among species in alveolar burdens that will result from well-defined inhalation exposures will provide investigators with a better understanding of alveolar burdens that would result from exposures of various mammalian species to the same aerosol. Alternatively, the exposure conditions could be tailored for each species to produce desired alveolar burdens of particles.

Predictable deposition, retention, and clearance patterns are possible for acute inhalation exposures of laboratory animal species and humans. Repeated exposures also occur for humans and are used routinely in laboratory animals to study the inhalation toxicology of a

broad spectrum of potentially hazardous particulates. The predicted biokinetics of particles acutely inhaled can be readily extrapolated to repeated exposures. However, the predictions become increasingly questionable as exposure conditions deviate away from those used for acute inhalation exposures. The following predictions for repeated inhalation exposures are therefore intended to be comparative, rather than absolute, and were made using the assumption that physical clearance parameters for the A region are the same for acute and repeated inhalation exposures.

Deposition data for two different aerosols, one with an MMAD of 0.5 and σ_g of 1.3, the other with an MMAD of 2.55 and a σ_g = 2.4 were chosen to calculate total alveolar retention (Table 10-43). The aerosol with an MMAD of 0.5 um and σ_g of 1.3 was chosen as the smallest particle diameter for which the laboratory animal dosimetry model calculates fractional deposition and to represent a relatively monodisperse distribution. The aerosol with an MMAD of 2.55 um and a σ_g of 2.4 was chosen to approximate a hypothetical PM10 aerosol in which the PM2.5 to PM10 sample size cut ratio is 0.6 (Dockery and Pope).

Table 10-44 summarizes the common and specific parameters used for predicting alveolar burdens for exposures of humans and six laboratory animal species of the two different aerosols at a concentration of 50 μg particles/m^3. Exposures were assumed to take place 24 h/day at the average minute respiratory ventilation and deposition fractions presented in Tables 10-20, 10-41, and 10-42. Daily alveolar deposition was expressed in units of μg particles/g lung to normalize deposition rates among the species. Particle dissolution-absorption rates were varied; half-times of 10, 100, and 1000 days were used to simulate particles that are relatively soluble, moderately soluble, and poorly soluble. The A clearance parameters used for predicting the results of repeated exposures were the same as the ones used for predicting the consequences of acute inhalation exposures, and are given in Table 10-17. The clearance parameters as recommended by the ICRP (ICRP66, 1994) were used in the human model LUDEP® version 1.1 software.

Tables 10-45, 10-46, and 10-47 show the calculated alveolar particle burdens of the 0.5 um MMAD (σ_g = 1.3) aerosol in various laboratory animal species and an adult human normal augmenter for a general population activity pattern, assuming a particle dissolution-absorption half-time of 10, 100, and 1,000 days, respectively. Tables 10-48, 10-49, and 10-50 show the analogous calculated alveolar particle burdens for the 2.55 um MMAD (σ_g =

TABLE 10-43. FRACTION OF INHALED PARTICLES DEPOSITED IN THE ALVEOLAR INTERSTITIAL REGION OF THE RESPIRATORY TRACT FOR SELECTED MAMMALIAN SPECIES AND ADULT MALE HUMANS

Aerosol Parameters	Fraction of Aerosol Deposited in Alveolar Interstitial Region					
	Mouse[a]	Syrian Hamster[a]	Rat[a]	Guinea Pig[a]	Monkey and Dog[b]	Human[c]
0.5 μm MMAD, σ_g = 1.3	0.083	0.030	0.005	0.279	0.140	0.077
2.55 μm MMAD, σ_g = 2.4	0.053	0.067	0.031	0.113	0.099	0.102

[a]Values calculated using specified laboratory animal model (U.S. Environmental Protection Agency, 1994; Ménache et al., 1995)
[b]Adapted from Snipes (1989).
[c]From (ICRP 66, 1994) average for general population activity pattern (8 h sleeping, 8 h sitting, and 8 h light activity) for adult male "normal augmenter" (see Table 10-18).

TABLE 10-44. SUMMARY OF COMMON AND SPECIFIC INHALATION EXPOSURE PARAMETERS USED FOR PREDICTING ALVEOLAR BURDENS OF PARTICLES INHALED BY MICE, RATS, SYRIAN HAMSTERS, GUINEA PIGS, MONKEYS, DOGS,AND HUMANS

A. Common Parameters:

Exposure atmosphere	50 $\mu g/m^3$
Particle MMAD, σ_g	0.5 μm, 1.3; or 2.55 μm, 2.4
Particle dissolution-absorption half-time	10, 100, or 1,000 days
Chronic inhalation exposure pattern	24 h/day; 7 days/week
Duration of continuous exposure	4, 13, or 104 week

B. Specific Parameters: (Particle deposition rates in the alveolar region; data calculated using information in Tables 10-19 10-20, 10-41, and 10-42

Species	Daily Deposition of 0.5 μm MMAD, σ_g = 1.3 aerosol (μg)	Daily Deposition of 2.55 μm MMAD, σ_g = 2.4 aerosol (μg)
Mouse	0.263	0.168
Syrian Hamster	0.123	0.275
Rat	0.091	0.565
Guinea pig	5.75	2.33
Monkey	7.82	5.53
Dog	29.03	20.53
Human[a]	76.69	101.59

[a]Average general population activity pattern (8 h sleeping, 8 h sitting, and 8 h light acitivty) for adult male "normal augmenter" (See Table 10-19).

2.4) aerosol. Note the different patterns for accumulations of A burdens of particles for these species and the fact that significant A burdens of particles can be reached with exposures to relatively low aerosol concentrations of 50 $\mu g/m^3$.

The exposure concentration is representative of environmental ambient aerosols that have been recorded for numerous American and European cities. An important point to make is that the composition of the ambient aerosols vary from one place to another and constituents of the aerosols undoubtedly cover a broad range of solubilization and absorption characteristics. Therefore, the composition of the retained particles would be expected to

TABLE 10-45. ALVEOLAR PARTICLE BURDENS (ug) OF 0.5 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 10 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.239	0.111	0.082	5.321	26.865	7.239	74.117
7	1.289	0.591	0.437	29.988	151.007	40.689	418.245
14	1.964	0.891	0.659	47.677	239.440	64.517	664.755
21	2.321	1.044	0.772	58.191	291.582	78.566	811.018
28	2.511	1.124	0.831	64.478	322.508	86.899	895.653
35	2.613	1.166	0.862	68.256	340.942	91.866	953.172
50	2.701	1.201	0.888	72.062	359.311	96.816	1002.474
75	2.730	1.212	0.897	73.717	367.165	98.932	1018.908
91	2.733	1.213	0.897	73.948	368.244	99.223	1027.125
100	2.734	1.214	0.898	74.000	368.486	99.288	1027.125
150	2.735	1.214	0.898	74.058	368.752	99.360	1027.125
200	2.735	1.214	0.898	74.060	368.760	99.362	1027.125

TABLE 10-46. ALVEOLAR PARTICLE BURDENS (ug) OF 0.5 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 100 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.255	0.119	0.088	5.664	28.593	7.704	76.493
7	1.629	0.746	0.552	38.058	191.603	51.627	514.384
14	2.950	1.332	0.985	72.809	365.276	98.423	986.040
21	4.030	1.796	1.328	104.777	523.773	141.130	1413.324
28	4.920	2.169	1.604	134.364	669.266	180.333	1807.740
35	5.660	2.472	1.828	161.880	803.494	216.499	2177.505
50	6.865	2.951	2.183	214.956	1059.363	285.444	2867.733
75	8.138	3.439	2.543	289.211	1410.924	380.171	3804.471
91	8.661	3.634	2.688	329.340	1598.196	430.631	4297.491
100	8.891	3.719	2.751	349.791	1693.027	456.183	4544.001
150	9.675	4.007	2.964	441.072	2112.820	569.296	5603.994
200	10.038	4.141	3.063	503.913	2400.421	646.790	6310.656
300	10.335	4.253	3.146	577.372	2738.209	737.806	7099.488
400	10.437	4.293	3.175	612.519	2901.850	781.897	7461.036
500	10.478	4.309	3.187	629.338	2981.247	803.292	7633.593
600	10.495	4.315	3.192	637.387	3019.777	813.675	7707.546
700	10.503	4.318	3.194	641.240	3038.482	818.713	7740.415
730	10.504	4.318	3.194	641.941	3041.920	819.639	7748.631

TABLE 10-47. ALVEOLAR PARTICLE BURDENS (ug) OF 0.5 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 1,000 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.163	0.265	0.544	2.294	20.221	5.448	101.325
7	1.041	1.669	3.429	15.416	135.498	36.505	681.370
14	1.884	2.977	6.117	29.491	258.316	69.594	1306.140
21	2.574	4.016	8.250	42.440	370.403	99.792	1872.134
28	3.143	4.850	9.963	54.424	473.292	127.513	2394.590
35	3.615	5.526	11.353	65.570	568.216	153.085	2884.393
50	4.385	6.599	13.557	87.068	749.162	201.836	3798.690
75	5.198	7.689	15.797	117.145	997.162	268.816	5039.523
91	5.533	8.126	16.694	133.399	1130.214	304.497	5692.593
100	5.680	8.316	17.085	141.683	1197.277	322.565	6019.128
150	6.180	8.960	18.408	178.656	1494.147	402.546	7423.229
200	6.412	9.260	19.025	204.110	1697.533	457.341	8359.297
300	6.601	9.511	19.539	233.865	1936.410	521.699	9404.209
400	6.667	9.600	19.721	248.101	2052.134	552.875	9883.128
500	6.693	9.635	19.793	254.913	2108.282	568.003	10111.700
600	6.704	9.649	19.823	258.174	2135.530	575.345	10209.660
700	6.709	9.655	19.835	259.734	2148.758	578.908	10253.200
730	6.710	9.656	19.837	260.018	2151.188	579.562	10264.080

TABLE 10-48. ALVEOLAR PARTICLE BURDENS (ug) OF 2.55 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 10 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.153	0.249	0.511	2.155	18.998	5.118	98.178
7	0.823	1.322	2.717	12.147	106.789	28.771	554.021
14	1.255	1.992	4.092	19.312	169.327	45.619	880.556
21	1.483	2.335	4.797	23.570	206.201	55.554	1074.300
28	1.604	2.513	5.163	26.117	228.071	61.446	1186.411
35	1.669	2.607	5.355	27.647	241.108	64.958	1262.602
50	1.725	2.685	5.516	29.189	254.098	68.458	1327.909
75	1.744	2.710	5.568	29.859	259.652	69.954	1349.678
91	1.746	2.713	5.574	29.953	260.415	70.160	1360.563
100	1.746	2.714	5.575	29.974	260.586	70.206	1360.563
150	1.747	2.714	5.576	29.997	260.774	70.257	1360.563
200	1.747	2.714	5.576	29.998	260.780	70.258	1360.563

TABLE 10-49. ALVEOLAR PARTICLE BURDENS (ug) OF 2.55 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 100 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.256	0.119	0.088	5.699	28.772	7.753	76.665
7	1.669	0.765	0.566	39.010	196.386	52.916	525.888
14	3.083	1.391	1.029	76.220	382.346	103.023	1027.125
21	4.290	1.910	1.413	111.979	559.632	150.792	1503.711
28	5.330	2.346	1.735	146.550	729.638	196.601	1963.863
35	6.232	2.715	2.008	180.139	893.479	240.746	2407.581
50	7.805	3.340	2.471	249.492	1227.773	330.822	3311.451
75	9.678	4.058	3.001	359.296	1747.511	470.863	4691.907
91	10.558	4.386	3.244	426.805	2062.527	555.745	5513.607
100	10.976	4.541	3.358	464.016	2235.077	602.237	5965.542
150	12.661	5.160	3.816	662.547	3147.853	848.183	8299.170
200	13.731	5.555	4.109	849.273	4002.444	1078.449	10353.420
300	15.085	6.068	4.488	1192.050	5579.528	1503.390	14051.070
400	15.970	6.410	4.741	1498.060	7005.263	1887.541	17173.530
500	16.626	6.661	4.927	1771.281	8295.952	2235.325	19885.140
600	17.140	6.854	5.069	2015.240	9464.616	2550.219	22185.900
700	17.553	7.002	5.179	2233.069	10522.820	2835.362	24157.980
730	17.661	7.040	5.207	2293.754	10820.340	2915.512	24733.170

TABLE 10-50. ALVEOLAR PARTICLE BURDENS (ug) OF 2.55 μm MMAD AEROSOL ASSUMING PARTICLE DISSOLUTION—ABSORPTION HALF—TIME OF 1,000 DAYS.

	Species						
Days	Mouse	Hamster	Rat	Guinea Pig	Dog	Monkey	Human
1	0.164	0.267	0.548	2.308	20.347	5.482	101.552
7	1.066	1.710	3.513	15.801	138.881	37.417	696.608
14	1.969	3.110	6.389	30.873	270.388	72.847	1360.563
21	2.741	4.271	8.774	45.357	395.762	106.624	1991.864
28	3.405	5.245	10.775	59.360	515.986	139.015	2601.396
35	3.981	6.070	12.471	72.965	631.852	170.230	3189.158
50	4.986	7.469	15.345	101.057	868.258	233.922	4386.454
75	6.182	9.073	18.640	145.533	1235.807	332.945	6215.049
91	6.744	9.807	20.148	172.878	1458.580	392.964	7303.500
100	7.011	10.153	20.589	187.950	1580.605	425.838	7902.147
150	8.088	11.537	23.702	268.365	2226.103	599.746	10993.34
200	8.771	12.421	25.519	343.998	2830.453	762.566	13714.47
300	9.636	13.568	27.874	482.840	3945.738	1063.038	18612.49
400	10.201	14.332	29.444	606.789	4953.990	1334.670	22748.61
500	10.620	14.895	30.600	717.457	5866.741	1580.586	26340.49
600	10.949	15.325	31.483	816.273	6693.198	1803.245	29388.15
700	11.212	15.657	32.166	904.505	7441.539	2004.869	32000.43
730	11.281	15.741	32.339	929.085	7651.941	2061.542	32762.34

change with time and the accumulated A burdens would consist of the more persistent types of particles or constituents of particles present in ambient aerosols. The more soluble, and perhaps more toxic, constituents of the aerosols will be rapidly absorbed into the circulatory system, metabolized, excreted, or redeposited in body organs.

Species differences are more apparent for the smaller diameter and more monodisperse particle aerosol (0.5 um MMAD, σ_g = 1.3) than for the larger diameter and more polydisperse particle aerosol (2.55 um MMAD, σ_g = 2.4). At the longer dissolution-absorption half-times, more disparity occurs between hamsters and humans, while the mouse moves into closer proximity. Notably, the rat remains at lower alveolar particle burdens than the humans at all dissolution-absorption half-times.

A different relationship of alveolar particle burdens among species is evident in Figures 10-43, 10-44, and 10-45 for the larger diameter and more polydisperse aerosol (2.55 um MMAD, σ_g = 2.4). At short dissolution-absorption half-times, the rat and human have very similar alveolar particle burdens, with the rat having a slightly greater burden at an assumed dissolution-absorpton half-time of 10-days. At an assumed dissolution-absorption half-time of 100 days, both the hamster and rat have alveolar particle burdens that are less than that of humans. By 1000 days, the mouse alveolar particle burden is similar to but lower than the human burden and the rat and hamster burdens are considerably lower. The remaining species (monkey, dog, and and guinea pig), change relationships of alveolar particle burdens relative to each other but have consistently higher burdens than do humans across the assumed dissolution-absorption half-times.

Data in Tables 10-45, 10-46, and 10-47 were used together with the data in Table 10-20 to calculate the ug of particles per gram of lung tissue for each aerosol at each of the assumed particle dissolution-absorption half-life times. Figures 10-40, 10-41, and 10-42 show the alveolar particle burdens normalized to lung tissue weight (ug particles per g lung tissue) for the 0.5 um MMAD (σ_g = 1.3) aerosol assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively. Figures 10-43, 10-44, and 10-45 show the alveolar particle burdens normalized to lung tissue weight (ug particles per g lung tissue) for the 2.55 um MMAD (σ_g = 2.4) aerosol assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively.

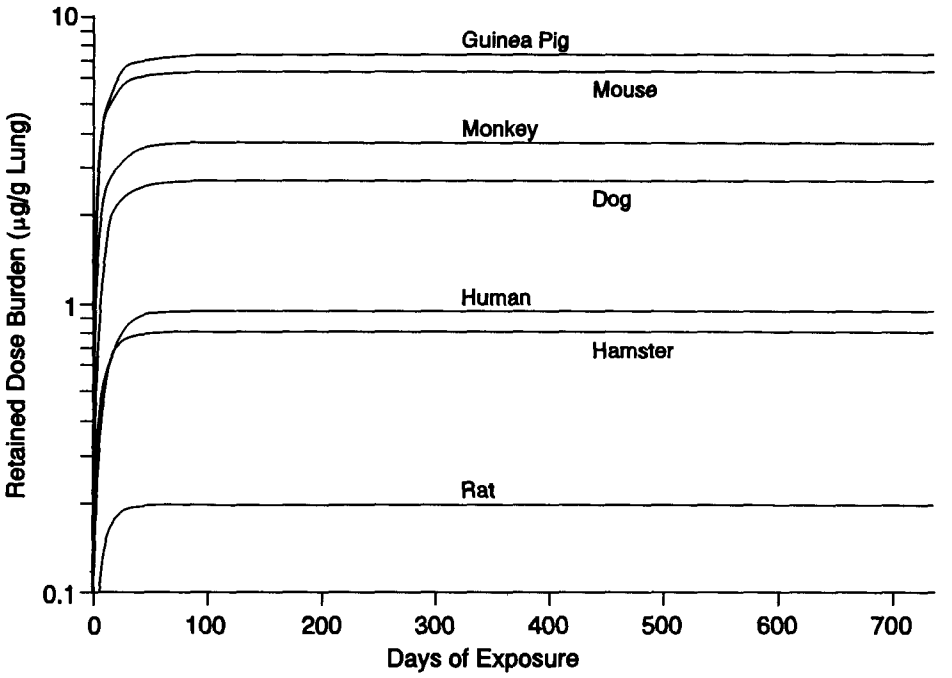

Figure 10-40. Predicted retained alveolar dose (ug/g lung) for 0.5 μm MMAD monodisperse (σ_g = 1.3) aerosol assuming a dissolution-absorption half-time of 10 days.

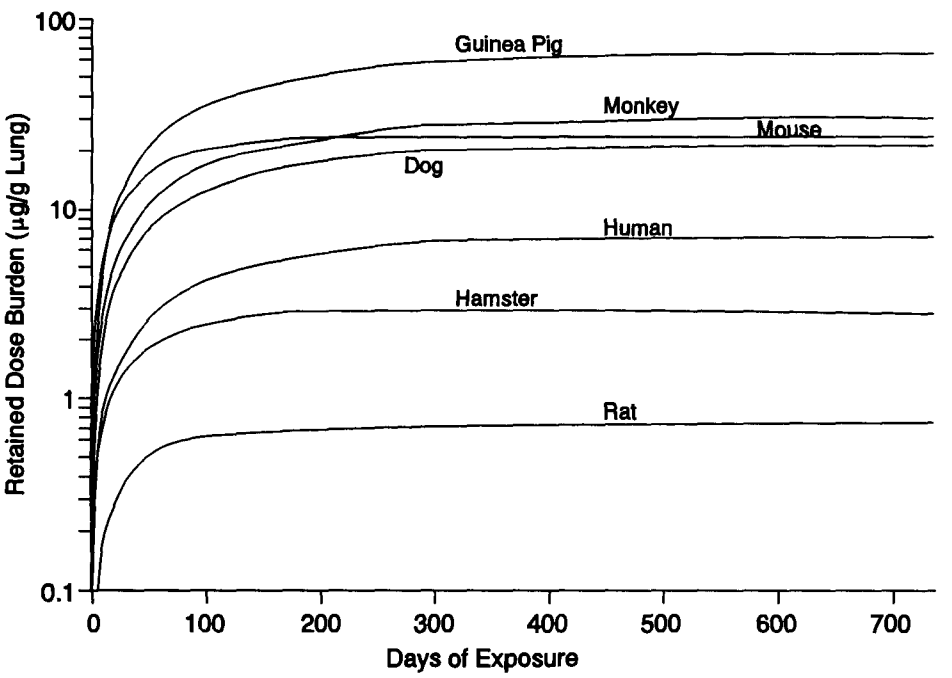

Figure 10-41. Predicted retained alveolar dose (ug/g lung) for 0.5 μm MMAD monodisperse (σ_g = 1.3) aerosol assuming a dissolution-absorption half-time of 100 days.

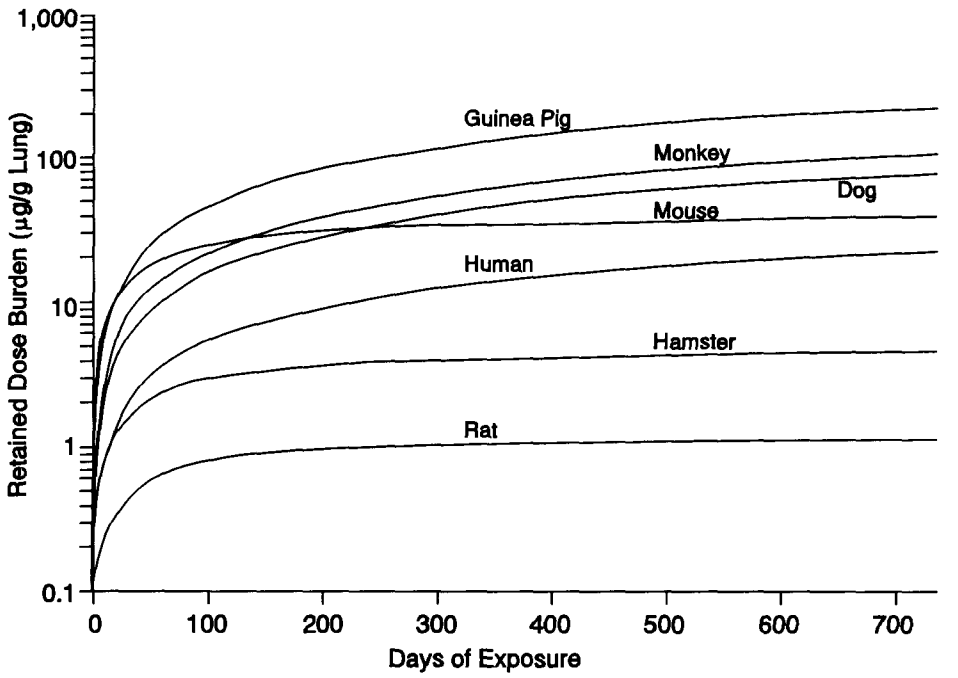

Figure 10-42. Predicted retained alveolar dose (ug/g lung) for 0.5 μm MMAD monodisperse (σ_g = 1.3) aerosol assuming a dissolution-absorption half-time of 1,000 days.

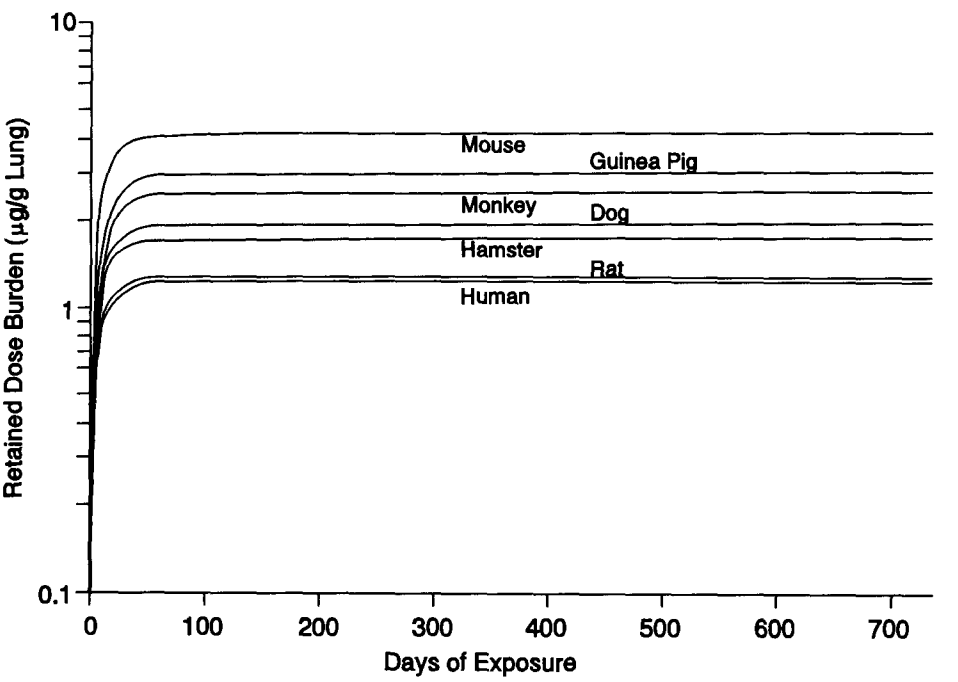

Figure 10-43. Predicted retained alveolar dose (ug/g lung) for 2.55 μm MMAD polydisperse aerosol (σ_g = 2.4) assuming a dissolution-absorption half-time of 10 days.

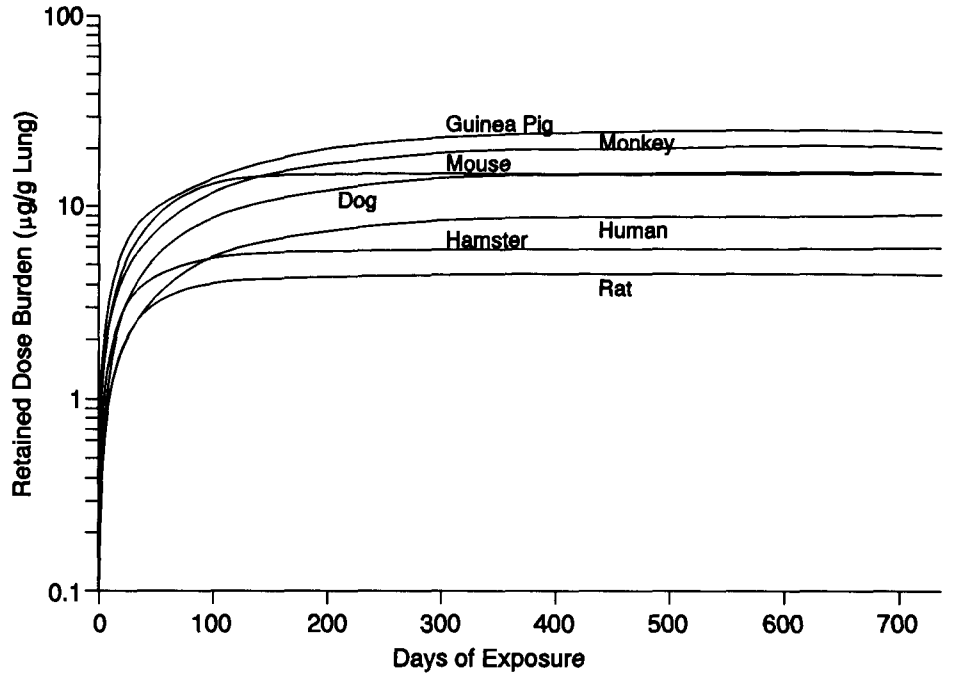

Figure 10-44. Predicted retained alveolar dose (ug/g lung) for 2.55 μm MMAD polydisperse aerosol (σ_g = 2.4) assuming a dissolution-absorption half-time of 100 days.

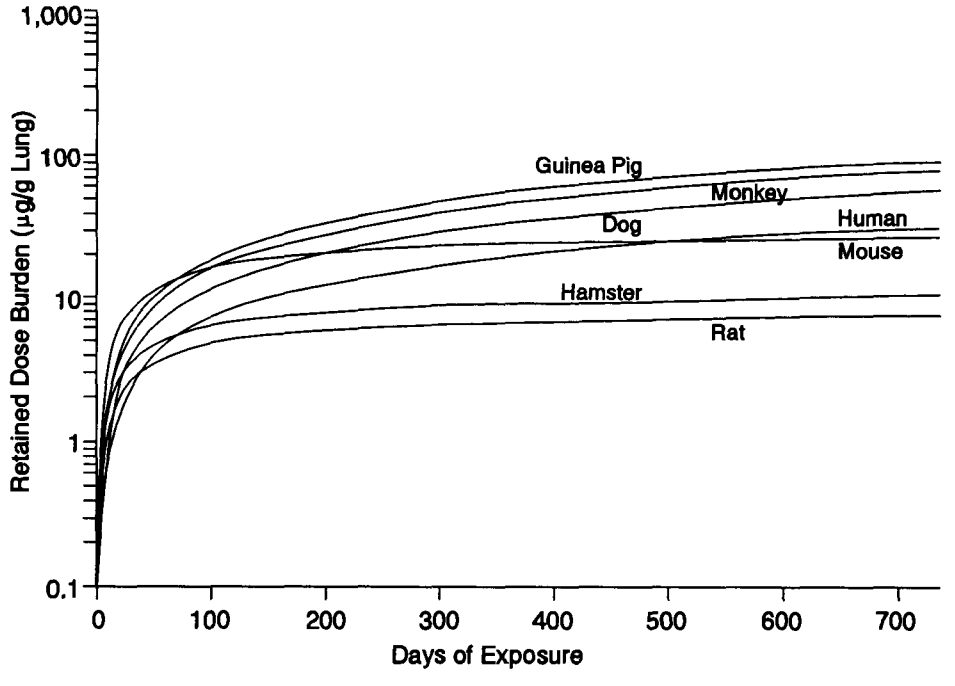

Figure 10-45. Predicted retained alveolar dose (ug/g lung) for 2.55 μm MMAD polydisperse aerosol (σ_g = 2.4) assuming a dissolution-absorption half-time of 1,000 days.

Figures 10-46, 10-47, and 10-48 show the alveolar retained dose ratios for both aerosols and assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively. Dose was normalized to lung tissue weight (ug particles per g lung tissue). These ratios could be calculated using Equation 10-52. Tables 10-45 through 10-50 provide the (AI_t) term. Tables 10-37 through 10-42 provide the (F_r) term. Normalizing factor data and ventilation rates for laboratory humans and laboratory animals are provided in Tables 10-19 and 10-20, respectively. These figures present the $RRDR_{A[ACT]}$ values that would be applied to a given concentration to calculate an HEC for each of seven species for these simulated continuous exposures. It is apparent that a substantial range of exposure concentrations would be required to produce the same specific A burdens in these mammalian species, and the exposure concentrations depend on the exposure protocol, or study duration. These results demonstrate the importance of understanding respiratory, deposition, and physical clearance parameters of humans and laboratory animals, as well as the dissolution-absorption characteristics of the inhaled particles. This combination of factors results in significant species differences in A accumulation patterns of inhaled particles during the course repeated or chronic exposures which must be considered in experiments designed to achieve equivalent alveolar burdens, or in evaluating the results of inhalation exposures of different mammalian species to the same aerosolized test materials.

These retained dose ratios are different than those predicted for deposited dose, reflecting both a difference in normalizing factor as well as differences in clearance rates and the dissolution-absorption characteristics of the inhaled particles. To illustrate, the predicted alveolar deposited dose ratio for the aerosol with a 0.5 μm MMAD and σ_g of 1.3 was 9.39 and 0.79 for the rat and guinea pig, respectively (see Section 10.7.4). If a dissolution-absorption half-time of 10 days is assumed for the same aerosol, the alveolar retained dose ratio is 0.22 and 7.84 for the rat and guinea pig, respectively. Assuming a more insoluble aerosol with a dissolution-half-time of 1,000 days results in a ratio of 0.49 and 2.76 for the rat and guinea pig, respectively. Again, this emphasizes the importance of understanding interspecies dosimetry and also of choosing a dose metric that is appropriate for the health effect or endpoint of interest since the magnitude and direction of interspecies differences also depends on the normalizing factors chosen.

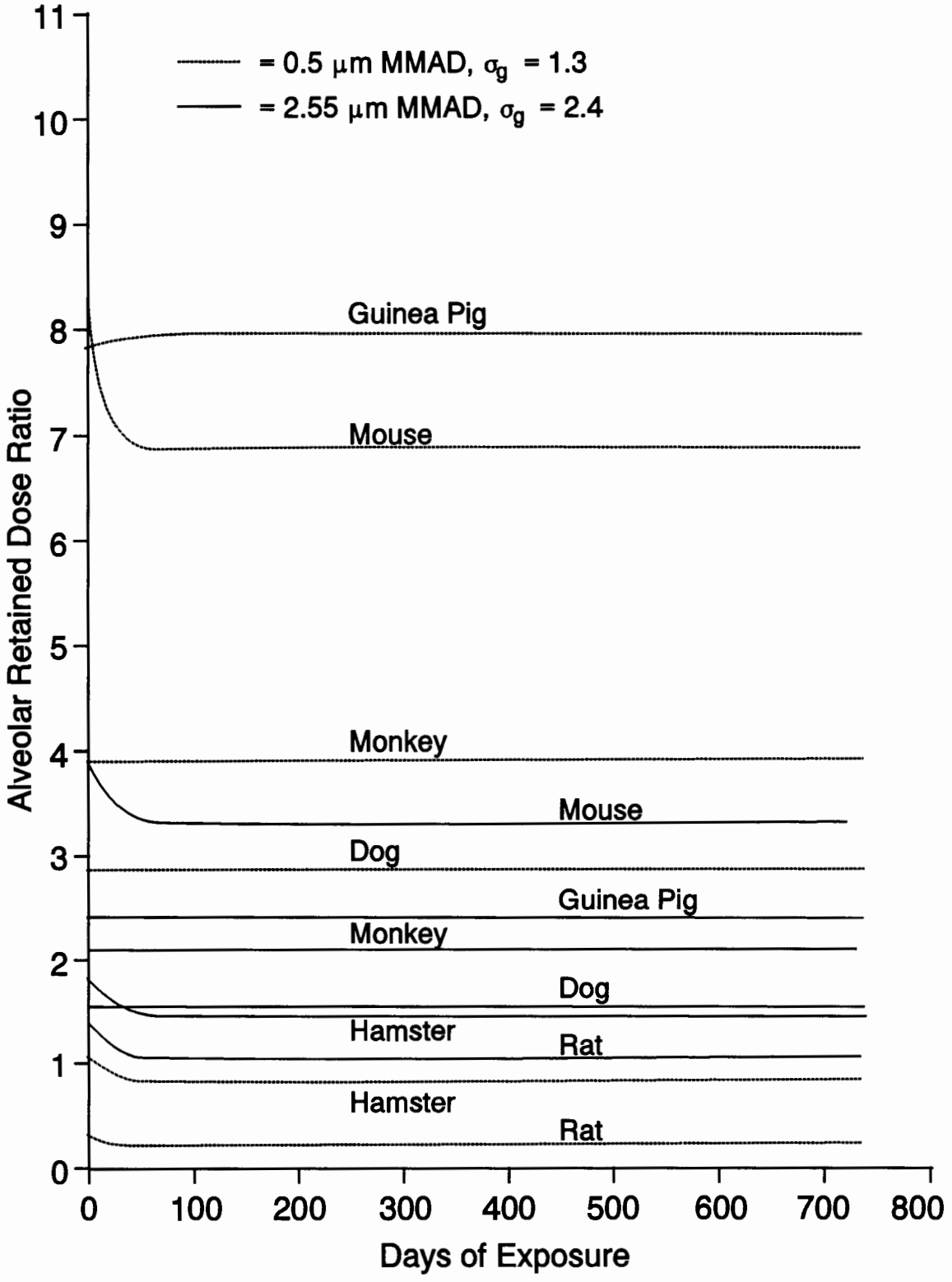

Figure 10-46. Predicted alveolar region retained dose ratios in various laboratory animals versus humans of 0.5 μm MMAD monodisperse (σ_g = 1.3) and 2.55 μm MMAD polydisperse (σ_g = 2.4) aerosols assuming a dissolution-absorption half-time of 10 days.

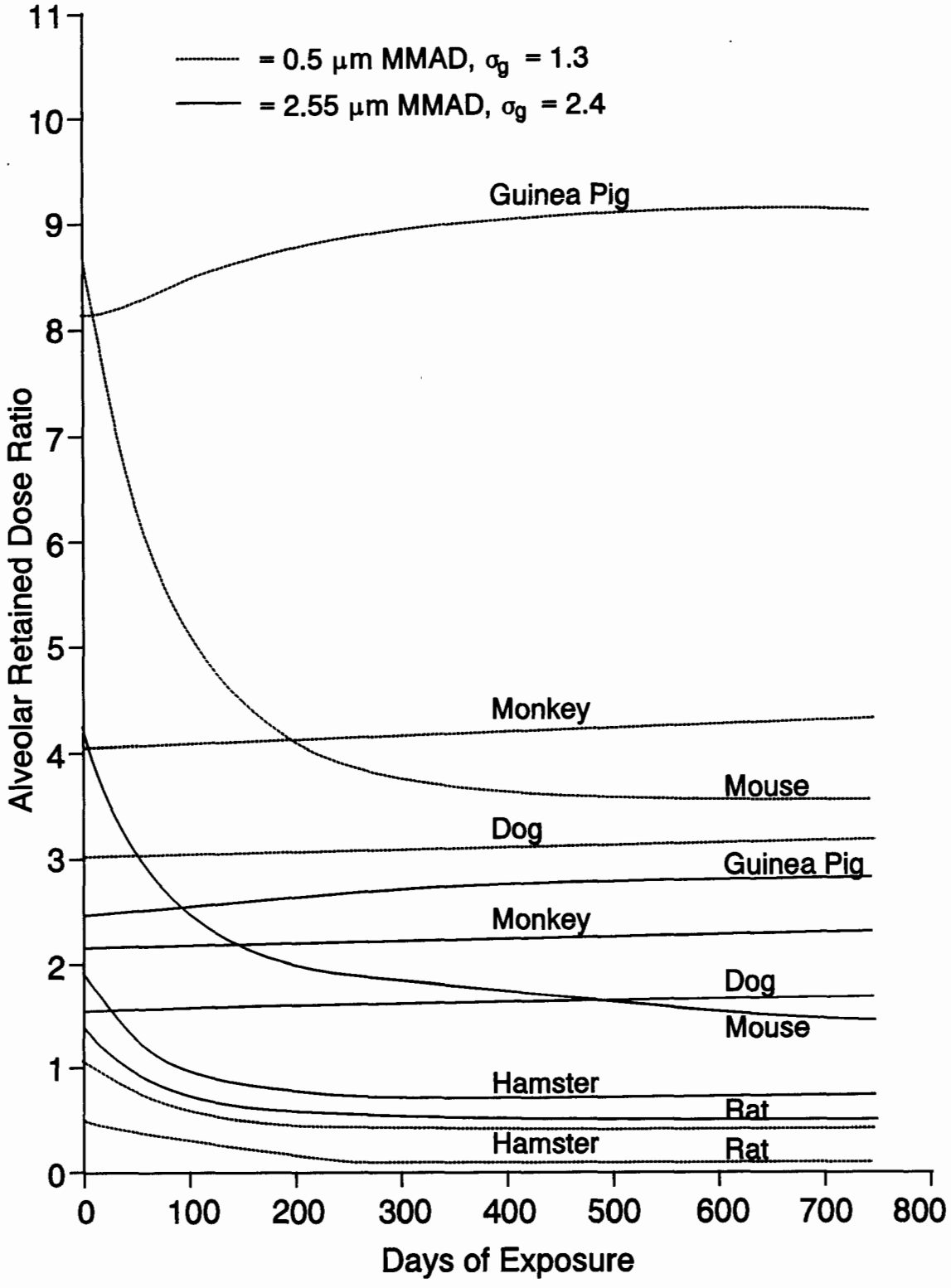

Figure 10-47. Predicted alveolar region retained dose ratios in various laboratory animals versus humans of 0.5 μm MMAD monodisperse (σ_g = 1.3) and 2.55 μm MMAD polydisperse (σ_g = 2.4) aerosols assuming a dissolution-absorption half-time of 100 days.

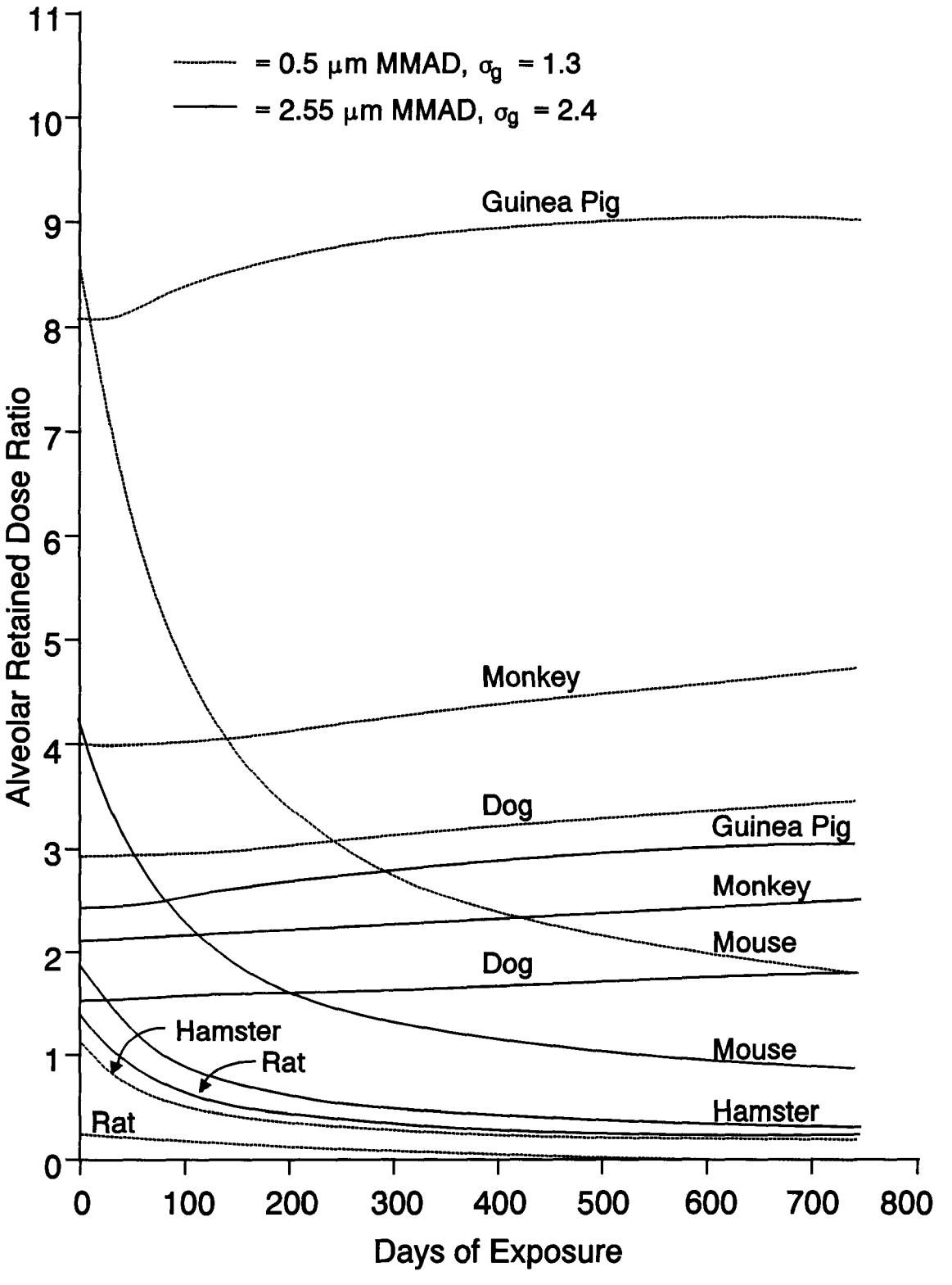

Figure 10-48. Predicted alveolar region retained dose ratios in various laboratory animals versus humans of 0.5 μm MMAD monodisperse (σ_g = 1.3) and 2.55 μm MMAD polydisperse (σ_g = 2.4) aerosols assuming a dissolution-absorption half-time of 1,000 days.

10.7.6 Summary

The dosimetry modeling exercise in this section has emphasized the importance of accounting for major determinants of particle deposition and clearance in order to calculate inhaled doses (either deposited or retained) that account for both within species and interspecies differences. For example, mouth breathing alters the deposition fraction of typical ambient aerosols in the tracheobronchial and alveolar regions when compared to nasal breathing. The differences in deposition between activity patterns emphasizes the need to take into account differences in ventilation rate and morphometry between the genders and at different ages. Since the LUDEP® version 1.1 software only allows simulation for adult male humans, these calculations await the next version. The ICRP has demonstrated differences between children of 1 year and adults across particles ranging from AMTD to AMAD of approximately 2.5-fold in the BB region and 2-fold in the alveolar region ICRP66, 1994). Differences in ventilation and morphometry as a consequence of disease can also be expected.

The various species used in inhalation toxicology studies that serve as the basis for exposure-dose-response assessment do not receive identical doses in a comparable respiratory tract region when exposed to the same aerosol. Such interspecies differences are important because the adverse toxic effect is likely more related to the quantitative pattern of deposition within the respiratory tract than to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose but also the specific pathways by which the inhaled material is cleared and redistributed. Thus, accounting for differences in dosimetry can change the apparent effect levels among species. To illustrate, for the same aerosol of 0.5 μm MMAD and σ_g of 1.3 at an exposure concentration of 100 $\mu g/m^3$, using deposition normalized to surface area for an effect observed in the tracheobronchial region, a human equivalent exposure concentration would be 939 $\mu g/m^3$ and 79 $\mu g/m^3$ based on rat versus guinea pig, respectively. This assumes the same sensitivity in humans to the deposited dose per surface area as in the rat or guinea pig. However, for chronic exposures to the same aerosol at the same concentration (100 $\mu g/m^3$), assuming it is relatively insoluble (i.e., assuming a dissolution-absorption half-time of 1,000 days), and based on a particle burden per gram of lung tissue, a human equivalent exposure concentration would be predicted as 22 $\mu g/m^3$ or 784 $\mu g/m^3$ based on the rat and guinea pig, respectively.

These examples show that relevance of a particular animal model should be considered together with dosimetry and the appropriateness of the metric for a given health endpoint. In general, the objective should be to provide a metric that may is mechanistically-motivated by the observed health effect of interest for extrapolation.

Smaller particle diameters have shown higher mass burdens of particle deposition in the TB region and of retained particle burden in the A region. This calls attention to the need for additional calculations based on particle number or surface area burdens. Considering that the bronchiolar region of the lung has a much smaller surface area than the alveolar region (factor of ≈ 170) the deposition of numbers of particles/unit surface area is ≈ 50 times higher in the bronchiolar region versus the alveolar region. This could indicate that the target site for reactive small particles may be the bronchiolar region, where subsequent particle-induced reactions may lead to impairment of breathing, thereby increasing symptoms which already may be present in persons with a compromised respiratory system like in COPD patients.

Dosimetry modeling can address important mechanistic factors of particle deposition and clearance including the aerosol particle diameter and distribution, intra and interspecies differences in deposition as as function of ventilation and morphometry, and intra and interspecies differences in clearance rates. Use of dosimetry modeling and judicious choice of appropriate dose metrics should be used to interpret the observed health effects data related to PM_{10} exposures. Predictions in this chapter were based on the use of mass as the exposure metric. Recent data suggest that particle number, or possibly particle surface area, may be a more appropriate exposure metric because the fine mode aerosols are small in mass but have extremely high concentrations of particle numbers. Also, normalizing factors such as number of alveoli or number of macrophages may be more appropriate for certain pathogenesis mechanisms. Creating these dose metrics for various species will depend on the availability of morphometric information.

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11. TOXICOLOGICAL STUDIES OF PARTICULATE MATTER

11.1 INTRODUCTION

This chapter reviews the results of exposure to PM in controlled human clinical studies, selected occupational studies, and animal toxicology studies. It focuses on those studies published since the 1982 PM Criteria Document (CD) (U.S. Environmental Protection Agency, 1982), which was the last PM CD to describe animal toxicology studies.

Particulate matter is a broad term that encompasses thousands of chemical species, many of which have not been investigated in controlled animal or human studies. However, even a full discussion of all the types of particles that have been studied is well beyond the scope of this chapter. Thus, criteria were used to select topics for presentation. High priority was placed on studies that (1) may elucidate or extend knowledge of the health effects of large portions of PM (e.g., sulfates, carbon), (2) that may contribute to enhanced understanding of the epidemiological studies (e.g., real-world particles; "surrogate" particles, defined as particles with low inherent toxicity that may cause effects due to their generic nature as a particle, such as their ultrafine size), or (3) that are ubiquitous. Although the latter is a criterion from the Clear Air Act, such widespread exposures also serve to increase public health interest. From these criteria, full summaries of acid aerosols, ultrafine particles, real-world particles, and "surrogate" particles are provided. Diesel exhaust particles generally fit the criteria, but because they are described in great detail elsewhere (U.S. Environmental Protection Agency, 1994), they are only summarized briefly here. Likewise, silica (U.S. Environmental Protection Agency, 1994) is only briefly presented. Diesel particles also differ from other particles in this classification because they are regulated pursuant to mobile source sections of the Clear Air Act (g/mi emission standards), although there is still a relationship of these regulations to the PM_{10} standard. Medium priority was placed on particles with high inherent toxicity that are of concern primarily because of point source emissions and more local exposures (as contrasted to ubiquitous pollutants). Metals having air concentrations greater than 1 ng/m^3 were placed in this class. Asbestos was also put in this class. The health effects of particles in this prioritization class

are summarized far more briefly here. It must be emphasized that this prioritization is not related to a judgement or decision about potency or health risk. For example, it should not be inferred that on an individual exposure basis, a "high priority" particle is of more inherent health concern than a "medium priority" particle. The split is primarily related to regulatory issues. The Clean Air Act requires a criteria document for criteria pollutants. Except for lead, individual metals are not criteria pollutants. Rather, they are regulated as hazardous air pollutants under the Clean Air Act. Thus, their inclusion here is only intended to be generally instructive because they can be part of the complex mixture of PM in the ambient air.

As noted above, lead is a criteria air pollutant, also regulated, like particulate matter, under Sections 108 and 109 of the Clean Air Act. Earlier extensive evaluations in Air Quality Criteria for Lead (U.S. Environmental Protection Agency, 1977) led to setting of the current National Ambient Air Quality Standard (primary as well as secondary) for lead at 1.5 $\mu g/m^3$ on a quarterly average basis (Federal Register, 1978 [PB-1910]). Subsequent to promulgation of that standard, the U.S. Environmental Protection Agency issued a revised Air Quality Criteria for Lead (1986) and a Supplement (U.S. Environmental Protection Agency, 1990). These and other such assessments found blood lead levels of 10 $\mu g/dl$ in young children and women of child bearing age (due to risk to the fetus in utero) to be associated with unacceptable risk of slowed prenatal and postnatal growth and neuropsychological development. Air levels below 0.50 to 0.75 $\mu g/m^3$ lead have been proposed as adequate to protect against such risk (World Health Organization, 1987). Typical ambient air levels of lead in U.S. urban areas almost invariably now fall below 0.10 to 0.25 $\mu g/m^3$. The reader is referred to the above-noted air quality criteria documents/supplement and Federal Register notices concerning the lead National Ambient Air Quality Standard for detailed information on particulate lead health effects.

Mixtures are important to understand because people are not exposed to single air pollutants, and the risks of the mixture can be different from those of the individual chemical. Little is known about mixtures, however. Most mixture studies involve two pollutants only. A significant exception to this is the body of work on the mutagenicity and carcinogenicity of particle-bound organics, which is also briefly summarized here, and on diesel emissions

The different nature of the data bases also influences the structure of the chapter. For example, community epidemiology studies that sought associations with some type of PM metric are described in Chapter 12 to permit full portrayal and integrated evaluation of the results. For the metals and diesel particles, included to reach a different goal, epidemiological studies are included here in Chapter 11 to facilitate a full hazard identification, and as appropriate, exposure-response information. Besides the summary of the effects portion of the literature, this chapter also attempts to identify and characterize key factors that may have significant influences on the health effects of PM.

Most of the investigations reported herein were conducted with animals, raising the question of their quantitative extrapolation to humans. Of the dosimetric and species sensitivity aspects of extrapolation, most is known about the former, which is presented in Chapter 10. Both Chapters 10 and 11 must be jointly considered for interpretation. For example, was one aerosol more toxic than another because it had a greater deposition in a sensitive lung target site or because it had higher potency?

Most of the animal toxicological and occupational epidemiological studies summarized here used very high particulate concentrations, relative to ambient, even when animal-to-human dosimetric differences are considered. This raises a question about the relevance of, for example, a rat study at 5,000 $\mu g/m^3$ in terms of direct extrapolation to humans in ambient exposure scenarios. In spite of these difficulties, the array of animal studies does illustrate certain toxicological principles for particles. To identify but a few here, the data base clearly shows that the site of respiratory tract deposition (and hence particle size) clearly influences the health outcome and that toxicity is dependent on the chemical species (e.g., cadmium is different from sulfuric acid, and cadmium chloride is different from cadmium oxide).

11.2 ACIDIC SULFATE PARTICLES

11.2.1 Controlled Human Exposure Studies of Acid Aerosols

11.2.1.1 Introduction

Human clinical exposure studies utilize controlled laboratory conditions to test responses to atmospheric pollutants. Advantages include the opportunity to study the species

of interest, humans, and the ability to carefully control the atmosphere with regard to pollutant concentration, aerosol characteristics, temperature, and relative humidity. Concentrations can be varied while other conditions are held constant to determine exposure-response relationships. Mixtures of pollutants or sequential exposures to different pollutants can be used to elucidate interactions.

Methods of inhalation used in clinical studies include mouthpiece, face mask, head-dome, and environmental chamber. Breathing through a mouthpiece alters breathing patterns, and bypasses the normal filtering and humidifying role of the nasal passages, thereby increasing delivery of particles to the lower airways. Environmental chamber and head-dome exposures allow the assessment of shifts between nasal and oral-nasal breathing that normally occur with exercise.

Several factors limit the utility of human clinical studies. To meet legal and ethical requirements, exposures must be without significant harm. Studies are typically limited to short-term exposures, since long-term exposures are impractical, and may be more likely to cause harm. Sample sizes are small, and therefore may not be representative of populations at risk. Finally, individuals likely to be at greatest risk (i.e., the very young and very old, those with severe obstructive lung disease, or combined heart and lung disease) have not been studied. The data from human clinical studies should therefore be used together with information from animal exposure studies, epidemiologic studies, and *in vitro* exposure studies, in the process of health assessment.

The endpoints most commonly measured in human clinical studies are symptoms and pulmonary function tests. The latter are well standardized, and their use in these studies has been reviewed (Utell et al., 1993). Effects in clinical studies can be directly compared to acute changes in field studies, as has been done extensively in studies of ozone health effects (U.S. Environmental Protection Agency, 1995).

Airway responsiveness is another endpoint commonly measured in human clinical studies. This test measures changes in lung function in response to pharmacologic bronchoconstricting agents, typically methacholine, carbachol, or histamine (see also Section 11.2.4). A dose-response curve is obtained for the agent, and airway responsiveness is expressed as the dose of the bronchoconstricting agent resulting in a specific change in lung function: e.g., the PD_{20} is the provocative dose resulting in a 20% fall in forced

expiratory volume in 1 sec (FEV_1). Individuals with asthma almost always have hyperresponsive airways, with a PD_{20} well below the normal range. Increase in airway reactivity in response to pollutant exposure could reflect airway inflammation or edema. However, smaller airway caliber as a consequence of the exposure will also increase measured responsiveness because of factors related to airways geometry. It is therefore important to measure responsiveness at a time when spirometric function has returned to baseline. Likewise, performing airway challenge testing prior to pollutant exposure may alter subsequent lung function responses to the pollutant by changing the baseline airways caliber. Differences among laboratories in the protocols and provocative agents used for airway challenge make comparison of experimental results problematic.

Endpoints in human clinical studies have extended beyond measures of air flow and lung volume. Mucocilary clearance is measured using inhaled radio-labelled aerosols. As reviewed in the Acid Aerosols Issue Paper (U.S. Environmental Protection Agency, 1989), exposure to acid aerosols alters mucociliary clearance in humans as well as in several animal species. Within the past decade, fiberoptic bronchoscopy has been used to sample the lower respiratory tract in healthy volunteers exposed to pollutants. Cells that populate the alveolar space, including alveolar macrophages (AM), lymphocytes, and polymorphonuclear leukocytes (PMN), can be recovered by bronchoalveolar lavage (BAL); bronchial epithelial cells can be sampled using bronchial brushing and endobronchial biopsies. Nasal lavage can be used to quantitate inflammation in the nose.

Features of experimental design of particular importance with regard to human clinical studies are method of exposure, exercise, and selection of control exposures. Exposure by mouthpiece reduces humidification of inhaled air that normally occurs in the nasal passages; entry of incompletely humidified air into the airways may cause bronchoconstriction in asthmatic subjects. Exercise plays an important role in enhancing pollutant effects by causing a change from nasal to oral-nasal breathing, hence decreasing upper airways deposition, and by increasing pollutant dose through increased $\dot{V}_E$.

Selection of control exposures is of particular importance. Typically, each subject serves as his/her own control to reduce intersubject variability. The control atmosphere depends on the study objectives, and may consist of clean air, or, when acidic aerosols are being tested, a neutral aerosol, such as sodium chloride (NaCl), to distinguish non-specific

effects of the aerosol from pollutant or hydrogen ion (H^+) effects. It is important that control exposures be performed under similar conditions of temperature, relative humidity, $\dot{V}_E$, and time of day; that control and pollutant exposure be separated by sufficient time to avoid carry-over effects; and that the order of the exposures be randomized among the study group. Investigators and subjects should be blinded to exposure atmospheres to the extent possible.

The majority of human clinical studies have focused on the pulmonary function effects of exposure to acid aerosols. These studies will therefore be summarized separately, first reviewing studies of effects on healthy subjects, followed by subjects with asthma. Subsequent sections will deal with effects other than lung function, and with studies of particulate pollutants other than acid aerosols. Within each section, studies will generally be reviewed in chronological order. Table 11-1 summarizes, in alphabetical order by author, controlled clinical studies of particle exposure published since 1988.

Human exposure studies of the effects of acid aerosols were reviewed in the *Acid Aerosols Issue Paper* (U.S. Environmental Protection Agency, 1989). That review reached the following conclusions:

1) In healthy subjects, no effects on spirometry have been observed after exposure to concentrations of H_2SO_4 less than 500 $\mu g/m^3$, and no consistent effects have been observed at levels up to 1,000 $\mu g/m^3$ with exposure durations up to 4 h. Studies of a variety of other sulfate and nitrate aerosols have similarly demonstrated an absence of spirometric effects on healthy subjects.
2) Combinations of sulfates with ozone or SO_2 have not demonstrated synergistic or interactive effects.
3) Asthmatic subjects experience modest bronchoconstriction after exposure to $\approx$400 to 1000 $\mu g/m^3$ H_2SO_4, and small decrements in spirometry have been observed in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$ for 30 min.
4) Some studies suggest that delayed effects may occur in healthy and asthmatic subjects following exposure to H_2SO_4.

TABLE 11-1. CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures[1]	MMAD[2] μm	GSD[3] μm	Duration	Exercise	Temp °C	RH[4] %	Symptoms	Lung Function	Other Effects	Comments
Anderson et al. (1992)	15 healthy 15 asthmatic 18 to 45 years	1): air 2): H_2SO_4 ≈ 100 μg/m^3 3): carbon black ≈200 μg/m^3 4): acid-coated carbon with ≈ 100 μg/m^3 H_2SO_4	1.0	2	60 min.	$\dot{V}_E$ ≈ 50 L/min	22	50	Healthy subjects more symptomatic in air.	Largest decrements in FVC with air exposure.	No change in airway responsiveness	Smoking status of subjects not stated.
Aris et al. (1990)	19 asthmatic 20 to 40 years	Mouthpiece study: HMSA[5] 0 to 1000 μM + H_2SO_4 50 μM vs H_2SO_4 50 μM	6.1			100 W on cycle		100	HMSA did not increase symptoms in comparison with H_2SO_4 alone.	No effects on SRaw[6]		
		Chamber study: HMSA 1 mM + H_2SO_4 5 mM vs H_2SO_4 5 mM	≈7		1 h		≈25					
Aris et al. (1991a)	10 healthy nonsmokers 21 to 31 years ozone sensitive	HNO_3 0.5 mg/m^3 or H_2O, or air followed by ozone 0.2 ppm	≈6		2 h 3 h	50 min of each h 40 L/min	22	100	No effects of fog exposure	No direct effects of fog exposures. Greatest decrements when ozone preceded by air.	No change in airway responsiveness	Fog may have reduced ozone effects on lung function.
							22	50				
Aris et al. (1991b)	18 asthmatics 23 to 37 years	Mouthpiece study: H_2SO_4 vs NaCl, ≈3 mg/m^3 with varying particle size, osmolarity, relative humidity	0.4 vs ≈6		16 min	With & without exercise.	≈24	<10 vs 100	No effects	Increases in SRaw with low RH conditions; no pollutant-related effects		Postulated that effects seen in other studies due to secretions or effects on larynx
		Chamber study: H_2SO_4 vs NaCl fog, 0.96 to 1.4 mg/m^3 with varying water content	6		1 h	100 W on cycle	≈27					

TABLE 11-1 (CONT'D). CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures	MMAD[1]	GSD[2]	Duration	Exercise	Temp °C	RH[3]	Symptoms	Lung Function	Other Effects	Comments
Avol et al. (1988a)	21 healthy 21 asthmatic 18 to 45 years	Air H_2SO_4: Healthy: 363, 1128, 1578 $\mu g/m^3$ Asthmatic: 396, 999, 1,460 $\mu g/m_3$	0.85 to 0.91	2.4 to 2.5	1 h	10 min X 3 47 to 49 L/min	21	50	Healthy: Slight increase in cough with highest concentrations. Asthma: dose-related increase in lower resp. sx.	Healthy: No effects on lung function or airway reactivity. Asthma: ↓FEV_1 0.26 L with H_2SO_4 1,460 $\mu g/m^3$		
Avol et al. (1988b)	22 healthy 22 asthmatic 18 to 45 years	H_2O fog H_2SO_4: Healthy: 647, 1,100, 2,193 $\mu g/m^3$ Asthmatic: 516, 1,085, 2,034 $\mu g/m_3$	9.7 to 10.7		1 h	10 min X 3 41 to 46 L/min	9	100	Dose-related increase in lower resp. sx. in both groups.	Healthy: No effects on lung function. Asthma: ↓peak flow 16% at 2,034 $\mu g/m^3$ H_2SO_4 .	No effects on airway responsiveness	Half the subjects received acidic gargle; no difference in effects.
Avol et al. (1990)	32 asthmatics 8 to 16 years	Air H_2SO_4 46, 127, and 134 $\mu g/m^3$	0.5	1.9	40 min	30 min rest, 10 min exercise 20L/min/m^2	21	48	No pollutant effect	No pollutant effect. One subject increased SRaw 14.2% with acid exposure.		Did not reproduce findings of Koenig et al., 1983.
Balmes et al. (1988)	12 asthmatics responsive to hypoosmolar saline aerosol 25 to 41 years	Mouthpiece, 5.9 to 87.1 g/m^3: NaCl 30 mOsm H_2SO_4 30 mOsm HNO_3 30 mOsm H_2SO_4+HNO_3 30 mOsm H_2SO_4 300 mOsm	≈5 to 6	1.5		At rest	≈23			Concentration of acid aerosol required to increase SRaw by 100% lower than for NaCl. No difference between acid species.		Exposures did not mimic environmental conditions. No mitigation by oral ammonia.

TABLE 11-1 (CONT'D). CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures	MMAD[1]	GSD[2]	Duration	Exercise	Temp °C	RH[3]	Symptoms	Lung Function	Other Effects	Comments
Culp et al. (1995)	16 healthy 20 to 39 yrs	NaCl 1000 $\mu g/m^3$ H_2SO_4 1,000 $\mu g/m^3$	0.9	1.9	2 h	10 min X 4 ≈40 L/min	22	40			Mucins from bronchoscopy: no effects on mucin recovery or changes in glycoproteins	
Fine et al. (1987b)	8 asthmatics 22 to 29 yrs	Mouthpiece: Buffered and unbuffered HCl and H_2SO_4 at varying pH	5.3 to 6.2	1.6 to 1.8		At rest			Cough with inhalation of unbuffered pH 2 aerosols	≈50% increase in airway resistance with buffered acid aerosols at pH 2. Little response to unbuffered acids.		Titratable acidity important determinant of response to acid aerosols.
Fine et al. (1987a)	10 asthmatics 22 to 34 yrs	Mouthpiece: Na_2SO_3 0 to 10 mg/ml, pH 9, 6.6, 4; buffered acetic acid pH 4; SO_2 0.25 to 8 ppm	5.6 to 6.1	1.6 to 1.7		At rest				For Na_2SO_3, broncho-constriction greater at lower pH; no response to acetic acid.		Suggests effects related to release of SO_2 or bisulfite, but not sulfite.
Frampton et al. (1992)	12 healthy 20 to 39 yrs	NaCl 1,000 $\mu g/m^3$ H_2SO_4 1000 $\mu g/m^3$	0.9	1.9	2 h	10 min X 4 ≈40 L/min	22	40	4/12 subjects: throat irritation with acid exposure.	No pollutant effects	BAL findings: No effects on cell recovery, lymphocyte subsets, AM function, fluid proteins.	
Frampton et al. (1995)	30 healthy 30 asthmatics 20 to 42 yrs	NaCl or H_2SO_4 100 $\mu g/m3$ followed by ozone 0.08, 0.12, or 0.18 ppm	0.45 0.64	4.05 2.50	3 h 3 h	10 min X 6. Healthy: 33 to 40 L/min; asthmatics: 31 to 36 L/min	21	40	No pollutant effects	Healthy subjects: no significant effects. Asthmatics: ozone dose-response following H_2SO_4 pre-exposure, but not NaCl		
Green et al. (1989)	24 healthy 18 to 35 yrs	Air; activated carbon 510 $\mu g/m^3$; HCHO 3.01 ppm; carbon 510 $\mu g/m^3$ + HCHO 3.01 ppm	1.4	1.8	2 h	15 of each 30 min., 57 L/min	22	65	Increased cough with carbon + HCHO	No direct effects of carbon. Additive effects of carbon + HCHO on FVC, FEV_3, peak flow; decrements less than 5%.		

TABLE 11-1 (CONT'D). CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures	MMAD[1]	GSD[2]	Duration	Exercise	Temp °C	RH[3]	Symptoms	Lung Function	Other Effects	Comments
Hanley et al. (1992)	22 asthmatics 12 to 19 yrs	Mouthpiece: 1): Air; H_2SO_4 70, 130 $\mu g/m^3$ 2): Air; H_2SO_4 70 $\mu g/m^3$ with and without lemonade	0.72	1.5	40 min. 45 min.	10 min 30 min ≈30 L./min	22	65	No effects	Significant decreases in FEV_1 (≈37 ml/μmol H+) and FVC at 2 to 3 min but not 20 min after exposure.	Significant correlation between baseline airways responsiveness and $\Delta FEV_1/H^+$ (R^2=0.3).	Large variability in oral NH_3 levels.
Koenig et al. (1989)	9 asthmatics with exercise-induced broncho-spasm 12 to 18 yrs	Mouthpiece: Air; H_2SO_4 68 $\mu g/m^3$; SO_2 0.1 ppm; $H_2SO_4+SO_2$; HNO_3 0.05 ppm			40 min.	10 min.	25	65	No effects	↓FEV_1 6% after H_2SO_4 compared with 2% after air.		
Koenig et al. (1992)	14 asthmatics with exercise-induced broncho-spasm 13 to 18 yrs	Mouthpiece: Air; H_2SO_4 35 or 70 $\mu g/m^3$	0.6	1.5	45 or 90 min.	≈23 L/min	22	65		↓FEV_1 6% after H_2SO_4 35 $\mu g/m^3$ for 45 min, 3% after 70 $\mu g/m^3$ (NS). Smaller changes after 90 min exposures.		Responses unrelated to $C \times T \times \dot{V}_E$
Koenig et al. (1993)	8 healthy 9 asthmatic 60 to 76 yrs	Mouthpiece: Air; $(NH_4)_2SO_4$ ≈70 $\mu g/m^3$; H_2SO_4 ≈74 to 82 $\mu g/m^3$ with and without lemonade	0.6	1.5	40 min	10 min 17.5 L/min for asthmatics, 19.7 for healthy	22	65		No significant effects. Correlation between increase in resistance and oral ammonia levels in asthmatics (R^2 = 0.575).		

TABLE 11-1 (CONT'D). CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures	MMAD[1]	GSD[2]	Duration	Exercise	Temp °C	RH[3]	Symptoms	Lung Function	Other Effects	Comments
Koenig et al. (1994)	28 asthmatics 12 to 19 yrs	Mouthpiece: Air; ozone 0.12 ppm+NO_2 0.3 ppm; ozone 0.12 ppm+NO_2 0.3 ppm+H_2SO_4 68 $\mu g/m^3$; ozone 0.12 ppm+NO_2 0.3 ppm+HNO_3 0.05 ppm	0.6	1.5	90 min X 2 days	$\dot{V}_E$ 3 X resting	22	65	No pollutant effects	No pollutant effects	No effects on airway responsiveness	6 subjects with moderate or severe asthma did not complete protocol
Kulle et al. (1986)	20 healthy 20 to 35 yrs	Air; activated carbon 517 $\mu g/m^3$; SO_2 0.99 ppm; carbon 517 $\mu g/m^3$ + SO_2 0.99 ppm.	1.5	1.5	4 h	15 min × 2, 35 L/min	22	60	No symptoms related to carbon exposure	No direct or additive effects of carbon exposure		
Laube et al. (1993)	7 healthy 20 to 31 yrs	Head dome: NaCl ≈500 $\mu g/m^3$ H_2SO_4 ≈500 $\mu g/m^3$	10.3 10.9		1 h	20 min	22 to 25	99	No pollutant effects	No pollutant effects	Tracheal clearance increased (4/4 subjects). Outer zone clearance increased (6/7 subjects). No effects on airway responsiveness	
Linn et al. (1989)	22 healthy 19 asthmatic 18 to 48 yrs	H_2O H_2SO_4 ≈2,000 $\mu g/m^3$	20 10 1		1 h	40 to 45 L/min	≈10	74 to 100	Increased total score with larger acid particles.	No pollutant effects	No effects on airway reactivity	4 asthmatic subjects unable to complete exposures because of symptoms.
Linn et al. (1994)	15 healthy 30 asthmatic 18 to 50 yrs	Air; ozone 0.12 ppm; H_2SO_4 100 $\mu g/m^3$; ozone+H_2SO_4	≈0.5	~2	6.5 h/dX 2 d	50 min X 6 29 L/min	21	50	Symptoms unrelated to atmosphere	↓FEV_1 & FVC in ozone, similar for healthy & asthmatic subjects. Greater fall in FEV_1 for acid+ozone than ozone alone, marginally significant interaction.	Increased airway responsiveness with ozone, marginal further increase with ozone+acid	Average subject lost 100 ml FEV_1 with ozone, 189 ml with ozone+acid Original findings replicated in 13 subjects

TABLE 11-1 (CONT'D). CONTROLLED HUMAN EXPOSURES TO ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subjects	Exposures	MMAD[1]	GSD[2]	Duration	Exercise	Temp °C	RH[3]	Symptoms	Lung Function	Other Effects	Comments
Morrow et al. (1994)	17 asthmatic 20 to 57 yrs 17 COPD 52 to 70 yrs	NaCl ≈100 $\mu g/m^3$ H_2SO_4 ≈90 $\mu g/m^3$			2 h	Asthmatics: 10 min X 4 COPD: 7 min X 1	21	30	No pollutant effects.	Asthmatics: ↓FEV_1 slightly greater after acid than after NaCl. COPD: No effects.		
Utell et al. (1989)	15 asthmatic 19 to 50 yrs	Mouthpiece: NaCl 350 $\mu g/m^3$; H_2SO_4 350 $\mu g/m^3$, high NH_3; H_2SO_4, low NH_3	0.80	1.7	30 min	10 min $\dot{V}_E$ 3X resting		20 to 25		Greater fall in FEV_1 with low NH_3 (19%) than with high NH_3 (8%).		
Yang and Yang (1994)	30 healthy 25 asthmatic 23 to 48 yrs	Mouthpiece: Bagged polluted air, TSP = 202 $\mu g/m^3$			30 min	At rest				Healthy subjects: no change Asthmatics: ↓FEV_1 ≈7%	Increased airway responsiveness in asthmatics reported; no allowance for change in airway caliber	No control exposure

[1]Exposures in environmental chamber unless otherwise stated.
[2]Mass median aerodynamic diameter. In some studies expressed as volume median diameter; see text.
[2]Geometric standard deviation.
[4]Relative humidity.
[5]Hydroxymethanesulfonic acid.
[6]Specific airways resistance.

5) Effects of sulfate aerosols are related to their acidity, and neutralization by oral ammonia tends to mitigate these effects.

6) Exposure to H_2SO_4 at concentrations as low as 100 $\mu g/m^3$ for 60 min alters mucociliary clearance.

7) Airway reactivity increases in healthy and asthmatic subjects following exposure to 1,000 $\mu g/m^3$ H_2SO_4 for 16 min.

8) Differences in estimated respiratory intake explain only a portion of the differences in responses among studies.

In the five years since the publication of the *Acid Aerosol Issue Paper*, several of these summary statements have been further confirmed. For example, recent studies confirm the absence of spirometric effects following acute exposure to H_2SO_4 and other acid aerosols in healthy subjects, at or below 1,000 $\mu g/m^3$. The observation of effects on adolescent asthmatics at levels as low as 68 $\mu g/m^3$ has not been confirmed, and studies utilizing longer exposures have raised further questions about the relationship between dosimetry and health effects. However, additional evidence supports the conclusion that lung function effects in asthmatic subject are related to hydrogen ion exposure, which is in part determined by the degree of neutralization by oral ammonia. Two recent studies examining sequential exposure to H_2SO_4 and ozone (Linn et al., 1994; Frampton et al., 1995) suggest that acid aerosols may potentiate the response to ozone in some asthmatic subjects. Finally, clinical studies of acid aerosols have been expanded to include endpoints associated with fiberoptic bronchoscopy and BAL.

11.2.1.2 Pulmonary Function Effects Of H_2SO_4 In Healthy Subjects

Since 1988, ten studies have examined the effects of H_2SO_4 exposure on pulmonary function in healthy subjects. Exposure levels ranged from 100 $\mu g/m^3$ to 2,000 $\mu g/m^3$, with exposure durations ranging from 16 min to 6.5 h on two successive days. All of these studies confirmed the findings from previous studies of an absence of spirometric effects on healthy subjects. Exposures at the highest concentrations (i.e. 1,000 $\mu g/m^3$ or greater) were associated with mild increases in lower respiratory symptoms, especially those exposures with particle sizes in the 10 to 20 μm range.

Two studies reported by Avol and colleagues (Avol et al., 1988a,b) examined effects of 1 h H_2SO_4 aerosol exposures in an environmental chamber. In the first study (Avol et al., 1988b), 22 healthy nonsmoking subjects between the ages of 18 and 45 years, some reporting allergies, were exposed for 1 h to fogs (volume median diameter (VMD) 9.7 to 10.3 μm, GSD not stated) consisting of H_2O (control) or H_2SO_4 at 647, 1,100, and 2,193 $\mu g/m^3$. Three 10-min periods of moderate exercise (46 L/min) were included. All subjects were exposed to each atmosphere, separated by one week. Half the subjects received an acidic gargle to reduce oral ammonia levels prior to exposure; no difference in effects was observed with or without the gargle, so data were combined in the analysis. Healthy subjects experienced a slight concentration-related increase in lower respiratory symptoms, but no effect was found on spirometry or on airway reactivity to methacholine measured 1 h after exposure.

A second study (Avol et al., 1988a) essentially duplicated this protocol for H_2SO_4 aerosols with a smaller particle size (MMAD = 0.85 to 0.91 μm, geometric standard deviation [GSD = 2.4 to 2.5]). Twenty-one healthy subjects, 12 with allergies by skin testing, were exposed on separate occasions to air and H_2SO_4 aerosol at each of three concentrations: 363, 1128, 1578 $\mu g/m^3$. A slight increase in cough was found at the two highest concentrations of H_2SO_4, but no effects were found on spirometry, specific airway resistance (SRaw), or airway reactivity to methacholine.

Linn et al. (1989) examined the effects of droplet size on 22 healthy subjects exposed to nominally 2,000 $\mu g/m^3$ H_2SO_4 for 1 h, with three, 10-min exercise periods. Distilled H_2O fog served as control aerosols. Aerosol VMDs were 1, 10, and 20 μm. Actual exposure concentrations were 1,496, 2,170, and 2,503 $\mu g/m^3$. Results were similar to the previous fog studies by this group, with no significant effects on lung function or airway reactivity to methacholine. Total symptom scores were increased with exposure to 10 μm and 20 μm H_2SO_4 particles, but not to 1 μm.

Frampton et al. (1992) exposed 12 healthy nonsmokers to aerosols of NaCl (control) or H_2SO_4 (MMAD = 0.9μm, GSD = 1.9) at 1,175 $\mu g/m^3$ for 2 h in an environmental chamber. Four 10-min exercise periods at V_E of $\approx$40 L/min were included. Subjects brushed their teeth and rinsed with mouthwash prior to and once during each exposure to reduce oral ammonia levels. Mild throat irritation was described by 4 of 12 subjects after

acid exposure and 3 of 12 subjects after NaCl exposure. No effects on lung function were found.

Five other recent studies (Anderson et al., 1992; Koenig et al., 1993; Laube et al., 1993; Linn et al., 1994; Frampton et al., 1995) have included healthy subjects in exposures to H_2SO_4 aerosols at levels below 1000 $\mu g/m^3$; none have shown meaningful effects on lung function. Anderson et al., (1992) studied the responses of 15 healthy subjects exposed for 1 h in a chamber to air, 100 $\mu g/m^3$ H_2SO_4, 200 $\mu g/m^3$ carbon black, and carbon black coated with H_2SO_4, (MMAD ≈ 1 μm). Lemonade or citrus juice gargles were used to reduce oral ammonia levels. Exposures containing acid were without effects on symptoms, lung function, or airway reactivity. Healthy subjects were actually more symptomatic and demonstrated greater increases in SRaw after air than after pollutant exposure, contrary to expectation. Koenig et al, (1993) studied eight elderly subjects age 60 to 76 years exposed to air, H_2SO_4, or ammonium sulfate at nominally 70 $\mu g/m^3$ (≈ 82 $\mu g/m^3$ H_2SO_4) for 40 min, delivered by mouthpiece. No effects were found on spirometry or total respiratory resistance. In a study designed to examine effects of acid fog on pulmonary clearance, Laube et al., (1993) exposed seven healthy volunteers to NaCl or H_2SO_4 at 470 $\mu g/m^3$, MMAD ≈ 11 μm, for 1 h with 20 min of exercise. Acid exposure did not alter symptoms or lung function. Two chamber studies designed to examine the effects of combined or sequential exposure to acid aerosols and ozone found no direct effects of exposure to ≈ 100 $\mu g/m^3$ H_2SO_4 on lung function of healthy subjects, using exposure durations of 3 h (Frampton et al., 1995) or 6.5 h for two successive days (Linn et al., 1994). Both studies included exercise and acidic mouthwash to minimize oral ammonia.

Thus for young, healthy adults, brief exposures to H_2SO_4 at mass concentrations more than an order of magnitude above ambient levels do not alter lung function. Some subjects report increased lower respiratory symptoms, including cough, at 1000 $\mu g/m^3$ and higher levels, particularly with larger particle sizes (> 5 μm). The elderly do not demonstrate decrements in lung function at low levels of exposure (≈ 82 $\mu g/m^3$). There are no data on the responses to particle exposure for healthy adolescents or children.

11.2.1.3 Pulmonary Function Effects Of H_2SO_4 In Asthmatic Subjects

Individuals with asthma often experience bronchoconstriction in response to a variety of stimuli, including exercise, cold dry air, or exposure to strong odors, smoke, and dusts. Considerable individual variability exists in the nature of stimuli that provoke a response, and in the degree of responsiveness. Thus, for clinical studies involving asthmatic subjects, subject selection and sample size deserve particular consideration. Differences among subjects may explain in part the widely differing results between laboratories studying effects of acid aerosols. For example, in some studies described below, asthmatic subjects were specifically selected to have exercise-induced bronchoconstriction (Koenig et al., 1989, 1992, 1994; Hanley et al., 1992), or responsiveness to hypo-osmolar aerosols (Balmes et al., 1988). The interval for withholding medications prior to exposure differed among various laboratories and different studies. In addition, the severity of asthma differed among studies; severity is often difficult to compare because published information describing clinical severity and baseline lung function is often incomplete. Table 11-2 lists the characteristics of asthmatic subjects exposed to acid aerosols and other particles.

Several studies have suggested that asthmatics are more sensitive than healthy subjects to effects of acid aerosols on lung function. Utell et al., (1982) found significant decrements in specific airway conductance (SGaw) in asthmatic subjects exposed by mouthpiece for 16 min to 450 and 1,000 $\mu g/m^3$ H_2SO_4. Moreover, exposure to neutralization products of H_2SO_4 produced smaller decrements in function, roughly in proportion to their acidity ($H_2SO_4 > NH_4HSO_4 > NaHSO_4$).

The role of H^+ in the responsiveness of asthmatics to acid aerosols was explored by Fine et al. (1987b), who found that titratable acidity and chemical composition, rather than pH alone, are key determinants of response in asthmatics. Eight asthmatic subjects were challenged by mouthpiece for 3 min at rest, with buffered or unbuffered hydrochloric acid (HCl) or H_2SO_4 at varying pH levels, and changes in SRaw were measured. Solutions were buffered with glycine, which, by itself, was found to have no direct effect on lung function. Aerosol MMAD ranged from 5.3 to 6.2 μm (GSD 1.6 to 1.8), simulating acid fogs. There was no group response to unbuffered acid, even at pH 2. However, SRaw increased in seven of eight subjects after inhalation of H_2SO_4 and glycine at pH 2, suggesting that titratable acidity or available H^+, rather than pH, plays a role in mediating acid fog-induced

TABLE 11-2. ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/FVC (%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Anderson et al. (1992)	15 (6/9)	19 to 45 years (29)	1): Air 2): H_2SO_4 ≈ 100 $\mu g/m^3$ 3): carbon black ≈ 200 $\mu g/m^3$ 4): acid-coated carbon	Not stated	Not stated	Not stated	69±14 (SD)	Methacholine: $PD_{20} \leq 56$ "breath-units"	Intermittent at ≈ 50 L/min
Aris et al. (1990)	19 (8/11)	20 to 40 years	Mouthpiece study: HMSA 0 to 1,000 mM + H_2SO_4 50 mM vs H_2SO_4 50 mM Chamber study: HMSA 1 mM + H_2SO_4 5 mM vs H_2SO_4 5 mM	Not stated	All but one on albuterol. 3 on inhaled steroids. No meds 24 h before study.	82±20 (SD)	Not stated	Methacholine: All responded to <2 mg/ml	Intermittent, 100 W on cycle ergometer
Aris et al. (1991b)	18	23 to 37 years	Mouthpiece study: H_2SO_4 vs NaCl to test changes in particle size, osmolarity (30 to 300 mOsm), relative humidity Chamber study: H_2SO_4 vs NaCl fog with varying water content	Not stated	Most subjects on albuterol. Several on inhaled steroids. No meds 24 h before study.	79±23 (SD)	Not stated	Methacholine: All responded to <1 mg/ml	Mouthpiece study: with & without exercise. Chamber study: intermittent exercise at 100 W on cycle ergometer.

TABLE 11-2 (CONT'D). ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/ FVC (%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Avol et al. (1988a)	21 (9/12)	18 to 45 years (30)	Air H_2SO_4 396, 999, 1,460 $\mu g/m^3$	Positive skin tests in 20	11 on no regular meds; 10 on regular meds. 3 unable to hold meds prior to exposure.	Not stated	73±14 (SD)	Hyperresponsive by methacholine challenge, not further specified	10 minX3 47 to 49 L/min
Avol et al. (1988b)	22 (9/13)	18 to 45 years (26)	H_2O fog H_2SO_4 516, 1,085, 2,034 $\mu g/m^3$	Positive skin tests in 18	"Majority had mild extrinsic disease". 9 on regular meds.	Not stated	45 to 98	Methacholine: $PD_{20} \leq 295$ "dose units"	10 minX3 41 to 46 L/min
Avol et al. (1990)	32 (12/20)	8 to 16 years	Air H_2SO_4 46 ,127, and 134 $\mu g/m^3$	All had history of allergy	18 on regular meds, 2 on no meds, rest intermittent. None on steroids.	Less than 70 in 25 subjects	Not stated	Hyperresponsive by exercise, cold air, or methacholine.	30 min rest, 10 min exercise 20L/min/m^2
Balmes et al. (1988)	12 (6/6)	25 to 41 years	Mouthpiece, doubling outputs, 5.9 to 87.1 g/m^3: NaCl 30 mOsm H_2SO_4 30 mOsm HNO_3 30 mOsm H_2SO_4+HNO_3 30 mOsm H_2SO_4 300 mOsm	Not stated	All on inhaled meds, 3 on inhaled steroids. No meds 24 h before study.	94±15 (SD)	61 to 89	Responsive to hypoosmolar saline aerosol, methacholine <2 mg/ml.	At rest

TABLE 11-2. ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/ FVC(%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Fine et al. (1987b)	8 (6/8)	22 to 29 years	Mouthpiece: Buffered and unbuffered HCl and H_2SO_4 at varying pH	Not stated	6 on inhaled meds and/or theophylline, no steroids. No meds 12 h before study.	41 to 108	74±11 (SD)	Methacholine: All responded to <3 mg/ml.	At rest
Fine et al. (1987a)	10 (5/5)	22 to 34 years (26.7)	Mouthpiece: Na_2SO_3 0 to 10 mg/ml, pH 9, 6.6, 4; buffered acetic acid pH 4; SO_2 0.25 to 8 ppm	Not stated	7 on inhaled meds, no steroids. No meds 12 h before study.				At rest
Frampton et al. (1995)	30 (20/10)	20 to 42 years	NaCl or H_2SO_4 100 μg/m3 followed by ozone 0.08, 0.12, or 0.18 ppm	All had positive skin tests. ↑IgE in 10.	All on intermittent or daily bronchodilators. None on steroids. Meds held 24 h before study.	81±4 (SE)	75±2 (SE)	Positive carbachol challenge if normal spirometry	10 min X 6 for each exposure.
Hanley et al. (1992)	22 (7/15)	12 to 19 years	Mouthpiece: 1): Air or H_2SO_4 70, 130 $\mu g/m^3$ 2): Air or H_2SO_4 70 $\mu g/m^3$, with and without lemonade	"All had allergic asthma". ↑IgE in 8.	All but 2 on meds, no steroids. No meds 4 h before study.	Not stated	Not stated	Methacholine: PD_{20} 0.25 to 25 mg/ml; not available for 3 subjects. 18 were responsive to exercise by treadmill test	1): 10 min 2): 30 min ≈30 L./min

TABLE 11-2 (CONT'D). ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/ FVC (%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Koenig et al. (1989)	9 (3/6)	12 to 18 years	Mouthpiece: Air H_2SO_4 68 $\mu g/m^3$ SO_2 0.1 ppm $H_2SO_4+SO_2$ HNO_3 0.05 ppm	5 "allergic asthma"	Not stated	Not stated	Not stated	Methacholine: All responded to <20 mg/ml. All had ↓FEV_1 >15% with treadmill test	"Moderate", on treadmill for 10 min.
Koenig et al. (1992)	14 (5/9)	13 to 18 years	Mouthpiece: Air H_2SO_4 35 or 70 $\mu g/m^3$	"Allergic asthma"	Not stated	Not stated	Not stated	Methacholine: PD_{20} 0.25 to 25 mg/ml; not available for 1 subject; 8 had pos. treadmill tests, 4 history of exercise responsiveness, 2 did not meet stated criteria for exercise responsiveness.	Intermittent ≈23 L/min
Koenig et al. (1993)	9 (7/2)	60 to 76 years	Mouthpiece: 1): Air 2): $(NH_4)_2SO_4$ ≈70 $\mu g/m^3$ 3&4): H_2SO_4 ≈74 $\mu g/m^3$ with and without lemonade	Not stated	All on "bronchodilator and/or anti-inflammatory treatment". Steroids not specified.	75	Not stated	Methacholine: $PD_{20} \leq 10$ mg/ml	10 min 17.5 L/min

TABLE 11-2 (CONT'D). ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/ FVC (%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Koenig et al. (1994)	28 (9/19)	12 to 19 years	Mouthpiece: 1): Air 2): ozone 0.12 ppm+NO_2 0.3 ppm 3): ozone 0.12 ppm+NO_2 0.3 ppm+H_2SO_4 68 $\mu g/m^3$ 4): ozone 0.12 ppm+NO_2 0.3 ppm+HNO_3 0.05 ppm	"Personal history of allergic asthma"	3 on no meds, rest on regular meds. 4 on inhaled steroids.	87	Not stated	Methacholine: $PD_{20}<25$ mg/ml. All but 1 responsive to exercise by treadmill test.	Intermittent $\dot{V}_E$ 3 X resting
Linn et al. (1989)	19 (13/6)	18 to 48 years (29)	H_2O H_2SO_4 $\approx$2,000 $\mu g/m^3$	"Some" subjects had history of allergy	All on bronchodilators at least weekly. No regular steroid use. No meds 12 h before study.	Not stated	70$\pm$11 (SD)	Hyperresponsiveness based on methacholine $PD_{20}<38$ "breath units", exercise responsiveness, or bronchodilator response.	Intermittent 40 to 45 L/min
Linn et al. (1994)	30 (17/13)	18 to 50 years (30)	1): Air 2): ozone 0.12 ppm 3): H_2SO_4 100 $\mu g/m^3$ 4): ozone+H_2SO_4	Some subjects had positive skin tests.	Wide range of medication usage. Some on inhaled steroids. No meds 4 h before study.	Not stated	72	Responsive to methacholine or exercise, or bronchodilator response	50 min X 6 29 L/min
Morrow et al. (1994)	17	20 to 57 years (35)	NaCl $\approx$100 $\mu g/m^3$ H_2SO_4 $\approx$90 $\mu g/m^3$	Positive skin tests	Requirement for bronchodilators	Not stated	65$\pm$8 (SD)	Positive carbachol challenge if normal spirometry	10 min X 4

TABLE 11-2 (CONT'D). ASTHMA SEVERITY IN STUDIES OF ACID AEROSOLS AND OTHER PARTICLES

Ref.	Subject # (F/M)	Age range (mean)	Exposures[1]	Allergies	Medications	FEV_1 (% pred.)	FEV_1/ FVC (%)	Airway Responsiveness	Exercise/ $\dot{V}_E$
Utell et al. (1989)	15	19 to 50 years	Mouthpiece: 1): NaCl 350 $\mu g/m^3$ 2): H_2SO_4 350 $\mu g/m^3$ high NH_3 3): H_2SO_4 low NH_3	Not stated	All on intermittent or daily bronchodilators. None on steroids. Meds held 24 h before study.	88±4 (SE)	70±3 (SE)	Positive carbachol challenge if normal spirometry	10 min $\dot{V}_E$ 3 X resting
Yang and Yang (1994)	25 (15/10)	23 to 48 years	Mouthpiece: Bagged polluted air, TSP = 202 $\mu g/m^3$	All ↑IgE	No steroids. Holding of medications not stated.	Not stated	Not stated	Hyperresponsive to methacholine	Rest

[1]Exposures in chamber unless otherwise stated.

bronchoconstriction. Nevertheless, the response occurred at H_2SO_4 concentrations estimated in excess of 10 mg/m^3, more than an order of magnitude higher than the concentration producing a response in the study of Utell et al. (1982).

Fine et al. (1987a) further examined the role of pH in sulfite-induced bronchoconstriction in asthmatics. Ten subjects with asthma were challenged with increasing concentrations of sodium sulfite (Na_2SO_3) at three different pH levels. Challenge with buffered acetic acid aerosols at pH 4 was used to control for the airway effects of acid aerosols. Subjects also inhaled increasing concentrations of SO_2 gas during eucapneic hyperpnea. Exposures consisted of 1 min of tidal breathing on a mouthpiece at rest. Particle MMAD ranged from 5.6 to 6.1 μm. Nine of ten subjects experienced bronchoconstriction with Na_2SO_3,with greater responses to aerosols made from solutions with lower pH. No response was seen following acetic acid. The authors concluded that bronchoconstriction in response to Na_2SO_3 aerosols may be caused by the release of SO_2 gas or by bisulfite ions, but not by sulfite ions and not merely by alterations of airway pH. These studies of Fine et al., as pointed out by the authors, addressed potential mechanisms for bronchoconstriction in response to acidic sulfates, but did not attempt to mimic the effects of environmental exposures.

Hypo-osmolar aerosols can induce bronchoconstriction in some asthmatics. To test the effects of varying osmolarity of acidic aerosols, Balmes et al. (1988) administered aerosols of NaCl, H_2SO_4, HNO_3, or H_2SO_4 + HNO_3 to 12 asthmatic subjects via mouthpiece. All solutions were prepared at an osmolarity of 30 mOsm, and delivered at doubling concentrations until SRaw increased by 100%. An additional series of challenges with H_2SO_4 at 300 mOsm was performed. The 12 subjects were selected from a group of 17 asthmatics on the basis of responsiveness to challenge with hypo-osmolar saline aerosol. Aerosol particle size was similar to coastal fogs, with MMAD ranging from 5.3 to 6.1. Delivered nebulizer output was quite high, ranging from 5.9 to approximately 87 g/m^3.

All hypo-osmolar aerosols caused bronchoconstriction. Lower concentrations of hypo-osmolar acidic aerosols were required to induce bronchoconstriction than with NaCl, and there was no difference between acidic species. No bronchoconstriction occurred with isosmolar H_2SO_4, even at maximum nebulizer output (estimated H_2SO_4 concentration greater than 40 mg/m^3). The authors concluded that acidity can potentiate bronchoconstriction

caused by hypo-osmolar aerosols. As in the studies of Fine et al. (1987a,b), these exposures did not mimic environmental conditions.

Koenig and colleagues have studied the responses of adolescents with allergic asthma to H_2SO_4 aerosols with particle sizes in the respirable range, and concentrations only slightly above peak, worst-case ambient levels. In one study (Koenig et al., 1983), ten adolescents were exposed to 110 $\mu g/m^3$ H_2SO_4 (MMAD = 0.6 μm) by mouthpiece for a total of 40 min, 30 min at rest followed by 10 min of exercise. The FEV_1 decreased 8% after exposure to H_2SO_4, and 3% after a similar exposure to NaCl, a statistically significant difference. In another study (Koenig et al., 1989), nine allergic adolescents were exposed to 68 $\mu g/m^3$ H_2SO_4 (MMAD = 0.6 μm) for 30 min at rest followed by 10 min of exercise ($\dot{V}_E$ = 32 L/min). Although only five subjects were described as having "allergic asthma", all subjects had exercise-induced bronchoconstriction; thus all subjects were asthmatic by generally accepted criteria (Sheffer, 1991). Effects were compared with similar exposures to air, 0.1 ppm SO_2, 68 $\mu g/m^3$ H_2SO_4 + 0.1 ppm SO_2, and 0.05 ppm HNO_3. The FEV_1 decreased 6% after exposure to H_2SO_4 alone, and 4% after exposure to H_2SO_4 + SO_2, compared to a 2% decrease after air. Increases in total respiratory resistance were not significant. These results were presented as preliminary findings, in that a total of 15 subjects were to be studied; formal statistical comparison of H_2SO_4 versus air was not presented. Findings from the full group of 15 subjects have not been published. These studies suggest that allergic asthmatics with exercise-induced bronchoconstriction may be more sensitive to effects of H_2SO_4 than adult asthmatics, and that small changes in lung function may be observed at exposure levels below 100 $\mu g/m^3$.

Two studies reported by Avol et al. (1988a,b) examined effects of H_2SO_4 aerosols and fogs on asthmatic subjects. The results for healthy subjects in these studies were described in Section 11.2.1.2. In the first study, 21 adult asthmatics, 20 of whom had positive skin tests to common allergens, were exposed to air or 396, 999, and 1,460 $\mu g/m^3$ H_2SO_4 (MMAD 0.85 to 0.91 μm) for one hour with intermittent exercise. The asthmatic subjects experienced concentration-related increases in lower respiratory symptoms, with some persistence of symptoms at 24 h. The FEV_1 decreased by a mean of 0.26 L after exposure to 999 $\mu g/m^3$, and 0.28 L after exposure to 1,460 $\mu g/m^3$. Results using analysis of variance (ANOVA) were significant for concentration effects on change in FEV_1 and FVC. However,

decrements at 396 $\mu g/m^3$ were identical to those seen with air exposure. The SRaw approximately doubled following exposure to both air and 396 $\mu g/m_3$ H_2SO_4, and approximately tripled following exposure to 999 and 1,460 $\mu g/m_3$. Although absolute change in SRaw related to concentration was not significant, percent change in SRaw was not analyzed as was done for FEV_1 and FVC; ANOVA of percent change for each of these measures may have proved more sensitive. These findings are similar to those of Utell, et al. (1983b), who found significant effects on SGaw following exposure to 450 and 1,000 $\mu g/m_3$, and significant effects on FEV_1 at 1,000 $\mu g/m_3$ (MMAD = 0.8 μm). However, exposures in the Utell study were performed at rest for a considerably shorter duration (16 minutes).

The second study (Avol et al., 1988b) utilized an identical protocol to examine effects of a large particle aerosol (MMAD = 10 μm). Twenty-two asthmatic subjects were exposed to fogs containing 516, 1,085 and 2,034 $\mu g/m_3$ H_2SO4, compared with H_2O-containing fog. Although concentration-related increases in respiratory symptoms were similar to those in the study of submicron aerosols, no significant effects were found on FEV_1, FVC, or SRaw, even at the highest concentration of greater than 2,000 $\mu g/m^3$. The findings from these two studies suggest that aerosols of submicron particle size may alter lung function to a greater degree than fogs in asthmatic subjects. However, the concentrations required to produce an effect differ strikingly from the studies of adolescent asthmatics of Koenig and colleagues.

Linn et al. (1989) utilized a similar exposure protocol to specifically examine effects of particle size. Nineteen asthmatic adults were exposed for 1 h to a pure water aerosol or approximately 2,000 $\mu g/m^3$ H_2SO_4 at 3 difference droplet sizes: 1, 10, and 20 μm. Subjects exercised for 3 10-min periods at $\dot{V}_E$ of 40 to 45 L/min. Grapefruit juice gargles were used to minimize oral ammonia. As in previous studies by this group, symptoms increased in acid atmospheres with larger particles. Four of the 19 asthmatic subjects were unable to complete one or more exposures because of respiratory symptoms. All but one of the aborted exposures was in an acid aerosol-containing atmosphere: three subjects did not complete the 1 μm acid exposure, one the 10 μm exposure, and three the 20μm exposure. The authors reported significant decrements in lung function in these subjects, requiring administration of a bronchodilator. As stated by the authors, "the patterns of these appreciable clinical responses by asthmatics suggests a causal relationship to acid exposure, without obvious

dependence on droplet size". These more dramatic responses to acid aerosols are not reflected in the mean responses, and suggest the existence of a few particularly susceptible individuals. Mean responses of FEV_1 to acid aerosol exposure were about -21%, with responses to exercise in clean air of about -12%. Some subjects experienced decreases in FEV_1 in excess of 50%, as a result of combined exercise and acid aerosol exposure. Analysis of variance found significant effects of acid × time on SRaw and FEV_1. There was no apparent effect of droplet size.

Utell et al. (1989) examined the influence of oral ammonia levels on responses to H_2SO_4. Fifteen subjects with mild asthma inhaled H_2SO_4 aerosols (350 $\mu g/m^3$, MMAD = 0.8 μm) via mouthpiece for 20 min at rest followed by 10 min of exercise. Sodium chloride aerosol served as control. Low oral ammonia levels were achieved using a lemon juice gargle and toothbrushing prior to exposure, and high levels were achieved by eliminating oral hygiene and food intake for 12 h prior to exposure. These procedures achieved a five-fold difference in oral ammonia levels. The FEV_1 decreased 19% with low ammonia versus 8% with high ammonia ($p < 0.001$). The FEV_1 also decreased 8% with NaCl aerosol. These findings extended the authors' previous findings (Utell et al., 1983b) of decrements in SGaw following exposure to 450 $\mu g/m^3$ H_2SO_4, and demonstrated the importance of oral ammonia in mitigating the clinical effects of submicron H_2SO_4 aerosols.

The findings of Koenig et al. (1989) in adolescent asthmatics prompted an attempt by Avol and colleagues (1990) to replicate the study using a larger group of subjects. Thirty-two subjects with mild asthma, aged 8 to 16 years, were exposed to 46 and 127 $\mu g/m^3$ H_2SO_4 (MMAD $\approx 0.5 \mu m$) for 30 min at rest followed by 10 min of exercise at 20 L/min/m^2 body surface area. Subjects gargled citrus juice prior to exposure to reduce oral ammonia. Bronchoconstriction occurred after exercise in all atmospheres, with no statistically significant difference between clean air and acid exposures at any concentration. Because these exposures were undertaken in an environmental chamber with unencumbered oral/nasal breathing, in contrast to mouthpiece exposure in the Koenig studies, a subsequent study was performed to examine the effects of oral breathing only. Twenty-one of these subjects were therefore exposed to 134 $\mu g/m^3$ H_2SO_4 while breathing chamber air through an open mouthpiece. Again, no acid effect was found. One subject who was "unusually susceptible to exercise-induced bronchospasm" also showed the largest decrements in lung function with

both exposures to the highest acid concentrations. It is possible that the subjects in the Koenig et al. (1989) study, all of whom demonstrated exercise-induced bronchoconstriction during a specific exercise challenge test, represented a more responsive subgroup of adolescent asthmatics. Only 15 of the 32 subjects in the Avol et al. (1990) study were known to have exercise-induced bronchoconstriction. Indeed, subsequent data from Dr. Koenig's laboratory (Hanley et al., 1992) suggest exercise responsiveness is predictive of H_2SO_4 responsiveness (see below).

Aris et al. (1990) examined the effects of hydroxymethanesulfonic acid (HMSA), which has been identified as a component of west coast acidic fogs. They postulated that HMSA might cause bronchoconstriction in asthmatics because, at the pH of airway lining fluid, it dissociates into CH_2O and SO_2 . In the first part of the study, nine asthmatics were serially challenged by mouthpiece with 0, 30, 100, 300 and 1,000 μM HMSA in 50 μM H_2SO_4 (MMAD = 6.1 μm). The SRaw was measured after each challenge. These findings were compared on a separate day to a similar series of exposures to 50 μM H_2SO_4 alone. No effect was found for HMSA on symptoms or airways resistance. An environmental chamber exposure study was then performed in which 10 asthmatic subjects were exposed to 1 mM HMSA + 5 mM H_2SO_4 for 1 h with intermittent exercise. The control was exposure to 5 mM H_2SO_4 alone. Three subjects underwent additional exposures to NaCl aerosol. Particle MMAD was approximately 7 μm. Both acid exposures slightly increased respiratory symptoms, but no significant effects on SRaw were found.

In a subsequent series of studies, Aris et al. (1991b) examined the effects of varying particle size, osmolarity, and relative humidity on airways resistance in response to H_2SO_4 aerosol. To study effects of particle size and osmolarity, 11 asthmatics inhaled five different aerosols for 16 min by mouthpiece at rest: (1) H_2SO_4 at 300 mOsm (VMD approximately 6 μm); (2) H_2SO_4 30 mOsm (VMD approximately 6 μm); (3) sodium chloride 30 mOsm (VMD approximately 6 μm); (4) H_2SO_4 (VMD approximately 0.4 μm); and (5) H_2SO_4, (VMD approximately 0.4 μm). Sulfuric acid concentrations were high, at approximately 3 mg/m^3. Airway resistance actually decreased slightly with all aerosol exposures and there were no significant effects on respiratory symptoms.

In a second mouthpiece study, nine subjects were exposed at rest (part 1) to H_2SO_4 at approximately 3 mg/m^3, with large (VMD $\approx$6 μm) versus small (0.3 μm) particle size and

low (< 10%) versus high (100%) relative humidity. Sodium chloride aerosols under similar conditions served as control. Because these exposures caused no decrements in SRaw, six subjects underwent exposures to small particle, low humidity H_2SO_4 versus sodium chloride while exercising at 40 L/min (part 2). Although SRaw increased significantly with exercise, there was no difference between H_2SO_4 and sodium chloride exposures. These results are shown in Figure 11-1. A significant increase in throat irritation was observed with the low humidity, small particle H_2SO_4 inhalation in part 1 of this study (n=9) but was not replicated in part 2 (n=6).

Finally, an environmental chamber exposure study was undertaken to examine effects of H_2SO_4 fogs (VMD approximately 6 μm) with varying water content on airways resistance. Ten subjects were exposed for 1 h with intermittent exercise to H_2SO_4 and NaCl at low (0.5 $\mu g/m^3$) and high (1.8 $\mu g/m^3$) liquid water content. The mean sulfate concentrations were 960 $\mu g/m^3$ for low water content fogs and 1,400 $\mu g/m^3$ for high liquid water content fog. Surprisingly, SRaw decreased slightly with most exposures, with no significant difference among the 4 atmospheres. The authors speculated that the decrements in pulmonary function following exposure to acid aerosols in previous studies may have been due to increases in airway secretions or effects on the larynx rather than bronchoconstriction.

Responsiveness of adolescent asthmatic subjects to H_2SO_4 aerosols was further explored by Hanley et al. (1992). Fourteen allergic asthmatics aged 12 to 19 years inhaled air or H_2SO_4 at targeted concentrations of 70 and 130 $\mu g/m^3$, for 30 min at rest and 10 min with exercise. In a second protocol, nine subjects were exposed to targeted concentrations of 70 $\mu g/m^3$ H_2SO_4, with and without drinking lemonade to reduce oral ammonia. Actual exposure concentrations ranged from 51 to 176 $\mu g/m_3$ H_2SO_4. Exposures lasted 45 min, including two 15-min exercise periods. Aerosol MMAD was 0.72 μm. For the purposes of this document, mean changes in FEV_1 were calculated from individual subject data provided in the published report. In the first protocol, FEV_1 fell 0.05 $\pm$ 0.08 L after air and 0.15 $\pm$ 0.14 L after nominal 70 $\mu g/m^3$ H_2SO_4. In the second protocol, FEV_1 fell 0.00 $\pm$ 0.23 L without lemonade gargle and 0.13$\pm$ 0.09 L with lemonade gargle. Results from the 22 subjects exposed in the two protocols were combined for the published analyses, and changes in pulmonary function were regressed against H^+ concentration for each subject. Decrements in FEV_1 and FVC were statistically significant at 2 to 3 min after exposure, but

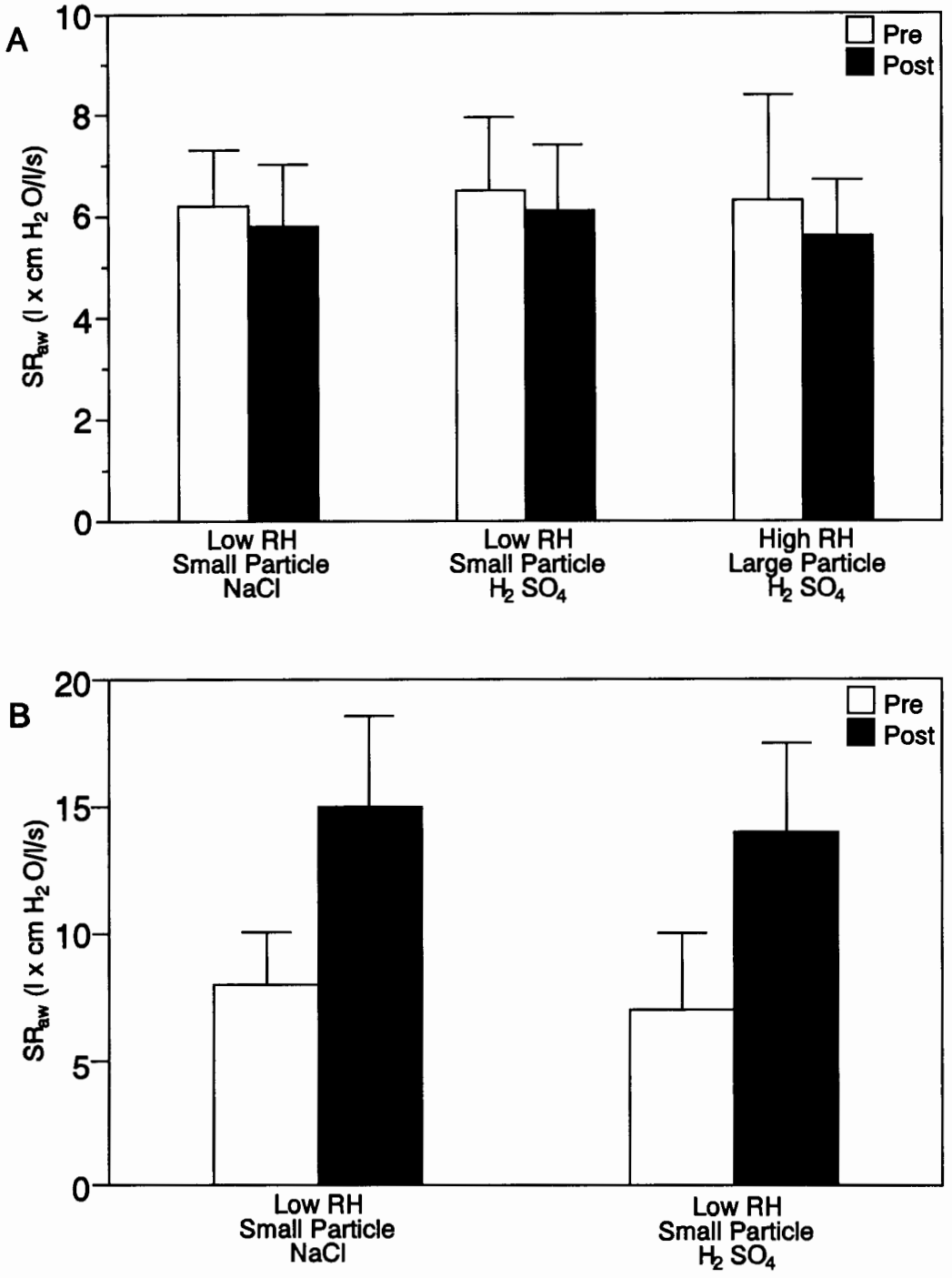

Figure 11-1. Mean ± SEM specific airway resistance (SRaw) before and after a 16-min exposure for (A) nine subjects who inhaled low relative-humidity (RH) NaCl, low-RH H_2SO_4, and high-RH H_2SO_4 aerosols at rest, and (B) six subjects who inhaled low-RH NaCl and low-RH H_2SO_4 aerosols during exercise.

Source: Aris et al., 1991b.

not at 20 min after exposure. Changes in $Vmax_{50}$ and total respiratory resistance were not significantly different. The findings corresponded to a fall in FEV_1 of approximately 37 ml/μM H^+. A significant correlation was found between exercise-induced bronchoconstriction, determined prior to exposure using a treadmill test, and the slope of Δ FEV_1/H^+. A similar observation linking baseline airways reactivity to H_2SO_4 responsiveness had been made previously by Utell et al., (Utell et al., 1983b).

Koenig et al. (1992) examined the effects of more prolonged mouthpiece exposures to H_2SO_4. Fourteen allergic asthmatic subjects aged 13 to 18, with exercise-induced bronchoconstriction, were exposed to air or 35 and 70 $\mu g/m^3$ H_2SO_4, for 45 min and 90 min, on separate occasions. Oral ammonia was reduced by drinking lemonade. The exposures included alternate 15-min periods of exercise at three times resting $\dot{V}_E$. The largest decrements in FEV_1 (6%) actually occurred with the shorter exposure to the lower concentration of H_2SO_4 (35 $\mu g/m^3$). Changes following exposure to 70 $\mu g/m^3$ and following 90 min exposures were not significant. The authors concluded that duration of exposure did not play a role in the response to H_2SO_4 aerosols. However, the absence of a concentration response in the studies suggests that the statistical findings may be due to chance. Therefore, the study does not appear to demonstrate a convincing effect of H_2SO_4 at these exposure levels.

Anderson et al. (1992) included 15 asthmatic adults in a study comparing the effects of exposure for 1 h to air, 100 $\mu g/m^3$ H_2SO_4, 200 $\mu g/m^3$ carbon black particles, and acid-coated carbon black. Decrements in FEV_1 were observed for all exposures, averaging about 9%. Analysis of variance for FVC showed a significant interaction of acid, carbon, and time factors ($p = 0.02$), but the largest decrements actually occurred with air exposure.

In the only study of elderly asthmatics, Koenig et al. (1993) exposed nine subjects, 60 to 76 years of age, by mouthpiece to air, $(NH_4)_2SO_4$, or 70 $\mu g/m^3$ H_2SO_4, with and without lemonade gargle. Exposures were 30 min at rest followed by 10 min of mild exercise ($\dot{V}_E$ = 17.5 L/min). Greater increases in total respiratory resistance occurred following H_2SO_4 without lemonade than following the other atmospheres, but the difference between atmospheres was not significant.

In a study comparing effects of H_2SO_4 exposure in subjects with asthma and COPD, Morrow et al. (1994) exposed 17 allergic asthmatic subjects in an environmental chamber to

90 $\mu g/m^3$ H_2SO_4 or NaCl (MMAD < 1 μm) for 2 h with intermittent exercise. Pulmonary function was measured after each of four 10 min exercise periods, and again 24 h after exposure, before and after exercise. Decrements in FEV_1 were consistently greater in H_2SO_4 than NaCl, although the difference was statistically significant only following the second exercise period. FEV_1 decreased $\approx$18% after H_2SO_4 compared with $\approx$14% after NaCl ($p = 0.02$). Reductions in SGaw were significantly different only following the fourth exercise period ($p = 0.009$). No changes were found in symptoms or arterial oxygen saturation, and there were no significant changes in lung function 24 h after exposure.

Finally, two recent studies have examined combined exposures to H_2SO_4 and ozone, one using a combined pollutant atmosphere for 6 h per day over 2 days, (Linn et al., 1994) and the other using sequential 3 h exposures to H_2SO_4 followed 1 day later by ozone (Frampton et al., 1995). These reports will be discussed in detail in section 11.2.1.7. However, neither study found any significant changes in lung function in asthmatics exposed to 100 $\mu g/m^3$ H_2SO_4 alone.

In summary, asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentrations differ widely among laboratories. Although the reasons for these differences remain largely unclear, subject selection differences in neutralization of acid by NH_3 may be an important factor. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to acid aerosols at exposure levels only slightly above peak ambient levels. Even in studies reporting an overall absence of effects on lung function, some asthmatic subjects appear to demonstrate clinically important effects.

11.2.1.4 Effects Of Acid Aerosols On Airway Responsiveness

Human airways may undergo bronchoconstriction in response to a variety of stimuli. Airway responsiveness can be quantitated by measuring changes in expiratory flow or airways resistance in response to inhalation challenge. Typically, the challenging agent is a non-specific pharmacologic bronchoconstrictor such as methacholine or histamine. Other agents include carbamylcholine (carbachol), cold dry air, sulfur dioxide, hypo-osmolar aerosols, or exercise. In allergic subjects, airway challenge with specific allergens can be performed, although the responses are variable, and late phase reactions can result in

bronchoconstriction beginning 4 to 8 h after challenge and lasting 24 h or more. Although many individuals with airway hyperresponsiveness do not have asthma, virtually all asthmatics have airway hyperresponsiveness, possibly reflecting underlying airway inflammation. Changes in clinical status are often accompanied by changes in airway responsiveness. Thus alterations in airway responsiveness may be clinically significant, even in the absence of direct effects on lung function. Godfrey (1993) and Weiss et al. (1993) have recently reviewed airways hyperresponsiveness and its relationship to asthma. Molfino et al. (1992) have provided a brief review of air pollution effects on airway responsiveness.

As noted in section 11.2.3, two studies (Utell et al., 1983b; Hanley et al., 1992) have suggested that the degree of baseline airway responsiveness may predict responsiveness to acid aerosol exposure in asthmatic subjects. This section will deal only with studies examining changes in airway responsiveness with exposure to particles.

Despite the absence of effects on lung function in healthy subjects, Utell et al. (1983a) observed, in healthy nonsmokers, an increase in airway responsiveness to carbachol following exposure to 450 $\mu g/m^3$ H_2SO_4. The increase occurred 24 h, but not immediately, after exposure. In addition, some subjects reported throat irritation between 12 and 24 h after exposure to H_2SO_4. These findings suggested the possibility of delayed effects. These investigators also observed increases in airway responsiveness among asthmatic subjects following exposure to 450 and 1000 $\mu g/m^3$, but not 100 $\mu g/m^3$ H_2SO_4. These findings have been reviewed (Utell et al., 1991).

Avol et al. (1988a,b) included airway responsiveness as an outcome measure in their studies of healthy and asthmatic subjects exposed to varying concentrations of H_2SO_4. No effects on responsiveness were reported, with either acidic fogs or submicron aerosols, at H_2SO_4 concentrations as high as 2000 $\mu g/m^3$. However, airway challenge was performed using only two concentrations of methacholine. This limited challenge may have been insufficiently sensitive to detect small changes in airway responsiveness.

Using a similar 2-dose methacholine challenge protocol, Linn et al. (1989) found no change in airway responsiveness of healthy subjects following exposure to 2000 $\mu g/m^3$ H_2SO_4 for 1 h, at particle sizes ranging from 1 to 20 μm. Anderson et al. (1992), in their study of responses to 100 $\mu g/m^3$ H_2SO_4, 200 $\mu g/m^3$ carbon black, and acid coated carbon, found no effects on airway responsiveness in healthy or asthmatic subjects. In this study, a

conventional methacholine challenge was used, administering doubling increases in methacholine concentration until FEV_1 decreased more than 20%.

In a study primarily designed to examine effects of acid fog exposure on mucociliary clearance, Laube et al. (1993) examined changes in airway responsiveness to methacholine in 7 asthmatic subjects exposed to 500 $\mu g/m^3$ H_2SO_4 or NaCl (MMAD $\approx$ 10 μm) for 1 h with 20 min of exercise. Responsiveness was measured at screening and 30 min after each exposure. No difference was observed between H_2SO_4 and NaCl exposures.

A recent study (Linn et al., 1994) has suggested that exposure to ozone with H_2SO_4 may enhance the increase in airway responsiveness seen with ozone exposure alone. Fifteen healthy and 30 asthmatic subjects were exposed to air, 0.12 ppm ozone, 100 $\mu g/m^3$ H_2SO_4, and ozone + H_2SO_4 for 6.5 h on 2 successive days, with intermittent exercise. Airway responsiveness was measured after each exposure day using a conventional methacholine incremental challenge, and compared with baseline measured on a separate day. An ANOVA using data from all subjects found an increase in airway responsiveness in association with ozone exposure ($p=0.003$), but showed no significant change following exposure to air or H_2SO_4 alone. Multiple comparisons did not reveal significant differences in airway responsiveness between ozone and ozone + H_2SO_4 in healthy or asthmatic subjects. However, asthmatic subjects showed the greatest increase in airway responsiveness following the first day of ozone + H_2SO_4, and ANOVA revealed a significant interaction of clinical status, ozone, acid, and day ($p=0.03$). Decreases in FEV_1 following methacholine challenge for healthy subjects were 8% after air, 6% after H_2SO_4, 9% after ozone, and 13% after ozone + H_2SO_4. Changes were smaller following the second exposure day, suggesting attenuation of responsiveness with repeated exposure, as seen in previous studies of ozone alone (U.S. Environmental Protection Agency, 1995). These studies suggest that exposure to low concentrations of H_2SO_4 may enhance ozone-induced increases in airway responsiveness in both healthy and asthmatic subjects.

Koenig et al. (1994) sought to determine whether exposure to H_2SO_4 or HNO_3 enhanced changes in lung function or airway responsiveness seen with exposure to ozone + nitrogen dioxide (NO_2). Adolescent asthmatic subjects were exposed to air, 0.12 ppm ozone + 0.3 ppm NO_2, ozone + NO_2 + 73 $\mu g/m^3$ H_2SO_4, and ozone + NO_2 + 0.05 ppm HNO_3. Exposures were by mouthpiece for 90 min, with intermittent exercise, on two consecutive

days. Airway responsiveness was measured by methacholine challenge at screening and on the day following the second pollutant exposure. No effects on airway responsiveness were found for any atmosphere. However, challenge following pollutant exposure utilized only doses of methacholine well below the level causing significant reductions in FEV_1 for these subjects at baseline, making it unlikely that small or transient changes in responsiveness would be detected. Six subjects did not complete the protocol because of illness, symptoms, and other factors which may or may not have been related to pollutant exposure; these data were not included in the analysis.

In summary, the data suggest that there is no significant effect of ambient level exposure to the particles tested on airway responsiveness in healthy or asthmatic subjects. Observations of possible delayed increases in responsiveness in healthy subjects exposed to 450 $\mu g/m^3$ H_2SO_4 (Utell et al., 1983a), and H_2SO_4 enhancement of ozone effects on airway responsiveness in healthy and asthmatic subjects (Linn et al., 1994) require confirmation in additional studies, utilizing standard challenge protocols.

11.2.1.5 Effects Of Acid Aerosols On Lung Clearance Mechanisms

Brief (1- to 2-h) exposures to H_2SO_4 aerosols have shown consistent effects on mucociliary clearance in three species: donkeys, rabbits, and humans. The direction and magnitude of the effect are dependent on the concentration and duration of the acid aerosol exposure, the particle size of the acid aerosol, and the size of the tracer aerosol. Clearance studies in animals are discussed in Section 11.2.2.5.

Initial studies in healthy nonsmokers by Leikauf et al. (1981) found that exposure to 110 $\mu g/m^3$ H_2SO_4 (MMAD $\approx 0.5\mu m$) for 1 h at rest accelerated bronchial mucociliary clearance, while a similar exposure to 980 $\mu g/m^3$ H_2SO_4 slowed clearance. A second study (Leikauf et al., 1984) utilizing a smaller tracer aerosol (4.2 μm) to assess more peripheral airways, found slowing of clearance with both 108 and 983 $\mu g/m^3$ H_2SO_4, in comparison with distilled water aerosol. Spektor et al. (1989) extended these studies, exposing ten healthy subjects to H_2SO_4 or distilled water aerosols for up to 2 h. Two different tracer aerosols were used, one administered before and the other after exposure. Following a 2 h exposure to 100 $\mu g/m^3$ H_2SO_4, clearance halftime tripled compared with control, with reduced clearance rates still evident 3 h after exposure. These findings suggested that brief,

resting exposures to H_2SO_4 at ≈ 100 $\mu g/m^3$ accelerate clearance in large bronchi but slow clearance in more peripheral airways.

Data from studies in asthmatics is less clear. Spektor et al. (1985) exposed ten asthmatic subjects to 0, 110, 319, and 911 $\mu g/m^3$ H_2SO_4 for 1 h. The effects were difficult to interpret because of inhomogeneous distribution of the tracer aerosol in the more severe asthmatics. However, clearance appeared decreased following acid exposure in the six subjects with the mildest asthma (not dependent on regular medications).

Laube et al. (1993) recently examined the effects of acid fog on mucociliary clearance in asthmatics. Seven nonsmoking subjects with mild asthma (baseline FEV_1 90 to 118% predicted) were exposed in a head dome to 500 $\mu g/m^3$ H_2SO_4 or NaCl (MMAD ≈ 10 μm) for 1 h with 20 min of exercise. Mucociliary clearance was measured using inhalation of a technetium-99M sulfur colloid aerosol after exposure to the test aerosol. Tracheal clearance was measured in four subjects, and was increased in all four after H_2SO_4 exposure (no statistical analysis was performed because of the small number of subjects). Outer zone lung clearance was increased in six of seven subjects after H_2SO_4 exposure ($p < 0.05$). The dose of H^+ inhaled orally correlated significantly with the change in outer zone lung clearance ($r = 0.79$, $p = 0.05$).

11.2.1.6 Effects Of Acid Aerosols Studied By Bronchoscopy And Airway Lavage

Fiberoptic bronchoscopy with BAL has proved a useful technique for sampling the lower airways of humans in clinical studies of oxidant air pollutants. The type and number of cells recovered in BAL fluid reflect changes in alveolar and distal airway cell populations, providing a relatively sensitive measure of inflammation. Increases in serum proteins recovered in BAL fluid can be a result of increased epithelial permeability, a consequence of injury and/or inflammation. Alveolar macrophages obtained by BAL can be assessed *in vitro* for functional changes important in inflammation and host defense. In addition, proximal airway cells and secretions can be recovered using airway washes or proximal airway lavage (Eschenbacher and Gravelyn, 1987).

Only one study has utilized bronchoscopy to evaluate the effects of exposure to acid aerosols. Frampton et al. (1992) exposed 12 healthy nonsmokers to aerosols of NaCl (control) or H_2SO_4 (MMAD = 0.9, GSD = 1.9) at 1000 $\mu g/m^3$ for 2 h. Four 10-min

exercise periods at ≈40 L/min were included. Subjects brushed their teeth and rinsed with mouthwash prior to and once during each exposure to reduce oral ammonia levels. Fiberoptic bronchoscopy with BAL was performed 18 h after exposure. No evidence for airway inflammation was found. Markers for changes in host defense, including lymphocyte subset distribution, antibody-dependent cellular cytotoxicity of alveolar macrophages, and alveolar macrophage inactivation of influenza virus, were not significantly different between H_2SO_4 and NaCl exposures.

In an effort to define possible effects of H_2SO_4 exposure on airway mucus, Culp et al. (1994) determined the composition of mucins recovered during bronchoscopy of subjects studied by Frampton et al. (1992), as well as from some subjects not exposed. Secretions were lipid extracted from airway wash samples and analyzed with regard to glycoprotein content, protein staining profiles, and amino acid and carbohydrate composition. Mucin composition was similar when non-exposed subjects were compared with NaCl-exposed subjects, indicating that aerosol exposure *per se* did not alter mucus composition. No differences were found between H_2SO_4 and NaCl exposure with regard to absolute yields of high-density material, proportion of glycoproteins, presence of glycoprotein degradation products, carbohydrate composition, or protein composition.

In these studies, bronchoscopy was performed 18 h after exposure in order to detect delayed effects. Transient effects of exposure to acid aerosols on alveolar macrophage function or mucous composition have therefore not been excluded.

11.2.1.7 Acid Aerosols And Other Pollutants

Previous studies have suggested that exposure to H_2SO_4 does not potentiate responses to other pollutants. A number of more recent studies have also failed to find interactions in effects of pollutant mixtures that include H_2SO_4. Anderson et al. (1992) found no effects on lung function following exposure to 200 $\mu g/m^3$ carbon black alone, or carbon particles coated with H_2SO_4. Aris et al. (1990) found no effects on airways resistance of exposure to mixtures of hydroxymethanesulfonic acid and H_2SO_4. Balmes et al. (1988) found no differences between the effects of H_2SO_4 and HNO_3 exposure in asthmatics, and no interaction with exposure to both aerosols by mouthpiece. Koenig et al. (1989) found that

exposure of adolescent asthmatic subjects to 68 $\mu g/m^3$ H_2SO_4 with 0.1 ppm SO_2 did not increase the responses seen with H_2SO_4 alone.

In one recent study (Koenig et al., 1994), 28 adolescent asthmatic subjects were exposed to air, 0.12 ppm ozone + 0.3 ppm NO_2, ozone + NO_2 + 68 $\mu g/m^3$ H_2SO_4, and ozone + NO_2 + 0.05 ppm HNO_3. Exposures were by mouthpiece for 90 min, with intermittent exercise, on two consecutive days. No significant effects on lung function were seen for any of the atmospheres. However, six subjects did not complete the study protocol for a variety of reasons; these subjects were characterized by the authors as having moderate to severe asthma, based on results of methacholine challenge. Although the reasons for withdrawal of these subjects were not clearly related to exposures, all discontinued participation following exposure to pollutants rather than to clean air. Thus, the subjects who were unable to complete the study may have been more responsive; because their data could not be included in the analysis, a significant pollutant effect on a minority of subjects may have been missed.

Two recent studies suggest that exposure to 100 mg/m^3 H_2SO_4 may enhance airway effects of exposure to ozone. Linn et al. (1994) exposed 15 healthy and 30 asthmatic subjects to air, 0.12 ppm ozone, 100 $\mu g/m^3$ H_2SO_4 (MMAD $\approx$0.5 μm), and ozone + H_2SO_4 for 6.5 h on two consecutive days. Each subject received all 4 pairs of exposures, each separated by one week. Subjects were exposed in small groups in an environmental chamber, with six, 50-min exercise periods each day. Acidic gargles were used to reduce oral ammonia. Lung function and methacholine responsiveness were measured at the end of each exposure day. Reductions in FEV_1 and FVC, and increases in airway responsiveness, were observed in association with ozone exposure in both healthy and asthmatic subjects. Some subjects in both the asthmatic and nonasthmatic group demonstrated greater declines in lung function after the first day of acid + ozone than after ozone alone (Figure 11-2), although the group mean differences were only marginally significant by ANOVA. From these data, a "hypothetical average subject", under the specific conditions of the study, would be expected to lose 100 ml FEV_1 during ozone exposure relative to clean air exposure, and would lose 189 ml FEV_1 during ozone + H_2SO_4 exposure. When the responsive subjects were re-studied months later, increased responsiveness to acid + ozone compared with ozone

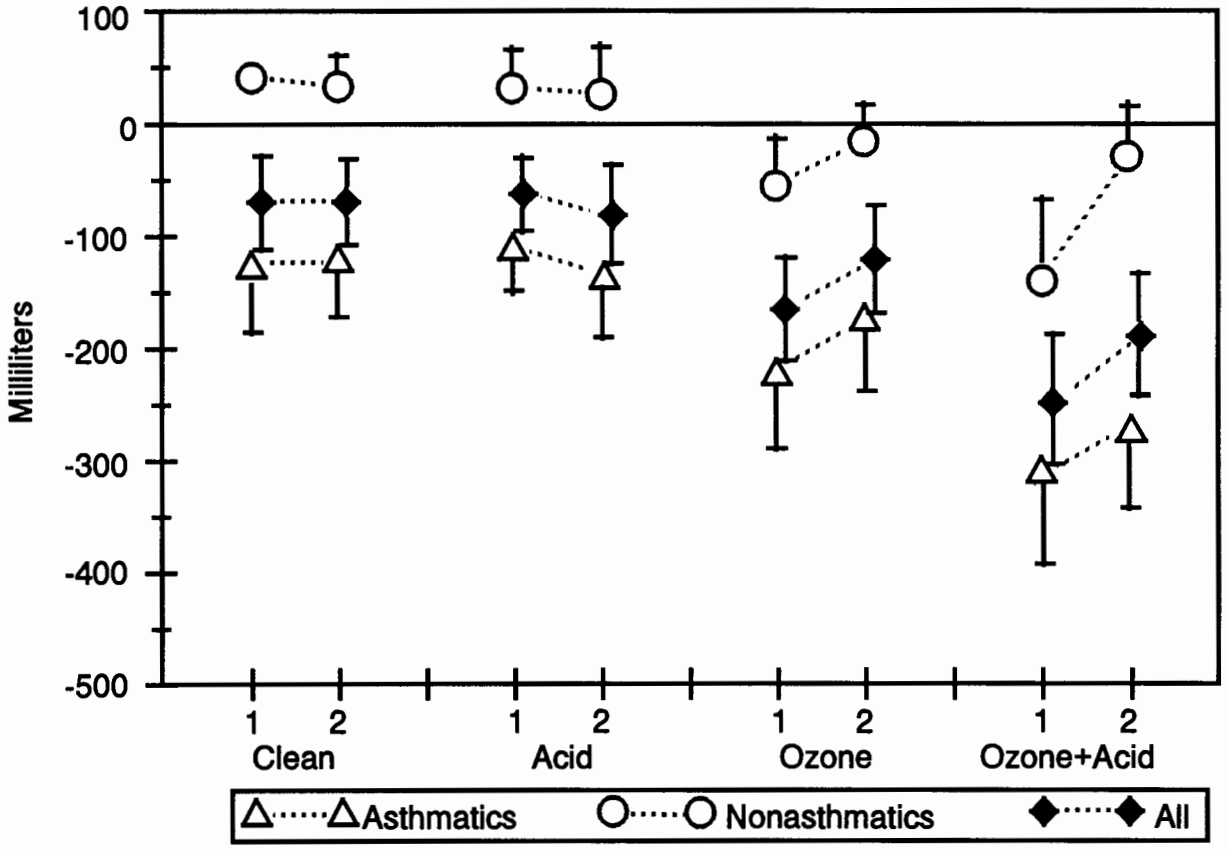

Figure 11-2. Decrements in FEV_1 (± SE) following 6.5-h exposures on 2 successive days.

Source: Linn et al. (1994).

was again demonstrated, although individual responses to O_3 + H_2SO_4 in the original and repeat studies were not significantly correlated.

Frampton et al. (1995) exposed 30 healthy and 30 asthmatic subjects to 100 $\mu g/m^3$ H_2SO_4 or NaCl for 3 h followed the next day by 0.08, 0.12, or 0.18 ppm ozone for 3 h. All exposures included intermittent exercise. Each subject received two of the three ozone exposure levels. Exposure to H_2SO_4 or NaCl did not alter lung functions. As shown in Table 11-3, changes in spirometry following exposure to ozone were small, consistent with the relatively low concentrations, short exposure duration, and moderate exercise levels ($\dot{V}_E$ 30.6 to 36.2 L/min for a total of 60 min). Figure 11-3 shows the percentage changes in

TABLE 11-3. PULMONARY FUNCTION RESPONSES AFTER AEROSOL AND OZONE EXPOSURES IN SUBJECTS WITH ASTHMA[a]

	FVC (L)		FEV_1 (L)		sGaw (cm H_2O/L/sec)	
Time of Measurement	NaCl	H_2SO_4	NaCl	H_2SO_4	NaCl	H_2SO_4
0.08 ppm Ozone						
Baseline	3.80 ± 0.17	3.73 ± 0.17	2.85 ± 0.11	2.79 ± 0.10	0.204 ± 0.021	0.209 ± 0.020
After exercise	3.64 ± 0.17	3.59 ± 0.18	2.84 ± 0.12	2.72 ± 0.12	-	-
Immediately after exposure	3.51 ± 0.18	3.64 ± 0.17	2.73 ± 0.12	2.79 ± 0.11	0.176 ± 0.024	0.177 ± 0.022
2 Hours after exposure	3.67 ± 0.17	3.70 ± 0.16	2.91 ± 0.12	2.89 ± 0.11	-	-
4 Hours after exposure	3.67 ± 0.15	3.74 ± 0.18	2.92 ± 0.10	2.92 ± 0.13	-	-
0.12 ppm Ozone						
Baseline	3.97 ± 0.22	3.95 ± 0.22	2.98 ± 0.17	3.05 ± 0.17	0.220 ± 0.015	0.236 ± 0.020
After exercise	3.72 ± 0.20	3.76 ± 0.19	2.94 ± 0.17	3.01 ± 0.16	-	-
Immediately after exposure	3.72 ± 0.21	3.76 ± 0.20	2.90 ± 0.19	2.97 ± 0.18	0.186 ± 0.019	0.209 ± 0.025
2 Hours after exposure	3.91 ± 0.22	3.85 ± 0.21	3.10 ± 0.18	3.08 ± 0.17	-	-
4 Hours after exposure	3.87 ± 0.22	3.87 ± 0.21	3.07 ± 0.18	3.04 ± 0.18	-	-
0.18 ppm Ozone						
Baseline	3.89 ± 0.23	3.99 ± 0.22	2.92 ± 0.16	3.04 ± 0.17	0.183 ± 0.016	0.207 ± 0.016
After exercise	3.76 ± 0.23	3.71 ± 0.22	2.90 ± 0.19	2.99 ± 0.16	-	-
Immediately after exposure	3.76 ± 0.23	3.74 ± 0.24	2.90 ± 0.19	2.96 ± 0.18	0.170 ± 0.016	0.179 ± 0.018
2 Hours after exposure	3.81 ± 0.25	3.87 ± 0.23	3.03 ± 0.19	3.03 ± 0.17	-	-
4 Hours after exposure	3.90 ± 0.24	3.84 ± 0.25	3.06 ± 0.17	2.99 ± 0.18	-	-

[a]Values are expressed as means ± SEM.

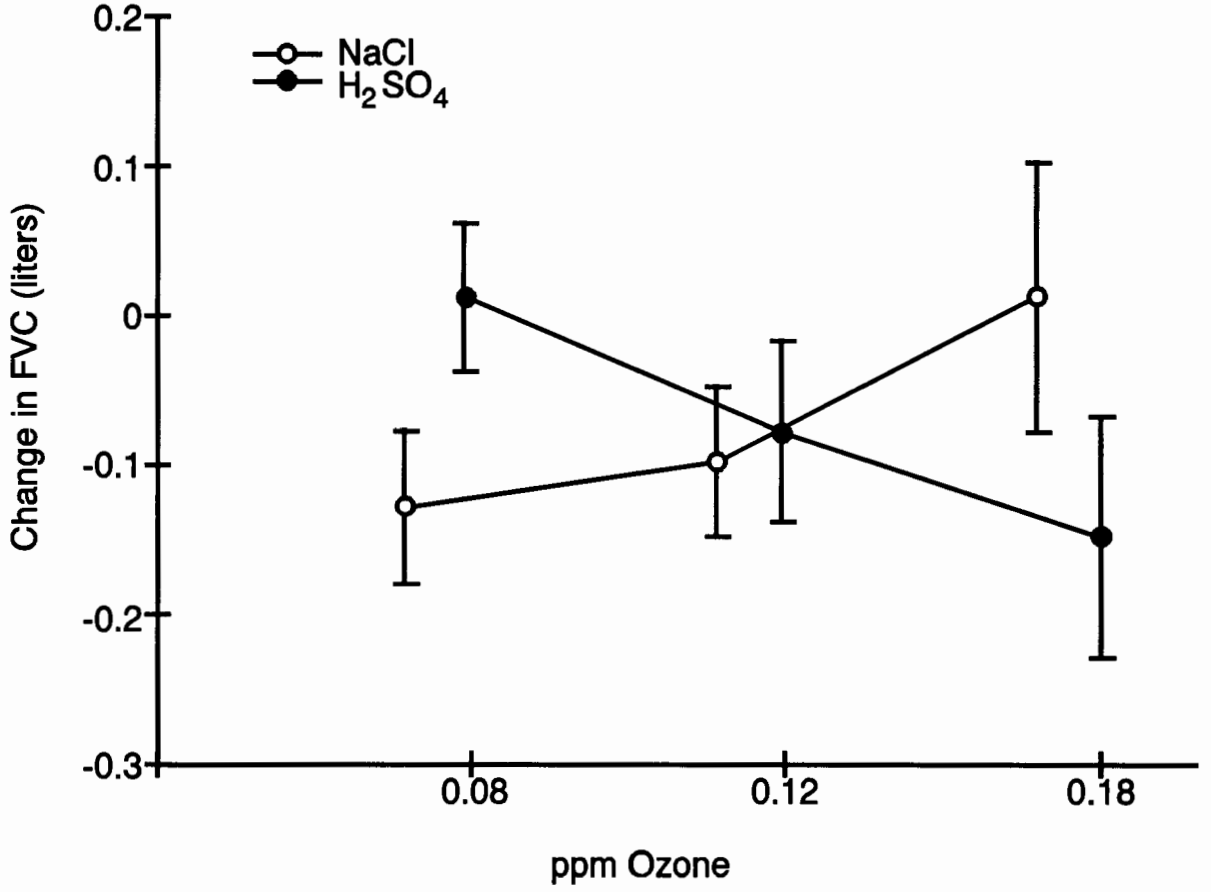

Figure 11-3. Asthmatic Subjects. The absolute change in FVC (liters) 4-h after exposure to each of the three ozone concentrations for the NaCl and H_2SO_4 aerosol preexposure conditions.

Source: Frampton et al., 1995.

FVC 4 h after ozone exposure; these changes were similar to those found immediately after exposure. With H_2SO_4 pre-exposure, FVC decreased following ozone in a concentration-response fashion. The ANOVA revealed significant main effects of ozone exposure as well as a significant interaction between aerosol and ozone exposure for effects on FEV_1 and FVC among the asthmatic subjects, but not the healthy subjects. Four-way ANOVA revealed an interaction between ozone and aerosol for the entire group ($p=0.0022$) and a difference between healthy subjects and subjects with asthma ($p=0.0048$). Surprisingly, decrements in FVC were found with 0.08 ppm ozone preceded by NaCl that were of similar magnitude to those seen with 0.18 ppm ozone preceded by H_2SO_4. The authors concluded that, for

asthmatic subjects, H_2SO_4 alters the response to ozone in comparison with NaCl pre-exposure. Interpretation of these findings would be facilitated by a similar study including air as a further control pre-exposure atmosphere. However, considered together, these two studies (Frampton et al., 1995 and Linn et al., 1994) suggest that H_2SO_4 aerosol exposure may enhance airway responsiveness to ozone.

11.2.1.8 Particulate Matter Other Than Acid Aerosols

Few studies have examined the effects of particles other than acid aerosols, despite the fact that ambient particulate matter consists of a mixture of soluble and insoluble material of varying chemical composition. Human safety considerations limit experimental exposures to particles considered to be essentially inert and non-carcinogenic. As reviewed in the 1982 Criteria Document (U.S. Environmental Protection Agency, 1982), Andersen et al. (1979) examined effects on healthy subjects of exposure to Xerox toner at concentrations ranging from 2 to 25 mg/m^3. These concentrations are not relevant to outdoor environmental exposures. Nevertheless, the studies were remarkable for the virtual absence of symptomatic or lung functional responses. Utell et al. (1980) exposed healthy young subjects with acute influenza to a $NaNO_3$ aerosol or NaCl (control), and observed significant reductions in specific airway conductance in response to the $NaNO_3$ aerosol, but not to NaCl aerosol, for up to 1 week following the acute illness. These studies suggested that individuals with acute viral illness may experience bronchoconstriction from particulate nitrate pollutants that do not have effects on healthy subjects. However, the concentration of particles in these experiments was $\approx$7 mg/m^3, more than 100 times greater than peak ambient concentrations.

Three more recent studies have attempted to examine effects of exposure to carbon black particles, either alone or in combination with other pollutants. First, Kulle et al. (1986) exposed 20 healthy nonsmokers (10 males and 10 females) to air, 0.99 ppm SO_2, 517 μg/m^3 activated carbon aerosol (MMAD = 1.5 μm, GSD = 1.5), and SO_2 + activated carbon for four hours in an environmental chamber. Two 15-minute exercise periods ($\dot{V}_E$ = 35 L/min) were included in the exposure. The exposure days were separated by one week and were bracketed by control air exposures on the day prior to and the day following the experimental exposure. Measurements included respiratory symptoms, spirometry, lung volumes, and airway responsiveness to methacholine. The carbon aerosol exposure resulted

in no significant effects on symptoms or lung function, and exposure to carbon + SO_2 did not enhance the very small effects on lung function seen with SO_2 alone. Results of methacholine challenge testing were not provided.

Second, a separate report from the same laboratory (Green et al., 1989) examined potential interactions between formaldehyde (HCHO) and carbon exposure. Twenty-four healthy nonsmokers without airway hyperresponsiveness were exposed for two hours to air, 3.01 ppm HCHO, 510 $\mu g/m^3$ activated carbon aerosol (MMAD = 1.4 μg, GSD = 1.8) and HCHO + carbon. Exposures incorporated exercise ($\dot{V}_E$ = 57 L/min) for 15 of each 30 minutes. The exposures were separated by one week. Measurements included symptoms, spirometry, lung volumes, and serial measurements of peak flow. There were no significant effects on symptoms or decrements in lung function with exposure to carbon alone. The combination of carbon and HCHO increased cough at 20 and 80 minutes of exposure when compared to either pollutant alone. There were also small (less than 5%) but statistically significant decrements in FVC, FEV_3, and peak flow with carbon + HCHO, compared with either pollutant alone. The authors speculated that the enhancement of cough with carbon + HCHO resulted from increased delivery of HCHO adsorbed to carbon.

Finally, the studies by Anderson et al. (1992), summarized previously, were designed to test the hypothesis that inert particles in ambient air may become coated with acid, thereby delivering increased concentrations of acid sulfates to "sensitive" areas of the respiratory tract. Carbon black particles (MMAD $\approx$1 μm, GSD $\approx$2 μm) were coated with H_2SO_4 using fuming H_2SO_4. Electron microscopy findings suggested successful coating of the particles. Fifteen healthy and 15 asthmatic subjects were exposed for 1 h to acid-coated carbon, with a total suspended particulate concentration of 358 $\mu g/m^3$ for asthmatic subjects and 505 $\mu g/m^3$ for healthy subjects. On separate occasions, subjects were also exposed to carbon black alone ($\approx$200 $\mu g/m^3$, estimated as the difference between total suspended particulate and non-carbon particulate concentrations), H_2SO_4 alone ($\approx$100 $\mu g/m^3$), and air. No adverse effects of particle exposure on lung function or airway responsiveness were observed for either study group.

Clinical studies of single particulate pollutants or simple mixtures may not be representative of effects that occur in response to complex ambient mixtures. In an attempt to examine effects of an ambient air pollution atmosphere under controlled laboratory

conditions, Yang and Yang (1994) exposed 25 asthmatic and 30 healthy subjects to polluted air collected in a motor vehicle tunnel in Taiwan. This compressed air sample contained 202 $\mu g/m^3$ particles as well as 0.488 ppm NO_2, 0.112 ppm SO_2, and 3.4 ppm carbon monoxide (CO). The chemical and size characteristics of the particles were not provided. Mouthpiece exposure to polluted air was performed at rest for 30 min, and lung function and methacholine responsiveness were assessed after exposure. Small but significant decrements in FEV_1 and FVC were observed in asthmatic, but not healthy subjects when compared with baseline measurements. However, no control exposure to air was performed, which seriously limits interpretation of these results. The small decrements in lung function could have resulted from exposure conditions other than the pollutants, such as humidity or temperature of the inhaled air, which were not specified.

Thus, few studies have examined effects of particles other than acid aerosols on lung function, although available data suggest inert particles in the respirable range have little or no acute effects at levels well above ambient concentrations. No studies have examined effects on mucociliary clearance, epithelial inflammation, or host defense functions of the distal respiratory tract in humans

11.2.1.9 Summary and Conclusions

Controlled human studies offer the opportunity to study the responses of human subjects under carefully controlled conditions, but are limited to short-term exposures to pollutant atmospheres without severe health risks. Outcome measures are limited by safety issues, but have been extended beyond measures of lung function and symptoms to include mucociliary clearance, BAL, and airway biopsies.

Human clinical studies of particle exposure remain almost completely limited to the study of acid aerosols, primarily of H_2SO_4, with the majority of these focussing on symptoms and pulmonary function. Only two studies (Frampton et al., 1992; Culp et al., 1995) have utilized BAL to examine effects of particle exposure in humans. No studies have examined effects of particle or acid aerosol exposure on airway inflammation in asthmatic subjects. There are no studies examining the effects of particle exposure on antigen challenge in allergic or asthmatic subjects.

Ten studies since 1988 have confirmed previous findings that healthy subjects do not experience decrements in lung function following single exposures to H_2SO_4 at levels up to 2,000 $\mu g/m^3$ for 1 h, even with exercise and use of acidic gargles to minimize neutralization by oral ammonia. Mild lower respiratory symptoms occur at exposure concentrations in the mg/m^3 range, particularly with larger particle sizes. Acid aerosols alter mucociliary clearance in healthy subjects, with effects dependent on exposure concentration and the region of the lung being studied.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels. Although the reasons for the inconsistency among studies remain largely unclear, subject selection and acid neutralization by NH_3 may be important factors. Even in studies reporting an overall absence of effects on lung function, occasional asthmatic subjects appear to demonstrate clinically important effects. Two studies from different laboratories have suggested that responsiveness to acid aerosols may correlate with degree of baseline airway hyperresponsiveness. There is a need to identify determinants of responsiveness to H_2SO_4 exposure in asthmatic subjects. In very limited studies, elderly and individuals with chronic obstructive pulmonary disease do not appear to be particularly susceptible to the effects of acid aerosols on lung function.

Two recent studies have examined the effects of exposure to both H_2SO_4 aerosols and ozone on lung function in healthy and asthmatic subjects. Both studies found evidence that 100 $\mu g/m^3$ H_2SO_4 may potentiate the response to ozone, in contrast with previous studies.

Human studies of particles other than acid aerosols provide insufficient data to draw conclusions regarding health effects. However, available data suggest that inhalation of inert particles in the respirable range, including three studies of carbon particles, have little or no effect on symptoms or lung function in healthy subjects at levels above peak ambient concentrations.

11.2.2 Laboratory Animal Studies

11.2.2.1 Introduction

This section reviews the effects of acidic aerosols on laboratory animals. Almost all of the available data have been derived from studies using acidic sulfates, namely ammonium bisulfate (NH_4HSO_4) and sulfuric acid (H_2SO_4).

11.2.2.2 Mortality

A number of studies reported in the previous CD (U.S. Environmental Protection Agency, 1982) examined the acute lethality of acid aerosols, mainly H_2SO_4, and there are little new data. As is evident with other toxicologic endpoints, large interspecies differences occurred, with the guinea pig appearing to be the most sensitive, compared to the mouse, rat and rabbit. But fairly high concentrations of H_2SO_4, generally above 4,000 $\mu g/m^3$, were required for lethality, even in a species as sensitive as the guinea pig. Furthermore within a particular species of experimental animal, the H_2SO_4 concentration required for lethality was dependent upon particle size, with smaller particles being less effective than larger ones.

As reported in the previous CD (U.S. Environmental Protection Agency, 1982), the cause of death due to acute, high-level H_2SO_4 exposure was laryngeal or bronchial spasm. Since these are irritant responses, differences in the deposition pattern of smaller and larger acid droplets may account for the aforementioned particle size dependence of lethal concentration; larger particles would deposit to a greater extent in the upper bronchial tree, where the bulk of irritant receptors are located. As the acid size is reduced, deeper pulmonary damage occurs prior to death. Lesions commonly seen are focal atelectasis, hemorrhage, congestion, pulmonary and perivascular edema, and desquamation of bronchiolar epithelium; hyperinflation is also often evident.

There are few data to allow assessment of lethality for acid sulfate aerosols other than H_2SO_4. Pattle et al. (1956) noted that if sufficient ammonium carbonate was added into the chamber in which guinea pigs were exposed to H_2SO_4 so as to provide excess NH_3, protection was afforded to acid levels which, in the absence of NH_3, would have produced 50% mortality. This implies that H_2SO_4 is more acutely toxic than its neutralization products [i.e., NH_4HSO_4 and/or $(NH_4)_2SO_4$]. Pepelko et al. (1980) exposed rats for 8 h/day for 3 days to $(NH_4)_2SO_4$ at 1,000,000 to 2,000,000 $\mu g/m^3$ (2 to 3 μm, MMAD); no

mortality resulted. On the other hand, 40 and 17% mortality was observed in guinea pigs exposed once for 8 h to 800,000 to 900,000, or 600,000 to 700,000 $\mu g/m^3$, respectively, of similarly sized-particles; no mortality was observed at levels $<600,000$ $\mu g/m^3$. Death was ascribed to airway constriction, rather than to extensive lung damage. As with H_2SO_4, guinea pigs were more sensitive than other species examined to the lethal effects of $(NH_4)_2SO_4$.

In summary, very high concentrations of acid sulfates are required to cause mortality in otherwise healthy animals. The mechanisms for this mortality are not expected to relate to human mortality observed in epidemiological studies.

11.2.2.3 Pulmonary Mechanical Function

Many studies examining the toxicology of inhaled acid aerosols at sublethal levels used changes in pulmonary function as indices of response. A survey of the database since publication of the previous CD (U.S. Environmental Protection Agency, 1982) is presented in Table 11-4.

One of the major exposure parameters which affects response is particle size. Studies by Amdur (1974) and Amdur et al. (1978a,b), summarized in the previous CD, showed that the irritant potency of H_2SO_4, $(NH_4)_2SO_4$, or NH_4HSO_4, as measured by pulmonary resistance in guinea pigs, increased with decreasing particle size (i.e., the degree of response per unit mass of sulfate $[SO_4^=]$ at any specific exposure concentration increased as particle size decreased, at least within the size range of 1 to 0.1 μm). If this is compared to the relationship between particle size and mortality, it is evident that the relative toxicity of different particle sizes also depends upon the exposure concentration. At high concentrations above the threshold for lethality, large particles were more effective in eliciting response, while at lower (sublethal) levels, smaller particles were more effective.

Pulmonary functional responses to H_2SO_4 described previously suggested a major site of action to be the conducting airways, as evidenced by exposure-induced alterations in resistance. However, some earlier data also suggested that high exposure levels may affect more distal lung regions, as evidenced by changes in pulmonary diffusing capacity (DL_{co}) noted in dogs exposed to 889 $\mu g/m^3$ (Lewis et al., 1973). Deep lung effects of H_2SO_4 are

TABLE 11-4. EFFECTS OF ACIDIC SULFATE PARTICLES ON PULMONARY MECHANICAL FUNCTION

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
H_2SO_4	Rat	Whole body	2,370	0.5 (MMD)	14 weeks	NC: V_T, f, R_L, Cd, pH, $PaCO_2$	Lewkowski et al. (1979)
H_2SO_4	Rat	Whole body	6,350	0.44 (MMD)	6 weeks	↓$PaCO_2$	Lewkowski et al. (1979)
H_2SO_4	Rat	Whole body	6,590	0.31 (MMD)	13 weeks	↑pH	Lewkowski et al. (1979)
H_2SO_4	Guinea pig, M Hartley	Whole body	1,000; 3,200	0.54 (MMD); 1.32	24 h/d, 3-30 d	Hypo- to hyperresponsive airways	Kobayashi and Shinozaki (1993)
H_2SO_4	Rabbit, M NZW	Nose-only (50%)	250	0.3 (MMAD); 1.6	1 h/day, 5 days/week, up to 12 mo	NC: R_L Hyperresponsive by 4 mo	Gearhart and Schlesinger (1986)
H_2SO_4	Guinea pig, M Hartley, 260-325 g	Nose-only (50%)	300	0.08 (MMD); 1.3	1 h	NC: VC, IC, VA, TLC; ↓DLco, (3 h post exp)	Chen et al. (1991)
H_2SO_4	Guinea pig, M Hartley, 290-410 g	Nose-only (50%)	200	0.06 (MMD); 1.4	1 h	NC: R_L	Chen et al. (1992b)
$(NH_4)_2SO_4$	Guinea pig, M Hartley, 10 wk	Whole body (50-60%)	1,000	0.4 (MMAD); 2.2	6 h/day, 5 days/week, 1 or 4 weeks	NC: RV; ↑FRC, VC, TLC, DLco, Cd, ΔN_2	Loscutoff et al. (1985)
$(NH_4)_2SO_4$	Rat, M SD, 14 wk	Whole body (50-60%)	1,000	0.4 (MMAD); 2.3	6 h/day, 5 days/week, 1 or 4 weeks	↑RV, ↑FRC, ΔN_2	Loscutoff et al. (1985)

Key to abbreviations:
NC: No significant change
↑: Significant increase
↓: Significant decrease
Cd: Dynamic compliance
DLco: Diffusing capacity, CO
f: Respiratory frequency
FRC: Functional residual capacity
IC: Inspiratory capacity
ΔN_2: Change in distribution of ventilation as measured by nitrogen washout technique
$PaCO_2$: Partial pressure of CO_2 in arterial blood
pH: Arterial pH
R_L: Pulmonary resistance
RV: Residual volume
TLC: Total lung capacity
V_T: Tidal volume
VA: Alveolar volume
VC: Vital capacity

also evident from studies of morphologic and lung defense endpoints, discussed in subsequent sections.

Studies reported in the previous CD (U.S. Environmental Protection Agency, 1982) indicated that the particle size of the acid aerosol affected the temporal pattern of any pulmonary function response. For example, the response to 100 $\mu g/m^3$ H_2SO_4 at 1 μm was slight and rapidly reversible, while that with 0.3 μm droplets was greater and more persistent. At any particular size, however, the degree of change in resistance and compliance in guinea pigs was observed to be concentration related.

Although the earlier studies by Amdur and colleagues appeared to provide a reasonable picture of the relative effects of acid particle size and exposure concentration on the bronchoconstrictive response of guinea pigs at sublethal exposure levels, there is some conflict between these results and reports by others discussed in the previous CD (U.S. Environmental Protection Agency, 1982). Whereas the former work supported a concentration dependence for respiratory mechanics alterations (i.e., animals in each exposure group responded uniformly and the degree of response was related to the exposure concentration), others found that individual guinea pigs exposed to H_2SO_4 at similar sizes showed an "all-or-none" constrictive response, i.e., in atmospheres above a threshold concentration, some animals manifested major changes in pulmonary mechanics ("responders"), while others were not affected at all ("nonresponders") (Silbaugh et al., 1981b). As the exposure concentration was increased further, the percentage of the group which was affected (i.e., the ratio of responders to nonresponders) increased, producing an apparent concentration response relationship. However, the magnitude of the change in pulmonary function was similar for all responders, regardless of exposure concentration. Sensitivity to this all-or-none response may be related to an animal's baseline airway caliber prior to H_2SO_4 exposure, because responders had higher pre-exposure values for resistance and lower values for compliance, compared to nonresponders. In any case, the threshold concentration for the all-or-none response was fairly high ($>10{,}000$ $\mu g/m^3$ H_2SO_4). Reasons for the discrepancy with the studies of Amdur and colleagues are not known; they may involve differences in guinea pig strains, ages, or exposure conditions, or differences in techniques used to measure functional parameters. In any case, the dyspneic response of the

guinea pig responders is similar to asthma episodes in humans, in both its rapidity of onset and in the associated characteristic obstructive pulmonary function changes.

A more recent approach used to evaluate the acute pulmonary functional response to H_2SO_4 involves co-inhalation of CO_2 (Wong and Alarie, 1982; Matijak-Schaper et al., 1983; Schaper et al., 1984). This procedure assesses the response to irritants by measuring a decrease in tidal volume (V_T) (based upon changes in inspiratory volume and pressure) which is routinely increased above normal by adding 10% CO_2 to the exposure atmosphere. Although the exact mechanism underlying a reduction in response to CO_2 is not clear, the assumption is that the change in ventilatory response after irritant exposure is due to direct stimulation of irritant receptors. A concentration-dependent decrease in CO_2-enhanced ventilation has been found in guinea pigs following 1-h exposures to H_2SO_4 (≈ 1 μm, MMD) at levels $\geq$40,100 $\mu g/m^3$ (Wong and Alarie, 1982). Subsequently, Schaper et al. (1984) exposed guinea pigs for 0.5 h to H_2SO_4 at 1,800 to 54,900 $\mu g/m^3$ (0.6 μm, AED). At concentrations $>10,000$ $\mu g/m^3$, the level of response (i.e., the maximum decrease in ventilatory response to CO_2) increased as a function of exposure concentration. At concentrations below 10,000 $\mu g/m^3$ there was no clear relationship between exposure concentration and response; any effects were transient, occurring only at the onset of acid exposure.

The results of the studies with CO_2 differ from those of both Silbaugh et al. (1981b) and Amdur and colleagues, in that there was neither an "all or none" response as seen by the former, nor was there a concentration-response relationship observed at H_2SO_4 concentrations $<10,000$ $\mu g/m^3$, as reported by the latter. In addition, Amdur and colleagues observed sustained changes in lung function, rather than a fading response, at low concentrations. The reasons for these differences are unknown, but may partly reflect inherent sensitivity differences in the measurement techniques used as noted above.

The specific mechanisms underlying acid sulfate-induced pulmonary functional changes are not known, but may be due to irritant receptor stimulation resulting from direct contact by deposited acid particles or from humoral mediators released as a result of exposure. In terms of the latter, a possible candidate in mediation of the bronchoconstrictive response, at least in guinea pigs, is histamine (Charles and Menzel, 1975). On the other hand, evidence for a direct response to H_2SO_4 in altering pulmonary function was found using the

CO_2 coinhalation procedure. Schaper and Alarie (1985) noted that the responses to histamine and H_2SO_4 differed in both their magnitude and temporal relationship, suggesting direct action of the inhaled acid or a role of other humoral factors.

Whatever the underlying mechanism, the results of pulmonary function studies indicate that H_2SO_4 is a bronchoactive agent that can alter lung mechanics of exposed animals primarily by constriction of smooth muscle; however, the threshold concentration for this response is quite variable, depending upon the animal species and measurement procedure used. In general, exposure to H_2SO_4 at levels $<1{,}000$ $\mu g/m^3$ does not produce physiologically significant changes in standard tests of pulmonary mechanics, except in the guinea pig. Although in this species such effects may be markers of exposure, their health significance in normal individuals is not always clear. On the other hand, all subgroups of an exposed population may not be equally sensitive.

11.2.2.3.1 Airway Responsiveness

Some lung diseases (e.g., asthma) involve a change in airway "responsiveness", which is an alteration in the degree of reactivity to exogenous (or endogenous) bronchoactive agents resulting in increased airway resistance at levels of these agents which would not affect airways of normal individuals. Such altered airways are called hyperresponsive. The use of pharmacologic agents capable of inducing smooth muscle contraction, a technique known as bronchoprovocation challenge testing, can assess the state of airway responsiveness after exposure to a nonspecific stimulus such as an inhaled irritant. Human asthmatics and, to some extent, chronic bronchitics, typically have hyperresponsive airways, but the exact role of this in the pathogenesis of airway disease is uncertain. Hyperresponsiveness may be a predisposing factor in clinical disease, or it may be a reflection of other changes in the airways which precede it. In any case, current evidence supports the hypothesis that an increase in airway responsiveness is a factor in the pathogenesis of obstructive airway disease (O'Connor et al., 1989).

The ability of H_2SO_4 aerosols to alter airway responsiveness has been assessed in a number of studies. Silbaugh et al. (1981a) exposed guinea pigs for 1 h to 4,000 to 40,000 $\mu g/m^3$ H_2SO_4 (1.01 μm, MMAD) and examined the subsequent response to inhaled histamine. Some of the animals showed an increase in pulmonary resistance and a decrease

in compliance at H_2SO_4 concentrations $\geq$19,000 $\mu g/m^3$ without provocation challenge; only the animals showing this constrictive response during acid exposure also had major increases in histamine sensitivity. This suggested that airway constriction may have been a prerequisite for the development of hyperresponsiveness. On the other hand, Chen et al. (1992b) found bronchial hyperresponsiveness, but no change in baseline resistance, in guinea pigs exposed for 1 h to 200 $\mu g/m^3$ H_2SO_4 (0.06 μm, MMD). Perhaps the smaller size of this aerosol was responsible for producing effects at a lower concentration.

Kobayashi and Shinozaki (1993) exposed guinea pigs to fairly high H_2SO_4 levels, namely 1,000 and 3,200 $\mu g/m^3$ (0.54 μm), 24 h/day for 3, 7, 14 or 30 days, and examined airway response to inhaled histamine. Unlike the study of Silbaugh et al. and similar to that of Chen et al., acid exposure did not change the baseline resistance measured prior to bronchoprovocation challenge. Exposure to 3,200 $\mu g/m^3$ of acid resulted in airway hyporesponsivess at 3 days, hyperresponsiveness at 14 days and a return to normal levels of responsivess by 30 days of exposure. Thus, acid exposure resulted in a transient alteration in airway function. The authors speculated that the hyporesponsiveness, and eventual return to normal, was due to changes in mucous secretion in the airways, which would affect the ability of the inhaled histamine challenge aerosol to contact airway receptors.

Airway responsiveness following chronic exposure to H_2SO_4 was examined by Gearhart and Schlesinger (1986), who exposed rabbits to 250 $\mu g/m^3$ H_2SO_4 (0.3 μm, MMD) for 1 h/day, 5 days/week, and assessed responsiveness after 4, 8 and 12 mo of exposure, using acetylcholine administered intravenously rather than inhaled. Hyperresponsiveness was evident at 4 mo, and a further increase was found by 8 mo; the response at 12 mo was similar to that at 8 mo, indicating a stabilization of effect. There was no change in baseline resistance. Thus, repeated exposures to H_2SO_4 produced hyperresponsive airways in previously normal animals.

The mechanism which underlies H_2SO_4-induced airway hyperresponsiveness is not clear. However, some recent studies have suggested possibilities. One may involve an increased sensitivity to mediators involved in airway smooth muscle control. For example, guinea pigs exposed to H_2SO_4 showed a small degree of enhanced response to histamine, but a much more pronounced sensitivity to substance P, a neuropeptide having effects on bronchial muscle tone (Stengel et al., 1993). El-Fawal and Schlesinger (1994) exposed

rabbits for 3 h to 50 to 500 $\mu g/m^3$ H_2SO_4 (0.3 μm), following which bronchial airways were examined in vitro for responsiveness to acetylcholine and histamine. Exposures at ≥ 75 $\mu g/m^3$ produced increased responsiveness to both constrictor agents. Detailed examination of the response in tracheal segments suggested that the acid effect may result from interference with airway contractile/dilatory homeostatic processes, in that there was a potentiation of the response of airway constrictor receptors and a diminution of the response of dilatory receptors.

11.2.2.4 Pulmonary Morphology and Biochemistry

Morphologic alterations associated with exposure to acid aerosols are outlined in Table 11-5.

Single or multiple exposures to H_2SO_4 at fairly high levels ($\gg 1{,}000$ $\mu g/m^3$) produce a number of characteristic morphologic responses (e.g., alveolitis, bronchial and/or bronchiolar epithelial desquamation, and edema). As with other endpoints, the sensitivity to H_2SO_4 is dependent upon the animal species. Comparative sensitivities of the rat, mouse, rhesus monkey and guinea pig were examined by Schwartz et al. (1977), using concentrations of H_2SO_4 $\geq 30{,}000$ $\mu g/m^3$ at comparable particle sizes (0.3 to 0.6 μm) and assessing airways from the larynx to the deep lung. Both the rat and monkey were quite resistant, while the guinea pig and mouse were the more sensitive species. The nature of the lesions in the latter pair were similar, but differed in location; this was, perhaps, a reflection of differences in the deposition pattern of the acid droplets. Mice would tend to have greater deposition in the upper respiratory airways than would the guinea pig (Schlesinger, 1985), which could account for the laryngeal and upper tracheal location of the lesions seen in the mice. The relative sensitivity of the guinea pig and relative resistance of the rat to acid sulfates is supported by results from other morphological studies (Busch et al., 1984; Cavender et al., 1977b; Wolff et al., 1986).

Repeated or chronic exposures to H_2SO_4 at concentrations $\leq 1{,}000$ $\mu g/m^3$ produce a response characterized by hypertrophy and hyperplasia of epithelial secretory cells. In morphometric studies of rabbits exposed to 125 to 500 $\mu g/m^3$ H_2SO_4 (0.3 μm) for 1 to 2 h/day, 5 d/week (Schlesinger et al., 1983; Gearhart and Schlesinger, 1988; Schlesinger et al., 1992b), increases in the relative number density of secretory cells (as determined by

TABLE 11-5. EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
H_2SO_4	Guinea pig	Whole body (70-90%)	32,600	1 (MMAD); 1.49	4 h	Focal atelectasis; epithelial desquamation in terminal bronchioles	Brownstein (1980)
H_2SO_4	Guinea pig, M/F Hartley, 2-3 mo	Whole body (80%)	1,200, 9,000, 27,000	0.8-1 (MMAD); 1.5-1.6	6 h	At 27,000 $\mu g/m^3$: interstitial edema only in "responders"; no change in "nonresponders" or at 1,000 and 10,000 $\mu g/m^3$. Concentration-dependent increase in height of tracheal mucus layer at all concentrations.	Wolff et al. (1986)
H_2SO_4	Rabbit, M mixed, 2.5-2.7 kg	Oral tube or nose-only (80%)	250-500	0.3 (MMAD); 1.6	1 h/day, 5 days/week, 4 weeks	Increased epithelial thickness in small airways; increase in secretory cells in mid to small airways	Schlesinger et al. (1983)
H_2SO_4	Rabbit, M mixed, 2.5-2.7 kg	Nose-only (80%)	250	0.3 (MMAD); 1.6	1 h/day, 5 days/week up to 52 weeks	Increase in secretory cell no. density throughout bronchial tree increase in number of small airways	Gearhart and Schlesinger (1988)
H_2SO_4	Rabbit, M NZ White, 3-3.5 kg	Nose-only (60%)	125	0.3 (MMD); 1.6	2 h/day, 5 days/week up to 12 mo	No bronchial inflammation; increase in secretory cell number density in small airways at 12 mo	Schlesinger et al. (1992b)
H_2SO_4	Rat	Whole body (40-60%)	2,000	0.3 (MMD); ≈ 2	8 h/day, 82 days	Some hypertrophy of epithelial cells, mainly at alveolar duct level; no effect on turnover rate of terminal bronchiolar epithelial or Type II cells	Juhos et al. (1978)
H_2SO_4	Rat	Whole body (50%)	700-1,200	0.03-0.04 (CMD); 1.8-2.1	Continuous, up to 180 days	No effect	Moore and Schwartz (1981)
H_2SO_4	Rat	Whole body ($\leq$60%)	45,000 68,000 172,000	0.52 (CMD) 0.4 (MMAD) 0.45 (CMD)	11 days 6 days 7 days	No effect in nasal passages, trachea, bronchi, alveolar region	Schwartz et al. (1977)
H_2SO_4	Rhesus monkey	Whole body ($\leq$60%)	150,000 361,000 502,000	0.3-0.5 (CMD) 0.43 (MMAD); 1.6 0.48 (MMAD); 1.5	3 days 7 days 7 days	No effect	Schwartz et al. (1977)

TABLE 11-5 (cont'd). EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
H_2SO_4	Guinea Pig	Whole body (≤60%)	30,000 38,000 71,000	0.31 (MMAD); 1.6 0.31 (MMAD); 1.6 0.52 (CMD)	7 days 7 days 4 days	At 71,000 $\mu g/m^3$: focal edema, necrosis of alveolar septa, inflammatory cell infiltration; necrosis of bronchiolar epithelium; focal epithelial necrosis in larger bronchi; ciliary denudation. At 38,000 $\mu g/m^3$: minimal effects; some change in density and length of cilia	Schwartz et al. (1977)
H_2SO_4	Mouse	Whole body (≤60%)	140,000 170,000	0.32 (MMAD); 1.4 0.62 (MMAD); 1.7	14 days 10 days	Lesions in larynx and upper trachea; epithelial ulceration, edema, inflammatory infiltration	Schwartz et al. (1977)
H_2SO_4	Rat	Whole body	1,000-100,000	0.6-1.1 (MMAD); 1.7-1.8	6 h	At 100,000 $\mu g/m^3$: some cilia loss; ulceration of larynx. < 100,000 $\mu g/m^3$: no effect	Henderson et al. (1980a)
H_2SO_4	Rat, M/F, F344/Crl 12-16 weeks	Whole body (80%)	1,100, 11,000, 96,000	0.8-1 (MMAD); 1.6-1.8	6 h	Laceration of larynx and cilia loss in bronchi at 96,000 $\mu g/m^3$; no deep lung lesions; some thickening of mucus lining in trachea at 11,000 and 96,000 $\mu g/m^3$	Wolff et al. (1986)
H_2SO_4	Rat, M Fischer, 250-300 g	Whole body (55%)	10,000 30,000 100,000	0.89 (MMD) 0.83 (MMD) 0.72 (MMD)	5 days 5 days 5 days	No effect	Cavender et al. (1977b)
H_2SO_4	Guinea pig	Whole Body (55%)	10,000 30,000 100,000	0.89 (MMD) 0.83 (MMD) 0.72 (MMD)	5 days 5 days 5 days	No effect } Mortality }	Cavender et al. (1977b)
$(NH_4)_2SO_4$	Guinea pig, M, Hartley adult	Whole Body	1,030	0.42 (MMD); 2.25	6 h/day, 5 days/week, 20 days	Interstitial thickening; hypertrophy and hyperplasia of Type II cells and secretory cells in bronchioli	Busch et al. (1984)
$(NH_4)_2SO_4$	Rat, M, SD/Crl, 70-75 g	Whole body	5000	0.8-1 (MMD); 1.8-2.0	7 days	No effect (proximal acinar region)	Last et al. (1983)
$(NH_4)_2SO_4$	Hamster, M, Syrian, 10 weeks	Whole body	187	0.3 (MMD); 2.02	6 h/day, 5 days/week, 15 weeks	Emphysematic lesions; no hyperplasia of bronchial glands or metaplasia of goblet cells	Godleski et al. (1984)
$(NH_4)_2SO_4$	Rat, M, adult	Whole body	300,000	1-2 (MMAD)	8 h/day, 1-14 days	No effect	Pepelko et al. (1980)

TABLE 11-5 (cont'd). EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
$(NH_4)_2SO_4$	Rat, M, SD adult	Whole body	1,030	0.42 (MMAD); 2.25	6 h/day, 5 days/week, 20 days	Interstitial thickening	Busch et al. (1984)
$(NH_4)_2SO_4$	Rat	Nose-only	70	0.2 (MMAD)	4 h/day, 4 days/week, 8 weeks	Increased alveolar septal thickness; decreased average alveolar diameter	Kleinman et al. (1995)

histochemical staining) have been found to extend to the bronchiolar level, where these cells are normally rare or absent. Depending upon the study, the changes began within 4 weeks of exposure and persisted for up to 3 mo following the end of exposure. The mechanism underlying increases in secretory cell numbers at low H_2SO_4 exposure levels is also unknown; it may involve an increase in secretory activity of existing cells, or a transition from another cell type.

A shift in the relative number of smaller airways (<0.25 μm) in rabbits was found by 4 mo of exposure to 250 $\mu g/m^3$ (0.3 μm) for 1 h/day, 5 days/week (Gearhart and Schlesinger, 1988). Changes in airway size distribution due to irritant exposure, specifically cigarette smoke, has been reported in humans (Petty et al., 1983; Cosio et al., 1977), and this seems to be an early change relevant to clinical small airways disease.

The specific pathogenesis of acid-induced lesions is not known. As with pulmonary mechanics, both a direct effect of deposited acid droplets on the epithelium and/or indirect effects, perhaps mediated by humoral factors, may be involved. For example, similar lesions have been produced in guinea pig lungs by exposure to either histamine or H_2SO_4 (Cavender et al., 1977a). In addition, some lesions may be secondary to reflex bronchoconstriction, to which guinea pigs are very vulnerable, rather than primary effects separable from constriction. Thus, damage at the small bronchi and bronchiolar level may be due not only to direct acid droplet-induced injury, but to indirect, reflex-mediated injury as well (Brownstein, 1980).

Morphologic and cellular damage to the respiratory tract following exposure to acid aerosols may be determined by methods other than direct microscopic observation. Analysis of bronchoalveolar lavage fluid can also provide valuable information, and this procedure has seen increasing use since publication of the previous CD. Levels of cytoplasmic enzymes, such as lactate dehydrogenase (LDH) and glucose-6-phosphate dehydrogenase (G-6PD), are markers of cytotoxicity; increases in lavageable protein suggest increased permeability of the alveolar epithelial barrier; levels of membrane enzymes, such as alkaline phosphatase, are markers of disrupted membranes; the presence of fibrin degradation products (FDP) provides evidence of general damage; and sialic acid, a component of mucoglycoprotein, indicates mucus-secretory activity. (It should, however, be noted that lavage analysis may not be able to provide identification of the site of injury nor indicate effects in the interstitial tissue.)

Henderson et al. (1980b) exposed rats for 6 h to H_2SO_4 (0.6 μm, MMAD) at 1,500, 9,500, and 98,200 $\mu g/m^3$, and found FDP in blood serum after exposure at all concentrations. No FDP was found in lavage fluid, but since the washing procedure did not include the upper respiratory tract (i.e., anterior to and including the larynx), FDP in the serum was concluded to be an indicator of upper airway injury. A concentration-dependent increase in sialic acid content of the lavage fluid was also observed, indicating increased secretory activity within the tracheobronchial tree.

Chen et al. (1992a) exposed guinea pigs to fine (0.3 μm) and ultrafine (0.04 μm) aerosols of H_2SO_4 at 300 $\mu g/m^3$ for 3 h/day for 1 or 4 days. Animals were sacrificed 24 h after each of these exposures. Following the single exposure to either size, lavage fluid showed increases in LDH and total protein, and the change in LDH was evident at 24 h with the fine, but not the ultrafine, particles. These responses did not occur following the 4 day exposure.

Wolff et al. (1986) exposed both rats and guinea pigs for 6 h to H_2SO_4 (0.8 to 1 μm, MMAD), at concentrations of 1,100 to 96,000 $\mu g/m^3$ for rats and 1,200 to 27,000 $\mu g/m^3$ for guinea pigs. No changes in lavageable LDH, protein, nor sialic acid were found in the rat. However, some of the guinea pigs exhibited bronchoconstriction after exposure to 27,000 $\mu g/m^3$, and only these animals showed increased levels of lavageable protein, sialic acid and LDH. In other studies, no changes in lavageable protein were found in the lungs of rats exposed for 3 days to 1,000 $\mu g/m^3$ (0.4 to 0.5 μm, MMAD) H_2SO_4 (Warren and Last, 1987), nor for 2 days to 5,000 $\mu g/m^3$ (0.5 μm, MMAD) $(NH_4)_2SO_4$ (Warren et al., 1986).

An important group of biological mediators of the inflammatory response, as well as of smooth muscle tone, are the eicosanoids, (e.g., prostaglandins and leukotrienes). Modulation of these mediators could be involved in damage to the respiratory tract due to inhaled particles. Preziosi and Ciabattoni (1987) exposed isolated, perfused guinea pig lungs for 10 min to aerosols of H_2SO_4 (no concentration or particle sizes were given). An increase in thromboxane B_2 but no change in leukotriene B_4 in the perfusate was found. Schlesinger et al. (1990b) exposed rabbits to 250 to 1,000 $\mu g/m^3$ H_2SO_4 (0.3 μm) for 1 h/day for 5 days. Lungs were lavaged and the fluid assayed for eicosanoids. A concentration-dependent decrease in levels of prostaglandins E_2 and $F_{2\alpha}$ and thromboxane B_2 were noted, while there was no change in leukotriene B_4. The effects, which were determined to be due to the

hydrogen ion rather than the sulfate ion, indicate that acid sulfates can upset the normally delicate balance of eicosanoid synthesis/metabolism which is necessary to maintain pulmonary homeostasis. Since some of the prostaglandins are involved in regulation of muscle tone, this imbalance may be involved in the development of airway hyperresponsivess found with exposure to acid sulfates.

Other biochemical markers of pulmonary damage have been used to assess the toxicity of acid sulfate particles. The proline content of the lungs may provide an index of collagen metabolism. No change in soluble proline content was found in rat lungs after exposure for 7 days to 4,840 $\mu g/m^3$ (0.5 μm, MMAD) $(NH_4)_2SO_4$, nor due to a 7 day exposure to 1,000 $\mu g/m^3$ (0.5 μm) H_2SO_4 (Last et al., 1986). A series of studies assessed collagen synthesis in rat lung minces after in vivo exposure; this is a possible indicator of the potential for pollutants to produce fibrosis. Exposure for 7 days to H_2SO_4 at 40, 100, 500, and 1,000 $\mu g/m^3$ (0.4 to 0.5 μm, MMAD) resulted in an increase in collagen synthesis rate only at 100 $\mu g/m^3$; higher levels had no effect (Warren and Last, 1987). No effect on collagen synthesis by rat lung minces was found due to 7-day exposures to $(NH_4)_2SO_4$ at 5,000 $\mu g/m^3$ (0.8 to 1 μm, MMAD) (Last et al., 1983).

Other parameters of pulmonary damage are changes in lung DNA, RNA, or total protein content. No significant changes in any of these parameters were found in rats after exposure to 1,000 $\mu g/m^3$ H_2SO_4 (<1 μm) for 3 days (Last and Cross, 1978), nor in protein content in rats exposed for up to 9 days to a similar concentration of H_2SO_4 (Warren and Last, 1987).

11.2.2.5 Pulmonary Defenses

Responses to air pollutants often depend upon their interaction with an array of non-specific and specific respiratory tract defenses. The former consists of nonselective mechanisms protecting against a wide variety of inhaled materials; the latter requires antigenic stimulation of the immune system for activation. Although these systems may function independently, they are linked, and response to an immunologic insult may enhance the subsequent response to nonspecific materials. The overall efficiency of lung defenses determines the local residence times for inhaled deposited material, which has a major

influence upon the degree of pulmonary response; furthermore, either depression or over-activity of these systems may be involved in the pathogenesis of lung diseases.

Studies of altered lung defenses resulting from inhaled acid aerosols have concentrated on conducting and respiratory region clearance function and nonspecific activity of macrophages; there are only a few studies of effects upon immunologic competence.

11.2.2.5.1 Clearance Function

Clearance, a major nonspecific defense mechanism, is the physical removal of material that deposits on airway surfaces. As discussed in Chapter 10, the mechanisms involved are regionally distinct. In the conducting airways, clearance occurs via the mucociliary system, whereby a mucus "blanket" overlying the ciliated epithelium is moved by the coordinated beating of the cilia towards the oropharynx. In the alveolar region of the lungs, clearance occurs via a number of mechanisms and pathways, but the major one for both microbes and nonviable particles is the alveolar macrophage (AM). These cells exist freely within the fluid lining of the alveolar epithelium, where they move by ameboid motion. The phagocytic ingestion of deposited particles helps prevent particle penetration through the alveolar epithelium and subsequent translocation to other sites. These cells contain proteolytic enzymes, which digest a wide variety of organic materials, and they also kill bacteria through oxidative mechanisms. In addition, AMs are involved in the induction and expression of immune reactions. Thus, the AM provides a link between the lung's non-specific and specific defense systems. These cells also are in the effector chain for lung damage (e.g., by release of proinflammatory cytokines).

Mucociliary Transport

The assessment of acid effects upon mucociliary clearance often involved examination only of mucus transport rates in the trachea, since this is a readily accessible airway and tracheal mucociliary clearance measurements are more straightforward to perform than are those aimed at assessing clearance from the entire tracheobronchial tree. Table 11-6 outlines studies of acid sulfate effects upon tracheal mucociliary clearance.

Although many of the studies involved fairly high concentrations of acid aerosols, most demonstrated a lack of effect. The most likely explanation for this is that the sizes of the

TABLE 11-6. EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT CLEARANCE

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
	Tracheal						
H_2SO_4	Dog, M/F Beagle, 3 years	Nose-only (80%)	1,000	0.3 (MMAD); 1.2	1 h	NC	Wolff et al. (1981)
			5,000	0.3 (MMAD); 1.2	1 h	NC	
			1,000	0.9 (MMAD); 1.3	1 h	↓	
			500	0.9 (MMAD); 1.3	1 h	↓	
H_2SO_4	Donkey, M/F adult	Nasopharyngeal catheter (45%)	200-1,400	0.4 (MMAD); 1.5	1 h	NC	Schlesinger et al. (1978)
H_2SO_4	Rat	Whole body (82%)	1,000-100,000	0.6-0.8 (MMAD); 1.5-2.6	6 h	↑	Wolff et al. (1980)
H_2SO_4	Rat	Nose-only (80%)	10,000-100,000	0.4-0.6 (MMAD); 1.3-1.4	0.5 h	↑	
H_2SO_4	Rat, M/F F344/Crl 12-16 weeks	Whole body (80%)	1,100, 11,000, 96,000	0.9-1 (MMAD); 1.6-1.8	6 h	↑ at 96,000 $\mu g/m^3$	Wolff et al. (1986)
H_2SO_4	Guinea pig, M/F Hartley 2-3 mo	Whole body (80%)	1,400, 9,000, 27,000	0.8-0.9 (MMAD); 1.5-1.6	6 h	↓ at 1,400 $\mu g/m^3$	
NH_4HSO_4	Sheep	Head-only (20-30%)	1,000	0.1 (CMD); 2.1	4 h	NC	Sackner et al. (1981)
$(NH_4)_2SO_4$	Donkey	Nasopharyngeal catheter (45%)	300-3,000	0.4 (MMAD); 1.5	1 h	NC	Schlesinger et al. (1978)
$(NH_4)_2SO_4$	Sheep	Head-only (20-30%)	1,100	0.1 (CMD); 2.1	4 h	NC	Sackner et al. (1981)
	Bronchial						
H_2SO_4	Rabbit, M NZW/mixed, 2.5-3 kg	Oral tube (75%)	100-2,200	0.3 (MMAD); 1.6	1 h	↑,↓ (depending on concentration and duration)	Chen and Schlesinger (1983); Schlesinger et al. (1984)
H_2SO_4	Rabbit, M mixed 2.5-2.7 kg	Oral tube or nose-only (80%)	250-500	0.3 (MMAD); 1.6	1 h/days, 5 days/week, 4 weeks	↑; persistent	Schlesinger et al. (1983)
H_2SO_4	Rabbit, M NZW 2.5-3 kg	Nose-only (80%)	250	0.3 (MMAD); 1.6	1 h/day, 5 days/week, 12 mo	↓ by 1 week; progressive slowing after 19 weeks; persistent	Gearhart and Schlesinger (1988)
H_2SO_4	Rabbit, M NZW 2.5-3 kg	Nose-only (60%)	1,250	0.3 (MMD); 1.6	2 h/day, 5 days/week up to 12 mo	↑ followed by ↓ PE; persistent	Schlesinger et al. (1992b)

TABLE 11-6 (cont'd). EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT CLEARANCE

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
	Bronchial						
H_2SO_4	Rabbit, M mixed 6 mo	oral tube nose-only	250; 250; 500	0.3 (MMAD); 1.6	1 h/day, 5 days/week, 4 weeks	↑ only some days at 250/oral and 500/nasal; persistant ↑ up to 14 days PE for all.	Schlesinger et al. (1983)
H_2SO_4	Donkey	Nasopharyngeal catheter (45%)	200-1,400	0.4 (MMAD); 1.5	1 h	↓ in some animals at all concentrations; progressive slowing in some animals with continued exposures.	Schlesinger et al. (1978)
H_2SO_4	Rat, M SD 200 g	Nose-only (39%; 85%)	3,600	1.0 (MMAD); 1.9-2.3	4 h	NC	Phalen et al. (1980)
NH_4HSO_4	Rabbit, M mixed 2.5-2.7 kg	Oral tube (78%)	600-1,700	0.4 (MMAD); 1.6	1 h	↓ at 1,700 $\mu g/m^3$	Schlesinger (1984)
$(NH_4)_2SO_4$	Rabbit, M mixed 2.5-2.7 kg	Oral tube (78%)	2,000	0.4 (MMAD); 1.6	1 h	NC	Schlesinger (1984)
$(NH_4)_2SO_4$	Rat, M SD 200 g	Nose-only (39%; 85%)	3,600	0.4 (MMAD); 1.9-2.3	4 h	NC	Phalen et al. (1980)
	Alveolar						
H_2SO_4	Rat, M SD 200 g	Whole body (30-80%)	3,600	1.0	4 h	NC	Phalen et al. (1980)
H_2SO_4	Rabbit, M NZW 2.5-3 kg	Oral tube	1,000	0.3 (MMAD); 1.5	1 h	↑	Naumann and Schlesinger (1986)
H_2SO_4	Rabbit, M NZW 2.5-3 kg	Nose-only (80%)	250	0.3 (MMAD); 1.6	1 h/day, 5 days/week, 1, 57, 240 day	↑	Schlesinger and Gerhart (1986)

TABLE 11-6 (cont'd). EFFECTS OF ACIDIC SULFATE PARTICLES ON RESPIRATORY TRACT CLEARANCE

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
	Alveolar (cont'd)						
H_2SO_4	Rabbit, M NZW 3-3.5 kg	Nose-only (80%)	500	0.3 (MMAD); 1.6	2 h/day, 14 days	↓	Schlesinger and Gearhart (1987)

Key to abbreviations:
NC: No significant change
↑: Significant increase
↓: Significant decrease
PE: Post exposure

aerosols were such that significant tracheal deposition did not occur. This is supported by the results of Wolff et al. (1981), who found tracheal transport rates in dogs to be depressed only when using 0.9 μm H_2SO_4; no effect was seen with a 0.3 μm aerosol at an equivalent mass concentration. In addition, the use of tracheal clearance rate as a sole toxicologic endpoint may be misleading, inasmuch as a number of studies have demonstrated alterations in bronchial clearance patterns in the absence of changes in tracheal mucous transport.

Studies assessing the effects of acid aerosols upon bronchial mucociliary clearance are also outlined in Table 11-6. Responses following acute exposure to H_2SO_4 indicate that the nature of clearance change (i.e., a slowing or speeding) is concentration dependent; stimulation of clearance generally occurs at low concentrations, and retardation generally occurs at higher levels. However, the actual concentration needed to alter clearance rate may depend upon the anatomic location within the bronchial tree from which clearance is being measured, in relation to the region which is most affected by the deposited acid. Studies in humans indicated that low H_2SO_4 concentrations (i.e., $\approx$100 to 500 $\mu g/m^3$) may accelerate clearance, compared to unexposed subjects, from the large proximal airways where little acid deposits, while slowing clearance from the distal ciliated airways where there is greater acid deposition. At higher concentrations, i.e., mucociliary clearance from both the proximal and distal bronchial tree may be depressed (Leikauf et al., 1984).

Comparison of responses to H_2SO_4 show interspecies differences in the sensitivity of mucociliary clearance to acid aerosols. As an example, the acceleration of tracheal transport found by Wolff et al. (1986) in the rat with $\approx$100,000 $\mu g/m^3$ H_2SO_4 seems anomalous since, in other species, levels $\geq$1,000 $\mu g/m^3$ depress mucociliary function. The reasons for this apparent discrepancy are not known. The rat is less susceptible to the lethal effects of H_2SO_4, and it does not have strong bronchoconstrictive reflex responses following H_2SO_4 exposures. These characteristics suggest that the mucociliary system of the rat may also differ in sensitivity from the other species studied, a view supported by the lack of effect of H_2SO_4 on bronchial clearance found by Phalen et al. (1980) following exposure at 3,600 $\mu g/m^3$ for 4 h and by the similarity in bronchial clearance response in donkeys and rabbits to single 1-h exposures of H_2SO_4 (Table 11-6). Although the lack of response of tracheal transport in the guinea pig at H_2SO_4 levels $>$1,000 $\mu g/m^3$ is also surprising, its response at

1,000 $\mu g/m^3$ is also different from that of the rat and more in line with other species (Wolff, 1986).

The relative potency of acid sulfate aerosols, in terms of altering mucociliary clearance, is related to their acidity (H^+ content). Schlesinger (1984) exposed rabbits for 1 h to submicrometer aerosols of NH_4HSO_4, $(NH_4)_2SO_4$, and Na_2SO_4. Exposure to NH_4HSO_4 at concentrations of $\approx$600 to 1,700 $\mu g/m^3$ significantly depressed clearance rate only at the highest exposure level. No significant effects were observed with the other sulfur oxides at levels up to $\approx$2,000 $\mu g/m^3$. When these results are compared to those from a study using H_2SO_4 (Schlesinger et al., 1984), the ranking of irritant potency was H_2SO_4 > NH_4HSO_4 > $(NH_4)_2SO_4$, Na_2SO_4; this strongly suggests a relation between the hydrogen ion concentration and the extent of alteration in bronchial mucociliary clearance.

The mechanism by which deposited acid aerosol alters clearance is not certain. The effective functioning of mucociliary transport depends upon optimal beating of cilia and the presence of mucus having appropriate physicochemical properties, and both ciliary beating as well as mucus viscosity may be affected by acid deposition. At alkaline pH, mucus is more fluid than at acid pH, so a small increase in viscosity due to deposited acid could "stiffen" the mucus blanket, perhaps promoting the clearance mechanism and, thus, increasing its efficiency (Holma et al., 1977). Such a scenario may occur at low H_2SO_4 exposure concentrations, where ciliary activity would not be directly affected by the acid, and is consistent with clearance acceleration observed at these concentrations with acute exposure. However, the exact relation between mucus viscosity and transport rate is not certain; differential alterations in rheological properties of the sol or gel layers may have different effects upon the system (Puchelle and Zahm, 1984).

High concentrations of H_2SO_4 may affect ciliary beating, as discussed in the previous CD (U.S. Environmental Protection Agency, 1982; Schiff et al., 1979; Grose et al., 1980). An additional mechanism by which deposited acid may affect mucociliary clearance is via altering the rate and/or amount of mucus secreted. A small increase in mucus production could facilitate clearance, while more excessive production could result in a thickened mucus layer which would be ineffectively coupled to ciliary beat. Finally, the airways actively transport ions, and the interaction between transepithelial ion transport and consequent fluid movement is important in maintaining the mucus lining. A change in ion transport due to

deposited acid particles may alter the depth and/or composition of the sol layer (Nathanson and Nadel, 1984), perhaps affecting clearance rate. In any case, the pathological significance of transient alterations in bronchial clearance rates in healthy individuals is not certain, but such changes are an indication of a lung defense response. On the other hand, persistent impairment of clearance may lead to the inception or progression of acute or chronic respiratory disease and, as such, may be a plausible link between inhaled acid aerosols and respiratory disease.

Short-term exposures to acid aerosols may lead to persistent clearance changes, as indicated previously (Schlesinger et al., 1978). The effects of long-term exposures were investigated by Schlesinger et al. (1983), who exposed rabbits to 250 or 500 $\mu g/m^3$ H_2SO_4 (0.3 μm, MMAD) for 1 h/day, 5 days/week for 4 weeks, during which time bronchial mucociliary clearance was monitored. Clearance was accelerated on individual days during the course of the acid exposures, especially at 500 $\mu g/m^3$. In addition, clearance was significantly faster, compared to preexposure levels, during a 2 week follow- up period after acid exposures had ceased.

Another long-term exposure at relatively low H_2SO_4 levels was conducted by Gearhart and Schlesinger (1988). Rabbits were exposed to 250 $\mu g/m^3$ H_2SO_4 for 1 h/day, 5 days/week for up to 52 weeks, and some animals were also provided a 3 mo follow-up period in clean air. Clearance was slower during the first month of exposure and this slowing was maintained throughout the rest of the exposure period. After cessation of exposure, clearance became extremely slow and did not return to normal by the end of the follow-up period. Differences in the nature of clearance change between this study and that of Schlesinger et al. (1983) may be due to differences in exposure protocol daily (duration) and/or concentration. In both studies, however, and as discussed earlier, histologic analyses indicated the development of increased numbers of epithelial secretory cells, especially in small airways, the likely consequence of which would be an increase in mucus production. In addition, the slowing of clearance seen by Gearhart and Schlesinger (1988) was also associated with a shift in the histochemistry of mucus towards a greater content of acidic glycoproteins; this would tend to make mucus more viscous.

The longest duration study at the lowest concentration of H_2SO_4 yet reported is that of Schlesinger et al. (1992b), in which rabbits were exposed to 125 $\mu g/m^3$ H_2SO_4 for 2 h/day,

5 days/week for up to 52 weeks. The variability of measured clearance time was increased with acid exposure, and acceleration of clearance was noted at various times during the one-year exposure period. However, following a 6-mo observation period, after exposures ceased, a trend towards slowing of clearance was noted (compared to both control and rates during acid exposure). In addition, and consistent with previous studies, an increase in the number density of epithelial secretory cells was observed in small airways (<0.5 mm) following 12 mo of acid exposure. This histological change had resolved by the end of the 6-mo post-exposure period.

Alveolar Region Clearance and Alveolar Macrophage Function

Only a few studies have examined the ability of acid aerosols to alter clearance of particles from the alveolar region of the lungs (Table 11-6). Rats exposed to 3,600 $\mu g/m^3$ H_2SO_4 (1μm) for 4 h showed no change in clearance (Phalen et al., 1980). On the other hand, acceleration of clearance was seen in rabbits exposed for 1 h to 1,000 $\mu g/m^3$ H_2SO_4 (0.3 μm, MMAD) (Naumann and Schlesinger, 1986).

Two studies involving repeated exposures to acid aerosols have been reported. In one, rabbits were exposed to 250 $\mu g/m^3$ (0.3 μm, MMAD) H_2SO_4 for 1 h/day, 5 days/week, and inert tracer particles were administered on days 1, 57 and 240 following the start of the acid exposures (Schlesinger and Gearhart, 1986). Clearance (measured for 14 days after each tracer exposure) was accelerated during the first test, and this acceleration was maintained throughout the acid exposure period. In the other study (Schlesinger and Gearhart, 1987), rabbits were exposed 2 h/day for 14 days to 500 $\mu g/m^3$ H_2SO_4 (0.3 μm, MMAD); retardation of early alveolar region clearance of tracer particles administered on the first day of exposure was noted. The results of these two studies suggest a graded response, whereby a low exposure concentration accelerates early alveolar region clearance and a high level retards it, such as was seen with mucociliary transport following acute H_2SO_4 exposure.

The mechanisms responsible for the altered alveolar region clearance patterns seen in the above studies are not known. Observed clearance is the net consequence of a number of differential underlying responses, which can include change in mucociliary transport rates and altered functioning of AMs.

A number of studies have examined the functional response of AMs following acidic sulfate aerosol exposures. To adequately perform their role in clearance, AMs must be competent in a number of functions, including phagocytosis, mobility and attachment to a surface. Alterations in any one, or combination, of these individual functions may affect clearance function. Naumann and Schlesinger (1986) noted a reduction in surface adherence and an enhancement of phagocytosis in AMs obtained by lavage from rabbits following a 1-h exposure to 1,000 $\mu g/m^3$ H_2SO_4 (0.3 μm). The acid exposure produced no change in the viability or numbers of recoverable AMs.

In a study with repeated H_2SO_4 exposures, AMs were lavaged from rabbits exposed to 500 $\mu g/m^3$ H_2SO_4 (0.3 μm) for 2 h/day for up to 13 consecutive days (Schlesinger, 1987a). Macrophage counts increased after 2 of the daily exposures, but returned to control levels thereafter. Neutrophil counts remained at control levels throughout the study, suggesting no acute inflammatory response. Random mobility of AMs decreased after 6 and 13 of the daily exposures. The number of phagocytically active AMs and the level of such activity increased after 2 exposures, but phagocytosis became depressed by the end of the exposure series. Although such studies demonstrate that H_2SO_4 can alter AM function, they have not as yet been able to provide a complete understanding of the cellular mechanisms which may underly the changes in pulmonary region clearance observed with exposure to acid aerosols.

The relative potency of acidic sulfate aerosols in terms of altering AM numbers or function has been examined. Aranyi et al. (1983) found no change in total or differential counts of free cells lavaged from mice exposed to 1,000 $\mu g/m^3$ $(NH_4)_2SO_4$ for 3 h/day for 20 days; this suggests a lack of inflammatory response to this sulfate aerosol. Additional studies seem to suggest that the response to acid sulfates of AM is a function of the H^+. Schlesinger et al. (1990a) examined phagocytic activity of AMs recovered from rabbits exposed for 1 h/day for 5 days to either 250 to 2,000 $\mu g/m^3$ H_2SO_4 (0.3μm) or 500 to 4,000 $\mu g/m^3$ NH_4HSO_4 (0.3 μm); the levels were chosen such that the H^+ concentration in the exposure atmospheres were equivalent for both sulfate species. Phagocytic activity of AMs was reduced following exposure to $\geq$1,000 $\mu g/m^3$ H_2SO_4 or to 4,000 $\mu g/m^3$ NH_4HSO_4; exposure to 2,000 $\mu g/m^3$ NH_4HSO_4 resulted in increased phagocytic activity. While these exposure concentrations were quite high, the interesting observation was that for a given level of sulfate, the response to H_2SO_4 was greater than that to NH_4HSO_4.

However, even when the data were assessed in terms of H^+ concentration in the exposure atmosphere, it was noted that exposure to the same concentrations of H^+ did not result in identical responses for the two different acid sulfate species; H^+ appeared to be more effective as the H_2SO_4 species. On the other hand, when AMs were incubated in acidic environments in vitro, the phagocytic activity response was identical, regardless of the sulfate species used, as long as the pH was the same. These results suggested an enhanced potency of H_2SO_4 during inhalation exposures. Experimental evidence provided by Schlesinger and Chen (1994) indicated that this difference noted in vivo was likely a reflection of different degrees of neutralization by respiratory tract ammonia of the two species of inhaled acid aerosols. It was shown that, for a given concentration of ammonia and within a given residence time within the respiratory tract, more total H^+ remained available from inhaled sulfuric acid than from inhaled ammonium bisulfate when the exposure atmospheres had the same total H^+ concentration. Thus, the greater observed potency of inhaled sulfuric acid compared to ammonium bisulfate for exposure atmospheres containing the same total H^+ concentration is likely due to a greater degree of neutralization of the latter, and a resultant greater loss of H^+ prior to particle deposition onto airway surfaces. Thus, the respiratory "fate" of inhaled acid sulfate particles should be considered in assessing the relationship between exposure atmosphere and biological response, since a lower H^+ concentration will likely deposit onto lung tissue than is inhaled at the mouth or nose.

Interspecies differences in the effects of acid sulfates on AM function were examined by Schlesinger et al. (1992a). Based upon in vitro exposures of AM to acidic media, a ranking of response in order of decreasing sensitivity to acidic challenge and subsequent effect on phagocytic activity was found to be: guinea pig > rat > rabbit > human.

As noted with other endpoints, the effect of H_2SO_4 upon AM function may be dependent upon particle size. Chen et al. (1992a) observed that 300 $\mu g/m^3$ H_2SO_4 enhanced the phagocytic activity of AMs recovered from guinea pigs after 4 days (3 h/day) of exposure to fine particles (0.3 μm), while an indentical exposure to ultrafine particles (0.04 μm) depressed phagocytic function.

The effects of acid sulfates upon the intracellular pH of AMs has been examined, because this may be one of the determinants of the rate of many cellular functions (Nucitelli and Deamer, 1982). Internal pH of AMs recovered from guinea pigs exposed to 300 $\mu g/m^3$

H_2SO_4 was depressed after a single 3-h exposure to both 0.3 and 0.04 μm particles, but the depression persisted for 24 h following exposure to the smaller size (Chen et al., 1992b). A depression in pH was also noted 24 h following 4 days of exposure to the ultrafine, but not the fine, aerosol. Thus, acid exposure produced a change in intracellular pH of the AMs and the effect was particle size dependent.

It is possible that this and other differences in response between fine and ultrafine particles reflect, to some extent, differences in the number of particles in aerosols of these two size modes, in that at a given mass concentration of acid sulfate, there are a greater number of ultrafine than fine particles. To examine this possibility, Chen et al. (1995) noted that changes in intracellular pH of macrophages obtained following inhalation exposure to H_2SO_4 aerosols were dependent both upon the number of particles impacting the cells, as well as upon the total mass concentration of H^+ in the exposure atmosphere, with a threshold existing for both exposure parameters. The role of size in modulating toxicity due to PM is discussed further in Section 11.5. It should, however, be noted that aside from number, differences in deposition and neutralization may also affect differential responses to fine and ultrafine particles.

A possible mechanism underlying the acid-induced alterations in intracellular pH was examined by Qu et al. (1993), who exposed guinea pigs to 969 $\mu g/m^3$ H_2SO_4 (0.3 μm MMD, σg 1.73) for 3 h or to 974 $\mu g/m^3$ for 3 h/day for 5 days. Macrophages were obtained following the end of each exposure protocol and examined for the ability of internal pH to recover from an added intracellular acid load. Both H_2SO_4 exposures resulted in a depression of internal pH recovery compared to air control. Subsequent analysis indicated that this alteration in internal pH regulation was attributable to effects on the Na^+/H^+ exchanger located in the cell membrane.

Macrophages are the source of numerous biologically active chemicals, and the effects of acid sulfate upon some of these have been investigated. Zelikoff and Schlesinger (1992) exposed rabbits to 50 - 500 $\mu g/m^3$ H_2SO_4 (0.3 μm) for 2 h. AM recovered by lavage following exposure were assessed for effects on tumor necrosis factor (TNF) release/activity and production of superoxide radical, both of which are biological mediators involved in host defense. Exposure to H_2SO_4 at $\geq$ 75 $\mu g/m^3$ produced a reduction in TNF cytotoxic activity, as well as a reduction in stimulated production of superoxide radical. Subsequently, Zelikoff

et al. (1994) exposed rabbits for 2 h/day for 4 days to sulfuric acid at 500, 750 or 1,000 $\mu g/m^3$. AM recovered from animals exposed at the highest acid level showed a reduction in TNF and interleukin (IL)-1α production/activity, both immediately and 24 h following the last exposure. On the other hand, increased release of TNF from macrophages obtained from guinea pigs was observed immediately following a single 3 h exposure, and 24 h following a 3 h/day 4 day exposure, to 300 $\mu g/m^3$ H_2SO_4 (0.3 μm or 0.04 μm) (Chen et al., 1992a); in addition, production of hydrogen peroxide by these cells was enhanced immediately after the 4 day exposure. These differences in TNF may reflect interspecies differences in response to acid exposure and/or differences in experimental conditions.

11.2.2.5.2 Resistance to Infectious Disease

The development of an infectious disease requires both the presence of the appropriate pathogen, as well as host vulnerability. There are numerous anti-microbial host defenses with different specific functions for different microbes (e.g., there are some differences in defenses against viruses and bacteria). The AM represents the main defense against gram positive bacteria depositing in the alveolar region of the lungs. The ability of acid aerosols to modify resistance to bacterial infection could result from a decreased ability to clear microbes, and a resultant increase in their residence time, due to alterations in AM function. To test this possibility, a rodent infectivity model has been frequently used. In this technique, mice are challenged with a bacterial aerosol after exposure to the pollutant of interest; mortality rate and survival time are then examined within a particular postexposure time period. Any decrease in the latter or increase in the former indicates impaired defense against respiratory infection. A number of studies which have used the infectivity model (primarily with *Streptococcus sp.*) to assess effects of acid aerosols were discussed in the previous CD (U.S. Environmental Protection Agency, 1982). It was evident that acute exposures to H_2SO_4 aerosols at concentrations up to 5,000 $\mu g/m^3$ were not very effective in enhancing susceptibility to this bacterially-mediated respiratory disease in the murine model. More recent studies with mice, shown in Table 11-7, continue to support this conclusion.

However, a study using another animal suggests that H_2SO_4 may indeed alter antimicrobial defense. Zelikoff et al. (1994) exposed rabbits for 2 h/day for 4 days to 500, 750, or 1,000 $\mu g/m^3$ H_2SO_4. Intracellular killing of a bacterium, *Staphylococcus aureus,* by

TABLE 11-7. EFFECTS OF ACID SULFATES ON BACTERIAL INFECTIVITY IN VIVO

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique (RH)	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	References
H_2SO_4	Mouse, F CD-1 30 days	Head-only (31%)	543	0.08 (VMD); 2.3	2 h	NC	Grose et al. (1982)
H_2SO_4	Mouse, F CD-1 30 days	Head-only (31%)	365	0.06 (VMD); 2.3	2 h/day, 5 days	NC	Grose et al. (1982)
$(NH_4)_2SO_4$	Mouse, F CD-1 30 days	Whole body	1,000	Submicrometer	3 h/day, 20 days	NC	Aranyi et al. (1983)

NC: No change

AMs recovered by lavage 24 h following the last exposure at the two highest acid concentrations was reduced; bacterial uptake was also reduced at the same time point, but only at the highest acid level. Thus, repeated H_2SO_4 exposures may reduce host resistance to bacteria in the rabbit, in contrast to no effect on mouse infectivity.

11.2.2.5.3 Specific Immune Response

Most of the database involving effects of acid aerosols on lung defense is concerned with non-specific mechanisms. Little is known about the effects of these pollutants on humoral (antibody) or cell-mediated immunity. Since numerous potential antigens are present in inhaled air, the possibility exists that acid sulfates may enhance immunologic reaction and, thus, produce a more severe response, and one with greater pulmonary pathogenic potential. Pinto et al. (1979) found that mice which inhaled H_2SO_4 for 0.5 h daily and were then exposed weekly to a particulate antigen (sheep red blood cells) exhibited higher serum and bronchial lavage antibody titers than did animals exposed to the antigen alone; unfortunately, neither the exposure mass concentration nor particle size of the H_2SO_4 was described. The combination of acid with antigen also produced morphologic damage, characterized by mononuclear cell infiltration around the bronchi and blood vessels, while exposure to acid or antigen alone did not. Thus, the apparent adjuvant effect of H_2SO_4 may be a factor promoting lung inflammation.

Osebold et al. (1980) exposed mice to 1,000 $\mu g/m^3$ H_2SO_4 (0.04 μm, CMD) to determine whether this enhanced the sensitization to an inhaled antigen (ovalbumin). The exposure regimen involved intermittent 4 day exposures, up to 16 total days of exposure; no increase in sensitization compared to controls was found. Kitabatake et al. (1979) exposed guinea pigs to 1,910 $\mu g/m^3$ (<1 μm, MMAD) for 0.5 h twice per week for 4 weeks, followed by up to 10 additional paired treatments with the H_2SO_4 for 0.5 h each; the animals were then exposed to aerosolized albumin for another 0.5 h. The breathing pattern of the animals was monitored for evidence of dypsnea. Enhanced sensitization was found after ≈ 4 of the albumin exposures. A subsequent challenge with acetylcholine suggested hyperresponsive airways.

Fujimaki et al. (1992) exposed guinea pigs to 300, 1,000, and 3,200 $\mu g/m^3$ H_2SO_4 for 2 or 4 weeks, following which lung mast cell suspensions were examined for antigen-induced

histamine release. Exposure for 2 weeks at the two highest concentrations resulted in enhanced histamine release, but this response dissipated by 4 weeks of exposure. Thus, H_2SO_4, at high concentrations, may affect the functional properties of mast cells; these cells are involved in allergic responses, including bronchoconstriction.

11.3 SIMPLE BINARY MIXTURES

Most of the toxicological data concerning effects of PM are derived from exposures using single compounds. Although such information is essential, it is also important to study responses which result from inhalation of typical combinations of materials, because population exposures are generally to complex mixtures. Toxicological interaction provides a basis whereby ambient pollutants may act with synergism (effect greater than the sum of the parts) or antagonism (effect less than the sum of the parts). Thus, the lack of any toxic effect following exposure to an individual pollutant should always be interpreted with caution, because mixtures may act differently than expected from the same pollutants acting separately. Most toxicologic studies of pollutant mixtures involved exposures to mixtures containing only two materials. These experiments are summarized below; complex mixture studies are discussed in Section 11.4.

The extent of any toxicological interaction involving acidic sulfate aerosols depends on the endpoint being examined, as well as on the co-inhalant. Most studies of interactions using acidic sulfates employed ozone as the co-pollutant. Depending upon the exposure regimen, endpoint, and animal species, either additivity, synergism, or antagonism was observed. These studies are summarized in the O_3 criteria document (U.S. Environmental Protection Agency, 1995). Interaction studies of H_2SO_4 and nitrogen dioxide (NO_2) are discussed in the criteria document on the latter pollutant (U.S. Environmental Protection Agency, 1993). The nature of interactions was dependent on the protocol; no unifying principles emerged.

The database for binary mixtures containing PM other than acid sulfates is quite sparse (Table 11-8). But, as with acidic sulfates, interaction depends upon pollutant combinations, exposure regimen and biological endpoints. Some interaction was noted following exposure of mice to mixtures of 9,400 $\mu g/m^3$ volcanic ash and 2.5 ppm SO_2 (Grose et al., 1985), in

TABLE 11-8. TOXICOLOGIC INTERACTIONS TO BINARY MIXTURES CONTAINING PM

Co-Pollutant			Acid Particle				Species, Gender Strain, Age and				
Chemical	$\mu g/m^3$	ppm	Chemical	$\mu g/m^3$ (μm)	Exposure Regime	Exposure Conditions	Body Weight	Endpoints	Response to Mixture	Interaction	Reference
SO_2		145	H_2SO_4	1,890 (<1 μm, MMAD)	0.5 h, twice weekly for 4 weeks; then 0.5 h twice weekly with antigen or constrictor challenge	Head-only	Guinea pig,	sensitization to inhaled antigen (albumin); responsivity to acetylcholine		Enhanced response compared to H_2SO_4 alone	Kitabatake et al. (1979)
Fly ash	70,000 (6 μm, MMAD)		H_2SO_4	1,000, 10,000, 100,000 (0.8 μm, MMAD, σg=1.7-1.8)	6 h	Chamber	Rat,	lavage indices (LDH, acid phosphatase, glutathione reductase)		Minimal interaction: response largely due to H_2SO_4; increase in LDH and glutathione reductase only in combined exposure	Henderson et al. (1980a)
HNO_3 (vapor)	380		H_2SO_4	180 (no size stated)	5 h/day, 5 days	Nose-only	Rat, M, Sprague-Dawley, 6 wk	macrophage phagocytosis; morphology	No change in cell turnover in nose, trachea, alveolar epithelium; no deep lung lesions; ↓ phagocytic activity.	Not determinable	Prasad et al. (1990)
SO_2	2,500	—	volcanic ash	9,400 (0.65 μm, MMAD, σg=1.8)	2 h	Whole body	mouse, F, CD-1, 4-8 weeks	infectivity to Group C *Streptococcus* or virus given 0 or 24 h after exposure	no change in susceptibility to infection	none	Grose et al. (1985)
SO_2	2,500	—	volcanic ash	9,400 (0.65 μm, MMAD, σg=1.8)	2 h	Whole body	rat, M, Sprague-Dawley, 60-70 days	lavaged cell nos. at 0 or 24 h PE	↑ PMN; ↑ lymphocytes; ↓ AM (no change in total cell no.)	possible at 0 h: effect greater than either pollutant alone; similar to SO_2 alone at 24 h	Grose et al. (1985)

TABLE 11-8 (cont'd). TOXICOLOGIC INTERACTIONS TO BINARY MIXTURES CONTAINING PM

Co-Pollutant			Acid Particle				Species, Gender Strain, Age and Body Weight				
Chemical	$\mu g/m^3$	ppm	Chemical	$\mu g/m^3$ (μm)	Exposure Regime	Exposure Conditions		Endpoints	Response to Mixture	Interaction	Reference
SO_2	2,500	—	volcanic ash	9,400 (0.65 μm, MMAD, σg=1.8)	2 h	Whole body	rat, M, Sprague-Dawley, 60-70 days	AM phagocytosis at 0 or 24 h PE	↓ phagocytic activity	possible at 0 hr: effect greater than either pollutant alone; at 24 h: similar to SO_2 alone	Grose et al. (1985)
SO_2	2,500	—	volcanic ash	9,400 (0.65 μm, MMAD, σg=1.8)	2 h/day, 5 days	Whole body	rat, M, Sprague-Dawley, 60-70 days	splenic lymphocyte response to mitogen (phytohemogglutinin)	decrease	possible synergism: no effect with either pollutant alone	Grose et al. (1985)
HCHO	1,000;	2.4-3	C black	1,000; 2,400-6,800 (2.45 μm, MMAD, σg=2.54)	4 h	Nose-only	mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered prior to pollutant; differential counts in lavage	none	none	Jakab (1992)
HCHO	—	4.1-5	C black	4,800-13,200	4 h	Nose-only	mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered prior to pollutant; differential counts in lavage	none	none	Jakab (1992)
SO_2	2,500	—	Volcanic ash	9,400 (0.65 μm, MMAD, σg=1.8)	2 h	Whole body	Rat, M, Sprague-Dawley, 60-70 days	tracheal ciliary beat frequency at 0, 24, 72 h PE	Decrease	None: same as ash alone	Grose et al. (1985)
HCHO	—	2.4-3	C black	2,400-6,800 (2.45 μm, MMAD, σg=2.54)	4 h	Nose-only	Mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered prior to pollutant; differential counts in lavage	None	None	Jakab (1992)
HCHO	—	1	C black	1,000; and 2,400-6,800 (2.45 μm MMAD, σg = 2.54)	4 h	Nose-only	Mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered prior to pollutant; differential counts in lavage	None	None	Jakab (1992)
HCHO	—	4.1-5	C black	4,800-13,200 (2.45 μm, MMAD, σg=2.54)	4 h	Nose-only	Mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered prior to pollutant; differential counts in lavage	None	None	Jakab (1992)

TABLE 11-8 (cont'd). TOXICOLOGIC INTERACTIONS TO BINARY MIXTURES CONTAINING PM

Co-Pollutant			Acid Particle								
Chemical	$\mu g/m^3$	ppm	Chemical	$\mu g/m^3$ (μm)	Exposure Regime	Exposure Conditions	Species, Gender Strain, Age	Endpoints	Response to Mixture	Interaction	Reference
HCHO	—	1.8-2.8; 5	C black	4,700-6,100; 10,000	4 h/day, 4 days	Nose-only	Mouse, F, Swiss, 20-23 g	infectivity of *S. aureus* administered 1 day after last pollutant exposure; differential counts in lavage	None	None	Jakab (1992)
HCHO	—	5	C black	10,000	4 h/day, 4 days	Nose-only	Mouse, F, Swiss, 20-23 g	F_c-receptor mediated Mø phagocytosis up to 40 days PE	↓ Phagocytic activity from day 3-day 25 PE, return to normal by day 40 PE	Possible synergism: no effect of C black or HCHO alone	Jakab (1992)
acrolein	—	2.5	C black	10,000 (2.4 μm, MMAD, σ=2.75)	4 h/day, 4 days	Nose-only	Mouse, F, Swiss, 20-23 g	infectivity to *S. aureus*, *P. mirabilis*, *L. monocytogenes*; influenza A virus administered 1 day PE	↓ Elimination of virus; ↓ killing of *L. monocytogenes*;	Possible synergism: no effect of either alone	Jakab (1993)
									↓ killing of *S. aureus*; ↑ killing of *P. mirabilis*	possible: no effect of C black	
									↑ PMN count 4 h after *P. mirabilis* challenge;	possibly: greater than either alone	
									no change total cell no. by lavage after *S. aureus*	none	

TABLE 11-8 (cont'd). TOXICOLOGIC INTERACTIONS TO BINARY MIXTURES CONTAINING PM

Co-Pollutant			Acid Particle								
Chemical	$\mu g/m^3$	ppm	Chemical	$\mu g/m^3$ (μm)	Exposure Regime	Exposure Conditions	Species, Gender Strain, Age	Endpoints	Response to Mixture	Interaction	Reference
SO_2	2,700	—	Volcanic ash	9,400 (0.65, MMAD, σg=1.78)	2 h/day, 5 days	Whole body	Rat, Sprague-Dawley (40 days)	pulmonary mechanics	Reduced tidal volume and peak expiratory flow; no effect on breathing frequency	None: effect due to SO_2	Raub et al. (1985)

Key abbreviations:
PE: post exposure
AM: alveolar macrophage
↑: increase
↓: decrease

that synergism was suggested in terms of immune cell activity and numbers but no interaction was found with overall bacterial infectivity. On the other hand, exposure of mice to various concentrations of carbon black and formaldehyde (HCHO) produced no evidence of interaction in terms of bacterial infectivity but possible synergism in terms of macrophage phagocytic activity (Jakab, 1992).

The infectivity study of Jakab (1993), in which mice were exposed to acrolein and carbon black (Table 11-8), is of interest because, as mentioned earlier, the microbial agents were selected on the basis of the defense mechanisms they elicited. The results indicated that while particle or acrolein exposure alone did not alter infectivity from any of the microbes, exposure to the mixture did, and also suggested differential effects on different aspects of antimicrobial defense. For example, the increase in intracellular killing of *P. mirabilis* was ascribed to the increase in PMN levels after bacterial challenge. The reduced effectiveness for *L. monocytogenes* and influenza virus were somewhat more persistent, which led the authors to suggest that the particle/gas mixture had a greater impact upon acquired immune defenses than on innate defense mediated by AMs and PMNs, this being the major defense against *S. aureus* and *P. mirabilis*.

11.3.1 Mixtures Containing Acidic Sulfate Particles

A few studies have examined the effects of exposure to multicomponent atmospheres containing acidic sulfate particles. Studies of mixtures containing O_3 or NO_2 are summarized elsewhere (U.S. Environmental Protection Agency, 1993, 1995).

Mannix et al. (1982) examined the effects of a 4 h exposure of rats to a SO_2-sulfate mix, consisting of SO_2 (13,000 $\mu g/m^3$) plus 1,500 $\mu g/m^3$ (0.5 μm, MMAD) of an aerosol containing $(NH_4)_2SO_4$ and $Fe_2(SO_4)_3$. No change in particle clearance from the tracheobronchial tree or pulmonary region was found.

A series of studies discussed in the previous CD (U.S. Environmental Protection Agency, 1982) involved exposure of dogs to simulated auto exhaust atmospheres (e.g., Hyde et al., 1978) for 16 h/day for 68 mo followed by a 32- to 36-mo period in clean air. The mixture consisted of 90 $\mu g/m^3$ H_2SO_4 + 1,100 $\mu g/m^3$ SO_2, with and without irradiated auto exhaust (which results in production of oxidants) and nonirradiated auto exhaust. The results were dependent on the time of examination, exposure, and the endpoint. The primary

finding was that groups exposed to SO_2 and H_2SO_4 showed emphysema like changes, observed 32- to 36-mo postexposure. The authors considered the specific changes to be analogous to an incipient stage of human centrilobular emphysema. Also, from the pulmonary function results, it did not appear that auto exhaust exacaberated the effects of the SO_2-H_2SO_4 mixture.

Prasad et al. (1988) exposed rats for 5 h/day for 5 days to an atmosphere consisting of 460 $\mu g/m^3$ diesel exhaust particles (0.15 μm), 380 $\mu g/m^3$ HNO_3 vapor, and 180 $\mu g/m^2$ H_2SO_4 (present as a surface coat on the diesel particles). Reduced activity of macrophage surface (Fc) receptors and phagocytosis were noted, but interaction could not be determined since the individual components were not tested separately.

In a later study, Prasad et al. (1990) examined particle clearance, lung histology and macrophage phagocytic activity following nose-only exposures of rats (Sprague-Dawley, M, 6 weeks) for 5 h/day for 5 days to atmospheres consisting of 390 $\mu g/m^3$ HNO_3 vapor, 550 $\mu g/m^3$ diesel exhaust particles, and 190 $\mu g/m^3$ H_2SO_4 coated on the diesel particles (0.15 μm). There was no change in tracheobronchial or pulmonary clearance of tracer particles with this mixture, compared to air controls. While no deep lung lesions nor any change in turnover rate of epithelial cells from the nose, trachea or alveolar region were noted, there was a decrease in the percentage of total macrophages assessed which had internalized diesel particles following exposure to the mixture, compared to cells recovered from animals exposed to the diesel particles alone. Furthermore, phagocytosis was depressed up to 3 days following exposure to the mixture. The enhanced effect of the particles with the surface acid coat is consistent with studies, described below, with other acid-coated particles.

Wong et al. (1994) exposed rats (M; F-344, nose-only) for 4 h/day, 4 days/week for 8 weeks to a complex mixture consisting of 350 $\mu g/m^3$ California road dust (5 μm MMAD) + 65 $\mu g/m^3$ $(NH_4)_2SO_4$ (0.3 μm) + 365 $\mu g/m^3$ NH_4NO_3 (0.6μm) + O_3 (0.2 ppm), as well as to O_3 alone. Animals were sacrificed at 4 or 17 days after the last exposure to assess stress inducible heat shock protein as an indicator of early pulmonary injury. An increase in heat shock protein was observed with the mixture at both time points, but the effect of O_3 was greater than that due to the mixture.

Amdur and Chen (1989) exposed guinea pigs to simulated primary emissions from coal combustion processes, produced by mixing ZnO, SO_2, and water in a high temperature

combustion furnace. The animals were exposed 3 h/day for 5 days to ultrafine (0.05 μm CMD, $\sigma g=2$) aerosols of zinc oxide (ZnO) at up to 5,000 $\mu g/m^3$ having a surface coating of H_2SO_4 resulting from this process (ZnO had no effect in this study). Levels of SO_2 in the effluent ranged from 0.2 to 1 ppm. Acid sulfate concentrations as low as 20 to 30 $\mu g/m^3$ as equivalent H_2SO_4 delivered in this manner resulted in significant reductions in total lung volume, vital capacity, and DLco. The effects appeared to be cumulative, in that the severity was increased with increasing exposure duration. These exposures also resulted in an increase in the protein content of pulmonary lavage fluid and an increase in PMNs. The investigators noted that much higher exposure levels of pure H_2SO_4 aerosol were needed to produce comparable results, suggesting that the physical state of the associated acid in the pollutant mixture was an important determinant of response. But one confounder in these studies was that the number concentration was greater for the coated particles than for the pure acid particles and, as mentioned earlier, both number and mass concentration likely play roles in biological responses to acidic sulfate aerosols.

Other studies have examined responses to acid-coated particles. Chen et al. (1989) exposed (nose-only) guinea pigs (male, Hartley, 250 to 300g) for 3 h to ultrafine ZnO (0.05 μm, $\sigma g=1.86$) onto which was coated 25 or 84 $\mu g/m^3$ H_2SO_4. Selected eicosanoids were examined in lavage fluid obtained at 0, 72, and 96 h post-exposure. Immediately following exposure, animals exposed to the higher acid concentration showed increased levels of prostaglandin F2α compared to those found in animals exposed to ZnO alone. Levels of prostaglandins E1 and 6-keto-PGF1α, thromboxane B2 and leukotriene B4 were similar to those found in animals exposed to the metal alone. During the post-exposure period, changes in prostaglandin E1, leukotriene B4 and thromboxane B2 were noted. But the authors suggested that there was no causal relationship between these changes and alterations in pulmonary function noted earlier (Amdur et al., 1986).

Chen et al. (1992b) exposed guinea pigs to acid-coated ZnO for 1 h, and examined airway responsiveness to acetylcholine administered 1.5 h after exposure. In this study, the equivalent concentrations of H_2SO_4 were 20 and 30 $\mu g/m^3$ coated on the 0.05 μm ZnO particles. Animals were also exposed to pure H_2SO_4 droplets at 202 $\mu g/m^3$ and having a similar size as the coated particles (0.06 μm, $\sigma g=1.36$). Hyperresponsiveness was found in animals exposed to the acid-coated particles, but not in those exposed to furnace gases

(particle-free control) or to the ZnO alone. A similar quantitative change was noted in those animals exposed to the pure droplet at about 10 times the concentration of the coated particles (Amdur and Chen, 1989).

Amdur et al. (1989) exposed guinea pigs for 3 h or for 3 h/day for 5 days to a similar atmosphere as above and examined pulmonary function. Levels of 30 $\mu g/m^3$ H_2SO_4 produced a significant depression in diffusing capacity (DLco). Repeated exposures at the equivalent of 21 $\mu g/m^3$ H_2SO_4 resulted in reduced DLco after the 4th exposure day; at the higher (30 $\mu g/m^3$) level of coated acid, DLco decreased gradually from the first exposure day.

The interaction of acid coated particles with ozone was examined by Chen et al. (1991). Guinea pigs (male, Hartley, 260 to 325 g) were exposed (nose-only) to sulfuric acid layer ZnO particles (0.050 μm CMD, $\sigma g=2$) at 24 or 84 $\mu g/m^3$ H_2SO_4 or pure acid (0.08 μm) at 300 $\mu g/m^3$ for 2 h, followed by 2 h rest period and 1 h additional exposure (whole body) to air or 0.15 ppm O_3. Other animals were exposed to acid coated ZnO having an equivalent acid concentration (24 $\mu g/m^3$) for 3 h/day for 5 days. This was followed by exposure for 1 h to 0.15 ppm O_3 on day 9, or to two additional 3 h exposures to 24 $\mu g/m^3$ H_2SO_4 layered-ZnO on days 8 and 9. In the single exposure series, animals exposed only to the higher coated acid concentration followed by ozone showed greater than additive changes in vital capacity and DLco, while those exposed first to the pure acid droplet did not show any change greater than that due to ozone alone. Animals exposed repeatedly and then to the two added acid exposures showed greater reductions in lung volumes and DLco than did those that did not receive the additional acid exposures. Finally, animals exposed to ozone after acid showed reduced lung volumes and DLco not observed in animals exposed to either ozone alone or acid alone. In terms of acid alone, neither single exposure to the coated acid affected the endpoints, while exposure to the pure acid decreased DLco. The investigators concluded that single or multiple exposures to the acid-layered ZnO resulted in an enhanced response to subsequent exposures to acid or ozone and that the manner in which the acid was delivered (i.e., as a pure droplet or as a surface coating) affected whether or not any interaction occurred. However, it is likely that the number concentration of particles was greater in the zinc oxide aerosol than in the pure acid aerosol, and the interaction may reflect this greater particle number. It should also be noted that ZnO itself may have produced

some biological response, or contributed to any interaction with the acid, in some of the studies reported for some endpoints.

11.3.2 Nitrates

11.3.2.1 Human Studies

Five studies have been conducted on human exposure to nitrate aerosols since 1979 (see Table 11-9). These studies have been discussed in the Acid Aerosol Issues Paper (U.S. Environmental Protection Agency, 1989). The only obvious effect was a decrease in G_{aw} and in PEFV curves in normal subjects with influenza exposed to 7,000 $\mu g/m^3$ of sodium nitrate ($NaNO_3$) aerosol. This is probably three orders of magnitude (i.e., approximately 1,000 times) above the nitrate concentration that may exist in the ambient air. These studies indicate that, at least as far as lung function is concerned, there is no present concern for pulmonary function effects from current ambient levels of nitrate aerosols.

Sackner et al. (1979) studied a diverse group of normal and asthmatic subjects exposed to concentrations reaching 1,000 $\mu g/m^3$ $NaNO_3$ for 10 min at rest. There were no significant effects on an extensive battery of pulmonary function tests.

Utell et al. (1979) studied both normal and asthmatic volunteers exposed to 7,000 $\mu g/m^3$ $NaNO_3$ (0.46 μm) aerosol for 16 min via mouthpiece. The major health effect end points measured in their study included R_{aw}, both full and PEFV curves, airway reactivity to carbachol, and aerosol deposition. Aerosol deposition as a percentage of inhaled aerosol averaged about 50% for normals and about 56% for asthmatics; the group differences were not significant. The exposure to $NaNO_3$ aerosol was indistinguishable from the control NaCl exposure in normals. Similarly, there were no effects of $NaNO_3$ exposure on asthmatics.

Utell et al. (1980) subsequently studied 11 subjects with influenza exposed to the same $NaNO_3$ regimen as above. The subjects were initially exposed at the time of illness and then were reexposed 1, 3, and 6 weeks later. Aerosol deposition ranged from 45 to 50% over the four exposure sessions. All subjects had cough and fever, and 10 of 11 subjects had viral or immunologic evidence of acute influenza. Baseline measurements of FVC and FEV_1 were within normal limits and did not change throughout the 6-week period. There were small but significant decreases in G_{aw} following $NaNO_3$ inhalation, but not after NaCl exposure. This

TABLE 11-9. EXPOSURE CONDITIONS AND RESPONSES IN SUBJECTS EXPOSED TO NITRATES[a]

Reference	Nitrate Species and Conc. ($\mu g/m^3$)	Exposure Duration (min)	Exercise Duration (min)	Exercise Ventilation (L/min)	Temp. (°C)	Relative Humidity (Percent)	Number of Subjects	Subject Char.	Aerosol MMAD	Effects
Kleinman et al. (1980)	NH_4NO_3 200	120	60	≈20	31	40	20	Normal	1.1	No significant changes in normals or asthmatics except possible decrease in R_T. No symptom effects.
							19	Asthma		
Sackner et al. (1979)	$NaNO_3$ 10,100,100	10	--	--	--	--	5	Normal	0.2	No changes.
							5	Asthma		
	1,000						6	Normal		
							6	Asthma		
	1,000						6	Normal		
							6	Asthma		
Stacy et al. (1983)	80 (NH_4NO_3)	240	30	55	30	60	12	Normal	0.55	No effects.
	80 (NH_4NO_3) +0.5 ppm NO_2						12	Normal		
Utell et al. (1979)	$NaNO_3$ 7,000	16 (×2) (32 Total)	--	--	--	25	10	Normal	0.46	No effects.
							11	Mild Asthmatics		
Utell et al. (1980)	$NaNO_3$ 7,000	16 (×2) (32 Total)	--	--		25	11	Influenza Patients	0.49	No symptoms. SG_{aw} decreased 17% and max 40% TLC decreased 12% after nitrate, within 2 days of onset of illness. Similar effects 1 week later, but not 3 weeks later.

[a]Abbreviations:
MMAD = Mass median aerodynamic diameter. $NaNO_3$ = Sodium nitrate. max40%TLC=Maximum expiratory flow at 40% of TLC on NH_4NO_3 = Ammonium nitrate. SG_{aw} = Specific airway conductance.a PEFV curve.
R_T = Total respiratory resistance.

difference was present during acute illness and 1 week later, but was not seen at 3 and 6 weeks after illness. The decrease in SG_{aw} seen on the initial exposure was accompanied by a decrease in partial expiratory flow at 40%TLC; this was also observed at the 1-week follow-up exposure. This study suggests that the presence of an acute viral respiratory tract infection may render humans more susceptible to the acute effects of nitrate aerosols. Nevertheless, the concentration of nitrates used in this exposure study exceed maximum ambient levels by more than 100-fold.

In addition to $NaNO_3$ aerosols, ammonium nitrate (NH_4NO_3) exposure has been studied by Kleinman and associates (1980). Twenty normal and 19 asthmatic subjects were exposed to a nominal 200 $\mu g/m^3$ of 1.1 μm NH_4NO_3 aerosol. The 2-h exposures included mild, intermittent exercise and were conducted under warm conditions (31 °C, 40% RH). There were no significant physiologically meaningful effects of the NH_4NO_3 exposure in either subject group.

Stacy et al. (1983) also studied the effects of 80 $\mu g/m^3$ of NH_4NO_3 in a group of healthy male adults. As in the Kleinman et al. (1980) study, there were no changes in lung function or symptoms.

Nitrates (e.g., sodium nitrate) have not been found to cause any deleterious effects (Utell et al., 1979, 1980; Kleinman et al., 1980; Stacy et al., 1983) at levels that might be expected in the atmosphere.

11.3.2.2 Animal Studies

The toxicologic database supporting any health effects from inhaled nitrates is limited. Sackner et al. (1979) exposed anesthetized dogs (via endotracheal tube) to sodium nitrate aerosols (0.1 to 0.2 μm) at 0.9 or 11 mg/m^3 for 7.5 min or at 5 mg/m^3 for 4 h. No effect on indices of pulmonary mechanical function, namely total respiratory resistance, functional residual capacity, compliance, or specific respiratory conductance, were noted up to 2 to 3 h postexposure. Sheep exposed (head only) to 0.9 mg/m^3 for 20 min or to 5 mg/m^3 for 4 h showed no change in tracheal mucous velocity compared to controls.

Ehrlich (1979) examined the effect of 3-h exposures to various nitrate salts on resistance to respiratory bacterial infection in mice. Animals were exposed to maximal concentrations as follows: lead nitrate (2 mg/m^3); calcium nitrate (2.8 mg/m^3); sodium

nitrate (3.1 mg/m^3); potassium nitrate (4.3 mg/m^3); ammonium nitrate (4.5 mg/m^3); and zinc nitrate (1.25 mg/m^3). Only zinc nitrate [$Zn(NO_3)_2$] resulted in any significant mortality increase, the extent of which seemed to be concentration related; the highest concentration increased mortality by about 20%. However, since the response was similar to that seen with zinc sulfate, the effect was likely due to the zinc ion (Zn^{+2}) rather than to the nitrate ion (NO_3^-).

Busch et al. (1986) exposed rats and guinea pigs (whole body) with either normal lungs or lungs with elastase-induced emphysema to 1 mg/m^3 of ammonium nitrate (0.6 μm MMAD, σg = 2.2) for 6 h/day, 5 days/week for 4 weeks. Using both light and electron microscopy, the investigators concluded that there were no biologically significant effects of nitrate exposure on lung structure. Loscutoff et al. (1985) exposed both normal and elastase-treated rats and guinea pigs (whole body) to ammonium nitrate (1 mg/m^3, 0.6 μm MMAD, σg = 2) for 6 h/day, 5 days/week for either 5 or 20 days and measured various pulmonary function indices, namely diffusing capacity (DL_{CO}), quasi-static compliance, residual volume, functional reserve capacity and single breath N_2-washout. No biologically significant changes were noted in rats due to ammonium nitrate exposure, nor was there any interaction between elastase treatment and aerosol exposure. Likewise, elastase treated guinea pigs were no more sensitive to aerosol exposure than were normals and the only effect of exposure was a slight change in the slope of the N_2-washout curve, although it was actually in the direction of improved function.

Charles and Menzel (1975) examined the effects of nitrate upon the release of histamine by guinea pig lung fragments, response to some pollutants may be a function of their ability to elicit biologic mediators. Lung fragments were incubated for 0.5 h with 20 to 200 mM ammonium nitrate. Histamine was released in proportion to the concentration of salt present. However, the response was not totally due to NO_3^-; ammonium (NH_4^+) ion was also a possible contribution. The relation of this actual in vivo exposures is, however, not clear. Other in vitro exposures suggest that NO_3^- may affect red blood cells by altering the transport of calcium across the cell membrane (Kunimoto et al., 1984).

11.4 COMPLEX MIXTURES

11.4.1 Introduction

The health effects of complex mixtures with particles are studied rarely because of their inherent difficulties. A major exception is diesel emissions which are described in the following, along with a few other reports on different mixtures. Older studies of complex mixtures are summarized in the previous CD (U.S. Environmental Protection Agency, 1982). They will not be reported here because they are not especially informative on first principles of mixtures or specific-classes of mixtures.

11.4.2 Mixtures Containing Other PM

There is little available data on complex mixtures of other PM. Fick et al. (1984) exposed rabbits (NZW, 1.5 to 2 kg) for 0.2 to 2 h to the pyrolysis products derived from Douglas fir wood (exposure concentrations and particle size were not stated). They noted an increase in the total number of cells recovered by lavage immediately postexposure, and the magnitude of this increase was related to the exposure duration. The ratio of AMs, PMNs and lymphocytes was constant at all exposure durations except for the longest, in which case lymphocyte numbers increased. A depression in the uptake and intracellular killing of *Pseudomonas aeruginosa* was found in AMs obtained from the smoke-exposed animals compared to cells from air controls. Furthermore, cells from the smoke-exposed animals were smaller, and had reduced surface adherence.

Clark et al. (1990) exposed dogs (mongrel, 15 to 20 kg) for 5 min to wood smoke (from fir plywood sawdust and kerosene; no specified particle size or exposure concentration) via an endotracheal tube. The lungs were examined for increased extravascular water around the pulmonary arteries, which was found to occur with smoke exposure but not in air sham controls. This response was suggested to be due to increased microvascular permeability without any increase in capillary pressure. A decrease in lung compliance was also noted with smoke exposure.

Another complex mixture examined was a combination of gaseous sulfur (IV), particulate sulfur (IV) and particulate sulfur (VI). A series of studies involved exposures (whole body) of Beagle dogs (M, 34 mo old) for 22.5 h/day, 7 days/week for up to 290 days to such an atmosphere, in which respirable sulfur IV (0.6 μm MMAD, $\sigma g=2$) was

maintained at a concentration of 300 $\mu g/m^3$ (Heyder et al., 1992; Maier et al., 1992; Kreyling et al., 1992; Schulz et al., 1992; Takenaka et al., 1992). Various biological endpoints were examined, and responses included reductions in nonspecific defense capabilities of AMs such as phagocytosis and production of reactive oxygen species; increases in protein and β-N-acetylglucosaminidase in lavage fluid; increased rate of clearance of test particles from lungs to blood (suggesting a change in the permeability of the epithelium); minor changes in pulmonary function; and some histopathological effects, such as hyperplasia of respiratory epithelium of the posterior nasal passages and a slight (but not statistically significant) decrease in the volume density of alveolar septa. The exact role played by specific components of this mixture could not be determined because responses to individual components were not examined.

11.4.3. Atmospheric Particulate Matter

11.4.3.1. Introduction

The 1982 Air Quality Criteria Document for Particulate Matter and Sulfur Dioxides (U.S. Environmental Protection Agency, 1982) reviewed studies showing that extractable organic matter from ambient air particulate matter collected from several urban localities was genotoxic in in vitro tests such as the Ames *Salmonella* mutagenicity test and mammalian cell transformation assays and was tumorigenic in subcutaneous injection and skin painting assays in rodents. Also discussed were rodent subcutaneous injection and skin painting studies showing tumorigenic activity of organic-solvent extracts of particulate matter emitted from combustion sources known to contribute to ambient air particulate matter, such as diesel engines, gasoline engines, and furnaces burning coal or oil. Polycyclic aromatic hydrocarbons (PAHs) were discussed as the best-studied class of potential carcinogenic compounds found in particulate extracts. The 1982 document also discussed evidence for the genotoxicity of SO_2 and bisulfite in in vitro tests, the equivocal evidence for an synergistic tumorigenic interaction between SO_2 and benzo[a]pyrene and the tumorigenic potential of some metals found in ambient air particulate matter. The conclusion was reached that "all the major types of airborne particulate matter may contain adsorbed compounds that are mutagenic and/or carcinogenic to animals and may contribute in some degree to the incidence of human cancer associated with exposure to urban air pollution".

Pertinent research completed since the publication of the previous Agency document, has included: mutagenicity or tumorigenicity testing of organic-solvent extracts of ambient air particulate matter collected from various localities, mutagenicity and tumorigenicity testing of particular emission sources that contribute to ambient air particulate matter, and fractionation studies of condensates or organic-solvent extracts of particulate emissions from specific sources. The research has focused mostly on particulate matter produced by the pyrolysis or combustion of carbon-containing material; relatively little attention has been given to the mutagenicity or carcinogenicity of acidic aerosols (i.e, particulate sulfates or particulate nitrates). This section presents an overview of the results of this research. This section also discusses epidemiological studies of the potential link between general air pollution and cancer in humans and recent research on the use of biomarkers of genetic damage to assess one class of carcinogens (polycyclic aromatic hydrocarbons, PAHs) found in ambient air particulate matter.

11.4.3.2. Particulate Matter and Cancer in Animals

Concern for the possible carcinogenicity of particulate matter has historical origins dating to 1775 when Percival Pott wrote about the frequent occurrence of scrotal cancer among chimney sweeps. However, experimental evidence of the carcinogenicity of particulate matter in animals was not produced until the middle part of this century in investigations that collected particulate matter from several urban locations, extracted the particulate matter with organic solvents and applied the extracts to the skin or to subcutaneous regions of mice.

In general, the results of animal carcinogenicity studies demonstrate that ambient air particulate matter contains extractable material that can produce tumors in animal systems when applied to the skin or injected subcutaneously. Table 11-10 summarizes experimental protocols used and tumor incidences obtained in animal carcinogenicity studies of samples of organic-solvent extracts of ambient air particulate matter. No reports were located regarding cancer bioassays with animals exposed by inhalation to aerosols of particulate matter collected from ambient air. Tumor incidences were not greatly elevated in most studies that exposed adult mice by skin painting or subcutaneous injection. Among the three such studies listed in Table 11-10, there are 17 treated groups of mice (Leiter et al., 1942; Kotin et al.,

TABLE 11-10. Carcinogenicity Tests of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Leiter et al., 1942	Particulate matter was collected by filtering air through cotton cloth at sites in downtown Pittsburgh and Chelsea, Massachusetts, by mechanical precipitation in a "labyrinth" for the intake and exhaust sites for the Holland Tunnel in New York City or by electrical precipitation on unoiled plates at sites in Pittsburgh and Chelsea. Period of collection was not specified. Particulate matter was extracted with benzene/ethylether.	Mice/C3H/M (n=20) Mice/strain A/M,F (n=10)	"Tars" were suspended in tricaprylin and single subcutaneous injections containing 21,000 to 71,000 μg tar were given in the right axilla of each mouse.	Chelsea: (Cloth sample): 2/38 (Precipitron sample): 0/39 Pittsburgh: (Precipitron sample): 4/32 (Cloth sample): 5/33 Holland: (New York intake): 0/30 (New York exhaust): 1/41 (New Jersey intake): 0/33 (New Jersey exhaust): 2/34	Numerator of incidence is for mice showing sarcomas at the injection site by the end of a 12-month observation period. Denominator is the time of mice surviving at the time of first tumor appearance, cited as 5 months. No injection site tumors were found during the observation period in 20 control C3H males that were given single subcutaneous injections of the vehicle, tricaprylin.

TABLE 11-10. Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Kotin et al., 1954	Collection, via large volume sample collector onto Whatman filter paper, occurred for 42 or 59 8-hour days at two Los Angeles sites, 1 with heavy industrial activity and 1 with heavy traffic congestion between August and October 15. Particulate matter from the 2 sites was pooled and extracted with benzene.	mice/C57 Black/M,F (n=38)	A benzene solution of the extracts (concentration was not specified) was painted on the skin in the interscapular area, 3-times weekly for life.	Los Angeles: 13/31	Numerator of incidence is for mice with papillomas at exposure site; an unspecified number of the papillomas progressed to carcinomas. Denominator of incidence is for number of mice surviving until the time of first tumor appearance, 15 months and 3 days. The authors did not clearly specify the duration of their observation period, but noted that nine mice still were alive at the time the report was written. Benzene controls were housed and painted in the same manner as treated mice. No skin tumors were found during the observation period in the 37 controls that were alive at the time of first tumor appearance.

TABLE 11-10 (Cont'd). Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Hueper et al., 1962	1-month collection on fiberglass filter membranes located in downtown and industrialized areas	mice/Black mice/M,F (n=36)	Monthly subcutaneous injections of 400 μg benzene extract, suspended in 0.1 mL tricaprylin, were given for 11 months, followed by 800 μg monthly until the 24th month.	Atlanta: 6/72 New Orleans: 1/72 Birmingham: 4/72 Los Angeles: 0/72 San Francisco: 3/72 Cincinnati: 3/72 Philadelphia: 3/72 Detroit: 5/72	Incidence was for observable tumors at injection sites. Maximal observation period was 2 years. No injection site tumors were found in 71 vehicle control mice.

TABLE 11-10 (Cont'd). Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Epstein et al., 1966	Particulate matter samples were collected with high-volume samplers at Continuous Air Monitoring Program sites in 6 U.S. cities during 1963. Samples were combined by site and extracted with benzene.	Mice/Swiss (ICR/Ha)/M,F (n=105=137)	Newborn mice were subcutaneously injected (in the neck) with 5,000, 10,000, and 15,000 μg of extracts suspended in tricaprylin on days 1, 7 and 14 of life. Mice were allowed to survive until the end of a 50-52 week period.	LIVER TUMORS: Controls: 4/67 M; 0/68 F Chicago: 3/11 M; 0/33 F Cincinnati: 5/6 M; 1/22 F Los Angeles: 1/13 M; 0/15 F New Orleans: 10/29 M; 0/30 F Philadelphia: 4/13 M; 0/27 F Washington: 4/13 M; 0/16 F PULMONARY TUMORS: Controls: 9/67 M; 4/68 F Chicago: 6/11 M; 7/33 F Cincinnati: 4/6 M; 3/22 F Los Angeles: 4/13 M; 1/15 F New Orleans: 7/29 M; 6/30 F Philadelphia: 1/13 M; 6/27 F Washington: 5/13 M; 7/16 F	Increased early mortality before weaning occurred in each treatment group compared with vehicle controls (16%) indicating that a maximum tolerated dose was exceeded. Percentage mortality before weaning was: 39% Chicago; 53% Cincinnati; 61% Los Angeles; 29% New Orleans; 35% Philadelphia; 53% Washington. Tumor incidences are for the number of mice with tumors at a given site divided by the number of mice alive at weaning minus those that were autolyzed or cannabilized. Malignant lymphomas were also found in a few treated groups at elevated incidences compared with controls, but neither the magnitude or the consistency of this finding was as great as the magnitude and consistency of the increases in liver and lung tumor incidence.

TABLE 11-10 (Cont'd). Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Asahina et al., 1972	Particulate matter was collected on air conditioner filters for a 6-month period from 8/65 to 2/66 at an office building in New York City. Samples were extracted with benzene, which was removed by evaporation.	Mice/Swiss (ICR/Ha)/M,F (n=53-86)	Newborn mice were subcutaneously injected (in the neck) with 0.1, 0.1 and 0.2 mL of extracts suspended in tricaprylin on days 1, 7 and 14 of life; each mouse received total doses of 0, 10,000, or 20,000 μg extract. Mice were allowed to survive until the end of a 50-52 week period.	LIVER TUMORS: Control: 3/31 M; 0/35 F 10 mg: 3/19 M; 0/28 F 20 mg: 4/13 M; 0/17 F PULMONARY ADENOMAS: Control: 2/31 M; 1/35 F 10 mg: 0/19 M; 3/28 F 20 mg: 3/13 M; 1/17 F LYMPHOMAS: Control: 0/31 M; 2/35 F 10 mg: 1/19 M; 1/28 F 20 mg: 0/13 M; 1/17 F	Increased early mortality before weaning occurred in treated mice (33% and 43% for 10,000 and 20,000 μg) compared with vehicle control mice (23%). Another group dosed with 40,000 μg showed 86% early mortality, thus precluding its use in meaningful cancer evaluation. Tumor incidences are for the number of mice with tumors at a given site divided by the number of mice alive at weaning minus those that were autolyzed or cannabilized. Injection site tumors were reported to be rare. The extract was fractionated into various fractions that were tested for tumorigenicity via the same protocol. Active fractions included a basic fraction, an aromatic fraction and an aliphatic fraction.

TABLE 11-10 (Cont'd). Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Epstein et al., 1979	Particulate matter was collected with high-volume samplers in several U.S. cities in 1962. The samples were composited and extracted with benzene. Extracts were stored at -4°C.	Mice/Swiss albino (ICR/HA)/M,F (n=90-233)	Newborn mice were subcutaneously injected (in the neck) with varying doses of extracts suspended in tricaprylin on days 1, 7 and 14 of life as indicated in the next column. Mice were allowed to survive until the end of a 50-52 week period.	LIVER TUMORS: CONTROLS: (0, 0, 0 mg on days 1, 7 & 14) 1/44 M; 0/38 F 5, 10, 10: 5/51 M; 0/46 F 5, 10, 15: 5/23 M; 0/27 F 5, 15, 15: 2/32 M; 0/28 F 5, 15, 20: 1/28 M; 0/24 F PULMONARY ADENOMAS, SOLITARY: 0, 0, 0: 5/44 M; 3/38 F 5, 10, 10: 13/51 M; 5/46 F 5, 10, 15: 7/23 M; 2/27 F 5, 15, 15: 5/32 M; 1/28 F 5, 15, 20: 5/28 M; 5/24 F TOTAL NUMBER OF TUMOR BEARING MICE: 0, 0, 0: 7/44 M; 4/38 F 5, 10, 10: 29/51 M; 20/46 F 5, 10, 15: 11/23 M; 9/27 F 5, 15, 15: 11/32 M; 11/28 F 5, 15, 20: 14/28 M; 19/24 F	Increased early mortality before weaning occurred in treated groups (32%-55%) compared with vehicle control mice (12%). Several other treatment groups were included (but not shown in this table) that injected 5,000 to 15,000 μg on only 1 or 2 of the three injection days; tumorigenic response was not as marked as in those shown in previous column. Lymphomas were also observed in treated and control mice. Tumor incidences are for the number of mice with tumors at a given site divided by the number of mice alive at weaning minus those that were autolyzed or cannabilized. A significant dose-related increase in total tumor incidence with increasing dose was evident when cumulative doses for all groups were expressed on a gram body weight basis and included in a regression analysis.

TABLE 11-10 (Cont'd). Carcinogenicity Testing of Samples of Ambient Air Particulate Matter in Animals.

Reference	Sample Collection	Species/Strain/Sex	Exposure Protocol	Particulate Matter Source and incidence of Animals with Tumors	Comments
Lewtas et al., 1991; Cupitt et al., 1994	Particulate matter was collected from two sites in Boise, Idaho for 4 months during the winter. Particulate matter was extracted with dichloromethane. Two composite samples were constructed: one dominated by wood smoke (WS) combustion products (78% WS, 11% MS, 11% residual) & one with a greater contribution from mobile sources (MS) (51% WS; 33% Ms, 16% residual).	Mice/Sencar/NS (n=40 per treatment group)	Mice were given single initiating dermal doses (in acetone) at dose levels of 0, 1,000, 2,000, 5,000 10,000, or 20,000 μg/mouse, followed by promoting doses of 2 μg TPA, 2x weekly for 26 weeks. Papillomas at application site were counted and tumor multiplicity was determined for each dose group.	Incidences of tumors were not reported, but estimated tumor initiation potencies were reported (i.e., slopes of the tumor multiplicity/dose curve estimated by regression analysis) Wood-smoke dominated sample: 0.095 papillomas/mouse/1,000 μg Wood smoke/Mobile sources sample: 0.215 papillomas/mouse/1,000 μg	Estimated tumor initiating potencies for ambient air particulate samples were intermediate between estimates for cigarette smoke condensate (0.0029 papillomas/mouse/1,000 μg) and coke oven particulates (2.10 papillomas/mouse/1,000 μg).

NS = not specified

1954; Hueper et al., 1962). Excluding the single outlying value of 42% (13/31) from the Kotin et al. (1954) study, the group percentages of mice with contact site tumors range from 0 to 15% with a mean of 4.8%. In contrast, assays with newborn mice generally show greater tumorigenic responses than the experiments with adult mice. For example, groups of newborn mice, subcutaneously injected on days 1, 7, and 14 of life with total doses of 25,000 to 40,000 μg of material extracted from a composite sample of ambient air particulate matter collected from several U.S. cities in 1962, showed total tumor percentages (hepatic, pulmonary and lymphatic tumors) after 1 year ranging from 33% (9/27) to 79% (19/24) (mean = 47%; median = 45%) compared with vehicle control percentages of 16% (7/44) and 10% (4/38) (Epstein et al., 1979; see Table 11-10). Although the newborn mouse assay is a sensitive experimental technique to detect potential carcinogens, direct extrapolation of these results to predict human response to ambient air particulate matter is questionable due to uncertainties involving potential sensitivity differences among species or age (e.g., newborns versus adults) and likely dispositional differences (pharmacokinetic and pharmacodynamic) associated with route of exposure (dermal or subcutaneous versus inhalation) and physicochemical properties of the material (extracted organic matter versus intact particulate matter with adsorbed organic matter). A further complication is that studies with organic-solvent extracts of particulate matter utilize a concentrating process to obtain the test material. For example, the 20,000 μg dose of material injected into the newborn mice in the Asahina et al. (1972) study was obtained from approximately 1,850 m^3 of air, which is approximately equivalent to the amount of air inhaled by human adults in 92 days (assuming an inhalation rate of 20 m^3/day).

In the only other available animal bioassay study, particulate matter extracts of ambient air, collected at two sites in Boise, Idaho from November, 1986 to February, 1987, were tested for tumor initiating activity in mouse skin tumor initiation assays (Lewtas et al., 1991; Cupitt et al., 1994). Using tracer species and receptor modeling methods, the contribution of residential wood smoke (WS) combustion and mobile engine (MS) combustion sources to the collected samples was determined and used to construct two composite samples; one dominated by wood smoke combustion products (78% WS; 11% MS; 11% residual) and another with a greater contribution from mobile sources (51% WS; 33% MS; 16% residual). Particulate matter samples were extracted with dichloromethane and solvent exchanged into

dimethylsulfoxide that was evaporated under dry nitrogen. Initiating doses of extracts dissolved in acetone at dose levels of 0, 1,000, 2,000, 5,000, 10,000, or 20,000 μg/mouse were applied to the dorsal skin of groups of 40 Sencar adult mice. Following a one-week period, 2 μg 12-o-tetradecanoylphorbol-13-acetate, a potent tumor promoter, was applied twice weekly for 26 weeks. At 26 weeks, papillomas at the application site were counted and tumor multiplicity (papillomas per mouse) was determined for each dose group. Slopes of the tumor multiplicity/dose curve were estimated by regression analysis and used as a measure of the tumor initiation potency of the samples. Estimated tumor initiation potencies for the two samples were 0.095 and 0.215 papillomas/mouse/1,000 μg for the wood-smoke-dominated and wood-smoke/mobile-sources samples, respectively. Comparison of the potency values for these ambient air extracts with those for extracts of particulate matter from specific sources of combustion showed them to be intermediate in the observed range between the extremes of 0.0029 papillomas/mouse/1,000 μg for cigarette smoke condensate and 2.10 papillomas/mouse/1,000 μmg for coke oven particulate emissions (see Figure 11-4). The comparative potency of organic extracts of different sources of particulate matter in the Sencar mouse skin tumor initiation assay has been proposed to be predictive of human lung cancer risk based on a correlation between human lung cancer risks (estimated from epidemiological data) for cigarette smoke, roofing tar emissions and coke oven emissions and their respective potencies in the mouse skin tumor initiation assay (Lewtas, 1993).

In summary, extracts of ambient air particulate matter collected from several sites produced small increases in contact site tumors in adult mice after epicutaneous or subcutaneous administration, significant increases in total lung, liver or lymphatic tumors in mice after subcutaneous administration shortly after birth and significant increases in skin tumors in adult mice after administration of initiating dermal doses followed by repeated promoting doses of a phorbol ester.

11.4.3.3. Genotoxicity of Particulate Matter

As discussed in the 1982 document (U.S. Environmental Protection Agency, 1982), supporting data for the carcinogenicity of particulate matter comes from numerous studies that have examined the in vitro genotoxicity of organic-solvent extracts of particulate matter

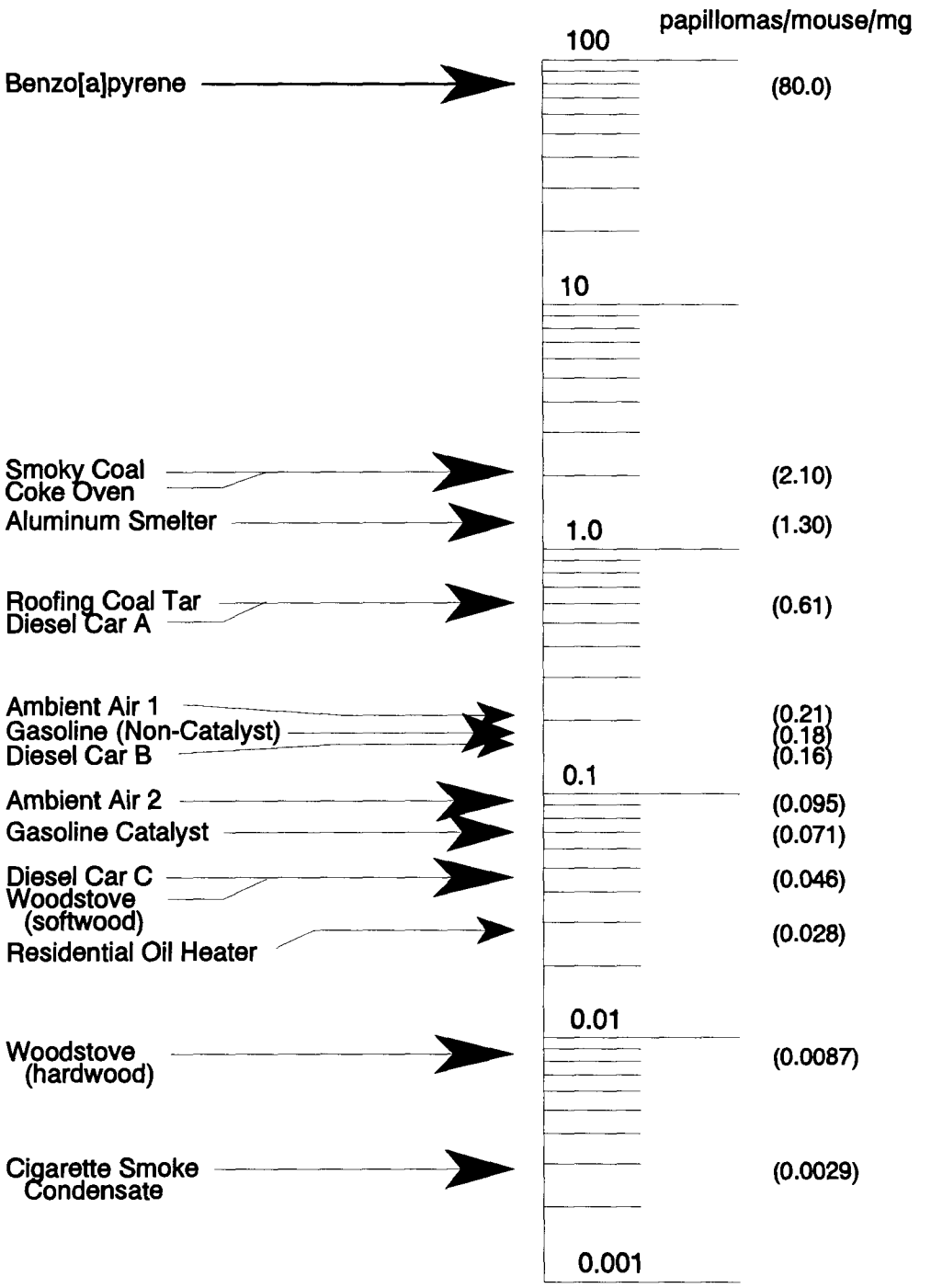

Figure 11-4. Comparative potency of a series of complex mixtures and benzo[a]pyrene in the Sencar mouse skin tumor initiation assay. The complex mixtures are organic-solvent extracts of particulate emissions. "Ambient Air 1" is 0.21; "Ambient Air 2" is 0.095. Numbers in parentheses are slopes from dose-response curves (Source: Lewtas, 1993)

in ambient air collected at various locations throughout the world. The limitations and potential inaccuracy of extrapolating positive results in genotoxicity tests to predict human cancer consequences is well known and has been discussed elsewhere (see for example the U.S. Environmental Protection Agency Cancer Guidelines, 1986 or Williams and Weisburger, 1991) Nevertheless, the positive evidence found for organic-solvent extracts of particulate matter in several types of genotoxicity assays is generally accepted as being supportive of the potential carcinogenicity of intact particulate matter.

The Ames *Salmonella* mutagenicity assay continues to be used widely to test the mutagenicity of organic-solvent extracts of particulate matter. Positive results have been published recently for particulate matter collected at sites in: Santiago, Chile (Adonis and Gil, 1993); Rome, Italy (Crebelli et al., 1991); Mexico City, Mexico (Espinosa-Aguirre et al., 1993); Ann Arbor, Michigan (Hoyer et al., 1992); Tokyo, Japan (Houk et al., 1992); Silesia, Poland (Motykiewicz et al., 1989); Padova, Italy (Nardini and Clonfero, 1992); Los Angeles, California (Pitts et al., 1985); Bormida Valley, Italy (Scarpato et al., 1993); Allegheny County, Pennsylvania (Siderpoulos and Specht, 1994); Sagamihara, Japan (Takagi et al., 1992); Fukuoka, Japan (Tokiwa et al., 1983); Pisa, Italy (Barale et al., 1989; Velosi et al., 1994); Morgantown, West Virginia (Whong et al., 1981); and Taipei, China (Wei et al., 1991). In general, recent results from Ames assays demonstrate the presence of both indirect mutagens requiring metabolic activation and direct mutagens not requiring activation. When compared, mutagenic activities have been higher during winter when domestic heating systems are operating than during warm months (Adonis and Gil, 1993; Motykiewicz et al., 1989; Nardino and Clonfero, 1992; Scarpato et al., 1993; Takagi et al., 1992; Tokiwa et al., 1983; Velosi et al., 1994; Whong et al., 1981; Wei et al., 1981). Polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene, dibenz[a,h]anthracene) are historically the earliest recognized carcinogenic components in extracts of particulate matter from combustion sources. They are known to require metabolic activation, and are thought to be significant, but not the sole, contributors to the mutagenicity. Other proposed contributors include oxygenated aliphatic hydrocarbons, oxygenated PAHs (e.g., PAH ketones, quinones and phenols) and heterocyclic (O, N or S) aromatic hydrocarbons (Lewtas, 1993; Motykiewicz et al., 1989). Comparison of mutagenic activities of particulate extracts in *Salmonella* strain TA98 with activity in strain TA98NR, a strain known to be resistant to 1-nitropyrene and

deficient in nitroreductases, has demonstrated the importance of direct-acting nitroarenes in many localities (Adonis and Gil, 1993; Crebelli et al., 1991; Espinosa-Aguirre et al., 1993; Nardino and Clonfero, 1992; Pitts et al., 1985; Takagi et al., 1992).

Less extensive genotoxicity testing of extracts of particulate matter has been conducted in mammalian systems, but the available results, from tests of ambient air samples from several sites in Europe and the U.S., have been predominately positive. Organic solvent extracts of particulate matter samples induced increases in sister chromatid exchange in cultured human lymphocytes and rodent cells (Lockard et al., 1981; Alink et al., 1983; de Raat, 1983; Hadnagy et al., 1986), and increased frequency of chromosomal aberrations in Chinese hamster V79 cells (Motykiewicz et al., 1988) and human lymphocytes (Krishna et al., 1984; Hadnagy et al., 1986).

Genotoxicity testing of intact ambient air particulate matter is limited. Crespi et al. (1985) reported that an intact particulate sample of an experimental, combustion-generated soot in the culture medium of metabolically competent human lymphoblast cells (designated AHH-1) produced dose-related mutations at the Hypoxanthine-Guanine-Phosphoribosyl-Transferase (HPRT) locus; a methylene chloride extract of the particles was approximately 1,000 times more active than the particle when equal weights of the intact particles and extracts of the particles were compared in the assay. Kelsey et al. (1994) found that particles collected from Kuwait ambient air during the 1991 oil fires and ambient air particles collected from Washington, D.C. (Standard Reference Material 1649 from the U.S. National Bureau of Standards) both produced increased frequency of sister chromatid exchanges in cultured human peripheral blood lymphocytes and slight increases in mutation frequency at the HPRT locus in AHH-1 human lymphoblast cells. The activities of the two particles were comparable on an equal particle mass basis.

11.4.3.4. Testing of Emission Sources Contributing to Particulate Matter

As discussed in chapter 5 of this document, important sources of particulate matter include stationary fuel combustion (e.g., domestic furnaces, electrical power generating plants), industrial processes (e.g., coke oven emissions, aluminum production emissions) and transportation-related fuel combustion (i.e., diesel or gasoline engine exhaust). Within the past 15 years, extensive research has been conducted on the short-term genotoxicity and

animal carcinogenicity of specific sources of carbon-containing particulate matter in ambient air. This section presents an overview of the findings of research on gasoline engine exhaust and emissions from burning of heating and cooking fuels, because of their potential importance in contributing to particulate matter in many localities (Lewis et al., 1988; Stevens et al., 1990). Diesel engine exhaust is discussed in Section 11.8.4).

11.4.3.4.1. Carcinogenicity and Genotoxicity of Gasoline Engine Emissions

Evidence of the carcinogenicity of gasoline engine exhaust particles is available from several assays with animals exposed by several routes. Extracts of gasoline engine exhaust particles also produced predominately positive results in extensive genotoxicity testing. Earlier studies (pre-1980) likely involved exhaust from engines using leaded gasoline, but later studies used exhaust from engines using unleaded gasoline. Although the presence of lead may have added to the carcinogenic potency of exhaust from engines using leaded gasoline, organic-solvent extracts of exhaust condensate from engines using non-leaded gasoline have also produced carcinogenic responses in animals and genotoxic effects in short-term tests (e.g., Nesnow et al., 1982a, b; 1983; Grimmer et al., 1983; Grimmer et al., 1984a; Rannug, 1983).

Organic-solvent extracts of particulate matter in gasoline engine exhaust induced skin tumors in mice given repeated dermal applications (Kotin et al., 1954; Wynder and Hoffman, 1962) and in mice given initiating dermal doses followed by tumor-promoting dermal doses of a phorbol ester (Nesnow et al., 1982a, b; 1983). Gasoline exhaust condensate produced injection site tumors in mice given subcutaneous injections (Pott et al., 1977), skin tumors in mice given biweekly dermal applications for 104 weeks (Grimmer et al., 1983), lung tumors in rats given lung implantations (Grimmer et al., 1984a), and lung tumors in Syrian golden hamsters given intratracheal instillations once every 2 weeks (2,500 or 5,000 μg/hamster per instillation) for life (Reznick-Schüller and Mohr, 1977). Bioassays conducted with fractionated extracts of gasoline exhaust condensate administered dermally or by lung implantation showed that most of the tumorigenic activity was associated with fractions containing PAHs with more than 3 to 4 rings (Grimmer et al., 1983; Grimmer et al., 1984a).

Carcinogenic responses in rats, hamsters, or mice exposed by inhalation to dilutions of gasoline engine exhaust were not found in several animal experiments. Brightwell et al.

(1986; 1989) found no significantly increased incidence of primary lung tumors in groups of Syrian golden hamsters or Fischer 344 rats exposed (16 hour/day, 5 days/week for up to 2 years) to two dilutions of exhaust from a 1.6-L gasoline engine or a gasoline engine equipped with a catalytic converter (particle concentrations were below the limit of detection of 210 $\mu g/m^3$) . Campbell (1936) found no increased incidence of tumors, compared with controls, in groups of mice exposed by inhalation to diluted exhaust from gasoline engines (particle concentrations were not determined) for 7 hours/day, 5 days/week for about 2 years. Yoshimura (1983), likewise, did not find carcinogenic responses in groups of ICR-JCL mice, Sprague-Dawley-JCL rats or Syrian golden hamsters exposed to diluted gasoline engine exhaust (particle concentrations were not reported) for 2 hours/day, 3 days/week for 12 months. Yoshimura (1983), however, reported that concurrent exposure to inhaled gasoline engine exhaust and ingested carcinogens from drinking water (diisopropanolnitrosamine for rats, ethyl carbamate for mice or diethylnitrosamine for hamsters) enhanced the carcinogenic response compared with the response to the respective carcinogen-contaminated drinking water alone. The frequency of pulmonary tumors increased with combined exposure to gasoline exhaust and ingested carcinogens in mice from 72.7 to 91.7 %, in rats from 8.7 to 30.3 %, and in hamsters from 3.8 to 10 %. The enhanced effect was seen at 12 months exposure in rats and hamsters and after 7 months in mice.

Organic-solvent extracts of gasoline engine exhaust particles, from engines with or without catalytic converters, was mutagenic, with or without exogenous metabolic activation, in the Ames assay with *Salmonella typhimurium* strains (Wang et al., 1978; Oshinishi et al., 1980; Claxton, 1981; Brooks et al., 1984; Norpoth et al., 1985; Lewtas, 1985; Westerholm et al., 1988). Rannug (1983) found that extracts of exhaust particles from engines operated with either leaded or lead-free gasoline displayed nearly equivalent mutagenic activities in the Ames assay with or without metabolic activation. Norpoth et al. (1985) fractionated extracts of exhaust particles and found that a fraction containing PAHs with 4 to 7 rings displayed the greatest mutagenic activity with metabolic activation in the Ames test. Handa et al. (1983) likewise reported that PAH-containing fractions of extracts of gasoline engine exhaust particles or condensates were mutagenic with exogenous metabolic activation in *S. typhimurium*.

Extracts of gasoline engine exhaust particles induced mutations in mouse BALB/c3T3 cells (Curren et al., 1981), mouse lympohoma L5178YTK+/- cells (Lewtas, 1982), and Chinese hamster ovary cells (Casto et al., 1981; Brooks et al., 1984). Organic-solvent extracts also induced sister chromatid exchanges in Chinese hamster ovary cells (Brooks et al., 1984; Lewtas and Williams, 1986), chromosomal aberrations in Chinese hamster ovary cells (Brooks et al., 1984), morphological transformations in BALB/3T3 mouse cells (Curren et al., 1981), and enhancement of viral-mediated transformation of Syrian hamster embryo cells (Casto et al., 1981). Inhalation exposure of mice to diluted gasoline engine exhaust 8 hours/day, for 10 days produced an increased frequency of micronucleated bone-marrow cells compared with controls; the particulate matter concentration in the test atmosphere was not reported (Massad et al., 1986).

11.4.3.4.2. Carcinogenicity and Genotoxicity of Emissions from Burning of Cooking and Heating Fuels

Smoke from the burning of fuels used in cooking and heating (e.g., oil, coal and wood) contains particulate matter with adsorbed organic compounds that are potential carcinogens. Although this type of emission source of particulate matter has received less experimental research attention than emissions from vehicular engines, several samples, including samples of soots from chimneys, have been examined for genotoxicity in short-term tests and carcinogenicity in animals.

Sufficient evidence is available for the carcinogenicity of particulate matter produced by the burning of cooking and heating fuels. Several samples of organic-solvent extracts of emissions from burning wood or coal showed tumor-initiating or complete carcinogenicity activity in mouse skin (Grimmer et al., 1984, 1985; Mumford et al., 1990; Lewtas, 1993). Long-term dermal application of organic-solvent extracts of air particles from unventilated homes in which smoky coal was burned produced skin tumors in mice (Mumford et al., 1990). Organic-solvent extracts of soot from the burning of solid oil shale fuel produced skin tumors in mice after repeated dermal application and lung tumors in rats after repeated intratracheal instillations (Vosamae, 1979). Supportive evidence comes from predominately positive results in genotoxicity testing of extracts of several particulate matter samples produced by the burning of wood or coal. Further supportive evidence comes from studies

in which inhalation exposure to aerosols of coal tars from coke oven emissions produced carcinogenic responses in mice and rats (Tye and Stemmer, 1967; MacEwen, 1976).

It should be noted that burning conditions for particular fuel sources are known to influence the amount of particulate matter produced, the chemical composition of the particulate matter, and the ability of organic solvent extracts of particulate matter to produce genotoxic (and presumably carcinogenic) effects.

Vosamae (1979) reported that twice weekly application for 5 months of a benzene extract of soot from the burning of solid oil shale fuel induced skin tumors in 58/78 mice that survived to the time of appearance of the first skin papillomas. Most of the skin tumors (36/58) progressively developed into malignant skin neoplasms. In an experiment with a similar protocol, a benzene extract of soot from the burning of liquid oil shale fuel produced skin tumors in only 9/141 mice that survived the 5-month treatment period.

Grimmer et al. (1984b, 1985) reported that a condensate from the flue of a hard-coal briquet-fired residential furnace produced significantly increased incidence of skin tumors in mice. Female CFLP mice were given twice weekly dermal doses of the material (0, 205, 616 or 1,884.9 μg) for 104 weeks. The condensate was fractionated and the fractions were tested by the same protocol. Fractions containing PAHs with more than 3 rings were the most active fractions and could account for approximately all of the carcinogenic activity of the whole condensate.

Organic-solvent extracts of particulate matter collected in unventilated Chinese homes burning smoky coal, smokeless coal, or wood were tested for skin tumor initiating activities in mice (Mumford et al., 1990). Female Sencar mice were given initiating dermal doses of 0, 1,000, 2,000, 5,000, 10,000, or 20,000 μg of the respective extracts followed by twice-weekly promoting dermal doses of tetradecanoylphorbol-13-acetate for 26 weeks. At the end of 26 weeks, dose-related increased incidences of skin papillomas were found in groups treated with the individual extracts. For each extract, slopes of the tumor multiplicity/dose curve were estimated by regression analysis and used as a measure of the tumor initiation potency of the samples. Estimated tumor initiation potencies were 0.49, 1.3, and 2.7 papillomas/mouse/1,000 μg of extract for the wood, smokeless coal, and smoky coal extracts, respectively. The smoky coal and wood extract samples were also assayed for complete carcinogenicity at dermal doses of 1,000 μg/mouse, given twice a week for 52

weeks, to female Sencar mice. The mice were held for observation for another 25 weeks. No skin tumors were found in a vehicle control group of 40 mice by the end of the experiment. The smoky-coal-treated group showed carcinomas in 38% of the mice at 52 weeks and 88% of mice at the end of the experiment. By the end of the experiment, only 5% (2/40) of the wood-treated mice developed skin tumors.

Lewtas (1993) reported that organic-solvent extracts of particulate emissions from a wood stove burning either softwoods or hardwoods were active in the mouse skin tumor initiating assay using the protocol described by Nesnow et al. (1982a,b) and Mumford et al. (1990). Estimated tumor initiation potencies for these samples were 0.046 papillomas/mouse/1,000 μg of extract for the softwood emission particles and 0.0087 papillomas/mouse/1,000 μg for the hardwood sample.

Vosamae (1979) gave groups of albino rats ten intratracheal instillations, at one week intervals, of 100,000 μg of an extract of soot obtained from burning oil shale solid fuel. One group received tar dissolved in Tween 40 and another group received tar dissolved in peach oil. Epidermoid lung neoplasms developed in 31/70 rats treated with the Tween 40 solution and still alive at the time of appearance of the first lung tumor. In the other treated group, only 3/57 rats developed benign lung epithelial lung tumors. Vehicle control groups showed no lung tumors.

Inhalation exposure to aerosols of coal tars from coke ovens produced carcinogenic responses in two rodent bioassays. Tye and Stemmer (1967) exposed male C3H/HeJ mice to aerosols of coal tars at concentrations of 0.2 mg/l (200,000 $\mu g/m^3$) (first 8 weeks) or 0.12 mg/L (120,000 $\mu g/m^3$) (remainder of experiment), for 2 hours, 3 times weekly for up to 55 weeks. Among the 32 treated mice (of an original 100) that survived to at least 46 weeks, the time at which the first tumor was noted, 4 showed lung adenocarcinomas, 19 showed intrabronchial adenomas, and 10 showed lung squamous metaplasia. In contrast, 32/50 air-control mice survived to 46 weeks and none of these survivors showed lung tumors by 55 weeks. MacEwen (1976) reported that 90-day continuous exposure to 10,000 $\mu g/m^3$ coal tar aerosols produced skin tumors in 44/55 ICR CF-1 mice and 18/43 CAF_1/JAX mice compared with 3/225 and 0/225 control mice of the respective strains. Continuous exposure of Sprague-Dawley rats to the same aerosol by the same protocol produced lung squamous

cell carcinomas in 38/38 male rats and 31/38 female rats; no lung tumors were found in 36 male or 37 female air-control rats (MacEwen, 1976).

Results from genotoxicity testing of particulate matter from the burning of cooking and heating fuels have been predominately positive.

Organic extracts of particle emissions from wood combustion in wood stoves or open fireplaces were mutagenic both with and without exogenous metabolic activation in the Ames *Salmonella* assay (Lewtas, 1985, 1988; Ramdahl et al., 1982; Alfheim et al., 1984a, b; Alfheim and Ramdahl, 1984; van Houdt et al., 1986; Lofroth et al., 1986; Mumford et al., 1987; Heussen, 1991). Extracts of soots from chimneys of domestic woodburning or coalburning stoves and fireplaces also were mutagenic in *Salmonella* (Medalia et al., 1983). Extracts of woodstove combustion emissions (particulate and vapor phases) induced sister chromatid exchange in Chinese hamster ovary cells (Hytonen et al., 1983; Alfheim et al., 1984b) and transformations of Syrian hamster embryo cells (Alfheim et al., 1984b). Testing of fractions of organic extracts of wood stove particulate emissions in the Ames assay showed that acidic or basic fractions had little activity; most of the activity was in a neutral fraction (Lewtas, 1988). Within the neutral fraction, the activity was distributed among aliphatic (27.9%), aromatic (23.3%), moderately polar (11.6%), and highly polar (32.6%) fractions, suggesting that several classes of neutral organic compounds play a role in the expression of the mutagenicity of particles produced by the burning of wood.

11.4.3.5. Discussion of Evidence for Genotoxicity and Carcinogenicity in Animals

Positive findings have been reported for a few cancer bioassays involving dermal or subcutaneous exposure of mice to extracts of several types of samples of particulate matter (Kotin et al., 1954; Leiter et al., 1942; Hueper et al., 1962; Epstein et al., 1966; 1979; Asahina et al., 1972; Lewtas et al., 1991). In addition, organic-solvent extracts of particulate matter samples collected from numerous worldwide localities were genotoxic in extensive testing with the Ames *Salmonella* reverse-mutation assay and, in less extensive testing, in short-term clastogenicity assays with cultured human or animals cells. Several studies have shown that significant portions of the genotoxic or carcinogenic activity of whole extracts of emitted particulate matter are accounted for by fractions containing complex mixtures of neutral organic molecules including PAHs, and that benzo[a]pyrene, one

of the most potent carcinogenic PAHs known, accounts for only a small portion of the total activity, usually less than 10% (see Lewtas, 1988, Grimmer et al., 1983, 1984a,b, 1985, 1987a,b). An area of significant uncertainty concerns the lack of data, including dose-response data, from long-term inhalation animal bioassays with samples of ambient air particulate matter.

11.4.3.6. Particulate Matter and Cancer in Humans

The 1982 Air Quality Criteria Document for Particulate Matter and Sulfur Dioxides (U.S. Environmental Protection Agency, 1982) and its 1986 Addendum (U.S. Environmental Protection Agency, 1986a) noted that epidemiological studies have found no clear evidence to substantiate hypothesized associations between increased cancer rates and elevations in atmospheric concentrations of particulate matter (as a class) or of sulfur oxides. The previous Agency documents acknowledged, however, the existence of epidemiological studies that provide evidence of increased cancer risk associated with occupational exposure to airborne particulate matter emitted from processes involving combustion or pyrolysis of carbon-containing material. Specific types of particulate matter pollution for which epidemiological evidence of an occupational lung cancer effect exists include coal gasification emissions (Doll et al., 1972), coke oven emissions (Lloyd et al., 1971; Redmond et al., 1976), and roofing tar emissions (Hammond et al., 1976). The documents concluded, however, that there was no well-accepted basis for the quantification of the "relative contributions or levels of such particulate matter components to possible carcinogenic effects of particulate matter pollution as a whole" (U.S. Environmental Protection Agency, 1982).

Results from several analytical epidemiological studies examining the potential link between general ambient air pollution and cancer have been published since the preparation of the previous Air Quality Criteria Documents. In contrast to many of the earlier epidemiological studies, these case-control and prospective cohort studies incorporated smoking history data and ambient air pollution data in their analyses. Because the hypothesized association between lung cancer mortality and air pollution continues to receive attention, the results and limitations of earlier descriptive epidemiological studies examining general air pollution and lung cancer mortality are first discussed in this section. More complete descriptions of these studies can be found in reviews by Friberg and Cederlöf

(1977), Doll (1978), Speizer (1983), and Pershagen and Simonato (1993). Review of recent analytical epidemiology studies (case-control and prospective cohort studies) follows the general discussion of the descriptive epidemiology studies.

Descriptive epidemiological studies showed that mortality from lung cancer in several countries during the 1950s and 1960s was more common in urban areas than rural areas (i.e., there was a lung cancer gradient; for reviews see Carnow and Meier, 1973; Higgins, 1976; Doll, 1978; Speizer, 1983; Pershagen and Simonato, 1993). Closer examination of the urban/rural lung cancer gradient in the descriptive studies showed that the gradient was less consistent in nonsmokers and in females compared with males (Doll, 1978; Pershagen and Simonato, 1993). These results, coupled with knowledge that the urban atmosphere can contain elevated concentrations of a variety of materials that caused cancer in laboratory animals and caused lung cancer in humans exposed to high levels under occupational conditions (e.g., metals such as nickel or chromium and PAHs adsorbed to particulates produced by the combustion of carbon-containing materials), led to the hypothesis that chronic exposure to urban air pollutants may cause lung cancer. Particulate products of the pyrolysis and combustion of fossil fuels and other carbon-containing material are especially of interest because of their relative importance in contributing to fine-particulate air pollution.

There are at least two major limitations to the descriptive studies of the urban/rural lung cancer gradient. The first is that major confounding factors (e.g., tobacco smoking and occupational exposures to lung carcinogens) are likely to contribute significantly to the apparent association between urban air pollution and lung cancer. Several investigators have postulated that a non-additive interaction between tobacco smoking and some component of the urban environment may be involved in the apparent increased lung cancer mortality risk in urban smokers (Doll, 1978; Vena, 1982; Jedrychowski et al., 1990; Pershagen and Simonato, 1993). The second major limitation is that these studies used only qualitative, surrogate measures of exposure (such as years of residency in areas with "high, medium or low" levels of air pollution). Quantitative monitoring of air pollution relevant to chronic exposure of individuals was not carried out, and exposure-response relationships, therefore, can not be explored.

The apparent urban/rural lung cancer gradient also has been examined in several prospective cohort studies and retrospective case/control studies that collected personal tobacco smoking histories and used place of residence as a surrogate index of exposure to air pollution (see Friberg and Cederlöf, 1978; Pershagen and Simonato, 1993 for review). Some of the studies also collected occupational history data. A major limitation to these studies, however, is that, like the descriptive epidemiological studies, attempts to quantify exposure levels to ambient air pollution were not part of the experimental designs (e.g., collection of air pollutant monitoring data specific to reported place of residence). Prospective cohort studies that compared urban and rural lung cancer mortality and found elevated smoking-adjusted relative risks for lung cancer mortality in urban groups generally did not find relative risks that exceeded 1.5 (see for example Buell et al., 1967). Some studies did not find elevated smoking-adjusted and/or occupation-adjusted relative risks in urban areas compared with rural areas (see for example Hammond, 1972; Hammond and Garfinkel, 1980). Similarily, mixed results were found among case-control studies that examined potential associations between smoking, place of residence, and lung cancer. For example, Haenzel and colleagues (Haenzel et al., 1962; Haenzel and Taeuber, 1964) studied residence and smoking histories for a sample of 10% of all U.S. lung cancer deaths in 1958-1959 (about 2100 white males and 683 white females; $\geq$ 35 years old) compared with a sample of the general U.S. population of about 25,000 males and 35,000 females identified through the U.S. census bureau. In both sexes, urban residence was associated with greater lung cancer mortality in cigarette smokers than in smokers with a rural residence; the urban/rural gradient was less evident in nonsmokers. Standardized mortality rate ratios (SMRs) for lung cancer, adjusted for age and smoking history, were consistently higher, by factors ranging from 1.41 to 2.00, for males or females who resided in urban areas for 10-39 years, 40 years or longer, or who were lifetime residents compared with males or females who resided in rural areas for similar periods (Haenzel et al., 1962; Haenzel and Taeuber, 1964). In contrast, Samet (1987) collected smoking, residence, and occupational histories for 422 lung cancer cases (283 males and 139 females) and 727 population controls (475 males and 252 females) in New Mexico, but found no consistent associations between residence history variables (e.g., number of years living in counties with more than 500,000 people)

and lung cancer risk using a multiple logistic regression analysis and adjustment for smoking history, age, and sex.

Several case-control studies that included attempts to semi-quantitatively characterize exposure to indices of ambient air pollution are available. In a case-control study, Jedrychowski et al. (1990) classified areas of Cracow, Poland into areas of low (total suspended particles [TSP] $< 150\ \mu g/m^3$ and $SO_2 < 104\ \mu g/m^3$), medium (TSP $> 150\ \mu g/m^3$ or $SO_2 > 104\ \mu g/m^3$, but not both) or high (TSP $> 150\ \mu g/m^3$ and $SO_2 > 104\ \mu g/m^3$) air pollution based on daily measurements made between 1973 and 1980 at 20 sampling sites. Information on occupation, smoking habits, and last place of residency were collected from next of kin for 901 male and 198 female subjects who died in Cracow between 1980 and 1985 with lung cancer and 875 male and 198 female controls who died in Cracow during the same period from causes other than respiratory disease. While a statistically significant increased relative risk for lung cancer (adjusted for age, smoking, and occupational exposure) was found for men who resided in the high-pollution areas (1.48; 95% CL: 1.08, 2.01), an increased relative risk was not not found not for men in the medium- or low-pollution areas, nor for women who resided in any of the areas. Katsouyanni et al. (1991) studied 101 female lung cancer patients and 89 female control patients with orthopedic conditions who all were permanent residents of Athens admitted to hospitals between 1987-1989. Exposure to increasing levels of air pollution appeared to be associated with increased risk for lung cancer, but the relative risk was small and not statistically significant. Using a logistic regression model that included risk variables for age, years of schooling, smoking, and estimated exposure to air pollution, an interaction between air pollution and smoking was apparent; comparison of the lowest and highest air-pollution exposure quartiles gave relative risks of 0.81 for non-smokers, 1.35 for 15-year smokers, and 2.23 for 30-year smokers. In a prospective cohort study, cancer incidence and mortality were monitored in approximately 6,000 nonsmoking, California Seventh-Day Adventists during a 6-year follow-up period between 1977 and 1982 (Abbey et al., 1991; Mills et al., 1991). Using Cox proportional hazards regression models that included covariates of age, sex, total years of past smoking, and educational attainment, statistically significant increased incremental risks during the follow-up period for all malignant neoplasm incidence were found for females (n = number of cancer cases = 175), but not males

(n = 108), when exposure was expressed as an incremental number of hours per year when TSP concentrations exceeded 100, 150, or 200 $\mu g/m^3$, but not concentrations of 60 or 75 $\mu g/m^3$. The largest increases in site-specific cancer risk estimates associated with TSP exposure occurred for respiratory cancers of the larnyx, lung and pleura, but small numbers of cancer cases limited the statistical power of the study to examine cancer incidence for each site separately (e.g., only 17 cancers of the larnyx, lung, or pleura occurred in the cohort).

In a recent prospective mortality study referred to as the "Six Cities Study", (discussed in detail in Chapter 12), Dockery et al. (1993) reported that air pollution was positively associated with death from cardiopulmonary disease, but the association between lung cancer mortality and fine particulate pollution was less certain, presumably because the incidence for lung cancer deaths in the cohort (8.4%) was much less than that for cardiopulmonary deaths (53.1%).

Recent analytical epidemiological studies that have examined the association between lung cancer and indices of exposure to air pollution including particulate matter, while also adjusting for tobacco smoking and other major potential risk factors, provide some evidence to support the hypothesis of an association between ambient air pollution found in certain localities and lung cancer. However, most investigators believe that the epidemiological evidence obtained thus far does not substantiate causality, although the hypothesis remains credible.

11.4.3.7. Biomarkers of Genetic Damage

One of the major methodological problems with the epidemiological studies examining the association between lung cancer and ambient air particulate matter pollution to date is that exposure of individuals is not directly monitored. This is a difficult problem to solve, because of the complex makeup of ambient air particulate matter, the uncertainty concerning which components may be responsible for any putative carcinogenic effect, and the potential for confounding occupational factors or "lifestyle" factors, such as smoking and diet, that might add to an individual's exposure to potentially carcinogenic agents. Nevertheless, several groups of investigators have been exploring the use of adducts between DNA and PAHs (PAH-DNA adducts) as biomarkers to aid in the assessment of individual exposure to one class of potential carcinogens in ambient air particulate matter.

Polycyclic aromatic hydrocarbons adsorbed to particulate matter are present in several complex mixtures, including tobacco smoke and coke oven emissions, that are well established as being carcinogenic to humans. Because carcinogenic PAHs are thought to initiate the multistage process of cancer via covalent modification of DNA, the measurement of PAH-DNA adducts in white blood cells (using benzo[a]pyrene-DNA adducts for a reference) has been examined as a means of quantifying the biologically effective dose of PAHs in humans exposed to coke oven emissions (Van Schooten et al., 1990), cigarette smoke (Phillips et al., 1990), or iron and steel foundry emissions (Perera et al., 1988).

Recently, PAH-DNA adduct levels in white blood cells have been measured in three populations with suspected differences in exposure to ambient air particulate matter: Polish coke oven workers, other residents of Polish towns around coke oven plants, and residents of a rural region of Poland (Hemminki et al., 1990; Perera et al., 1992; Grzybowska et al., 1993). Using blood samples collected in the winter, the general pattern of adducts and the average levels of adducts were similar in coke oven workers and residents of towns with coke oven plants, while the levels in the rural residents were 2 to 3 times lower (Hemminki et al., 1990). Subsequently, analysis of blood samples drawn in the summer showed that coke-plant town residents had average adduct levels that were lower than the average for coke oven workers and similar to rural residents (Grzybowska et al., 1993). The authors commented that the seasonal change in the relative levels of adducts in the town residents may be reflective of the use of coal combustion for domestic heating in the winter; the same seasonal variation was found in the mutagenic activity in Ames tests of extracts of samples of ambient air particulate matter from the same region (Motykiewicz et al., 1989). Large degrees of variation in levels of PAH-DNA adducts were noted among individuals within each "exposure" group.

Several investigators have noted some potential limitations in the use of PAH-DNA adducts as biomarkers of exposure to ambient air particulate matter. Kriek et al. (1993) and Lewtas et al. (1993) both noted that substantial interindividual variation in PAH-DNA adducts has been observed in several populations, and that this variation may be due, in part, to individual variation in metabolic activities (e.g., PAH metabolism or DNA repair), in addition to individual differences in exposure levels. In a study that monitored personal exposure to benzo[a]pyrene in air and placental PAH-DNA adducts in pregnant Chinese

women who used smoky coal for domestic purposes in vented or unvented homes, Mumford et al. (1993) did not find a significant exposure-response relationship between monitored benzo[a]pyrene concentrations in air and levels of PAH-DNA adducts or the percentage of samples with detectable PAH-DNA adducts. Mumford et al. (1993) suggested that dietary intake of PAH may have been responsible for the lack of an exposure-response relationship, and that PAH-DNA adducts may be used as a qualitative, but not quantitative, measure of exposure to combustion emissions. Heussen et al. (1994) measured white-blood-cell PAH-DNA adducts (using the ^{32}P-postlabeling technique) in five individuals before and after a 1-week exposure to residential air in homes with open fireplaces, but found no "combustion-related" increase in DNA adducts, even though extracts of air samples showed an increased mutagenic activity in Ames tests, with and without metabolic activation, after one week of open-fireplace use. Heussen et al. (1994) proposed that the exposure conditions may have presented too low a concentration of particulate PAHs or too short a duration for the production of increased PAH-DNA adducts in the exposed subjects, or that unknown, nonaromatic compounds, rather than PAHs, may account for the observed mutagenic activity of the air samples.

Although PAH-DNA adducts are being examined as biomarkers for exposure to ambient air particulate matter from combustion sources, their use as a biomarker for general ambient air particulate matter is limited due to the complexity of the chemical makeup of ambient air particulate matter and the potential variability across localities.

11.4.4 Diesel Exhaust Emissions

Diesel engines emit both gas phase pollutants (hydrocarbons [HCs], oxides of nitrogen [NO_x], and carbon monoxide [CO]) and carbonaceous PM. A description of the diesel engine, its combustion system, pollutant formation mechanisms and emission factors as well as the cancer and noncancer health effects of diesel exhaust emissions has been reviewed in another document (U.S. Environmental Protection Agency, 1994). The information summarized here is drawn from that document.

In addition to the potential carcinogenicity of diesel exhaust, there has been concern that diesel PM may contribute to other health problems, especially those associated with the respiratory tract. Other components of diesel exhaust, such as sulfur dioxide (SO_2), nitrogen

dioxide (NO_2), formaldehyde, acrolein, and sulfuric acid may contribute to some of these potential health effects. The discussion begins with noncancer effects, proceeds to mutagenicity and carcinogenicity, and ends with a summary of potential mechanisms.

Within the text, exposures are expressed in terms of the concentration of diesel particles. Other major measured components in the studies are presented in the tables which have additional details about the studies, including references. The diesel assessment document (U.S. Environmental Protection Agency, 1994) should be consulted for a complete evaluation of diesel emissions.

11.4.4.1 Noncancer Health Effects

Effects of Diesel Exhaust on Humans

The effects of short term exposure to diesel exhaust have been investigated primarily in occupationally-exposed workers (Table 11-11). Symptoms of acute exposure to high levels of diesel exhaust include mucous membrane, eye, and respiratory tract irritation (including chest tightness and wheezing) and neuropsychological effects of headache, lightheadedness, nausea, heartburn, vomiting, weakness, and numbness and tingling in the extremities. Diesel exhaust odor can cause nausea, headache, and loss of appetite.

In studies of humans exposed to diesel exhaust, minimal and not statistically significant changes were reported over the course of a workshift in respiratory symptoms and pulmonary function in underground miners, bus garage workers, dock workers, and locomotive repairmen. In diesel bus garage workers, there was an increased reporting of burning and watering of the eyes, cough, labored breathing, chest tightness, and wheezing, but no reductions in pulmonary function associated with exposure to diesel exhaust. In stevedores pulmonary function was adversely affected over a workshift exposure to diesel exhaust but normalized after a few days without exposure.

The chronic effects of exposure to diesel exhaust have been evaluated in humans in epidemiologic studies of occupationally exposed workers. Most of the epidemiologic data indicate the absence of an excess of chronic respiratory disease associated with exposure to diesel exhaust. In a few of these studies, a higher prevalence of respiratory symptoms, primarily cough, phlegm, or chronic bronchitis, were observed among the exposed. Reductions in several pulmonary function parameters including FVC and FEV_1, and to a

TABLE 11-11. HUMAN STUDIES OF DIESEL EXHAUST EXPOSURE

Study	Description	Findings
Kahn et al. (1988)	13 Cases of acute exposure, Utah and Colorado coal miners.	Acute reversible sensory irritation, headache; nervous system effects, broncho-constriction were reported at unknown exposures.
El Batawi and Noweir (1966)	161 Workers, two diesel bus garages.	Eye irritation (42%), headache (37%), dizziness (30%), throat irritation (19%), and cough and phlegm (11%) were reported in this order of incidence by workers exposed in the service and repair of diesel powered buses.
Battigelli (1965)	Six subjects, eye exposure chamber, three dilutions.	Time to onset was inversely related and severity of eye irritation was associated with the level of exposure to diesel exhaust.
Katz et al. (1960)	14 Persons monitoring diesel exhaust in a train tunnel.	Three occasions of minor eye and throat irritation; no correlation established with concentrations of diesel exhaust components.
Hare and Springer (1971) Hare et al. (1974)	Volunteer panelists who evaluated general public's response to odor of diesel exhaust.	Slight odor intensity, 90% perceived, 60% objected; slight to moderate odor intensity, 95% perceived, 75% objected; almost 75% objected; almost 95% objected.
Linnell and Scott (1962)	Odor panel under highly controlled conditions determined odor threshold for diesel exhaust.	In six panelists, the volume of air required to dilute raw diesel exhaust to an odor threshold ranged from a factor of 140 to 475.
Battigelli (1965)	13 Volunteers exposed to three dilutions of diesel exhaust for 15 min to 1 h.	No significant effects on pulmonary resistance were observed as measured by plethysmography.
Reger et al. (1978)	Five or more VC maneuvers by each of 60 coal miners exposed to diesel exhaust at the beginning and end of a work shift.	FEV_1, FVC, and PEFR were similar between diesel and non-diesel-exposed miners. Smokers had an increased increased number of decrements over shift than nonsmokers.
Ames et al. (1982)	Pulmonary function of 60 diesel-exposed compared with 90 non-diesel-exposed coal miners over work shift.	Significant work shift decrements occurred in miners in both groups who smoked; no significant differences in ventilatory function changes between miners exposed to diesel exhaust and those not exposed.
Jorgensen and Svensson (1970)	240 Iron ore miners matched for diesel exposure, smoking and age were given bronchitis questionnaires and spirometry pre- and postwork shift.	Among underground (surrogate for diesel exposure) miners, smokers and older age groups, frequently of bronchitis was higher. Pulmonary function was similar between groups and subgroups except for differences accountable to age.

TABLE 11-11 (cont'd). HUMAN STUDIES OF DIESEL EXHAUST EXPOSURE

Study	Description	Findings
Gamble et al. (1978)	200 Salt miners performed before and after workshift spirometry. Personal environmental NO_2 and inhalable particle samples were collected.	Smokers had greater but not significant reductions in spirometry than ex- or nonsmokers. NO_2, but not particulate, levels significantly decreased FEV1, FEF_{25}, FEF_{50}, and FEF_{75} over the workshift.
Gamble et al. (1987a)	232 Workers in four diesel bus garages were administered acute respiratory questionnaires and before and after workshift spirometry. Compared to lead, acid battery workers previously found to be unaffected by their exposures.	Prevalence of burning eyes, headache, difficult or labored breathing, nausea, and wheeze were higher in diesel bus workers than in comparison population.
Ulfvarson et al. (1987)	Workshift changes in pulmonary function were evaluated in crews of roll-on/ roll-off ships and car ferries and bus garage staff. Pulmonary function was evaluated in six volunteers exposed to diluted diesel exhaust, 2.1 ppm NO_2, and 0.6 mg/m^3 particulate matter.	Pulmonary function was affected during a workshift exposure to diesel exhaust, but it normalized after a few days with no exposure. Decrements were greater with increasing intervals between exposures. No effect on pulmonary function was observed in the experimental exposure study.
Battigelli et al. (1964)	210 Locomotive repairmen exposed to diesel exhaust for an average of 9.6 years in railroad engine houses were compared with 154 railroad yard workers of comparable job status but no exposure to diesel exhaust.	No significant differences in VC, FEV_1, peak flow, nitrogen washout, or diffusion capacity nor in the prevalence of dyspnea, cough, or sputum were found between the diesel exhaust-exposed and nonexposed groups.
Gamble et al. (1987b)	283 Male diesel bus garage workers from four garages in two cities were examined for impaired pulmonary function (FVC, FEV_1, and flow rates). Study population with a mean tenure of 9 $\pm$ 10 years S.D. was compared to a nonexposed "blue collar" population.	Analyses within the study populations population showed no association of respiratory symptoms with tenure. Reduced FEV_1 and FEF_{50} (but not FEF_{75}) were associated with increasing tenure. The study population had a higher incidence of cough, phlegm, and wheezing unrelated to tenure. Pulmonary function was not affected in the total cohort of diesel-exposed of diesel-exposed but was reduced with 10 or more years of tenure.

TABLE 11-11 (cont'd). HUMAN STUDIES OF DIESEL EXHAUST EXPOSURE

Study	Description	Findings
Purdham et al. (1987)	Respiratory symptoms and pulmonary function were evaluated in 17 stevedores exposed to both diesel and gasoline exhausts in car ferry operations; control group was 11 on-site office workers.	No differences between the two groups for respiratory symptoms. Stevedores had lower baseline lung function consistent with an obstructive ventilatory defect compared with controls and those of Sydney, Nova Scotia, residents. Caution in interpretation is warranted due to small sample size. No significant size. No significant changes in lung function over workshift nor difference between two groups.
Reger et al. (1982)	Differences in respiratory symptoms and pulmonary function were assessed in 823 coal miners from six diesel equipped mines compared to 823 matched coal miners not exposed to diesel exhaust.	Underground miners in diesel-use mines reported more symptoms of cough and phlegm and had lower pulmonary function. Similar trends were noted for surface workers at diesel-use mines. Pattern was consistent with small airway disease but factors other than exposure to diesel exhaust thought to be responsible.
Ames et al. (1984)	Changes in respiratory symptoms and function were measured during a 5-year period in 280 diesel-exposed and 838 nonexposed U.S. underground coal miners.	No decrements in pulmonary function or increased prevalence of respiratory symptoms were found attributable to diesel exhaust. In fact, 5-year incidences of cough, phlegm, and dyspnea were greater in miners without exposure to diesel exhaust than in miners exposed to diesel diesel exhaust.
Attfield (1978)	Respiratory symptoms and function were assessed in 2,659 miners from 21 underground metal mines (1,709 miners) and nonmetal mines (950 miners). Years of diesel usage in the mines were surrogate for exposure to diesel exhaust.	Questionnaire found an association between an increased prevalence of cough and aldehyde exposure; this finding was not substantiated by spirometry data. No adverse symptoms or pulmonary function decrements were related to exposure to NO_2, CO, CO_2, dust, or quartz.
Attfield et al. (1982)	Respiratory symptoms and function were assessed in 630 potash miners from six potash mines using a questionnaire, chest radiographs and spirometry. A thorough assessment of the environment of each mine was made concurrently.	No obvious association indicative of diesel exposure was found between health indices, dust exposure, and pollutants. A higher prevalence of cough and phlegm, but no differences in FVC and FEV_1, were found in these diesel-exposed potash workers when compared to predicted values from a logistic model based on blue- collar staff working in nondusty jobs.

TABLE 11-11 (cont'd). HUMAN STUDIES OF DIESEL EXHAUST EXPOSURE

Study	Description	Findings
Gamble et al. (1983)	Respiratory morbidity was assessed in 259 miners in 5 salt mines by respiratory symptoms, radiographic findings and spirometry. Two mines used diesels extensively, 2 had limited use, one used no diesels in 1956, 1957, 1963, or 1963 through 1967. Several working populations were compared to the salt mine cohort.	After adjustment for age and smoking, salt miners showed no symptoms, increased prevalence of cough, phlegm, dyspnea or air obstruction (FEV_1/FVC) compared to aboveground coal miners, potash workers or blue collar workers. FEV_1, FVC, FEF_{50}, and FEF_{75} were uniformly lower for salt miners in comparison to all the comparison populations. No changes in pulmonary function were associated with years of exposure or cumulative exposure to inhalable particles or NO_2.
Gamble and Jones (1983)	Same as above. Salt miners were grouped into low, intermediate and high exposure categories based on tenure in jobs with diesel exposure.	A statistically significant dose-related association of phlegm and diesel exposure was noted. Changes in pulmonary function showed no association with diesel tenure. Age- and smoking-adjusted rates of cough, phlegm, and dyspnea were 145, 169, and 93% of an external comparison population. Predicted pulmonary function indices showed small but significant reductions; there was no dose-response relationship.
Edling and Axelson (1984)	Pilot study of 129 bus company employees classified into three dieselexhaust exposure categories clerks (0), bus drivers (1), and bus garage workers.	The most heavily exposed group (bus garage workers) had a fourfold increase in risk of dying from cardiovascular disease, even after correction for smoking and allowing for 10 years of exposure and 15 years or more of inductionlatency time.
Edling et al. (1987)	Cohort of 694 male bus garage employees followed from 1951 through 1983 were evaluated for mortality from cardiovascular disease. Subcohorts categorized by levels of exposure were clerks (0), bus drivers (1), and bus garage employees (2).	No increased mortality from cardiovascular disease was found among the members of these five bus companies when compared with the general population or grouped as sub-cohorts with different levels of exposure.

Source: quoted from U.S. Environmental Protection Agency, 1994.

lesser extent forced expiratory flow at 50 and 75% of vital capacity (FEF_{50} and FEF_{75}), have also been reported. Two studies, each with methodological problems, detected statistically significant decrements in pulmonary function when compared with matched controls. These two studies coupled with other reported nonsignificant trends in respiratory flow-volume

measurements suggest that diesel exhaust exposure may impair pulmonary function among occupational populations. A preliminary study of the association of cardiovascular mortality and exposure to diesel exhaust found a fourfold higher risk ratio. A more comprehensive study by the same investigators, however, found no significant difference between the observed and expected number of deaths caused by cardiovascular disease.

The results of the epidemiologic studies addressing noncarcinogenic health effects resulting from exposure to diesel exhaust must be interpreted cautiously because of a myriad of methodological problems, including incomplete information on the extent of exposure to diesel exhaust, the presence of confounding variables (smoking, occupational exposures to other toxic substances, and the short duration and low intensity of exposure). These limitations restrict definitive conclusions about diesel exhaust being the cause of any noncarcinogenic health effects, observed or reported.

Effects Of Diesel Exhaust On Animals

In short-term and chronic exposure studies, toxic effects have been related to high concentrations of diesel particulate matter. Data from short-term exposures indicate minimal effects on pulmonary function, even though histological and cytological changes were observed in the lungs (Table 11-12). Exposures for several months or longer to levels markedly above environmental ambient concentrations resulted in accumulation of particles in the lungs, increases in lung weight, increases in AMs and leukocytes, macrophage aggregation, hyperplasia of alveolar epithelium, and thickening of the alveolar septa. Similar histological changes, as well as reductions in growth rates and alterations in indices of pulmonary function, have been observed in chronic exposure studies. Chronic studies have been carried out using rats, mice, guinea pigs, hamsters, cats, and monkeys. Reduced resistance to respiratory tract infections has been reported in mice exposed to diesel exhaust.

Reduced growth rates have been observed most often in studies with exposures of at least 2,000 $\mu g/m^3$ diesel particulate matter which lasted for 16 h or more per day (Table 11-13). No effects on growth or survival were noted at levels of 6,000 to 8,000 $\mu g/m^3$ of PM when the daily exposures were only 6 to 8 h/day.

Changes in pulmonary function have been noted in a number of different species chronically exposed to diesel exhaust (Table 11-14). The lowest exposure levels that resulted

TABLE 11-12. SHORT-TERM EFFECTS OF DIESEL EXHAUST ON LABORATORY ANIMALS

Species/Sex	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	References
Rat, F-344, M; Mouse, A/J; Hamster, Syrian	20 h/day 7 days/week 10-13 weeks	1,500 0.19 μm, MMD	2,100,000 to 2,730,000	6.9	0.49	—	Increase in lung wt; increase in thickness of alveolar walls; no species difference	Kaplan et al. (1982)
Rat, F-344, M, F; Mouse, CD-1, M, F	7 h/day 5 days/week 19 weeks	210 1,000 4,400	140,000 665,000 2,926,000	— — —	— — —	— — —	No effects on lung function; increase in PMNs and proteases and AM aggregation in both species	Mauderly et al. (1981)
Cat, Inbred, M	20 h/day 7 days/week 4 weeks	6,400	3,584,000	14.6	2.1	2.1	Few effects on lung function; focal pneumonitis or alveolitis	Pepelko et al. (1980a)
Rat, Sprague-Dawley, M	20 h/day 7 days/week 4 weeks	6,400 6,800[a]	3,584,000 3,808,000	16.9 16.1[a]	2.49 2.76[a]	2.10 1.86[a]	Decreased body wt; arterial blood pH reduced; vital total lung capacities increased	Pepelko (1982a)
Guinea Pig, Hartley, M, F	20 h/day 7 days/week 4 weeks	6,800[a]	3,808,000	16.7	2.9	1.9 (<0.01 ppm O_3)[a]	Exposure started when animals were 4 days old; increase in pulmonary flow; bradycardia	Wiester et al. (1980)
Rat, F-344, M	20 h/day 5.5 days/week 4 weeks	6,000 6.8 μm, MMD	2,640,000	—	—	—	Macrophage aggregation; increase in PMNs; Type 2 cell proliferation; thickened alveolar walls	White and Garg (1981)
Guinea Pig, Hartley M, F	20 h/day 7 days/week 8 weeks	6,300	7,056,000	17.4	2.3	2.1 (<0.01 ppm O_3)[a]	Increase in relative lung wt; AM aggregation; hypertrophy of goblet cells; focal hyperplasia of alveolar epithelium	Weister et al. (1980)

[a]Irradiated exhaust.
PMN = Polymorphonuclear leukocyte.
AM = Alveolar macrophage.

Source: quoted from U.S. Environmental Protection Agency, 1994.

TABLE 11-13. EFFECTS OF CHRONIC EXPOSURES TO DIESEL EXHAUST ON SURVIVAL AND GROWTH OF LABORATORY ANIMALS

Species/Sex	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	References
Rat, F-344, M, F; Monkey, cynomolgus, M	7 h/day 5 days/week 104 weeks	2,000 0.23–0.36 μm, MMD	7,280,000	11.5	1.5	0.8	No effects on growth or survival	Lewis et al. (1989)
Rat, F344, M; Guinea Pig, Hartley, M	20 h/day 5 days/week 106 weeks	250 750 1,500 0.19 μm, MMD	2,650,000 7,950,000 15,900,000	2.7[a] 4.4[a] 7.1[a]	0.1[b] 0.27[b] 0.5[b]	— — —	Reduced body weight in rats at 1,500 $\mu g/m^3$	Schreck et al. (1981)
Hamster, Chinese, M	8 h/day 7 days/week 26 weeks	6,000 12,000	8,736,000 17,472,000	— —	— —	— —	No effect on growth	Vinegar et al. (1981a,b)
Rat, Wistar, M	6 h/day 5 days/week 87 weeks	8,300 0.71 μm, MMD	21,663,000	50.0	4.0–6.0	—	No effect on growth or mortality rates	Karagianes et al. (1981)
Rat, F-344, M, F; Mouse CD-1	7 h/day 5 days/week 130 weeks	350 3,500 7,000 0.25 μm, MMD	1,592,000 15,925,000 31,850,000	2.9 16.5 29.7	0.05 0.34 0.68	— — —	No effect on growth or mortality rates	Mauderly et al. (1984, 1987b)
Rat, Wistar, F; Mouse, MMRI, F	19 h/day 5 days/week 104 weeks	4,240 0.35 μm, MMD	41,891,0000	12.5	1.5	1.1	Reduced body wts; increased mortality in mice	Heinrich et al. (1986a)
Rat, F-344 M, F	16h/day 5 days/week 104 weeks	700 2,200 6,600	5,824,000 18,304,000 54,912,000	— — 32.0	— — —	— — —	Growth reduced at 2,200 and 6,600 $\mu g/m^3$	Brightwell et al. (1986)
Rat[c] F-344/Jcl.	16 h/day 6 days/week 130 weeks	110[d] 410[d] 1,080[d] 2,310[d] 3,720[e] 0.2–0.3 μm, MMD	1,373,000 5,117,000 13,478,000 28,829,000 46,426,000	1.23 2.12 3.96 7.10 12.9	0.08 0.26 0.70 1.41 3.00	0.38 1.06 2.42 4.70 4.57	Concentration-dependent decrease in body weight; earlier deaths in females exposed to 3,720 $\mu g/m^3$, stabilized by 15 mo	Research Committee for HERP Studies (1988)

[a]Estimated from graphically depicted mass concentration data.
[b]Estimated from graphically presented mass concentration data for NO_2 (assuming 90% NO and 10% NO_2).
[c]Data for tests with light-duty engine; similar results with heavy-duty engine.
[d]Light-duty engine.
[e]Heavy-duty engine.

Source: Quoted from U.S. Environmental Protection Agency (1994).

TABLE 11-14. EFFECTS OF DIESEL EXHAUST ON PULMONARY FUNCTION OF LABORATORY ANIMALS

Species/Sex	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	References
Rat, F-344 M, F	7 h/day 5 days/week 104 weeks	2,000 0.23–0.36 μm MMD	7,280,000	11.5	1.5	0.8	No effect on pulmonary function	Lewis et al. (1989)
Monkey, M Cynomolgus	7 h/day 5 days/week 104 weeks	2,000 0.23-0.36 μm, MMD	7,280,000	11.5	1.5	0.8	Decreased expiratory flow; no effect on vital or diffusing capabilities	Lewis et al. (1989)
Rat, F-344, M	20 h/day 5.5 days/week 87 weeks	1,500 0.19 μm, MMD	14,355,000	7.0	0.5	—	Increased functional residual capacity, expiratory volume and flow	Gross (1981b)
Rat, Wistar, F	7-8 h/day 5 days/week 104 weeks	3,900 0.1 μm, MMD	14,196,000- 16,224,000	18.5	1.2	3.1	No effect on minute volume, compliance or resistance	Heinrich et al. (1982)
Hamster, Chinese, M	8 h/day 7 days/week 26 weeks	6,000 12,000	8,736,000 17,472,000	— —	— —	— —	Decrease in vital capacity, residual volume, and diffusing capacity; increase in static deflation lung volume	Vinegar et al. (1980, 1981a,b)
Rat, F-344, M, F	7 h/day 5 days/week 130 weeks	350 3,500 7,000 0.23–0.26 μm, MMD	1,593,000 15,925,000 31,850,000	2.9 16.5 29.7	0.05 0.34 0.68	— — —	Diffusing capacity, lung compliance reduced at 3,500 and 7,000 $\mu g/m^3$	Mauderly et al. (1988) McClellan et al. (1986)
Hamster, Syrian M, F	19 h/day 5 days/week 120 weeks	4,240 0.35 μm, MMD	48,336,000	12.5	1.5	1.1	Significant increase in airway resistance	Heinrich et al. (1986a)
Rat, F-344; Hamster Syrian	16 h/day 5 days/week 104 weeks	700 2,200 6,600	5,824,000 18,304,000 54,912,000	— — —	— — —	— — —	Large number of pulmonary function changes consistent with obstructive and restrictive airway diseases at 6,600 $\mu g/m^3$ (no specific data provided)	Brightwell et al. (1986)
Rat, Wistar, F	19 h/day 5 days/week 140 weeks	4,240 0.35 μm, MMD	56,392,000	12.5	1.5	1.1	Decrease in dynamic lung compliance; increase in airway resistance	Heinrich et al. (1986a)
Cat, inbred, M	8 h/day 7 days/week 124 weeks	6,000[a] 12,000[b]	41,664,000 83,328,000	20.2 33.3	2.7 4.4	2.1 5.0	Decrease in vital capacity, total lung capacity, and diffusing capacity after 2 years; no effect on expiratory flow	Pepelko et al. (1980b, 1981) Moorman et al. (1985)

[a]1 to 61 weeks exposure.
[b]62 to 124 weeks of exposure.

Source: Quoted from U.S. Environmental Protection Agency (1994).

in impaired pulmonary function varied among the species tested but were in excess of 1,000 $\mu g/m^3$.

Histological changes occurring in the respiratory tract tissue of animal exposed chronically to high concentrations of diesel exhaust include alveolar histiocytosis, macrophage aggregation, tissue inflammation, increases in polymorphonuclear leukocytes, hyperplasia of bronchiolar and alveolar Type 2 cells, thickened alveolar septa, edema, fibrosis, and emphysema (Table 11-15). Biochemical changes in the lung associated with these histopathological findings included increases in lung DNA, total protein, and activities of alkaline and acid phosphatase, and glucose-6-phosphate dehydrogenase; increased synthesis of collagen; and release of inflammatory mediators such as leukotriene LTB and prostaglandin $PGF_{2\alpha}$. Some studies have also suggested that there may be a threshold of exposure to diesel exhaust below which pathologic changes do not occur. These no-effect levels were reported to be 2,000 $\mu g/m^3$ for cynomolgus monkeys, 110 to 350 $\mu g/m^3$ for rats, and 250 $\mu g/m^3$ PM for guinea pigs exposed for 7 to 20 h/day, 5 to 5.5 days/week for 104 to 130 weeks.

The pathological effects of diesel exhaust particulate matter appear to be strongly dependent on the relative rates of pulmonary deposition and clearance (Table 11-16). At particle concentrations of about 1,000 $\mu g/m^3$ or above, pulmonary clearance becomes reduced, with concomitant focal aggregations of particle-laden AMs. The principal mechanism of reduced particle clearance appears to be the result of impaired AM function. This impairment seems to be nonspecific and applies to insoluble particles deposited in the alveolar region. Other data suggest that the inability of particle-laden AMs to translocate to the mucociliary escalator is correlated to the average composite particle volume per AM in the lung. Data from rats indicate that when this particle volume exceeds a critical level, impairment appears to be initiated. Such data for other laboratory species and humans, unfortunately, are very limited.

There is a considerable body of evidence that the major noncancerous health hazards posed by exposure to diesel exhaust are to the lung. These data also denote that the exposures that cause pulmonary injury are lower than those inducing detectable increases in lung tumors. These same data further indicate that the inflammatory and proliferative changes in the lung play a key role in the etiology of pulmonary tumors in exposed rats.

TABLE 11-15. HISTOPATHOLOGICAL EFFECTS OF DIESEL EXHAUST IN THE LUNGS OF LABORATORY ANIMALS

Species/Sex	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	References
Rat, F-344, M Mouse A/J, M; Hamster, Syrian, M	20 h/day 7 days/week 12-13 weeks	1,500 0.19 μm, MMD	2,520,000- 2,730,000	—	—	—	Inflammatory changes; increase in lung weight; increase in thickness of alveolar walls	Kaplan et al. (1982)
Monkey, Cynomolgus, M	7 h/day 5 days/week 104 weeks	2,000 0.23–0.36 μm, MMD	7,280,000	11.5	1.5	0.8	AM aggregation; no fibrosis, inflammation or emphysema	Lewis et al. (1989)
Rat, F-344, M, F	7 h/day 5 days/week 104 weeks	2,000 0.23–0.36 μm, MMD	3,640,000	11.5	1.5	0.8	Multifocal histiocytosis; inflammatory changes; Type II cell proliferation; fibrosis	Bhatnagar et al. (1980) Pepelko (1982a)
Rat, Sprague-Dawley, M; Mouse, A/HEJ, M	8 h/day 7 days/week 39 weeks	6,000	13,104,000	—	—	—	Increase in lung protein content and collagen synthesis but a decrease in overall lung protein synthesis in both species; prolyl-hydroxylase activity increased in rats in utero	Bhatnagar et al. (1980) Pepelko (1982a)
Hamster, chinese, M	8 h/day 5 days/week 26 weeks	6,000 12,000	6,240,000 12,480,000	— —	— —	— —	Inflammatory changes; AM accumulation; thickened alveolar lining; Type II cell hyperplasia; edema; increase in collagen	Pepelko (1982b)
Hamster, Syrian, M, F	7-8 h/day 5 days/week 120 weeks	3,900 0.1 μm, MMD	16,380,000- 18,720,000	18.5	1.2	3.1	Inflammatory changes, 60% adenomatous cell proliferation	Heinrich et al. (1982)
Rat, Wistar, M	6 h/day 5 days/week 87 weeks	8,300 0.71 μm, MMD	21,663,000	50.0	4.0-6.0	—	Inflammatory changes; AM aggregation; aleovar cell hypertrophy; interstitial fibrosis, emphysema (diagnostic methodology not described)	Karagianes et al. (1981)
Rat, F-344, F	8 h/day 7 days/week 104 weeks	4,900	28,538,000	7.0	1.8	13.1	Type II cell proliferation; Inflammatory changes; bronchial hyperplasia; fibrosis	Iwai et al. (1986)
Rat, F-344, M, F; Mouse CD-1, M, F	7 h/day 5 days/week 130 weeks	350 3,500 7,000 0.23 μm, MMD	1,592,000 15,925,000 31,850,000	2.9 16.5 29.7	0.05 0.34 0.68	— — —	Alveolar and bronchiolar epithelial metaplasia in rats at 3,500 and 7,000 $\mu g/m^3$; fibrosis at 7,000 $\mu g/m^3$ in rats and mice; inflammatory changes	Mauderly et al. (1987a,b) Henderson et al. (1988)

TABLE 11-15 (cont'd). HISTOPATHOLOGICAL EFFECTS OF DIESEL EXHAUST IN THE LUNGS OF LABORATORY ANIMALS

Species/Sex	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	References
Rat, M, F, F-344/Jcl.	16 h/day 6 days/week 130 weeks	110[a] 410[a] 1,080[a] 2,310[a] 3,720[b]	1,373,000 5,117,000 13,478,000 28,829,000 46,336,000	1.23 2.12 3.96 7.10 12.9	0.08 0.26 0.70 1.41 3.00	0.38 1.06 2.42 4.70 4.57	Inflammatory changes; Type II cell hyperplasia and lung tumors seen at >400 $\mu g/m^3$; shortening and loss of cilia in trachea and bronchi	Research Committee for HERP Studies (1988)
Hamster, Syrian, M, F	19 h/day 5 days/week 120 weeks	4,240	48,336,000	12.5	1.5	1.1	Inflammatory changes; thickened alveolar septa; bronchiolo-alveolar hyperplasia; emphysema (diagnostic methodology not described)	Heinrich et al. (1986a)
Mouse, NMRI, F	19 h/day 5 days/week 120 weeks	4,240	48,336,000	12.5	1.5	1.1	Inflammatory changes; bronchioloalevolar hyperplasia; alveolar lipoproteinosis; fibrosis	Heinrich et al. (1986a)
Rat, Wistar, F	19 h/day 5 days/week 140 weeks	4,240	56,392,000	12.5	1.5	1.1	Thickened alveolar septa; AM aggregation; inflammatory changes; hyperplasia; lung tumors	Heinrich et al. (1986a)
Guinea Pig, Hartley, M	20 h/day 5.5 days/week 104 weeks	250 750 1,500 6,000	2,860,000 8,580,000 17,160,000 68,640,000	— — — —	— — — —	— — — —	Minimal response at 250 and ultrastructural changes at 750 $\mu g/m^3$; thickened alveolar membranes; cell proliferation; fibrosis at 6,000 $\mu g/m^3$; increase in PMN at 750 $\mu g/m^3$ and 1,500 $\mu g/m^3$	Barnhart et al. (1981, 1982) Vostal et al. (1981)
Cat, inbred, M	8 h/day 7 days/week 124 weeks	6,000[c] 12,000[d]	41,664,000 83,328,000	20.2 33.2	2.7 4.4	2.1 5.0	Inflammatory changes; AM aggregation; bronchiolar epithelial metaplasia; Type II cell hyperplasia; peribronchiolar fibrosis	Plopper et al. (1983) Hyde et al. (1985)

[a]Light-duty engine.
[b]Heavy-duty engine.
[c]1 to 61 weeks exposure.
[d]62 to 124 weeks of exposure.

AM = Alveolar macrophage.
PMN = Polomerphonuclear leukocyte.

Source: Quoted from U.S. Environmental Protection Agency (1994).

TABLE 11-16. EFFECTS OF EXPOSURE TO DIESEL EXHAUST ON THE PULMONARY DEFENSE MECHANISMS OF LABORATORY ANIMALS

Species	Exposure Period	Particles ($\mu g/m^3$)	C x T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	Reference
ALVEOLAR MACROPHAGE STATUS								
Guinea Pig, Hartley	20 h/day 5.5 days/week 8 weeks	250 1,500 0.19 μm, MMD	220,000 1,320,000	2.9 7.5	— —	— —	No significant changes in absolute numbers of alveolar macrophages (AMs)	Chen et. al. (1980)
Rat, F-344, M	7 h/day 5 days/week 104 weeks	2,000 0.23–0.36 μm MMD	7,280,000	11.5	1.5	0.81	Little effect on viability, cell number, oxygen consumption, membrane integrity, lyzomal enzyme activity, or protein content of AMs; decreased cell volume and ruffling of cell membrane and depressed luminescence of AM	Castranova et al. (1985)
Rat, F-344, M	20 h/day 5.5 days/week 26, 48, or 52 weeks	250[a] 750[a] 1,500[b] 0.19 μm, MMD	715,000- 8,580,000	2.9 4.8 7.5	— — —	— — —	AM cell counts proportional to concentration of DP at 750 and 1,500 $\mu g/m^3$; AM increased in lungs in response to rate of DP mass entering lung rather than toral DP burden in lung; increased PMNs were proportional to inhaled concentrations and/or duration of exposure; PMNs affiliated with clusters of aggregated AM rather than DP	Strom (1984) Vostal et al. (1982)
Rat F-344/Crl, M, F Mouse, CD, M,F	7 h/day 5 days/week 104 weeks (rat), 78 weeks (mouse)	350 3,500 7,000 0.25 μm, MMD	1,274,000[c] 12,740,000[c] 25,480,000[c]	2.9 16.5 29.7	0.05 0.34 0.68	— — —	Significant increases of AM in rats and mice exposed to 7,000 $\mu g/m^3$ DP for 24 and 18 mo, respectively, but not at concentrations of 3,500 or 350 $\mu g/m^3$ DP for the same exposure durations; PMNs increased in a dose-dependent fashion in both rats and mice exposed to 3,500 or 7,000 $\mu g/m^3$ DP and were greater in mice than rats	Henderson et al. (1988)
CLEARANCE								
Rat	7 h/day 5 day/week 12 weeks	200 1,000 4,500 0.25μm, MMD	84,000 420,000 1,890,000	— — —	— — —	— — —	Evidence of apparent speeding of tracheal clearance at the 4,500 $\mu g/m^3$ level after 1 week of ^{99m}Tc macroaggregated-albumin and reduced clearance of tracer aerosol in each of the three exposure levels at 12 weeks; indication of a lower percentage of ciliated cells at the 1,000 and 4,500 $\mu g/m^3$ levels	Wolff and Gray (1980)

TABLE 11-16 (cont'd). EFFECTS OF EXPOSURE TO DIESEL EXHAUST ON THE PULMONARY DEFENSE MECHANISMS OF LABORATORY ANIMALS

Species	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	Reference
Rat, F-344 M, F	7 h/day 5 days/week 18 weeks <0.5 μm, MMD	150 940 4,100	94,500 592,000 2,583,000	— — —	— — —	— — —	Lung burdens of DP were concentration-related; clearance half-time of DP almost double in 4,100 $\mu g/m^3$ group compared to 150 $\mu g/m^3$ group.	Griffis et al. (1983)
Rat, F-344, M	7 h/day 5 days/week 26-104 weeks	2,000 0.23-0.36 μm MMD	1,820,000- 7,280,000	11.5	1.5	0.8	No difference in clearance of $^{59}Fe_3O_4$ particles 1 day after tracer aerosol administration; 120 days after exposure tracer aerosol clearance was enhanced; Lung burden of DP increased significantly between 12 to 24 months of exposure	Lewis et al. (1989)
Rat, Sprague-Dawley	4-6 h/day 7 days/week 0.1 to 14.3 weeks	900 8,000 17,000	2,500- 10,210,000	— — —	5.0 2.7 8.0	0.2 0.6 1.0	Impairment of tracheal mucociliary clearance in a concentration-response manner	Battigelli et al. (1966)
Rat, F-344, M, F	7 h/day 5 days/week 130 weeks	350 3,500 7,000 0.25 μm, MMD	1,593,000 15,925,000 31,850,000	2.9 16.5 29.7	0.1 0.3 0.7	— — —	No changes in tracheal mucociliary clearance after 6, 12, 18, 24, or 30 mo of exposure; increases in lung clearance half-times as early as 6 mo at 7,000 $\mu g/m^3$ level and 18 mo at 3,500 $\mu g/m^3$ level; no changes seen at 350 $\mu g/m^3$ level; after 24 mo of diesel exposure, long-term clearance half-times were increased in the 3,500 and 7,000 $\mu g/m^3$ groups	Wolff et al. (1987)
MICROBIAL-INDUCED MORTALITY								
Mice, CD-1, F	—	—	—	—	—	—	No change in mortality in mice exposed intratracheally to 100 μg of DP prior to exposure to aerosolized *Streptococcus* sp.0	Hatch et al. (1985)

TABLE 11-16 (cont'd). EFFECTS OF EXPOSURE TO DIESEL EXHAUST ON THE PULMONARY DEFENSE MECHANISMS OF LABORATORY ANIMALS

Species	Exposure Period	Particles ($\mu g/m^3$)	C × T ($\mu g \cdot h/m^3$)	CO (ppm)	NO_2 (ppm)	SO_2 (ppm)	Effects	Reference
Mice CD-1, F	7 h/day 5 days/week 4, 12, or 26 weeks	2,000 0.23–0.36 μm MMD	280,000- 1,820,000	11.5	1.5	0.8	Mortality similar at each exposure duration when challenged with Ao/PR/8/34 influenza virus; in mice exposed for 3 and 6 mo, but not 1 mo, there were increases in the percentages of mice having lung consolidation, higher virus growth, depressed interferon levels and a four-fold reduction in hemagglutin antibody levels	Hahon et al. (1985)
Mice, CR/CD-1, F	8 h/day 7 days/week 2 h up to 46 weeks	5,300 to 7,900	11,000- 20,350,000	19 to 22	1.8 to 3.6	0.9 to 2.8	Enhanced susceptibility to lethal effects of *S. pyogenes* infections at all exposure durations (2 and 6 h; 8, 15, 16, 307, and 321 days); inconclusive results with *S. typhimurium* because of high mortality rates in controls; no enhanced mortality when challenged with A/PR8-3 influenza virus	Campbell et al. (1980, 1981)

[a]Chronic exposure lasted 52 weeks.
[b]Chronic exposure lasted 48 weeks.
[c]Calculated for 104-week exposure.
DP = Diesel exhaust particles.
AM = Alveolar macrophage.
PMN = Polymorphonuclear leukocyte.

Source: Quoted from U.S. Environmental Protection Agency (1994).

11.4.4.2 Mutagenicity

Since 1978, over 100 publications have appeared in which genotoxicity assays have been employed with diesel emissions, the volatile and particulate fractions (including extracts), or individual chemicals found in diesel emissions. These studies are reviewed in the Health Assessment Document for Diesel Emissions (U.S. Environmental Protection Agency, 1994). The subject has been reviewed in the recent International Agency for Research on Cancer (IARC) monograph (International Agency for Research on Cancer, 1989) which contains an exhaustive description of the available studies and other review articles (Claxton, 1983; Pepelko and Peraino, 1983) and the proceedings of several symposia on the health effects of diesel emissions (U.S. Environmental Protection Agency, 1980; Lewtas, 1982; Ishinishi et al., 1986; International Agency for Research on Cancer, 1989).

Extensive studies with *Salmonella* have unequivocally demonstrated direct-acting mutagenic activity in both particulate and gaseous fractions of diesel exhaust. The induction of gene mutations has been reported in several in vitro mammalian cell lines after exposure to extracts of diesel particles. Dilutions of whole diesel exhaust did not induce sex-linked recessive lethals in *Drosophila* or specific-locus mutations in male mouse germ cells.

Structural chromosome aberrations and sister chromatid exchanges (SCE) in mammalian cells have been induced by particles. Whole exhaust induced micronuclei, but not SCE or structural aberrations, in bone marrow of male Chinese hamsters exposed to whole diesel emissions for 6 mo. In 7-week exposures, neither micronuclei nor structural aberrations were increased in bone marrow of female Swiss mice. Likewise, whole diesel exhaust did not induce dominant lethals or heritable translocations in male mice exposed for 7.5 and 4.5 weeks, respectively.

11.4.4.3 Diesel Carcinogenicity Studies

Epidemiologic Studies of Diesel Exhaust Carcinogenicity

It is difficult to study the health effects of diesel exhaust in the general population because diesel emissions are diluted in the ambient air; hence, exposure is very low. Thus, populations occupationally exposed to diesel exhaust are studied to determine the potential health effects in humans. The occupations involving potential exposure to diesel exhaust are

miners, truck drivers, transportation workers, railroad workers, and heavy-equipment operators.

All the occupational studies considered in this section have a similar problem—an inability to measure accurately the actual exposure to diesel exhaust. Most studies compared persons in job categories that would presumably have some exposure to diesel exhaust with either standard populations (that have presumably no exposure to diesel exhaust) or with men working in other job categories in industries with little or no potential for diesel exhaust exposure. The study of the U.S. railroad workers was the only one in which the job categories were verified based on an industrial hygiene survey. A few studies included measurements of diesel fumes, but there was no standard method for the measurement. Neither was any attempt made to correlate these exposures with the cancers observed in any of these studies, nor was it clear exactly which extract should be measured to assess the occupational exposure to diesel exhaust.

An excess risk of lung cancer was observed in four out of seven cohort studies and seven out of eight case-control studies. Of these studies, three cohort (Howe et al., 1983; Wong et al., 1985; Boffetta and Stellman, 1988) and three case-control studies (Garshick et al., 1988; Hayes et al., 1989; Steenland et al., 1990) observed an exposure-response relationship by using duration of employment as a surrogate for exposure. However, because of the lack of actual data on exposure to diesel exhaust in these studies and other methodologic limitations, such as lack of latency analysis, etc., the evidence of carcinogenicity in humans falls short of being sufficient, and hence, is considered to be limited. An additional five cohort studies (Gustavsson et al., 1990; Gubéran et al., 1992; Emmelin et al., 1993; Swanson et al., 1993; Hansen, 1993) and three case-control studies (Boffetta et al., 1990; Cordier et al., 1993; Notani et al., 1993) have been published after the initial EPA analysis and are reviewed in the Addendum to Chapter 8 of the Health Assessment Document for Diesel Exhaust (U.S. Environmental Protection Agency, 1994). The reviews of these studies indicate that the designation of "limited" evidence of carcinogenicity in humans will not change.

Animal Carcinogenicity Studies

Based on positive inhalation exposure data in rats and mice, intratracheal instillation in rats, and injection or skin painting in mice and supported by positive mutagenicity studies, the animal evidence for carcinogenicity of diesel exhaust is considered to be adequate (U.S. Environmental Protection Agency, 1994). The contribution of the various fractions of diesel exhaust to the carcinogenic response is less certain. The effects of the gaseous phase are equivocal. The presence of known carcinogens adsorbed to diesel particles and the demonstrated tumorigenicity of particle extracts in a variety of injection, instillation- and skin-painting studies provides evidence for the involvement of the organic fraction. Studies showing that pure carbon particles can also induce tumors, on the other hand, indicate that the carbon core of the diesel particle is also involved in the carcinogenic process.

The potential for diesel exhaust to induce tumors in laboratory animals has been extensively investigated. Inhalation studies are presented in Table 11-17. Studies employing rats exposed for two years or more to high PM concentrations (up to 8,000 $\mu g/m^3$), resulting in large particle loads in the lungs, were generally positive in demonstrating diesel exhaust-induced increases in lung tumors. Inhalation of diesel exhaust was negative in mice, except for studies involving exposure of two strains from birth. Attempts to induce significant increases in lung tumor incidence in Syrian golden hamsters, cats, or monkeys were unsuccessful. The negative results in cats and monkeys may be explained by an inadequate exposure duration (2 years) in these longer-lived species, whereas hamsters are generally less sensitive to lung tumor induction by inhalation than are rats or mice.

Although inhalation of sufficient doses of diesel exhaust will induce lung cancer in rats and in at least some strains of mice, the relationship between exposure levels and response is less clearcut. Significant increases in lung tumors were not reported at concentrations less than about 2,000 $\mu g/m^3$ PM; the response at higher concentrations varies considerably. A significant percentage of this variation can probably be attributed to the exposure regime. A better method than concentration alone for assessing exposure-response relationships could be achieved by comparing cumulative exposure (concentration $\times$ daily exposure duration $\times$ days of exposure). Only those studies conducted for a sufficient length of time ($\geq$24 mo) for expression of carcinogenic responses have been included in this analysis. Examination of

TABLE 11-17. SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]				Comments
								Adenomas	Adenocarcinoma + Squamous Cell Carcinomas	Squamous Cysts	All Tumors	
Mauderly et al. (1987)	Rat/F344	M + F, 230[b]	Clean air	0	None	7 h/day,	NA	(0)	(0.9)	(0)	(0.9)	
		M + F, 223	Whole exhaust	350	None	5 days/week		(0)	(1.3)	(0)	(1.3)	
		M + F, 221	Whole exhaust	3,500	None	up to		(2.3)	(0.5)	(0.9)	(3.6)[c]	
		M + F, 227	Whole exhaust	7,100	None	30 mo		(0.4)	(7.5)	(4.9)	(12.8)[c]	
								Adenomas	Carcinomas	Squamous Cell Tumors	All Tumors	
Heinrich et al. (1986a,b)	Rat/ Wistar	F, 96	Clean air	0	None	19 h/day,	NA	0/96 (0)	0/96 (0)	0/96 (0)	0/96 (0)	
		F, 92	Filtered exhaust	0	None	5 days/week		0/92 (0)	0/92 (0)	0/92 (0)	0/92 (0)	
Mohr et al. (1986)		F, 95	Whole exhaust	4,000	None	for up to 35 mo		8/95 (8.4)	0/95 (0)	9/95 (9.4)	17/95 (17.8)[c]	
								Adenomas	Adenocarcinoma	Squamous Cell Tumors	All Tumors	
Heinrich et al. (1986a,b)	Mouse/ NMRI	M + F, 84	Clean air	0	None	19 h/day,	NA	9/84 (11)	2/84 (2)	—	11/84 (13)	
		M + F, 93	Filtered exhaust	0	None	5 days/week		11/93 (12)	18/93 (19)[c]	—	29/93 (31)[c]	
		M + F, 76	Whole exhaust	4,000	None	for up to 30 mo		11/76 (15)	13/76 (17)[c]	—	24/76 (32)[c]	
	Hamsters/ Syrian	M + F, 96	Clean air	0	None	19 h/day,	NA	0/96 (0)	0/96 (0)	0/96	0/96 (0)	
		M + F, 96	Filtered exhaust	0	None	5 days/week		0/96 (0)	0/96 (0)	0/96	0/96 (0)	
		M + F, 96	Whole exhaust	4,000	None	for up to 30 mo		0/96 (0)	0/96 (0)	0/96	0/96 (0)	
										Squamous Cell Carcinoma	All Lung Tumors	
Henrich et al. (1989a)	Rat/ Wistar	F, NS	Clean air	0	DpN[d]	19 h/day,	NA			(4.4)	(84.8)	
		F, NS	Whole exhaust	4,200	DpN[d]	5 days/week				(46.8)[c]	(83.0)	
		F, NS	Filtered exhaust	0	DpN[d]	for 24 to				(4.4)	(67.4)	
		F, NS	Clean air	0	DpN[e]	30 mo				(16.7)	(93.8)	
		F, NS	Whole exhaust	4,200	DpN[e]					(31.3)[c]	(89.6)	
		F, NS	Filtered exhaust	0	DpN[e]					(14.6)	(89.6)	

TABLE 11-17 (cont'd). SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]				Comments
								Adenomas	Adenosquamous Carcinomas	Squamous Cell Carcinomas	All Tumors	
Takaki et al. (1988) Light-duty engine	Rat/F344	M + F, 123	Clean air	0	None	16 h/day,	NA	1/23 (0.8)	2/123 (1.6)	1/23 (0.8)	4/123 (3.3)	
		M + F, 123	Whole exhaust	100	None	6 days/week,		1/23 (0.8)	1/23 (0.8)	1/23 (0.8)	3/123 (2.4)	
		M + F, 125	Whole exhaust	400	None	for up to		1/25 (0.8)	0/125 (0)	0/125 (0)	1/125 (0.8)	
		M + F, 123	Whole exhaust	1,100	None	30 mo		0/23 (0)	5/123 (4.1)	0/123 (0)	5/123 (4.1)	
		M + F, 124	Whole exhaust	2,300	None			1/24 (8.1)	2/124 (1.6)	0/124 (0)	3/124 (2.4)	
								Adenomas	Adenosquamous Carcinomas	Squamous Cell Carcinomas	All Tumors	
Ishinishi et al. (1988b) Heavy-duty engine	Rat/F344	M + F, 123	Clean air	0	None	16 h/day,	NA	0/123 (0)	1/123 (0.8)	0/123 (0)	1/123 (0.8)	
		M + F, 123	Whole exhaust	500	None	6 days/week,		0/123 (0)	0/123 (0)	1/123 (0.8)	1/123 (0.8)	
		M + F, 125	Whole exhaust	1,000	None	for up to		0/125 (0)	0/125 (0)	0/125 (0)	0/125 (0)	
		M + F, 123	Whole exhaust	1,800	None	30 mo		0/123 (0)	4/123 (3.3)	0/123 (0)	4/123 (3.3)	
		M + F, 124	Whole exhaust	3,700	None			0/124 (0)	6/124 (4.8)	2/124 (1.6)	8/124 (6.5)[c]	
				0								
				0								
				4,900				Adenomas	Adenocarcinoma and Adeno-Squamous Carcinoma	Large Cell and Squamous Cell Carcinomas	All Tumors	
Iwai et al. (1986)	Rat/F344	F, 24	Clean air	0	None	8 h/day,	NA	1/22 (4.5)	0/22 (0)	0/22 (0)	1/22 (4.5)[f]	
		F, 24	Filtered exhaust	0	None	7 days/week,		0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	
		F, 24	Whole exhaust	4,900	None	for 24 mo		3/19 (0)	3/19 (15.8)	2/19 (10.5)	8/19 (42.1)[c,g]	
									Adenoma	Carcinoma		
Takemoto et al. (1986)	Rat/F344	F, 12	Clean air	0	None	4 h/day,	NA		0/12 (0)	0/12 (0)		
		F, 21	Clean air	0	DIPN[h]	4 days/week,			10/21 (47.6)	4/21 (19)		
		F, 15	Whole exhaust	2,000-4,000	None	18-24 mo			0/15 (0)	0/15 (0)		
		F, 18	Whole exhaust	2,000-4,000	DIPN[h]				12/18 (66.7)	7/18 (38.9)		

TABLE 11-17 (cont'd). SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]		Comments
								Adenoma	Adeno-Carcinoma	
Takemoto et al. (1986) (cont'd)	Mouse/ IRC	M + F, 45	Clean air	0	None	4 h/day, 4 days/week, for 19-28 mo	NA	3/45 (6.7)	1/45 (2.2)	
		M + F, 69	Whole exhaust	2,000-4,000	None			6/69 (8.7)	3/69 (4.3)	
	Mouse/ C57BL	M + F, 12	Clean air	0	None	4 h/day, 4 days/week for 19-28 mo	NA	1/12 (8.3)	0/12 (0)	
		M + F, 38	Whole exhaust	2,000-4,000	None			8/38 (21.1)	3/38 (7.9)	
								Primary Lung Tumors		
Brightwell et al. (1989)	Rat/344	M + F, 260	Clean air	0	None	16 h/day, 5 days/week, for 24 mo	NA	3/260 (1.2)		Tumor incidence for all interim sacrifice periods
		M + F, 144	Filtered exhaust (medium exposure)	0	None			0/144 (0)		
		M + F, 143	Filtered exhaust (high exposure)	0	None			0/143 (0)		
		M + F, 143	Whole exhaust	700	None			1/143 (0.7)		At highest conc., ♀ 24/25 (96%) at 24-mo sacrifice ♂ 12/27 (44%) at 24-mo sacrifice
		M + F, 144	Whole exhaust	2,200	None			14/144 (9.7)[c]		
		M + F, 143		6,600	None			55/143 (38.5)[c]		
								Primary Lung Tumors		
	Hamster/ Syrian Golden	M + F,	Clean air	0	None	16 hours/day, 5 days/week, for 24 mo	NA	7/202 (3.5)		Respiratory tract tumors not related to exhaust exposure for any of the groups
		M + F, 202	Clean air	0	DEN[j]			4/104 (3.8)		
		M + F, 104	Filtered exhaust (medium dose)	0	DEN[j]			9/104 (8.7)		
		M + F, 104	Filtered exhaust (high dose)	0	DEN[j]			2/101 (2.0)		
		M + F, 101	Whole exhaust	700	DEN[j]			6/102 (5.9)		
		M + F, 102	Whole exhaust	2,200	DEN[j]			4/101 (3.9)		
		M + F, 101	Whole exhaust	6,600	DEN[j]			1/204 (0.5)		
		M + F, 204	Filtered exhaust (high dose)	0	None			0/203 (0)		
		M + F, 203	Whole exhaust	6,600	None					

TABLE 11-17 (cont'd). SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]	Comments
								Adenomas	
Karagianes et al. (1981)	Rat/Wistar	M, 40	Clean air	0	None	6 h/day, 5 days/week, for up to 20 mo	NA	0/6 (0)	
		M, 40	Whole exhaust	8,300	None			1/6 (16.6)	
								Lung Tumors	
Orthoefer et al. (1981) (Pepelko and Peirano, 1983)	Mouse/ Strong A	M, 25	Clean air	0	None	20 h/day, 7 days/week, for 7 weeks		3/22 (13.6)	0.13 Tumors/ mouse
			Whole exhaust	6,400	None		26 weeks	7/19 (36.8)	0.63 Tumors/ mouse
			Whole exhaust	6,400	UV irradiated		26 weeks	6/22 (27.3)	0.27 Tumors/ mouse
								Lung Tumors	
	Mouse/ Jackson A	M + F, 40	Clean air	0	None	20 h/day, 7 days/week, for 8 weeks	8 weeks	16/36 (44.4)	0.5 Tumors/ mouse
		M + F, 40	Whole exhaust	6,400	None		8 weeks	11/34 (32.3)	0.4 Tumors/ mouse
	Mouse/ Jackson A	F, 60	Clean air	0	None	20 h/day, 7 days/week, for approx. 7 mo.		4/58 (6.9)	0.09 Tumors/ mouse
		F, 60	Clean air	0	Urethan[l]			9/52 (17.3)	0.25 Tumors/ mouse
		F, 60	Whole exhaust	6,400	None			14/56 (25.0)	0.32 Tumors/ mouse
		F, 60	Whole exhaust	6,400	Urethan[k]			22/59 (37.3)	0.39 Tumors/ mouse
		M, 429	Clean air	0	None			73/403 (18.0)	0.23 Tumors/ mouse
		M, 430	Whole exhaust	6,400	None			66/368 (17.9)	0.20 Tumors/ mouse

TABLE 11-17 (cont'd). SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]			Comments
								Adenomas	Carcinomas	All Tumors	
Pepelko and Peirano (1983)	Mouse/ Sencar	M + F, 260	Clean air	0	None	Continuous	NA	(5.1)	(0.5)	(5.6)	
			Clean air	0	BHT[l]	for 15 mo		(12.2)	(1.7)	(2.8)	
			Clean air	0	Urethan[k]			(8.1)	(0.9)	(9.0)	
			Whole exhaust	12,000	None			(10.2)[c]	(1.0)	(11.2)[c]	
			Whole exhaust	12,000	BHT[l]			(5.4)	(2.7)	(8.1)	
			Whole exhaust	12,000	Urethan[l]			(8.7)	(2.6)	(11.2)	
									All Tumors		
	Mouse/ Strain A	M + F, 90	Clean air	0	None		NA		21/87 (24)		0.29 Tumors/ mouse
			Clean air	0	Exposure (darkness)				59/237 (24.9)		0.27 Tumors/ mouse
			Whole exhaust	12,000	Exposure				10/80 12.5)		0.14
			Whole exhaust	12,000	(darkness)				22/250 (0.10)		0.10
			Clean air	0	Urethan[m]				66/75 (88)		2.80
			Whole exhaust	12,000	Urethan[m]				42/75 (0.95)		0.95
									Broncho-alveolar Carcinoma		
Kaplan et al. (1983) White et al. (1983)	Rat/F344	M, 30	Clean air	0	None	20 h/day,	8 mo		0/30 (0)		
		M, 30	Whole exhaust	250	None	7 days/week,	8 mo		1/30 (3.3)		
		M, 30	Whole exhaust	750	None	for up to	8 mo		3/30 (10.0)		
		M, 30	Whole exhaust	1,500	None	15 mo	8 mo		1/30 (3.3)		
									Pulmonary Adenoma		
	Mouse/ A/J	M, 388	Clean air	0	None	20 h/day,	NA		130/388 (33.5)		
		M, 388	Whole exhaust	250	None	7 days/week,			131/388 (33.8)		
		M, 399	Whole exhaust	750	None	for up to			109/399 (27.3)		
		M, 396	Whole exhaust	1,500	None	8 mo			99/396 (25.0)		
									Pulmonary Adenomas		
Kaplan et al. (1982)	Mouse/ A/J	M, 458	Clean air	0	None	20 h/day,	6 mo		144/458 (31.4)		
		M, 18	Clean air	0	Urethan[k]	7 days/week,			18/18 (100)		
		M, 485	Whole exhaust	1,500	None	for 3 mo			165/485 (34.2)		

TABLE 11-17 (cont'd). SUMMARY OF ANIMAL CARCINOGENICITY STUDIES

Study	Species/ Strain	Sex/ Total Number	Exposure Atmosphere	Particle Concentration ($\mu g/m^3$)	Other Treatment	Exposure Protocol	Postexposure Observation	Tumor Type and Incidence (%)[a]			Comments
								Adenomas	Carcinomas	All Tumors	
Ishinishi et al. (1988b)	Rat/F344	NS, 5	Whole exhaust	100	None	16 h/day, 6 days/week, for 12 mo	6 mo	0/5 (0)	0/5 (0)	0/5 (0)	
		NS, 8	Whole exhaust	100	None		12 mo	0/8 (0)	0/8 (0)	0/8 (0)	
		NS, 11	Whole exhaust	100	None		18 mo	0/11 (0)	0/11 (0)	0/11 (0)	
Light duty		NS, 5	Whole exhaust	1,100	None		6 mo	0/5 (0)	0/5 (0)	0/5 (0)	
		NS, 9	Whole exhaust	1,100	None		12 mo	0/9 (0)	0/9 (0)	0/9 (0)	
		NS, 11	Whole exhaust	1,100	None		18 mo	0/11 (0)	0/11 (0)	0/11 (0)	
Heavy duty		NS, 5	Whole exhaust	500	None	16 h/day, 6 days/week, for 12 mo	6 mo	0/5 (0)	0/5 (0)	0/5 (0)	
		NS, 9	Whole exhaust	500	None		12 mo	0/9 (0)	0/9 (0)	0/9 (0)	
		NS 11	Whole exhaust	500	None		18 mo	0/11 (0)	0/11 (0)	0/11 (0)	
		NS, 5	Whole exhaust	1,800	None		6 mo	0/5 (0)	0/5 (0)	0/11 (0)	
		NS, 6	Whole exhaust	1,800	None		12 mo	0/6 (0)	0/6 (0)	0/6 (0)	
		NS, 13	Whole exhaust	1,800	None		18 mo	0/13 (0)	1/13 (7)	1/13 (7)	
Lewis et al. (1986)	Rat/F344	M + F, 288[n]	Clean air	0	None	7 h/day, 5 days/week, 24 mo[o]	NA	No tumors		0/192 (0)	
			Whole exhaust	2,000	None					0/192 (0)	

[a]Table values indicate number exposed/number with tumors (% animals with tumors).
[b]Number of animals examined for tumors.
[c]Significantly different from clean air controls.
[d]Diphenylnitrosamine; 6.25 mg/kg/week sc during first 25 weeks of exposure.
[e]Diphenylnitrasamine; 12.5 mg/kg/week sc during first 25 weeks of exposure.
[f]Splenic lymphomas also detected in controls (8.3%), filtered exhaust group (37.5%) and whole exhaust group (25%).
[g]5.3% incidence of large cell carcinomas.
[h]1 g/kg, ip 1/week for 3 weeks starting 1 mo into exposure.
[i]Includes adenomas, squamous cell carcinomas, adenocarcinomas, adeno squamous cell carcinoma, and mesotheliomas.
[j]4.5 mg/DEN/kg, sc, 3 days prior to start of inhalation exposure.
[k]Single ip dose 1 mg/kg at start of exposure.
[l]Butylated hydroxytoluene 300 mg/kg, ip for Week 1, 83 mg/kg for Week 2, and 150 mg/kg for Weeks 3 to 52.
[m]12 mg/m^3 from 12 weeks of age to termination of exposure. Prior exposure (in utero) and of parents was 6 mg/m^3.
[n]120-121 males and 71-72 females examined histologically.
[o]Not all animals were exposed for full term, at least 10 males were killed at 3-, 6-, and 12-mo exposure.

NS = Not specified.
NA = Not applicable.

Source: Quoted from U.S. Environmental Protection Agency (1994).

the rat data, shown and plotted in Figure 11-5 reveals that most studies indicate a trend of increasing tumor incidence at exposures exceeding 1×10^7 $\mu g \cdot h/m^3$.

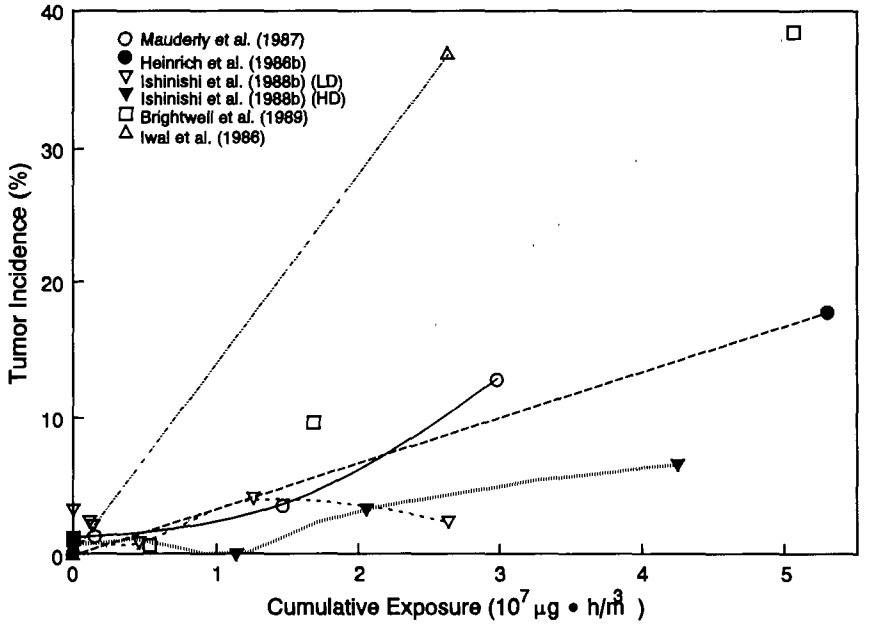

Figure 11-5. Cumulative exposure data for rats exposed to whole diesel exhaust.

Particle Effect in Diesel Exhaust-Induced Carcinogenicity

The relative contribution of the carbon core of the diesel particles versus organics adsorbed to the surface of the particles to cancer induction is still somewhat uncertain. The primary evidence for the importance of the adsorbed organics is the presence of known carcinogens among these chemicals. These include polycyclic aromatics as well as nitroaromatics. Organic extracts of particles have also been shown to induce tumors in a variety of injection, intratracheal instillation and skin painting studies, and Grimmer et al. (1987) has, in fact, shown that the great majority of the carcinogenic potential following intratracheal instillation resided in the fraction containing four- to seven-ring PAHs.

Evidence for the importance of the carbon core is provided by studies of Kawabata et al. (1986), that showed induction of lung tumors following intratracheal instillation of CB that contained no more than traces of organics and studies of Heinrich (1990) that

indicated that exposure via inhalation to CB (Printex 90) particles induced lung tumors at concentrations similar to those effective in diesel studies. Other particles of low solubility such as titanium dioxide (Lee et al., 1986) have also been shown to induce lung tumors, although at much higher concentrations than necessary for carbon particles or diesel exhaust. Pyrolyzed pitch, on the other hand, essentially lacking a carbon core but having PAH concentrations at least three orders of magnitude greater than diesel exhaust, was no more effective in tumor induction than was diesel exhaust (Heinrich et al., 1986b). These studies suggest that the insoluble carbon core of the particle is at least as important as the organic components and possibly more so for lung tumor induction at high particle concentrations ($>2{,}000\ \mu g/m^3$).

Diesel PM is composed of an insoluble carbon core with a surface coating of relatively soluble organic constituents. Studies of diesel particle composition have shown that the insoluble carbon core makes up about 80% of the particle mass and that the organic phase can be resolved into a more slowly dissolving component and a more quickly dissolving component. Since macrophage accumulation, epithelial histopathology, and reduced clearance have been observed in rodents exposed to high concentrations of chemically inert particles (Morrow, 1992), it appears possible that the toxicity of diesel particles results from the carbon core rather than the associated organics. However, the organic component of diesel particles consists of a large number of polycyclic aromatic hydrocarbons and heterocyclic compounds and their derivatives. A large number of specific compounds have been identified. These components of diesel particles may also be responsible for the pulmonary toxicity of diesel particles. It is not possible to separate the carbon core from the adsorbed organics in order to compare the toxicity. As an approach to this question, a study has been performed in which rats were exposed to either diesel exhaust or to carbon black, an inert analog of the carbon core of diesel particles. Rats were exposed for 16 h/day, 5 days/week, for up to 24 mo to either 2,500 or 6,500 $\mu g/m^3$ of the particle (duration adjusted concentrations = 1,200 and 3,100 $\mu g/m^3$) (Nikula et al., 1991). Although the study is primarily concerned with the role of particle associated organics in the carcinogenicity of diesel exhaust, non-neoplastic effects are also mentioned. According to the preliminary report, both diesel exhaust and carbon black exposure resulted in macrophage hyperplasia, epithelial hyperplasia, bronchiolar-alveolar metaplasia, and focal fibrosis. Although the

analyses have not yet been completed, the preliminary report states that the number and intensity of the lesions seems to correspond to the exposure time and concentration and that the morphological characteristics of the lesions were similar in the animals exposed to diesel and to carbon black. The preliminary results suggest that the chronic noncancer effects of diesel exhaust exposure are caused by the persistence of the insoluble carbon core of the particles, rather than by the extractable organic layer. On this basis, the variety for non-cancer effects is based on the calculation of the human equivalent dose with the retained mass of the carbon core per unit of pulmonary surface area as the expression of dose which is considered equivalent across species.

Metabolism and Mechanism of Action of Carcinogenic Compounds of Diesel Exhaust

The role of the carbonaceous core (soot particle) and a particle overload effect in the pulmonary carcinogenesis of diesel exhaust is also of concern. Several studies (Vostal, 1986; Kawabata, 1986; Heinrich, 1990; Wolff et al., 1990; Oberdörster and Yu, 1990) have provided data indicating that the carbonaceous core may have a promotional effect related to the ability of the particle to induce chronic inflammation and promote epithelial cell proliferation. More recent work (Mauderly et al., 1994; Nikula et al., 1994) has shown that carbon black was also carcinogenic in rats exposed to particle concentrations of 2,500 or 6,500 $\mu g/m^3$ for 24 mo. The carbon black particles were similar to the soot particles of diesel exhaust but contain markedly lower amounts of adsorbed organic compounds.

A study by Wolff et al. (1990) addressed this topic by comparing the inflammatory responses in rats exposed to diesel exhaust (10,000 $\mu g/m^3$) or CB particles (10,000 $\mu g/m^3$). Although the level of lung DNA adducts was slightly higher for diesel exhaust exposure, both exposures resulted in inflammatory responses, as determined by increased numbers of neutrophils and macrophages and increased acid proteinase in the BAL fluid.

Oberdörster and Yu (1990) evaluated the significance of a particle effect in the tumorigenic response of the lung to diesel exhaust exposure. Using data from studies examining the effects of long-term inhalation exposure to diesel exhaust, TiO_2 particles, CB, or toner particles, it was reported that only the surface area of retained particles in the lung showed a reasonable concentration-response relationship relative to tumor incidence and that particle overload (retained mass or volume of particles) alone may not be the determining

factor in lung tumor formation. In this respect, it was shown that particles lacking adsorbed organics (pure CB or TiO_2 particles) and diesel exhaust particles exhibited a similar relationship between particle surface area and tumor incidence. The investigators hypothesized a tumorigenic effect would probably require that a "critical" surface area of retained particles be attained for the manifestation of any mechanisms of tumorigenicity.

The possibility of a particle effect in the tumorigenic response has also been demonstrated by Heinrich (1990) in which female Wistar rats (72 per group) were exposed to Printex 90 CB particles for 10 mo followed by a 20-mo exposure-free observation period or for 20 mo followed by a 10-mo exposure-free observation period. A particle concentration of 6,090 $\mu g/m^3$ was used in both protocols. The Printex 90 particles had an extremely low organic content ($\approx$1,000-fold less than that of diesel exhaust particles). The tumor rates for the 10- and 20-mo exposure durations were 17% (14% malignant) and 8% (all malignant), respectively. Although the lower tumor incidence for the longer exposure period was not consistent, the results demonstrate that the tumor incidences for CB particles with an organic content 1,000-fold less than diesel exhaust particles are equivalent to those reported for diesel exhaust exposures. The fact that these particles were able to exert a significant tumorigenic response implicates the carbon core of diesel exhaust particles as possible tumor initiators in diesel exhaust-induced carcinogenicity at high particle concentrations.

The potential importance of the particle in the pulmonary carcinogenicity of inhaled diesel exhaust in rats was reported by Mauderly et al. (1994). In this long-term exposure study, rats were exposed 16 h/day, 5 days/week for 24 mo to whole diesel exhaust or CB (free of adsorbed organics) at particle concentrations of 2,500 or 6,500 $\mu g/m^3$. Controls were exposed to clean air. Lung weights were increased in rats exposed to the highest concentrations of both diesel exhaust or CB but were slightly higher for the diesel exhaust group. The lung burdens of particulate matter were significantly greater for the diesel exhaust-exposed rats at 18 and 23 mo. A substantial transfer of particles from the lungs to lung-associated lymph nodes was observed, but no difference was noted between the diesel exhaust and CB exposure groups. Inflammation and cytotoxicity detected in lavage fluid was greater for diesel exhaust-exposed rats, but the difference was proportional to the higher lung burden of retained particles noted for these animals. Preliminary data based on approximately 100 male and 100 female rats indicated that the numbers of lung tumors

observed grossly at necropsy were nearly identical for the diesel exhaust and CB exposure groups. Tumor type observed included squamous cysts, squamous cell carcinomas, papillary adenocarcinomas, tubular adenocarcinomas, and solid carcinomas. The growth of tumors transplanted into athymic mice has also been similar for diesel exhaust and CB exposures, 74 and 73%, respectively. In summary, these preliminary observations suggest that no difference exists in the type or incidence of lung tumors in rats following long-term exposure to diesel exhaust or CB, and that the particle-associated organics may not significantly involved in the pulmonary carcinogenicity of diesel exhaust in rats.

The carcinogenic potential of many PAHs is well-documented, and, therefore, the potential involvement of PAHs in diesel exhaust-induced carcinogenesis must be considered. However, the recent reports by Heinrich (1990), Mauderly et al. (1994), and Nikula et al. (1994) provide data that call into question the importance of PAHs in diesel exhaust-induced carcinogenesis in these types of experiments that use exceptionally high particle concentrations. Bond et al. (1990a) reported that DNA adduct levels were similar in Type 2 cells of rats exposed either to diesel exhaust or carbon black particles. Although speculative at this time, the information in these studies suggest that PAHs may not be instrumental in diesel exhaust-induced carcingenicity. Bond et al. did report DNA adducts in both carbon- and diesel-exposed rats, but adducts were induced at lower concentrations by diesel exhaust. The greater lung burden and toxicity of diesel particles at comparable concentrations indicate that organics do play a role in toxicity and possibly carcinogenicity, although probably not a major role.

Cancer Assessment

The U.S. Environmental Protection Agency (1994) has developed a draft qualitative and quantitative cancer assessment for diesel emissions. The summary to follow was drawn from that document. That draft is currently undergoing external review by the public and the Clean Air Scientific Advisory Committee. On the basis of limited evidence for carcinogenicity of diesel engine emissions in humans, supported by adequate evidence in animals and positive mutagenicity data, diesel engine emissions are considered to best fit the weight-of-evidence Category B1. Agents classified into this category are considered to be

probable human carcinogens. This is in agreement with the 2A classification by the International Agency for Research on Cancer.

Risk estimates can be derived from either human or animal experiments. Each type of study has its own strengths and limitations. Estimates based on human studies reflect direct observation of an association between exposure and human cancer. These human estimates, however, are limited by the difficulty of reconstructing reliable estimates of exposures many years in the past and distinguishing the influence of confounding exposures to other carcinogens. Conversely, estimates based on animal studies benefit from precisely measured exposures and the absence of many potentially confounding factors; but use of animal estimates involves uncertainty in the extrapolation of dose and response rates to humans, as well as extrapolation from experimental to ambient concentrations over about three orders of magnitude.

From human studies, published unit risk estimates range from 6×10^{-4} to $3 \times 10^{-3}/\mu g/m^3$. An upper bound risk estimate of $3 \times 10^{-3}/\mu g/m^3$ was reported for London transport workers. (In view of the nonpositive findings of this study, a lower bound estimate would encompass 0.) Upper bound risk estimates of 6×10^{-4} and $2 \times 10^{-3}/\mu g/m^3$ were calculated for railroad workers, assuming mean occupational exposure concentrations of 500 or 125 $\mu g/m^3$, respectively.

From animal experiments, upper bound unit risk estimates can be calculated using the linearized multistage procedure, a default method used when the mechanism of action is unknown, the information required by a mechanistic model is unavailable, or the suspected mechanism or background conditions are consistent with linearity at low incremental exposures. The linearized multistage procedure was applied to three rat experiments that collectively span a 50-fold range of doses and yielded unit risk estimates ranging from 1.6 to $7.1 \times 10^{-5}/\mu g/m^3$ (the upper 95% bound of the cancer risk from a lifetime exposure). These estimates are based on two assumptions: (1) that carbon particles are primarily responsible for both toxic and carcinogenic effects, and (2) that equivalent sensitivity occurs across species when dose is expressed as mass per unit surface of the alveolar region. Dosimetric adjustments were made from rats to humans and from experimental regimes to continuous lifetime exposure. In addition, an alternative low-dose extrapolation model was developed to

account for possible tumor-initiating effects of the particles. Much of the data needed to estimate the model's parameters, however, are lacking.

In view of the uncertainty inherent in these types of calculations, the human and animal estimates should be viewed as complementary. For a bounding estimate intended to determine whether an exposure level has a potential to pose a hazard to human health, the published human estimates may be practical for exposure levels in the range of observations in these studies. On the other hand, projection of the public health impact of an exposure level may benefit from using estimates derived from animal experiments, because of the closely controlled conditions and their precisely measured exposure levels, absence of many confounding factors, and narrow confidence limits around the tumor incidence rates. A unit risk estimate of $3.4 \times 10^{-5}/\mu g/m^3$ for continuous lifetime exposure, which is the geometric mean of the upper bound estimates calculated from the three rat experiments, is therefore recommended (U.S. Environmental Protection Agency, 1994).

11.5 ULTRAFINE PARTICLES

Particles used in toxicological studies are mainly in the fine and coarse mode size range. This section addresses the hypothesis that ultrafine particles can cause acute lung injury and focuses on experimental studies in which ultrafine particles generated as fumes were used. The ultrafine (nucleation mode) particle phase has a median diameter of $\approx$20 nm (see Figure 3-13). Ultrafine particles with a diameter of 20 nm have an approximately 6 order of magnitude higher number concentration than a 2.5 μm diameter particle, when inhaled at the same mass concentration and particle surface area is also highly increased (Table 11-18). Although many classes of ultrafine particles can be found in the atmosphere (e.g., smog, metallurgical dusts and fumes, carbon black, combustion nuclei, oil smokes), few have been studied as particles in this size fraction.

Inhalation studies in rats with aggregated ultrafine particles have shown that these particles still required high concentrations (in the mg/m^3) range and repeated exposures to produce effects in laboratory animals, although they were more active than larger-sized particles of the same composition. These particles included ultrafine TiO_2 aggregates (Ferin et al., 1992; Oberdörster et al., 1992; Heinrich, 1994) as well as aggregated carbon black

TABLE 11-18. NUMBERS AND SURFACE AREAS OF MONODISPERSE PARTICLES OF UNIT DENSITY OF DIFFERENT SIZES AT A MASS CONCENTRATION OF 10 $\mu g/m^3$

Particle Diameter μm	Particle Number per cm^3 air	Particle Surface Area μm^2 per cm^3 air
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24

particles (Heinrich, 1994; Mauderly et al., 1994; Nikula et al., 1994). Effects observed after subchronic or chronic exposure of rats included chronic inflammation, pulmonary fibrosis, and induction of lung tumors. No acute effects were observed, even at the highest exposure concentrations. Although the studies of TiO_2 and carbon black involved particles of submicron size (0.2 to 0.3 μm), they are still considerably larger than 20 nm ultrafine particles. Thus, these results may not fully reflect the toxicity of 20 nm particles.

From these studies, it appeared that particle surface area is an important parameter for expressing exposure-response and dose-response relationships of inhaled highly insoluble particles. This means that aggregated ultrafine particles, because of their highly increased surface area, could be fitted into the overall dose-response curve with other larger-sized particles (Oberdörster et al., 1992, 1994). The finding that ultrafine particles can penetrate into the interstitium more easily than larger-sized particles (Takenaka et al., 1986; Ferin et al., 1992) is also very important. This transport across the epithelium appears to be facilitated if ultrafine particles deaggregate upon deposition and are present as singlet particles.

In contrast, specific types of inhaled singlet ultrafine particles can induce severe acute lung injury at low inhaled mass concentrations relative to aggregated ultrafine particles. These model ultrafine particles were generated by heating of polytetrafluoroethylene (Teflon®; PTFE); the resulting condensation aerosol consisted of singlet ultrafine particles. More than 25 years ago it was recognized that the toxicity of pyrolysis products of PTFE is associated with particulate phase rather than with gas phase constituents (Waritz and Kwon,

1968). However, it was demonstrated more recently that these particles are of ultrafine size (Lee and Seidel, 1991; Seidel et al., 1991). These particles form upon heating of Teflon® to a critical temperature of ≈420 to 450 °C and have a median diameter of ≈26 nm, with a geometric standard deviation of 1.4 (Oberdörster et al., 1995a). The toxicity of PTFE fumes has been recognized for a long time, dating back to the 1950's when exposures of rabbits, guinea pigs, rats, mice, cats, and dogs resulted in acute mortality (Treon et al., 1955). Further studies in experimental animals by several investigators (Scheel et al., 1968; Coleman et al., 1968; Griffith et al., 1973; Lee et al., 1976; Alarie and Anderson, 1981) confirmed that these fumes are highly toxic to birds and mammals. Extensive pulmonary epithelial and interstitial damage and alveolar flooding occurred after only short-durations of exposure. Accidental exposures of humans to fumes generated from polymers also demonstrated the high toxicity of these fumes for humans (Nuttall et al., 1964; Goldstein et al., 1987; Dahlqvist et al., 1992). Associated effects include pulmonary edema, nausea and headaches, together characterized by the term "polymer fume fever" in analogy to the well-known symptoms of metal fume fever (Rose et al., 1992).

The toxicity of polymer fumes was initially associated with toxic gas phase products, such as hydrogen fluoride (HF), carbonyl fluoride, and perfluoroisobutylene (PFIB). However, detailed studies by Waritz and Kwon (1968) as well as more recent studies have shown that the high toxicity is associated with the particulate phase. For example, HF studies showed that concentrations as high as 1300 ppm are needed to cause effects in the respiratory tract of exposed rats; these effects occur only in the upper respiratory tract, not in the lung periphery where the fume particles have been shown to be most effective (Stavert et al., 1991). Concentrations of HF in fumes generated at the critical temperature are only ≈10 ppm, and therefore, cannot be responsible for the observed toxicity of the fumes (Oberdörster et al., 1995a). The more toxic gas phase compounds, carbonyl fluoride and PFIB are generated only at temperatures approaching 500°C when heating PTFE (Coleman et al., 1968; Waritz and Kwon, 1968). Furthermore, rat inhalation studies with PFIB alone showed that lung pathology was detected only when a high concentration of 90,000 $\mu g/m^3$ was exceeded (Lehnert et al., 1993). Further proof that the particles of polymer fumes represent the toxic entity is provided by studies in which the particulate phase was removed

by filters and subsequently the gas phase compounds did not show toxicity in exposed rats (Waritz and Kwon, 1968; Warheit et al., 1990; Lee and Seidel, 1991).

It has also been suggested that highly toxic radicals on the surface of the polymer fume particles may cause the acute effects. However, studies by Seidel et al. (1991) with fumes from different polymers showed similar toxicities to the lung regardless as to whether significant amounts of radicals could be detected on those particles or not. Although this still does not exclude that some reactive toxic compounds may be attached to the particle surface, all of these studies provide convincing evidence that the ultrafine particles are the cause of the PTFE fume-associated, acute lung injury. It has also been shown that aging of the fumes leading to particle aggregation diminishes their toxicity, indicating that the presence of ultrafine particles as singlets is highly important for the toxicity of these particles (Lee and Seidel, 1991; Warheit et al., 1990).

To exclude the possibility that oxygen-derived radicals from the generation process may be responsible for the observed pulmonary toxicity, PTFE particles were generated in a nitrogen atmosphere (Waritz and Kwon, 1968) or in an argon gas atmosphere (Oberdörster et al., 1995b). Results showed that the inhaled PTFE fumes generated in this way showed the same high pulmonary toxicity in rats that was observed with PTFE fumes generated in air. The toxicity consisted of severe hemorrhagic, pulmonary edema and influx of PMNs into the alveolar space within 4 h after a 15-min exposure of healthy rats to an ultrafine particle mass concentration of about 40 to 50 $\mu g/m^3$; this was accompanied by high mortality (Oberdörster et al., 1995b). It was also determined by these investigators that a number concentration of 1×10^5 PTFE particles/cm^3 is equivalent to a mass concentration of ≈ 8 $\mu g/m^3$. Pulmonary lavage data showed that up to 80% of lavageable cells consisted of PMNs. Acute mortality was also observed in up to 50% of rats exposed to these concentrations of 5×10^5 particles/cm^3. Epithelial as well as endothelial cell damage occurred, resulting in both interstitial and alveolar edema. Analysis of the particle disposition in lung tissue using electron energy loss spectroscopy revealed that, shortly after the exposure, ultrafine particles could be found in epithelial cells as well as interstitial and endothelial sites. The authors concluded that freshly-generated ultrafine PTFE particles inhaled as singlets at low mass concentrations can cause severe acute lung injury and that ultrafine particles, in general, penetrate readily through epithelial-endothelial barriers.

Nose-only exposures to as low as $\approx 10\ \mu g/m^3$ (1×10^5 particles/cm^3) of ultrafine PTFE particles for 30 min were found to result in significant inflammatory responses in exposed rats (Oberdörster et al., 1995c).

Additional studies with ultrafine PTFE particles directed at evaluating mechanistic events in the lung by using in situ hybridization techniques on lung tissue showed that the highly inflammatory reaction was characterized by significant increases in message for the pro-inflammatory cytokine TNFa and the low molecular weight protein metallothionein (Johnston et al., 1995). Furthermore, increases in abundance for messages encoding IL-1α, IL-1β, IL-6, TNFα and the antioxidants MnSOD and metallothionein were found in RNA extracted from lung tissues. In addition to the increase in message of these pro-inflammatory cytokines and antioxidants, abundance for message of inducible NOS was also increased, whereas message for VEGF (vascular endothelial growth factor) was decreased in the acute phase (Johnston et al., 1995). The authors suggested that the acute lung damage affecting epithelial and endothelial barrier functions may be due to the activities of reactive oxygen and reactive nitrogen species originating from highly activated inflammatory cells and produced via inducible NOS.

In summary, certain freshly-generated ultrafine particles, when inhaled as singlets at very low mass concentrations (10 to 50 $\mu g/m^3$), can be highly toxic to the lung. Mechanisms responsible for this high toxicity could include: (1) high pulmonary deposition efficiencies of these particles; (2) the large numbers per unit mass of these particles; (3) their increased surface area available for reaction; and (4) the presence of radicals on the particle surface depending on the process of generation of the particles. Results of studies with ultrafine model particles indicate that particle number may be the more important dose parameter.

11.6 METALS

11.6.1 Introduction

The metals discussed in this section are those commonly found to be present in the ambient atmosphere of U.S. urban areas in concentrations greater than 1 ng/m^3 (see Chapter 6). These sections are intended as general summaries on each metal since the majority, with the exception of lead, do not have current documentation or health risk

standards. Each section briefly discusses physical and chemical properties of the metal and/or important compounds; their pharmokinetics, including deposition, uptake, distribution, metabolism and elimination; associated data on acute and chronic health effects in humans and animals; and comparative toxicity in humans and laboratory animals.

11.6.2 Aluminum

11.6.2.1 Chemical and Physical Properties

Aluminum metal is a tin-white, malleable, ductile, solid that does not occur naturally in its elemental form. It is the third most abundant element in the earth's crust and is found in a large variety of minerals and ores (Sleppy, 1992). Aluminum belongs to Group IIIA of the periodic system of elements and exhibits a valence of +3 in all compounds, except for a few high-temperature gaseous species for which the valence may be +1 or +2 (Staley and Haupin, 1992). Aluminum is a good reducing agent and reacts with oxygen and moisture in air to form an aluminum oxide film on the exposed surfaces (Budavari, 1989; Brady and Humiston, 1986; Staley and Haupin, 1992). It can form organometallic compounds by direct aluminum-to-carbon bonds or by bonds represented as Al-X-R, where X may be oxygen, nitrogen, or sulfur, and R is a suitable organic radical (Staley and Haupin, 1992).
In aqueous solutions, aluminum is amphoteric (Brady and Humiston, 1986; Sleppy, 1992). Elemental aluminum and aluminum oxide (Al_2O_3) are insoluble in water, whereas some other aluminum compounds are moderately water soluble. For example, aluminum chlorohydrate ($Al_2ClH_5O_5$ or $Al_2(OH)_5Cl \cdot 2H_2O$) dissolves in water to form slightly turbid colloidal solutions; and aluminum trichloride ($AlCl_3 \cdot 6H_2O$) and aluminum fluoride (AlF_3) are moderately soluble in hot water (Budvari, 1989).

11.6.2.2 Pharmacokinetics

Absorption and Distribution

Most aluminum compounds enter the lung as particles of poorly soluble compounds (Ganrot, 1986). Some of these particles are taken up by alveolar macrophages through phagocytosis, then transported through the respiratory system and ultimately swallowed. The remaining aluminum is taken up by macrophages in lung tissue, where it is retained indefinitely.

Following oral exposure in laboratory animals, aluminum is distributed in the blood. Al^{+3} ions are present almost exclusively in the plasma where they competitively bind to the iron-binding sites of transferrin (Ganrot, 1986; Moshtaghie and Skillen, 1986). Considerable binding of Al^{+3} also occurs in the metabolically active areas of bone (Ganrot, 1986). The density of transferrin receptors in different organs influences aluminum distribution. The cells accumulating the most aluminum are large, long-lived postmitotic cells such as neurons (Ganrot, 1986). Within these cells, Al^{+3} accumulates in the lysosomes, cell nucleus, and chromatin. In organs composed of postmitotic cells, this accumulation is expected to increase the concentration of Al^{+3}. However, in other organs, the accumulation of Al^{+3} and the elimination of dead cells that are replaced by cells with a lower Al^{+3} concentration leads to a steady state aluminum concentration.

Several laboratory animal studies indicate that aluminum is absorbed by the lungs following inhalation exposure (Steinhagen et al., 1978; Stone et al., 1979; Thomson et al., 1986). Although these studies indicate that absorption by the lungs has occurred, aluminum levels in other tissues, urine, and plasma were not assessed. Following short or long term inhalation exposure to aluminum chlorohydrate, elevated aluminum levels were found in the lung (rats, Guinea pigs), adrenal glands (rats), and peribronchial lymph nodes (Guinea pigs) (Stone et al., 1979; Steinhagen et al., 1978). Rats and hamsters had elevated aluminum levels in lymph nodes and lymphatic drainage areas following repeated exposure to aluminum dusts (Christie et al., 1963). No appreciable accumulation was found in the brain, heart, spleen, kidneys, or liver of either species.

Aluminum is normally found in human tissue, with a total body burden of aluminum in healthy humans of about 30–50 mg (Alfrey, 1981; Alfrey et al., 1980; Cournot-Witmer et al., 1981; Ganrot, 1986). About 50% of the body burden is in the skeleton and 25% in the lungs (Ganrot, 1986). Most aluminum detected in lungs is probably due to accumulated inhaled insoluble aluminum compounds (Ganrot, 1986).

Metabolism

In the body, aluminum exists in four different forms: as free ions, as low-molecular-weight complexes, as physically bound macromolecular complexes, and as covalently bound macromolecular complexes (Ganrot, 1986). The free ion, Al^{+3}, easily binds to many

substances and structures, so that its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism.

Aluminum also forms low-molecular-weight complexes that are often very stable chelates with organic acids, amino acids, nucleotides, phosphates, and carbohydrates. The complexes, especially the nonpolar ones, are metabolically active. Because aluminum has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, much of it likely exists in the body as physically bound macromolecular complexes with such substances. These macromolecular complexes are expected to be much less metabolically active than the small, low-molecular-weight complexes. Aluminum also forms complexes with structures that are so stable that they are essentially irreversible macromolecular complexes. For example, evidence suggests that the nucleus and chromatin are often aluminum binding sites in cells (Crapper McLachlan, 1989; Dryssen et al., 1987; Ganrot, 1986; Karlik and Eichorn, 1980.)

Excretion

In humans, most inhaled aluminum is excreted through the kidney. Urinary levels in six volunteers rapidly increased to 14 to 414 μg/L from pre-exposure levels (3 μg/L) after a one-day exposure (8-h workshift) to a time-weighted average (TWA) concentration of 2,400 μg Al/m^3 (Sjogren et al., 1985). Urinary Al levels of seven welders occupationally exposed to Al fumes or dust for 6 mo increased three-fold after an 8-h workshift compared to preshift concentrations (Mussi et al., 1984). During longer exposure periods (25 workers exposed for 0.3–21 years to approximately 1,500 μg/m^3 Al), urinary Al levels averaged 82 μg/L, compared to 29 μg/L following a 16 to 37 day exposure-free interval (Sjogren et al., 1988).

There is a relationship between the duration of AL exposure and urinary concentrations in humans (Sjogren et al., 1985, 1988). Welders exposed to 250 μg/m^3 (8-h workshift) for more than 10 years had a urinary Al half-life of at least 6 mo, compared to nine days for individuals exposed for less than a year (Sjogren et al., 1988). The excretion half-life was eight hours following a single AL exposure (Sjogren et al., 1985). However, when measured after an exposure-free period, urinary concentrations were related to the total number of years exposed. Apparently, the longer the exposure in humans, the greater the

retention of AL. No studies were located regarding excretion in laboratory animals following inhalation of AL or its compounds.

11.6.2.3 Health Effects

Human Data

No data were located on effects in humans of acute inhalation exposure to AL. Longer-term studies were limited and consisted of occupational case studies and epidemiology studies in AL smelter and potroom workers. The studies did not specify the concentration or form of AL exposure, except as "aluminum dust," and reported confounding exposure to known carcinogens and respiratory irritants. Based on these data, the respiratory tract is the primary target of AL inhalation. Respiratory effects are usually largely limited to irritation, and are generally transient and not severe. No data were located that indicate exposure to AL causes death or cancer in humans. Human toxicity data are summarized in Table 11-19.

Many AL industry workers are exposed to AL dusts found in potrooms where hot aluminum metal is recovered from AL ore. However, these workers are also simultaneously exposed to other toxicants such as polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, sulfur dioxide, hydrogen fluoride, other respirable dusts, and many also smoke. Common reported symptoms include asthma, cough, and decreased pulmonary function (Abramson et al., 1989; Chan-Yeung et al., 1983; Simonsson et al., 1985). No effect on bronchitis incidence or pulmonary function was reported in a longitudinal study of aluminum die-casting workers, where confounding exposures may be lower (Discalz; et al., 1992), but AL exposure levels were not reported.

Case reports show that some aluminum workers develop lung fibrosis when exposed to AL dusts (De Vuyst et al., 1986; Gaffuri et al., 1985; Musk et al., 1980). However, AL exposures in these studies were not quantified, and the workers also experienced confounding exposure to other dusts and fumes. Workers inhaling AL oxide dust (96% ≤ 1.2 μm diameter) at unspecified levels as a prophylactic treatment for silicosis have not developed respiratory problems (Dix, 1971). Based on this, the McIntyre Research Foundation recommended an AL powder concentration of 30,000 particles of respirable size per cm^3 for 10 minutes daily (duration not stated). Stokinger (1981) converted this to a mass

TABLE 11-19. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ALUMINUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Al/m^3						
N/A	NS	Occup Duration NS	Al dusts	NS	Human (54) M	Clinical, radiographic, pathological, environmental features: One worker with lung fibrosis, pneumonia, encephalopathy, seizures. Al found in lungs but not brain. No x-ray abnormalities in 43 other workers.	McLaughlin et al. (1962)
N/A	NS	Occup 1–30 yr	Al dusts	NS	Human (2103) M	Historical cohort study, CS: Concomitant exposure to PAHs in coal tar pitch and tobacco smoke. Excessive deaths from pancreatic, lung, lymphatic, and brain cancers.	Milham (1979)
N/A	NS	Occup 1–21 yr	Al dusts	NS	Human (5891) M	Historical cohort study, CS: Concomitant exposure to PAHs in coal tar pitch and tobacco smoke. Inc lung cancer.	Gibbs and Horowitz (1974)
N/A	NS	Occup 26 yr	Al dusts	NS	Human (6455) M	Mortality survey, CS: Concomitant exposure to PAHs in coal tar pitch and tobacco smoke. Slight inc in mortality due to lung cancer.	Mur et al. (1987)
N/A	NS	Occup 10–24 yr	Alumina dust (Al_2O_3)	NS	Human (4) M	Radiographic examination of lung; histology of transbronchial biopsies; pulmonary levels of Al: Normal lung function and radiographs. Al concentrations (ppm wt.w.) of 400, 530, 590, 1080 in lungs. No fibrosis at 400. Slight fibrosis in lung of one worker at 1080. Note: Concomitant exposure to PAHs in coal tar pitch and tobacco smoke.	Gaffuri et al. (1985)

TABLE 11-19 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ALUMINUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Al/m^3$						
N/A	NS	Occup Duration NS	Al dusts	NS	Human (1) M	Occup history, Al identified by electron probe analysis of lung biopsy: Case report showing granulomatous response (extensive interstitial granulomas composed of macrophages, foreign body giant cells, and birefringent crystalline structures) in lung, similar to that observed in rabbits following Al dust inhalation.	Chen et al. (1978)
N/A	NS	Occup Duration NS	Al dusts	NS	Human NS	Review of epidemiological studies: Suggests exposure produces asthma-like syndrome due to irritant rather than allergic mechanism. Evidence of reduced lung function consistent with chronic airflow limitation.	Abramson et al. (1989)
N/A	NS	Occup Duration NS	Al dusts	NS	Human (797) M	Epidemiology study, spirometry, chest radiography, environmental monitoring: Cough, wheezing, altered pulmonary function (dec mean FEV and maximal mid-expiratory flow rate).	Chan-Yeung et al. (1983)
N/A	0-53,000 as AlF_3	Occup 2 yr	AlF_3 or Al sulphate	25-35% AlF_3 dust $<5\ \mu m$	Human (19) M	Methacholine provocation tests, CS: Nocturnal wheezing, breathlessness, reversible airways obstruction, dyspnea, hyperreactivity (dec FEV_1).	Simonsson et al. (1985)
N/A	UK	Occup Duration NS	Al silicate dusts used for cat litter	UK	Human (13) M, (4) F	CS: Fibrosis in three workers, potentially due to silica.	Musk et al. (1980)

TABLE 11-19 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ALUMINUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Al/m^3$						
N/A	NS	Occup Duration NS	Al dusts (metallic Al, Al oxide)	NS	Human (1) M	Mineralogical analysis of BAL, lung tissue, mediastinal lymph node: Severe lung fibrosis and bronchial carcinoma. Metallic Al particles (0.5μm-5 μm) found in BAL, lung tissue, and lymph nodes.	De Vuyst et al. (1986)
N/A	NS	Occup Avg. 11.6, 14.8 yr	Al dusts	NS	Human (76) M	Spirometry, bronchitis prevalence: No effect on FVC, FEV_1. Low incidence of bronchitis, occurring mostly in smokers. Note: Longitudinal study of aluminum die-casting workers.	Discalzi et al. (1992)
N/A	NS	Occup Duration NS	Alumina, silica	NS	Human (344) M	CS, chest x-ray, gross and microscopic pathology: In 35 cases, interstitial lung fibrosis (non-nodular), profound emphysema, cough, dyspnea.	Shaver and Riddel (1947)

Abbreviations:

Al = aluminum; AlF_3 = aluminum trifluoride; ALK = alkaline phosphatase; BAL = bronchoalveolar lavage; BC = blood chemistry; CS = clinical signs; d = day; dec = decreased; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; inc = increased; M = male; N/A = not applicable; NS = not specified in the literature reviewed; occup = occupational; PAH = polycyclic aromatic hydrocarbons; PF = pulmonary function; resp = respiratory; wt.w = wet weight; yr = years.

concentration of 350,000 $\mu g/m^3$, assuming a particle diameter of 2 μm and a specific gravity of AL of 2.7.

Epidemiological studies of AL workers have not shown an increase in deaths due to cardiovascular diseases (Gibbs and Horowitz, 1979; Milham, 1979; Mur et al., 1987; Rockette and Arena, 1983; Theriault et al., 1984; Waldron-Edward et al., 1971). Nor has there been excess mortality from Alzheimer's or other neurological diseases in workers inhaling large quantities of AL dust (Gibbs, 1985). No studies were located regarding other systemic, developmental, or reproductive effects in humans following inhalation exposure to AL or AL compounds.

Several studies were found regarding cancer in workers from AL reduction factories following inhalation exposure (Gibbs and Horowitz, 1979; Milham, 1979; Mur et al., 1987; Rockette and Arena, 1983; Theriault et al., 1984). These studies show excessive deaths from cancer of the lung, pancreas, lymphatic system, brain, or bladder; however, the authors concluded that is unclear whether these cancers were caused by exposure to AL dusts or by concomitant exposure to carcinogens (tobacco smoke or PAHs from coal tars) in the factories. Exposure concentrations for AL were not provided in the studies.

Laboratory Animal Data

Limited information is available regarding respiratory effects in laboratory animals following inhalation exposure to aluminum dusts, as summarized in Table 11-20. Two studies involved exposure of rats, Guinea pigs, and hamsters to aluminum chlorohydrate, a common component of antiperspirants (Drew et al., 1974; Steinhagen et al., 1978). Other studies used aluminum oxide (Christie et al., 1963) or pure aluminum flakes (Thomson et al., 1986). These studies report a proliferation of macrophages detected in lavage fluid or in alveolar walls. Granulomatous reactions characterized by giant vacuoled macrophages, sometimes accompanied by pneumonia, were also reported.

Rats exposed to either aluminum trichloride ($AlCl_3$, 360 μg Al/m^3) or aluminum trifluoride (AlF_3, 420 μg Al/m^3) dusts for 5 mo had increased lysozyme levels resulting from damaged pulmonary alveolar macrophages. In addition, exposure to aluminum trichloride produced increased protein levels in lavage fluid and increased alkaline phosphatase activity,

TABLE 11-20. LABORATORY ANIMALS EXPOSURE CONDITIONS AND EFFECTS FOR ALUMINUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Al/m^3						
Acute Studies							
N/A	10,000 50,000 100,000 200,000 1,000,000	4 h	Al flakes (99% pure)	2.62–3.28 μm (geo. mean 2.82 μm) >90% <5 μm in diameter MMAD 1.58 μm, τg = 1.91	Rat, F344 (6) M	BPL, BW, PF, HP: No alteration in PF. Persistent changes in enzymatic and cytological lavage fluid parameters (ALK, protein, LDH, G6P) at ≥50,000 $\mu g/m^3$ with multi-focal microgramulomas in lungs and hilar lymph nodes.	Thomson et al. (1986)
N/A	0 33,000	4 h/d 3 d	AlClH aerosol	NS	Hamster, NS (10–30) M	MFO activity, BW, CS, HP: Inc lung weight, incr in neutrophils and macrophages in bronchial walls.	Drew et al. (1974)
N/A	0 10,000	6 h/d 20 d	AlClH aerosol	NS	Hamster, NS (24) M	MFO activity, HP: Granulomatous nodules in lungs and bronchoalveolar junction at 10,000 $\mu g/m^3$. Thickened alveolar walls, probably adaptive macrophage response from particulate accumulation.	Drew et al. (1974)
Chronic Studies							
N/A	0 50 500 5,000	6 h/d 5 d/wk 6 mo	AlClH dust	84% EAD (μm): 6.20, 5.78, 5.34 σg: 3.88, 4.82, 3.49	Rat, F344 (10) M, (10) F	BW, HP, BC: Lung nodules at 500 $\mu g/m^3$. Enlarged lymph nodes. Exposure-related granulomatous reactions characterized by giant vacuoled macrophages containing basophilic material and eosinophilic cellular debris at ≥500 $\mu g/m^3$.	Steinhagen et al. (1978)

TABLE 11-20 (cont'd). LABORATORY ANIMALS EXPOSURE CONDITIONS AND EFFECTS FOR ALUMINUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Al/m^3						
N/A	0 50 500 5,000	6 h/d 5 d/wk 6 mo	AlClH dust	84% EAD (μm): 6.20, 5.78, 5.34 σg: 3.88, 4.82, 3.49	Guinea pig, Hartley (10) M, (10) F	BW, HP, BC: Lung nodules at 500, inc lung weight at 5,000 μg/m^3. Exposure-related granulomatous reactions characterized by giant vacuoled macrophages containing basophilic material and eosinophilic cellular debris at $\geq$500 μg/m^3.	Steinhagen et al. (1978)
N/A	420	6 h/d 5 d/wk 5 mo	AlF_3 dust	UK	Rat, S-D (50) M	BW, BC: Incr lysozyme levels from damaged PAMs at 420 μg/m^3. No apparent effect on G6P or ALK, suggesting no adverse effect on Type I or II cells.	Finelli and Que Hee (1981)
N/A	360	6 h/d 5 d/wk 5 mo	$AlCl_3$ dust	UK	Rat, S-D (50) M	BW, BC: Incr lysozyme levels from PAMs at 360 μg/m^3. No apparent effect on G6P, suggesting no adverse effect on Type I alveolar cells. Incr ALK at 360 μg/m^3, suggesting effect on Type II cells. Transient inc in lavage protein levels.	Finelli and Que Hee (1981)

Abbreviations:

Al = aluminum; $AlCl_3$ = aluminum trichloride; AlClH = aluminum chlorohydrate; AlF_3 = aluminum trifluoride; ALK = alkaline phosphatase; BAL = bronchoalveolar lavage; BPL = bronchopulmonary lavage; BC = blood chemistry; BW = body weight; CS = clinical signs; d = day; dec = decreased; F = female; EAD = equivalent aerodynamic diameter; G6P = glucose-6-phosphate dehydrogenase; h = hour; HP = histopathology; inc = increased; LDH = lactate dehydrogenase; M = male; MFO = mixed function oxidase; MMAD = mass median aerodynamic diameter; mo = month; N/A = not applicable; NS = not specified in the literature reviewed; PAH = polycyclic aromatic hydrocarbons; PAMs = pulmonary alveolar macrophages; PF = pulmonary function; resp = respiratory; wk = week; wt.w = wet weight; yr = years.

suggesting that aluminum trichloride affects Type II alveolar cells (Finelli and Que Hee, 1981). These types of changes are often considered to be an adaptive response to many types of dusts. Pulmonary function in rats was not affected following exposure to alumina (Al_2O_3) fibers for 86 weeks (Pigott et al., 1981).

No changes in heart, kidney or liver weights or histology were seen in animals exposed to aluminum chlorohydrate in antiperspirants (Drew et al., 1974; Steinhagen et al., 1978). In rats, liver weights increased (by 9.4%) after 3 mo exposure to aluminum trichloride (360 μg Al/m^3), and kidney weights increased by 9% or 12% after exposure to aluminum trichloride (360 μg Al/m^3) or aluminum trifluoride (420 μg Al/m^3), respectively. Body weight was not affected in male rats after exposure for 5 mo (Finelli and Que Hee, 1981). No studies were located regarding other systemic, developmental, or reproductive effects in animals following inhalation exposure to aluminum or aluminum compounds.

Only one study was found that addressed cancer in animals following inhalation exposure to aluminum (Kobayashi et al., 1968). However, the results are not reliable because the study is seriously flawed (insufficient number of animals, lack of sufficient controls and exposure duration).

11.6.2.4 Factors Affecting Susceptibility

No data were located that addressed populations especially susceptible to the inhalation effects of aluminum. However, since the respiratory system is the major target of inhaled aluminum, individuals with impaired respiratory function may be at increased risk. The developing respiratory tract of children may also pose an increased susceptibility.

Other information on potential susceptible populations comes from other exposure routes. Although inhaled aluminum compounds are absorbed, it is unclear if the extent of absorption is high enough for systemic toxicity to be an issue. However, Alzheimer's disease patients may have increased vulnerability to the aluminum effects. The metal has been hypothesized to play a role in the development of Alzheimer's, and Alzheimer's patients may have an altered blood-brain barrier, which may allow increased Al accumulation in the brain (Shore and Wyatt, 1983). However, there are numerous uncertainties regarding any involvement of aluminum in the etiology of Alzheimer's disease.

Dialysis patients and others with renal dysfunction may have increased sensitivity to aluminum. Tissue levels of aluminum are increased in dialysis patients (Alfrey, 1980; Alfrey et al., 1980), partly due to increased exposure, such as from aluminum hydroxide dosing. However, dialysis patients also have elevated parathyroid hormone levels, which may enhance aluminum absorption, as well as decreased renal function, which decreases excretion.

11.6.3 Antimony

11.6.3.1 Chemical and Physical Properties

Antimony is a member of Group 5A of the periodic table. Because it exhibits both metallic and nonmetallic properties, it is classified as a metalloid. Antimony has four possible oxidation states: −3, 0, +3, and +5. The +3 state is the most common and stable (Agency for Toxic Substances and Disease Registry, 1992), although elemental antimony (oxidation state 0) is stable as well, and not readily attacked by air or moisture (Li et al., 1992). In solutions, antimony does not exist as a simple cation (i.e., Sb^{+3} or Sb^{+5}). Rather, hydrolyzed forms are found, $Sb(OH)_3$ for trivalent antimony, and $Sb(OH)_6^-$ for pentavalent antimony. Under oxidizing conditions, $Sb(OH)_6^-$ is the dominant species in solutions with a pH greater than 3 and under reducing conditions, $Sb(OH)_3$ is the dominant species. A wide variety of organoantimony compounds are known which can be broadly subdivided into Sb(III) and Sb(V) compounds (Freedman et al., 1992).

Antimony compounds for which inhalation toxicity data exist vary in their relative solubility in water. Antimony trioxide (Sb_bO_3) is insoluble in cold water and decomposes in hot water, whereas the pentsulfide (Sb_2O_5) is very slightly soluble in water. Antimony trisulfide (Sb_2S_3) is moderately soluble in water at 18 °C, but the pentoxide (Sb_5S_5) is insoluble. Antimony trichloride ($SbCl_3$), on the other hand, is moderately soluble at low temperatures (ca. 0 °C) but soluble in all proportions at 80 °C, whereas antimony potassium tartrate $K(SbO)\ C_4H_4O_6 \cdot ½\ H_2O$ is only moderately soluble in either cold or hot water.

11.6.3.2 Pharmocokinetics

Absorption and Distribution

No quantitative data were located on absorption of antimony from the respiratory tract of humans. Indirect evidence of absorbed antimony is provided by occupational studies that reported elevated antimony levels in blood and urine of antimony-trioxide exposed workers (Brieger et al., 1954; Cooper et al., 1968).

The retention and clearance of antimony from the lungs depends primarily on solubility (Leffler et al., 1984) and particle size (Felicetti et al., 1974a; Leffler et al., 1984). After exposure to radiolabeled antimony tartrate aerosol (in trivalent and pentavalent forms), whole-body counting in mice found antimony to be initially cleared rapidly from the lungs, followed by a slower, steady decrease in antimony levels. This biphasic clearance is due to the more rapid absorption of soluble material (i.e., trivalent form) from the lungs into the systemic circulation and longer lung retention of less soluble (i.e., pentavalent) and smaller particles. It was also observed that 1.6 μm antimony particles deposited in the upper respiratory tract to a greater degree than 0.7 or 0.3 μm particles (Felicetti et al., 1974a; Thomas et al., 1973).

Data from both live and deceased smelter workers indicate that antimony is retained in the lungs for long periods of time (Gerhardsson et al. 1982; McCallum 1963, 1967; McCallum et al. 1971; Vanoeteren et al. 1986a, 1986b, 1986c). Gerhardsson et al. (1982) measured antimony content in lungs from 40 deceased smelter workers and found antimony levels in the exposed men (316 mg/kg) to be 12-times greater ($p < 0.001$) than levels in nonexposed referents. Also, lung antimony concentration did not decrease with increasing postexposure period, indicating a long biological half-life for lung antimony. Studies by Vanoeteren et al. (1986a, 1986b, 1986c) also confirm that antimony accumulates in lung and is retained for long periods of time.

In a chronic inhalation study of rats by Bio/dynamics Incorporated (1990), the rate at which antimony trioxide was cleared by the lungs depended on the concentration, with clearance half-times of 2.3, 3.6, and 9.5 mo for the low-, mid, and high-concentration groups. Substantial amounts of antimony were still found in lungs of the rats after one year of exposure (10.6, 120, and 1,460 μg/g lung tissue, respectively).

Antimony is transported throughout the body via blood, with relative partitioning between erythrocytes and plasma a function of valency; in hamsters levels were greater in the erythrocytes following exposure to the trivalent form compared to the pentavalent (Felicetti et al., 1974b). Species differences exist in blood clearance of antimony, with levels persisting longer in rats than in mice and dogs (Felicetti et al., 1974a; Thomas et al., 1973). Antimony accumulates in the liver, thyroid, skeleton, and fur of animals; the largest burden is in the fur (Felicetti et al., 1974a,b). In hamsters that inhaled antimony tartrate, liver uptake of trivalent antimony was more rapid than that of the pentavalent form (Felicetti et al., 1974b), but the opposite was true for the skeleton.

Metabolism

Antimony can covalently bind with sulfhydryl groups and phosphate, as well as interact reversibly with endogenous ligands (e.g., proteins). Pentavalent antimony can be reduced to trivalent antimony. In both humans and animals, inorganic antimony (as opposed to organic antimony) is not methylated *in vivo* (Bailly et al., 1991), but is excreted primarily in the bile (conjugated to glutathione) and urine.

Excretion

Occupational studies found elevated urinary antimony levels in workers exposed to antimony trioxide (Cooper et al., 1968; Ludersdorf et al., 1987). In animals, trivalent and pentavalent antimony are eliminated in the urine and feces. The urine/feces ratio of antimony is dependent on valence state; with urinary excretion dominating after pentavalent antimony injection and mainly fecal excretion after trivalent form administration (Edel et al., 1983; Felicetti et al., 1974b). Some antimony in the feces after inhalation exposure is probably due to unabsorbed antimony cleared from lungs via mucociliary action into the gastrointestinal tract. There is a biphasic clearance of trivalent antimony tartrate from the body; 90% was excreted within 24 h after exposure, followed by a slower phase with a half-life of 16 days (Felicetti et al., 1974b).

11.6.3.3 Health Effects

Human Data

Acute inhalation exposure information on antimony is largely lacking for humans. Quantitative data on antimony exposure are mainly taken from occupational studies in which workers were exposed for extended periods to antimony trichloride, antimony oxide, or antimony ore, or a mixture of these compounds. The studies are very limited due to inadequate information on particle size of the antimony dust and concurrent exposure to other chemicals. Toxicity data for humans are summarized in Table 11-21.

Occupational exposure to antimony trioxide and/or pentoxide dust at extremely high concentrations (2 to 138 mg) over long periods (months to years) result in antimony pneumoconiosis, an inflammation of the lungs due to the irritation caused by the inhalation of dust (Cooper et al., 1968; Potkonjak and Pavlovich, 1983; Renes, 1953). Pneumoconiosis is characterized by chronic coughing, wheezing, and upper airway inflammation. No particular clinical findings or lung function changes distinguish this pneumoconiosis (called antimoniosis) from other types of simple pneumoconioses. Chext x-rays are characterized by numerous small opacities densely distributed in the middle and lower lung fields (Potkonjak and Pavlovich, 1983). Opacities are usually of the *p*, pinhead type. Sporadically *pq* type are seen, but not *r* type nor massive fibrosis (*pmf*). Other respiratory effects include chronic bronchitis, chronic emphysema, pleural adhesions, and irritation in exposed workers (Potkonjak and Pavlovich, 1983). Alterations in pulmonary function (airway obstruction, bronchospasm, and hyperinflation) have also been reported in workers exposed to airborne antimony (Cooper et al., 1968; Potkonjak and Pavlovich, 1983).

As for non-respiratory system impacts, ocular conjunctivitis and dermatosis in workers have resulted from exposure to airborne antimony (Potkonjak and Pavlovich, 1983; Renes, 1953), possibly due to direct ocular contact with antimony. Among reported systemic effects, cardiovascular effects (increased blood pressure, altered electrocardiogram [ECG] recordings) were observed in workers exposed to mg levels of antimony trisulfide for 8 months to 2 years (Brieger et al., 1954; Renes, 1953). Also, gastrointestinal symptoms (abdominal pain, diarrhea, vomiting, ulcers) have been reported in workers chronically exposed to mg levels of the trichloride, trisulfide, or oxide Sb compounds (Brieger et al., 1954; Renes, 1953; Taylor, 1966). Nerve tenderness and a tingling sensation were also

TABLE 11-21. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Sb/m^3						
Acute Studies							
NA	73,000	NR (accidental exposure)	Antimony trichloride fumes	NR	Human (7) M	Clinical observations: Gastrointestinal symptoms (abdominal pain, nausea, vomiting) and headache occurred. Transient upper respiratory tract irritation was reported, but possibly due to concomitant exposure to hydrogen chloride vapor. Note: Ingestion is also possible route.	Taylor (1966)
Chronic Studies							
NA	10,070-11,810	2 wk–5 mo (occup)	Mixture of fumes (35-68% Sb; 2-5% As; 0.01-0.04% Se; 0.04-0.3% Pb; 0.1-0.4% Cu)	NR	Human (78) M	Clinical symptoms, chest X-ray (6 men only), physical examination: Symptoms include abdominal cramps, diarrhea, vomiting, and dermatitis. Laryngitis (11%), pharyngitis (8%), pneumonitis (5.5%), rhinitis (20%), septal perforations (3.5%), and tracheitis (19%) were reported. Nerve tenderness and tingling also reported.	Renes (1953)
NA	8,870-45,950	17.91 yr (avg) (9–31 yr) (occup)	Antimony trioxide (38.73-88.86%) and antimony pentoxide (2.11-7.82%) dusts	80% < 5 μm	Human (51) M	Physical examination, lung function, chest x-ray (2-5 times over 25-year period): X-rays revealed diffuse, densely distributed punctate opacities in mid-lung, enlarged, dense shadows and emphysematous changes in upper and lower regions (pneumonoconiosis). Chronic coughing. Conjunctivitis and upper airway inflammation due to dust irritation. Dermatosis in 32 of 51 workers. Other effects included chronic bronchitis, emphysema, inactive tuberculosis, and pleural adhesions. No tumors were evident. Note: Dusts also contained free silica (0.82-4.72%), ferric trioxide (0.9-3.81), and arsenic oxide (0.21-6.48%).	Potkonjak and Pavlovich (1983)

TABLE 11-21 (cont'd) HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sb/m^3$						
NA	2,150	8 h/d 5 d/wk 8 mo–2 yr (occup)	Antimony trisulfide dust	NR	Human (113) M	Physical examination: Ulcers (7/111), altered ECG (T-waves) (37/75), and altered BP (38/113). No skin or respiratory irritation reported.	Brieger et al. (1954)
NA	80-138,000	1-15 yr (occup)	Antimony ore and antimony trioxide dust	NR	Human (28) NS	Pulmonary function tests (14 subjects), chest x-ray (13 subjects): X-ray revealed pneumoconiosis in 3/13 workers, and suspected pneumoconiosis in an additional 5.	Cooper et al. (1968)

Abbreviations:

BP = blood pressure; ECG = electrocardiogram; d = days; dec = decreased; h = hour; inc = increased; F = female; M = male; MMAD = mass median aerodynamic diameter; NA = not applicable; NS = not specified; NR = not reported; occup = occupational; σ_g = geometric standard deviation of distribution; WBC = white blood cells; wk = weeks; wt = weight; yr = years.

reported in workers exposed to high concentrations of antimony oxide (Renes, 1953). However, no clear causal relationship have been established between the antimony exposures and the above effects due to possible impact of concurrent exposure to other chemicals (e.g., hydrogen chloride, sodium hydroxide) in the workplace.

Only one report evaluated effects of antimony exposure on reproductive or developmental endpoints. Belyaeva (1967) reported increased incidence of spontaneous abortions and disturbances in menstrual cycle in exposed female workers at an antimony metallurgical plant (antimony trioxide, antimony pentasulfide, and metallic antimony). Body weights of children from exposed mothers lagged behind those from controls after 1 year. No quantitative exposure data were available and no description of the control group was provided; but antimony was detected in the blood of exposed workers at 10 times higher levels than for controls and was also found in other body fluids.

The study by Potkonjak and Pavlovich (1983) reported that cancer incidence was not affected in workers exposed to 8,900 to 46,000 μg Sb/m^3 for 9–31 years.

Laboratory Animal Data

Toxicity data for laboratory animals are summarized in Table 11-22. Like humans, laboratory animals develop respiratory signs associated with pneumonoconiosis, progressing to proliferation of alveolar macrophages to fibrosis. For example, Brieger et al. (1954) found lung inflammation in rabbits exposed to 19,900 μg/m^3 antimony trisulfide for 5 days. Also, a concentration-related increase in numbers of alveolar macrophages occurred in rats exposed to antimony trioxide (7 to 210 μg Sb/m^3) for 13 weeks or 1 year (Bio/dynamics Incorporated, 1985, 1990). Microscopic lung examination revealed interstitial inflammation at the 6, 12, 18 and 24 mo sacrifices. Granulomatous inflammation/granulomas were seen in all exposure groups at 18 and 24 mo. Increased numbers of alveolar and intraalveolar particle-laden macrophages were seen at every exposure duration in all but the control groups, but there were no indications that the increases in particle-laden macrophages in lungs of the low and mid concentration group rats were anything but a normal compensatory response. However, clearance half-times in the high concentration groups were 3 times greater than in the low and mid concentration groups, indicating that clearance mechanisms may be compromised at the higher exposure levels. With respect to interstitial inflammation

TABLE 11-22. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sb/m^3$						
Acute Studies							
NA	19,940	7 h/d 5 d/wk 5 d	Antimony trisulfide aerosol	$\leq 2\ \mu m$	Rabbit, NS (5) NS	ECG recording, autopsy: Effects included altered ECG (not specified), parenchymatous changes in myocardium, liver, and renal tubular epithelium, and inflammation of lungs.	Brieger et al. (1954)
Subchronic and Chronic Studies							
NA	0 17,480	7 h/d 5 d/wk 52 wk	Antimony ore (antimony trisulfide, stibnite) dust	MMAD = 4.78	Rat, Wistar (90) M, (90) F	Body wt, gross and light microscopy: Clinical observation of hemorrhage around ears during first 2 mo. Foci on pleural surfaces of lung lobes. Alveolar wall thickening (interstitial fibrosis, alveolar wall cell hypertrophy and hyperplasia) and cuboidal cell metaplasia at 6 mo and inc interstitial fibrosis at 12 mo. Inc tumor incidence (squamous cell carcinomas, bronchioloalveolar adenomas and carcinomas) in females.	Groth et al. (1986); Wong et al. (1979)
NA	2,200	7 h/d 5 d/wk 6 wk	Antimony trisulfide aerosol	$\leq 2\ \mu m$	Rat, Wistar (10) M	ECG recording, autopsy: Lung exhibited congestion and focal areas of hemorrhage (mild), considered to be secondary to heart failure. Heart had hyperemia, "flabbiness" of myocardium, and swelling of myocardial fibers. Respiratory inflammation, renal and hepatic parenchymatous degeneration, and myocardial damage and altered ECG (elevation of the RS-T segments and flattening of T-waves) at 2,200 $\mu g/m^3$.	Brieger et al. (1954)

TABLE 11-22 (cont'd) LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sb/m^3$						
NA	4,020	7 h/d 5 d/wk 6 wk	Antimony trisulfide aerosol	$\leq 2\ \mu m$	Rabbit, NS (6) M	ECG recording, hematology, clinical chemistry, liver function tests, histopathology: Myocardial damage (dilation of heart, flabby myocardium, swelling of myocardial fibers), altered ECG (altered T-waves).	Brieger et al. (1954)
NA	3,810 (7 wk) 3,980 (10 wk)	7 h/d 5 d/wk 7 or 10 wk	Antimony trisulfide aerosol	$\leq 2\ \mu m$	Dog, NS (2) F per regimen	ECG recording, hematology, clinical chemistry, histopathology: No effects at 7 wk, but swelling of myocardial fibers, altered ECG (not specified) at 10 wk.	Brieger et al. (1954)
NA	0 210 920 4,110 19,610	6 h/d 5 d/wk 13 wk (up to 13 wk postexposure)	Antimony trioxide dust	MMAD = 2.9, 3.9, 2.9, and 3.4 μm for respective levels; σ_g = 1.6, 1.5, 1.6, and 1.5, respectively	Rat, Fischer (50) M, (50) F	Body wt, organ wts, hematology, clinical chemistry, gross and histopathology examinations of major organs: Reduced body wt at two high levels. Lung lesions included degenerating macrophages and cellular debris in lumen of alveoli in all exposed groups. Multifocal pneumonocyte hyperplasia, nonsuppurative alveolitis, and focal alveolar wall thickening at two highest concentrations. Corneal irregularities and alopecia in high-concentration group.	Bio/dynamics Incorporated (1985)
NA	0 209,000	4 h/d 63-78 d	Antimony trioxide NS	NR	Rat, NS (10–24) F	Maternal, reproductive, and developmental evaluation: Dec number of pregnancies in 33% of animals and in number of offspring. Histopathology of uterine and ovarian tissues revealed lack of ova in follicles, misshapen ova, cysts, and uterine metaplasia.	Belyaeva (1967)
NA	0 1,600 4,200	6 h/d 5 d/wk 12 mo	Antimony trioxide dust	MMAD 0.4–0.44 σ_g = 1.5–1.6	Rat, Fischer (49) F	Histopathology of spleen, adrenals, ovaries, uterus, skeletal muscle, bone, brain, thyroid, thymus, pancreas, digestive glands, lymph nodes, heart, liver, kidney, esophagus, stomach, small intestine): Respiratory focal fibrosis at both concentrations	Watt (1980)

TABLE 11-22 (cont'd) LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Sb/m^3						
NA	0 7 480 4,010	6 h/d 5 d/wk 1 yr ($\leq$12 mo postexposure)	Antimony trioxide dust	MMAD = 3.7 (avg) σ_g = 1.7	Rat, Fischer (65) M, (65) F	Clinical signs, body wt, hematology, organ wts, gross and microscopic examination: Inc number of alveolar macrophages, interstitial inflammation, hyperplasia of reticuloendothelial cells occurred at 7 μg/m^3 and above (6 and 12 mo postexposure).	Bio/dynamics Incorporated (1990)
NA	83,600-104,500	25 h/wk 14.5 mo	Antimony trioxide dust	MMAD = 0.6 μm	Rat, Sragué-Dawley (50) M	Gross and microscopic histopathology of lungs ($\geq$2 mo): Pleural foci at 9 mo; increased mottling with increasing duration. Proliferation, swelling, and desquamation of alveolar lining cells early. Lipid pneumonia, fatty degeneration in alveolar macrophages, progressing to necrosis, accumulation of intracellular lipids. Absence of fibrosis in lymph nodes.	Gross et al. (1952)
NA	83,600-104,500	100 h/wk 14.5 mo	Antimony trioxide dust	MMAD = 0.6 μm	Rat, NS (50) M	Gross and microscopic histopathology of lungs ($\geq$2 mo): Mottling at 9 mo. Proliferation, swelling, and desquamation of alveolar macrophages. Lipid pneumonia, fatty degeneration in alveolar macrophages, progressing to necrosis, accumulation of intracellular lipids. Death in 18%, due to pneumonia.	Gross et al. (1955)

TABLE 11-22 (cont'd) LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sb/m^3$						
NA	0 36,000	7 h/d 5 d/wk 52 wk	Antimony trioxide aerosol	MMAD = 2.8	Rat, Wistar (90) M, (90) F	Body wt, gross and light microscopy examination: Clinical observation was hemorrhage around ears during first 2 mo. Foci on pleural surfaces of lung lobes. Alveolar wall thickening (interstitial fibrosis, alveolar wall cell hypertrophy and hyperplasia) and cuboidal cell metaplasia at 6 mo and inc interstitial fibrosis at 12 mo. Inc incidence of tumors (squamous cell carcinomas, bronchioloalveolar adenomas and carcinomas) in female rats.	Groth et al. (1986); Wong et al. (1979)
NA	0 1,600 4,200	6 h/d 5 d/wk 1 yr	Antimony trioxide dusts	Low: 0.44 μm, σ_g = 2.23 High: 0.4 μm, σ_g = 2.13 (Ferret's diameter)	Pig, Sinclair miniature (2-3) F	Hematology, clinical chemistry, ECG, organ wt, histopathology: Inc lung weight and nonneoplastic pulmonary effects (focal fibrosis, hyperplasia, pigmented macrophages, multinucleated giant cells) at 1,600 and 4,200 $\mu g/m^3$. Severity inc with concentration.	Watt (1983)
NA	0 1,600 4,200	6 h/d 5 d/wk 1 yr	Antimony trioxide dusts	Low: 0.44 μm, σ_g = 2.23 High: 0.4 μm, σ_g = 2.13 (Ferret's diameter)	Rat, Fischer (49) F	Hematology, clinical chemistry, ECG, organ wt, histopathology: Inc incidence of lung tumors (scirrhous carcinoma, squamous cell carcinoma, bronchoalveolar adenomas) at 4,200 $\mu g/m^3$. Inc lung weight and nonneoplastic pulmonary effects (focal fibrosis, hyperplasia, pigmented macrophages, multinucleated giant cells) at 1,600 and 4,200 $\mu g/m^3$. Severity inc with concentration.	Watt (1983)

TABLE 11-22 (cont'd) LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ANTIMONY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Sb/m^3						
Subchronic and Chronic Animal (cont'd)							
NA	38,100	2 h/d 7 d/wk 2 wk initially, then 3 h/d for 8-265 d	Antimony trioxide	≤ 1 μm	Guinea pigs (24) NS	Electrocardiogram, hematology, organ wt, histopathology: Interstitial pneumonitis, inc lung wt, subpleural petechial hemorrhages. Liver effects included inc wt, cloudy swelling, and fatty degeneration. Dec WBC and splenic hyperplasia and hypertrophy were reported.	Dernehl et al. (1945)

Abbreviations:

BP = blood pressure; ECG = electrocardiogram; d = days; dec = decreased; h = hours; inc = increased; F = female; M = male; MMAD = mass median aerodynamic diameter; mo = months; NA = not applicable; NS = not specified; NR = not reported; σ_g = geometric standard deviation of distribution; WBC = white blood cells; yr = years.

and granulomatous inflammation, statistical significance of incidence data was not reported in the study, but the data were subsequently evaluated using trend and pairwise (Fisher Exact) tests to the statistical significance of increases in severity grades and incidence (Allen and Chapman, 1993). An evaluation of male and female graded responses for interstitial and granulomatous inflammation using logistic regression techniques found no effect in females at any concentration level and marginally significant effects (for increased severity of interstitial inflammation) at the high concentration level for males during the exposure period (first 12 months). However, in the second, follow-up year, 4,500 μg Sb2O3/m^3 caused increases in both the incidence and severity of these responses for both male and female rats sacrificed at 18 and 24 months ($p < 0.05$). At higher concentrations (1,600 to 83,600 μg Sb/m^3), more severe respiratory effects (interstitial fibrosis, hyperplasia, and lipoid pneumonia) occurred in rats (Bio/dynamics, 1990; Dernehl et al., 1945; Gross et al., 1952, 1955; Groth et al., 1986; Watt, 1980, 1983; Wong et al., 1979).

Inhaled antimony trisulfide dust exposures (in mg ranges) for acute to subacute durations produced degenerative changes in the myocardium and related ECG abnormalities in several laboratory animal species (Brieger et al., 1954). With a five-day exposure, ECG alterations (unspecified) occurred in rabbits exposed to 19,940 μg/m^3. With longer exposures (6–10 weeks), rats, rabbits, and dogs exhibited altered ECGs and swelling of myocardial fibers at concentrations at least four times lower (2,000 to 4,000 μg/m^3) than required to produce similar changes following acute exposure in rabbits. However, no changes in ECG readings were seen in pigs exposed to similar concentrations for a year (Watt, 1983).

Renal effects (tubular epithelial changes) have been reported in rabbits acutely exposed to high concentrations (19,940 μg/m^3) antimony trisulfide (Brieger et al., 1954). No changes in the kidney were observed in rats after subchronic exposure to lower concentrations of antimony trioxide (Bio/dynamics Incorporated, 1985) or acute exposure to antimony trisulfide (Bio/dynamics Incorporated, 1990; Groth et al., 1986; Wong et al., 1979).

Alopecia (hair loss) and eye irritation occurred in rats exposed to antimony trioxide for 13 weeks at 4,100 or 19,600 μg/m^3 (Bio/Dynamics Incorporated, 1985). Cataracts were observed in rats exposed to antimony trioxide for a year (Bio/Dynamics Incorporated, 1990). An ophthalmoscopic examination was performed on all rats at pretest, 6, 12, 18 and 24 mo.

Mild, compound-related ocular irritation was noted at 6 mo, but no signs of compound related ocular disease were noted at 12 or 18 mo. Examination of all surviving rats at 24 mo revealed increased incidence of conjunctivitis, and cataracts (females only; principally posterior subcapsular cataracts). Statistical analysis of the cataract response at 24 mo was performed for both male and female rats (Allen and Chapman, 1993). Trend test and pairwise comparisons (Fishers Exact) revealed no concentration-response relationship for the male rats; at the high concentration, however, a statistically significant increase in female cataracts was clearly indicated by both trend and pairwise tests ($p < 0.01$).

Exposure to high concentrations of antimony trioxide (209,000 μg antimony/m^3) prior to conception and throughout gestation resulted in decreased number of offspring born to rats (Belyaeva, 1967). In dams that failed to conceive, metaplasia of the uterus and disturbances in the ovum-maturing process were observed.

Animal data suggest that antimony is carcinogenic in rats. Lung tumors developed in rats exposed to antimony trioxide or antimony trisulfide ($\geq$4,200 μg Sb/m^3) for a year (Groth et al., 1986; Watt, 1980, 1983; Wong et al., 1979). However, no effect was seen in rats exposed to 4,010 μg/m^3 as antimony trioxide (Bio/dynamics Incorporated, 1990) or in guinea pigs exposed to 4,200 μg/m^3 as antimony trioxide (Watt, 1983).

11.6.3.4 Factors Affecting Susceptibility

Individuals with preexisting chronic respiratory or cardiovascular problems may have greater susceptibility to toxic effects of antimony (Brieger et al. 1954; Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953). The developing respiratory tract in children may also pose increased susceptibility. Animal data also suggest renal effects following extended antimony exposure (Brieger et al. 1954; Price et al. 1979). Although there is no evidence to indicate whether similar effects would be occur in humans, it is possible that individuals with kidney dysfunction may be unusually susceptible.

11.6.4 Arsenic

11.6.4.1 Physical/Chemical Properties

Arsenic is a metalloid belonging to Group 5A of the periodic table. Arsenic has valence states of -3, 0, $+3$ and $+5$ (Weast, 1989), although the $+3$ and $+5$ forms of

arsenic are the most common states (World Health Organization, 1987). Elemental arsenic is oxidized to arsenic trioxide (+3 oxidation state) upon exposure to air (American Conference of Governmental Industrial Hygienists, 1991). Arsenic occurs in the environment in both organic and inorganic compounds (Ishinishi, 1986). Arsenic trioxide, in particulate form, is the most common compound of arsenic found in ambient air (Ishinishi, 1986), but it may be oxidized to arsenic pentoxide (+5 oxidation state). In aerated water, As^{+3} is oxidized to As^{+5}, especially at alkaline pH (Agency for Toxic Substances and Disease Registry, 1992). Elemental arsenic is insoluble in water, but arsenic trioxide and arsenic pentoxide are both moderately soluble.

Workers in smelters, glass factories, arsenical pesticide manufacture, pesticide applicators, and wood preserving plants are potentially exposed to relatively high levels of arsenic as dusts and vapors. Another source of potential occupational arsenic exposure is the use of gallium arsenide in semiconductor technology. Smelter workers are exposed primarily to trivalent arsenic (arsenic trioxide) and wood preservers to pentavalent arsenic. The general population near these types of manufacturing plants are exposed by inhalation to low but detectible levels of arsenic.

11.6.4.2 Pharmacokinetics

Absorption and Distribution

In smelter workers exposed to arsenic trioxide, urinary excretion accounted for about 40 to 60% of the inhaled dose (Pinto et al., 1977). Smith et al. (1977) showed that amounts of different arsenic species (As (III), As (V), methylarsonic acid and dimethylarsinic acid) in urine samples of copper smelter workers exposed to inhaled inorganic arsenic (primarily As_2O_3) correlated well with each other and with exposure. Particles > 5 μm diameter were more closely correlated with excretion of arsenic compounds, although the correlation for exposure to particles < 5 μm was also highly significant ($p < 0.001$). The authors attributed this to greater deposition efficiency of particles > 5 μm and to that size fraction accounting for more than half of the total airborne arsenic.

No laboratory animals studies on absorption of arsenic via inhalation were found. In hamsters, intratracheal instillation of relatively soluble oxy compounds of arsenic (sodium arsenate, sodium arsenite, arsenic trioxide) resulted in 60 to 90% clearance from the lungs in

one day, whereas arsenic trisulfide and lead arsenite (only slightly soluble) largely remained in the lungs and were only slowly absorbed (Marafante and Vahter, 1987); calcium arsenate was solubilized and cleared from the lungs more slowly (Pershagen et al., 1982). Leffler et al. (1984) instilled dust from a smelter (19% arsenic and 1.6% antimony) into hamster lungs and found a lung clearance half-life of 20 h for arsenic and 40 h for antimony, compared to a half-life of 13 h for arsenic trioxide (5 $\pm$ 2 μm MMAD).

Soluble arsenic salts are rapidly and completely absorbed from the gastrointestinal tract of humans. Less than 5% of an oral dose of 1–8 mg arsenic was eliminated in the feces (Bettley and O'Shea, 1975). Similar absorption was seen in the monkey (Charbonneau et al., 1978) and in mice (Vahter and Noren, 1980). Marafante and Vahter (1987) found a good correlation between the solubility of arsenic compounds in dilute HCl and their absorption from the gastrointestinal tract of hamsters. After a single oral dose of 2 mg ^{74}arsenic/kg for each compound, the absorption based on 3-day fecal elimination was 51% for sodium arsenite, 88% for sodium arsenate, 31% for lead arsenate, and 17% for arsenic trisulfide.

Inorganic arsenic is freely distributed to all tissues after it is absorbed into the bloodstream. Tissue levels of arsenic in humans have been studied using autopsy data. Kadowaki (1960) found the highest levels in nails (0.89 μg/g) followed by hair, bone, teeth, and skin and lower levels in soft tissues. Hair arsenic levels are increased in occupationally exposed workers, as high as 44 μg/g Bencko et al. (1986).

No inhalation data were found for the distribution of arsenic in laboratory animal species, but in mice given a single oral dose of ^{74}arsenic as arsenate or arsenite, the highest tissue concentrations were seen within 2 h in the kidneys, liver, and bile, and tissue levels decreased by 72 h (Vahter and Norin, 1980). Arsenate was cleared more rapidly than arsenite from soft tissues (except kidney). In contrast, rats retained up to 50% of a single injected dose of radioactive arsenate in red blood cells 2 days after dosing, and 26% remained after 64 days. The persistence in blood is due to strong binding of arsenic to free sulfhydryl groups in rat hemoglobin; once bound to the hemoglobin availability and, thus, the toxicity of arsenic is greatly reduced in rats (Mast et al., 1990; Vahter et al., 1982). For this reason, the rat is not an appropriate toxicokinetic model for extrapolation of metabolic data to humans. Dimethylarsenic, a metabolite of inorganic arsenic, has low affinity for tissues, is rapidly excreted, and is not distributed in tissues.

Metabolism

Inorganic arsenic metabolism is similar in humans and laboratory animals (mice, rabbits, and hamsters). Arsenate (As^{+5}) is reduced to arsenite (As^{+3}),which is methylated to form monomethyl arsenic acid (MMA). MMA is then reduced (As^{+5} to As^{+3}) and methylated to form dimethyl arsinic acid (DMA). The methylated forms of arsenic as well as inorganic arsenic species, are excreted in the urine; methylation facilitates the urinary excretion. Glutathione (GSH) appears to be the electron receptor in the reduction reactions, and the reduction is predominantly enzymatically mediated, although GSH can non-enzymatically reduce As^{+5}. Methylation is mediated by two methyltransferases, and S-adenosylmethionine is the methyl donor and electron acceptor (Levine et al., 1988).

Excretion

In humans, the predominant methylated form in urine is DMA, with lesser amounts of MMA. Six adult males given a single oral tracer dose of ^{74}arsenic/kg as arsenate (capsule). Of the dose excreted in the urine after 5 days (58% of administered), 51% was DMA, 21% MMA, and the remainder inorganic species. Interindividual variability in methylation was indicated by a DMA range of 40–56% and an MMA range of 15–25%.

Although there were no data on excretion of arsenic in laboratory animals after inhalation, oral and intravenous studies suggest that methylation of arsenic is required for efficient excretion. In mice given a single oral or intravenous dose of ^{74}arsenic as arsenate (As^{+5}), reduced arsenite (As^{+3}) and DMA were detected in the bladder urine in one h; in mice given As^{+3}, very little As^{+5} was found in plasma or urine, but DMA was found in urine. In rabbits given an intravenous injection of As^{+5}, As^{+3} was found in the bladder urine at 0.5 h, but DMA did not appear until 2 h. These findings indicated that reduction was prerequisite to methylation (Vahter and Endvall, 1983). In a similar study, Marafante et al. (1985) found after intravenous dosing of rabbits with ^{74}As as arsenate that reduction of As^{+5} was more rapid than methylation. That is, within 15 min, 10% of total arsenic in plasma was As^{+3}; As^{+5} concentrations in plasma decreased with a half time of one h; As^{+3} was cleared with half times of 10 min and 2 h; and DMA levels in plasma peaked at 4 h. After 24 h, urinary DMA, As^{+3}, and unchanged As^{+5} accounted for 35%, 5%, and 25% of the administered dose.

11.6.4.3 Health Effects

Human Data

Data on toxicity of inhalation exposures are mainly limited to qualitative occupational studies for workers breathing arsenic dusts (arsenic trioxide). Respiratory effects, including lung cancer, and peripheral neurological effects are toxic endpoints with inhalation exposure. Chronic encephalopathy has also been associated with exposure to arsenic fumes in case reports.

In humans, acute symptoms are seen after airborne exposure to high levels of arsenic trioxide in an occupational setting. Symptoms include severe irritation of the nasal mucosa, larynx, and bronchi (Holmqvist, 1951; Pinto and McGill, 1953). It is not clear if these effects were chemically related to arsenic or a result of irritation due to the dusts inhaled. Irritation of mucous membranes of the nose and throat leading to hoarseness, laryngitis, bronchitis, or rhinitis and sometimes perforation of the nasal septa have been reported in workers exposed to arsenic dusts (Pinto and McGill, 1953), but effect levels cannot be set due to insufficient exposure data.

Hyperpigmentation and hyperkeratosis are skin changes characteristic of chronic exposure to arsenic and are seen in individuals exposed to arsenic through inhalation or ingestion. The only available chronic inhalation studies are those for occupational exposures. Occupational exposure to sodium arsenite dusts in a factory manufacturing sheep dip was reported by Perry et al. (1948). Among 31 chemical workers with high exposure to arsenic (mean value about 400 $\mu g/m^3$, average time of employment 24 years), there was a 90% incidence of hyperpigmentation and a 29% incidence of hyperkeratoses. In 56 controls (from the same plant and possibly subject to some level of exposure), there was a 16% incidence of hyperpigmentation and a 4% incidence of hyperkeratoses. Perry et al. (1948) noted that although most of the exposed workers wore dust masks, it was likely that they were not used properly. Considerable exposure to arsenic did occur as indicated by the high urinary arsenic levels, which averaged 243 mg arsenic/L in the high exposure chemical workers. Considering the high incidence of hyperpigmentation in the "controls", and the possibility that direct skin contact and accidental ingestion of the dust were likely, total uptake of arsenic may have been much higher than that indicated by the air concentrations.

Feldman et al. (1979) studied 70 copper smelter workers and a control group of 41 non-smelter workers, on whom clinical neurologic examinations were conducted; of the smelter group, 37 were classified as high exposure and 33 as low based on arsenic levels in nails, hair, and urine. Weak associations were found between arsenic exposure and clinical neurologic findings, decreased action potential amplitude, and slower motor and sensory nerve conduction velocity. Associations were weak since there were only three cases of motor neuropathy and five cases of mixed sensorimotor neuropathy in the arsenic-exposed workers.

Morton and Caron (1989) reported two cases of chronic encephalopathy associated with high exposure to arsenic fumes in a wood treatment plant. Beckett et al. (1986) also reported a case of acute encephalopathy due to occupational exposure to arsenic in a smelting plant for a subject who had worked intermittently for 20 years with the smelting process and had previous exposures, one of which (5 years earlier) caused cough, diarrhea, rash, and neuro-behavioral symptoms. The urinary levels were 21 μg/L arsenic, which is only slightly higher than normal.

Lagerkvist et al. (1986) reported that increased peripheral vasospastic disorders and Reynaud's phenomenon were found in Swedish arsenic workers exposed to airborne arsenic dusts. The effect on the blood vessels was quantified by measurement of systolic blood pressure in fingers and toes after local cooling.

No reproductive or developmental studies were located for humans following inhalation exposure to arsenic.

Studies in smelter worker populations have shown an association between lung cancer mortality and arsenic exposure (Axelson et al., 1978; Enterline and Marsh, 1982). An excess of lung cancer deaths in pesticide workers chronically exposed to arsenic has been shown in mortality studies and cohort studies (Ott et al., 1974; Mabuchi et al., 1979; Matanoski et al., 1981).

Laboratory Animal Data

Laboratory animal toxicity data from inhalation exposures to arsenic compounds are summarized in Table 11-23. Limited acute data were available on the inhalation toxicity of arsenic in animals. Aranyi et al. (1985) exposed mice to an aerosol of arsenic trioxide for 3

TABLE 11-23. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ARSENIC AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ As/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
0 270 500 940		3 h/d 1, 5, or 20 d	As_2O_3 aerosol	MMAD = 0.4 μm; σ_g = 2.6	Mice, CD1 (42-292) F	Simultaneously challenged with an aerosol of viable *Streptococcus zooepidemicus* or radiolabeled 35S-Klebsiella pneumonia to determine mortality: Mortality in Streptococcal assay, decreased bacteriocidal activity.	Aranyi et al. (1985)
Chronic Studies							
0 60 200		continuously for 18 mo	As_2O_3 aerosol	MMAD <0.3 μm	Rats, Wistar (20-40) M	Body wt, hematology, clinical chemistry, and macroscopic and microscopic examination: No effects.	Glaser et al. (1985)
5,200 19,100 39,000		6 h/d 7 d/wk Gd 4–17	GaAs aerosol	MMADs = 1.1, 1.2, and 1.3 μm, respectively; σ_g = 2	Pregnant Mice, Swiss CD (22–24) F	Maternal, reproductive, and developmental endpoints: Reduced maternal weight ($p<0.05$) on gd 9–15 for the two high-concentration dams. Dyspnea occurred in 50% of animals for the 5,200 and 19,000-$\mu g/m^3$ groups and in all animals in the 39,000-$\mu g/m^3$ group in some portion of the exposure period; incidence, duration, and severity were concentration-related. The 19,000 and 39,000-$\mu g/m^3$ groups had grey and/or mottled lungs. Developmental toxicity (concentration-related dec number of live fetuses/litter and corpora lutea/dam and inc number of early resorptions/litter was observed in exposed groups; significant only in the 39,000-$\mu g/m^3$ group; dec mean fetal body wt was concentration-related; significant in the two high-concentration groups; concentration-related increase in reduced ossification of sternebrae per litter; significant in the two high-concentration groups).	Mast et al. (1990)

TABLE 11-23 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ARSENIC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg As/m^3						
5,200 19,100 39,000		6 h/d 7 d/wk Gd 4–19	GaAs aerosol	MMADs = 1.1, 1.2, and 1.3 μm, respectively; σ_g = 2	Pregnant Sprague Dawley Rats (30–31) F	Maternal, reproductive, and developmental endpoints: Maternal toxicity at 19,000 μg/m^3 and above (pulmonary effect (dyspnea). Developmental toxicity at 19,000 μg/m^3 and above (reduced fetal body weight at two high concentration groups; concentration-related; increased incidence of skeletal variations, specifically ossification of sternebrae (significant) and incompletely ossified vertebral centra, was concentration-related and significant in the two high-concentration groups).	Mast et al. (1990)

Abbreviations:

As_2O_3 = arsenic trioxide; d = days; dec = decreased; F = females; h = hours; GaAs = gallium arsenide; Gd = gestational day; inc = increased; M = males; MMAD = mass median aerodynamic diameter; mo = months; Na_3As = sodium arsenite dust; NS = not specified; σ_g = geometric standard deviation of distribution; wk = weeks; wt = weight.

h at levels of 0, 270, 500, or 940 μg arsenic/m^3. Additional groups were exposed for 3 h/day for 5 or 20 days. At the end of exposure, mice were given an aerosol exposure of viable streptococci, and death of exposed and controls was recorded over 14 days. Separate groups were challenged with aerosols of ^{35}S-labeled *Klebsiella pneumoniae* to evaluate macrophage functionality (bacterial killing) in a 3-h period. In the streptococcal assay, a concentration-related increase in mortality occurred. Bacteriocidal activity was markedly decreased after a single exposure to 940 μg arsenic/m^3, but no consistent or significant effects were seen at lower exposure levels after one or several exposures.

In a chronic inhalation study, male Wistar rats (20–40/group) were continuously exposed to 0, 60, or 200 μg arsenic/m^3 as arsenic trioxide for 18 mo (Glaser et al., 1986). No effects on body weight, hematology, clinical chemistry, or macroscopic and microscopic examination outcomes were observed.

Carcinogenicity bioassays for arsenic have been conducted mainly in rats and mice. Ishinishi et al. (1977) reported that 15 weekly intratracheal instillations of arsenic trioxide (260 μg), copper ore (3.95% arsenic), or refinery flue condensate (10.5% arsenic) to Wistar rats did not increase the incidence of tumors over those of controls during the lifespan of the animals. In a study by Pershagen et al. (1984), 15 weekly intratracheal instillations of arsenic trioxide (250 μg As/m^3) in hamsters increased the incidence of respiratory tract adenomas and papillomas, but the hamsters had also received a carrier dust (charcoal carbon) that increased the lung retention of arsenic. However, in one inhalation study Berteau et al. (1978) found that female mice exposed to 1% aqueous aerosol of sodium arsenite, 20 to 40 min/day, 5 days/week, for 55 weeks did not show an increase in tumor incidence.

Mast et al. (1990) conducted an inhalation developmental study in rats and mice exposed 6 h/day to gallium arsenite (5,000, 19,000, or 39,000 μg arsenic/m^3) on days 4–17 (mice) or 4 to 19 (rats) of gestation. Maternal toxicity was observed at the two highest concentrations in both mice (reduced body weight, dyspnea, mottled lungs) and rats (dyspnea). Slight growth retardation (statistically significant decrease in fetal body weight) was seen in pups at the two highest levels. A significant decrease in incomplete ossification of sternebrae was also observed with exposure to 19,000 μg/m^3 and above. No significant increases in malformations were seen.

11.6.4.4 Factors Affecting Susceptibility

The respiratory system is most sensitive to arsenic toxicity in humans following inhalation exposure (Holmqvist 1951; Pinto and McGill 1953). Therefore, individuals with pre-existing respiratory conditions (such as asthma, bronchitis) may have greater susceptibility than healthy individuals to respiratory effects from arsenic exposure. The developing respiratory tract in children may also pose an increased susceptibility. Developmental toxicity has also been observed and thus fetuses may also represent a susceptible population.

11.6.5 Barium

11.6.5.1 Chemical and Physical Properties

Barium is a silvery-white, relatively soft, ductile metal belonging to the alkaline-earth group of elements in Group 2 (IIA) of the periodic system of elements (Boffito, 1992; DiBello et al., 1992). Elemental barium is not found free in nature (DiBello et al., 1992), the element being fairly volatile and extremely reactive. Barium reacts readily and exothermically with oxygen and halogens at room temperature. It also reacts vigorously with water, releasing hydrogen and forming barium hydroxide, $Ba(OH)_2$ (Boffito, 1992). Barium forms compounds in the +2 valence state; in aqueous solution, barium is present as a cation with a +2 charge (DiBello et al., 1992), with some compounds, e.g., barium carbonate ($BaCO_3$) and barium chloride ($BaCl_2$) being slightly soluble in warm water (ca 20 to 25 °C) (Lide, 1992). Barium forms organometallic compounds such as barium acetate and barium 2-ethylhexanoate (DiBello et al., 1992).

11.6.5.2 Pharmacokinetics

Human

Limited information exists on pharmacokinetic properties of barium with inhalation exposure in humans. Increased urinary levels of barium (250 mEq/mL) reported by Shankle and Keane (1988) in humans following inhalation indicate that barium is absorbed by this route. Analysis of barium in humans, as discussed by Schroeder et al. (1972) indicates that barium is distributed predominantly to the skeleton and teeth. Barium exposure in this study presumably occurred via the oral route. Case studies have shown that excretion of oral doses

of barium in humans is about 3% in urine, with most of the remainder in feces (Tipton et al., 1966). Barium is not metabolized in the body but may be metabolically transported or incorporated into complexes or tissues.

Laboratory Animals

Laboratory animal data indicate that clearance of inhaled barium compounds from the lungs is related to the compound's solubility, with an initial rapid elimination phase for both soluble barium chloride and for insoluble barium sulfate. Because of its chemical similarity to calcium, barium accumulates in bone; about 25% of absorbed barium is transported to the skeleton, and the remainder is excreted in the urine and feces within 2 weeks (Cuddihy et al., 1974). The biological half-life of radioactive barium sulfate in the pulmonary region has been calculated to be 8 days in dogs exposed via inhalation (Morrow et al., 1964), and 10 days in rats injected intratracheally (Cember et al., 1961).

Cuddihy and Griffith (1972) studied the distribution of barium after co-inhalation of radiolabeled barium chloride and lanthanum chloride by dogs. By 5 days postexposure, a much higher percentage of the initial body burden remained in the skeleton (about 30%) than was in the lungs (about 0.2%). Similar studies were conducted with radiolabeled barium chloride and radiolabeled barium sulfate (Cuddihy et al., 1974). Data for skeletal burden were not available for barium sulfate, but lung burden accounted for less than half of the total body burden by day 5, indicating that clearance had occurred (Cuddihy et al., 1974). Distribution to blood was more rapid and extensive following exposure to barium chloride, with peak levels of about 10% of the initial body burden shortly after exposure, compared with a peak of about 2% of the initial body burden for barium sulfate (Cuddihy and Griffith, 1972; Cuddihy et al., 1974). For both compounds, initial elimination in urine and feces accounted for about 13% of the initial body burden each. For barium sulfate, some of the barium in the blood, urine, and feces probably represents barium cleared from the lungs by mucociliary action and either absorbed (blood and urine) or not absorbed (feces) from the gastrointestinal tract.

Data from intratracheally instilled barium may provide some information on the fate of barium compounds deposited in the lungs following inhalation exposure. Radioactive barium sulfate injected directly into the trachea of rats was taken up into the epithelial membranes

and remained there for at least several weeks (Gore and Patrick, 1982; Takahashi and Patrick, 1987). These studies also show that barium in the trachea can be cleared to the lymphatic system (Takahashi and Patrick, 1987). Data from rats exposed to barium sulfate via intratracheal injection found that about 7% of the initial lung burden was finally cleared to blood (Spritzer and Watson, 1964).

11.5.5.3 Health Effects

Studies evaluating barium effects following inhalation exposure are limited to case reports of occupational exposure in humans and two experimental animal studies. These studies are not adequate for firmly establishing the health effects of barium by inhalation because of serious study limitations. The case reports are inadequate because data were available for only a few exposed subjects and because exposure conditions (duration, frequency, dose) were not well characterized. Laboratory animal studies were also poorly characterized (lack of controls, number of animals not reported, duration and frequency of exposure not indicated, inadequate methods and results). Due to these major limitations of available data, results should be regarded as providing only preliminary or suggestive evidence for health effects due to inhalation exposure to barium.

Human Data

Human toxicity data for inhalation exposure are provided in Table 11-24. Workers exposed chronically to dust from barium sulfate had minimal radiologically observable evidence of pneumoconiosis, accompanied by infrequent reporting of minor respiratory symptoms (Doig, 1976). Essing et al. (1976) also reported few respiratory symptoms, slight decrease in lung function (4/12), and a thickening of lung structure (5/12) after inhalation of steatite (talcum) dust containing barium carbonate.

Shankle and Keane (1988) reported gastrointestinal effects (subjective symptoms), neurological effects (absence of deep tendon reflexes and progressive weakness in extremities), hypokalemia, and renal failure after a male worker accidentally inhaled large amounts of barium carbonate powder. The kidney and nervous system are known targets of oral exposure to barium; it is unclear whether the observed effects resulted from the absorption of inhaled barium, from barium that was inhaled and ingested after mucociliary

TABLE 11-24. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR BARIUM AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Ba/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
NA	NR	Occup Single incident - powder blown in face	$BaCO_3$ powder	NR	Human (1) M	Subjective symptoms, physical examination, urinalysis: Abdominal cramps, nausea, vomiting, diaphoresis, excess salivation, progressive weakness. Absent deep tendon reflexes. Hematuria, elevated serum creatinine, hypokalemia, barium level of 250 mEq/mL.	Shankle and Keane (1988)
Chronic Studies							
NA	NR	Occup 1947: 3.5-15 yr 1961: 1 mo-18 yr 1963: 21 mo-18 yr	$BaSO_4$ dust	1961 dust count range: 2734-11365 particles per cu. ml	Human 1947: (5) M 1961: (11) M 1963: (14) M	Subjective symptoms, clinical examinations, chest radiography, spirometry (1966, 1969, 1973 follow-ups only): Slight coughs, slight sputum. Basal crepitations in 1/5 (1947) 1/11 (1961). Opacities varying in intensity and profusion in 1/5 (1947), 7/11 (1961) and 9/14 (1963). Follow-up radiography indicated progressive regression after exposure cessation. Pulmonary function tests were average or better.	Doig (1976)
NA	600-2,300	7-27 yr occup	Steatite dust - 6% $BaCO_3$	NR	Human (12) M	Subjective symptoms, physical examination, spirometry, plethysmographic lung function test, blood gas analysis, ECG, x-rays: Coughing with or without discharge. Adiposity (8/12), inc BP (3/12). Slight dec in lung function (4/12). Incomplete right bundle branch block (2/12). Thickening of lung structure (5/12), pronounced calcifications in walls of pelvic vessels and femoral artery (1/12).	Essing et al. (1976)

Abbreviations:

avg = average; B = both male and female; Ba = barium; $BaCl_2$ = barium chloride; $BaCO_3$ = barium carbonate; $BaSO_4$ = barium sulfate; BP = blood pressure; BW = body weight; d = day; dec = decreased; ECG = electrocardiography; HP = histopathology; h = hour; inc = increased; M = male; mEq = milliequivalent; min = minute; mo = month; NA = not applicable; NR = not reported; occup = occupational exposure; ppm = parts per million; wk = week; yr = years.

clearance, or from barium that was directly ingested. Essing et al. (1976) also reported nonrespiratory effects after chronic inhalation exposure to barium carbonate, including cardiovascular effects (increased blood pressure in 3/12, incomplete right bundle branch block in 2/12, and pronounced calcifications in walls of pelvic vessels and femoral artery in 1/12). Because the subjects were also smokers and overweight, it is unclear if these effects were related to barium exposure.

Laboratory Animal Data

Toxicity data for laboratory animals are summarized in Table 11-25. Limited available data indicate that the respiratory tract and possibly other organ systems are targets of inhaled barium. Hicks et al. (1986) reported bronchoconstriction and increased blood pressure in guinea pigs intratracheally administered 60 μg Ba/m^3/min as an aerosolized barium chloride solution. Taresenko et al. (1977) exposed rats by inhalation to barium carbonate for 1 or 4 mo. Rats exposed to 23,380 μg Ba/m^3 for 1 mo exhibited desquamative bronchitis and focal thickening of interalveolar septa. Exposure of rats for 4 mo at 3,640 μg Ba/m^3 resulted in pulmonary lesions; other organs (heart, liver, kidneys) also demonstrated histopathology in the form of granular dystrophy and reduced biliary excretion was seen. The reproductive organs in both male and female rats (at doses of 3,640 and 9,380 μg Ba/m^3, respectively) were also affected (decreased sperm production in males, shortened estrous cycle in females) by inhalation exposure to barium carbonate and impaired reproductive capabilities occurred in exposed males mated with unexposed females.

Other effects observed by Tarasenko et al. (1977) in rats exposed for 1 mo to 23,380 μg Ba/m^3 included hematological changes, enzyme inhibition, metabolic changes and vascular tonus (all of which were unspecified). Decreased body weight, hematological changes, increased urinary calcium, inhibition of serum activities of cholinesterase and alkaline phosphatase were observed after the 4 mo exposure protocol (3,640 μg Ba/m^3).

11.6.5.4 Factors Affecting Susceptibility

Populations that may have increased susceptibility to barium via inhalation exposure include patients with cardiovascular problems (particularly hypertension), smokers, others with a history of lung disease, and those taking certain prescription drugs. The developing

TABLE 11-25. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR BARIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Ba/m^3						
NA	23,380	h/d NR d/wk NR 1 mo	$BaCO_3$ aerosol	80% of particles were < 2 μm	Rat, Albino NR	HP of respiratory tract and lungs, heart, liver and kidneys; urine and blood analyses, bromsulfophthalein test: Desquamative bronchitis, focal thickening of interalveolar septa; granular dystrophy in other organs studied. Blood changes, unspecified enzyme inhibition, metabolic changes, vascular tonus, dec biliary excretion.	Tarasenko et al. (1977)
NA	0 Males: 805 3,640 Females: 2,170 9,380	4 h/d 6 d/wk 4 mo	$BaCO_3$ dust	NR	Rat, Albino (NR) B	BW, urine and blood analyses, ECG, bromsulfophthalein test for liver function, HP of lungs, liver, heart, kidneys, testicles and ovaries; reproductive parameters: Dec BW. Dec blood Hb, dec thrombocyte count dec blood glucose, dec blood protein, inc leukocyte count, inc blood phosphorous, inc urinary calcium, inhibition of cholinesterase and alkaline phosphatase activities. Inc arterial BP. Dec biliary function. Pulmonary lesions (perivascular and peribronchial sclerosis with focal thickening of the interalveolar septa); granular dystrophy in liver, heart and kidneys; dec number and motility of spermatozoids, desquamated epithelium of ducts. Impaired fertilization, dec viability of offspring, inc embryonal mortality (females mated with exposed males). All above effects observed in males exposed to 3640 μg Ba/m^3. Shortened estrous cycle, ovarian structural abnormalities, underdeveloped offspring (females exposed to 9380 μg Ba/m^3).	Tarasenko et al. (1977)

Abbreviations:

avg = average; B = both male and female; Ba = barium; $BaCl_2$ = barium chloride; $BaCO_3$ = barium carbonate; $BaSO_4$ = barium sulfate; BP = blood pressure; BW = body weight; d = day; dec = decreased; ECG = electrocardiography; HP = histopathology; h = hour; inc = increased; M = male; mEq = milliequivalent; min = minute; mo = month; NA = not applicable; NR = not reported; occup = occupational exposure; ppm = parts per million; wk = week; yr = years.

respiratory tract of children may also be susceptible. Long-term (7 to 27 years) occupational exposure to high (600 to 2,300 $\mu g/m^3$) levels of barium was found to increase blood pressure and other cardiovascular effects (Essing et al., 1976); suggesting possible increased risk for individuals with high blood pressure or other cardiovascular problems with barium inhalation. Although inhalation of barium has been associated with only minimal lung effects (Doig, 1976; Essing et al., 1976), individuals with impaired lung function due to lung disease or smokers might experience increased respiratory symptoms upon exposure to high (mg) concentrations of inhaled barium.

Other information on factors increasing susceptibility to barium are limited to data from oral or parenteral administration. However, some or all may be relevant to the inhalation exposure route, since barium may be absorbed from the lungs. Oral and parenteral administration of barium has been shown to decrease serum potassium in humans and laboratory animals (Foster et al., 1977; Gould et al., 1973; Phelan et al., 1984; Roza and Berman, 1971); thus, individuals taking diuretics may have a severe hypokalemic reaction to barium absorption.

11.6.6 Cadmium

11.6.6.1 Chemical and Physical Properties

Cadmium is a metallic element found in Group 2B of the periodic table, which has possible valences of 0, +1, and +2; it forms almost all of its compounds in the +2 oxidation state. Rarely, the +1 oxidation state may be produced in the form of dimeric Cd_2^{2+} species. This species is unstable in water or other donor solvents, and dissociates to Cd^{2+} and Cd (Herron, 1992). Cadmium metal is slowly oxidized in moist air and when heated in air, it rapidly forms cadmium oxide (Carr, 1992). Cadmium exists in the environment as both inorganic salts and organocadmium compounds. Elemental cadmium and its most commonly encountered compound in ambient air, cadmium oxide (CdO) are both insoluble in water; whereas cadmium chloride ($CdCl_2$) and cadmium sulfide (CdS) are moderately water soluble.

11.6.6.2 Pharmacokinetics

Absorption and Distribution

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine particles; when inhaled, some fraction of this particulate matter is deposited in the airways or the lung, and the rest is exhaled. While some soluble cadmium compounds (cadmium chloride, cadmium oxide, and cadmium sulfate) may undergo limited absorption from particles deposited in the tracheobronchial region, the main site of absorption is the alveoli. No direct data are available on cadmium deposition, retention, or absorption in the human lung. However, the detection of cadmium in the kidney (Ellis et al., 1985; Roels et al., 1983) and in the urine (Elinder et al., 1985a, b; Jarup et al., 1988; Kawada et al., 1990; Smith et al., 1980; Thun et al., 1989) of occupationally exposed workers indicates that inhaled cadmium is absorbed.

Retention in the lung following cadmium inhalation has been reported as >40% in rats (Moore et al., 1973). Based on the estimated amount of cadmium inhaled in mice exposed to cadmium chloride, lung retention at an unspecified time of after exposure was 0.2 to 4% and whole body retention was 10.5 to 23% (Potts et al., 1950). Princi and Geever (1950) found that blood cadmium levels of dogs exposed to cadmium oxide were higher than those of dogs exposed to comparable levels and particle sizes of cadmium sulfide, consistent with the higher solubility and absorption of cadmium oxide in body fluids compared to cadmium sulfide (Princi and Geever, 1950). Glaser et al. (1986) exposed rats via inhalation to cadmium oxide (100 $\mu g/m^3$), cadmium chloride (100 $\mu g/m^3$), or cadmium sulfide (100 $\mu g/m^3$), and found the ratio of lung to kidney levels was higher for the sulfide than for the other two, suggesting increased pulmonary retention. Also, the oxide and chloride were distributed to the cytosolic compartment of lung tissue, while only $\approx$30% of cadmium sulfide was in the cytosolic compartment (Glaser et al., 1986).

Oberdörster and Cox (1989) exposed rats to cadmium chloride aerosol via nose-only inhalation and administered cadmium oxide or cadmium sulfide to rats via intratracheal instillation. The pulmonary retention half-time for all three compounds was shorter in rats (months) than for monkeys (years). The pulmonary retention half-time of cadmium chloride in rats was $\approx$85 days. Pulmonary retention of cadmium oxide dust in the rats was biphasic, with retention half-times of 9 days and $\approx$7 mo. Cadmium sulfide had a faster biphasic half

time of 11 and 76 days. It appears that the cadmium sulfide particles were retained in the lungs and cleared by the alveolar macrophages and mucociliary action. The results of Klimisch (1993) also suggest that inhaled cadmium compounds are more bioavailable to the kidney than are ingested ones. Biphasic clearances were also observed in the monkey. The order of long-term retention half-times in the monkey was cadmium oxide < cadmium chloride < cadmium sulfide. The authors suggested that cadmium sulfide dust, like other insoluble particles, is at least partly transported to the lymph nodes. Cadmium oxide clearance from rat lungs may occur via rapid bronchial clearance followed by a much slower alveolar clearance, due to impairment by cadmium-induced inflammation. Deposition of cadmium in the rat and human lung has also been modeled by Oberdörster (1989, 1991).

Absorbed cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure. Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with greatest concentrations in liver, kidney, pancreas, and vertebrae (Friberg, 1950). In workers dying from inhalation of cadmium, lung cadmium levels were somewhat lower than liver or kidney cadmium concentrations (Beton et al., 1966). The concentration of cadmium in liver of occupationally-exposed workers generally increases in proportion to intensity and duration of exposure (Davison et al., 1988; Ellis et al., 1985). The concentration of cadmium in kidney may rise more slowly after exposure (Gompertz et al., 1983) and begins to decline after the onset of renal damage at a critical concentration of 160 to 285 μg/g (Roels et al., 1981).

The amount of cadmium in the liver and kidney was much higher in rats following cadmium oxide exposure than following cadmium chloride exposure (Glaser et al., 1986). However, Oberdorster and Cox (1989) found significant kidney cadmium accumulation in rats following nose-only exposure to cadmium chloride. They also found liver and kidney Cd accumulation following intratracheal exposure to cadmium oxide dust but not cadmium sulfide dust exposure. The reason for the difference between the two studies is unclear.

Oberdörster (1990) described the distribution of Cd from the blood into the liver. Cd is then probably transported as Cd-metallothionein from the liver to the kidney, where it has a very long biological half time. Little is transported to the urine, except following significant

renal tubular damage. The liver is a major storage organ of the metal (Mason, 1990), and the kidney a well-defined target organ for Cd toxicity and storage.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood (Lauwerys et al., 1978). Accumulation of cadmium in the placenta at levels about six to seven times higher than maternal or fetal cord blood cadmium concentration has also been reported (Kuhnert et al., 1982).

Metabolism

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium(+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules.

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein, metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals, as well as organic compounds. Metallothionein binding decreases the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appears to be adequate to bind all cadmium accumulated (Goyer et al., 1989). When metallothionein-bound cadmium is transported to the kidney, it is readily diffusible and filterable at the glomerulus and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes, 1978). Cadmium-induced renal toxicity is probably associated with cadmium not bound to metallothionein (Goyer et al., 1989). Renal damage is believed to occur if the localization of cadmium or an excessive concentration of cadmium prevent it from becoming bound to metallothionein. The route of cadmium exposure does not appear to affect metallothionein metabolism in liver and kidney, although inhalation exposure induces metallothionein in the lung (Glaser et al., 1986; Hart, 1986).

Excretion

Braithwaite et al. (1991) studied 14 male workers (mean age 51 years) with mean occupational Cd exposure of 15 years. All subjects had been exposed to levels >50 $\mu g/m^3$;

urinary and blood analyses were performed and in-vivo liver and kidney cadmium measured using a neutron activation technique. Subjects were divided into two groups, those with >500 μg/g of ß-2-microglobin in the urine, and those with less. Subjects with elevated excretion of ß-2-microglobin had statistically significantly higher mean concentrations of cadmium in blood, urine, and liver, and a higher range of kidney cadmium burden. Strong correlations were evident between urinary cadmium concentration and kidney cadmium and estimated body burden of cadmium, supporting the theory that urinary excretion of cadmium derives mainly from the kidney following tubular damage. Although urinary cadmium is most frequently measured, most inhaled or ingested cadmium is excreted in the feces. This excreted cadmium represents mostly material that was swallowed, but not absorbed from the gastrointestinal tract.

Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; then, urinary cadmium excretion increases markedly (Roels et al., 1981). Bio/Dynamics Incorporated (1980) found that cadmium retention in rats was higher for soluble cadmium compounds (cadmium carbonate and cadmium oxide) than for insoluble cadmium pigments, and that excretion was much higher in the feces than in the urine.

Cadmium has a very-long biological half-life, that in humans is estimated to be 10 to 30 years in kidney and 4.7 to 9.7 years in liver (Ellis et al., 1985). Absorbed cadmium is rapidly cleared from plasma, and taken up by the erythrocytes. Transport in plasma occurs via proteins including albumin, globulins, transferrin and metallothionein. Urinary cadmium excretion plateaus at human exposures above 500 $\mu g/m^3 \times$ year, possibly because of renal saturation at this level and the inability of the kidney to further increase excretion (Smith et al., 1980)

11.6.6.3 Health Effects

Humans Data

As shown in Table 11-26, there is very strong evidence that the kidney and respiratory tract are the main target organs of cadmium toxicity.

TABLE 11-26. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
Acute Studies							
N/A	NS	5 hr accident	CdO fumes, dust	NS	Human (5) M	Case reports; symptoms, HP of lungs in one fatal case: Mild symptoms during exposure; cough, chest pain, dyspnea, fever at 4-10 hrs post-exposure and severe chest pain, wheezing, persistent cough at 8 hr-7 d. Cause of one death was pulmonary edema. Cd level for fatal case est at 7,500 μg/m^3. based on level in lungs.	Beton et al. (1966)
N/A	NS	1 hr accident	NS solder fumes	NS	Human (1) M	Case report; symptoms, x-ray: Up to 4 yrs post-exposure, dyspnea, cough, myalgia, fever. Initial chest x-ray showed infiltrates.	Barnhart and Rosenstock (1984)
Chronic Studies							
N/A	0 50	0-12 yr occup	CdO dust	"95% of CdO dust had a particle size (MMAD) <5 μm"	Human (87-240) B	Urinary ß-2m: Tubular proteinuria (defined as >95th percentile of normal population) was correlated with exposure duration. Workers employed 6-12 yr had 3.2 times the rate as those employed 0-3 yr. Prevalence of proteinuria was, 19% for workers with 6-12 yr exposure to $\approx$50 μg/m^3, compared with 3% in controls. Note: Concomitant exposure to nickel hydroxide.	Kjellstrom et al. (1977)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	see comments	>3 mo occup	CdO dust	NS	Human (326) M, (114) F	Proteinuria (beta-2-microglobulin): 1% proteinuria (i.e., nonresponse) at $<359\ \mu g/m^3 \times$ yr, 9% proteinuria at 359-1,710 yr $\times\ \mu g/m^3$ (avg 691 yr $\times\ \mu g/m^3$). Modeling predicted 4% proteinuria at cumulative exposure of 500 yr $\times\ \mu g/m^3$. Proteinuria defined as >97.5th percentile of normals. Majority of workers with tubular proteinuria had higher cum blood Cd than workers with same cum exposure, but no proteinuria, suggesting cum blood Cd is more sensitive than cum air Cd. This is the same cohort as Kjellstrom et al., 1977. Note: Cum exposure based on individual exposure and work area measurements	Jarup et al. (1988)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	20-45,200 dep on area	>6 yr median 25 yr occup	CdO dust, fume $CdSO_4$ mist	NS	Human (11-16) M	Medical evaluation, urinary Cd, creatinine clearance, uric acid, ß-2m; pulmonary function: High exposure group (urinary Cd 45.7 μg/L; >6 yr at >200) had dec creatinine clearance, inc uric acid and ß-2m excretion compared to the low exposure group (urinary Cd 13.1 μg/L; not worked in areas with fume or dust exposure). Also dec tubular reabsorption of phosphorus, dec plasma bicarbonate in high exp group. When divided by total exp subgroups, no effect on ß-2m excretion at <700 μg/m^3 × yr; 15% incidence of ß-2m-uria at 700-3,500 μg/m^3 × yr. No sig decline of FVC with total exposure. Note: Individual TWA exposure calculated from personal and area sampling and adjusted for use of respirators.	Smith et al. (1980)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	3-1,500	1-46 yr occup	CdO dust, fumes; $CdSO_4$ mist	NS	Human (82) M	Urinary total protein, ß-2m, kidney and liver Cd content measured by *in vivo* NAA: Liver Cd significantly correlated with exposure. Renal abnormality observed in most workers with liver Cd levels >40 ppm and exposure >400-500 $\mu g/m^3 \times$ yr. Avg kidney concentration for active workers was 230 ppm and 125 ppm in those with abnormal and normal kidney function, respectively. TWE (in $\mu g/m^3 \times$ yr): Normals: 0.105 (active), 0.379 (retired); Proteinuria: 1.69 (active), 3.14 (retired). A logistic model predicted 7% proteinuria at an exposure of 100 $\mu g/m^3 \times$ yr.	Ellis et al. (1985)
N/A	3-1,166	19 yr geom mean occup	Cd, CdO, CdS dust or fume	NS	Human (45) M	Blood pressure, urinary Cd, ß-2m, RBP, calcium, phosphate: Inc kidney stones, hypertension, prostatic disease. Inc excretion of ß-2m and RBP in exposed group, dec tubular reabsorption of calcium, phosphorus. No enzymuria (indicator for tubular epithelium necrosis). Small inc in mean serum creatinine, indicating glomerular dysfunction. Using logistic regression to model prevalence of renal abnormalities, sharp increase at 300,000 $\mu g/m^3 \times$ days (820 $\mu g/m^3 \times$ yr). Note: Exposure generally dec with time. Cumulative exposure est based on work history, adjusted by 0.25 for times and areas where respirators used.	Thun et al. (1989); followup to Ellis et al. (1985) and Smith et al. (1980)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	7-390 (TWA)	1-14 yr occup ave 3.7 yr	NS NiCd battery manu-facture	NS	Human (65) F	Urinary ß-2m and NAG, serum creatinine and urea: Urinary ß-2m and NAG correlated with blood Cd. Age-adjusted urinary NAG sig inc at urinary Cd > 3 μg/g creatinine.	Chia et al. (1989)
N/A	0, 340-600	1-39 yr occup	CdO dust	NS	Human (75) M	Kidney function (several measures) in copper-cadmium workers: Several measures of kidney function fit a threshold model versus exposure. Total protein, retinol binding protein, albumin, and ß-2m had a threshold est at 1,100 μg/m^3 × yr. Tubular resorption of urate and phosphate had higher thresholds. Measures (creatinine clearance, serum creatinine, ß-2m) of glomerular filtration rate (GFR) indicated a reduction in GFR with exposure, but there was no a well-defined threshold. Tubular proteinuria incidence inc at exposure >1,000 μg/m^3 × yr.	Mason et al. (1988)
N/A	0 10-200	4-24 yr occup	NS solder fumes	NS "respirable cadmium"	Human (58) M, (2) F	Medical history, urinary Cd, ß-2m, other proteins, GFR: No difference from controls in subjective complaints or incidence of kidney stones. However, within the exposed group, kidney stones sig more common among those with urinary Cd >6.3 nmol/mmol creatinine than among those with lower levels. Excretion of ß-2m, orosomucoid, and albumin correlated with Cd. For ß-2m, apparent threshold at 9nmol Cd/mmol creatinine. Avg GFR sig less than expected.	Elinder et al. (1985a)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 95-19,580 (avg 520)	4-24 yr occup	NS solder fumes	NS "respirable cadmium"	Human (58) M, (2) F	Urinary Cd, ß-2m: Cumulative Cd exposure est at 350-900 μg/m^3 × yr. A few cases with slight tubular proteinuria at <1,000 μg/m^3 × yr; at >3,000 μg/m^3 × yr, 74% prevalence of slight ß-2m-uria, and 54% prevalence of pronounced ß-2m-uria. Proteinuria did not reverse after exposure ended and two subjects developed proteinuria after cessation of exposure. Note: Exposure levels are from personal samplers on workers using cadmium-containing solders.	Elinder et al. (1985b)
N/A	0 3-350 (range) 0.18 and 3.0 (avg)	Avg 10.4 yr occup	NS cadmium pigment dust	NS "respirable cadmium"	Human (9-53) NS	Urinary Cd, ß-2m, NAG, metallothionein: Cd in urine correlated better with urinary metallothionein than the other two proteins. ß-2m was unaffected at this level of exposure, which resulted in urinary Cd geometric mean of 1.02 μg/g creatinine. Note: Avg exposure levels reported separately for two different job categories.	Kawada et al. (1990)
N/A	NS	NS	NS smelter	NS	Human (36-40) M	Urinary Cd, NAG, AAP, GGT: NAG and AAP sig elevated in exposed group. Based on probit modeling based on data grouped by Cd level, 10% chance of elevated NAG value at 6.3 μg Cd/g creatinine and 10% chance of elevated AAP value at 5.0 μg Cd/g creatinine.	Mueller et al. (1989)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 390 110 (avg of different areas)	≥21 yr occup	NS Brazing fumes	NS	Human (33-41) M	Incidence of proteinuria: Overall incidence of proteinuria was 21% in exposed group, and ave exposure of cohort was 780 μg/m^3 × year. Mean cumulative exposure of workers with normal and abnormal renal function was 459 and 1,137 μg/m^3 × year, respectively.	Falck et al. (1983)
N/A	NS	10.4 yr avg occup	Cd form not stated	NS	Human (58) M	Urinary Cd, transferrin, albumin, ß-2m, retinol binding protein, and other proteins: Elevated ave urinary levels of transferrin, albumin an ß-2m, compared to controls. Prevalence of inc levels sig only for transferrin and albumin, HMW proteins. Cd: 6.23 μg/g creatinine (range, 0.87-165).	Bernard et al. (1990)
N/A	0 50 150 500	5-24 yr avg 14 yr occup	NS solder fumes	NS "respirable cadmium"	Human (31-57) B (2) F	Pulmonary function, kidney function: Proteinuria found in 42% of the entire exposed cohort several years after exposure ceased, and inc with duration of exposure. No effect on pulmonary function (FVC, FEV_1, etc.) in any group of workers exposed to cadmium-containing solders for 5-24 years. Control for smoking and renal damage did not change lack of effect. Main body of information in Elinder et al. (1985a,b). Exposed group was divided into high, medium, and low, and ave exposure estimated for each group.	Edling et al. (1986)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 36-600	≥1 yr occup	"Cd fume" Cu-Cd alloy manufctr	NS	Human (101) M	Pulmonary function (FEV_1, FVC, TLCO), x-ray, liver cadmium (NAA analysis): Exposed workers had sig lower FEV_1, FVC, TLCO compared to referents; the effect was related to cum exposure and to liver cadmium. Reduction in FEV_1 was seen at cum exposure as low as $<400\ \mu g/m^3 \times$ yr and at liver Cd <12.5 ppm; no statistical test of these groups alone was conducted. Note: Exposure levels est based on area and breathing zone measures.	Davison et al. (1988)
N/A	0, "low", >200	≥6 yr median: 26.4 yr (low), 27.1 yr (high) occup	Cd fume, Cd sulfate aerosol	NS	Human (12-17) M	Pulmonary function, urinary Cd: Workers with high exposure had dec FVC compared with low exposure workers and controls. No effect on FEV_1. Chest x-rays showed interstitial fibrosis in 29% of exposed workers. Dec FVC was inversely correlated with urinary Cd, and with months of work in Cd fume, but not Cd sulfate areas. Avg urinary Cd was 13.1 $\mu g/L$ in "low" group and 45.7 $\mu g/L$ in >0.2 group.	Smith et al. (1976)
N/A	30 40 90	1-11 yr ave 5, 8 yr occup	CdO dust	NS	Human (8) M, (36) F	Recovery of lung function after reduction or cessation of exposure in cadmium battery workers, medical history: Total lung capacity inc after reduction of exposure. After cessation of exposure, vital capacity, FEV, prevalence of respiratory symptoms improved. Two subcohorts: reduced exposure and no longer exposed	Chan et al. (1988)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	1-356 (total dust), max resp dust = 650	4.4 yr ave (F) 7.5 yr ave (I) 27.5 yr (II)	CdO dust and fume	NS	Human (90) M (grp I) (25) M (grp II) (26) F	Pulmonary function (FVC, MEFR, PEFR); chest x-ray, urinary Cd, ß-2m: F workers exposed only in one area, to 10 (total [apparently Cd] dust), 4 (respirable dust). No effect on lung or kidney function in this group. Group I (M), exposed <20 yr, had slight (~6%), stat. sig dec in FVC, FEV_1, PEFR, but no sig effect on urinary proteins. Group II (M), exposed >20 yr, had inc frequency of cough, mod (9-12%) dec in FVC, FEV_1, PEFR, proteinuria (inc HMW protein and/or LMW protein), dec hematocrit.	Lauwerys et al. (1979)
N/A	50-350	>20 yr ave 32 yr	CdO dust and fume	NS	Human (18) NS	Chest x-ray, pulmonary function, urinary protein: Grade I dyspnea more frequent in exposed group. Slight, but nonsig dec in spirometric indices (FEV_1, PEFR, VC, etc.). Proteinuria in 7/18 workers, suggesting kidney is more sensitive than lung.	Lauwerys et al. (1979)
N/A	NS	14.5 yr ave occup	Cd fume	NS	Human (31) M	Urinary Cd, IQ, attention, psychomotor speed, vigilance, memory, conceptual reasoning, mood: High urinary Cd cohort performed less well than low urinary Cd group on measures of attention, psychomotor speed, memory Note: Historical level of ≈300 μg/m^3 reported in one measure.	Hart et al. (1989b)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	mean 808 $\mu g/m^3$ × yr	>1 yr	CdO fume	NS	Human (101) M	Serum testosterone, LH, FSH; urinary Cd: No effect on testicular endocrine effects. RBP, creatinine in urine correlated with cumulative exposure index. Reproductive function was not assessed.	Mason (1990)
N/A	7,000-1,500,000 dep on area	>6 mo	CdO dust	NS	Human (590) M	Mortality, cohort study: Sig inc cancer of the respiratory system (lung, trachea, bronchus) (SMR = 165) and nonmalignant gatrointestinal disease (not correlated with exp) (SMR = 383). Lung cancer mortality sig inc with cum exp. Note: Some workers also exposed to arsenic.	Thun et al. (1985)
N/A	20,000-1,000,000	>1 yr	CdO dust	NS	Human (522) M	Mortality, cohort study: Inc deaths due to nephritis and nephrosis, related to exposure duration (SMR=300). SMR for lung cancer = 133 (not sig), SMR for prostate cancer = 108. SMR inc with latency period. Based on combining data from 6 populations, SMR for lung cancer = 1.21, p = 0.008, prostate cancer SMR=162, p=0.02. Note: Exposure levels were lower at later measurement periods; coexposure to nickel.	Elinder et al. (1985c)

TABLE 11-26 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	NS	<2-≥15 yr occup	CdO (cadmium hydroxide dust)	NS	Human (2559) M, (466) F	Mortality lung cancer deaths: Trend in lung cancer deaths approached significance among early workers, but only because of sig excess at high exposure. Among later workers, no trend was found. Note: No control for smoking.	Sorahan (1987)

Abbreviations:

avg = average; AAP = alanine aminopeptidase (brush border enzyme); ALKP = alkaline phosphatase; AM = alveolar macrophages; AP = acid phosphatase; B = both male and female; ß-2m = ß-2-microglobulin; ß-2m-uria = ß-2-microglobulinuria; BAL = bronchoalveolar lavage; Cd = cadmium; $CdCl_2$ = cadmium chloride; CdO = cadmium oxide; CdS = cadmium sulfide; $CdSO_4$ = cadmium sulfate; cum = cumulative; d = day; dec = decreased; dep = depending; EM = electron microscopy; exp = exposure; est = estimated; FEV_1 = forced expiratory flow in 1 second; FSH = follicle stimulating hormone; FVC = forced vital capacity; GFR = glomerular filtration rate; geom = geometric; GFR = glomerular filtration rate; GGT = gamma glutamyltranspeptidase; HMW = high molecular weight; hr = hour; HP = histopathology; inc = increased; LDH = lactate dehydrogenase; LH = luteinizing hormone; LMW = low molecular weight; MEFR = maximal expiratory flow rate; MMAD = mass median aerodynamic diameter; mo = month; N/A = not applicable; NAA = neutron activation analysis; NAG = N-acetyl-D-glucosaminidase; NS = not specified; occup = occupational; PEFR = peak expiratory flow rate; PMN = polymorphonuclear cells; ; ppm = parts per million; ; RBC = red blood cell; RBP = retinol binding protein; sig = significant(ly); SRBC = sheep red blood cells; TWA = time weighted average; TWE = cumulative exposure index; TLCO = carbon monoxide transfer factor; UK = unknown, document in retrieval; VC = vital capacity; VMD = volume median diameter; wk = week; wt = weight; yr = years.

Signs of renal damage have been observed in several studies of workers occupationally exposed to cadmium (Chia et al., 1989; Elinder et al., 1985a, 1985b; Falck et al., 1983; Kjellstrom et al., 1977; Mason et al., 1988; Smith et al., 1980; Thun et al., 1989). The proteinuria caused by cadmium exposure is characterized by the presence in urine of a number of low-molecular-weight proteins, including $ß_2$-microglobulin, lysozyme, and retinol binding protein. These low-molecular-weight proteins are all readily filtered by the glomerulus and are normally reabsorbed in the proximal tubule of the kidney. Therefore, elevated urinary excretion of these proteins is symptomatic of proximal tubular damage. Urinary excretion of high-molecular-weight proteins such as albumin also occurs in occupationally exposed workers (Bernard et al., 1990; Elinder et al., 1985b; Mason et al., 1988; Thun et al., 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al., 1990) or severe tubular damage (Elinder et al., 1985a; Mason et al., 1988). The tubular proteinuria caused by cadmium exposure may be accompanied by depressed tubular resorption of other solutes such as enzymes, amino acids, glucose, calcium, copper, and inorganic phosphate (Elinder et al., 1985a,b; Falck et al., 1983; Mason et al., 1988). The urinary concentrations of some of these compounds, particularly renal enzymes, has been suggested to be more sensitive than low-molecular-weight proteins for detecting tubular dysfunction in exposed humans. An additional renal effect seen in workers after high levels of cadmium inhalation exposure is increased frequency of kidney stone formation (Elinder et al., 1985a; Falck et al., 1983; Thun et al., 1989); likely secondary to disruption of calcium metabolism due to kidney damage.

Tubular dysfunction generally develops only after cadmium reaches a minimum threshold level or "critical concentration" in the renal cortex. The critical concentration of cadmium in renal cortex associated with increased incidence of renal dysfunction in an adult human population chronically exposed to cadmium has been estimated to be about 200 μg/g wet weight by several investigators (Ellis et al., 1985; Roels et al., 1983).

Several quantitative evaluations of kidney toxicity have been performed using cumulative dose (exposure duration times cadmium concentration) as the independent variable. An early study found a, 19% prevalence of proteinuria after 6 to 12 year exposure to 50 $\mu g/m^3$ (Kjellstrom et al., 1977), but a subsequent follow-up study found only a 4% prevalence at about this level of exposure (Jarup et al., 1988). The definition of proteinuria

used in these studies is an excretion exceeding 95th percentile of a normal population. Thus a prevalence of 5% or less can be considered unrelated to cadmium exposure. Among the workers in the follow-up study, the prevalence of proteinuria was 9% at an average cumulative exposure of 691 year × $\mu g/m^3$ (Jarup et al., 1988). Other recent analyses found thresholds for proteinuria at 820 $\mu g/m^3$ × year (Thun et al., 1989) or ≈1 mg/m^3 × year (Elinder et al., 1985b; Mason et al., 1988). In another cohort, with an average 30-year exposure of 26 $\mu g/m^3$, the average exposures of workers with and without proteinuria were 459 and 1,137 $\mu g/m^3$ × year, respectively (Falck et al., 1983).

Cessation of cadmium exposure generally does not lead to any decrease in proteinuria in occupationally-exposed workers (Elinder et al., 1985b; Mason et al., 1988; Thun et al., 1989), possibly because kidney cadmium levels decline very slowly postexposure. In fact, recent evidence shows that kidney damage may be induced after exposure ceases. Elinder et al. (1985b) observed the development of proteinuria in workers after exposure cessation.

The respiratory tract is also a major target of cadmium, with intense irritation resulting from acute high-level exposure; lower-level chronic exposure produces dyspnea and decreased lung function. Data on effects of acute inhalation exposure to cadmium are very limited. However, based on secondary sources, World Health Organization (1987) reported that chemical pneumonitis is expected at cadmium fume concentrations above 1,000 $\mu g/m^3$. High levels of cadmium oxide fumes or dust are intensely irritating to respiratory tissue, producing severe tracheobronchitis, pneumonitis, and pulmonary edema within several hours (Beton et al., 1966). Repeated exposure within one to two days does not cause recurrent symptoms; however, if the repeated exposure occurs several days later, symptoms may reoccur (Barnhart and Rosenstock, 1984).

Emphysema and dyspnea are the major symptoms of chronic cadmium exposure (Friberg, 1950). However, this study included no control for cigarette smoking. Some recent studies that controlled for smoking have found that cadmium-exposed workers had evidence of lung impairment in pulmonary function tests (Chan et al., 1988; Davison et al., 1988; Smith et al., 1976), but similar studies have found no impairment (Edling et al., 1986). One possible reason for the conflicting results is that lung injury caused by high-level cadmium exposure may be partially reversible (Chan et al., 1988), so that several years after exposures have been significantly reduced, lung function may be close to normal.

Although neurotoxicity is not generally associated with cadmium inhalation exposure, few studies have specifically assessed neurological effects. A recent study found decreased performance on measures of attention, psychomotor speed, and memory in a cohort with high urinary cadmium, compared to a group with lower cadmium exposure (Hart et al., 1989b).

The relationship between occupational exposure to cadmium and increased risk of cancer (particularly lung and prostate cancer) has been explored in a number of epidemiologic studies. The data are conflicting, and confounding factors such as exposure to other metal carcinogens and smoking may explain observed increases in cancer rates. Overall, the results provide weak evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium.

Recent analyses of English and Swedish cohorts have found some increases in lung cancer at levels >300 $\mu g/m^3$, but no clear relationship between lower levels and duration of cadmium exposure and increased risk of lung cancer (Elinder et al.,, 1985c; Sorahan, 1987). In an American cohort, a statistically significant 2.8-fold excess risk of lung cancer was found in the highest exposure group (cumulative exposures greater than 8,000 $\mu g/m^3$ $\times$ years) and an exposure-related trend was observed (Thun et al., 1985). In the Swedish study, some workers were also exposed to nickel, a known human lung carcinogen (Elinder et al., 1985c). Smoking was not corrected for in the analysis of any cohort. A small excess of prostate cancer has also been observed in studies of men occupationally exposed to cadmium, but appears to be limited to groups with very high cadmium exposures (Elinder et al., 1985c).

Laboratory Animal Data

Laboratory animal toxicity data are summarized in Table 11-27. Data from an early animal study confirm that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after 4 mo of inhalation exposure, and histologic lesions were found after an additional 3 to 4 mo of exposure (Friberg, 1950). Subsequent studies that assessed urinary protein levels found no effect, presumably because the exposure levels and durations of follow-up prior to sacrifice were insufficient to produce a critical concentration in the kidney (Glaser et al., 1986; Prigge, 1978a).

TABLE 11-27. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
Acute Studies							
N/A	0 250 450 4,500	2 hr	$CdCl_2$ aerosol	250: MMAD=0.50, σ_g=2.07 480: MMAD=0.63, σ_g=2.00 4,500: MMAD=0.56, σ_g=2.39	Rat, Crl:CD (SD)BR (16-20) M	HP of lung: At 4,500 $\mu g/m^3$, no lesions at 0 hr post-exposure, but at 72 hr, pneumonitis characterized by proliferation of Type II epithelial cells, hemorrhage, edema, and inc macrophage populations. Pneumonitis more severe following CdO than $CdCl_2$ exposure.	Grose et al. (1987)
N/A	0 250 450 4,500	2 hr	CdO aerosol	250: MMAD=1.28, σ_g=1.47 450: MMAD=1.33, σ_g=1.45 4,450: MMAD=1.56, σ_g=1.54	Rat, Crl:CD (SD)BR (16-20) M	HP of lung: At 4,500 $\mu g/m^3$, no lesions at 0 hr post-exposure, but at 72 hr, pneumonitis characterized by proliferation of Type II epithelial cells, hemorrhage, edema, and inc macrophage populations. Pneumonitis more severe following CdO than $CdCl_2$ exposure.	Grose et al. (1987)
N/A	0 250 450 4,500	2 hr	$CdCl_2$ aerosol	250 MMAD=0.50, σ_g=2.07 450: MMAD=0.63, σ_g=2.00 4,500: MMAD=0.56, σ_g=2.39	Rabbit, DLA: (NZW) (2-4) M	HP of lung: At 4,500 $\mu g/m^3$, moderate thickening of alveolar wall at 0 hr and mild multifocal pneumonitis at 72 hr post-exposure.	Grose et al. (1987)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 250 450 4,500	2 hr	CdO aerosol	250: MMAD=0.50, σ_g=2.07 450 MMAD=0.63, σ_g=2.00 4,500 MMAD=0.56, σ_g=2.39	Rabbit, DLA: (NZW) (2-4) M	HP of lung: At 4,500 $\mu g/m^3$, slight increase in macrophages at 0 or 72 hr. At 4,500 $\mu g/m^3$, mild multifocal pneumonitis at 72 hr post-exposure.	Grose et al. (1987)
N/A	0 5,000	1 hr	$CdCl_2$ aerosol	MMAD = 1.4 μm σ_g = 1.8	Rat, Long Evans (7) M	Lung wt, HP, EM; BAL fluid analysis: Pulmonary edema, accompanied by sig. dec ALKP levels 24 hrs post-exposure. ALKP was sig inc on day 4. Superoxide dismutase, glucose-6-phosphate dehydrogenase, lysosomal enzymes inc.	Boudreau et al. (1988)
N/A	0 6,500	1 hr	$CdCl_2$ aerosol	"diameter 1.1 μm"	Rat, UK (6) M	HP of resp tract: Mild pulmonary edema at 24 hrs, severe interstitial inflammation by day 5, recovery except for a few foci of mild inflammation by day 11. Cd lung content had a half-time of 27 d.	Bus et al. (1978)
N/A	0 500 5,300	3 hr	CdO aerosol	500: MMAD=0.26, σ_g=2.31 5,300: MMAD=0.33, σ_g=3.18	Rat, Wistar (4) M	Lung HP, BAL fluid: Mild inflammation, inc AM, and epithelial hyperplasia at 500 $\mu g/m^3$; lesions repaired at 7-15 d post-exposure. At 5,300 $\mu g/m^3$, damage more severe, and not entirely repaired at 15 d. Inc dehydrogenase activities related to antioxidant defenses and lung repair at both levels.	Buckley and Bassett (1987)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 10,000	1 hr/d 5-15 d	$CdCl_2$ form UK	"mean diameter = 3.5 μm" σ_g UK	Rat, UK (8) M	HP of lung: Acute vascular congestion, alveolar hemorrhage, and PMN cell proliferation. Granulation tissue response resulted in fine scar tissue resembling human centrilobular emphysema.	Snider et al. (1973)
N/A	0 1,100 10,100	30 min	$CdCl_2$ aerosol	MMAD = 1.7 μm σg = 1.7	Hamster, Syrian (8) NS	HP of lung, BAL fluid analysis: Inflammation (BAL showed inc nucleated cell number and AP at both levels, ALKP activity at high level) at 2 hr to 3 wk post-exposure. HP (done only at high level) showed nothing immediately, but necrosis of bronchiolar epithelium at 1 d after exposure. Also lymphatic infiltration of bronchiolar walls) but no effect on alveoli.	Henderson et al. (1979)
N/A	0 88,000	1 hr	$CdCl_2$ aerosol	MMAD = 0.7 μm σg = 3.43	Mouse, C57Bl/6 (10) F	Immune response: At 5-18 d post-exposure, dec primary IgM response. Dec spleen cell viability.	Krzystyniak et al. (1987)
N/A	0 110 190	2 hr	$CdCl_2$ aerosol	$\geq$99% of particles $\leq$3 μm	Mouse, CD-1 (17) F	Immune response to SRBC injected 2 hr post exposure: Dec IgM level in spleen cells at 4 d post-exposure.	Graham et al. (1978)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
Subchronic and Chronic Studies							
N/A	0 300 1,000 2,000	6 hr/d 5 d/wk 62 d	$CdCl_2$ aerosol	300: VMD=0.66, σ_g=1.10; 1,000 and 2,000: VMD=0.73, σ_g=1.15	Rat, F344 (8) M, (8) F	Organ wt, HP of lung, reproductive fitness (exposed rats mated with unexposed rats 6 d after last exposure): Hyperplasia of terminal bronchioles, cell flattening, inflammation and proliferation of fibroblasts at $\geq$300 $\mu g/m^3$. At 1,000 $\mu g/m^3$, also lymphoid hyperplasia, microgranulomas, inc lung wt due to inc elastin and collagen. All animals died at 2,000 $\mu g/m^3$. No effect on viable embryos, late deaths, resorptions, corpora lutea, preimplantation loss.	Kutzman et al. (1986)
N/A	0 1,600	3 hr/d 5 d/wk 1-6 wk	CdO aerosol	Aerodynamic diameter determined by EM was 1.76 μm particle size variability averaged 7-10%	Rat, Lewis (15) M	BAL, HP of lung: Lung damage indicated by cytologic and biochemical alterations in BAL fluid (e.g., inc ALKP, AP, LDH, protein, PMNs). Aggregates of PMNs in interstitium, thickening of alveolar septa at 2 wks of exposure. Effects peaked at 2 wks of exposure, then decreased.	Hart (1986)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 1,600	3 hr/d 5 d/wk 4 wk	CdO aerosol	Aerodynamic diameter determined by EM was 1.76 $\pm$0.04 μm	Rat, Lewis (20) M	BAL analysis, HP of lung: Lung damage indicated by cytologic and biochemical alterations in BAL (e.g., inc Type 2 pneumocytes, lymphocytes, PMNs, nonprotein sulfhydryl, inc ALKP, AP, LDH). No effect of 1,600 $\mu g/m^3$ alone on HP, but pre-exposure dec effects (diffuse alveolitis, edema) of challenge with 8,400 $\mu g/m^3$. Hypothesized adaptive synthesis of metallothionein. BAL changes in challenged animals were lower in those that had been pretreated. Note: measured effects after single 3-hr challenge with to 8,400 $\mu g/m^3$.	Hart et al. (1989a)
N/A	0 100	22 hr/d 7 d/wk 30 d	$CdCl_2$ aerosol	MMAD = 0.29 μm σ_g = 1.56	Rat, Wistar (6) M	BAL analysis, RBC count, serum alanine aminotransferase levels, urinary protein: Inc number and size of macrophages, returning to normal 2 mo post-exposure. No effect on other parameters.	Glaser et al. (1986)
N/A	0 100	22 hr/d 7 d/wk 30 d	CdO aerosol	MMAD = 0.24 μm σ_g = 1.44	Rat, Wistar (6) M	BAL analysis, RBC count, serum alanine aminotransferase levels, urinary protein: Inc number and size of macrophages, returning to normal 2 mo post-exposure. Inc serum alanine aminotransferase. No effect on other parameters.	Glaser et al. (1986)
N/A	0 1,000	22 hr/d 7 d/wk 30 d	CdS aerosol	MMAD = 0.21 μm σ_g = 1.48	Rat, Wistar (6) M	BAL fluid analysis, RBC count, serum alanine aminotransferase levels, urinary protein: Inc number and size of macrophages, returning to normal 2 mo post-exposure. No effect on other parameters.	Glaser et al. (1986)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 25 50 100	23.5 hr/d 63-90 d 100 $\mu g/m^3$ exposure for 63 d	$CdCl_2$ aerosol	Median aerodynamic diameter = 0.19 μm σ_g = 1.5	Rat, Wistar (12) F	HP of lungs, liver, kidney; urinalysis, hematology: Bronchiolar proliferation, emphysematic areas, xanthoma cell areas, histiocytic cell granulomas at all levels. Inc hemoglobin and hematocrit at $\geq$50 $\mu g/m^3$. No liver or kidney lesions or proteinuria Kidney cadmium = 32.88 ppm wet wt at 100 $\mu g/m^3$.	Prigge (1978a)
N/A	0 4,100 5,700	3 hr/d 21-23 d/mo 7-9 mo	Mostly CdO dust	$\approx$95% of particles <5 μm, $\approx$55% <1 μm	Rabbit, UK (8-9) M, (4) F	HP of lung, kidney; urinalysis, hematology (4,100 $\mu g/m^3$ only): Concentration-related incidence and severity of bronchitis, fibrosis, edema, and emphysematous changes. Slight anemia and eosinophilia at 4,100 $\mu g/m^3$. Significant proteinuria after 4 mo exposure, with histologic renal lesions (isolated foci, interstitial infiltrates) at 7-9 mo. Note: Dust also contained $\approx$20% iron and small amounts of Si and Ni.	Friberg (1950)
N/A	0 400	6 hr/d 5 d/wk 4-6 wk	$CdCl_2$ aerosol	MMAD 0.5-1 μm	Rabbit, NS (8) M	HP of lung: Inc lung wt, interstitial infiltration of PMNs and lymphocytes, intra-alveolar accumulation of large, vacuolated macrophages, inc phospholipid content.	Johansson et al. (1984)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 20 160	5 hr/d 5 d/wk 5-6.5 mo	CdO aerosol	MMAD <0.65 μm 99.2% of total aerosol mass had particle size <4.7 μm	Rat, Wistar (7-15) F	Behavioral tests of pups (forepaw muscle strength, exploratory activity, conditioned learning); pup viability: No effect on no. pups/litter, but pup viability dec at 20 μg/m^3. Dec exploratory activity in both sexes at 160 μg/m^3, and in males at 20 μg/m^3. Conditioned learning dec in females at 160 μg/m^3 at 3 and 7 mo. Dec ambulation in open field in males at 160 μg/m^3. Note: Dams exposed for 5 mo prior to mating, during mating, and during gestation.	Baranski (1984)
N/A	0 20 160 1,000	5 hr/d 5 d/wk 4-5 mo	CdO aerosol	Fraction <5 μm was 98.3-99.4% of total dust mass	Rat, Wistar (5-16) F	Developmental toxicity, including neurotoxicity; maternal toxicity: No effects on reproductive: Delayed ossification at all levels. Dec locomotor activity and conditioned reflex at up to 4 mo of age at all levels. No effect on reproductive success at $\leq$160 μg/m^3. At 1,000 μg/m^3, sig fewer pregnancies and inc mortality. Note: Dams exposed for 4-5 mo prior to mating, during mating and during gestation	Baranski (1985)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 20 160 1,000	5 hr/d 5 d/wk 20 wk	CdO aerosol	Fraction <4.7 μm was 98.3-99.4% of total aerosol mass	Rat, Wistar (13-14)	Length of estrous cycle: Estrous cycle sig lengthened compared to pre-exposure at all exposure levels, but not in controls. Longer estrous cycle compared to control rats at same age seen only at 1,000 $\mu g/m^3$. All rats died by 20 wk at 1,000 $\mu g/m^3$.	Baranski and Sitarek (1987)
N/A	0 200 400 600	24 hr/d 21 d	$CdCl_2$ aerosol	Median aerodynamic diameter = 0.6 μm σg = 1.6	Rat, Wistar (12) F	Maternal wt gain, fetal body wt, urinalysis, HP of lung, serum biochemistry: Maternal wt gain significantly dec at all levels. Fetal body wt significantly dec at 600 $\mu g/m^3$. Liver Cd in dams and fetuses were 3265 and 40.4 ng/g wet wt, respectively, at 400 $\mu g/m^3$. Dec serum ALKP in dams at all levels and in fetuses at 600 $\mu g/m^3$. No proteinuria. Mild bronchiolitis at 200 $\mu g/m^3$.	Prigge (1978b)
N/A	0 13.4 25.7 50.8	23 hr/d 7 d/wk 18 mo	$CdCl_2$ aerosol	MMAD = 0.55 μm σg = 1.8	Rat, Wistar (40) M	HP of lung: Adenomatous hyperplasia in the bronchioalveolar area in 1/41 control rats, and 6/40, 5/40, 3/40 in low-, mid-, and high-concentration groups. Due to lack of a concentration-response, not clear if the effect was exposure related. Concentration-related incidence of lung tumors (0%, 15%, 53%, 71%). Types were epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas.	Takenaka et al. (1983)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cd/m^3$						
N/A	0 30 90	22 hr/d 7 d/wk 18 mo (0.03) or 6 mo (0.09)	$CdCl_2$ aerosol	avg MMD of 0.2-0.5 μm σ_g NS	Rat, Wistar (20) M, (20) F	HP of lung: Lung tumors (bronchioalveolar adenoma, adenocarcinoma, squamous cell tumors) at $\geq$0.03 in both sexes. Note: Exposure for only 6 mo at 90 $\mu g/m^3$ due to toxicity. Animals observed for 12 (30 $\mu g/m^3$) or 18 (90 $\mu g/m^3$) mo post-exposure.	Oldiges et al. (1989)
N/A	0 90	22 hr/d 7 d/wk 18 mo	$CdSO_4$ aerosol	avg MMD of 0.2-0.5 μm σ_g NS	Rat, Wistar (20) M, (20) F	HP of lung: Lung tumors (bronchioalveolar adenoma, adenocarcinoma, squamous cell tumors) in both sexes. Note: Animals observed for 12 mo post-exposure	Oldiges et al. (1989)
N/A	0 90 270 810 2,430	22 hr/d 7 d/wk 18 mo	CdS aerosol	avg MMD of 0.2-0.5 μm σ_g NS	Rat, Wistar (20) M, (20) F	HP of lung: Lung tumors (bronchioalveolar adenoma, adenocarcinoma, squamous cell tumors) at 90 $\mu g/m^3$ in both sexes and at 270, 810, and 2,430 for shorter durations (3-16 mo). Note: Total exposure + post-exposure observation time 27-30 mo.	Oldiges et al. (1989)
N/A	0 30 90	22 hr/d 7 d/wk 18 mo	CdO dust	avg MMD of 0.2-0.5 μm σ_g NS	Rat, Wistar (20) M, (20) F	HP of lung: Lung tumors (bronchioalveolar adenoma, adenocarcinoma, squamous cell tumors) at both levels in both sexes. Similar tumors were also observed in animals exposed 40 hr/wk for 6 mo. Co-exposure to ZnO dust. Note: In main exp, exp to 90 $\mu g/m^3$ for 7-11 mo. Exposure + post-observation time 31 mo.	Oldiges et al. (1989)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 10 30	22 hr/d 7 d/wk 18 mo	CdO fume	"primary CdO particles in the size range of 10 nm"	Rat, Wistar (20) M, (20) F	HP of lung: Lung tumors (bronchioalveolar adenoma, adenocarcinoma) at 30, but not at 10 μg/m^3 in both sexes. Note: Exposure + post-exposure observation time 31 mo.	Oldiges et al. (1989)
N/A	0 30 90	8 or, 19 hr/d 5 d/wk 42-69 wk	$CdCl_2$ aerosol	NS	Mouse, Han: NMRI (82-89) F	HP of lung: Inc incidence of alveolar lipoproteinosis, interstitial fibrosis, bronchoalveolar hyperplasia. No effect on lung tumors, or on probability of dying with a lung tumor in life table analysis to correct for shorter lifespan of exposed animals.	Heinrich et al. (1989)
N/A	0 30 90	8 or, 19 hr/d 5 d/wk 95-96 wk	$CdSO_4$ aerosol	NS	Mouse, Han: NMRI (95-96) F	HP of lung: Inc incidence of alveolar lipoproteinosis, interstitial fibrosis, bronchoalveolar hyperplasia. No effect on lung tumors, or on probability of dying with a lung tumor in life table analysis to correct for shorter lifespan of exposed animals.	Heinrich et al. (1989)
N/A	0 90 270 1,000	8 or, 19 hr/d 5 d/wk 41-64 wk	CdS aerosol	NS	Mouse, Han: NMRI (71-101) F	HP of lung: Inc incidence of alveolar lipoproteinosis, interstitial fibrosis, bronchoalveolar hyperplasia. No sig effect on lung tumors. However, life table analysis to correct for shorter lifespan of exposed animals found inc probability of dying with a lung tumor at 90 μg/m^3.	Heinrich et al. (1989)
N/A	0 10 30 90	8 or, 19 hr/d 5 d/wk 98-105 wk	CdO fume	NS	Mouse, Han: NMRI (93-105) F	HP of lung: Inc incidence of alveolar lipoproteinosis, interstitial fibrosis, bronchoalveolar hyperplasia. Sig inc incidence of lung tumors.	Heinrich et al. (1989)

TABLE 11-27 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CADMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cd/m^3						
N/A	0 10 30 90 270	8 or, 19 hr/d 5 d/wk 34-64 wk	CdO dust	NS	Mouse, Han: NMRI (86-107) F	HP of lung: Inc incidence of alveolar lipoproteinosis, interstitial fibrosis, bronchoalveolar hyperplasia. Sig inc incidence of lung tumors. Inc probability of dying with a lung tumor in life table analysis.	Heinrich et al. (1989)

Abbreviations:

avg = average; AAP = alanine aminopeptidase (brush border enzyme); ALKP = alkaline phosphatase; AM = alveolar macrophages; AP = acid phosphatase; B = both male and female; ß-2m = ß-2-microglobulin; ß-2m-uria = ß-2-microglobulinuria; BAL = bronchoalveolar lavage; Cd = cadmium; $CdCl_2$ = cadmium chloride; CdO = cadmium oxide; CdS = cadmium sulfide; $CdSO_4$ = cadmium sulfate; cum = cumulative; d = day; dec = decreased; dep = depending; EM = electron microscopy; exp = exposure; est = estimated; FEV_1 = forced expiratory flow in 1 second; FSH = follicle stimulating hormone; FVC = forced vital capacity; GFR = glomerular filtration rate; geom = geometric; GFR = glomerular filtration rate; GGT = gamma glutamyltranspeptidase; HMW = high molecular weight; hr = hour; HP = histopathology; inc = increased; LDH = lactate dehydrogenase; LH = luteinizing hormone; LMW = low molecular weight; MEFR = maximal expiratory flow rate; MMAD = mass median aerodynamic diameter; mo = month; MMD = mass median diameter; N/A = not applicable; NAA = neutron activation analysis; NAG = N-acetyl-D-glucosaminidase; NS = not specified; occup = occupational; PEFR = peak expiratory flow rate; PMN = polymorphonuclear cells; ; ppm = parts per million; ; RBC = red blood cell; RBP = retinol binding protein; sig = significant(ly); SRBC = sheep red blood cells; TWA = time weighted average; TWE = cumulative exposure index; TLCO = carbon monoxide transfer factor; UK = unknown, document in retrieval; VC = vital capacity; VMD = volume median diameter; wk = week; wt = weight; yr = years.

Other studies in animals confirm that inhalation exposure to cadmium leads to respiratory injury. Acute exposure to cadmium oxide or cadmium chloride causes increased lung weight, inhibition of macrophages, cytoplasmic swelling and edema of type I cells, and eventually, replacement by type II cells (Boudreau et al., 1989; Buckley and Bassett, 1987; Bus et al., 1978; Grose et al., 1987; Henderson et al., 1979; Palmer et al., 1989). Intermediate-duration exposure causes similar respiratory toxicity (Glaser et al., 1986; Johansson et al., 1984; Kutzman et al., 1986; Prigge, 1978a). However, some tolerance to cadmium appears to develop, with lung lesions that develop after a few weeks of exposure not progressing or even reversing after longer exposure (Hart, 1986; Hart et al., 1989a). Multiple mechanisms appear to be responsible for this tolerance, including the synthesis of lung metallothionein and an increase in type II cells (Hart et al., 1989a). Chronic inhalation exposure to several forms of cadmium aerosols causes bronchioalveolar hyperplasia, proliferation of connective tissue, and interstitial fibrosis in rats (Takenaka et al., 1983).

Two studies found that inhalation exposure to cadmium can suppress the primary humoral immune response of mice, and cadmium can be cytotoxic to spleen cells (Graham et al, 1978; Krzystyniak et al., 1987).

Developmental toxicity (delayed ossification, decreased locomotor activity, and impaired conditioned learning) occurred in offspring of female rats exposed to cadmium oxide (20 μg Cd/m^3) for 4 to 5 mo prior to mating and during gestation (Baranski, 1984, 1985). Maternal weight gain and fetal weight were reduced in pregnant rats exposed to cadmium chloride aerosols at concentrations of 200, 400, or 600 μg Cd/m^3 during gestation (Prigge, 1978b). The decrease in fetal weight was statistically significant only at 600 μg/m^3 (Prigge, 1978b). These studies indicate that cadmium is a developmental toxin in animals by the inhalation route.

Decreased fertility was found in female rats exposed for 4 to 5 mo to 1,000 μg Cd/m^3; however, this concentration also caused substantial maternal toxicity (Baranski, 1985). Male and female rats exposed to cadmium concentrations of up to 1,000 μg/m^3 for 62 days and subsequently mated with unexposed controls showed no decrement in reproductive success, as measured by viable embryos and preimplantation losses (Kutzman et al., 1986).

Studies in rats demonstrate that chronic inhalation exposure to cadmium can cause lung cancer (Oldiges et al., 1989; Takenaka et al., 1983). These studies reported primary lung

tumors (bronchioalveolar adenoma, adenocarcinoma, squamous cell tumors) following exposure to cadmium chloride, cadmium sulfate, or cadmium sulfide aerosols, and cadmium oxide dust or fumes. No lung cancers were produced in hamsters exposed under a similar protocol (Heinrich et al., 1989), and only relatively weak evidence of association with lung cancer was found among mice exposed to cadmium oxide dusts or cadmium oxide fumes (Heinrich et al., 1989). In an abstract by Oberdörster et al. (1994) it was suggested that mice may have increased resistance to cadmium-induced lung cancer compared to rats because of their greater capacity for metallothionein induction. However, inflammation and cell proliferation were greater in the mouse lung than in the rat lung.

11.6.6.4 Factors Affecting Susceptibility

No studies were located that specifically evaluated factors affecting susceptibility. However, because the kidney and respiratory tract are targets of inhaled cadmium, people with compromised function of these organs would be expected to be at increased risk. Populations with decreased kidney function include diabetics and individuals with an age-related decline in kidney function.

Although immune function has not been assessed in workers exposed to cadmium, two studies in mice found decreased immune response following acute inhalation exposure to cadmium (Graham et al., 1978; Krzystyniak et al., 1987). This suggests that people with a compromised immune system may be at increased risk. Pregnant women may also have an increased susceptibility, based on the finding of Prigge (1978b) that toxic effects were observed in pregnant rats at lower concentrations than in nonpregnant female rats. Laboratory animal studies also suggest that the developing fetus may be at increased risk (Baranski, 1984, 1985).

Palmer et al. (1986) found that thyroidectomy results in increased injury from cadmium inhalation as a result of a decreased repair response. Their observations of enhanced Type II cell damage, decreased Type II cell proliferation, decreased macrophage levels, and decreased antioxidant levels suggest that thyroidectomy results in reduced capacity for efficient clearance of cell debris from the lungs. These results suggest that people with reduced thyroid function may be more susceptible to the respiratory toxicity of cadmium. These groups include the elderly and people with certain acute or chronic illnesses (such as

cirrhosis and diabetes). Major illnesses, malnutrition, glucocorticoids, and surgical trauma may also affect the levels of thyroid hormones.

Individuals with a genetically-determined decreased metallothionein inducibility would be less able to sequester cadmium, and thus would probably be more susceptible to cadmium-related renal toxicity.

11.6.7 Chromium

11.6.7.1 Chemical and Physical Properties

Chromium is a metallic element and belongs to Group VI of the periodic system of elements. Chromium forms compounds in oxidation states ranging from -2 to +6, of which +2, +3 and +6 are the most common (Agency for Toxic Substances and Disease Registry, 1993; Page and Loar, 1993; U.S. Environmental Protection Agency, 1984). Chromium forms both cationic and anionic salts (Hazardous Substances Data Bank [Data Base], 1995; Westbrook, 1993). Divalent chromium [+2 or chromous; Cr(II)] is relatively unstable and is readily oxidized to the chromium (+3) [Cr(III)] state. Trivalent chromium (+3 or chromic) is the most stable oxidation state and tends to form kinetically inert hexacoordinate complexes with water and other ligands. Cr (III) forms stable complexes with amino acids and peptides. Hexavalent chromium [+6 or chromate; Cr(IV)], the second most stable oxidation state, is rapidly reduced to Cr(III) after it penetrates biological membranes and in the presence of organic matter (Agency for Toxic Substances and Disease Registry, 1993; U.S. Environmental Protection Agency, 1984). The Cr(IV) oxidation state is also reduced to Cr(III), since it is apparently an intermediate in the reduction of Cr(IV) to Cr (III) (Page and Loar 1993). In solution, Cr(VI) exists as a complex anion.

Solubility in water is an important factor related to differential toxicologic effects of chromium and its compounds. Elemental chromium and its Cr^{+3} and Cr^{+4} oxides (Cr_2O_3 and CrO_2) are insoluble in water, as are zinc ($ZnCrO_4$) and ferrochromate ($FeCr_2O_4$). Several other chromium compounds are slightly to moderately soluble in hot water, such as the Cr^{+6} oxide (CrO_3), the trichloride ($CrCl_3$), and potassium, sodium, calcium, and lead chromates ($K_2Cr_2O_7$, $NaCrO_4$, $CaCrO_4$, $PbCrO_4$, respectively).

11.6.7.2 Pharmacokinetics

Hexavalent and trivalent chromium, the most common species of chromium in the environment, have different patterns of absorption, distribution, metabolism, and excretion. Generally, trivalent chromium [Cr(III)] is relatively non-toxic because it cannot cross biological membranes. Exposure to hexavalent chromium [Cr(VI)], which is more soluble and better absorbed, leads to documented toxicological and carcinogenic effects. However, the ultimate carcinogen within the cell is suspected to be trivalent chromium, and possibly tetravalent, pentavalent and radical chromium intermediates as well (Jones, 1990). Accordingly, interaction between the kinetics and the oxidation state of chromium has significant toxicological consequences.

Absorption and Distribution

The absorption of inhaled chromium compounds depends on several factors, including the physical and chemical properties of the material (oxidation state, size, solubility, and the activity of alveolar macrophages). The presence of chromium in the serum and urine of workers occupationally exposed to chromium indicates that chromium can be absorbed from the lungs (Foa et al., 1988; Gylseth et al., 1977; Lindberg and Vesterberg, 1983a; Minoia and Cavalleri, 1988). Chromium (VI) compounds are usually much better absorbed than chromium (III). There is no specific information available about the absorption of chromic acid mist, a compound of particular toxicological concern.

Among rats exposed to aerosols of Cr (VI) as potassium dichromate or Cr (III) as chromium trichloride, clearance was dependent on particle size, but Cr (VI) entered the blood stream more rapidly and extensively than Cr (III) (Suzuki et al., 1984). Clearance of Cr (VI) particles of 1.5 or 1.6 μm was biphasic, with half-lives of 31.5 h and 737 h. Cr (VI) particles of 2 μm followed a uniphasic clearance curve, with a half-life of 151-175 h. The clearance curve for Cr (III) was uniphasic, with a half-life of 164 h. The study authors calculated that the amount of Cr (VI) transferred to the blood was always at least three-fold greater than the amount of Cr (III) transferred.

The absorption of $CrCl_3$ [Cr(III)] and Na_2CrO_4 [Cr(VI)] were compared following intratracheal administration to rabbits (Wiegand et al., 1984). Initially, whole blood concentrations of the two compounds were similar, indicating comparable initial absorption

rates into the body. Subsequently, Cr(VI) was taken up more completely; at the end of the experiment (4 h post-exposure), only 47% of Cr(VI) remained in the respiratory tract, while 85% of Cr(III) was found in the respiratory tract at that time. Further absorption of Cr(III) may be forestalled by the formation of complexes within the respiratory tract.

Human data on chromium distribution following inhalation exposure are limited but indicate that levels are highest in the lung (Gerhardsson et al., 1984). A study of Japanese chrome platers and chromate refiners found that chromium levels in the hilar lymph node, lung, spleen, liver, kidney, and heart were elevated compared to those of unexposed males (Teraoka, 1981). In rats injected intratracheally with radiolabelled $Na_2Cr_2O_4 \cdot 2H_2O$ [Cr(VI)], the percent of administered radioactivity in various tissues at 6 h was the following: lung (42.9%), gastrointestinal tract (20.3%), residual carcass (10.4%), skin (3.2%), liver (2.6%), kidney (2.3%), serum (1.8%), red blood cells (1.5%), and testis (0.12%). After 40 days, the radioactivity was primarily found in the lung (12.3%) and residual carcass (5.3%); all other tissues contained less then 0.75% of the administered radioactivity (Weber, 1983). Following intratracheal administration to rabbits, absorption into the blood was strictly compartmentalized; Cr(VI) absorbed by the blood was primarily present in the erythrocytes, while Cr(III) was confined to the plasma (Wiegand et al., 1984).

There were no reliable data on whether inhaled chromium can cross the placenta. Cr(VI) administered via the oral or injection routes can cross the placenta, while Cr(III) crosses at much lower levels (Agency for Toxic Substances and Disease Registry, 1993). The relevance of these findings to inhalation exposure is unclear.

Metabolism

Hexavalent and trivalent chromium form different complexes inside the body. The metabolism of Cr(VI) includes its reduction to Cr(III) via Cr(V) and Cr(IV) species; there are no known instances of biological oxidation of Cr(III). Because cellular membranes are selectively permeable to Cr(VI), the locus of reduction has profound consequences for the effect of chromium. Cr(VI) enters the cell and undergoes metabolic interactions, including reduction, intracellularly. Cr(III), including extracellularly reduced Cr(VI), has more limited metabolic interactions and toxicological consequences. The available information does not describe reduction or metabolism of chromic acid.

Extracellular reduction of chromium has been noted primarily in the respiratory, digestive, and urinary tracts. As reviewed by Jones (1990), reduction in the lungs is mediated by the epithelial lining fluid, the pulmonary alveolar macrophages, the lung peripheral parenchyma, and the bronchial tree. In a detailed examination of chromium reduction in the epithelial lining fluid of rats that received intratracheal injections of Na_2CrO_4 [Cr(VI)], Suzuki and Fukuda (1990) found that approximately 80% of the chromium was reduced in the lungs after 18 min. Ascorbic acid appeared to carry out most of the initial reduction, with glutathione acting as the reducing agent after ascorbic acid levels were depleted.

Reduction in the urinary tract is suggested by Minoia et al. (1983). In dichromate workers who were mainly exposed to Cr(III) or Cr(VI) compounds, urinary chromium was present only as Cr(III).

Elimination

Human (Foa et al., 1988; Gylseth et al., 1977; Lindberg and Vesterberg, 1983a; Minoia and Cavalleri, 1988) and animal (Langard et al., 1978) data indicate that chromium is eliminated in the urine, but there is little information on the rate. In addition, no studies were located that assessed chromium in feces. Studies assessing urinary chromium following occupational exposure were reported in the section on absorption. Elimination of chromium was slow in rats exposed for 4 days to $ZnCrO_4$ [Cr(VI)]. Chromium levels in the urine were almost constant for 4 days postexposure, and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langard et al., 1978).

11.6.7.3 Health Effects

Human Data

No data were located on the effects in humans of acute inhalation exposure to chromium. Longer term studies were generally limited to occupational case studies and epidemiology studies. Based on these data, the respiratory tract is the primary target of chromium inhalation. Renal effects have also been observed, as well as gastrointestinal irritation, probably from swallowing chromium via mucociliary clearance. Exposure levels reported in epidemiological studies, especially more recent ones, should be viewed with

caution, because levels of chromium dusts in the workplace have improved in recent years, and some symptoms may have resulted from earlier, higher exposure levels. In addition, nasal effects may have partially resulted from the transfer of chrome from the hands to the nose by direct dermal contact. Human toxicity data are summarized in Table 11-28.

Workers in the chrome electroplate industry are frequently exposed to CrO_3 (VI) aerosols ("chromic acid mist"). The electroplating process results in the electrolysis of water, and the hydrogen and oxygen produced cause the formation of a chromic acid aerosol. Commonly observed upper respiratory symptoms include irritation and atrophy of nasal mucosa, progressing to nasal ulceration and perforation at higher exposure levels and/or durations. Other reported symptoms include epitaxis (nosebleeds) and rhinorrhea (nasal discharge) (Cohen et al., 1974; Gomes, 1972; Kleinfeld and Rosso, 1965; Lucas and Kramkowski, 1975; Royle, 1975). Effect levels can not be determined from these studies because there was no stratification of exposure levels. No effects were observed in a group of 32 chrome workers exposed to levels up to 6 $\mu g/m^3$ Cr(VI) as CrO_3 (Markel and Lucas, 1973). Pulmonary function tests have found that chromium also can cause obstructive lung disease. Respiratory effects of chromium are probably due to the direct action of chromium at the site of contact.

Swedish chrome plating workers exposed to ≥ 2 $\mu g/m^3$ Cr(VI) as CrO_3, had crusty, atrophied nasal mucosa, but no nasal symptoms were reported in workers exposed to < 1 $\mu g/m^3$. Also, slight statistically significant transient effects on forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were observed at > 2 $\mu g/m^3$ (Lindberg and Hedenstierna, 1983). Emphysema and obstructive lung disease, characterized by decreased FVC and FEV_1, were observed in a group of ferrochromium workers, exposed to Cr(III) and Cr(VI) at total chromium levels of 20 to 190 $\mu g/m^3$ (Langard, 1980). Asthma from chromium inhalation has been reported (Park et al. 1994), but the chemical form and exposure levels were unknown. The pathogenic mechanism of chromium-induced asthma is not known; data are conflicting regarding the existence of an IgE-mediated reaction.

Occupational inhalational exposure to chromium compounds has resulted in the early signs of renal damage, as indicated by the presence of low molecular weight proteins in urine. Franchini and Mutti (1988) reported increased levels of retinol binding protein and tubular antigen in the urine of chromate and dichromate industry workers with >15 μg

TABLE 11-28. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 <2 (TWA) 2-20 (TWA) peak 46	0.2-23.6 yr (median 2.5) yr occup	CrO_3 (VI) mist	NS	Human (NS) M,F	Respiratory symptoms, PF, changes in nasal mucosa (cluster exposure groups): Nasal mucosal atrophy and irritation in all groups based on TWA. When classified by peak exposures, no effects at 0.2-1.2 $\mu g/m^3$, but effects were seen in the cohort with peak exposure at 2.5-11 $\mu g/m^3$, and in the highest peak exposure group. Slight, transient dec. FVC, FEV_1 at 2-20 $\mu g/m^3$. Severity correlated better with peak exposure levels than with mean exposure. Subjects were divided into "low exposure" (<2 $\mu g/m^3$, 16M, 5F), "high exposure" (>2-20 $\mu g/m^3$, 21M, 1F), and "mixed" (CrO_3 and other acids, metallic salts, 48 M, 13 F), and controls (119 M). Note: 36 subjects were also divided into peak exposure categories: 0.2-1.2 $\mu g/m^3$ (n=10); 2.5-11 $\mu g/m^3$ (n=12); and 20-46 $\mu g/m^3$ (n=14).	Lindberg and Hedenstierna (1983)
N/A	180-1,400	2 wk-1 yr occup	CrO_3 (VI) mist	NS	Human (9) M	Respiratory symptoms: Septal perforation of nose, ulcerated nasal septum, moderate injection of nasal septum, epitaxis. Negative chest roentgenograms.	Kleinfeld and Rosso (1965)
N/A	<52 52-100 110-160 160-210 310-360 >520	<1 yr occup	CrO_3 (VI) vapor	N/A	Human (258) NS	Nasal mucosa, dental effects, clinical signs: Nasal ulceration and perforation, epitaxis, rhinorrhea at ≥52 $\mu g/m^3$.	Gomes (1972)
N/A	<1-20 mean = 4	3-16 yr occup ave 7.5 yr	CrO_3 (VI) aerosol	NS	Human (11) M	Respiratory and GI clinical signs: Nasal septal ulceration and perforation, epitaxis, rhinorrhea, stomach pain, duodenal ulcers in exposed workers. Levels based on personal monitoring. Pathology attributed to direct skin contact.	Lucas and Kramkowski (1975)

TABLE 11-28 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	<1-6	NS->5 yr occup	CrO_3 (VI) mist	NS	Human (32) NS	Physical exam and questionnaire with emphasis on eye, nose, and throat: No effects observed. Nasal mucosal inflammation was attributed to recent upper respiratory tract infection.	Markel and Lucas (1973)
N/A	0.1 7.1 Avg. Total Cr. = .3 Avg. Cr (VI) = 2.9	0.3-132 mo 26.9 mo ave occup	CrO_3 (VI)	NS	Human (30) M, (7) F	Respiratory symptoms: nasal ulceration and perforation, rhinorrhea, epitaxis in exposed workers.	Cohen et al. (1974)
N/A	<16 - >52	<1 yr->5 yr occup	CrO_3 (VI) NS	NS	Human (997-1117) M,F	Respiratory symptoms: Inc prevalence of bronchial asthma, exposure-duration-related inc in nasal perforations, nasal ulcers in chrome platers. In 10/12 plants, level was $<16\ \mu g/m^3$.	Royle (1975)
N/A	NS	3-108 mo occup	Cr dust (compound NS)	NS	Human (4) M	Clinical symptoms, skin-prick test, BPT: Case study of 4 cases of occupational asthma caused by chromium. All had positive response to $Cr_2(SO_4)_3$ [Cr(III)] on skin prick or patch test, and a positive response in BPT to $Cr_2(SO_4)_3$. Healthy controls and intrinsic asthmatics did not respond on the BPT. Note: All were smokers.	

TABLE 11-28 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	2-20 mean = 6	0.1-26 yr occup ave 5.3 yr	CrO_3 (VI) NS	NS	Human (24-27) M	Renal function: Inc. urinary beta-2-microglobulin at 0.002 among chrome platers. Increase not found in ex-chrome platers. No effect on urinary albumin. Most of the current workers had irritation of the airways; four had ulcerated or perforated nasal septum.	Lindberg and Vesterberg (1983b)
N/A	50-1,000	avg 7 yr occup	CrO_3 (VI)	NS	Human (43) M	Urinalysis: Dose-related increase in retinol binding protein (RBP) and tubular antigen. No effect on RBP at Cr levels $<15\ \mu g/g$ creatinine. Note: Exposure usually $<50\ \mu g/m^3$, sometimes as high as 1,000 $\mu g/m^3$.	Franchini and Mutti (1988)
N/A	20-158	2-12 yr occup	Cr_2O_3 (III)	dust, not further described	Human (236) M	Renal function: No effect on urinary albumin, renal tubular epithelium antigens.	Foa et al. (1988)
N/A	130-61	1-32 yr avg 7 yr occup	Chromium (0)	UK	Human (230) M	Urinalysis: No effect on excretion of urinary enzymes, total protein, or ß2-microglobulin in a well-designed epidemiological study.	Triebig et al. (1987)
N/A	20-190 total Cr	>15 yr occup	Ferro-chromium (III, VI) dust 11-33% Cr(VI)	NS	Human (25-60) M	Pulmonary function, chest x-ray: Obstructive lung disease, emphysema, dec FVC and FEV_1 in exposed workers.	Langard (1980)
N/A	0 10-1,350	4-19 yr occup	$PbCrO_4$ and $ZnCrO_4$ (VI)	NS	Human (24) M	Lung cancer deaths: Three cases of bronchial carcinoma observed, compared to 0.079 expected based on national rates (SMR = 3,797). Exposure of the 3 affected workers estimated at 500-1,500 for 6-9 yrs; 2 of the 3 were smokers.	Langard and Norseth (1975)

TABLE 11-28 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 usually 10-30	≥3 yr occup	$ZnCrO_4$ (VI)	NS	Human (24) M	Lung cancer deaths: Inc lung cancer rate. Four new cases of lung cancer were found among 133 workers, with 3/4 in subcohort employed for ≥3 yrs before exposure was reduced in 1973. O/E = 6/0.135, SMR = 4,444. Types of lung cancer: Highly differentiated epithelial cell carcinoma, adenocarcinoma, anaplastic small cell carcinoma, oat-cell carcinoma. Note: Exposure levels had been higher previously.	Langard and Vigander (1983) (follow-up to Langard and Norseth, 1975)
N/A	40-290	1-49 yr occup	Ferro-chromium (VI and III) dust	NS	Human (976) M	Lung cancer incidence: 7 cases among study group. Compared to local rate, risk ratio = 389 (p=0.06). Compared to internal reference group, risk ratio = 850 (p=0.026). Perforation of nasal cavity in 2 workers.	Langard et al. (1980)
N/A	40-290	1-49 yr occup	Ferro-chromium mix (VI and III)	NS	Human (976) M	Cancer incidence: Inc in lung, prostate, and kidney cancers that were not statistically significant. Incidence ratios were 154, 151, and 273, respectively. Note: Workers with first exposure <20 years prior to study were excluded to allow for latent period for cancer development.	Langard et al. (1990)
N/A	<50 $\mu g/m^3$-yr to ≥6,000 $\mu g/m^3$-yr (Total Cr)	NS occup	Reported only as Insoluble [Cr(III)] and Soluble [Cr(VI]	NS	Human (332) M	Lung cancer deaths: Inc. lung cancer rate. The age-adjusted lung cancer death rate due to Cr(III) was 0 at <250 $\mu g/m^3$-year, and increased with exposure above that level. Similarly, for total Cr, there were no lung cancer deaths at <500 $\mu g/m^3$-year, and rate increased with exposure. For Cr(VI), death rate inc with exposure, but lung cancer deaths were observed at <250 $\mu g/m^3$-yr. A cohort of employees exposed in 1931-1937 were followed to 1974. Lung cancer deaths clustered at 27-36 years of observation.	Mancuso (1975)

TABLE 11-28 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cr/m^3						
N/A	0 218, 413 "usual conc of Cr(VI)"	90 d- >5 yr occup	Mix VI and III	NS	Human (2101)NS	Lung cancer deaths: Inc lung cancer deaths. O/E = 59/29.16, based on local population; SMR = 202 ($p<0.01$). Usual exposure estimated for earlier exposure years; no data were available for later years. Cumulative exposures were estimated to be 670 μg Cr(VI)/m^3-yrs for short-term employees and 3,647 μg Cr(VI)/m^3-yrs for long-term employees. Cr(III) levels not estimated. Exposure dec in later years. Note: Usual conc estimated as avg of mean annual air concentrations for several years.	Hayes et al. (1979); Braver et al. (1985)
N/A	>500- >2,000	1 mo- 29 yr occup	$PbCrO_4$ and $ZnCrO_4$ (VI) dust	NS	Human (1879) M	Cancer deaths: Significant trend for lung cancer with duration of employment, limited to those employed for $\geq$10 yrs and with $\geq$30 yr since initial employment (0/E = 6/1.87; SMR = 321 for this group). Positive trend for stomach cancer with duration of employment, although no significant excess. Note: Exposure levels determined only during "later years".	Hayes et al. (1989)

Abbreviations:

ALAT = alanine aminotransferase; AM = aveolar macrophage; AP = alkaline phosphatase; avg = average; BAL = bronchoalveolar lavage; BP = bronchopulmonary lavage; BPT = bronchoprovocation test; BW = body weight; conc = concentration; CrO_2 = chromium dioxide [chromium (IV) oxide]; CrO_3 = chromic acid [chromium (VI) oxide]; Cr_2O_3 = chromium (III) oxide; d = day; dec = decreased; F = female; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; GI = gastrointestinal; h = hour; inc. = increased; M = male; N/A = not applicable; NS = not specified; occup = occupational exposure; $PbCrO_4$ = lead chromate; PF = pulmonary function; PMN = polymorphonuclear cells; ppm = parts per million; SMR = standard mortality ratio; SRBC = sheep red blood cells; TWA = time-weighted average; wk = week; wt = weight; WBC = white blood cell count; yr = years; $ZnCrO_4$ = zinc chromate.

chromium/g creatinine in urine. Exposure was to 50-1,000 $\mu g/m^3$ Cr(VI) as CrO_3 for an average of 7 years. Levels of ß-2-microglobulin were elevated in the urine of chrome platers exposed to 2-20 $\mu g/m^3$ Cr(VI) as CrO_3, but urinary albumin was unaffected (Lindberg and Vesterberg, 1983b). The study found no effect in a group of ex-chrome platers, indicating that elevated ß-2-microglobulin levels are reversible. There was no evidence of impairment of renal function in ferrochromium workers exposed to up to 158 $\mu g/m^3$ Cr(III) as Cr_2O_3 (Foa et al., 1988), or in steel plant workers exposed to up to 610 $\mu g/m^3$ Cr(0) as metallic chromium dust (Triebig et al., 1987). The renal toxicity of chromium is supported by studies showing renal failure and necrosis of renal tubules following fatal or near-fatal oral ingestion of chromium (Agency for Toxic Substances and Disease Registry, 1993).

Chromium inhalation may also result in gastrointestinal effects. Stomach pain and duodenal ulcers were reported in a group of chrome platers exposed to an average of 4 $\mu g/m^3$ CrO_3 (VI) (Lucas and Kramkowski, 1975); there was no control group. If these effects are due to chromium, they probably result from mouth breathing and/or ingestion of chromium removed from the lungs by mucociliary clearance.

There are numerous occupational epidemiology studies on the potential carcinogenicity of chromium. Only the studies that are most appropriate for risk assessment or fill qualitative data gaps are presented here. Overall, the data indicate that Cr(VI) can cause lung cancer. Data on other cancers are less clear. Analysis of the data is confounded by the high prevalence of smoking, but several of the authors used a control population matched for percent smokers. Lung cancer deaths were increased (SMR = 202) in a cohort of 2,101 workers exposed to chromates at 410 $\mu g/m^3$ (Cr(VI), and risk increased in longer-term employees (Braver et al., 1985; Hayes et al., 1979). In a study of 24 pigment workers exposed to $PbCrO_4$ and $ZnCrO_4$ at 10-1,350 $\mu g/m^3$ Cr(VI), three cases of bronchial carcinomas were observed, compared with 0.079 expected based on national rates (SMR = 3,797) (Langard and Norseth, 1975). In a followup study, three additional cases were reported in this subpopulation (O/E = 6/0.135; SMR = 4,444), and one case in a larger cohort that had been exposed after air concentrations of chromium were reduced (Langard and Vigander, 1983). In a retrospective cohort study of chromate pigment workers, lung cancer deaths were increased only in the subpopulation with $\geq$10 years exposure and $\geq$30 years since initial exposure (Hayes et al., 1989). In a cohort study of a ferrochromium plant

where exposure to a mixture of Cr(VI) and Cr(III) ranged from 40 to 290 $\mu g/m^3$ total Cr, the incidence of lung, prostate, and kidney cancers were increased above the general population, but the increase was not statistically significant (Langard et al., 1990). In a group of dichromate [Cr(VI)] producing workers, lung cancers were elevated (relative risk 1.8), and two cases of nasal cancer were found (Alderson et al., 1981). Increased lung cancer risk has also been reported for chromate workers (Taylor, 1966). Mancuso (1975) measured exposure to both Cr(VI) and Cr(III) in a chromate plant, and calculated that the age-adjusted death rate increased both with exposure to Cr(VI) and with exposure to Cr(III). However, the association with Cr(III) exposure may have been due to the correlation between Cr(III) and Cr(VI) exposure.

Laboratory Animal Data

Laboratory animal data support the respiratory tract as the main target of chromium inhalation following either acute or chronic exposure. These data, summarized in Table 11-29, indicate that all forms of chromium can result in mild irritation, increased alveolar macrophage activity and/or accumulation of macrophages in the lung. However, most respiratory tract tissue damage is attributed to Cr(VI) compounds.

In the one acute study analyzed, hamsters exposed to 900 to 25,000 $\mu g/m^3$ Cr(III) as $CrCl_3$ for 30 min had increased acid phosphatase in bronchoalveolar lavage (BAL) fluid and focal accumulation of macrophages. Rabbits exposed to chromium (0) dust at concentrations up to 3,100 $\mu g/m^3$ for 4 weeks had increased alveolar macrophage activity, but no tissue damage (Johansson et al. 1980). Similarly, in rabbits exposed to aerosols of $Cr(NO_3)_3$ at up to 2,300 $\mu g/m^3$ Cr(III), effects were limited to accumulation of macrophages and decreased macrophage response to stimulation (Johansson et al., 1986a,b, 1987). In the one study of Cr(IV) toxicity, exposure of rats to CrO_2 at 310 μg Cr/m^3 for 2 years resulted in dust-laden alveolar macrophages and type II pneumocyte hyperplasia (Lee et al., 1988).

Respiratory effects of Cr(VI) compounds are consistent with an inflammatory reaction. Increased macrophage levels in response to Cr(VI) have been observed in several studies (Glaser et al., 1985, 1986; Johansson et al., 1986a,b). These changes can result in granulomas, giant cells, and fibrosis (Steffee and Baetjer, 1965). The BAL fluid of rats exposed to $Na_2Cr_2O_7$ had increased percent lymphocytes and increased response to sheep red

TABLE 11-29. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Cr/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
N/A	0 900 25,000	30 min	$CrCl_3$ (III) aerosol	count median diameter = 1.2 μm σ_g ~1.5	Hamster, Syrian (16) M, (16) F	Lung lavage (enzymes, cytology), lung HP: Inc. acid phosphatase in lavage fluid and lung tissue, focal accumulation of MP and PMN cells at 900 and 25,000 $\mu g/m^3$.	Henderson et al. (1979)
Subchronic and Chronic Studies							
N/A	0 600 3,100	6 h/d 5 d/wk 4 wk	Cr (0) dust	<320 mesh	Rabbit, NS (4) M	AM activity, BAL, lung wt and HP: No effect on lung wt. Inc activity of AM. Uptake of chromium dust by AMs.	Johansson et al. (1980)
N/A	0 600	6 h/d 5 d/wk 4-6 wk	$Cr(NO_3)_3 \cdot 9H_2O$ (III) aerosol	MMAD ~1 μm	Rabbit, NS (8) M	HP of lung by EM and light microscopy: Inc intraalveolar or intrabronchial accumulation of macrophages, nodular accumulation of macrophages. No epithelial destruction or abnormal proliferation. Decreased macrophage response to stimulation.	Johansson et al. (1986a,b)
N/A	0 900	6 h/d 5 d/wk 4-6 wk	Na_2CrO_4 (VI) aerosol	MMAD ~1 μm	Rabbit, NS (8) M	HP of lung by EM and light microscopy: Inc AM in BAL fluid. Inc intraalveolar or intrabronchial accumulation of macrophages, nodular accumulation of macrophages. No epithelial destruction or abnormal proliferation.	Johansson et al. (1986a,b)
N/A	0 600 2,300	6 h/d 5 d/wk 4 mo	$Cr(NO_3)_3 \cdot 9H_2O$ (III) aerosol	MMAD ~1 μm	Rabbit, NS M	BAL, HP of lung by light microscopy and EM: Increased levels of AM. Nodular accumulation of macrophages in terminal airspaces, interstitial infiltration of inflammatory cells at 600 and 2,300 $\mu g/m^3$.	Johansson et al. (1987)

TABLE 11-29 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Cr/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 25 50 100 200	22 h/d 7 d/wk 28 d	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI) aerosol	MMAD = 0.20 μm σ_g = 1.5	Rat, Wistar (20) M	BW; HP of lung, stomach, liver; organ wt, blood biochem, BAL, immune function: Inc. lung, spleen wt at $\geq$50 $\mu g/m^3$. HP normal. ALAT, AP, creatinine normal. Response to SRBC and AM phagocytosis increased in BAL fluid at all levels. Inc. percent lymphocytes in BAL fluid at 25 and 50 $\mu g/m^3$.	Glaser et al. (1985)
N/A	0 25 50 100 200	22 h/d 7 d/wk 90 d	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI) aerosol	MMAD = 0.20 μm σ_g = 1.5	Rat, Wistar (20) M	BW; HP of lung, stomach, liver; organ wt, blood biochem, BAL, immune function: Inc. lung, spleen wt at $\geq$50 $\mu g/m^3$. HP normal. ALAT, AP, creatinine normal. Response to SRBC increased at all levels. Macrophage activity, percent lymphocytes in BAL fluid inc at 25 and 50, dec at 200 $\mu g/m^3$. Lung clearance dec at 200 $\mu g/m^3$. Inc lung wt, serum phospholipids and triglycerides at 200 $\mu g/m^3$.	Glaser et al. (1985)
N/A	0 50 100 200 400	22 h/d 7 d/wk 30-90 d	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI) aerosol	50-100: (MMAD=0.28 μm, σ_g=1.63) 200-400: MMAD=0.39 μm, σ_g=1.72	Rat, Wistar (30) M	Blood biochem, hemato., urinalysis, and BAL; gross and HP exam of upper airway epithelia, lung, kidneys: Reversible inc. in WBC at $\geq$100 $\mu g/m^3$ at 30 d and at $\geq$50 $\mu g/m^3$ at 90 d. At $\geq$50 $\mu g/m^3$ and 30 d exposure, lung wt inc, slight hyperplasia, macrophage infiltration. Incidence declined with longer exposure, indicating repair. Inc protein in BAL fluid.	Glaser et al. (1990)
N/A	0 3,630	30 min/d 2 d/wk 12 mo	CrO_3 (VI) aerosol	"mist size 10 μm"	Mouse, ICR (10-19) F	HP of respiratory tract: Emphysema, nasal septum perforation. On epithelium of the trachea and bronchus, loss of cilia, proliferation of goblet or basal cells, and squamous metaplasia, with severity related to exposure duration. Adenomas and adenocarcinomas observed.	Adachi et al. (1986)

TABLE 11-29 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 1,810	120 min/d 2 d/wk 12 mo	CrO_3 (VI) aerosol	"mist size ~5 μm--85%"	Mouse, C57BL (20-23) F	Gross and HP of respiratory tract: Emphysema, nasal septum perforation, lung metaplasia. In animals sacrificed 6 mo after the last exposure, also hyperplasia of larynx/trachea and papillomas of nasal epithelia.	Adachi (1987)
N/A	0 25 500 100	22 h/d 7 d/wk 18 mo	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI) aerosol	MMAD = 0.36 μm σ_g = 1.69	Rat, Wistar (20) M	Body wt, HP of lungs, liver, kidney, adrenals, hematology, blood biochem, urinalysis: Lung and liver weight significantly increased at 100 $\mu g/m^3$. Weak accumulations of pigmented macrophages in alveolar region of lung at 25 $\mu g/m^3$ and moderate levels at higher exposure levels. Lung tumors (adenocarcinoma and adenomas) and squamous cell carcinoma of pharynx at 100 $\mu g/m^3$.	Glaser et al. (1986)
N/A	0 100	22 h/d 7 d/wk 18 mo	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI): Cr_5O_{12} (III) 3:2 mixture	Cr(VI): MMAD = 0.36 μm σ_g = 1.69; Cr(III): MMAD = 0.39 μm σ_g = 1.71	Rat, Wistar (20) M	Body wt, HP of lungs, liver, kidney, adrenals, hematology, blood biochem, urinalysis: Lung wt increased. Moderate accumulations of pigmented macrophages; focal thickened septa, bronchoalveolar hyperplasia, and interstitial fibrosis. Hematocrit, Hb, RBC, WBC, but not differential white blood cell counts were increased. Inc cholesterol. Lung tumor (adenoma).	Glaser et al. (1986)
N/A	0 Avg. 1.600-2,100	4-5 h/d 4 d/wk 2 yr	Finely ground chromium roast (VI) and $K_2Cr_2O_7$ (VI) dust	NS	Rat, Wistar (78) NS	HP of lungs and tissues with gross lesions: Lung abscesses, bronchopneumonia, alveolar and interstitial inflammation, giant cell, granulomatoma. No exposure-related evidence of carcinogenesis. $K_2Cr_2O_7$ was added to chromate roast at a level of 1%.	Steffee and Baetjer (1965)

TABLE 11-29 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 Avg. 1,600-2,100	4-5 h/d 4 d/wk 4.5 yr	Finely ground chromium roast (VI) and $K_2Cr_2O_7$ (VI)	NS	Guinea pig (50) M,F	HP of lungs and gross lesions: Inc incidence of granulomata and inflammatory response. Alveolar and interstitial inflammation, alveolar hyperplasia, interstitial fibrosis. No evidence of carcinogenicity.	Steffee and Baetjer (1965)
N/A	0 1,040-1,560	4 h/d 5 d/wk 101 wk	Mixed chromium dust (VI) 13.7% CrO_3 6.9% Cr_2O_3	Mass median diameter of airborne particles 0.8 μm Distribution: <0.5 μm, 23%; 0.5-1, 46%; 1-2, 14%; 2-3, 9%; 3-4, 4%; 4-5, 2%; ≥5, 5%	Rat, Wistar/Mc-collum mix (57) M, (53) F	HP of lungs: Pneumonia, inflammation, consolidation, and congestion of lungs. No statistically significant effect on lung cancer incidence. Note: Chromate dust obtained from a chemical plant.	Baetjer et al. (1959)
N/A	0 Avg. 1,600-2,100	4-5 h/d 4 d/wk 4.5 yr	Finely ground chromium roast (VI) and $K_2Cr_2O_7$ (VI)	NS	Guinea pig, NS (50) M,F	HP of lungs and gross lesions: Inc incidence of granulomata and inflammatory response. Alveolar and interstitial inflammation, alveolar hyperplasia, interstitial fibrosis. No evidence of carcinogenicity.	Steffee and Baetjer (1965)

TABLE 11-29 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 1,040-1,560	4 h/d 5 d/wk 101 wk	Mixed chromium dust (VI) 13.7% CrO_3 6.9% Cr_2O_3	Mass median diameter of airborne particles 0.8 μm Distribution: <0.5 μm, 23%; 0.5-1, 46%; 1-2, 14%; 2-3, 9%; 3-4, 4%; 4-5, 2%; ≥5, 5%	Rat, Wistar/Mc-collum mix (57) M, (53) F	HP of lungs: Pneumonia, inflammation, consolidation, and congestion of lungs. No statistically significant effect on lung cancer incidence. Note: Chromate dust obtained from a chemical plant	Baetjer et al. (1959)
N/A	0 4,300	5 h/d 5 d/wk 18 mo	$CaCrO_4$ (VI) dust	Size (μm) / % Particles smaller than: <0.1 4.5 <0.2 48.7 <0.3 69.6 <0.4 82.2 <0.5 91.2 <0.6 95.9 <0.7 97.3 <0.8 98.7 <0.9 99.6 ≤1.0 99.9	Mouse, C57BL/6 (136) M, (136) F	HP of heart, trachea, lung: Epithelial changes in bronchial tree ranging from epithelial necrosis and atrophy to marked hyperplasia. Inflammatory infiltration of subepithelial tissues. Bronchiolization of alveoli, dilation of alveolar ducts, accumulation of alveolar cells and foam cells. Increased incidence of lung tumors. The tumors were identified as alveologenic adenomas and adenocarcinomas. Hyperplasia and atrophy of tracheal and submandibular lymph nodes, occasional small ulcerations in stomach and intestinal mucosa.	Nettesheim et al. (1971)

TABLE 11-29 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR CHROMIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cr/m^3$						
N/A	0 310 15,500	6 h/d 5 d/wk 2 yr	CrO_2 aerosol (IV) (0.31-stabilized, un-stabilized; 15.5 stabilized)	Aerodynamic diameter = 2.6-2.8 μm σ_g = 2.76-3.26	Rat, Sprague-Dawley (120) M, (120) F	Body wt, organ wt, hematology, blood biochem, urinalysis, HP of major organs, including trachea, lung, nasal turbinates: No effect on body wt, hematology, blood biochem, urinalysis. Mediastinal lymph nodes and lungs were black at 0.31 (stabilized and unstabilized) and at 15.5. All groups had densely dust-laden alveolar macrophages, and there was a low incidence of type II pneumocyte hyperplasia. At 15.5, also observed inc lung wt, degenerative foamy alveolar macrophages, and hyperplasia of type II pneumocytes, collagenized fibrosis, squamous metaplasia. Two females at 15.5 had cystic keratinizing squamous cell carcinoma (considered metaplastic, not neoplastic).	Lee et al. (1988)

Abbreviations:

ALAT = alanine aminotransferase; AM = aveolar macrophage; AP = alkaline phosphatase; ave = average; BAL = bronchoalveolar lavage; BP = bronchopulmonary lavage; BW = body weight; conc = concentration; CrO_2 = chromium dioxide [chromium (IV) oxide]; CrO_3 = chromic acid [chromium (VI) oxide]; $Cr(NO_3)_3$ = chromium nitrate; Cr_2O_3 = chromium (III) oxide; $CrCl_3$ = chromium trichloride; d = day; dec = decreased; EM = electron microscopy; F = female; GI = gastrointestinal; gen = generation; HP = histopathology; h = hour; inc. = increased; $K_2Cr_2O_7$ = potassium dichromate; M = male; MMAD = mass median aerodynamic diameter; MP = macro-phages; Na_2CrO_4 = sodium chromate; $Na_2Cr_2O_7$ = sodium dichromate; N/A = not applicable; NS = not specified; occup = occupational exposure; $PbCrO_4$ = lead chromate; PF = pulmonary function; PMN = polymorphonuclear cells; ppm = parts per million; SMR = standard mortality ratio; SRBC = sheep red blood cells; TWA = time-weighted average; wk = week; wt = weight; WBC = white blood cell count; yr = years.

blood cells (Glaser et al., 1985) The incidence of macrophage infiltration declined with longer exposures, suggesting that repair occurred (Glaser et al., 1990). Glaser et al. (1990) also suggested that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of Cr(VI) compounds.

Respiratory tissue alterations have also been observed in animals. Lower levels, such as up to 400 $\mu g/m^3$ Cr(VI) as $Na_2Cr_2O_7$, result in hyperplasia (Glaser et al., 1990). Mice exposed to 1,810 or 3,630 $\mu g/m^3$ Cr(VI) as CrO_3 for 1 year developed nasal septal perforation, loss of cilia, and metaplasia of the lung, trachea, and bronchus (Adachi, 1987; Adachi et al., 1986). Epithelial changes of the bronchial tree ranging from necrosis and atrophy to hyperplasia were observed in mice exposed to 4,300 μg Cr/m^3 as $CaCrO_4$ dust for 18 mo (Nettesheim et al., 1971).

Chromium can also act as a sensitizing agent. Miyamoto et al. (1975) sensitized guinea pigs to chromium by repeated dermal painting and intradermal exposure to potassium dichromate, and then exposed the animals via inhalation to an aerosolized solution of potassium dichromate (concentration not specified) for 30-45 min. The inhalation challenge elicited a stronger reaction in the lungs (edema, infiltration of lymphocytes into the interstitial spaces) of actively sensitized guinea pigs than in control guinea pigs. The observed changes were characterized as a delayed-type hypersensitivity reaction.

Few animal data are available on non-respiratory effects of chromium. However, Glaser et al. (1986) reported increased liver weight in rats exposed to 100 $\mu g/m^3$ Cr(VI) as $Na_2Cr_2O_7$ for 18 mo.

Animal studies also support the carcinogenicity of Cr(VI). Rats treated with 100 $\mu g/m^3$ Cr(VI) as $Na_2Cr_2O_7$ had adenocarcinoma and adenomas of the lung and squamous cell carcinomas of the pharynx, but exposure-related tumors were not observed at lower levels (Glaser et al., 1986). Lung tumors were also observed in mice treated with $CaCrO_4$ (Nettesheim et al.. 1971).

No developmental effects were reported in rats exposed to 200 $\mu g/m^3$ Cr(VI) as sodium dichromate for three generations (Glaser et al., 1984, as cited in Agency for Toxic Substances and Disease Registry, 1993). Further experimental details were not available in the secondary reference, and the original reference is in German. There were no other studies on developmental toxicity by the inhalation route and no studies were located that

observed reproductive outcome in animals that inhaled chromium compounds. However, there were no histological effects of the testes in rats exposed to 200 $\mu g/m^3$ Cr(VI) as sodium dichromate for 28 or 90 days (Glaser et al., 1985) or 100 $\mu g/m^3$ Cr(VI) as sodium dichromate for 18 mo (Glaser et al., 1986, 1988). Oral data indicate that Cr(VI) compounds are reproductive and developmental toxicants, while Cr(III) compounds may cause reproductive toxicity, but not developmental toxicity (Agency for Toxic Substances and Disease Registry, 1993).

11.6.7.4 Factors Affecting Susceptibility

Because the respiratory system is a major target of chromium inhalation toxicity, individuals with impaired respiratory function may have increased susceptibility to chromium. The developing respiratory tract of children may also pose an increased susceptibility. Repeated exposure to chromium may result in hypersensitivity (Miyamoto et al. 1975), which can be manifested as increased respiratory toxicity. Differences in chromium metabolism can also increase susceptibility. Individuals who reduce Cr(VI) in the bloodstream to Cr(III) more slowly have been identified (Korallus 1986). Because Cr(III) cannot cross biological membranes and is much less toxic than Cr(VI), slow reducers are more likely to be adversely affected by chromium exposure. The ability to reduce Cr(VI) in the bloodstream may be related to plasma ascorbic acid levels. Smokers may also be more susceptible to lung cancer related to chromium exposure, since inhalation of cigarette smoke may result in squamous metaplasia of the respiratory mucosa (Albert, 1991).

Since occupational studies have shown early signs of renal damage following inhalation exposure to chromium (Franchini and Mutti, 1988; Lindberg and Vesterberg, 1983b), individuals with pre-existing kidney dysfunction may be more susceptible to the nephrotoxic effects of chromium.

11.6.8 Cobalt

11.6.8.1 Chemical and Physical Properties

Cobalt is a metallic element found in Group 8B of the periodic table. It exhibits the valence states of 0, +1, +2, +3, +4, and +5. The common forms of cobalt in the 0 oxidation state are cobalt metal and the cobalt carbonyls (Agency for Toxic Substances and

Disease Registry, 1991). Most cobalt compounds are formed with cobalt in the +2 or +3 oxidation state, although cobalt(III) compounds tend to exist as complexes rather than as simple salts. In aqueous solution, Co^{+2} is stable; however, Co^{+3}, a strong oxidizing agent, is reduced to Co^{+2} in aqueous solutions. Cobalt exists in the environment both as inorganic salts, and as organocobalt compounds (Richardson, 1993). Elemental cobalt is insoluble in water, as are cobalt (II) oxide (CoO) and cobalt (III) oxide (Co_2O_3), whereas cobalt (II) sulfate ($CoSO_4$) and cobalt (II) chloride ($CoCl_2$) are moderately soluble in hot water (at ca. 80 to 100 °C).

11.6.8.2 Pharmacokinetics

Absorption and Distribution

No data were located regarding absorption of cobalt following inhalation or oral exposure to cobalt powder, hard metal, or cobalt sulfate. However, the kinetics of cobalt excretion in the urine suggest that there is a component that is absorbed rapidly (within < 1 day) and a component that is absorbed over the course of at least several weeks (Alexandersson, 1988; Roshchin et al., 1989). Based on lung activity levels on Days 15 and 80 post-exposure in workers who accidentally inhaled ^{60}Co aerosol for 10 to 20 min, the lung clearance half-time was in the range 25 to 78 days; only minor activity was in the liver (Beleznay and Osvay, 1994). Hamsters exposed via inhalation to 12,200 μg cobalt/m^3 as cobalt oxide for 7 h/day for 2 days had virtually no cobalt in the lungs at 6 days post-exposure. At 24 h post-exposure, most of the inhaled dose was detected in the gastrointestinal tract (60%), with the lungs containing only approximately 3% of the dose, the liver and kidney less than 1% each, and the remaining carcass 23% (Wehner and Craig 1972). Dogs administered a radiolabeled cobalt nitrate aerosol intratracheally rapidly eliminated most of the dose from the lungs and body (Kreyling et al., 1986). However, 3% of the dose was retained in the lungs with a biological half-life of 400 days. The rapid elimination of most of the cobalt nitrate is probably related to its hygroscopic (water absorbing) properties.

Serum cobalt levels of 32 workers in a hard-metal factory showed a progressive increase from the beginning to the end of the work week (Posma and Dijstelberger, 1985). Cobalt levels in the air ranged from 12 to 2,550 μg/m^3, depending on the work area, and

mean serum cobalt levels ranged from 2.0 to 18.3 μg/L, depending on the work area. Blood cobalt levels in workers exposed to cobalt powder at concentrations ranging from 49 to 1,050 $\mu g/m^3$ were 4.9 to 47.9 μg/L (Angerer et al., 1985). Elevated cobalt levels were found in the lungs of copper smelter workers autopsied at least 5 years after retirement (Gerhardsson et al., 1984), indicating that cobalt has a long half-life in the lungs. Neither the form of cobalt nor the exposure level were reported. The mediastinal lymph nodes of hard-metal workers have also been found to have elevated cobalt levels (Hillerdal and Hartung, 1983). Elevated cobalt levels were found in a cobalt worker who died of myocardial disease (Kennedy et al., 1981). The highest tissue levels of cobalt administered intratracheally to albino rats (strain unspecified) as cobalt sulfate were observed within 24 h of dosing, in the lungs, liver, and kidney (Roshchin et al., 1989). Cobalt accumulated in myocardial tissue (the only tissue analyzed) of rats fed 0.2 mg/kg cobalt as cobalt sulfate for 8 weeks (Clyne et al., 1990).

Using leaching experiments on neutron-activated hard-metal dust, Edel et al. (1990) found that cobalt is about 17% soluble in lung cytosol and about 12% soluble in plasma. Three biochemical pools of cobalt were identified in the lung cytosol. About 56% of the cobalt was associated with low molecular weight components, constituting the diffusible cobalt pool, and about 34% was associated with proteins of molecular weight 70,000 to 80,000, which may include transferrin. A third pool ($\approx$8%) was associated with high molecular weight components. These data are consistent with the immunology data indicating that cobalt binds to proteins to form an allergen (Shirakawa et al., 1989).

Metabolism

Cobalt is an essential nutrient and is a constituent of cyanocobalamin (Vitamin B_{12}). Vitamin B_{12} plays an essential role in the maturation and development of erythrocytes and is required for the action of several enzymes (Lehninger, 1975).

Excretion

Excretion of cobalt occurs primarily in the urine, although fecal excretion is also significant in the first few days post exposure (Kreyling et al., 1986). Urinary cobalt levels in four hard-metal workers at the end of a work week ranged from about 100 to about

4,500 nmol/L (unexposed controls had 6.8 nmol/L), and correlated with exposure level (Alexandersson, 1988). Blood cobalt levels measured Friday at the end of the shift were 178 nmol/L in workers exposed to about 90 $\mu g/m^3$, compared with 8.5 nmol/L in the controls. The two subjects with the highest urinary cobalt levels exhibited biphasic excretion. The decrease in urinary concentration was rapid for the first 24 hours and slower for the next 46 hours. Even after a 4-week vacation, blood and urine levels (39 nmol/L and 83 nmol/L, respectively) in ten workers were elevated above the control values. Urinary cobalt levels of 26 workers in a hard-metal factory correlated with exposure level and showed a progressive increase from the beginning to the end of the work week (Scansetti et al., 1985). By the third week after a vacation break, excretion over the weekend was not sufficient to reduce levels to normal.

Cobalt sulfate administered intratracheally to rats was also eliminated in a biphasic manner (Roshchin et al., 1989). Palmes et al. (1959) found that urinary cobalt rose rapidly and declined rapidly in rats exposed via inhalation to mixed cobalt oxides; biphasic elimination was observed, with a half-life of about 1 day for the rapid phase.

11.6.8.3 Health Effects

Human Data

The respiratory tract is the primary target of inhalation exposure to cobalt and its compounds in humans, as summarized in Table 11-30. Much of the data on inhalation exposure of humans to cobalt and its compounds come from studies of workers exposed to hard-metal dust. Hard-metal contains 75 to 95% tungsten carbide, 5 to 20% cobalt as a binder, and small amounts of other metals such as titanium, nickel, chromium, niobium, vanadium, and tantalum (Shirakawa et al., 1989). The particles generated are <2.0 μm in diameter. Although cobalt constitutes only 5 to 20% of the material, the respiratory effects of hard-metal exposure are believed to be due to the cobalt, rather than the tungsten carbide because: (1) these effects have been seen following exposure to cobalt in the absence of tungsten carbide, and (2) laboratory animal studies indicate that tungsten carbide alone does not produce these effects. However, data noted below from acute and intermediate-duration animal studies indicate that the tungsten carbide exacerbates the toxic effects of cobalt exposure. Data also come from studies of diamond polishers exposed to a mixture of cobalt

TABLE 11-30. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Co/m^3$						
Acute							
N/A	avg 38 range 14-76	6 h	Hard-metal dust	"75% of dust in room was respirable"	Human (15) M	PF (e.g., FVC, FEV_1, PF), clinical symptoms: Subjects (all naive) were exposed in hard-metal factory. Sig dec in FVC and nonsig dec in FEV_1 were observed, compared to pre-exposure values. Coughing, expectoration, sore throat reported, but not rales or wheezing.	Kusaka et al. (1986)
Chronic							
N/A	avg 126 range 6-610	10 yr occup	Hard-metal dust	"75% of dust in room was respirable"	Human (34-68) M, (8-16) F	PF (e.g., FVC, FEV_1, PF), medical exam: No changes in pulmonary function between pre- and post-shift values. However, all measured ventilatory indices were lower than those of the controls, and $FEV_{1\%}$ was sig lower. Note: Three of the exposed subjects had asthma related to hard metal.	Kusaka et al. (1986)
N/A	17-32,470 mean of peak values	17.3, 25 yr avg at 2 plants occup	Hard-metal dust	NS	Human (281) M, (9) F	PF (FVC, FEV_1), x-ray, complete physical of affected workers: Interstitial infiltrates in 9 of 290 subjects chosen based on high exp or exp duration. Two subjects had restriction and 2 had obstructive lung defects. Cough, sputum, wheeze in some affected subjects. Symptoms progressed with further exposure. Interstitial fibrosis in one biopsy.	Sprince et al. (1984)
N/A	48 (mean present exp)	7 yr avg occup	Hard-metal dust	NS[1]	Human (828) M, (211) F	Cross sectional study; Medical history, PF (flow volume, DL_{CO}), x-ray: Work related wheeze 9.2% at ≤ 50, 18.1% at 50-100, 15.4% at >100 ($p=0.016$). DL_{CO} correlated with cumulative exp. Profusion observed in 2.6% of subjects and interstitial lung disease (based on profusion, FVC or DL_{CO}, or FEV_1/FVC) in 0.7%. Relative odds of profusion 5.1 for avg lifetime exp >100. Interstitial lung disease also found in 3 workers with avg lifetime exp <8. Suggests susceptible subpopulation.	Sprince et al. (1988)

TABLE 11-30 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Co/m^3$						
N/A	0, 5-10, 10, 60 (avg exp in last few yr)	1-19 yr occup	Hard-metal dust	NS[1]	Human (30-60) B	Case-control study; Clinical exam, x-ray, dynamic spirometry, Co in urine and blood: No statistically sig effect observed in 5-10 group. Inc chest tightness and chronic bronchitis in 10 group. All groups showed dec compared to controls in spirometry (FEV_1, FEV%) Monday morning before work; effect sig at 60 for FEV_1. FVC not affected. Effects indicate obstructive change. In 60 group, dec FEV_1 correlated with yrs exp. Note: Controls individually matched with regard to length of employment, smoking. 60 $\mu g/m^3$ largest group, strongest statistical power.	Alexandersson and Swensson (1979)
N/A	0 30-272 mean, dep on area	avg 13.2-17.8 yr occup	Hard-metal, "soft powder"	NS	Human (69-351) M, (19-74) F	Cross sectional study; Medical history, bronchial hyperreactivity, PF (FEV, flow volume, CO): Cough and sputum more frequent in exp workers. Inc incidence of obstructive and restrictive syndrome, with larger effect in women. Exposure-related changes in the steady state carbon monoxide uptake (TCO_{SS}). Marked inc in bronchial hyperreactivity in women. Slight abnormalities in x-rays more frequent in men. Those with abnormal x-rays had lower FVC, FEV_1, CO indices.	Meyer-Bisch et al. (1989)
N/A	4-55	NS occup	Hard-metal dust	NS[1]	Human (3) NS	Case studies; BAL, lung biopsy, CS, lung function: interstitial pneumonitis, interstitial fibrosis, dec FVC, cough, dyspnea, inc macrophages in BAL fluid.	Barnhart et al. 1991

TABLE 11-30 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Co/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 15.2, 136 (geom. means) range 6-2875	6 yr avg occup	Cobalt/ diamond dust	NS	Human (11-34) M, (12-14) F	PF (e.g., FVC, FEV_1, PEFR), urinary Co, resp symptoms: Dec values of FVC, FEV_1, MEF_{75}; resp symptoms (cough, sputum, dyspnea) more common in exposed group. Among exp nonsmokers, higher urinary Co and lower PF values in those exp >5 yr, compared to those exp <5 yr. Symptoms compatible with moderate restrictive syndrome; obstructive component also possible. Concomitant oral exp likely.	Gennart and Lauwerys (1990)
N/A	50-1000	5-18 yr occup	Cobalt/ diamond dust	NS	Human (2) F, (4) M	Medical history, lung function tests, bronchoscopy, chest x-rays; BAL fluid analysis: All cases had tracheobronchitis, mild increases in total cells in BAL fluid. Inc T-lymphocytes and inversion of helper/suppressor ratio in 3 cases. Cytology of one worker with interstitial lung disease was comparable to that of 5 other "symptomless" workers among those with the longest exposures.	Mosconi et al. (1991)
N/A	1-57	>6 mo (case-control) 7.3 yr avg (cross-sectional) occup	Cobalt sulfate, cobalt metal dust	~25% of all dust particles <3 μm	Human (151, 224) B	Case-control study of asthma, cross-sectional study of chronic bronchitis and decreased pulmonary capacity: Occupational asthma (relative risk 4.1); symptoms reversed in most subjects when exposure removed. 5/15 gave positive response when challenged with cobalt chloride. In cross-sectional study, symptoms of chronic bronchitis (cough, phlegm, and wheezing) more elevated in cobalt workers who smoked than other smokers. No evident effect on nonsmoking pop. Note: Workers in 3 areas studied; in one, personal monitoring was 1-57 $\mu g/m^3$. In second, it was 1.3-9.5 $\mu g\ Co/m^3$ as cobalt sulfate on dust particles, and air in third had 10 to 100 $\mu g/m^3$ metallic cobalt. Concomitant to SO_2 expos.	Roto (1980)

TABLE 11-30 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Co/m^3						
N/A	100-3,000	10.7 yr avg (range 2-31 yr) occup	cobalt salts and oxides (not further described)	NS	Human (46) M	Resp symptoms (questionnaire), PF (FEV_1, FVC), chest x-ray: No sig difference on any parameter. Note: Two potentially sensitive workers had left work area before the study and were not included. One had developed asthma and the other had a positive cobalt skin patch test. Note: Exposure based on personal monitoring; most exposure $\leq$1,100 $\mu g/m^3$.	Morgan (1983)
N/A	49-1,046	11.3 yr avg occup	Cobalt metal powder	NS	Human (40)NS	Chest x-ray, ECG, hematology: No effects observed.	Angerer et al. (1985)
N/A	NS	1-40 yr occup	Cobalt metal dust cobalt chloride aerosol	NS	Human NS	Cancer mortality: Cohort study of 1,143 workers at plant; number of Co workers NS. Inc death rate from malignant tumors (SMR = 1.65) and lung cancer (SMR = 4.66, $p<0.05$) in unstated number of cobalt workers. In a case control analysis of 7 cobalt workers and 20 matched controls, higher lung cancer mortality in cobalt workers, but effect not statistically sig.	Mur et al. (1987)

Abbreviations:

avg = average; B = both male and female; BAL = bronchoalveolar lavage; Co = cobalt; CO = carbon monoxide; CS = clinical signs; d = day; dec = decreased; dep = depending; DL_{CO} = diffusing capacity for carbon monoxide; ECG = electrocardiogram; EM = electron microscopy; exp = exposure; F = female; FEV_1 = forced expiratory flow in 1 second; $FEV_{1\%}$ = forced expiratory flow at 1%; FVC = forced vital capacity; geom = geometric; h = hour; HP = histopathology; inc = increased; LM = light microscopy; M = male; MEF_{75} = mean expiratory flow at 75%; MMAD = mass median aerodynamic diameter; mo = month; N/A = not applicable; nonsig = nonsignificant; NS = not specified; occup = occupational; PF = pulmonary function; PEFR = peak expiratory flow rate; pop = population; ppm = parts per million; resp = respiratory; sig = significant(ly); SMR = standard mortality ratio; TCO_{SS} = steady state carbon monoxide uptake; VC = vital capacity; wk = week; wt = weight; yr = years.

and diamond dust (Gennart and Lauwerys, 1990). Diamond polishing dust was analyzed by Van den Oever et al. (1990) and found to contain no fibrinogenic materials and none of the metals present in hard metal, except cobalt. In the one human epidemiological study of exposure to cobalt metal dust, results of exposure to cobalt metal were reported together with results for cobalt sulfate (Roto, 1980).

Human respiratory effects of cobalt inhalation are asthma and interstitial lung disease (fibrosis). Symptoms related to interstitial lung disease include small opacities (indicative of interstitial infiltrates) on radiographs, work-related wheeze, and reduced values of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DL_{CO}) (Sprince et al., 1984, 1988). Others have observed decreased FEV_1 and FEV% (but unchanged FVC), indicating obstructive alterations (Alexandersson and Swensson, 1979). Hard metal workers in Italy were found to have reduced carbon monoxide diffusing capacity (Suardi et al., 1994). There are also data suggesting that certain subpopulations may be more sensitive than others. Among a cohort of 1,039 tungsten carbide workers, most of the affected workers experienced short-term exposures to cobalt levels exceeding 300 $\mu g/m^3$, but three affected subjects were exposed to <50 μg cobalt/m^3 (Sprince et al. 1988).

Symptoms similar to those observed following exposure to hard-metal dust (dyspnea, cough, and decreased FVC, FEV_1, and mean expiratory flow at 75% of FVC [MEF_{75}]) occurred in workers in a plant producing diamond-cobalt saws, where exposure was to cobalt, without tungsten carbide (Gennart and Lauwerys, 1990). The study authors concluded that the results were compatible with a moderate restrictive syndrome, but an obstructive component could not be ruled out. Both obstructive (defined as normal vital capacity with decreased FEV_1 or MMEF) and restrictive (defined as decreased VC and TLC, with normal FEV_1/VC ratio) syndromes were observed in a cross-sectional study of hard-metal workers exposed to levels of 45 to 272 μg cobalt/m^3, or 30 to 210 μg cobalt/m^3, depending on the factory. Cough, sputum, and bronchial hyperreactivity were also observed (Meyer-Bisch et al., 1989).

There are several case studies of respiratory symptoms in workers occupationally exposed to cobalt. Ohori et al. (1989) presented four case studies of giant-cell interstitial pneumonia (characterized by decreased FVC and interstitial fibrosis) that developed in people

who had worked with hard metal for 3 to 13 years. No exposure levels were available, but the particle size was described as less than 2.0 μm in diameter. Symptoms of occupational asthma (dyspnea and airway hyperresponsiveness) and interstitial lung disease (crackles and leucocytosis following cobalt challenge) were found in a diamond polisher with a history of dyspnea and chest tightness associated with exposure to diamond-cobalt disks (Van Cutsem et al., 1987).

Asthma due to cobalt inhalation clearly has an immunological component. Cobalt-specific antibodies and elevated immunoglobulin IgE levels have been detected in occupational asthma, but no exposure levels were reported (Shirakawa et al., 1989). Cobalt hypersensitivity is specific to the cobalt-sensitized population (Roto, 1980). In order to provoke an antibody-mediated response, cobalt metal would have to be converted to ionized cobalt on the bronchial mucosa to act as a hapten; the complete antigen would be formed by complexing with host proteins (Shirakawa et al., 1988). Significantly elevated IgA levels and slightly but significantly decreased IgE levels were reported in a study of 35 cobalt production workers where exposure was not assessed (Bencko et al., 1986). The finding in this study of elevated levels of serum proteins known as acute reactants (α_1-antitrypsin, α_2-macroglobulin, transferrin, ceruloplasmin, and lysozyme) suggests that cell-mediated immunity may also be involved. Irritation from cobalt particles probably contributes to interstitial lung disease, but this effect may also have an immunotoxic component. Three cases of diamond polishers with occupational asthma attributed to cobalt exposure had positive cobalt inhalation challenge tests, and exposure to cobalt temporarily increased nonspecific hyperreactivity (Gheysens et al., 1985). By contrast, the reaction to histamine challenge in a control diamond polisher with documented asthma was unaffected by pre-exposure to cobalt, indicating that the effect of cobalt was not due to nonspecific irritation.

Other studies have used bronchoalveolar lavage to study the possible role of allergic mechanisms in respiratory symptoms related to cobalt exposure. Mosconi et al. (1991) examined workers producing cobalt-diamond stone cutting who were exposed to 50 to 1000 μg cobalt/m^3. They found a marked increase in the levels of T lymphocytes, suggestive of chronic hypersensitivity. In three of the workers, the helper/suppressor ratio was reversed. In an abstract, Barnhart et al. (1991) reported pneumoconiosis, accompanied by elevated macrophage and lymphocyte levels in bronchoalveolar lavage fluid, in hard-metal workers

exposed to low cobalt levels (4 to 55 μg cobalt/m^3). Eosinophils were found in bronchoalveolar lavage or in lung biopsies from case studies of hard-metal workers with dyspnea, indicating that cell-mediated immunity plays a role in the toxic response to cobalt (Davison et al., 1983).

Workers exposed to hard-metal or cobalt dust developed acute hypersensitivity pneumonitis, interstitial fibrosis, and multinucleated giant cell pneumonitis (Cugell et al., 1990). Increases of lymphocytes and neutrophils in bronchoalveolar lavage fluid indicated active alveolitis. A metal-coating worker developed shortness of breath and interstitial fibrosis with numerous macrophages and multinucleated giant cells following exposure for 7 years (Beckett, 1992). Fischbein et al. (1986) described two cases of interstitial lung disease in hard-metal workers. Clinical signs included dyspnea and a productive cough. Lung biopsy found interstitial fibrosis and giant cell interstitial pneumonia. Interstitial lung disease leading to death, possibly as a complication of oxygen therapy, was reported in a case study of a diamond polisher (Nemery et al., 1990). Autopsy revealed pronounced mural fibrosis of the lung with an active interstitial and intraalveolar inflammatory exudate and multinucleated giant cells in the alveolar lumina.

Rubin et al. (1986) found no evidence of lung fibrosis in 315 employees of two hard-metal factories. No data on exposure levels were provided. It is not clear why no effect was observed, but it could be because sensitive workers had left the department. Morgan (1983) found no x-ray changes or effect on lung function in 46 workers exposed to 100 to 3,000 μg cobalt/m^3 in the manufacture of cobalt salts; most exposures were below 1,100 μg cobalt/m^3. The study did not include two affected workers (one with asthma and one with a positive cobalt skin test) who had moved out of the work area prior to the study. Pulmonary function tests and x-ray analysis revealed no respiratory effects on 40 workers who had been exposed to cobalt powder for an average of 11.3 years (Angerer et al., 1985). Average cobalt levels were 49 to 1,046 μg/m^3. No details of the physiological analysis were reported. Small sample size or the removal of a sensitive subpopulation could account for the lack of respiratory effects in the Morgan (1983) and Angerer et al. (1985) studies. Alternatively, the latter study suggests that respiratory effects may not occur following exposure to cobalt powder at cobalt levels that would produce fibrosis in populations exposed to cobalt in hard metal.

Cardiovascular effects of cobalt were first noticed following large oral doses of cobalt (Morin et al., 1971), but there is evidence suggesting that inhalation exposure to cobalt can also cause cardiovascular effects. Horowitz et al. (1988) found a weak correlation between reduced left ventricular function and duration of cobalt exposure in 30 hard-metal workers who had been exposed to undetermined cobalt levels for 10 ± 5 years. This result was attributed to early cor pulmonale related to hard-metal pneumoconiosis. Kennedy et al. (1981) reported a case of fatal myocardial disease due to occupational exposure to cobalt powder; elevated cobalt levels were found in the myocardium. Subsequent personal monitoring of workers at the factory revealed cobalt levels "well in excess" of 100 $\mu g/m^3$. The cardiotoxic effects of cobalt have been attributed to cobalt producing a biochemical block at the same point in the myocardial metabolic pathway as where a thiamine deficiency would be evident (Heggtveit et al., 1970). Another case of fatal cardiomyopathy due to occupational cobalt exposure was described by Barborik and Dusek (1972).

In comparing 12 hard-metal workers with pulmonary symptoms and 26 controls, the exposed workers had verbal memory and attention deficits (Jordan et al., 1990). No exposure information was available and no tests were conducted to determine the hard metal component responsible for observed effects. Meecham and Humphrey (1991) reported that a worker exposed to cobalt powder for 20 mo developed optic atrophy and nerve deafness. Both symptoms lessened after exposure stopped; 3 mo postexposure, blood cobalt was 234 $\mu g/L$ (normal < 2 $\mu g/L$).

Mur et al. (1987) assessed the effect of exposure to cobalt metal dust and cobalt chloride on cancer mortality in an electrochemical plant. Among exposed workers, the lung cancer death rate was elevated (SMR = 4.66; $P < 0.05$). In a small case-control study, cobalt exposure was more common among the lung cancer deaths than in the general plant population, but the effect was not statistically significant. In addition, there were concomitant exposures to other chemicals, such as arsenic and nickel.

No studies were located on the reproductive or developmental effects in humans of inhaled cobalt compounds.

Laboratory Animal Data

Inhalation toxicity data for laboratory animals are summarized in Table 11-31. Studies in laboratory animals confirm the respiratory tract as the major target of cobalt toxicity. Acute exposure to high levels have also found effects on the thymus and testes. Animal studies differ from the available human studies in reporting effects on the upper respiratory tract, including the nose and larynx, that were not reported in humans. This may be due to the use of a soluble cobalt compound in the laboratory animal studies, to the greater sensitivity of URT evaluation (e.g., histopathology) in laboratory animal studies, to differences in URT dosimetry between laboratory animal species and humans, to the the high exposures used in experimental studies, or to species sensitivity. Polycythemia (nonadverse increases red blood cells) occurs at higher cobalt concentrations as a result of the role of cobalt and vitamin B_{12} in hematopoiesis.

Only two studies were found on the effects of acute exposure of animals to cobalt compounds. Rats exposed to mixed cobalt oxides at $\geq$7,000 $\mu g/m^3$ for 30 min had pulmonary edema (Palmes et al., 1959). Bucher (1991) exposed rats and mice to 38, 190, 1,900, 19,000, or 76,000 μg cobalt/m^3 as cobalt sulfate for 6 hours/day, 5 days/week, for 16 exposures. Effects at $\leq$1,900 $\mu g/m^3$ were poorly described, but red discoloration of the lungs was reported at 1,900 $\mu g/m^3$ in rats. Histopathological changes included inflammation and necrosis of the respiratory epithelium of the larynx, trachea, brochioles, and respiratory turbinates of the nose. These effects were seen at $\geq$19,000 $\mu g/m^3$ in rats, and $\geq$1,900 $\mu g/m^3$ in mice, the only levels that were histologically analyzed.

In F344/N rats and B6C3F_1 mice exposed to a cobalt sulfate aerosol at 0, 110, 380, 1,140, 3,800, or 11,400 $\mu g/m^3$ for 6 hours/day, 5 days/week for 13 weeks, compound-related lesions were limited to the respiratory tract (Bucher, 1991; Bucher et al., 1990). At the lowest concentration, squamous metaplasia of the larynx and infiltration of histiocytes to the alveolar space were observed in both rats and mice. Effects at higher concentrations ($\geq$3,800 $\mu g/m^3$) included fibrosis, inflammation, and degeneration of the olfactory epithelium, but no evidence of heart damage, based on histopathology or enzyme levels.

Among miniature swine exposed to pure cobalt metal powder to 100 or 1,000 $\mu g/m^3$ for 6 hours/day, 5 days/week for 3 mo, total compliance and tidal volume were decreased,

TABLE 11-31. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Co/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
N/A	0 7000 26000 83000 90000 106000 116000 137000 179000 236000	30 min	Cobalt mixed oxide, cobalt carbonate dust	"the overall median size was 0.1 μm diameter, or 0.3 μm mass median diameter. There are many particles of about 0.01 μm diameter."	Rat, NS (5) NS	Lung and body wt, gross necropsy: Pulmonary edema at 7000 and up. Gross damage (defined as "any one or more of hemorrhage, edema, consolidation, congestion, pleuritis, bronchiectasis, emphysema, or atelectasis") observed at all levels. Animals were sacrificed 24 h postexposure. Note: In a separate experiment, deaths were observed at $\geq$78000 following a 30 min exposure. Note: The exposure material was not well characterized, but was produced as breakdown products of cobalt carbonyl.	Palmes et al. (1959)
N/A	0 38 190 1900 19000 76000	6 h/d 5 d/wk 16 exp	Cobalt sulfate ($CoSO_4 \cdot 7H_2O$) aerosol	1 μm MMAD range: 0.83-1.10 μm	Rat, F344/N (5) M, (5) F	Histology of major organs (3 top levels), wt gain, lethality: No effect on wt gain or survival at $\leq$1900. Resp tract lesions reported at 1900, but not further described, except "red discoloration and increased firmness in the lungs." Survival dec at $\geq$19000 in males and at 76000 in females. HP described at only at $\geq$19000, and included (at both levels) inflammation and necrosis of resp epithelium of larynx, trachea, bronchioles, and respiratory turbinates of nose; degeneration of olfactory epithelium of nose; squamous metaplasia of the larynx. Hemorrhage into alveolar spaces at 76000. Also lymphoid necrosis of thymus in animals that died, and atrophy of testis at 19000.	Bucher (1991)

TABLE 11-31 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Co/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 38 190 1900 19000 76000	6 h/d 5 d/wk 16 exp	Cobalt sulfate ($CoSO_4 \cdot 7H_2O$) aerosol	1 μm MMAD range: 0.83-1.10 μm	Mouse, $B6C3F_1$ (5) M, (5) F	Histology of major organs (3 top levels), wt gain, lethality: Survival dec at $\geq$19,000 $\mu g/m^3$. Animals also lost wt at 19,000 $\mu g/m^3$. HP showed the following at $\geq$1900: inflammation and necrosis of the respiratory epithelium of larynx, trachea, bronchioles, and respiratory turbinates of nose; degeneration of olfactory epithelium of nose. At 19,000 $\mu g/m^3$, squamous hyperplasia of the larynx and regeneration of the bronchiolar epithelium in the lung. Animals that died also had lymphoid necrosis of thymus, necrosis of hepatocytes. Note: No HP done at 38 or 190 $\mu g/m^3$.	Bucher (1991)
Subchronic and Chronic							
N/A	0 9000	7 h/d 5 d/wk 3 mo	Cobalt mixed oxides, cobalt carbonate dust	"the overall median size was 0.1 μm diameter, or 0.3 μm mass median diameter. There are many particles of about 0.01 μm diameter."	Rat, NS (41-75) NS	Body wt, gross necropsy, HP of major organs, hematology, urinary cobalt: Lung edema, nodules consisting of large macrophages with foamy cytoplasm. Also moderate interstitial and peribronchial fibrosis, mild emphysema, moderate peribronchial lymphoid hyperplasia. Inc hemoglobin in exposed animals (not necessarily adverse). No effect on organs other than lung. Note: 11 deaths at beginning of experiment attributed to infection weakening resistance to cobalt. Note: The exposure material was not well characterized, but was produced as breakdown products of cobalt carbonyl.	Palmes et al. (1959)
N/A	0 400 2000	6 h/d 5 d/wk 14-16 wk	Cobalt chloride	MMAD ~1μm σ_g NS	Rabbit, NS (8) M	LM and EM of lung: Interstitial inflammation and abnormal accumulation of enlarged alveolar macrophages at both levels. Also nodular aggregation of type II cells, and focal swelling of type I and type II cells, with some type II cells missing microvilli. Incidence and severity inc with exp concentration.	Johansson et al. (1987)

TABLE 11-31 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Co/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 110 380 1140 3800 11400	6 h/d 5 d/wk 13 wk	Cobalt sulfate ($CoSO_4 \cdot 7H_2O$) aerosol	1 μm MMAD range: 0.83-1.10 μm	Rat, F344/N (10) M, (10) F	Histology of resp tract, hematology, thyroid function, urinalysis, serum chemistry, sperm morphology, vaginal cytology, estrous stage, wt. gain, lethality: Squamous metaplasia of the larynx, infiltration of histiocytes to alveolar space at 110. More severe effects on lung, nose, and larynx at higher levels. Inc relative kidney and lung wt in males at all levels, and inc lung wt in females at $\geq$380. No effects on sperm parameters or estrous cycle. Note: Total amount of Co in 16 h urine ranged from 2.5 to 105 μg in males and from 2.0 to 67 μg in females (from low to high exposure level).	Bucher et al. (1990); Bucher (1991)
N/A	0 110 380 1140 3800 11400	6 h/d 5 d/wk 13 wk	Cobalt sulfate ($CoSO_4 \cdot 7H_2O$) aerosol	1 μm MMAD range: 0.83-1.10 μm	Mouse, $B6C3F_1$ (10) M, (10) F	Histology of resp tract, hematology, thyroid function, urinalysis, serum chemistry, sperm morphology, vaginal cytology, estrous stage, wt. gain, lethality: Compound-related HP was limited to resp tract and were concentration related. At 110, squamous metaplasia of the larynx, infiltration of histiocytes to alveolar space. Similar effects at 380. More severe effects on lung, nose, and larynx at higher levels, including degeneration of olfactory epithelium, squamous metaplasia of respiratory epithelium of nose at $\geq$3800. Inc absolute and relative lung wt at $\geq$3800. Dec epididymal wt in males at 11400, and sig dec sperm motility at $\geq$1140. Estrous cycle sig longer at 11400.	Bucher et al. (1990); Bucher (1991)
N/A	0 100 1000	6 h/d 5 d/wk 3 mo	Cobalt metal powder	size range 0.4 to 3.6 μm σ_g NS	Swine, Miniature (5) NS	PF, ECG, x-ray, biopsy, urinary Co: Dec compliance and tidal volume at $\geq$100; cardiomyopathy; no visible effect on x-ray; no interstitial fibrosis or alveolar exudate Note: Exp for a week, not exp for 10 days to allow for the development of sensitization, and then exp for 3 mo.	Kerfoot et al. (1975)

TABLE 11-31 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR COBALT AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Co/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 1000	6 h/d 5 d/wk 13 wk	Cobalt dust	MMAD = ~4.1μm σ_g = 1.9	Rat, F344 (24) M	PF (lung volume, static and dynamic mechanics, DL_{CO}), HP of lung: No effect on lung function. End-airway inflammation, mild-to-moderate interstitial thickening. Foamy macrophages, suggesting lipid accumulation. Note: Observed HP more severe in combination with 15000 $\mu g/m^3$ tungsten carbide.	Costa et al. (1990)
N/A	0 500 2000	6 h/d 5 d/wk 1-8 mo	Cobalt chloride	NS	Rabbit, NS (NS) M	LM and EM of lung, morphology and function of alveolar macrophages, phospholipid levels: Nodular proliferation of type II alveolar cells and macrophage stimulation after 1 mo of exposure at 500. At 4 mo, nodular hyperplasia of type II cells, accumulation of enlarged macrophages, hyperreactive type II cells, interstitial inflammation at $\geq$500.	Johansson and Camner (1986)
N/A	0 7,900	7 h/day 5 days/week 14 mo	Cobalt oxide aerosol	"Respirable" aerosol	Hamster, Syrian golden (51) M	HP: Pneumoconiotic lesions with emphysema component; tumor incidence: No carcinogenic effects seen. Note: Few study details available.	Wehner etal. (1972)

Abbreviations:

avg = average; B = both male and female; BAL = bronchoalveolar lavage; Co = cobalt; CO = carbon monoxide; CS = clinical signs; d = day; dec = decreased; dep = depending; DL_{CO} = diffusing capacity for carbon monoxide; ECG = electrocardiogram; EM = electron microscopy; exp = exposure; F = female; FEV_1 = forced expiratory flow in 1 second; $FEV_{1\%}$ = forced expiratory flow at 1%; FVC = forced vital capacity; geom = geometric; h = hour; HP = histopathology; inc = increased; LM = light microscopy; M = male; MEF_{75} = mean expiratory flow at 75%; MMAD = mass median aerodynamic diameter; mo = month; N/A = not applicable; nonsig = nonsignificant; NS = not specified; occup = occupational; PF = pulmonary function; PEFR = peak expiratory flow rate; pop = population; ppm = parts per million; resp = respiratory; sig = significant(ly); SMR = standard mortality ratio; TCO_{SS} = steady state carbon monoxide uptake; VC = vital capacity; wk = week; wt = weight; yr = years.

but there was no histological evidence of inflammation, interstitial pneumonitis, or fibrosis (Kerfoot et al., 1975). Cardiomyopathy was observed at both levels.

Male rabbits exposed to 500 or 2,000 $\mu g/m^3$ cobalt as cobalt chloride for 6 hours/day, 5 days/week for 4 mo developed nodular hyperplasia of type II alveolar cells and accumulation of enlarged macrophages in reactive areas (Johansson and Camner, 1986).

Evidence from several studies in animals suggests that the symptoms of hard-metal disease are due to cobalt rather than tungsten carbide, but the presence of tungsten carbide can exacerbate the respiratory effects of cobalt exposure. Costa et al. (1990) reported in an abstract that end-airway inflammation and interstitial thickening was more severe in rats exposed to 1,000 μg cobalt/m^3 and tungsten carbide (15,000 $\mu g/m^3$) than in rats exposed to 1,000 μg cobalt/m^3 alone. Lasfargues et al. (1992) found higher mortality and more severe lung inflammation in rats exposed by intratracheal installation to suspensions of tungsten carbide-cobalt (cobalt dose 10,000 $\mu g/kg$), compared with rats exposed to cobalt (10,000 $\mu g/kg$) alone. Urinary cobalt was higher when the cobalt was co-administered with tungsten carbide, suggesting that tungsten carbide may increase cobalt absorption. In an *in vitro* study, Lison and Lauwerys (1990) found that adding tungsten carbide increased cobalt uptake in mouse and rat macrophages, and increased the resulting cytotoxicity.

In the one study located that assessed the carcinogenicity of inhalation exposure to cobalt, treatment of hamsters with 7,900 μg cobalt/m^3 as cobalt oxide for 7 h/day, 5 days/week for 14 mo did not increase the incidence of benign or malignant tumors; however, pneumoconiosis with lung consolidation was seen in animals with increasing age and exposure time (Wehner and Craig, 1972).

No studies were located on the reproductive or developmental effects in animals of inhaled cobalt compounds.

11.6.8.4 Factors Affecting Susceptibility

Because the primary target of inhaled cobalt is the respiratory tract, individuals with respiratory impairments may be at increased risk for toxic effects. Some cobalt-exposed workers develop an immune reaction to cobalt that is associated with asthma (Roto 1980; Shirakawa et al., 1988, 1989). People who have developed this hypersensitivity would be expected to be affected by cobalt toxicity at much lower levels than others. The developing

respiratory tract of children may also pose an increased susceptibility. Sprince et al. (1988) also reported that certain individuals were more sensitive than others to interstitial lung disease resulting from cobalt exposure. Because some of the more sensitive workers were not reported to have experienced previous exposure to a sensitizing concentration, it appears that some unknown mechanism may account for their increased susceptibility. Two different mechanisms may be operating to determine sensitive subpopulations for the two different endpoints (asthma and interstitial lung disease).

Oral (Morin et al., 1971) and inhalation (Horowitz et al. 1988; Kennedy et al. 1981) exposure to cobalt has been associated with cardiovascular effects. This suggests that people with cardiovascular disease may have increased susceptibility to cobalt toxicity.

11.6.9 Copper

11.6.9.1 Chemical and Physical Properties

Copper is a reddish colored, malleable, ductile metal that has a bright metallic luster. It may be found in nature in its elemental form. Copper is the first element of group 11 (IB) of the periodic system of elements. Copper demonstrates four oxidation states, 0, +1, +2, and +3, of which +1 and +2 are the most important (George, 1993; Hazardous Substance Data Bank, 1995; Richardson, 1993). When elemental copper is exposed to water or moist air, copper sulfides and oxides are initially formed. Further oxidation and reaction with water yields basic copper sulfates, such as $CuSO_4 \cdot Cu(OH)_2$ and $CuSO_4 \cdot 3Cu(OH)_2$ (George, 1993). Copper(+1) disproportionates spontaneously in aqueous solutions to elemental copper and copper(+2) (Richardson, 1993). Copper(+2) is the most stable oxidation state (Brady and Humiston, 1986). Copper forms compounds with the anions of both strong and weak acids (George, 1993). It also forms organometallic compounds (Richardson, 1993). Elemental copper is insoluble in water, whereas copper (+1) chloride (CuCl), copper (+2) chloride dihydrate ($CuCl_2 \cdot 2H_2O$) and copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) are poorly soluble at low temperatures (ca 0 °C) and moderately soluble at high temperatures (ca. 100 °C).

11.6.9.2 Pharmacokinetics

There is limited information on the pharmacokinetic properties of copper following inhalation exposure. There are no studies available regarding the rate and extent of distribution or excretion of copper following inhalation exposure of humans or laboratory animals. Most of the following information provided on copper absorption, distribution, metabolism and excretion are based on oral exposure data.

Serum copper levels were reported in humans in the range of 100 to 220 μg/dL in humans following chronic occupational exposure to copper dust (Suciu et al., 1981). Armstrong et al. (1983) reported human urinary copper levels ranging from <20 to 180 ug/L after acute exposure to copper fumes. In animals, Batsura (1969) reported that copper oxide was observed in alveolar capillaries 3 h after rats were exposed to a welding dust aerosol generated from pure copper wires.

According to oral exposure studies, absorbed copper loosely binds to and is transported by plasma albumin (Marceau et al., 1970), or the plasma protein transcuprein (Weiss and Linder, 1985). At the liver it is incorporated into ceruloplasmin and released into the plasma. Copper metabolism involves the transfer to and from various organic ligands, most notably sulfhydryls and imidazole groups on amino acids and proteins. Copper is stored bound to metallothionein and amino acids and in association with copper-dependent enzymes. There are several studies that have shown an increase in metallothionein synthesis in animals injected with copper compounds; however, metallothionein synthesis has not been investigated following inhalation exposure (Mercer et al., 1981; Sugawara et al., 1991; Wake and Mercer, 1985). Mehra and Bremner (1984) suggested that increased levels of metallothionein may be associated with resistance to copper toxicity in pigs. Exposure to high levels of dietary copper has also been shown to induce ceruloplasmin biosynthesis in the liver (Haywood and Comerford, 1980). As previously stated, copper is incorporated into ceruloplasmin in the liver and then released into the plasma. Bile is the major excretion pathway for copper based on oral exposure studies. Oral administration of radioactive copper, as copper acetate, resulted in 72% excreted in the feces (Bush et al., 1955). Normally, 0.5 to 3.0% of daily copper intake is excreted into the urine (Cartwright and Wintrobe, 1964). Biliary copper is associated with low molecular weight copper binding

components as well as macromolecular binding species (Gollan and Dellar, 1973). Farrer and Mistilis (1967) reported that the reabsorption of biliary copper is negligible.

11.6.9.3 Health Effects

Human Data

The data on human exposure to copper by inhalation are limited. The major target organ appears to be the respiratory system, but the data are limited to occupational studies. Data are primarily based on subjective symptoms without indications of pulmonary function changes as a result of occupational exposure as discussed in Table 11-32. The observed symptoms may also be due to exposure to copper by both oral and inhalation routes since exposures were confounded. The lack of control workers is also a limitation in evaluating the human data available for copper exposure by inhalation.

Acute inhalation exposure to copper in humans has primarily resulted in a combination of respiratory symptoms (Armstrong et al., 1983). Upper respiratory irritation has been reported with exposure to copper fumes; however, exposure data were not provided (American Conference of Governmental Industrial Hygienists, 1991). Armstrong et al. (1983) reported the following symptoms (in order of number of workers affected): fever, dyspnea, chills, headache, nausea, myalgia, cough, shortness of breath, a sweet metallic taste and vomiting in factory workers accidentally exposed to copper fumes for 1 to 10 h as a result of cutting pipes known to contain copper. These symptoms are consistent with metal fume fever, an acute disease induced by inhalation of metal oxides that temporarily impairs pulmonary function but does not progress to chronic lung disease (Stokinger, 1981). Airborne copper concentration during the exposure period was not reported. It was reported that 5 of 12 workers hospitalized following the acute exposure had urine copper levels greater than 50 μg/L. Since the major route of excretion of copper is biliary, the elevated urine copper levels reported suggest that the exposure concentration was relatively high. Copper levels were not determined for control workers in this study which limits the interpretation of the urinary copper values as an indicator of copper inhalation exposure. Armstrong et al. (1983) also reported evidence of minimal elevation of serum lactate dehydrogenase (in 3 of 14 workers evaluated) and leukocytosis (in 21 of 24 workers evaluated). Nonspecific complaints of discomfort and chills were reported among several

TABLE 11-32. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COPPER AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ Cu/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
N/A	NS	1-10 h occup	Cu fumes	NS	Human (26) NS	Subjective symptoms and clinical tests (CBC, LDH determination, urinalysis) after outbreak of metal fume fever: Fever, dyspnea, chills, headache, nausea, myalgia, cough, shortness of breath, sweet metallic taste, vomiting. Leukocytosis, elevated LDH levels, 5/12 workers had urine copper levels >50 $\mu g/L$. Workers were cutting pipes known to contain approx 90% Cu, 10% Ni, trace amounts of Zn.	Armstrong et al. (1983)
N/A	75,000-120,000	few weeks occup	Cu dust	"extremely fine"	Human (NS)	Subjective symptoms: Complaints of discomfort similar to onset of common cold; chills or warmth; stuffiness of the head. Note: Actual exposures may have been higher when work being carried out. Symtpoms ceases when ventilation improved.	Gleason (1968)
N/A	NR	1-60 mo occup	Cu (II) dust	NS	Human (10) M	Nose and throat examinations, subjective symptoms: 6/11 workers had nasal mucosa characterized by increased vascularity and superficial epistatic vessels. Symptoms included runny nose and mucosal irritation in mouth and eyes.	Askergren and Mellgren (1975)

TABLE 11-32 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR COPPER AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration μg Cu/m^3	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain (Number) Sex,	Assays performed: Effect(s)	Reference
Chronic Studies							
N/A	464,000 (464,000 1st year; 132,000 2nd year; 111,000 3rd year; NR 4th year)	4 year occup	Cu dust 99.9%	NS	Human (75-100) NS	Annual examinations in the following categories: Respiratory: Radiography showed linear pulmonary fibrosis and in some cases nodulation. Symptoms included coughing, sneezing, yellowish-green expectoration, and thoracic pain. Gastrointestinal: Symptoms included anorexia, nausea, and diarrhea. Hepatic: Hepatomegaly (39% in first yr, 50% in second yr, 70% in third yr, 56% in fourth year). Neurological: Symptoms in >17% included headache, vertigo, drowsiness, polyneuritic syndromes with subjective troubles of sensitivity (paresthesia and spontaneous pains in limbs), irritability, disturbances in motor reactions, neurasthenic syndrome. Serum copper levels in polyneuritic syndrome were 100-180 ug/dL, in neurasthenic syndrome they were 180-220 ug/dL. Reproductive: Sexual impotence in 16% of workers.	Suciu et al. (1981)

Abbreviations:

1st = first; 2nd = second; 3rd = third; 4th = fourth; approx = approximately; Cu = copper; $CuSO_4$ = copper sulfate; $CuCl_2$ = copper chloride; d = day; dec = decreased; HP = histopathology; inc = increased; h = hour; LDH = lactate dehydrogenase; LM = light microscopy; M = male; $\mu g/m^3$ = micrograms per cubic meter; MMAD = mass median aerodynamic diameter; mo = month; NA = not applicable; NBT = nitroblue tetrazolium; Ni = nickel; NS = not specified; occup = occupational exposure; ppm = parts per million; SEM = scanning electron microscopy; σ_g = geometric standard deviation of distribution; wk = week; yr = years; Zn = zinc.

workers within a few weeks of beginning operation of a copper plate polishing operation. Exposure levels of 75 to 120 $\mu g/m^3$ were measured (Gleason, 1968).

In a epidemiological study by Suciu et al. (1981), factory workers exposed to copper dust received annual physical and clinical examinations during a 4 year exposure period. The reported air copper levels were not reported for the first year, were 464,000 μg Cu/m^3 in the second year; 132,000 μg Cu/m^3 in the third year; and 111,000 μg Cu/m^3 in the fourth year. Although inhalation was considered to be the major route of exposure for these workers, it was likely that a portion of the airborne copper was trapped in the upper respiratory tract and swallowed. This assumption was made based on the gastrointestinal effects that were observed in these workers in addition to the respiratory effects. Respiratory effects reported included symptoms of coughing, sneezing, yellowish-green expectoration, dyspnea, and thoracic pain. Radiography revealed linear pulmonary fibrosis and in some cases nodulation. Gastrointestinal symptoms included anorexia, nausea and diarrhea. Hepatic effects included hepatomegaly (39% in first year, 50% in second year, 70% in third year and 56% in fourth year). Neurological symptoms in >17% of the workers included headache, vertigo, drowsiness, polyneuritic syndromes with subjective troubles of sensitivity (parathesia and spontaneous pains in limbs), irritability, disturbances in motor reactions and neurasthenic syndrome. Serum copper levels were also determined and were at levels of 100 to 180 μg/dL in polyneuritic syndrome subjects, and 180 to 220 μg/dL in neurasthenic syndrome subjects. Sexual impotence was reported in 16% of workers examined. Limitations of this study include the absence of a control group, poor description of study design and the lack of statistical analysis of data.

Respiratory effects were also noted in a report by Askergren and Mellgren (1975). Nose and throat examinations were performed in sheet-metal workers exposed to copper dust. Six of 11 workers had nasal mucosa characterized by increased vascularity and superficial epistatic vessels. This was accompanied by symptoms of runny nose and mucosal irritation in the mouth and eyes.

Laboratory Animal Data

As with human exposure, the respiratory system appears to be the primary site of injury following inhalation exposure to copper. Table 11-33 summarizes the available toxicity data

TABLE 11-33. LABORATORY ANIMAL EXOPOSURE CONDITIONS AND EFFECTS FOR COPPER AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Cu/m^3						
N/A	0 560 1,210 3,300	3 h/day	$CuSO_4$ aerosol	MMAD = 0.54 μm σ_g = 2.07	Mouse, CD1 (23-100) B	Tracheobronchial lavage for total and differential cell count, viability and ATP content, tracheal HP, tracheal cilia beating frequency, subgroups simultaneously challenged with *Streptococcus zooepidemicus* aerosol to determine mean survival time, subgroups simultaneously exposed to ^{35}S-*Klebsiella pneumoniae* aerosol to determine pulmonary bactericidal activity: Dec mean survival time $\geq$560 μg/m^3. Dec bactericidal activity at 3,300 μg/m^3. No effect on lavage parameters, tracheal cilia beating frequency or histology.	Drummond et al. (1986)
N/A	0 1,210 3,300	3 h/day	$CuSO_4$ aerosol	MMAD = 0.54 μm σ_g = 2.07	Hamster, Syrian golden (4) NS	Tracheal cilia beating frequency, tracheal HP: Dec cilia beating frequency and abnormal epithelium at 3,300 μg/m^3.	Drummond et al. 1986

TABLE 11-33 (cont'd). LABORATORY ANIMAL EXOPOSURE CONDITIONS AND EFFECTS FOR COPPER AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain (Number) Sex,	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Cu/m^3$						
N/A	0 120 130	3 h/day 5 days/week 1-2 weeks	$CuSO_4$ aerosol	MMAD = 0.54 μm $\sigma_g = 2.07$	Mouse, CD1 (4) NS	Respiratory tract HP (SEM), subgroups simultaneously challenged with *S. zooepidemicus* aerosol to determine mean survival time, subgroups simultaneously exposed to ^{35}S-*K. pneumoniae* aerosol to determine pulmonary bactericidal activity: Slight alveolar thickening and irregularities after 5 exposures at 120 $\mu g/m^3$, extensive thickening with many walls fused into irregular masses after 10 exposures at 130 $\mu g/m^3$. Dec mean survival time after 10 exposures at 130 $\mu g/m^3$. Dec bactericidal activity in both exposure groups.	Drummond et al. (1986)
N/A	0 120 130	3 h/d 5 d/wk 1-2 wk	$CuSO_4$ aerosol	MMAD = 0.54 μm $\sigma_g = 2.07$	Hamster, Syrian golden (4) NS	Respiratory tract HP (SEM), tracheal cilia beating frequency: No change in frequency. Normal epithelium.	Drummond et al. (1986)
N/A	0 600	6 h/d 5 d/w 1 mo	$CuCl_2$ aerosol	MMAD range = 0.5-11 μm	Rabbit, NS (8) M	Pulmonary lavage for number and variance of macrophages, LM and SEM of alveolar macrophages, oxidative metabolism determined by ability to reduce NBT, macrophage bacterial capacity: Slightly increased amount of lamellated cytoplasmic inclusions.	Johansson et al. (1983)

TABLE 11-33 (cont'd). LABORATORY ANIMAL EXOPOSURE CONDITIONS AND EFFECTS FOR COPPER AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain (Number) Sex,	Assays performed: Effect(s)	Reference
ppm	μg Cu/m^3						
N/A	0 600	6 h/d 5 d/wk 4-6 wk	$CuCl_2$ aerosol	NS	Rabbit, NS (8) M	Microscopy: Minor lymphocytic or eosinophilic inflammatory infiltrates noted, however, incidence was similar to controls. Volume density of alveolar type II cells increased slightly.	Johansson et al. (1984)
N/A	0 600	6 h/d 5 d/wk 4-6 wk	$CuCl_2$ aerosol	NS	Rabbit, NS (8) M	Lysozyme (muramidase) concentration and number of alveolar macrophages: No effect.	Lundborg and Camner (1984)

Abbreviations:

B = both males and females; Cu = copper; $CuSO_4$ = copper sulfate; $CuCl_2$ = copper chloride; d = day; dec = decreased; HP = histopathology; inc = increased; h = hour; LDH = lactate dehydrogenase; LM = light microscopy; M = males; $\mu g/m^3$ = micrograms per cubic meter; MMAD = mass median aerodynamic diameter; mo = month; NA = not applicable; NBT = nitroblue tetrazolium; Ni = nickel; NS = not specified; ppm = parts per million; SEM = scanning electron microscopy; σ_g = geometric standard deviation of distribution; wk = week; yr = years; Zn = zinc.

for laboratory animals. Drummond et al. (1986) reported a decrease in tracheal cilia beating frequency following a single exposure to 3,300 μg Cu/m^3 (as a copper sulfate aerosol) in hamsters, but not in mice exposed to the same level. This respiratory effect was not seen with repeated exposures at lower levels. Histological examination of the trachea revealed abnormal epithelium in hamsters at 3,300 μg Cu/m^3, supporting the observation of decreased Cu/m^3 or 10 exposures at 130 μg Cu/m^3) led to alveolar thickening and respiratory tract irregularities, which worsened with increased duration of exposure. cilia beating frequency. In mice repeatedly exposed to copper sulfate (5 exposures at 120 μg

Immunological effects were observed in mice (Drummond et al., 1986) and in rabbits (Johansson et al., 1983) exposed to copper sulfate aerosols. Mice exposed to either a single concentration of 560 μg Cu/m^3 or 10 exposures to 130 μg Cu/m^3, and simultaneously challenged with an aerosol of *Streptococcus zooepidemicus* had decreased survival time (Drummond et al., 1986). Decreased bactericidal activity was also observed in mice after exposure to an aerosol of *Klebsiella pneumonia* after single or repeated exposures to copper sulfate aerosols (Drummond et al., 1986), suggesting that copper can inhibit the function of alveolar macrophages. After inhalation exposure, Johansson et al. (1983) also observed a slight increase in the amount of lamellated cytoplasmic inclusions in alveolar macrophages. Exposures of rabbits to copper chloride aerosols for 4 to 6 weeks resulted in a minor increase in volume density of alveolar Type 2 cells and minor levels of lymphocytic or eosinophilic inflammatory infiltrates (Johansson et al., 1984).

11.6.9.4 Factors Affecting Susceptibility

Because the respiratory system is a target of inhaled copper (Armstrong et al., 1983; Suciu et al., 1981), individuals with respiratory impairments may be at increased risk, and the developing respiratory tract in children may also be more susceptible.

Other information on factors increasing susceptibility to copper are limited to data from oral exposure, but many of these factors may be relevant for inhalation as well, since several inhaled copper compounds are absorbed from the lungs. For example, patients with Wilson's disease (hepatolenticular degeneration) have an impaired ability to maintain copper homeostasis, and so are highly susceptible to copper toxicity. Wilson's disease is an autosomal recessive disorder characterized by increased retention of hepatic copper,

decreased biliary copper excretion, decreased plasma ceruloplasmin, and hypercupruria (Schroeder et al., 1966).

Because of the liver's key role in copper storage, ceruloplasmin synthesis, and copper excretion into bile, metabolic or pathologic dysfunction would probably disrupt copper homeostasis, thus making persons with liver damage more susceptible to copper toxicity. Similarly, homeostasis is maintained by increasing urinary copper excretion when copper intake is high, such that people with impaired renal function might have difficulty in increasing renal copper excretion to handle a high copper intake; but it is dubious that environmental inhalation exposure to copper would be high enough for these issues to be a factor.

Infants under one year of age have increased susceptibility to copper toxicity because they have not yet developed the homeostatic mechanisms for clearing copper from the body and preventing its entry via the intestine. This was seen in a study where two infant siblings exposed to high levels of copper in tap water developed hepatosplenomegaly, but no effects were observed in an older sibling or the parents (Mueller-Hoecker et al., 1988). Also, those with inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase are likely to be more susceptible to toxic effects of oxidative stressors such as copper (Calabrese and Moore, 1979). The threshold for copper toxicity may be lower for such individuals with this deficiency (Chugh et al., 1975).

11.6.10 Iron

11.6.10.1 Chemical and Physical Properties

Pure elemental iron is silvery-white or gray and a relatively soft, ductile, malleable metal (Knepper, 1981). Elemental iron is rarely found in nature because it readily combines with other elements such as oxygen and sulfur (Knepper, 1981). Iron is in Group VIII of the periodic system of elements. Oxidation states of iron may range from -4 to +6, of which +2 (ferrous) and +3 (ferric) are the most important (McArdle, 1981). Iron forms a large number of inorganic compounds (e.g., oxides, carbonates, sulfates, chlorides, and sulfides) and some carbonyls, e.g., iron pentacarbonyl (Elinder, 1986). In aqueous solutions, iron(+2) ions are oxidized to iron(+3). Iron(+3) ions hydrolyze in solution to form aquo species (Knepper, 1981). In dry air, elemental iron is stable but readily oxidizes in moist air

forming "rust" which is mainly hydrated iron oxide (Budavari, 1989). Elemental iron and its most common compound, ferric oxide (Fe_2O_3), are insoluble in water, as is ferric or iron pentacarbonyl, FeC_5O_5 or $Fe(CO)_5$. Certain other iron compounds, e.g., ferric chloride ($FeCl_3$), ferric sulfate $Fe_2(SO_4)_3$, and ferric nitrate $Fe(NO_3)_3$ are water soluble.

11.6.10.2 Pharmacokinetics

No quantitative data were located on absorption of iron from the lungs of humans. In rats, lung clearance of deposited iron oxide particles is slow after inhalation of iron oxide (mass median aerodynamic diameter [MMAD] of 0.3 μm) (Elinder, 1986). Creasia and Nettesheim (1974) also reported increased iron accumulation in lungs after repeated exposure of hamsters to ferric oxide.

The body normally contains about 3–5 grams of iron. Two-thirds of the iron in the body are bound to hemoglobin in red blood cells. Therefore, whole blood concentration of iron is directly proportional to the hemoglobin concentration. Approximately 10% of iron in the body is found in myoglobin and iron-requiring enzymes. The remaining is bound to iron-storage proteins (ferritin and hemosiderin) found mainly in the liver, bone marrow, and spleen (Elinder, 1986). In tissues, the highest concentrations of iron are found in liver and spleen, followed by kidney, heart, and skeletal muscle.

Transferrin, a β_1-globulin, is important in the metabolism of iron as it binds to iron and transports iron in the plasma to storage tissues (e.g., bone marrow) (Elinder, 1986). Iron can exist in two stable oxidation states, ferrous Fe(II) and ferric Fe(III). In most biological fluids, Fe(II) is rapidly oxidized to its thermodynamically stable form, Fe(III), which forms insoluble Fe(III) hydroxide complexes. These redox reactions are important in iron metabolism because iron shuttles continuously between its ferrous and ferric state during storage and transport processes (Marx, 1984). Iron is eliminated primarily in the urine and feces (Elinder, 1986). Iron can also be eliminated via sweat, hair, and nails.

11.6.10.3 Health Effects

Human Data

Most of the available human inhalation data on iron are based on occupational exposures to iron oxide, with effects limited to respiratory symptoms and dysfunction. There

are no acute human inhalation data on the effects of iron exposure. Health effects information via inhalation route is limited on iron pentacarbonyl. No information was located on the soluble iron salts including ferric chloride, ferric nitrate, and ferric sulfate. Inhalation toxicity information on humans is summarized in Table 11-34.

Occupational exposure occurs from mining of iron ores, consisting mainly of oxide forms. During the mining and during smelting and welding process, workers are often exposed to dust containing iron oxides and silica, as well as other metals and substances. It is known that exposure to iron oxides results in roentgenological changes in the lung due to deposition of inhaled iron particles (Doig and McLaughlin, 1936; Musk et al., 1988; Plamenac et al., 1974), designated variously as siderosis, iron pneumoconiosis, hematite pneumoconiosis, iron pigmentation of the lung, and arc welder lung (Elinder, 1986). Siderosis is prevalent in 5 to 15% of iron workers exposed for more than 5 years (Buckell et al., 1946; Schuler et al., 1962; Sentz and Rakow, 1969). Exposure levels were reported to exceed 10,000 μg iron/m^3 by Sentz and Rakow (1969); but no exposure data were presented for the other studies. A Romanian study (Teculescu and Albu, 1973) reported a 34% prevalence of siderosis in workers exposed to ferric oxide dust (3,500 to 269,000 μg/m^3); but radiological evidence of lung fibrosis was not observed. Complaints of chronic coughing were reported by 80% of the workers. Morgan (1978) found a male subject exposed chronically to ferric oxide (magnetite; Fe_3O_4) had symptoms of coughing and sputum for 8–9 years and exhibited an abnormal chest x-ray, but pulmonary function tests revealed no abnormalities. Stokinger (1984) reviewed the literature on occupational exposure to iron oxide fumes, and concluded that most investigators considered the roentgenological pulmonary changes, secondary to inhalation of iron dust (i.e., siderosis), as benign and did not suspect them to progress to fibrosis. Although several case reports have described iron oxide workers, with coughing and shortness of breath, exhibiting diffuse fibrosis in their chest x-rays (Charr, 1956; Friede and Rachow, 1961; Stanescu et al., 1967), concurrent exposure to other chemicals may have contributed to this finding (Chan-Yeung et al., 1982; Sitas et al., 1989).

Several studies report high incidence of lung cancer mortality among workers exposed to iron oxide in mines and smelters; but, in all cases, there was simultaneous exposure to other potentially carcinogenic substances (Boyd et al., 1970; Faulds, 1957). Improvements

TABLE 11-33. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR IRON AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Fe/m^3						
Chronic Human							
NA	≥10,000	2 mo-12 yr (occup)	Iron oxide fume	NR	Human (73) M	Subjective symptoms, chest x-ray: Siderosis in 3 males. Note: concurrent exposure to several other chemicals; exposure characterized after plant levels reduced; workers from 5 different plants.	Sentz and Rakow (1969)
NA	NS	≥6 yr (occup)	Iron oxide and metallic iron dust	NR	Human (138) M, (33) F	Occupational history, subjective symptoms, chest x-ray: Siderosis in 15 individuals, of which 1 complaint of shortness of breath and 6 of cough. Note: Concurrent exposure to HCl, silica, and combustible matter (carbon, oil, fiber).	Buckell et al. (1946)
	NS	≥7 yr (occup)	Iron oxide dust	NR	Human (13) M (control) (16) M (exposed)	Clinical exam, medical and work history questionnaire, lung function tests: Slight dyspnea (7 cases) and cough (3 cases) in exposed group. Significant decrease in static and functional compliance. Note: Welders may have been exposed to other chemicals in metallurgical plant.	Stanescu et al. (1967)

TABLE 11-34 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR IRON AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Fe/m^3$						
NA	3,500 - 269,000	10 yr (avg) (4-13 yr) (occup)	Iron oxide dust	<1 μm - 30% 1-3 μm - 45% 3-5 μm - 23% 5-10 μm - 2%	Human (113) M	Medical history and physical exam, chest x-ray: 34% prevalence of siderosis; complaints of chronic coughing and breathlessness. No evidence of fibrosis.	Teculescu and Albu (1973)
NA	3,500 - 269,000	10 yr (avg) (4-13 yr) (occup)	Iron oxide dust	<1 μm - 30% 1-3 μm - 45% 3-5 μm - 23% 5-10 μm - 2%	Human (14) M	Medical history and physical exam, chest x-ray, pulmonary function test: siderosis; 64% of workers had chronic cough. No evidence of fibrosis. Normal pulmonary function. Note: 4 smokers, 3 ex-smokers.	Teculescu and Albu (1973)

Abbreviations:

avg = average; d = day(s); h = hours; MMAD = mass median aerodynamic diameter; NA = not applicable; NK = not known, waiting for study retrieval; NR = not reported; NS = not specified; occup = occupational; yr = years.

in dust control and ventilation of mines after 1967 have also resulted in reduction of lung cancer mortality in iron ore mine workers (Kinlen and Willows, 1988). It is hard to draw definite conclusions about the role of iron oxide particles in development of lung cancer in humans (Elinder, 1986). Stokinger (1984) concluded that when confounding factors (smoking, concurrent exposure to other chemicals) are considered, there is no evidence that inhaled iron oxides might be a human carcinogen.

No studies were located regarding the reproductive and developmental effects of iron oxides in humans.

Laboratory Animal Data

As shown in Table 11-35, two acute inhalation studies reported clinical signs relating to respiratory distress in rats exposed to iron pentacarbonyl for 4 h or 1 mo (BASF Corporation, 1991; Bio/Dynamics Incorporated, 1988). However, histopathology was not performed on the lungs. Acute exposure of rats to 500,000 μg iron/m^3 as iron oxide for greater than 30 min also resulted in coughing, respiratory difficulties, and nasal irritation (Hewitt and Hicks, 1972 as cited in Elinder, 1986) and histopathology of the lungs revealed iron oxide particles in macrophage cells. Ten intratracheal installations of ferric oxide to hamsters produced loss of ciliated cells, and hyperplasia and proliferation of non-ciliated epithelial cells in the lungs (Port et al., 1973). At a longer duration of 1 mo, hamsters inhaling 14,000 μg iron/m^3 as ferric oxide dust (MMAD of 0.11 μm) revealed respiratory tract cell injury and alveolar fibrosis (Creasia and Nettesheim, 1974).

Carcinogenicity of iron in animals was reported in an early study by Campbell (1940). Mice inhaling iron oxide at unspecified concentrations for 10 mo developed lung tumors (32.7% versus 9.6% in controls); however, study details were limited (Campbell, 1940), and this finding has not been confirmed in later studies in hamsters (Creasia and Nettesheim, 1974). Iron oxide may serve as a carcinogenic cofactor either by retarding clearance of inhaled carcinogens or by inducing cytopathological changes that make the cells of the respiratory tract more prone to develop cancer when exposed to carcinogenic substances.

There was a lack of animal information on the effect of iron exposure on other systemic organs including the reproductive system.

TABLE 11-35. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR IRON AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Fe/m^3$						
NA	500,000	>30 min	Iron oxide	NK	Rats, NS (NS)	Clinical signs: Coughing, respiratory difficulties, nasal irritation	Hewitt and Hicks, (1972) as sited in Elinder (1986)
NA	14,000	1 mo	Iron oxide	MMAD = 0.11 μm	Hamsters, NS (NS)	Histopathology: Respiratory tract cell injury (not specified), alveolar fibrosis	Creasia and Nettesheim (1974)
0	0	6 h/d	Iron	NA	Rats, Wistar	Clinical signs: Impaired respiration,	BASF
0.02	200	5 d/wk	pentacarbonyl		(10) NS	blood nasal discharge at two highest	Corporation
0.08	700	4 wk	vapor			concentrations only.	(1991)
0.28	2,300						
0.9	6,800						
2.8	22,000						
0	0	4 h	Iron	NA	Rats, S-D	Clinical signs, gross examination:	Bio/Dynamics
2.1	17,000		pentacarbonyl		(5) M,	Labored breathing, rales,	Incorporated
7	55,000		vapor		(5) F	lacrimation, nasal discharge at three	(1988)
11	87,000					highest concentrations. Red lungs	
23	182,000					and turbinates; however, findings are equivocal on basis of gross examination only.	

Abbreviations:

d = day(s); h = hours; MMAD = mass median aerodynamic diameter; NA = not applicable; NK = not known, waiting for study retrieval; NR = not reported; NS = not specified; occup = occupational; wk = week(s).

11.6.10.4 Factors Affecting Susceptibility

Individuals with preexisting respiratory conditions would likely be more susceptible to iron oxide because human and laboratory animal studies indicate that the respiratory system is the major target organ for iron toxicity. The developing respiratory tract of children may also pose increased susceptibility. There may be other factors affecting susceptibility to iron; but there is a lack of data to determine other such factors.

11.6.11 Mercury

11.6.11.1 Physical/Chemical Properties

Mercury is a liquid metal found in Group 2B of the periodic table. It exhibits three valence states, 0, +1, and +2, and readily forms compounds in the +1 and +2 states (Singer and Nowak, 1981). Many mercury compounds are unstable, and are easily reduced to metallic mercury and compounds of lower oxidation state (Singer and Nowak, 1981). Metallic mercury, the most reduced form of mercury, is stable at ordinary temperatures, and does not react with air or oxygen (Drake, 1981). In its gaseous form, it constitutes over 95% of the mercury found in the atmosphere (Agency for Toxic Substances and Disease Registry, 1994). Mercury exists in the environment as both inorganic salts and organomercurial compounds (Singer and Nowak, 1981). Elemental mercury is insoluble, as is mercuric sulfide (HgS). Mercuric compounds slightly to moderately soluble, depending on temperature, include, for example, mercuric ($HgCl_2$) and mercurous (Hg_2Cl_2) chloride and mercuric acetate, Hg $(C_2H_3O_2)_2$.

11.6.11.2 Pharmacokinetics

Elemental mercury and inorganic mercury compounds (mercuric chloride) are most likely inhaled by humans. Inhalation exposure to organic mercury compounds is low. Therefore, data on the pharmacokinetics and health effects of mercury are focused primarily on elemental mercury vapors and inorganic mercury compounds.

Absorption and Distribution

Elemental mercury is highly lipophilic and absorption of the inhaled vapor is substantial, followed by rapid diffusion across the alveolar membranes of the lungs into

blood. Studies indicate that following exposure to 100 to 200 $\mu g/m^3$ elemental mercury vapor, approximately 74 to 80% of inhaled elemental mercury vapor is retained in human tissues (Hursh et al., 1976; Teisinger and Fiserova-Bergerova, 1965). Indirect evidence of rapid absorption was provided by elevated mercury levels found in red blood cells, plasma, and excreta of five volunteers who inhaled radiolabeled mercury for 14 to 24 min (Cherian et al., 1978). Elevated blood levels of mercury were also observed in humans following a brief occupational exposure (3 days) to >100 $\mu g/m^3$ elemental mercury vapor (Barregard et al., 1992).

There are few reports regarding the respiratory absorption of elemental and inorganic mercury compounds in animals. Elevated levels of mercury were detected in blood and tissues of pregnant or nursing guinea pigs after short-term exposure (2 to 2.5 h) to elemental mercury vapors (6,000 to 10,000 $\mu g/m^3$) (Yoshida et al., 1989, 1992). Following repeated exposure (5 weeks) of rats to mercury vapor (1,000 $\mu g/m^3$), high levels were detected in the blood and brain (Warfvinge et al., 1992).

Elemental mercury distributes throughout the body due to its lipophilic nature, crossing blood-brain and placental barriers with ease (Clarkson, 1989; Dencker et al., 1983; Yoshida et al., 1992). Mercury distributes to all tissues and reaches peak levels within 24 h, except in the brain where peak levels are achieved within 2 to 3 days (Hursh et al., 1976). The longest retention of mercury after inhalation of mercury vapor occurs in the brain.

A 4-h exposure of mice to elemental mercury vapor produced the highest mercury retention in the brain compared to other organs (Berlin et al., 1966). Mercury was found primarily in the neocortex, basal nuclei, and the cerebellar Purkinje cells (Warfvinge et al., 1992). After 12 to 14 h of exposure of rats to a relatively small amount of elemental mercury vapor (550 $\mu g/m^3$), accumulation of mercury was observed within all cell types examined (ganglion cells, satellite cells, fibroblasts, and macrophages).

The kidney is the major organ of mercury deposition after inhalation exposure to elemental mercury vapor. Mercury concentrations in the kidney are orders of magnitude higher than in other tissues (Rothstein and Hayes, 1964). The kidney contains metallothionein, a metal-binding protein that is also found in fetal and maternal livers. In the kidney, the production of metallothionein is stimulated by exposure to mercury. The increased levels of metallothionein increase the amount of mercuric ion binding and

accumulation in the kidney (Piotrowski et al., 1973). Three classes of sulfhydryl groups have been identified in the kidney, with the metallothionein having the greatest affinity for mercury (Clarkson and Magos, 1966). Low-molecular-weight complexes of mercury have been identified in the urine, suggesting that they may exist in the kidney and contribute to the kidney's accumulation of mercury (Piotrowski et al., 1973).

After exposure to mercury vapor, mercury is distributed throughout the body in different chemical and physical states. Elemental mercury dissolves in the blood upon inhalation; mercury concentration in red blood cells is twice that measured in the plasma (Cherian et al., 1978). Elemental mercury in the blood is oxidized to its divalent form in the red blood cells. The divalent cation exists as a diffusible or nondiffusible form. The nondiffusible form is mercuric ions that bind to proteins (albumin and globulins) and are held in high-molecular-weight complexes, existing in equilibrium with the diffusible form.

Metabolism

Metabolism of all forms of mercury is similar for humans and animals. Once absorbed, elemental and inorganic mercury enter an oxidation-reduction cycle. Elemental mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs of humans and animals. Evidence from animal studies suggests the liver as an additional site of oxidation. Absorbed divalent cation from exposure to mercuric mercury compounds can, in turn, be reduced to the elemental or monovalent form and released as exhaled elemental mercury vapor. In the presence of protein sulfhydryl groups, mercurous mercury (Hg_2^{++}) disproportionates to one divalent cation (Hg^{2+}) and one molecule at the zero oxidation state (Hg^0). The conversion of methylmercury or phenylmercury to divalent inorganic mercury can probably occur soon after absorption, also feeding into the oxidation-reduction pathway.

Elemental mercury vapor is inhaled through the lungs and rapidly enters the bloodstream. The dissolved vapor can undergo rapid oxidation, primarily in the red blood cells, to its inorganic divalent form by the hydrogen peroxide-catalase pathway (Clarkson, 1989). It is believed that the rate of oxidation is dependent on: (1) concentration of catalase in the tissue; (2) endogenous production of hydrogen peroxide; and (3) availability of mercury vapor at the oxidation site (Magos et al., 1978). In red blood cells *in vivo*, hydrogen peroxide production is probably a rate-determining step because Nielsen-Kudsk

(1973) found that stimulation of hydrogen peroxide production in red cells increased the uptake of mercury vapors in red cells. At low doses, the percent of dose in the blood is higher than after a high dose, indicating that a higher proportion of the dose is oxidized by blood (Magos et al., 1989). The hydrogen peroxide-catalase pathway in red cells may become saturated at higher dose levels (Magos et al., 1989).

The oxidation of elemental mercury may also occur in the brain, liver (adult and fetal), lungs, and probably all other tissues to some degree (Clarkson, 1989; Magos et al., 1978)). In rat liver homogenates, hydrogen peroxide catalase is the predominant oxidative pathway in tissues. Its capacity is very high. Unlike oxidation in red cells, the rate-limiting step in *in vitro* oxidation in the liver is dependent on the rate of mercury delivery to the enzyme (Magos et al., 1978). Unoxidized elemental mercury can still reach the brain because the oxidation of elemental mercury is a slow process compared with the circulation time from the lung to the brain. Once in the brain, elemental mercury can be oxidized to the divalent form. Because the oxidized form does not readily cross the blood-brain barrier, mercury can be trapped in the brain. Autoradiographic studies suggest that mercury oxidation also occurs in the placenta and fetus (Dencker et al., 1983), although the extent of oxidation is not known. Based on the fact that the rate of oxidation in red cells is non-linear (i.e., can become saturated at higher doses) (Magos et al., 1989), it is assumed that the rate of distribution of elemental mercury to the brain and fetus is probably nonlinear.

High affinity binding of divalent mercuric ion to thiol or sulfhydryl groups of proteins is believed to be a key underlying mechanism for biologic activity of mercury (Clarkson, 1972). However, since proteins containing sulfhydryl groups are rather ubiquitous, occurring in both extracellular and intracellular membranes and organelles, and most sulfhydryl groups play an integral part in the structure or function of many proteins, the precise intracellular target for mercury is not easily determined. Possible mechanisms include inactivation of various enzymes, structural proteins, or transport processes.

There is evidence to suggest that the divalent inorganic mercury cation is reduced by mammalian tissue to elemental mercury after its oxidation. Rats and mice pretreated parenterally with mercuric chloride exhale elemental mercury vapor (Clarkson and Rothstein, 1964). Liver and kidney homogenates in animals also release mercury vapor after exposure to mercuric chloride.

Excretion

The urine and feces are the main excretory pathways of mercury in humans, with a body burden half-life of approximately 1 to 2 mo (Clarkson, 1989). After an acute mercury exposure in humans, urinary excretion accounts for 13% of the total body burden. After long-term exposure, urinary excretion increases to 58%. Humans inhaling mercury vapor for less than an hour expired approximately 7% of the retained dose of mercury (Cherian et al., 1978; Hursh et al., 1976). The half-life for this elimination pathway was 14 to 25 h; therefore, excretion via expired air is negligible by 5 to 7 days after exposure (Cherian et al., 1978). Using a two-compartment model, elimination half-lives in urine of workers exposed for 20 to 45 h to >100 $\mu g/m^3$ elemental mercury vapor were estimated to be 28 and 41 days for a fast and slow phase, respectively (Barregard et al., 1992). For high level exposure to inorganic divalent mercury, the urine is probably the major elimination route with a half-life similar to that of elemental mercury (Clarkson, 1989). An elimination half-life from urine was estimated to be 25.9 days following an acute exposure to a high level of mercuric chloride (13,8000 $\mu g/kg$) (Suzuki et al., 1992). Exhalation in the lungs and secretion in saliva, bile, and sweat may also contribute a small portion to the excretion process (Joselow et al., 1968b). There was no human data on the elimination of mercury in the feces.

The overall elimination rate of inorganic mercury from the body is the same as the rate of elimination from the kidney, where most of the body burden is localized. Inorganic mercury is also readily cleared from the lung. Elimination from the blood and the brain is thought to be a biphasic process with an initial rapid phase in which the decline in the body burden is associated with high levels of mercury being cleared from tissues, followed by a slower phase with mercury clearance from the same tissues (Takahata et al., 1970). An even longer terminal elimination phase is also possible because of accumulation or persistence of mercury, primarily in the brain (Takahata et al., 1970).

Data are limited on elimination of elemental and inorganic mercury in animals. Initial excretion of mercury is predominantly in the fecal matter following inhalation of elemental mercury vapor, but as mercury concentrations increase in the kidney, urinary excretion increases (Rothstein and Hayes, 1964). After inhalation of elemental mercury for 8 weeks,

approximately 10 to 20% of the total excreted mercury is by exhalation (Rothstein and Hayes, 1964).

11.6.11.3 Health Effects

Inhalation of elemental mercury vapor has been associated with systemic toxicity in both humans and animals. At low levels of exposure, the major target organs of elemental mercury induced toxicity are the kidneys and the central nervous system. At high exposure levels, respiratory, cardiovascular, and gastrointestinal effects also occur. It should be noted that the temperature at which exposure occurs affects the vapor pressure and presence of condensed droplets which, in turn, influence the primary route by which exposure occurs (Milne et al., 1970). Inhaled droplets, for example, are more likely to be ingested instead of inhaled. This is due to particles cleared from the upper respiratory tract by mucociliary action which are swallowed and absorbed via the gastrointestinal route.

A great deal of the information on effects associated with inhalation exposure to elemental mercury vapor comes from studies conducted several decades ago, when methods for determining exposure levels were less precise than current methods. No studies were located concerning effect levels following inhalation exposure to inorganic salts of mercury (e.g., mercuric or mercurous salts, oxides, etc.). Information on inhalation exposure to organic mercury compounds (e.g., alkylmercury compounds) in humans is limited to case reports and includes only qualitative data on gastrointestinal, renal, muscular, and neurological effects. In many cases, it is difficult to determine whether effects observed in exposed persons were directly attributable to mercury exposure.

The central nervous system is probably the most sensitive target organ for elemental mercury vapor exposure. Nervous system disorders following exposure to elemental mercury vapors are both consistent and pronounced. Short- and long-term exposures elicit similar neurological effects. Symptoms intensify and may become irreversible as exposure duration and/or concentration increases. Most occupational studies discuss chronic exposure to a time-weight average concentration or a concentration range (i.e., subjects are not grouped by exposure levels), thereby preventing the assessment of dose-response relationships within the populations studied. However, the average exposure levels for affected groups are similar in many of these studies. There are a large group of studies that

reported urinary and/or blood mercury levels, but did not monitor air mercury levels in the occupational settings. It should also be noted that mercury vapor concentrations in the general work environment may be lower than those in the microenvironment immediately surrounding workers (Stopford et al., 1978); therefore, actual exposure levels may be higher than the estimated air mercury values.

Human Data

The human toxicity data are summarized in Table 11-36. Several case studies have reported adverse neurological effects following acute inhalation of high concentrations of mercury vapor. A wide variety of cognitive, personality, sensory, and motor disturbances have been reported. The most prominent symptoms include tremors (initially affecting the hands and sometimes spreading to other parts of the body), emotional lability (characterized by irritability, excessive shyness, confidence loss, and nervousness), insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, muscle twitching), headaches, polyneuropathy (paresthesia, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities), and performance deficits in tests of cognitive function (Hallee, 1969; Jaffe et al., 1983; Karpathios et al., 1991; Lilis et al., 1985; McFarland and Reigel, 1978; Snodgrass et al., 1981). In case reports of individuals exposed to inorganic mercury vapor for 1 to 6 mo, similar effects were reported (Fagala and Wigg, 1992; Friberg et al., 1953; Sexton et al., 1978; Taueg et al., 1992). Effects included dizziness, joint pains, weakness, insomnia, numbness and tingling in her palms, decreased pinprick and vibration sensations in the lower extremities, intention tremor, a slowing of the background rhythms on electroencephalograms, irritability, outbursts of temper, shyness, sensitivity, auditory hallucinations, and photophobia, personality change, insomnia, headaches, and weakness.

Information on the neurological effects in humans from chronic mercury vapor exposure is available primarily from occupational studies. Chronic-duration exposures to elemental mercury vapor have resulted in tremors (which may be mild or severe depending on degree of exposure), unsteady walking, irritability, poor concentration, short-term memory deficits, tremulous speech, blurred vision, performance decrements in psychomotor skills (e.g., finger tapping, reduced hand-eye coordination), paresthesias, and decreased

TABLE 11-36. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR MERCURY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
0.001-0.006	10-50	NS (occup)	Hg vapor[b]	NA	Human (21) NS	Urinary protein: Inc proteinuria.	Stewart et al. (1977)
0.005	41[a] (urine)	NS (occup)	Hg vapor	NA	Human (63) NS	Renal function parameters, urinary protein: Renal dysfunction (increased β2-microglobulin, inc high molecular weight proteins).	Buchet et al. (1980)
0.005	41[a] (urine)	NS (occup)	Hg vapor	NA	Human (20) NS	BML: 50 $\mu g/g$ creatinine; 30 $\mu g/L$ blood. Inc urinary brush border proteins.	Mutti et al. (1985)
0.006-0.12	50-1,000	3.5, 21 yr (occup)	Hg vapor	NA	Human (101-111) M	BML: >50 $\mu g/g$ creatinine. Subjective symptoms, physical examination: No effect.	Bunn et al. (1986)
0.012 0.02	100 180	1->10 yr (avg) (occup)	Hg vapor	NA	Human (567) NS	Subjective symptoms, tremors: Insomnia, nervousness, weight loss, objective tremors at 180 $\mu g/m^3$.	Smith (1970)
0.003	25	>1 yr (avg) (occup)	Hg vapor	NA	Human (9-10) M, (60-62) F	Subjective symptoms, psychometric tests, tremor: Inc tiredness, memory disturbance.	Langworth et al. (1992a)
0.007	59	7.9 yr (avg) (occup)	Hg vapor	NA	Human (53-77) M	Nerve conduction test: Altered sensory nerve conduction and visual evoked response.	Ellingson et al. (1993)

TABLE 11-36 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR MERCURY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
0.18-0.4	1,500-3,300	389 min/d duration NS (occup)	Hg vapor	NA	Human (76-117) M	Subjective symptoms; objective neurobehavior and psychomotor function tests; biochemical measurements for blood, liver, and kidney functions: Lower scores than controls for motor coordination, reaction time, and short-term memory.	Kishi et al. (1993)
0.004 (0.001-0.01)	330 (avg) (8-850)	10.4 yr (avg) (occup)	Hg vapor	NA	Human (19) M, (69) F	Subjective symptoms; neurobehavioral tests: Fatigue and confusion; impaired performance on tests.	Liang et al. (1993)
0.002-0.05	20-450	8-9 mo (case report)	Hg vapor	NA	Human (1) M	Clinical signs: Fatigue, irritability.	Friberg et al. (1953)
0.012-0.12	100-1,000	51-176 d (case report)	Hg vapor	NA	Human (5) M, (6) F	Signs and symptoms: Nervousness, insomnia, inattentiveness, altered EEGs and personality changes.	Sexton et al. (1978)
0 0.013-0.095	0 106-783	NS (occup)	Hg vapor	NA	Human (41-55) M	Blood chemistry, serum immunoglobin levels: Inc α-2-macroglobulin and ceruloplasmin; dec IgG and increased IgA and IgM. Note: No information on employment duration, daily exposure, or confounding factors; exposure measured just before study, and not during time of exposures.	Bencko et al. (1990)

TABLE 11-36 (cont'd). EXPOSURE CONDITIONS AND EFFECTS FOR MERCURY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
0.003	26 (TWA)	1-41 yr (avg = 15.3 yr) (occup)	Hg vapor	NA	Human (25-26) M	Hand tremor measurements: Inc frequency of mild intention tremors with weight load (neurophysiological impairment) (related to duration).	Fawer et al. (1983)
0.002 (0.001-0.006)	14 (avg) (8-49)	0.7-24 yr (occup)	Hg vapor	NA	Human (27-60) M, (27-38) F	Neurobehavioral and intelligence tests: Impaired performance on neurobehavioral tests (finger tapping, trail making, symbol digit, digit span, logical memory recall, visual reproduction recall, Bender gestalt time scores).	Ngim et al. (1992)
0 0.009 (0.003-0.03)	0 76 (avg) (25-270)	1-5 yr (occup)	Hg vapor	NA	Human (79-84) M	Questionnaire, subjective symptoms, neurological examination: Difficulty with heel-to-toe gait (15%), static tremor (19%), symptoms (metallic taste and difficulty sleeping).	Ehrenberg et al. (1991)
0.007-0.36	630	NS (occup)	Hg vapor	NA	Human (81) NS	Plasma β-galactosidase, β-glucuronidase, β-N-acetylglucosaminidase, and β-glucosidase levels: Proteinuria (15/81).	Foa et al. (1976)
0.0004 0.006	3.3 (blood) 46 (urine)[a]	10 yr (avg) (occup)	Hg vapor	NA	Human (36) M	Clinical and neurological status, EEG, cognitive tests: Dec verbal intelligence and memory.	Piikivi et al. (1984)
0.003	25 (blood)[a]	15.6 yr (avg) (occup)	Hg vapor	NA	Human (41) M	BML: 15 μg/L urine; 56 μg/L blood EEG: 15% had slower and attenuated EEGs.	Piikivi and Toulonen (1989)

TABLE 11-36 (cont'd). EXPOSURE CONDITIONS AND EFFECTS FOR MERCURY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
0.003	≈25 (blood)[a]	14 yr (avg) (occup)	Hg vapor	NA	Human (60) M	BML: 19.3 μg/L urine; 11.6 μg/L blood Subjective symptoms, psychological performance tests: Inc in subjective measures of memory disturbances and sleep disorder; anger, fatigue, and confusion also reported.	Piikivi and Hanninen (1989)
0.005	≈30 (blood)[a]	15.6 yr (avg) (occup)	Hg vapor	NA	Human (41) M	BML: 17 μg/L urine; 10 μg/L blood Subjective and objective symptoms of autonomic function, EEG: Inc subjective symptoms of cardiovascular dysfunction and slight decrease in pulse rate variations (cardiovascular reflex response).	Piikivi (1989)
0.003	≈25 (urine)[a]	13.7 yr (avg) (occup)	Hg vapor	NA	Human (60) M	BML: 19.3 μg/L urine; 11.6 μg/L blood Urinary albumin and N-acetyl-beta-glucosaminidase (NAG): No effects.	Piikivi and Ruokonen (1989)
0.006	≈46 (urine)[a]	5.5 yr (avg) (occup)	Hg vapor	NA	Human (62) M	BML: 17 μg/L urine; 14 μg/L blood Serum and urinary proteins: No effects.	Lauwerys et al. (1983)
0.007	≈59 (urine)[a]	7.9 yr (avg) (occup)	Hg vapor	NA	Human (58) NS	BML: 56 μg/g creatinine Renal function: No effects.	Bernard et al. (1987)
0.007	≈55 (urine)[a]	8 yr (avg) (occup)	Hg vapor	NA	Human (100) M	BML: 72 μg/g creatinine Renal function: No effects.	Stonard et al. (1983)

TABLE 11-36 (cont'd). EXPOSURE CONDITIONS AND EFFECTS FOR MERCURY AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	μg Hg/m^3						
0.005	≈41 (urine)[a]	5 yr (avg) (occup)	Hg vapor	NA	Human (43) M	BML: 67 μg/g creatinine Clinical examination, psychomotor tests: preclinical psychomotor dysfunction.	Roels et al. (1982)
0.007	≈58 (urine)[a]	5 yr (avg) (occup)	Hg vapor	NA	Human (43) M	BML: 50 μg/g creatinine; 10-20 μg/L blood Clinical examination, β2-microglobulin in urine and serum, serum protein: Proteinuria and albuminia.	Roels et al. (1982)
0.006	≈52 (urine)[a]	7.7 yr (avg) (occup)	Hg vapor	NA	Human (54) M	BML: 71 μg/g creatinine; 21 μg/L blood Hand tremor tests: Postural and intentional tremor.	Roels et al. (1989)
0.0035	≈29 (urine)[a]	0.5-19 yr (avg) (occup)	Hg vapor	NA	Human (21) M	BML: 63 μg/g creatinine; 24 μg/L blood Postural tremor of the finger: Inc tremor parameters with urinary excretion of Hg.	Verberk et al. (1986)
0.006-0.012	50-100 (blood and urine)[c]	2->10 yr (avg) (occup)	Hg vapor	NA	Human (38) M, (4) F	BML: 35 μg/g creatinine Symptoms questionnaire, neurological performance tests, nerve conduction test, saccadic eye movement, opthalomogic examination, urinary NAG: Subjective neurological symptoms; numbness or pain in extremities; decreased motor nerve condutction velocity; inc NAG levels. BML: 100-250 μg/L; 2.8-5 μg/L blood	Rosenman et al. (1986)

[a]Extrapolated from blood or urine levels based on conversion factor from Roels et al. (1987).
[b]Elemental mercury.
[c]Extrapolated from blood and urine levels based on conversion factors from Rosenman et al. (1986).

Abbreviations:
avg = average; BML = biological monitoring level; dec = decreased; EEG = electroencephalography; F = females; Hg = mercury; Ig = immunoglobulin; inc = increased; M = males; NAG = *N*-acetyl-β-glucosaminidase; NA = not applicable; NS = not specified; occup = occupational; TWA = time weighted average.

nerve conduction (Albers et al., 1988; Chaffin et al., 1973; Fawer et al., 1983; Kishi et al., 1993; Langolf et al., 1978; Langworth et al., 1992a; Liang et al., 1993; Piikivi et al., 1984; Smith et al., 1970). The majority of studies suggest that motor system disturbances are reversible upon exposure cessation, while cognitive impairments, primarily memory deficits, may be permanent (Chaffin et al., 1973).

Several studies have shown significant effects on tremor or cognitive skills at low exposure levels (Ehrenberg et al., 1991; Fawer et al., 1983; Piikivi et al., 1984; Piikivi and Hanninen, 1989; Piikivi and Toulonen, 1989; Roels et al., 1982,, 1989; Rosenman et al., 1986; Verberk et al., 1986). Decreases in performance on tests that measured intelligence (similarities test) and memory (digit span and visual reproduction tests) were observed in chlor-alkali workers exposed for an average of 16.9 years to low levels of mercury when compared to an age-matched control group (Piikivi et al., 1984). Dentists with an average of 5.5 years of exposure to low levels of mercury showed impaired performance on several neurobehavioral tests (Ngim et al., 1992). Difficulty with heel-to-toe gait was observed in thermometer plant workers subjected to mean personal breathing zone air concentrations of 76 $\mu g/m^3$ (range of 25 to 270 $\mu g/m^3$) (Ehrenberg et al., 1991). Chlor-alkali workers exposed to low air levels of inorganic mercury reported an increase in memory disturbances, sleep disorders, anger, fatigue, confusion, and hand tremors compared to the controls (Piikivi and Hanninen, 1989).

Peripheral nerve function has generally been reported to be affected at higher exposure levels. Changes include progressive sensory loss and diminished sensation reflexes in the legs (Ellingsen et al., 1993; Shapiro et al., 1982), prolongation of brainstem auditory evoked potentials (Discalzi et al., 1993), and prolonged somatosensory evoked potentials (Langauer-Lewowicka and Kazibutowska, 1989).

The kidney is a sensitive target organ of toxicity following inhalation exposure to elemental mercury. This sensitivity may be, in part, because of the relatively high accumulation of mercury in the kidney. Acute high-concentration inhalation exposure in humans has resulted in effects ranging from mild transient proteinuria or slight changes in urinary acid excretion (Bluhm et al., 1992), to frank proteinuria, hematuria, and/oliguria (Campbell, 1948; Hallee, 1969; Snodgrass et al., 1981), and acute renal failure with

degeneration or necrosis of the proximal convoluted tubules (Campbell, 1948; Jaffe et al., 1983; Kanluen and Gottlieb, 1991; Rowens et al., 1991).

The results from a number of studies show renal toxicity in workers chronically exposed to mercury vapor (Barregard et al., 1988; Bernard et al., 1987; Buchet et al., 1980; Cardenas et al., 1993; Ehrenberg et al., 1991; Foa et al., 1976; Kazantis et al., 1962; Langworth et al., 1992b; Piikivi and Ruokonen, 1989; Roels et al., 1982; Stewart et al., 1977; Stonard et al., 1983; Tubbs et al., 1982). Effects include proteinuria, proximal tubular and glomerular changes, albuminuria, glomerulosclerosis, and increased urinary *N*-acetyl-β-glucosaminidase. Gstraunthaler et al. (1983) has suggested that epithelial cell damage in the kidney is the result of enhanced free radical formation and lipid peroxidation. Attempts to define threshold levels for effects have had mixed results. Urinary excretion of albumin, β2-microglobulin, or retinol binding protein were not affected at 72 μg mercury/g creatinine (Bernard et al., 1987). However, other studies have shown increases in urinary albumin with urinary mercury levels greater than 50 μg mercury/g creatinine (Buchet et al., 1980) and increases in urinary *N*-acetyl-β-glucosaminidase at urinary mercury levels of greater than 50 or 100 μg mercury/g creatinine.

Respiratory symptoms are a prominent effect of acute-duration high level exposure to elemental mercury vapors. The most commonly reported symptoms include cough, dyspnea, and chest tightness or burning pains in the chest (Hallee, 1969; Kanluen and Gottlieb, 1991; King, 1954; Lilis et al., 1985; McFarland and Reigel, 1978; Milne et al., 1970; Rowens et al., 1991; Snodgrass et al., 1981; Taueg et al., 1992). In the more severe cases, respiratory distress, pulmonary edema (alveolar and interstitial), lobar pneumonia, fibrosis, and desquamation of the bronchiolar epithelium have been observed. The ensuing bronchiolar obstruction by mucus and fluid results in alveolar dilation, emphysema, pneumothorax, and possibly death (Campbell, 1948; Jaffe et al., 1983; Kanluen and Gottlieb, 1991; Taueg et al., 1992). Little information is available regarding exposure levels resulting in the above symptoms. At chronic exposures, no respiratory symptoms and no abnormalities were noted upon examining chest X-rays or the results of pulmonary function tests in a group of chlor-alkali workers exposed for an average of greater than 6 years to low levels of mercury (Smith et al., 1970).

Exposure to mercury vapors has resulted in cardiovascular effects (increased heart rate and blood pressure) following acute inhalation exposure to high concentrations of elemental mercury vapor (Haddad and Sternberg, 1963; Hallee, 1969; Snodgrass et al., 1981). Exposures of longer durations due to spills or occupational exposures have also been reported to result in increased blood pressure (Fagala and Wigg, 1992; Friberg et al., 1953; Karpathios et al., 1991; Taueg et al., 1992) and increased heart rate (Fagala and Wigg, 1992). Chronic-duration occupational exposures, however, have given mixed results regarding effects on blood pressure and heart rate. Two studies of workers exposed to relatively low levels of mercury showed no effects on blood pressure or electrocardiography (Smith et al., 1970). In contrast, workers exposed to lower concentrations of mercury vapors for at least 5 years reported an increased incidence of palpitations and cardiovascular reflex responses were slightly reduced compared to unexposed matched controls (Piikivi, 1989). These studies are limited, however, because exposure to other chemicals may have contributed to the effects observed and other risk factors were not consistently considered.

Gastrointestinal effects have been reported in humans after acute-duration exposure to high concentrations of elemental mercury vapors. Stomatitis (inflammation of the oral mucosa), abdominal pains, nausea and/or vomiting, and diarrhea (Kanluen and Gottlieb, 1991). A correlation was also observed between mercury exposure levels and unspecified oropharyngeal symptoms in workers from a chlor-alkali plant (Smith et al., 1970).

Initial exposure to high concentrations of elemental mercury vapors produces a syndrome similar to "metal fume fever", an acute disease induced by intense inhalation of metal oxides, that temporarily impairs pulmonary function but does not progress to chronic lung disease. This disease is characterized by fatigue, fever, chills, and elevated leukocyte count. Evidence of moderate-to-high leukocytosis with neutrophilia was reported following acute inhalation exposure to elemental mercury vapor (Campbell, 1948; Hallee, 1969; Jaffe et al., 1983; Lilis et al., 1985; Rowens et al., 1991), as well as subacute or chronic exposures (Fagala and Wigg, 1992). In volunteers with dental amalgam, significantly decreased hemoglobin and hematocrit, and increased mean corpuscular hemoglobin concentration were found compared to controls without dental amalgams (Siblerud, 1990). δ-Aminolevulinic acid dehydratase activity in erythrocytes was decreased in workers exposed to elemental mercury in the manufacture of tungsten rods (Wada et al., 1969). In workers

exposed to 106 to 783 $\mu g/m^3$ mercury vapors, there was a significant increase in α_2-macroglobulin and ceruloplasmin (an α-globulin protein active in storage and transport of copper) compared to unexposed workers (Bencko et al., 1990).

The immune reaction to mercury exposure appears to be idiosyncratic, with either increases or decreases in immune activity depending on a genetic predisposition. Therefore, it is not surprising that several studies of workers exposed to elemental mercury vapor have failed to show marked changes in immune function parameters in large populations. For example, no effect on serum immunoglobulins (IgA, IgG, or IgM) and no increase in autoantibody titers were observed in a group of chlor-alkali workers exposed for an average of 13.5 years (Langworth et al., 1992b). Similarly, no increases in antilaminin antibodies were observed in workers exposed for an average of 7.9 years (Bernard et al., 1987), and no increase in antiglomerular basement membrane antibodies or IgE was seen in workers exposed for between 1.5 and 25 years (Cardenas et al., 1993). Slight decreases in IgA and IgG were observed in workers after more than 20 years of exposure to elemental mercury vapors when compared to unexposed controls (Moszczynski et al., 1990).

Evidence for a human autoimmune response has been obtained in a few studies. Examination of the kidneys of two workers with proteinuria revealed granular deposition of IgG and the C3 complement factor in the glomeruli (Tubbs et al., 1982). One of 89 workers examined by Langworth et al. (1992b) showed a weak reaction to antiglomerular basement membrane, and 8 of 44 workers examined by Cardenas et al. (1993) showed an abnormally high anti-DNA antibody titer. Increases in IgA and IgM were observed in workers in a mercury refinery (Bencko et al., 1990) and increases in anti-DNA antibodies were observed in workers from a chlor-alkali plant (Cardenas et al., 1993).

Epidemiological studies have found no evidence indicating that inhalation of elemental mercury produces cancer in humans (Cragle et al., 1984; Kazantzis, 1981).

Several studies evaluated fertility (i.e., ability to conceive within a year; number of children conceived with correlation to age of parents) following subchronic or chronic inhalation exposure to elemental mercury in humans (Alcser et al., 1989; Lauwerys et al., 1985); no effects were observed compared to unexposed control groups. Although no effect on fertility was observed in exposed workers, the rate of spontaneous abortions was correlated with increased mercury concentrations in the urine of fathers exposed before the

pregnancy to elemental mercury in chlor-alkali plants (Cordier et al., 1991). In addition, women occupationally exposed to elemental mercury vapors (dentists and dental assistants, factory workers) had more reproductive failure (spontaneous abortions, stillbirths, congenital malformations) and irregular, painful, or hemorrhagic menstrual disorders than a control group of women not exposed to mercury (Sikorski et al., 1987) and complications of parturition (toxicosis, abortions, prolonged parturition, hemorrhagic parturition) (Mishonova et al., 1980). However, these studies lacked adequate information regarding exposure concentrations and durations.

Laboratory Animal Data

In laboratory animals, as in humans, adverse neurological and behavioral effects are prominent following inhalation exposure to elemental mercury vapor. However, animals appear to be less sensitive than humans. Table 11-37 summarizes the laboratory animal data. Marked cellular degeneration and widespread necrosis were observed in the brains of rabbits following exposures to elemental mercury vapor at 28,800 $\mu g/m^3$ for durations ranging from 2 to 30 h (Ashe et al., 1953). With longer exposures (1 to 13 weeks) and lower concentrations, rabbits exhibited effects ranging from mild, unspecified, pathological changes to marked cellular degeneration and some necrosis in the brain (Ashe et al., 1953), and slight tremors and clonus (Fukuda, 1971). Rats exhibited a decline in conditioned avoidance response (reversible) with exposure to 3,000 $\mu g/m^3$ for 12 to 42 weeks; however, no histopathological changes were evident (Kishi et al., 1978). Mice exposed to an unspecified concentration of elemental mercury vapor intermittently for over 3 weeks exhibited progressive neurological dysfunction (i.e., wobbling and unresponsiveness to light), beginning 22 days after initial exposure, and died 4 days postexposure (Ganser and Kirschner, 1985). No studies were conducted using standard battery of tests on neurological endpoints (e.g., functional and observational neurological changes).

Respiratory effects in laboratory animals have been observed following acute inhalation exposure of elemental mercury vapors. Rats exposed to 27,000 $\mu g/m^3$ of elemental mercury vapors for 2 h displayed dyspnea and death due to asphyxiation (Livardjani et al., 1991). Respiratory tract lesions included lung edema, necrosis of the alveolar epithelium, and

TABLE 11-37. LABORATORY ANIMAL EXPSOURE CONDITIONS AND EFFECTS FOR MERCURY VAPOR AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
Animal Acute Studies							
0 3.3	0 27,000	1 or 2 hr	Hg vapor	NA	Rats, Wistar (4) M	Clincal observations, superoxide dismutase activity, histopathology of major organs (stated in summary only): Death by asphyxiation, respiratory effects (lung edema, hyaline membranes, necrosis of alveolar epithelium). Note: Air continuously recycled in chamber.	Livardjani et al. (1991)
3.5	28,800	1-30 hr	Hg vapor	NA	Rabbits, NS (1-2) NS	Clinical signs, histopathology: Cellular degeneration (not specified) and necrosis in lungs, heart, colon, liver, kidney, and brain. Note: Data not presented in detail.	Ashe et al. (1953)
Subchronic and Chronic Animal							
0.73	6,000	7 hr/d 5 d/wk 1-11 wk	Hg vapor	NA	Rabbits, NS (1-3) NS	Clinical signs, histopathology: Cellular degeneration and ncrosis in liver, necrosis in kidneys, unspecified histopathological changes in lungs, heart, colon, and brain. Note: Data not presented in detail.	Ashe et al. (1953)

TABLE 11-37 (cont'd). LABORATORY ANIMAL EXPSOURE CONDITIONS AND EFFECTS FOR MERCURY VAPOR AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	μg Hg/m^3						
0.105	860	7 hr/d 5 d/wk 12 wk	Hg vapor	NA	Rabbits, NS (1-4) NS	Clinical signs, histopathology: Unspecified histopathological changes (transient) in heart, kidney, and brain. Clinical signs not reported. Note: Data not presented in detail.	Ashe et al. (1953)
0.012	100	7 hr/d 5 d/wk 72 wk	Hg vapor	NA	Rat, NS (1-2) NS	Clinical signs, histopathology of kidneys: No effects.	Ashe et al. (1953)
0.012	100	7 hr/d 5 d/wk 72 wk	Hg vapor	NA	Rabbit, NS (1-4) NS	Clinical signs, histopathology of kidneys: No effects.	Ashe et al. (1953)
0.012	100	7 hr/d 5 d/wk 72 wk	Hg vapor	NA	Dog, NS (2) NS	Clinical signs, histopathology of kidneys: No effects.	Ashe et al. (1953)
0 0.37	0 3,000	3 hr/d 5 d/wk 12-42 wk	Hg vapor	NA	Rats, NS (7) M	Behavioral tests; histopathology of lung, liver, kidney, brain, spinal cord, and sciatic nerve: Irritability; dense deposits in tubular cells and lysosomal inclusions in renal cortex; decline in conditioned avoidance response; tremor. No histopathological changes in the brain.	Kishi et al. (1978)
0 0.5	0 4,000	6 hr/d 4 d/wk 13 wk	Hg vapor	NA	Rabbits, NS (6) M	Clinical signs, electromyographic recording: tremors and clonus.	Fukuda (1971)

TABLE 11-37 (cont'd). LABORATORY ANIMAL EXPSOURE CONDITIONS AND EFFECTS FOR MERCURY VAPOR AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Hg/m^3$						
0 0.12	0 1,000	6 or 24 hr/d 5 wk	Hg vapor	NA	Rat, Brown Norway (3-4/sex)	Serum IgE concentration, anti-laminin antibody titer, urinary protein: Inc serum IgE; anti-laminin autoantibody titer, IgG deposits along glomerular capillary walls.	Hua et al. (1993)
0 0.006	0 50	1 or 4h/d 7 d ppd11-17	Hg vapor	NA	Rats, Sprague-Dawley (6) M	Spontaneous motor activity (at 2 and 4 mo of age) and spatial learning tasks (at 6 mo): impaired spatial learning (radial arm maze), increased locomotor activity.	Fredriksson et al. (1992)
0 0.3	0 2,500	6 hr/d 5 d/wk 3 wk (prior to mating and Gd 7-20)	Hg vapor	NA	Rat, NS (24) F	Maternal, reproductive, and developmental parameters: Dec number of live pups/litter; death of remaining infants by postpartum day 6; maternal toxicity (spasms, tremor, death, decreased milk production).	Baranski and Szymczyk (1973)
Mercuric Chloride							
NA	NS	1 h/d 4 d/wk 2 mo	H_gCl_2 aerosol	NS	Brown, Norway Rat/5B	Immunomorphological studies, indirect immunofluorescent studies, proteinuria: Proteinura and autoimmune effect in kidney, lung, and spleen (linear pattern of fixation of the fluorescinated anti-rat IgG antiserum along glomerular capillary wall and mesangium in kidneys, lung vessels and interstitium, and/or white pulp of spleen).	Bernaudin et al. 1981

TABLE 11-37 (cont'd). LABORATORY ANIMAL EXPSOURE CONDITIONS AND EFFECTS FOR MERCURY VAPOR AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number), Sex	Assays performed: Effect(s)	Reference
ppm	μg Hg/m^3						
NA	0 0.17 1.6	4 h/d 4 d Gd 9-12	H_gCl_2 aerosol	NS	CFLP Mice/ F NS	Reproductive and developmental parameters: Inc dead or resorbed fetuses; delayed ossification at 0.17 μg/m^3. Limitation: Data reported as number of embryos only, not as number of affected litters; no statistical analysis; aerosol exposure not well characterized; maternal toxicity not evaluated.	Selypes et al. 1984

[a]Elemental mercury.

Abbreviations:
avg = average; d = day(s); dec = decreased; ppd = post partum day; F = females; Gd = gestational day; Hg = mercury; H_gCl_2 = mercuric chloride; h = hours; Ig = immunoglobulin; inc = increased; M = males; NAG = *N*-acetyl-β-glucosaminidase; NA = not applicable; NS = not specified; ppd = post partum day; TWA = time weighted average; yr = years.

hyaline membranes, and occasional lung fibrosis. Longer exposure to mercury vapor (1 to 20 h) produced effects ranging from mild to moderate pathological changes (unspecified) (Ashe et al., 1953). Congested lungs were observed in rats exposed to 1,000 $\mu g/m^3$ elemental mercury vapors for 6 weeks (continuously for 100 h/week) (Gage, 1961). However, in rats exposed to 3,000 $\mu g/m^3$ mercury vapor for 12 to 42 weeks (intermittently for 3 h/day), pathological examination revealed no significant changes in the respiratory system (Kishi et al., 1978).

The study by Ashe et al. (1953) has also reported cardiovascular and liver effects in animals following acute and subchronic exposures; however, pathological lesions in the liver and heart tissues were not specified. The study was not well conducted, was deficient in quantitative data, and used a small number of animals.

Increased serum IgE, anti-laminin autoantibody titer, and IgG deposits along glomerular capillary walls were observed in Brown Norway rats exposed to 1,000 $\mu g/m^3$ mercury vapor for 5 weeks (Hua et al., 1993). Inhalation exposure to mercuric chloride aerosol for 2 mo also resulted in proteinuria and autoimmune effects in the kidney, lung, and spleen in Brown - Norway rats (Bernaudin et al., 1981).

In rats, exposure to elemental mercury vapor for 21 days caused prolongation of the estrous cycle (Baranski and Szymczyk, 1973). The study authors speculated that the effects on the estrous cycle were caused by the action of mercury on the central nervous system (i.e., damage to the hypothalamic regions involved in the control of estrous cycling).

Reproductive and developmental effects in rats exposed to elemental mercury are indicated by Baranski and Szymczyk (1973). Adult female rats were exposed to mercury vapor at 2,500 $\mu g/m^3$ for 3 weeks prior to fertilization and during gestational days 7 to 20. A decrease in the number of living fetuses was observed in these dams compared to unexposed controls, and all pups born to the exposed dams died by the 6th day after birth. However, no difference in the occurrence of developmental abnormalities was observed between exposed and control groups. The cause of death of the pups in the mercury-exposed group was unknown, although an unspecified percentage of the deaths was attributed by the authors to a failure of lactation in the dams. Death of pups was also observed in another experiment in which dams were only exposed prior to fertilization to the same dose level,

supporting the conclusion that high mortality in the first experiment was due, at least in part, to poor health of the mothers (Baranski and Szymczyk, 1973).

Neurodevelopmental effects have also been reported with exposure to elemental mercury vapor in rat; subtle behavioral changes (delayed spatial learning, lower locomotor, rearing, and total activity) when the rats were tested at 4 and 6 mo of age (Fredriksson et al., 1992). Offspring of rats exposed for 1 h/day showed increases in the time necessary to finish a task in the radial arm maze (spatial learning). Offspring of rats exposed for 4 h/day showed increases in both the time to finish the task and in the number of errors committed. When tested for locomotor activity at 2 mo, an increase in rearing was observed in the 4 h/day group, but repeat testing at 4 mo showed lower locomotor, rearing, and total activity than controls. The 1 h/day exposure group showed no difference from controls at 2 mo, and increased activity and decreased rearing at 4 mo when compared to controls. An inhalation developmental study in rats (Selypes et al., 1984) reported increased dead or resorbed fetuses and delayed ossification following in utero exposure to mercuric chloride during gestational day 9-12. However, the study had several limitations, including lack of information regarding maternal toxicity, number of affected litters, statistical analysis, and aerosol characterization.

11.6.11.4 Factors Affecting Susceptibility

Because the kidney, respiratory tract, and nervous system are targets of mercury toxicity following inhalation exposure, individuals with functional impairments of these tissues are considered to be at greater risk of suffering from the toxic effects of mercury.

Inhalation and oral laboratory animal studies (Aten et al., 1992; Bernaudin et al., 1981; Druet et al., 1978; Hultman and Enestrom, 1992) and limited human data (Lindqvist et al., 1974; Tubbs et al., 1982) also indicate that there may be persons with a genetic predisposition to develop an autoimmune glomerulonephritis upon exposure to mercury. In this form of renal toxicity, proteinuria is observed following the reaction of autoantibodies with renal tissues and deposition of immune material (i.e., IgG and complement C3) in the renal mesangium and glomerular blood vessels. Both susceptible and resistant mice and rat strains have been identified, and susceptibility appears to be governed by both major histocompatibility complex (MHC) genes and nonMHC genes (Aten et al., 1991; Druet

et al., 1978; Hultman and Enestrom, 1992; Hultman et al., 1992; Michaelson et al., 1985; Sapin et al., 1984).

Other data on factors affecting susceptibility are from oral and dermal exposures. Metabolism of mercury is expected to be similar after absorption for all exposure routes, and as such, the following information on susceptibility may be relevant for the inhalation route. Individuals with a dietary insufficiency of zinc, glutathione, antioxidants, or selenium, or those who are malnourished may be more susceptible to the toxic effects of mercury poisoning because of the diminished ability of these substances to protect against mercury toxicity.

Probably the most widely recognized form of hypersensitivity to mercury poisoning is the uncommon syndrome known as acrodynia, also called erythredema polyneuropathy and pink disease (Warkany and Hubbard, 1953). Infantile acrodynia was first described in 1828, but many adult cases have since been reported. While acrodynia is seen in a small number of children (0.1%) after short-term exposures and with urine levels of 50 μg/L or more, there are some cases in the literature in which mercury exposure was known to have occurred, but without elevated (above background) Hg levels in urine. There could be many reasons for this, but the most likely is that urine levels are not a simple measure of body burden or of target tissue, i.e., brain levels. Acrodynia is characterized by itching, flushing, swelling, and/or desquamation of the palms of the hands or soles of the feet, morbiliform rashes, excessive sweating and/or salivation, tachycardia, elevated blood pressure, insomnia, weakness, irritability, fretfulness, and peripheral sensory disturbances (Warkany and Hubbard, 1953). The occurrence of acrodynia was determined to be an idiosyncratic reaction to mercury exposure. Despite widespread exposure of children to mercury-containing laxatives, antiascariasis medications, and teething powders in the 1940s and 1950s, only a few children developed acrodynia. The basis for this hypersensitivity and methods for identifying the susceptible population are unknown, although the lack of stabilized thermoregulatory and other homeostatis in neonates is suspected.

Neonates may also be especially susceptible to mercury toxicity. Both inorganic and organic forms of mercury are excreted in the milk (Sundberg and Oskarsson, 1992; Yoshida et al., 1992). Furthermore, suckling rats exhibit a very high absorption of inorganic mercury as a percentage of the diet (30–40%) compared to adult rats, which absorb ca. 1%

of inorganic mercury from the diet (Kostial et al., 1978). The highest oral toxicity to inorganic mercury as expressed by the LD_{50} was for 2-week-old rats; by 3 to 6 weeks of age, rats showed a dramatic drop in sensitivity to inorganic mercury poisoning (Kostial et al., 1978). The transfer of mercury to suckling rats via milk was found to result in greater concentrations of the metal in brains of the offspring than in the mother (Yang et al., 1973).

11.6.12 Manganese

11.6.12.1 Physical and Chemical Properties

Manganese (Mn) is a reddish-gray or silver-colored metal with an atomic weight of 54.94, a melting point of 1244°C, and a density of 7.20 at 20°C (Sax and Lewis, 1987). Although widely distributed in the earth's crust, ranking as the twelfth most abundant element and the fifth most abundant metal, manganese does not occur naturally as the pure metal. Oxides, carbonates, and silicates are the most important manganese-containing minerals. Manganese is mainly used in metallurgical processes but has various other uses (e.g., in dry-cell batteries, glass, leather, textiles, fertilizers). Organic carbonyl compounds are used as fuel-oil additives, smoke inhibitors, and anti-knock additives in gasoline (U.S. Environmental Protection Agency, 1984, 1994).

Crustal manganese enters the atmosphere by a number of natural and anthropogenic processes, which include wind erosion and the suspension of road dusts by vehicles. The resulting mechanically generated aerosols consist primarily of coarse particles ≥ 2.5 μm mass median aerodynamic diameter (MMAD). The smelting of natural ores and the combustion of fossil fuels also result in injection of crustal manganese into the atmosphere in the form of fume or ash in the fine-particle range (≤ 2.5 μm MMAD). Nearly one-half of all industrial and combustive emissions of manganese are from ferroalloy manufacture and about one-tenth from fossil-fuel combustion.

The most common forms of manganese compounds in coarse particles of crustal origin are oxides or hydroxides of oxidation state +2, +3, or +4, and manganese carbonate. The manganese emitted by metallurgical processes consists of oxides. The manganese from combusted methylcyclopentadienyl manganese tricarbonyl (MMT), used in some countries as a fuel additive, is emitted primarily as Mn_3O_4 particles < 1 μm MMAD. Minute amounts of organic manganese compounds such as MMT may be present in ambient air under certain

conditions. However, MMT itself is rapidly photodegraded to inorganic manganese in sunlight. The estimated half-time is 10 to 15 seconds (U.S. Environmental Protection Agency, 1984).

Background concentrations of manganese have been reported as 0.05 to 5.4 ng/m^3 over the Atlantic Ocean (Duce et al., 1975) and 0.01 ng/m^3 at the South Pole (Zoller et al., 1974). For the period of 1979 to 1983, the median ambient concentration of particulate manganese with an MMAD $\leq$ 10 μm for sites in the U.S. Environmental Protection Agency (EPA) Inhalable Particulate Network was approximately 20 ng/m^3, with a 10th percentile level of 10 ng/m^3 and a 99th percentile value of over 200 ng/m^3 (U.S. Environmental Protection Agency, 1994).

The size of manganese particles in the atmosphere varies from place to place, depending on the dominant sources in an area. Based on dichotomous sampler data for 22 sites in the United States (Davis et al., 1984), the proportion of particulate matter $\leq$10 μm MMAD (PM_{10}) manganese that was in the fine-mode ($\leq$2.5 μm MMAD) ranged from 3 to 66%.

11.6.12.2 Pharmacokinetics

Quantitative pharmacokinetic data directly comparing different routes of exposure for manganese are not available, but several experimental studies have demonstrated that tissue manganese levels are well regulated when the exposure is by ingestion. Very few cases of manganese toxicity by ingestion have been observed. However, when inhaled, manganese that enters the bloodstream passes first by the brain, before being processed by the liver. Depending on its ability to cross the blood brain barrier, this manganese may reach areas of the central nervous system (CNS) and produce the characteristic neurotoxic effects of manganese. Although manganese is eliminated primarily by biliary excretion, it appears that inhaled manganese may not be as well regulated by this mechanism as is ingested manganese.

The water-solubility of a manganese compound appears to affect the time course of respiratory tract absorption but not necessarily the amount ultimately absorbed. Mena et al. (1969) observed no difference between the absorption of 1 μm particles of $MnCl_2$ and Mn_2O_3 in healthy adults. Drown et al. (1986) found that following intratracheal instillation of

$MnCl_2$ and Mn_3O_4 in rats, the soluble chloride cleared four times faster than the insoluble oxide from the respiratory tract; however, despite this initial difference, after 2 weeks the amounts of labeled Mn in the respiratory tract were similar for the two compounds. Extrathoracic deposition is another possible route of exposure. Studies such as those of Perl and Good (1987) and Evans and Hastings (1992) have indicated that neurotoxic metals such as aluminum and cadmium can be directly transported to the brain olfactory bulbs via nasal olfactory pathways.

Experimental studies using radiolabeled manganese indicate that the metal is eliminated more slowly from the brain than from most other organs or the body as a whole. Pharmacokinetic analyses based on inhalation of manganese chloride by macaque monkeys (Newland et al., 1987) indicated that clearance from the brain was slower than from the respiratory tract and that the rate of clearance depended on the route of exposure. Brain half-times were 223 to 267 days after inhalation versus 53 days following subcutaneous administration (Newland et al., 1987) or 54 days in humans given manganese intravenously (Cotzias et al., 1968). These long half-times were thought to reflect both slower clearance of brain stores and replenishment from other organs, particularly the respiratory tract. In rats, Drown et al. (1986) also observed slower clearance of labeled Mn from the brain than from the respiratory tract. Several occupational physicians have reported large individual differences in workers' susceptibility to manganese intoxication, which Rodier (1955) speculated might be due in part to differences in the ability to clear particulate manganese from the lung. However, large differences between individuals in their absorption of ingested manganese have also been noted (Davidsson et al., 1991). The basis for the wide range in individual susceptibility to manganese toxicity remains to be elucidated.

Some experimental evidence suggests that the mechanisms of manganese toxicity may depend on the oxidation state of manganese. However, both the trivalent form (Mn^{3+}) and the divalent form (Mn^{2+}) have been demonstrated to be neurotoxic. Also, both forms of manganese can cross the blood-brain barrier, although research suggests that Mn^{3+} is predominantly transported bound to the protein transferrin (Aschner and Gannon, 1994), whereas Mn^{2+} may enter the brain independently of such a transport mechanism (Murphy et al., 1991).

11.6.12.3 Health Effects

The toxicity of manganese varies according to the route of exposure. By ingestion, manganese has relatively low toxicity at typical exposure levels and is considered a nutritionally essential trace element. However, by inhalation, manganese has been known since the early 1800s to be toxic to workers. Manganism is characterized by various psychiatric and movement disorders, with some general resemblance to Parkinson's disease in terms of difficulties in the fine control of some movements, lack of facial expression, and involvement of underlying neuroanatomical and neurochemical factors. Respiratory effects (e.g., pneumonitis) and reproductive dysfunction (e.g., reduced libido) are also frequently reported features of occupational manganese intoxication. The available evidence is inadequate to determine whether or not manganese is carcinogenic; some reports suggest that it may even be protective against cancer. Based on this mixed but insufficient evidence, the U.S. Environmental Protection Agency (IRIS, 1988) has placed manganese in a Group D weight-of-evidence category, which signifies that it is not classifiable as to human carcinogenicity.

Human Data

Various epidemiological studies of workers exposed to manganese at average levels below the current American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV) (5 mg/m^3)[1] have shown neurobehavioral, reproductive, and respiratory effects, both by objective testing methods and by workers' self-reported symptoms on questionnaires (e.g., Roels et al., 1987, 1992; Iregren, 1990; Mergler et al., 1994). Neurobehavioral effects generally have reflected disturbances in the control of hand movements (e.g., tremor, reduced hand steadiness) and/or the speed of movement (e.g., longer reaction time, slower finger-tapping speed). Reproductive effects have included a decrease in the number of children born to manganese-exposed workers (compared to matched controls) and various self-reported symptoms of sexual dysfunction. In recent studies at low to moderate occupational exposure levels, respiratory effects have been reflected primarily in self-reported symptoms of respiratory tract illnesses rather than in

[1]The American Conference of Governmental Industrial Hygienists (1992) has given notice of intent to lower the TLV to 0.2 mg/m^3.

differences between objective spirometric measurements in manganese-exposed and control workers. However, the lack of studies using more sensitive investigational methods and the existence of some limited evidence from an epidemiological study of school children (Nogawa et al., 1973) raise a degree of concern about pulmonary function effects in relation to lower level manganese exposure.

Several epidemiological studies of workers have provided consistent evidence indicating that neurotoxicity is associated with low-level occupational manganese exposure. Roels et al. (1992) conducted a cross-sectional study of neurobehavioral and other endpoints in a group of 92 male alkaline-battery plant workers exposed to MnO_2 dust and compared their performance to a matched control group of 101 male workers without industrial manganese exposure. The geometric mean occupational-lifetime integrated respirable dust concentration was 793 μg Mn/m^3 $\times$ years (range: 40 to 4433). The equivalent value for total dust was 3505 μg Mn/m^3 $\times$ years (range: 191 to 27,465). The authors noted that the monitored concentrations were representative of the usual exposures of the workers because work practices had not changed during the preceding 15 years of the plant's operation. Because the respirable fraction (5 μm MMAD) is more representative of the toxicologically significant particles (i.e., the smaller particles that are inhaled and deposit predominantly in the lower respiratory tract), the respirable dust measurements were considered to be more accurate than total dust as an indicator of exposure in relation to the observed health effects.

According to the 1992 report of Roels et al., manganese-exposed workers performed significantly worse than matched controls on several measures of neurobehavioral function, particularly eye-hand coordination, hand steadiness, and visual reaction time. Similar neurobehavioral impairments were also found in an earlier study by Roels et al. (1987) of a different occupational population exposed to mixed manganese oxides and salts at approximately the same levels of total dust (respirable dust was not measured). A recent study of manganese workers in Canada by Mergler et al. (1994) also indicated that, among other effects, performance on tests of the ability to make rapid alternating hand movements, to maintain hand steadiness, and to perform other aspects of fine motor control was significantly worse, compared to matched controls. Workers in that study were exposed to an average respirable manganese dust concentration of 35 μg/m^3 at the time of the study, but earlier exposure levels had been somewhat higher (Mergler et al., 1994). In addition,

reports of a Swedish study of manganese-exposed steel workers (Iregren, 1990; Wennberg et al., 1991, 1992) provided compelling evidence of comparable neurobehavioral impairments, including slower reaction time and finger-tapping speed. The median total dust concentration in the Swedish study was 140 μg Mn/m^3, with respirable dust reported as constituting 20 to 80% of individual workers' total dust exposures. Thus, the lowest-observed-adverse-effect level (LOAEL) from this study would presumably be somewhat lower than that from Roels et al. (1992), but the exposure histories in the Swedish study are less fully characterized.

None of the investigators in the above studies have reported a no-observed-adverse-effect level (NOAEL). If the period of occupational manganese exposure in the Roels et al. (1992) study had been longer than the relatively short average duration of only 5.3 years and if the age of the workers had been greater than the relatively young average of 31.3 years, it is possible that the observed effects would have occurred at even lower levels of exposure. Some reports in the literature indicate that manganese toxicity may not be clinically evident until some years after exposure occurred or terminated (e.g., Cotzias et al., 1968; Rodier, 1955), and other reports point to a greater sensitivity of elderly persons, compared to middle-aged or young adults, for acute as well as chronic manganese toxicity (e.g., Kawamura et al., 1941). It is possible that the compensatory or reserve capacity of certain neurological mechanisms may be stressed by manganese exposure earlier in life, with manifestations of impairments only becoming evident much later, perhaps at a geriatric stage. One reason for the latter concern is that Parkinson's disease is typically a geriatric disease in which symptoms are only seen when the loss of brain cells that produce dopamine (which is also apparently involved in manganese toxicity) reaches 80% or more. Indeed, some neurologists think that a long latency period of perhaps several decades may precede various parkinsonian syndromes. These points lead to a concern that if manganese reduces the compensatory or reserve capacity of the nervous system, parkinsonian-type effects might occur earlier in life than they would otherwise.

Laboratory Animal Data

Evidence from several laboratory animal studies supports findings in manganese-exposed humans. For example, inhaled manganese has been shown to produce

significant alterations in dopamine levels in the caudate and globus pallidus of Rhesus monkeys (Bird et al., 1984) and behavioral changes in mice (Morganti et al., 1985). However, species differences may complicate interpretation of certain neurobehavioral findings in laboratory animals. Unlike primates, rodents do not have pigmented substantia nigra, which is a brain region of relatively high manganese uptake and involvement in consequent neurobehavioral dysfunction. Nevertheless, rodent and primate studies show various neurochemical, neuropathological, and neurobehavioral effects resulting from manganese exposure. However, because most laboratory animal studies of manganese neurotoxicity involve exposure by routes other than inhalation, they are not described here (see U.S. Environmental Protection Agency, 1984).

Other endpoints of manganese toxicity have also been investigated with laboratory animal models of inhalation exposure. Experimental animal data qualitatively support human study findings in that manganese exposure results in an increased incidence of pneumonia in rats exposed to 43,000 to 139,000 μg Mn/m^3 as MnO_2 (mean MMAD = 0.76 μm; mean σ_g = 2.28) for 2 weeks (Shiotsuka, 1984), pulmonary congestion in monkeys exposed to 700 or 3,000 μg Mn/m^3 as MnO_2 (80% < 1 μm) for 5 mo (Nishiyama et al., 1977), pulmonary emphysema in monkeys exposed to 700 to 3,000 μg Mn/m^3 as MnO_2 (80% < 1 μm) for 10 mo (Suzuki et al., 1978), and bronchiolar lesions in rats and hamsters exposed to 117 μg Mn/m^3 as Mn_3O_4 (0.29 μm) for 56 days (Moore et al., 1975). Also, Lloyd-Davies and Harding (1949) induced bronchiolar epithelium inflammation, widespread pneumonia, and granulomatous reactions in rats administered 10,000 μg MnO_2 (80% < 1 μm) by intratracheal injection, and pulmonary edema in rats administered 5,000 to 50,000 μg $MnCl_2$ (as a 5% solution in saline) in the same fashion. However, no significant pulmonary effects were detected in other studies of rats and monkeys exposed to as much as 1,150 μg Mn/m^3 as Mn_3O_4 (equivalent aerodynamic diameter $\approx$ 0.11 μm; σ_g = 3.07) for 9 mo (Ulrich et al., 1979a,b,c) and rabbits exposed to as much as 3,900 μg Mn/m^3 as $MnCl_2$ (MMAD $\approx$ 1 μm) for 4 to 6 weeks (Camner et al., 1985).

Laboratory animal studies have also shown that inhaled manganese may increase susceptibility to infectious agents such as *Streptococcus pyogenes* in mice (Adkins et al., 1980), *Enterobacter cloacae* in guinea pigs (Bergstrom, 1977), *Klebsiella pneumonia* in mice (Maigetter et al., 1976), and *Streptococcus hemolyticus* in mice (Lloyd-Davies, 1946).

In general, manganese concentrations were relatively high (>10,000 $\mu g/m^3$) in these studies. However, Adkins et al. (1980) concluded that, based on the regression line of the relationship between concentration and mortality in manganese-exposed mice, exposure to 620 $\mu g/m^3$ would result in a mortality rate at least 10% greater than the control rate.

The developmental effects of manganese have been investigated primarily from the viewpoint of the nutritional role of this element and therefore have generally involved oral exposure. Some studies indicate that neonates of various species have a greater body burden of manganese than mature individuals have, possibly because neonates do not develop the ability to eliminate manganese (and thereby maintain manganese homeostasis) until some time after birth (Miller et al., 1975; Cotzias et al., 1976; Wilson et al., 1992). Moreover, some evidence suggests that the neonate's inability to maintain manganese homeostasis is due to a limitation in the elimination of manganese rather than in its gastrointestinal absorption (Bell et al., 1989), which would suggest a potentially greater vulnerability of young individuals to excessive manganese exposure regardless of the route of exposure.

Several studies have demonstrated neurochemical alterations in young rats and mice exposed postnatally to manganese by routes other than inhalation (e.g., Kontur and Fechter, 1988; Seth and Chandra, 1984; Deskin et al., 1981; Cotzias et al., 1976). The only inhalation study of the developmental toxicity of manganese appears to be that of Lown et al. (1984). Female HA/ICR mice were exposed to MnO_2 7 h/day, 5 days/week for 16 weeks prior to conception and between gestational days 1 and 18. For the first 12 weeks, the air concentration was 49,100 μg Mn/m^3; all later exposures were at 85,300 μg Mn/m^3. To separate prenatal and postnatal exposure effects, a cross-fostering design was used. Although mothers exposed to MnO_2 prior to conception produced significantly larger litters, prenatally exposed offspring showed reduced scores on various neurobehavioral activity measures and retarded growth that persisted into adulthood. Balance and coordination were affected by either gestational or post-partum exposure to MnO_2.

11.6.12.4 Comparative Toxicity

The neuropathological bases for manganism have been investigated by many researchers and have indicated the involvement of the corpus striatum and the extrapyramidal motor system (e.g., Archibald and Tyree, 1987; Donaldson and Barbeau, 1985; Eriksson et al.,

1987, 1992). Neuropathological lesions have generally been associated with the basal ganglia, with neuronal degeneration in the putamen and globus pallidus (e.g., Newland et al., 1987; Yamada et al., 1986). The substantia nigra, a pigmented area of the midbrain with connections to the striatum and globus pallidus, contains dopamine cells that project to the striatum and play an important role in the control of movement. Manganese tends to accumulate in the substantia nigra and the basal ganglia and damage dopamingergic neurons in those structures (Bird et al., 1984). Rodents lack the degree of melanin pigmentation that characterizes the substantia nigra of humans and nonhuman primates, and thus rodents are not thought to be as susceptible to the neurotoxic effects of manganese as are humans. However, this difference between rodents and humans is not a qualitative difference, and rodents do show various effects indicative of manganese neurotoxicity.

In terms of the neurochemistry of manganese toxicity, several studies have shown that dopamine levels are affected by manganese exposure in humans, monkeys, and rodents, with various indications of an initial increase in dopamine followed by a longer term decrease (e.g., Cotzias et al., 1976; Bird et al., 1984; Barbeau, 1984). Some theories of manganese neurotoxicity have focused on the role of excessive manganese in the oxidation of dopamine resulting in free radicals and cytotoxicity (e.g., Donaldson et al., 1982; Barbeau, 1984). In addition, the fundamental role of mitochondrial energy metabolism in manganese toxicity has been indicated by the studies of Aschner and Aschner (1991), Gavin et al. (1990), and others. Brouillet et al. (1993) have suggested that the effects of manganese on mitochondrial function result in various oxidative stresses to cellular defense mechanisms (e.g., GSH) and, secondarily, free radical damage to mitochondrial DNA. In view of the slow release of manganese from mitochondria (Gavin et al., 1990), such an indirect effect would help account for a progressive loss of function in the absence of ongoing manganese exposure (Brouillet et al., 1993), as manganese toxicity may continue or progress in humans despite the termination of exposure (Cotzias et al., 1968; Rodier, 1955).

Because of the involvement of the dopaminergic system and extrapyramidal motor system in both Parkinson's disease and manganism, symptoms of the two diseases are somewhat similar, and several writers have suggested the possibility of a common etiology; however, many neurological specialists make a clear distinction in the etiologies and clinical features of Parkinson's disease and manganism (Barbeau, 1984; Langston et al., 1987).

11.6.12.5 Factors Affecting Susceptibility

Epidemiological studies of workers and experimental studies laboratory animals exposed to manganese have shown neurobehavioral, reproductive, and respiratory effects. People with impairments in the function or reserve capacity of these systems are potentially susceptible to the effects of manganese toxicity. Some reports in the literature indicate that manganese toxicity may not be clinically evident until some years after exposure occurred or terminated (Cotzias et al., 1986; Rodier, 1955). It is possible that the compensatory or reserve capacity of certain neurological mechanisms may be stressed by manganese earlier in life, with manifestations of impairments only becoming evident much later, perhaps at a geriatric stage. The neurobehavioral effects of manganism are characterized by various psychiatric and movement disorders that resemble Parkinson's disease, a disease that is typically a geriatric disease. If manganese reduces the compensatory or reserve capacity of the nervous system, then Parkinsonian-type effects might occur earlier in life or be exacerbated later in life. Because the epidemiologic studies only investigated healthy working adult males, there is concern that the effects of manganese on the developing nervous system have not been adequately investigated, and suggests that the prenatal and/or postnatal populations may be at increased risk. People with iron or calcium deficiencies and individuals with liver impairment may also have an increased potential for excessive manganese body burdens due to increased absorption or altered clearance mechanisms.

11.6.13 Magnesium

11.6.13.1 Chemical and Physical Properties

Magnesium is a metallic element in Group 2A of the periodic table. It forms all of its compounds in the +2 oxidation state. Upon exposure to air, the surface of magnesium metal is oxidized from its elemental valence of 0 to form magnesium oxide. This magnesium oxide film protects the metallic magnesium from further oxidation. In water, under ordinary atmospheric conditions, metallic magnesium is oxidized as well to form magnesium hydroxide [$Mg(OH)_2$] (Lockwood et al., 1981). Magnesium exists in the environment as both inorganic salts, and organomagnesium compounds (Copp and Wardle, 1981). Elemental magnesium is insoluble in cold water and decomposes in hot water to magnesium hydroxide,

$Mg(OH)_2$, whereas two of its more common compounds, i.e., magnesium oxide (MgO) and magnesium carbonate ($MgCO_3$) are slightly soluble in water.

11.6.13.2 Pharmacokinetics

Data on the absorption, distribution, metabolism, and excretion of inhaled magnesium compounds are limited. However, the observation of increased serum magnesium levels in workers exposed to magnesium oxide dust (Pleschitzer, 1936) indicates that some of the magnesium is absorbed, either directly following deposition in the lung, or from the gastrointestinal tract following clearance from the lung. Any magnesium oxide that is absorbed is hydrated to magnesium hydroxide (American Conference of Governmental Industrial Hygienists, 1991). Lung deposition of magnesium carbonate and magnesium carbonate dusts has been observed in animals following prolonged exposure at high concentrations; further experimental details were not available (Zeleneva, 1970).

Further data on magnesium toxicokinetics are limited to information from oral dosing. Absorbed magnesium is distributed throughout the body. A normal adult body contains a total of about 21 g of magnesium, of which about 11 g are in the skeleton, 9.5 g are in the cells, and 0.5 g are in extracellular water (Wacker and Vallee, 1958). Magnesium is an essential element and is a cofactor in many enzymatic reactions. It is associated with metabolically active ATP, and so is essential to such functions as muscle contraction, nerve conduction, carbohydrate utilization, and macromolecule synthesis. Absorbed magnesium is excreted in the urine, but absorption from the intestine is poor, leading to elimination in the feces (Aikawa et al., 1958). The kidney plays a key role in maintaining magnesium homeostasis (Labeeuw and Pozet, 1988).

11.6.13.3 Health Effects

Limited data are available regarding the health effects in humans or laboratory animals of inhalation exposure to magnesium compounds. Data are available only on magnesium oxide fume and magnesite. Magnesium oxide occurs as a powder at room temperature, but magnesium oxide fume results when magnesium is burned at high temperatures. Magnesite is the mineral magnesium carbonate; roasting magnesite produces magnesium oxide.

Humans

Toxicity data for humans are summarized in Table 11-38. Data on acute magnesium inhalation are limited to one study in which volunteers inhaled freshly generated magnesium oxide fume at 246,000, 252,000, 258,000, or 348,000 μg magnesium/m^3 for 1 to 9 min (Drinker et al., 1927). The total amount inhaled was estimated at 15,000 to 29,000 μg. Less than 10 min after exposure, body temperature rose slightly, followed 5 to 6 h later by fever and elevated white blood cell counts; recovery was complete by the next morning. The response was considered milder than that observed with zinc oxide fume, but the authors suggested that more prolonged exposures would lead to more severe symptoms. This study appears to be the basis for the statement in Stokinger (1981) that the TC_{LO} for magnesium oxide is 400,000 μg/m^3 (238,000 μg magnesium/m^3). The mechanism for the development of fever following exposure to magnesium oxide is not known, but it has been compared to metal fume fever from zinc oxide exposure, which is attributed to an immune response (see zinc section below).

Among workers exposed to magnesium oxide dust, symptoms were limited to conjunctivitis and nasal catarrh (Pleschitzer, 1936). Blood magnesium levels were elevated up to twice normal levels, but exposure levels were not available. Serum calcium was also elevated in 70% of those examined. Details on parameters assessed and exposure conditions were not reported in the secondary references available.

There are a few epidemiological studies of chronic exposure to magnesium carbonate dusts; because all were in Russian, this description is based on a secondary reference (American Conference of Governmental Industrial Hygienists, 1991). Pneumoconiosis was reported in these studies, but appears to be due to coexposure to other materials, such as silica or asbestos. Thus, the severity of pneumoconiosis has been reported to be related to the crystalline silica (Tokmurzina and Dzangosina, 1970) or asbestos content (Keane and Zavon, 1966) of the dust. Pneumoconiosis was reported in 2.1% of a cohort of 619 workers exposed for 6 to 20 years to "high concentrations" of crude magnesite (magnesium carbonate) or roasted magnesite (magnesium oxide). The magnesite also contained 1 to 3% silicon dioxide (Zeleneva, 1970). Most of the cases were among the workers exposed to roasted (calcined) magnesite; actual exposure levels were not reported. A "benign pneumoconiosis," often associated with bronchitis and emphysema, was suggested by the

TABLE 11-38. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR MAGNESIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Mg/m^3$						
Acute Studies							
NA	246,000 252,00 258,000 348,000	1-9 min	MgO fume	UK	Human UK	CS, white blood cell count: Slight rise in temperature at 10 min; fever and elevated white blood cell counts at 5-6 hr postexposure. Complete recovery by the next morning.	Drinker et al. (1927)
Chronic Studies							
NA	"high concen-trations"	6-20 yr occup	$MgCO_3$, MgO dust	UK	Human (619) UK	Medical exam, x-ray: Pneumoconiosis, often associated with bronchitis and emphysema in 2.1% of cohort. Note: Most cases were among those exposed to magnesium oxide. The magnesium carbonate contained 1-3% silicon dioxide.	Zeleneva (1970)

Abbreviations:

CS = clinical signs; hr = hour; Mg = magnesium; MgO = magnesium oxide; $MgCO_3$ = magnesium carbonate; min = minutes; NA = not applicable; occup = occupational; yr = years.

clinical phenomena and latent periods. Toxic effects outside the respiratory system have not been reported following human exposure to magnesium carbonate dusts (American Conference of Governmental Industrial Hygienists, 1991).

Heldaas et al. (1989) investigated cancer mortality in a group of magnesium metal workers exposed to various magnesium compounds (magnesium oxide, magnesium metal dust, and magnesium chloride). Elevated cancer incidences were observed for cancer of the lip (6 observed versus 2.3 expected), stomach (21 observed versus 12.8 expected), and lung (32 observed versus 18.2 expected). The rate of lung cancer and all cancers increased with increased duration of employment and for lung cancer was statistically significant for all employment periods. However, the relevance of this study to magnesium carcinogenicity is unclear, since there were confounding exposures to coal tar, asbestos, and hexachlorobenzene and other chlorinated aromatics. Magnesium has been proposed to antagonize the tumorigenic potential of nickel and lead, based on the results of intraperitoneal injection of magnesium along with either of the other two compounds (Poirier et al., 1984).

Laboratory Animal Data

The limited toxicity data for laboratory animals are summarized in Table 11-39. A reaction similar to metal fume fever was observed in cats that inhaled freshly formed magnesium oxide fume for 15 min to 3 h (Drinker and Drinker, 1928). Carbon dioxide was included at 10% to stimulate deep respiration. Exposure levels were not reported, but the estimated amount of inhaled magnesium ranged from 21,000 μg to 156,000 μg (apparently for a single exposure level of varying durations). After 3 h of exposure, symptoms included dyspnea and lethargy, and the animals were cold to the touch. The animals rapidly returned to normal after exposure; necropsy of one cat showed normal lungs. This is an old study, conducted prior to development of standard toxicological methods and few experimental details are available; still, the reaction described is similar to that with zinc, but milder. It is unclear why hypothermia was found in cats and fever in humans.

Intratracheal installation of finely divided metallic magnesium particles in a salt solution in guinea pigs resulted in a slight pneumonic reaction that was attributed to the fluid rather than the administered magnesium (Gardner and Delahant, 1943). Microscopic vacuoles in

TABLE 11-39. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR MAGNESIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Mg/m^3						
NA	NS	15 min-3 hr	MgO fume	UK	Cat, NS (UK)	CS, necropsy (lungs): Uniform, but slight hypothermia. After 3 h exposure, dyspnea and lethargy; animals were cold to the touch. The animals rapidly returned to normal. Necropsy of one cat showed normal lungs. Note: Exposure was apparently to one concentration for varying durations. Total amount magnesium inhaled estimated at 21,000-156,000 μg. Note: Symptoms were described as milder than those in animals exposed to zinc oxide fume.	Drinker and Drinker (1928)

Abbreviations:

CS = clinical signs; hr = hour; MgO = magnesium oxide; min = minutes; NA = not applicable; NS = not specified in the literature reviewed;

the cytoplasm of mononuclear cells lining the alveolar walls were also observed, and were attributed to the liberation of hydrogen. Healing and resolution occurred within 6 weeks, with no residual fibrosis.

Studies on the effects in laboratory animals of magnesite dust are limited to reports in Russian (Katsnel'son et al., 1964; Zeleneva, 1970), and experimental details are lacking. Slight fibrosis was observed in animals exposed via inhalation to magnesium oxide or magnesium carbonate dusts, although magnesium oxide dust was more fibrogenic. The report implied that the experimental procedure involved prolonged exposure at high levels (American Conference of Governmental Industrial Hygienists, 1991).

Chronic data on the effects in laboratory animals of magnesium oxide were limited to a single carcinogenicity study of intratracheal instillation. Elevated levels of hystiocytic lymphomas compared with historical control levels were observed in hamsters that were administered 1,200 μg magnesium per week as magnesium oxide dust for 30 weeks (Stenback et al., 1973).

11.6.13.4 Factors Affecting Susceptibility

Based on the limited data in humans and laboratory animals suggesting that the respiratory tract is a target of magnesium inhalation, individuals with a compromised respiratory tract may be at increased risk from magnesium inhalation toxicity. The developing respiratory tract of children may also pose an increased susceptibility.

Other information on factors affecting susceptibility is based on general information on magnesium toxicity, and relates only to absorbed magnesium. The relevance of these data to magnesium inhalation would depend on the absorption of the magnesium compound of interest. People with reduced renal function, have reduced magnesium excretion and may develop hypermagnesemia. This population may include those with renal failure, as well as the elderly, since the elderly may have an age-related decrease in renal clearance (Beliles 1994; Ratzan et al. 1980).

11.6.14 Molybdenum

11.6.14.1 Chemical and Physical Properties

Molybdenum, a silvery-gray metal or grey-black powder, belongs to Group VIB of the periodic system of elements (Barr, 1981; Friberg and Lener, 1986). Molybdenum forms compounds in the valence states of 0, +2, +4, +5, or +6, of which +6 is the most stable valence state (Barr, 1981; Barry, 1981). Molybdenum does not occur naturally in the native state (Friberg and Lener, 1986). Over fifty inorganic molybdenum compounds are known and organomolybdenum compounds also exist (Friberg and Lener, 1986). Molybdenum compounds may disproportionate to mixtures in which molybdenum occurs in different oxidation states (Barry, 1981). Molybdenum is resistant to oxidation at temperatures up to about 1650 °C (Barr, 1981). Budavari (1989) reports that molybdenum is slowly oxidized to the trioxide in the presence of steam but is not attacked by water. Elemental molybdenum and its dioxide (MoO_2) are insoluble in water, whereas the trioxide (MoO_3) is slightly soluble in water at 18 °C and moderately soluble at 70 °C. Other compounds also vary in their solubility. Ammonium molybdate $(NH_4)_2\ MoO_4$, decomposes in water, but ammonium paramolybdate, $(NH_4)_6\ MO_7O_{24}$, is fairly water soluble as is sodium molybdate, Na_2MO_4. Both molybdenum disulfide (or molybdenite, MoS_2) and calcium molybdate ($CaMoO_4$), on the other hand, are insoluble.

11.6.14.2 Pharmacokinetics

Molybdenum is an essential micronutrient and acts as a cofactor for three enzymes: xanthine oxidase (which affects uric acid formation), aldehyde oxidase, and sulfite oxidase (Friberg and Lener, 1986).

Indirect evidence for absorption of molybdenum following inhalation exposure comes from studies showing increased molybdenum concentrations in plasma (0.9 to 36.5 μg/100 mL versus 0 to 3.4 μg/100 mL for controls) and urine (120 to 11,000 μg Mo/L versus 20 to 230 μg Mo/L for controls) of workers at a molybdenum roasting plant exposed to concentrations of soluble molybdenum dusts (mainly MoO_3 and other molybdenum oxides) ranging from 100 to 4500 μg Mo/m^3 (8-h time-weighed average = 9500 μg Mo/m^3) (Walravens et al., 1979). Following inhalation exposure of Guinea pigs to molybdenum compounds, tissue levels indicated that absorption was limited for all tested compounds

(Fairhall et al., 1945). The major portion of molybdenum was found in the lungs following exposure to molybdenum sulfide (286,000 μg Mo/m^3) and calcium molybdate (159,000 μg Mo/m^3) with minute amounts in the liver, kidney, spleen, and bones. Exposure to molybdenum trioxide dust (205,000 μg Mo/m^3) resulted in similar low levels in the lungs and other organs. Levels in all tissues were negligible following exposure to molybdenum trioxide fume (191,000 or 53,000 μg Mo/m^3). No studies were found on metabolism or excretion of molybdenum or molybdenum compounds in humans or animals following inhalation exposure. Orally administered hexavalent molybdenum is readily absorbed (Van Campen and Mitchell, 1965) and is distributed to the kidneys, liver, and bone (Huber et al., 1971; Robinson et al., 1964). Excretion is mostly in the urine (Neilands et al., 1948) although biliary excretion in the feces has also been reported (Lener and Bibr, 1979).

11.6.14.3 Health Effects

There are few studies on health effects in humans or laboratory animals of inhalation exposure to molybdenum compounds, and those that do exist were generally not conducted according to modern toxicology standards. The major toxic endpoint for such inhalation exposure in humans and laboratory animals is the respiratory system.

Human Data

Inhalation toxicity data for humans are summarized in Table 11-40. No studies were located on the acute inhalation toxicity of molybdenum compounds in humans. Walravens et al. (1979) conducted an occupational survey of 25 workers in a molybdenum-roasting plant in Colorado, where exposure was to molybdenum oxides. The 8-h time weighted average exposure was approximately 9,500 μg Mo/m^3, and the average length of worker exposure was 4.0 years (range 0.5 to 20 years). Clinical findings included elevated serum ceruloplasmin (average 50.47 mg/100 mL versus 30.50 mg/100 mL for controls) and smaller increments in serum uric acid concentrations. Although hyperuricosuria (indicative of gout-like symptoms) was not seen, high employee turnover could have removed workers sensitive to the gout-causing action of molybdenum. Nonspecific worker complaints included joint pains, headaches, backaches and hair and skin changes.

TABLE 11-40. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR MOLYBDENUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Mo/m^3						
NA	9,500 (8 h TWA)	4.0 yr avg (range 0.5-20 yr) occup	Soluble Mo oxides dust (mainly MoO_3)	"respirable dust less than 10 μm diameter"	Human (25) M	BC, subjective symptoms on medical questionnaire: Inc serum ceruloplasmin and serum uric acid, inc Mo in plasma and urine. No Mo-induced gout reported. Note: Soluble Mo in total dust was TWA exposure of 9,500 μg/m^3; Mo in respirable dust was 1,000-4,500 μg/m^3. Note: High employee turnover.	Walravens et al. (1979)
NA	670-12,700	4-7 yr occup	Mo trioxide dust	UK	Human (19) B	Case study, subjective symptoms, chest x-ray: Pneumoconiosis in 3 workers. 1 female, difficulty breathing, general weakness, dizziness; one male, dry cough; second male, difficulty breathing, pain in chest, expectoration.	Mogilevskaya (1963)
NS	≤600,000	NS occup	Molybdenum, form UK	UK	Human (500) UK	Medical exam: nonspecific symptoms and CNS changes. Note: Concomitant exposure to copper dust, possibly to radon in mine.	Eolayan (1965)

Abbreviations:

avg = average; BC = blood chemistry; BW = body weight; cardio = cardiovascular; CS = clinical signs; d = day; dec = decreased; est = estimated; F = female; h = hour; HP = histopathology; inc = increased; M = male; Mo - molybdenum N/A = not applicable; NS = not specified in the literature reviewed; occup = occupational; UK = unknown, original reference in retrieval; wk = week; wt = weight; yr = years.

In a Russian study of, 19 workers exposed to molybdenum compounds, three subjects showed signs of pneumoconiosis upon x-ray examination. Exposure in all cases was primarily to molybdenum trioxide dust. A female exposed to 670 to 2,000 μg Mo/m^3 (with occasional excursions to $\geq$16,700 μg Mo/m^3) for 5 years had difficulty breathing, general weakness, and dizziness; a male exposed to 4,000 to 12,700 μg Mo/m^3 as molybdenum trioxide aerosol for 4 years experienced a dry cough. Another male worker who was exposed to the same levels of molybdenum (not stated whether dust or aerosol) for 7 years had difficulty breathing, pain in the chest, and morning expectoration; this worker had also suffered from a pulmonary hemorrhage at an earlier unspecified time (Mogilevskaya, 1963).

A Russian occupational survey of 500 workers from a molybdenum and copper mine where molybdenum concentrations could have been as high as 60,000 to 600,000 μg Mo/m^3 reported nonspecific symptoms and some central nervous system changes (Eolayan, 1965); however, the exact form of molybdenum and specific symptoms are not available.
In workers at a copper-molybdenum factory (exposure to both molybdenum and copper), toxic effects were reported in the liver, based on serum biochemistry (Avakyan et al., 1978). The observed effects were attributed to a disruption of the balance between copper and molybdenum. Further study details will require translation of the article.

Although the exact mechanism of molybdenum is not known, it is believed that molybdenum forms a complex with copper that reduces the bioavailability of copper. Tetrathiomolybdate reduces the activity of ceruloplasmin, a copper-containing enzyme (Winston, 1981). The gout-like symptoms reported in some Armenian residents may be the result of increased xanthine oxidase activity in response to increased molybdenum levels. The xanthine oxidase may then cause increased uric acid levels which are the primary cause of gout (Yarovaya, 1964).

Oral exposure to high levels of molybdenum has been reported to cause gout-like symptoms. This has been seen in residents of Armenia where the soil is rich in molybdenum (77,000 μg Mo/kg) and copper (39,000 μg Cu/kg). Intake levels via food have been estimated to be 10,000 μg molybdenum (compared with 1,000 to 2,000 μg in control areas) (Koval'skiy et al., 1961; Koval'skiy and Yarovaya, 1966; Yarovaya, 1964). Some exposure via inhalation of soil cannot be ruled out, although the symptoms reported did not include any pulmonary effects.

No studies were located regarding reproductive or developmental effects in humans of inhalation exposure to molybdenum compounds.

Laboratory Animal Data

The toxicity data for laboratory animals are summarized in Table 11-41. In a series of 4-h rat inhalation studies, rats were exposed to technical grade molybdenum trioxide (2,610,000 μg Mo/m^3), pure molybdenum trioxide (3,890,000 μg Mo/m^3), ammonium dimolybdate (1,160,000 μg Mo/m^3), or sodium molybdate (899,000 μg Mo/m^3) (Barltrop, 1991). The dust level for pure molybdenum trioxide was so high that the animals were not visible. Clinical signs for all but ammonium dimolybdate were limited to partial or complete closing of the eyes, which was attributed to the high dust level. Other clinical signs of discomfort observed with ammonium dimolybdate (wetness around the mouth, restlessness, and hunched posture) molybdic may also have been a result of the high dust levels. Systemic effects were limited to decreased body weight losses for the first 3 days postexposure. Respiratory effects were limited to one male exposed to sodium molybdate that had an increased lung to body weight ratio and congested lungs. This study indicates that acute exposure to very dust levels of these molybdenum compounds is minimally toxic.

Effects on cellular respiration of the respiratory tract mucosa were reported in rats in a Russian abstract (Georgiadi, 1978). Further details were not available in English.

A study of rats receiving a single intratracheal dose (0.5 mL) of a 2% solution of LPA (55% cobalt, 35% molybdenum, and 10% silicon) showed weight loss for 3 to 4 days post-exposure after which weight gain was normal. Transient histopathological signs included peribronchial or peribronchiolar pneumonia with edema. Alveolar lesions, including epithelialization, bronchiolar proliferation and atelectasis and minimal fibrosis were reversible with time (Du Pont, 1971). Diffuse pneumoconiosis with interstitial pneumonia was seen in rabbits 9 mo after receiving powdered molybdenum as intratracheal doses of 70,000 to 80,000 μg/kg (Mogilevskaya, 1963, Dzukaev, 1970).

A Russian study of the comparative toxicity of four molybdenum dusts to rats after 1 h of exposure found no effects (unspecified) during a 4-week observation period for metallic molybdenum (25,000,000 to 30,000,000 μg Mo/m^3), molybdenum dioxide (7,500,000 to 9,000,000 μg Mo/m^3), or molybdenum trioxide (8,040,000 to 10,050,000 μg Mo/m^3).

TABLE 11-41. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR MOLYBDENUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Mo/m^3						
Acute Studies							
NS	0 2,610,000	4 h	Mo trioxide (technical) dust	36% by wt <3.5μm MMAD=4.2 μm σ_g=2.19	Rat, SD (5) M, (5) F	CS, BW, food/water consumption, gross necropsy, HP of lungs: No deaths, transient clinical signs (closing of eyes), post-mortem unremarkable, normal lung:BW ratio. Both sexes lost wt until day 2-3, then gained wt at a normal rate. Food consumption was dec days 2-3. Eye closing due to high dust levels.	Barltrop (1991)
NS	0 3,890,000	4 h	Mo trioxide (pure) dust	72% by wt <3.5μm MMAD=2.9 μm σ_g=1.83	Rat, SD (5) M, (5) F	CS, BW, food and water consumption, gross necropsy, HP of lungs: No deaths, post-mortem unremarkable, normal lung:BW ratio. Both sexes lost wt until day 3, then gained wt at a normal rate. Food intake dec days 1-3. Dust levels so high animals not visible during exposure	Barltrop (1991)
NS	0 1,160,000	4 h	Ammonium dimolydbate dust "56.4% Mo"	23% by wt <3.5μm MMAD=6.3 μm σ_g=2.75	Rat, SD (5) M, (5) F	CS, BW, food/water consumption, gross necropsy, HP of lungs: No deaths, transient clinical signs (partial eye closing, wet around mouth, restless behavior, hunched posture), post-mortem unremarkable, normal lung:BW ratio. Both sexes lost wt until day 2-3, then gained wt at a normal rate. Food intake dec days 1-2. CS attributed to high dust levels.	Barltrop (1991)

TABLE 11-41 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR MOLYBDENUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Mo/m^3						
NS	0 899,000	4 h	Sodium molydbate dust	26% by wt <3.5μm MMAD=6.9 μm σ_g=2.71	Rat, SD (5) M, (5) F	CS, BW, food/water consumption, gross necropsy, HP of lungs: No deaths, transient clinical signs (partial closing of eyes). Both sexes lost wt until day 3, then gained at normal rate. Food intake dec days 2-3. One exposed male had inc lung:bw ratio and congested lungs, but no HP. No effects on other animals. Closing of eyes due to high dust levels.	Barltrop (1991)
NS	70,000-80,000	single dose (intra-tracheal)	Powdered Mo	UK	Rabbits, UK (NS)	HP: Diffuse pneumoconiosis with interstitial pneumonia after 9 mo observation.	Mogilevskaya (1963)
NS	25 to 30	1 h	Mo metal dust	UK	Rat, UK (UK)	CS: No effect.	Mogilevskaya (1963)
NS	7.5 to 9.0	1 h	Mo dioxide dust	UK	Rat, UK (UK)	CS: No effect.	Mogilevskaya (1963)
NS	8.0 to 10.0	1 h	Mo trioxide dust	UK	Rat, UK (UK)	CS: No effect.	Mogilevskaya (1963)
NS	2.4 to 4.0	1 h	Ammonium paramolyb-date dust	UK	Rat, UK (UK)	CS: Irritation of upper respiratory passages and conjunctivae.	Mogilevskaya (1963)
Chronic Studies							
NS	12 to 15	1 h/d 30 d	Mo metal dust	UK	Rat, UK (UK)	CS, HP: Slight growth depression, dust deposits in lungs, thickening of intraalveolar septa.	Mogilevskaya (1963)
NS	6 to 7.5	1 h/d 30 d	Mo dioxide dust	UK	Rat, UK (UK)	CS, HP: Slight growth depression, dust deposits in lungs, thickening of intraalveolar septa.	Mogilevskaya (1963)

TABLE 11-41 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR MOLYBDENUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Mo/m^3						
NS	5.4 to 6.7	1 h/d 30 d	Mo trioxide dust	UK	Rat, UK (UK)	CS, HP: Dec weight gain (by 28%), macroscopic hemorrhage, perivascular edema, alveolar hemorrhage.	Mogilevskaya (1963)
NS	40,000-200,000	1 h/d 30 d	Ammonium paramolyb-date dust	UK	Rat, UK (UK)	CS, HP: All animals died, severe dust deposits in lungs, thickening of intraalveolar septa.	Mogilevskaya (1963)
NS	286,000 (avg)	1h/d 5 d/wk 5 wk	Mo disulfide dust	NS	Guinea pig, NS (25) M	CS: One death, all other animals appeared "normal," except for inc respiratory rate.	Fairhall et al. (1945)
NS	205,000	1h/d 5 d/wk 5 wk	Mo trioxide dust	"Average 1.63 μm"	Guinea pig, NS (51) M	CS, HP: Weight loss, loss of appetite, diarrhea, muscular incoordination, loss of hair and 50% mortality; alveolar and bronchial exudate; some swelling and vacuolization of hepatic cells.	Fairhall et al. (1945)
NS	53,000 191,000	1h/d 5 d/wk 5 wk	Mo trioxide fume	"Average 1.55 μm"	Guinea pig, NS (12) M	CS: One death at 191,000 μg Mo/m^3, no other toxic effects at either concentration.	Fairhall et al. (1945)
NS	159,000	1h/d 5 d/wk 5 wk	Calcium molybdate dust	NS	Guinea pig, NS (24) M	CS: 20% mortality, no other toxic effects.	Fairhall et al. (1945)

Abbreviations:

avg = average; BC = blood chemistry; BW = body weight; cardio = cardiovascular; CS = clinical signs; d = day; dec = decreased; est = estimated; F = female; h = hour; HP = histopathology; inc = increased; M = male; Mo - molybdenum N/A = not applicable; NS = not specified in the literature reviewed; occup = occupational; SD = Sprague-Dawley; UK = unknown, original reference in retrieval; wk = week; wt = weight; yr = years.

Exposure to 240,000 to 400,000 μg Mo/m^3 ammonium paramolybdate resulted in irritation of the upper respiratory passages and conjunctivae (Mogilevskaya, 1963).

A study with Guinea pigs exposed to various molybdenum compounds for 1 h/day, 5 days/week for 5 weeks was conducted by Fairhall et al. (1945). Molybdenum disulfide dust (286,000 μg Mo/m^3 average concentration) caused death in 1/25 animals within 3 days, despite normal appearance of other animals in the group. Exposure of 51 guinea pigs to 205,000 μg Mo/m^3 as molybdenum trioxide dust resulted in the most severe symptoms, with a loss of weight, loss of appetite, diarrhea, muscular incoordination, loss of hair and a 50% mortality rate, with histopathologic signs in the lung showing alveolar and bronchial exudate. Molybdenum trioxide fumes (either, 191,000 or 53,000 μg Mo/m^3) caused significantly fewer effects than the dust, with only 1/12 animals at the higher exposure dying and no other toxic effects seen in the other animals at either concentration. Guinea pigs exposed to 159,000 μg Mo/m^3 as calcium molybdate had a 20% mortality rate among the 24 exposed animals but no other adverse effects.

In a subchronic study by Mogilevskaya (1963), rats were exposed to metallic molybdenum (12,000,000 to 15,000,000 μg Mo/m^3), molybdenum dioxide (6,000,000 to 7,500,000 μg Mo/m^3), molybdenum trioxide (5,360,000 to 6,700,000 μg Mo/m^3), or ammonium paramolybdate (40,000 to 200,000 μg Mo/m^3)] for 1 h/day for 30 days. These levels were slightly lower than those used in the acute study in the same paper. Metallic molybdenum and molybdenum dioxide produce no adverse effects, except for a slight growth depression; examination of the lungs revealed dust deposition and thickening of the intraalveolar septa. Molybdenum trioxide exposure resulted in decreased weight gain (28% of control) with histopathologic examination of the lung revealing macroscopic hemorrhage, marked perivascular edema and hemorrhage into the alveolar space. Ammonium paramolybdate had high toxicity (all animals died) with severe dust deposits in the lungs and thickening of the intraalveolar septa, which contained connective tissue fibers.

No studies were located regarding reproductive or developmental effects in animals of inhalation exposure to molybdenum compounds.

11.6.14.4 Factors Affecting Susceptibility

No data were located that addressed populations especially sensitive to the effects of inhaled molybdenum compounds. However, since the respiratory tract is the major target of molybdenum inhalation, individuals with impaired respiratory function would be expected to be at increased risk. The developing respiratory tract of children may also pose an increased susceptibility.

Other susceptible populations can be hypothesized based on the mechanism of toxicity of absorbed molybdenum. Since molybdenum decreases the bioavailability of copper (Winston, 1981), people with impaired copper metabolism, such as those with Wilson's disease, would be expected to be at increased risk. Similarly, since high levels of molybdenum can cause gout-like symptoms, individuals with pre-existing gout may have an increased susceptibility. However, it is unclear if absorption of molybdenum from inhalational exposure to environmental levels would be high enough to affect these two groups.

11.6.15 Nickel

11.6.15.1 Physical/Chemical Properties

Nickel is a metallic element belonging to transition Group 8B of the periodic table. It forms compounds in which the nickel atom has oxidation states of -1, 0, $+1$, $+2$, $+3$, and $+4$. Under environmental conditions, the $+2$ state is the only one of importance; other oxidation states occur in special complexes and oxides (Agency for Toxic Substances and Disease Registry, 1992). Nickel is stable in air at ordinary temperatures, but can burn in oxygen, forming nickel(+2) oxide (Windholz, 1983). Nickel exists in aqueous solutions as the hexahydrate ion $[Ni(H_2O)_6]^{2+}$. In alkaline solutions, nickel(+2) hydroxide can be oxidized to nickel(+4) oxide (Agency for Toxic Substances and Disease Registry, 1992). Nickel exists in the environment as both organic and inorganic compounds (Antonsen, 1981). Elemental nickel, nickel oxide (NiO), and nickel subsulfide (Ni_3S_2) are all insoluble in water, whereas nickel chloride ($NiCl_2$) and nickel sulfate ($NiSO_4$) are both relatively water soluble.

11.6.15.2 Pharmacokinetics

Absorption and Distribution

Respiratory tract deposition and uptake of nickel is dependent on particle size and solubility (Grandjean, 1974). In humans, 30 to 35% of inhaled nickel is retained in the the respiratory tract, of which only a portion ($\approx$ 20% of inhaled) will be absorbed into the bloodstream (Bennett, 1984; Grandjean, 1984; Sunderman and Oskarson, 1991). The remainder is either swallowed or expectorated. Absorption is evident from nickel in the urine of exposed workers (Bernacki et al., 1978; Torjussen and Andersen, 1979). Higher concentrations of urinary nickel were found in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) compared to insoluble nickel compounds (nickel oxide, nickel subsulfide), indicating that the soluble compounds were more readily absorbed from the respiratory tract (Bernacki et al., 1978; Torjussen and Andersen, 1979). The nickel content of the nasal mucosa in workers exposed to insoluble nickel compounds was higher than the content in workers exposed to soluble nickel compounds, again suggesting greater absorption of the soluble compounds (Torjussen and Andersen, 1979).

Data in rats and mice indicate that insoluble nickel compounds are retained in the lungs in greater amounts and for a longer period of time than soluble nickel compounds (Benson et al., 1987, 1988; Dunnick et al., 1989; English et al., 1981; Tanaka et al., 1985). The lung burden of nickel in these rodents increase with increasing particle size (Tanaka et al., 1985, 1988). Nickel retention was about 6 times (mice) to 10 times (rats) greater in animals expose to insoluble nickel subsulfide compared to soluble nickel sulfate (Benson et al., 1987, 1988). Elimination half-times from the lung of rats were calculated to be 7.7, 11.5, and 21 mo for nickel oxide with mass median aerodynamic diameters (MMADs) of 0.6, 1.2, and 4.0 μm, respectively (Tanaka et al., 1985, 1988). In addition, the lung burdens of nickel generally increased with longer exposure duration and higher levels of the various nickel compounds (Dunnick et al., 1988, 1989).

Slow clearance of nickel oxide from the lungs was observed in hamsters (Wehner and Craig, 1972). The retention was not dependent on the duration of exposure or exposure concentration. Approximately 20% of the inhaled concentration of nickel oxide (30 to 130 mg Ni/m^3) was retained in the lungs 3 days after a 3-week exposure. By 45 days after the last exposure to nickel oxide, 45% of the initial lung burden was still present in the lungs

(Wehner and Craig, 1972). First-order clearance kinetics were reported for nickel in mice lungs after a 2-h exposure (Graham et al., 1978). After 4 days of exposure, 72% of the deposited fraction was cleared from the lungs.

The clearance of nickel compounds from lungs was also studied following intratracheal administration (Carvalho and Ziemer, 1982; Valentine and Fisher, 1984). Nickel subsulfide was cleared from lungs in two phases, an initial half-time of 1.2 days (38% of dose cleared) followed by a half-time of 12.4 days (42% of dose). After 35 days, 10% remained in the lungs (Valentine and Fisher, 1984). Soluble nickel chloride is cleared from lungs more rapidly than nickel subsulfide, with 71% of the initial nickel chloride dose cleared by 24 h and 0.1% remaining after 21 days (Carvalho and Ziemer, 1982).

Once absorbed, nickel is transported in the bloodstream. Soluble nickel ion (Ni[II]) forms complexes with water or with water and other ligands. These complexes can be rapidly translocated into different tissues. In plasma, about 75% of nickel is bound to high molecular weight proteins (e.g., α_2-macroglobulin, gamma-globulin, transferrin, albumin) (Coogan et al., 1989). Elevated serum nickel levels have been found in occupationally exposed individuals compared to nonexposed controls (Angerer and Lehnert, 1990; Elias et al., 1989; Torjussen and Andersen, 1979). Levels were higher in workers exposed to soluble nickel compounds compared to workers exposed to insoluble nickel compounds (Torjussen and Andersen, 1979).

Nickel has been detected primarily in the lungs of exposed individuals, with much lower levels of nickel in the liver and kidneys (Resuke et al., 1987; Sumino et al., 1975). Nickel has also been found in the nasal mucosa of exposed workers, with higher levels found in workers exposed to insoluble nickel compounds (Torjussen and Andersen, 1979).

In rats exposed to nickel oxide, the lung burden of nickel increased with longer exposures and increasing particle size (Kodama et al., 1985; Tanaka et al., 1985). Nickel was found in the liver, kidney, and spleen following exposure to nickel oxide, nickel subsulfide, and nickel sulfate; however, these levels were very low compared to lung content (Benson et al., 1987, 1988; Tanaka et al., 1985).

Metabolism

The metabolism of nickel consists of ligand exchange reactions (Coogan et al., 1989). In humans and laboratory animals, nickel binds to albumin, L-histidine, and α-2-macroglobulin in the serum. The principal binding locus of nickel to serum albumins in humans, rats, and bovines is the histidine residue at the third position from the amino terminus. Dogs do not seem to have this binding locus, and most of the nickel (>85%) in the serum was not bound to protein (Agency for Toxic Substances and Disease Registry, 1992). A proposed transport model involves the ability of L-histidine to remove nickel from albumin via a ternary complex composed of albumin, nickel, and L-histidine. The low-molecular weight L-histidine nickel complex can then cross biological membranes (Coogan et al., 1989). Once inside the cell, nickel interacts with deoxyribonucleic acid (DNA), resulting in crosslinks and strand breaks.

Excretion

Absorbed nickel is excreted in the urine, regardless of the route of exposure (Angerer and Lehnert, 1990; Bernacki et al., 1978; Elias et al., 1989; Hassler et al., 1983; Torjussen and Andersen, 1979). A half-life of 17 to 53 h has been reported in exposed welders (Onkelinx and Sunderman, 1980). A two-compartment model has been developed for the whole-body kinetics of nickel(II) (Onkelinx and Sunderman, 1980); the model consists of a rapid clearance phase, followed by a slow clearance phase. In nickel-exposed workers, an increase in urinary nickel excretion was found from the beginning to the end of the shift, indicating a fraction that was rapidly eliminated. An increase in urinary excretion was also found as the week progressed, indicating a fraction that was excreted more slowly (Ghezzi et al., 1989). Higher nickel levels were found in the urine of workers exposed to soluble nickel compounds, indicating that the soluble compounds are more readily absorbed than insoluble compounds (Bernacki et al., 1978; Torjussen and Andersen, 1979). Nickel has also been excreted in the feces of nickel workers, but this was most likely due to mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract (Hassler et al., 1983).

In laboratory animals, the route of excretion following intratracheal administration of nickel depends on the solubility of the nickel compound. In rats given soluble nickel chloride

or nickel sulfate, ≈70% of the given dose was excreted in the urine within 3 days (Carvalho and Zeimer, 1982; Clary, 1975; English et al., 1981; Medinsky et al., 1987). By day 21, 96.5% of the given dose of nickel chloride had been excreted in the urine (Carvalho and Zeimer, 1982). Following intratracheal administration of less soluble compounds (nickel oxide, nickel subsulfide), a greater fraction of the dose is excreted in the feces as a result of mucociliary clearance. Following administration of nickel oxide to rats or nickel subsulfide to mice, approximately equal amounts of the initial dose were excreted in the urine and the feces (English et al., 1981; Valentine and Fischer, 1984). A total of 90% of the initial dose of nickel subsulfide was excreted within 35 days, and 60% of the initial dose of nickel oxide was excreted within 90 days. This is consistent with nickel oxide being less soluble and not as rapidly absorbed as nickel subsulfide (English et al., 1981; Valentine and Fischer, 1984).

11.6.15.3 Health Effects

Both soluble and insoluble nickel compounds, as well as elemental nickel, can produce toxicity in humans following inhalation exposure. Generally, soluble nickel compounds (nickel chloride, nickel sulfate, and nickel nitrate) are considered more toxic than the insoluble nickel compounds (nickel oxide and nickel subsulfide). The respiratory system is the primary target of nickel toxicity following inhalation exposure. The potential for respiratory carcinogenicity is evident in both human and laboratory animal studies.

Human Data

Most human data on respiratory effects of nickel are based on occupational or chronic duration studies. Human toxicity data are summarized in Table 11-42. Asthma induced by occupational exposure to nickel has been documented (Dolovich et al., 1984; McConnell et al., 1973; Novey et al., 1983). The asthma can result from either primary irritation or from an allergic response. Reduced vital capacity and expiratory flows were observed in stainless steel welders (Kilbam et al., 1990); alveolar volume and total thoracic gas volume were unaffected. Because the welders were also exposed to high levels of chromium, the role of nickel in the etiology of the impaired lung function is not known. In addition, no quantitative exposure information is available from these studies.

TABLE 11-42. EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	(Sample or group size) Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 80-310	(occup) 1-16 years	Ni aerosol	NR	Human (821) M, (758) F	Clinical examination including pulmonary x-ray, ECG, lung function tests, and blood count, hospital records of birth data and congenital defects: Increased abortions (relative risk 1.8) and increased incidence of malformations (16.9% versus 5.8% in controls) occurred.	Chashschin et al. (1994)
NA	NR	(occup) ≥5 years	Ni dust	NR	Human (845) M	Deaths recorded for men who died before 1967, and causes of deaths identified: Of 482 men that died, 113 had lung cancer and 39 nasal cancer. More observed deaths compared to expected deaths for both types of cancers, particularly nasal sinus cancer, in those workers who were first employed before 1925 but not in workers first employed in 1925-1944. The higher incidences may be attributed to various reasons: high exposures to dust, more smokers, and older workers employed prior to 1925. Also, between 1920-1925, personal protection for workers against dust was introduced into the plant, which may have attributed to the decreased number of cancers.	Doll et al. (1970)

Abbreviations:

ECG = electrocardiogram; F = females; LM = light microscopy; M = males; mo = months; NA = not applicable; NR = not reported; occup = occupational; SMR = standard mortality ratio; wt = weight.

The carcinogenic effect of nickel has been well documented in occupationally exposed workers (Chovil et al., 1981; Doll et al., 1977; Magnus et al., 1982). Lung and nasal cancer (primarily squamous cell carcinomas) were the predominant cancers in the exposed workers. Respiratory cancers were related primarily to exposure to soluble nickel compounds at concentrations $>1{,}000$ μg Ni/m^3 and to exposure to less soluble compounds at concentrations $\geq 10{,}000$ μg Ni/m^3 (primarily oxidic and sulfidic compounds) (Doll, 1990). A higher incidence of respiratory tract cancer was observed among workers exposed to both soluble and less soluble nickel compounds compared to those exposed to less soluble nickel compounds alone, suggesting compound interaction. There was no evidence suggesting that metallic nickel causes respiratory tract cancer (Doll, 1990).

In a cohort of 2,247 refinery workers, an excess of lung cancer was found by 3 to 14 years after first employment, while an increase in nasal cancer was not observed until 15 to 24 years after first employment (Magnus et al., 1982). The risk of respiratory tract cancers markedly decreased when the date of first exposure was later than ≈ 1930 (Doll et al., 1970, 1977; Pedersen et al., 1973). This was a result of reducing nickel dust exposure by altering the machinery used in the refining process and by the use of cotton face pads by the workers (Doll et al., 1977). The interaction between smoking and nickel exposure for the development of respiratory tract cancer was found to be additive rather than multiplicative (Magnus et al., 1982). Nevertheless, the workers in these studies were exposed to a variety of other metals, including uranium, iron, lead, and chromium, so it cannot be concluded that nickel was the sole causative agent.

Immunological, renal, and dermal effects have also been observed in refinery workers exposed to nickel. Significant increases in levels of immunoglobulin G (IgG), IgA, and IgM, respectively, and a significant decrease in IgE levels were observed in workers exposed to nickel (compound not specified) (Bencko et al., 1983, 1986). A significant increase in other serum proteins that may be involved in cell mediated immunity (including α-antitrypsin, α-2-macroglobulin, ceruloplasmin) also were observed. The increase in immunoglobulins and serum proteins indicated that the immune system was stimulated by nickel exposure. Increased urinary β-2-microglobulin levels in the kidneys has been observed in exposed individuals (Sunderman and Horak, 1981). Contact dermatitis is one of the most prevalent effects of nickel exposure. Immunological studies indicated that the dermatitis is an allergic

response to nickel. The contact dermatitis may be the result of dermal contact with airborne nickel or a response to inhaled nickel in individuals sensitized to nickel (Agency for Toxic Substances and Disease Registry, 1992).

In a cross-sectional study of 821 male and 758 female workers in a nickel refinery plant, increased abortions (relative risk of 1.8) and increased incidence of malformations (musculoskeletal system and cardiovascular defects) (16.9% versus 5.8% in unexposed controls) occurred in the exposed workers (Chashschin et al., 1994).

Laboratory Animal Data

As in humans, the respiratory tract is the major target organ of nickel toxicity in laboratory animals following inhalation exposure. The laboratory animal toxicity data are summarized in Table 11-43. Acute duration studies are limited; studies evaluated effects following at least 2 wks of exposure to nickel oxide (Lovelace, 1986a,b). Rats and mice inhaling nickel oxide developed respiratory effects including hyperplasia of alveolar macrophages, inflammation, and interstitial infiltrates. At exposures of longer duration, bronchial gland hyperplasia was observed 20 mo after a 1-mo exposure to 500 μg Ni/m^3 as nickel oxide (Horie et al., 1985). Chronic inflammation, fibrosis, macrophage hyperplasia, interstitial inflammatory infiltrates, and increased lung weight occurred in rats and mice following exposure to nickel sulfate hexahydrate, nickel subsulfide or nickel oxide for 16 days or 13 weeks (Benson et al., 1987, 1988, 1989, 1990; Dunnick et al., 1988, 1989). Olfactory epithelial atrophy of the nose also occurred with exposure to nickel sulfate and nickel subsulfide, but not nickel oxide, in both species (Benson et al., 1990). Rats appeared to be more sensitive than mice to nickel toxicity (Benson et al., 1990; Lovelace, 1986a,b). The toxicity depended on the solubility of the compounds and not on lung burden, since the compound with the lowest toxicity (nickel oxide) had the highest lung burden. The studies indicate the following toxicity ranking: nickel sulfate > nickel subsulfide > nickel oxide.

Enzyme changes were observed in alveolar macrophages of rats exposed to nickel oxide or nickel chloride aerosols for 18 days (Murthy et al., 1983). Biochemical (altered lysozyme, alkaline phosphatase, and β-glucuronidase activities) and morphological alterations (hyperplasia and lamellated material in the cytoplasm) in alveolar macrophages were associated with impaired cellular function in rabbits exposed to metallic nickel or nickel

TABLE 11-43. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration μg Ni/m^3	Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
Acute Studies							
NA	0, 100 250, 350 500	2 hr	$NiCl_2$ aerosol	99% ≤ 3 μm	Mouse, Swiss (14-29) F	Hemolytic plaque technique to determine number of specific antibody-producing spleen cells: Immunosuppression was observed at ≥ 250 $\mu g/m^3$.	Graham et al. (1978)
NA	0 900 2,000 4,000 7,800 23,600	6 hr/d 5 d/wk 12 d	NiO aerosol	MMAD = 3 μm σ_g = 1.9	Rats, F344 (5/sex)	Clinical signs, gross and histopathology examination: Lung lesions occurred at 2,000 $\mu g/m^3$ and above, increasing in severity with each level. At 2,000 $\mu g/m^3$, hyperplasia of alveolar macrophages in 3/10 animals. At 4,000 $\mu g/m^3$ and above, effects included hyperplasia of alveolar macrophages, focal inflammation in alveoli and alveoli septa, focal interstitial infiltrate, hyperplasia of peribronchial lymphoid tissue, enlarged and vacuolated Type II cells. At high level, thymus lesions were reported (degeneration with debris laden macrophages).	Lovelace (1986a)
NA	0 900 2,000 4,000 7,800 23,600	6 hr/d 5 d/wk 12 d	NiO aerosol	MMAD = μm σ_g = 1.9	Rats, F344 (5/sex)	Clinical signs, body wt, gross and histopathology examination: Lung lesions occurred at the two highest levels. At 9,000 $\mu g/m^3$, mild hyperplasia of alveolar macrophages. At highest level, decreased body wt and moderate lung effects occurred (hyperplasia of alveolar macrophages, inflammation, focal interstitial infiltrates, necrotic or vacuolated macrophages.	Lovelace (1986b)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
Subchronic and Chronic Studies							
NA	0 2,000 (SD = 1)	6 hr/d 5 d/wk 4.5 wk	Ni dust	NR	Rabbit, NS (8) M	Lung weight, AM function and size: Inc lung weight and AM activation.	Jarstrand et al. (1978)
NA	130	6 hr/d 5 d/wk 4 or 8 mo	metallic Ni dust	NR	Rabbit, NS (6)	EM and LM of lavaged AM, phagocytic function and activity: Inc volume density of Type II cells and impaired AM function occurred, but AM activity was not affected.	Johansson et al. (1983)
NA	0 1,700	6 hr/d 5 d/wk 1 mo	metallic Ni dust	Unspecified size, but 40% respirable, i.e., penetrated a preseparator	Rabbit, NS (8) M	Morphometric measurements Inc volume density of Type II alveolar epithelial cells in lungs.	Johansson and Camner, (1980)
NA	0 600	6 hr/d 5 d/wk 1 mo	$NiCl_2$ aerosol	MMAD ≈ 1 μm	Rabbit, NS (8) M	Fibronectin and lysozyme in lung lavage fluid: Dec fibronectin concentration and lysozyme activity.	Berghem et al. (1987)
NA	0 230 300 430	6 hr/d 5 d/wk 4 wk	$NiCl_2$ aerosol	4% >8 μm 1% 4-8 μm 9% 2-4 μm 32% 1-2 μm 49% 0.1-1 μm 4% 0.25-0.5 μm 1% <0.25 μm	Rabbit, NS (4-8) M	LM and EM of lungs, bactericidal and phagocytic activities of AM: Inc number of AM in lavage fluid, laminated structures and active cell surface in AM, decreased bactericidal capacity.	Wiernik et al. (1983)
NA	0 120	12 hr/d 6 d/wk >2 wk	$NiCl_2$ aerosol	MMAD = 0.32 μm σ_g = 1.51	Rat, Wistar (10) M	Lavaged AM, HP of lungs: Hyperplastic bronchial epithelium, lymphocytic infiltration.	Bingham et al. (1972)
NA	0 109	8 hr/d 5 d/wk 18 d	$NiCl_2$ aerosol	MMAD = 0.32 μm	Rat, Wistar ($\geq$3) M	Enzyme activities in AMs and lavage fluid: Inc AM acetylesterase and dec lysozyme activities; inc alkaline phosphate in lavage fluid.	Murthy et al. (1983)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 130	6 hr/d 5 d/wk 4-6 wk (3 d post)	$NiCl_2$ dust	MMAD = 0.5-1 μm	Rabbits, NS (6) M	Macrophage concentration and lysozyme activity in lung lavage fluid: Inc lavaged AMs, dec lysozyme activity in lavage fluid and in lavaged AMs.	Lundborg and Camner, (1984)
NA	0 110 220 440 880 1,800	6 hr/d 6 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.16-2.71 μm σ_g = 1.99-2.7	Rat, F344 (10/sex)	Body wt gain, CS, HP mortality, sperm morphology and vaginal cytology: Labored respiration at 1,800 μg/m^3; Inc lung wt at 110 μg/m^3; lung lesions (chronic inflammation, goblet cell hyperplasia, inc number of vacuolated AMs) at 440 μg/m^3; thinning of olfactory epithelium at 220 μg/m^3; enlarged bronchial and mediastinal lymph nodes draining the lungs due to inc number of lymphocytes within cortex of nodes at all levels.	Benson et al. (1990)
NA	0 110 220 440 880 1,800	6 hr/d 6 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.16-2.71 μm σ_g = 1.99-2.7	Mouse, B6C3F1 (10/sex)	Body wt gain, CS, HP mortality, sperm morphology and vaginal cytology: Inc lung wt at 440 μg/m^3; lung lesions (AM hyperplasia at 220 μg/m^3, then inflammation, fibrosis, lymphoid hyperplasia at higher conc.); olfactory epithelial atrophy at 440 μg/m^3.	Benson et al. (1990)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 110 450 1,800	6 H/d 5 d/wk 65 d	Ni_3S_2 aerosol	MMAD = 2.4 μm σ_g = 2.2	Mouse, B6C3F1 (40) F	Alveolar macrophages, antibody-forming cell response, spleen cell proliferative response, NK cell activity, host resistance to B16F10 tumor: Inc number of lung-associated lymph nodes (LALN), increased nucleated cells in LALN (1,800 μg/m^3) and lavage fluid (450 μg/m^3); increased Ab-forming cells in LALN (1,800); dec mixed lymphocyte response (1,800 μg/m^3); dec AM phagocytic activity of AMs (450 μg/^{3}); dec NK cell activity of spleen (1,800 μg/m^3).	Haley et al. (1990)
NA	0 27 110 450	6 hr/d 5 d/wk 65 d	$NiSO_4$ aerosol	MMAD = 2.3 μm σ_g = 2.4	Mouse, B6C3F1 (40) F	Alveolar macrophages, antibody-forming cell response, spleen cell proliferative response, NK cell activity, host resistance to B16F10 tumor: Inc number of lung-associated lymph nodes (LALN) at 450 μg/m^3; increased Ab-forming cells in LALN (450 μg/m^3).	Haley et al. (1990)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 53,200 ± 11,100	7 hr/d 5 d/wk lifespan	NiO aerosol	MMAD = 0.3 μm σ_g = 2.2	Hamster, Syrian golden (5) M	Gross and HP exam of lung, trachea, larynx, heart, liver, kidneys, spleen, bladder, skinned head; Pneumoconiosis characterized by interstitial pneumonitis, diffuse granulomatous pneumonia, fibrosis of alveolar septa, bronchial and bronchiolar hyperplasia, bronchiolization of alveolar epithelium, squamous metaplasia, emphysema, atelectasis.	Wehner et al. (1975)
NA	0 110 200 400 900 1,800	6 hr/d 5 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.4 μm σ_g = 2.2	Rat, F344/N (10/sex)	Body and organ wts, clinical signs, histopathology: dec body wt gain at 200, inc lung weight in 110, alveolar macrophage hyperplasia at all levels and chronic inflammation at 110 μg/m^3; olfactory epithelial atrophy at 400 μg/m^3.	Dunnick et al. (1989)
NA	0 110 200 400 900 1,800	6 hr/d 5 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.4 μm σ_g = 2.2	Mouse, B6C3F1 (10/sex)	Body and organ weights, clinical signs, histopathology: Inc lung weight in 900 μg/m^3; alveolar macrophage hyperplasia at 200 μg/m^3, chronic inflammation at 900 μg/m^3; foci of fibrosis at 900 μg/m^3; olfactory epithelial atrophy at 400 μg/m^3.	Dunnick et al. (1989)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Ni/m^3$						
NA	0 020 050 100 200 400	6 hr/d 5 d/wk 13 wk	$NiSO_4$ aerosol	MMAD = 2.3 μm σ_g = 2.4	Mouse, B6C3F1 (10/sex)	Body and organ wts, clinical signs, histopathology: Inc lung weight in 200 (males) and 400 (females); alveolar macrophage hyperplasia at 100, chronic inflammation at 400 $\mu g/m^3$; olfactory epithelial atrophy at 400 $\mu g/m^3$.	Dunnick et al. (1989)
NA	0 020 050 100 200 400	6 hr/d 5 d/wk 13 wk	$NiSO_4$ aerosol	MMAD = 2.3 μm σ_g = 2.4	Rat, F344/N (10/sex)	Body and organ wts, clinical signs, HP: Inc lung weight in 50 (females); alveolar macrophage hyperplasia at all levels and chronic inflammation at 100 $\mu g/m^3$; olfactory epithelial atrophy at 200 $\mu g/m^3$ (males) and 50 $\mu g/m^3$ (females).	Dunnick et al. (1989)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 400 900 1,800 3,600 7,300	6 hr/d 5 d/wk 16 days	Ni_3S_2 aerosol	AVG: MMAD=2.8, σ_g=2 0.4 (MMAD=2.67-3.15; σ_g=1.84-2.34) 0.9 (MMAD=2.88-2.98; σ_g=1.83-1.91) 1.8 (MMAD=2.75-2.82; σ_g=1.76-2.14) 3.6 (MMAD=2.48-2.80; σ_g=2.10-2.14) 7.3 (MMAD=2.50-2.64; σ_g=1.70-2.01)	Rat, F344/N (5/sex)	Body and organ wts, histopathology: Labored respiration, emaciation and dehydration at 3,600; reduced body wt gain (13%) at 1,800; inc absolute lung wt at 3,600 (males) and 1,800 (females); respiratory effects (necrotizing pneumonia, emphysema, goblet cell hyperplasia of bronchioles, pigment accumulation in alveoli) at 7,300; inflammation at 400; atrophy of olfactory epithelium and degeneration of respiratory epithelium at all conc. (increased incidence but not severity with conc.); hepatic atrophy at 3,600; testicular degeneration at 1,800 μg/m^3.	Benson et al. (1987)
NA	0 400 900 1,800 3,600 7,300	6 hr/d 5 d/wk 16 days	Ni_3S_2 aerosol	avg: MMAD=2.8, σ_g=2 (refer to above for each specific concentration)	Mouse, B6C3F1 (5/sex)	Body and organ wts, HP, natural killer (NK) cell activity of spleen cells: Labored respiration at 7,300 emaciation, dehydration, and dec body wt gain at 3,600; inc absolute lung wt at 7,300; lung fibrosis at 3,600 (50% animals); atrophy of olfactory epithelium and degeneration of respiratory epithelium) at 900; hepatic atrophy; spleen and thymus atrophy; testicular degeneration at 3,600 μg/m^3.	Benson et al. (1987)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 700	6 hr/d 5 d/wk 78 wk (30 wk post)	Ni_3S_2 aerosol	diameter 70% <1 μm 25% 1-1.5 μm	Rat, F344 (22-32) M	Body wt, HP in major organs: Reduced body wt, inc lung lesions (pneumonitis, atelectasis, bronchitis, bronchiectasis, emphysema), inc incidence of lung tumors (adenomas, adenocarcinomas, squamous cell carcinomas).	Ottolenghi et al. (1974)
NA	0 200 100 400	6 hr/d 5 d/wk 13 wk	$NiSO_4$ aerosol	MMAD = 1.9 μm σ_g = 2.1	Rat, F344/N (6/sex)	Biochemical and cytological evaluation of BAL fluid, necropsy of lungs: Inflammation suggested by inc LDH, b-glucuronidase, and total protein at 100 μg/m^3.	Benson et al. (1989)
NA	0 400 1,800	6 hr/d 5 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.8 μm σ_g = 2.2	Rat, F344/N (6/sex)	Biochemical and cytological evaluation of BAL fluid, necropsy of lungs: Inc LDH, b-glucuronidase, and total protein; inflammation, macrophage hyperplasia, and interstitial infiltrates at 400 μg/m^3.	Benson et al. (1989)
NA	0 20 100 400	6 hr/d 5 d/wk 13 wk	$NiSO_4$ aerosol	MMAD = 1.9 μm σ_g = 2.1	Mouse, B6C3F1 (8/sex)	Biochemical and cytological evaluation of BAL fluid, necropsy of lungs: Inflammation suggested by inc LDH and b-glucuronidase, macrophage hyperplasia and interstitial infiltrates at 100 μg/m^3; chronic inflammation and fibrosis at 400 μg/m^3.	Benson et al. (1989)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Ni/m^3$						
NA	0 400 1,800	6 hr/d 5 d/wk 13 wk	Ni_3S_2 aerosol	MMAD = 2.8 μm σ_g = 2.2	Mouse, B6C3F1 (8/sex)	Biochemical and cytological evaluation of BAL fluid, necropsy of lungs: Inc LDH, b-glucuronidase, and total protein at 400; chronic inflammation and fibrosis at 1,800 and macrophage hyperplasia and interstitial infiltrates at 400 $\mu g/m^3$.	Benson et al. (1989)
NA	0 800 1,600 3,300 6,700 13,300	6 hr/d 5 d/wk 16 d	$NiSO_4 \cdot 6H_20$ aerosol	MMAD = 1.9 μm σ_g = 2.2	Rat, F344/N (5/sex)	Clinical signs, body wt gain, mortality, NK cell activity, gross necropsy, histopathology: Labored respiration, emaciation, lethargy, reduced body wt gain, inc lung wt, lung inflammation, degeneration in bronchiolar mucosa (less vacuolation of epithelial cells, goblet cell hypertrophy), nasal lesions (degeneration of respiratory epithelium and atrophy of olfactory epithelium) at 800; lymphoid hyperplasia in lymph nodes at 800 and lymphocyte depletion in cortex at 6,700; testicular degeneration at 13,300 $\mu g/m^3$.	Benson et al. (1988)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 800 1,600 3,300 6,700 13,300	6 hr/d 5 d/wk 16 d	$NiSO_4 \cdot 6H_20$ aerosol	MMAD = 1.9 μm σ_g = 2.2	Mouse, B6C3F1 (5/sex)	Clinical signs, body wt gain, mortality, NK cell activity, gross necropsy, HP: Emaciation, lethargy, reduced body wt gain, decreased lung wt. Due to high mortality, only 0, 800, and 1,600 groups had HP exam: Lung inflammation and atrophy of olfactory epithelium at 800; spleen and thymus atrophy due to lymphoid depletion at 1,600 (in mice that died only); testicular degeneration at 1,600 μg/m^3.	Benson et al. (1988)
NA	0 120	12 hr/d 6 d/wk >2 wk	NiO aerosol	MMAD = 0.25 μm σ_g = 3.6	Rat, Wistar (10) M	Lavaged alveolar macrophages, histopathology of lungs: Inc number of alveolar macrophages, macrophage accumulation in alveolar spaces, thickening of alveolar wall with dec lymphocyte infiltration.	Bingham et al. (1972)
NA	0 400 900 2,000 3,900 7,900	6 hr/d 5 d/wk 13 wk	NiO aerosol	MMAD = 2.8 μm σ_g = 1.8	Rat, F344/N (10/sex)	Body and organ wts, clinical signs, histopathology: Inc lung weight in all males and at ≥900 in females; alveolar macrophage hyperplasia at all levels and chronic inflammation at ≥3,900 μg/m^3.	Dunnick et al. (1989)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 400 900 2,000 3,900 7,900	6 hr/d 5 d/wk 13 wk	NiO aerosol	MMAD = 2.8 μm σ_g = 1.8	Mouse, B6C3F1 (10/sex)	Body and organ wts, clinical signs, histopathology: increased lung weight in 3,900 (females); AM hyperplasia at all levels chronic inflammation at $\geq$7,900 $\mu g/m^3$.	Dunnick et al. (1989)
NA	0 120	8 hr/d 5 d/wk 18 d	NiO aerosol	MMAD = 0.25 μm	Rat, Wistar ($\geq$3) M	Enzyme activities in AMs and lavage fluid: inc. acetylesterase and decreased lysozyme activities and inc. acetylesterase, alkaline phosphatase, b-glucuronidase, and lysozyme activities in lavage fluid.	Murthy et al. (1983)
NA	0 800 1,600 3,200	continuously on gd1-21	NiO aerosol	NR	Pregnant Rat, Wistar (10-13) F	Body wt; wt change and HP on lung, liver, and kidney; hematology: Maternal effects decreased (11%) body wt gain, inc. lung wt, increased leukocytes at 800 $\mu g/m^3$; fetal effects-decreased wt, increased leukocytes and serum urea at 1,600 $\mu g/m^3$.	Weischer et al. (1980)
NA	0 200 400 800	continuously for 28 days	NiO aerosol	NR	Rat,Wistar (10) F	Body wt; HP on lung, liver, and kidney; hematology: Lungs-thickened septa, macrophage foci, emphysema, peribronchial infiltration of round cells, edema; kidney-tubular degeneration; dec body wt gain and kidney wt at 800; inc lung wt and alkaline phosphatase at 200; inc SGOT activity at 400; inc RBC at 800 $\mu g/m^3$.	Weischer et al. (1980)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 400 2,000 7,900	6 hr/d 5 d/wk 13 wk	NiO aerosol	MMAD = 3 μm σ_g = 1.9	Mouse, B6C3F1 (8/sex)	Biochem. and cytological eval. of BAL fluid, necropsy of lungs: Inflammation suggested by inc LDH, B-glucuronidase and total protein at 2,000; macrophage hyperplasia at 400; interstitial infiltrates at 2,000; chronic inflammation at 7,900 μg/m^3.	Benson et al. (1989)
NA	0 400 2,000 7,900	6 hr/d 5 d/wk 13 wk	NiO aerosol	MMAD = 3 μm σ_g = 1.9	Rat, F344 (6/sex)	Biochem. and cytological eval. of bronchoalveolar fluid; necropsy of lungs: Inc B-glucuronidase, total protein at 2,000; macrophage hyperplasia at 400; chronic inflammation, interstitial infiltrates at 2,000 μg/m^3.	Benson et al. (1989)
NA	0 200 900	7 hr/d 5 d/wk 3, 6 or 12 mo	NiO aerosol	MMAD = 0.6 μm σ_g = 1.6	Rat, Wistar (5)M	Organ weights, histopathology of lung, liver, spleen, and kidneys: Epithelial hyperplasia of alveoli and alveoli sacs (bronchial metaplasia) at 200 μg/m^3 at 12 mo.	Tanaka et al. (1988)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	μg Ni/m^3						
NA	0 900 2,000 3,900 7,900 23,600	6 hr/d 5 d/wk 16 d	NiO aerosol	MMAD = 3 μm σ_g = 1.9	Rat, F344/N (5/sex)	Body wt and organ wts, mortality, clinical signs, microscopic pathology: Inc lung wt at 7,900; hyperplasia of alveolar macrophages, focal suppurative inflammation, focal interstitial cellular infiltrate and particles in alveoli and alveolar macrophages at 900; atrophy of olfactory epithelium and atrophy of thymus and hyperplasia of lymph nodes at 23,600 μg/m^3.	Dunnick et al. (1988)
NA	0 900 2,000 3,900 7,900 23,600	6 hr/d 5 d/wk 16 d	NiO aerosol	MMAD = 3 μm σ_g = 1.9	Mouse, B6C3F1 (5/sex)	Body wt and organ wts, mortality, clinical signs, microscopic pathology: Lung lesions at 7,900 (focal mixed inflammatory cell infiltrate, bronchial epithelium hyperplasia, diffuse alveolar macrophage hyperplasia); atrophy of thymus and hyperplasia of lymph nodes at 23,600 μg/m^3.	Dunnick et al. (1988)
NA	0 500 1,100 5,100 5,500 6,300	6 hr/d 5 d/wk 1 mo	NiO aerosol	MMAD = 1.2 μm σ_g = 2.2	Rat, Wistar (2-5) M	Histopathology (up to 20 mo postexposure): Bronchial gland hyperplasia at 20 mo at 500 and 6,300 μg/m^3.	Horie et al. (1985)

TABLE 11-43 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR NICKEL AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Sex, Strain	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Ni/m^3$						
NA	0 25-818	continuously for 4 wk or 4 mo	NiO aerosol	MMAD = 0.41-0.49 μm σ_g = 1.61-1.91 (specified for each level)	Rat, Wistar (12) NS	Alveolar macrophage analysis; humoral immune system (plaque test and lysis test): Dec number of alveolar macrophages, inc phagocytic activity; dec humoral immune response (dec antibody synthesis against injected sheep erythrocytes).	Spiegelberg et al. (1984)
NA	0 470 2,000 7,900	6 hr/d 5 d/wk 65 d	NiO aerosol	MMAD = 2.8 μm σ_g = 1.8	Mouse, B6C3F1 (40) F	Alveolar macrophages, antibody-forming cell response, spleen cell proliferative response, NK cell activity, host resistance to B16F10 tumor: Inc number of lung-associated lymph nodes (LALN) at 450; inc nucleated cells in LALN at 2,000; dec alveolar macrophage activity at 470 $\mu g/m^3$.	Haley et al. (1990)

Abbreviations:

AM = alveolar macrophages; CS = clinical signs; EM = electronic microscopy; F = female; HP = histopathology; LM = light microscopy; M = male; NA = not applicable; Ni_3S_2 = nickel subsulfide; $NiCl_2$ = nickel chloride; NiO = nickel oxide; $NiSO_4$ = nickel sulfate; $NiSO_4 \cdot 6H_20$ = nickel sulfate hexahydrate; NR = not reported; wt = weight.

chloride for 1 to 8 mo (Berghem et al., 1987; Jarstrand et al., 1978; Johansson and Camner, 1980, 1986; Johansson et al., 1983; Lundborg and Camner, 1984; Wiernik et al., 1983). Increase in volume density of alveolar Type 2 cells was also seen after 1 mo exposure.

Acute to subchronic exposures have resulted in immunological changes in rats, mice, and rabbits. Immunosuppression was observed in mice exposed to nickel chloride for 2 h (Graham et al., 1978). Longer-term exposure caused effects in respiratory macrophages (Haley et al., 1990; Spiegelberg et al., 1984). A decrease in alveolar macrophage phagocytic activity was observed in mice exposed to nickel subsulfide, nickel sulfate, or nickel oxide for 65 days (Haley et al., 1990). A decrease in natural killer cell activity was observed in the mice exposed to nickel subsulfide. Atrophy of lymphoid organs (spleen and thymus) and lymphoid hyperplasia in bronchial and mediastinal lymph nodes were observed in rats and mice exposed for 16 days to nickel sulfate, nickel subsulfide, and nickel oxide (Benson et al., 1987, 1988: Dunnick et al., 1988). A decrease in the number of alveolar macrophages and in the humoral response was observed in rats after $\leq$4 mo of exposure to nickel oxide, indicating that inhalation exposure to nickel may make animals more susceptible to infection (Spiegelberg et al., 1984). The increase in susceptibility was also exhibited by rabbits exposed to metallic nickel for 3 to 6 mo (Johansson et al., 1981). All of the animals exposed for 6 mo had foci of pneumonia, which may have resulted from an impaired function of the alveolar macrophages. The inhibitory effects of nickel on the cellular immune response may be related to the development of nickel-induced tumors in animals, as well as to the high risk of lung cancer in nickel-exposed workers (Shen and Zhang, 1994).

After a 12-mo exposure, bronchial epithelial metaplasia were observed in rats exposed to nickel oxide (Tanaka et al., 1988). An increase in respiratory lesions (pneumonitis, atelectasis, bronchitis, bronchiectasis, and emphysema), compared to controls, was observed in rats exposed to nickel subsulfide for 78 weeks, followed by a 30-week observation period (Ottolenghi et al., 1974). Alveolar proteinosis and marked lung enlargement were observed in rats exposed chronically to 60 μg Ni/m^3 as nickel oxide (Takenaka et al., 1985). At the end of the experiment, two animals also had focal fibrosis. Pneumoconiosis was observed in hamsters following a lifetime exposure to 42,000 μg Ni/m^3 as nickel oxide alone or in combination with cigarette smoke (Wehner, 1986; Wehner et al., 1975, 1979). The pneumoconiosis was characterized by lung changes of interstitial pneumonitis, diffuse

granulomatous inflammation, bronchial and bronchiolar epithelial hyperplasia, fibrosis of the alveolar septa, bronchiolization of the alveolar epithelium, and emphysema and/or atelectasis. Despite the high lung burden of nickel, pneumoconiosis was not observed initially, indicating the low acute toxicity of nickel oxide. The pneumoconiosis increased in severity as a function of exposure time and age. Emphysema was observed in the animals that died before developing pneumoconiosis.

Nickel has been shown to be carcinogenic in animals, with nickel subsulfide being the most potent (Coogan et al., 1989). Lung cancer was found in rats exposed chronically to nickel subsulfide (Ottolenghi et al., 1974). Tumors included adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma. Lung tumors were not observed in rats following exposure to nickel oxide ((Horie et al., 1985); however, the exposure duration (1 mo) was not sufficient to evaluate the potential for carcinogenicity.

Other systemic changes associated with nickel inhalation exposure have included decreased body weight gain, decreased liver weight, and altered serum glucose in rats exposed to nickel oxide for less than a month (Weischer et al., 1980). Atrophy of the liver was observed in mice and rats exposed to nickel subsulfide for 16 days (Benson et al., 1987).

A decrease in fetal body weight was observed in the offspring of rats exposed to nickel oxide on gestation days 1-21 (Weischer et al., 1980). No effects on the number of fetuses or on the number and weight of placentas were observed. Testicular degeneration was observed in rats and mice exposed to nickel sulfate and nickel subsulfide for 16 days (Benson et al., 1987, 1988). No exposure-related effects were seen in sperm number, motility, or morphology, or on the length of the estrous cycle in rats or mice exposed nickel for 13 weeks (Dunnick et al., 1989). Higher exposure concentrations were used in the 16-day studies, which explains why testicular effects were observed after 16 days but not 13 weeks of exposure.

11.6.15.4 Factors Affecting Susceptibility

Individuals with respiratory difficulties may have greater susceptibility to the toxicity of inhaled nickel, since pulmonary dysfunction and asthmatic symptoms have been shown to occur in exposed workers (Dolovich et al., 1984; Kilbam et al., 1990; McConnell et al., 1973; Novey et al., 1983). The developing respiratory tract of children may also pose an

increased susceptibility. Data have suggested that smoking and nickel exposure may have an additive effect on the development of respiratory tract cancer (Magnus et al., 1982).

Greater susceptibility to nickel toxicity may result in individuals with comprised immunological systems. Human and animal data have shown that nickel can cause changes in immunoglobulin levels (Bencko et al., 1983, 1986) and immunosuppression (Benson et al., 1987, 1988; Dunnick et al., 1988, Haley et al., 1990).

Individuals sensitized to nickel may be unusually susceptible, because exposure to nickel by any route may trigger an allergic response (Dolovich et al., 1984; McConnell et al., 1973; Novey et al., 1983). Epidemiology studies indicate that blacks have a higher nickel sensitivity than whites and that women of either racial group have higher reaction rates (Nethercott and Holness, 1990; Prystowsky et al., 1979). The incidence of reactions may be higher in women because they wear more metal jewelry than do men.

A relationship between human lymphocyte antigens (HLA-DRw6) and nickel sensitivity was observed in patients who had a contact allergy and positive results in a patch test for nickel only (Mozzanica et al., 1990). The patients had no occupational exposure history. The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen, compared to normal controls. The relative risk for patients with DRw6 to develop a sensitivity to nickel was approximately 1:11. The presence of DRw6 may be monitored to determine the potential risk of individuals to become sensitized to nickel.

11.6.16 Potassium

11.6.16.1 Chemical and Physical Properties

Potassium is one of the alkali metals in Group 1A of the periodic table. It forms compounds in the +1 oxidation state, and is never found free in nature. Metallic potassium is rapidly oxidized in air, and decomposes in water with the evolution of hydrogen (Weast, 1989). Potassium is unique among alkali and alkaline-earth metals in forming the superoxide KO_2 in air. This compound is unstable in contact with molten potassium, and will react to yield K_2O. Potassium can react to form inorganic salts and organopotassium compounds such as KCO (Greer et al., 1982). Potassium dichromate ($K_2Cr_2O_7$) is moderately soluble in water.

11.6.17.2 Pharmacokinetics

Serum potassium concentration was unaffected in six atopic subjects after a single inhalation of 10% potassium chloride from an ultrasonic nebulizer (Dixon et al., 1989). However, due to the large potassium content in the body, it is unclear if a change in serum levels would have been detected, even if the entire amount sprayed from the nebulizer were deposited in the lungs and absorbed into the blood.

No other data were located on the pharmacokinetics of potassium following inhalation exposure to potassium compounds. Therefore, this discussion is based on general principles of chemistry and biochemistry (Mudge, 1985). Many potassium compounds are soluble in water and would be expected to be absorbed from the lungs. Potassium is an essential element. It is found throughout the body as the intracellular cation and in the extracellular compartment. An active ion transport system using magnesium-adenosine triphosphate (Mg-ATP) as the energy source (see the section on magnesium) maintains a potassium gradient across the plasma membrane. This gradient plays a crucial role in nerve conduction and muscle action. Orally administered potassium is completely absorbed from the gastrointestinal tract and excreted in the urine. The kidney plays a major role in the maintenance of potassium homeostasis. The body responds to increased potassium by increasing excretion and by increasing tissue uptake, thereby returning extracellular potassium levels to normal.

11.6.16.3 Health Effects

Data on the effects of inhalation exposure to potassium are summarized in Table 11-44. The one study that investigated the health effects of inhaled potassium compounds was an abstract that investigated the effects of inhaling potassium chloride and sodium chloride in 6 male atopic subjects with increased nonspecific bronchial reactivity (Dixon et al., 1989). In a randomized double-blind study, the subjects inhaled 10% potassium chloride on one day and 0.9% sodium chloride on a different day using an ultrasonic nebulizer. Cardiovascular parameters and vital capacity were measured at intervals from 1 to 150 breaths after exposure. All subjects coughed and bronchoconstricted after potassium chloride dosing, but there was no cough and less bronchoconstriction after sodium chloride. Partial flow at 30%

TABLE 11-44. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR POTASSIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ K/m^3$						
NA	See comments	See comments	KCl	NR	Human (6) M	Cardiac output, heart rate, stroke volume, ventricular ejection time, oxygen saturation, serum K, vital capacity: Cough only after KCl, not after NaCl. Bronchoconstriction (40% fall in Vp30) was observed with KCl, but not 0.9% or 10% NaCl. Serum K+ and cardiovascular parameters unaffected, suggesting direct effect on respiratory tissue. Effect attributed to KCl, not nonspecific osmotic effect. Note: Subjects were atopic, with increased non-specific bronchial reactivity. Note: Exposure was double-blinded and randomized, with subjects exposed to 10% KCl or 0.9% NaCl by ultrasonic nebulizer on separate days. Exposure to 10% NaCl was in a separate experiment.	Dixon et al. (1989)

Abbreviations:

K+ = potassium ion; KCl = potassium chloride; M = male; min = minute; NA = not applicable; NaCl = sodium chloride; NR = not reported; ppm = parts per million; Vp30 = partial flow at 30% vital capacity.

vital capacity (Vp30) was decreased by >40% after potassium chloride exposure, but not after sodium chloride. Plasma potassium levels, oxygen saturation, and cardiovascular parameters were unaffected. The abstract further states that a second randomized double-blind study was conducted with the same subjects inhaling "0.9% sodium chloride or 10% sodium chloride." However, since the next statement is "all subjects coughed and bronchoconstricted after potassium chloride; there was no cough and less bronchoconstriction after sodium chloride," it appears that the second study may actually have been conducted with 0.9% potassium chloride and 10% sodium chloride. Thus, the second study would have assessed whether the observed effects could have been attributed to potassium, or nonspecifically to inhaled salts. Based on the observed results, the authors concluded that hyperreactive subjects bronchoconstrict in response to potassium, and the effect cannot be explained by osmotic challenge alone.

A Russian study assessed the effects on the upper respiratory tract of workers at a plant that produced nitrogen-phosphorus-potassium fertilizer; further details were not available (Kilin, 1972).

A study in Russian reported embryotoxic effects (apparently in animals) following inhalation exposure to potassium ferricyanide; no English-language abstract was included (Besedina and Grin, 1987). However, the observed embryotoxicity is likely to be due to the ferricyanide ion, rather than to potassium ion.

Other reports on the effects on inhalation exposure to potassium are limited to studies in which potassium was the counter-ion used for assessing the toxicity of specific anions. Studies on potassium dichromate are discussed in the section on chromium, and a study on potassium bromate is discussed in the section on bromine.

Sudden increases in oral or intravenous potassium intake can cause hyperkalemia. Because of the role of potassium in nerve conduction and muscle contraction, the primary effect of hyperkalemia is on the electrical activity of the heart (Mudge, 1985). Although similar effects could theoretically result from inhalation exposure, one would expect the required exposure concentrations to be quite high, due to the large amount of total body potassium and the significant daily throughput via the oral route.

11.6.16.4 Factors Affecting Susceptibility

Because the data on potassium inhalation toxicity are quite limited, only limited hypotheses can be made regarding susceptible subpopulations. The finding of increased cough and bronchoconstriction among atopic subjects who inhaled a potassium chloride aerosol (Dixon et al., 1989) suggests that this group may be at increased risk of respiratory toxicity following potassium inhalation. However, the tested concentration was much higher than levels likely to be involved in environmental exposure.

Because the kidney is important in maintaining potassium homeostasis, individuals with impaired kidney function may be less able to adjust to an increased potassium body burden if large amounts of potassium are absorbed from the lung. In addition, hyperkalemia may occur as a result of conditions such as acidosis, untreated Addison's disease, and hyperglycemia in diabetic patients who are deficient in aldosterone (Mudge, 1985). People with such conditions may be more susceptible to systemic effects of inhaled potassium compounds. Because the heart is the primary target of hyperkalemia (Mudge, 1985), people with cardiovascular disease may also be more susceptible to increased systemic levels of potassium. However, because of the homeostatic balances on potassium levels, such systemic increases would likely be limited to individuals with altered potassium metabolism.

11.6.17 Selenium

11.6.17.1 Chemical and Physical Properties

According to Elkin (1982), selenium belongs to Group 16 (VIA) of the periodic system of elements and most of its chemical properties are very similar to sulfur. Solid elemental selenium has several allotropic forms: amorphous, crystalline or red, and gray or metallic. The gray form is stable at ordinary temperatures. Liquid selenium is brownish red and produces dark red vapors when it boils. The important oxidation states of selenium are -2, 0, $+2$, $+4$, and $+6$. The $+2$ state is not known to occur in nature. Selenium reacts with active metals and gains electrons to form ionic compounds containing the selenide ion Se^{2-}. Selenium forms covalent compounds, including organoselenium compounds, with most other substances. Crystalline selenium does not react with water, even at high temperatures, and is generally stable in water over a wide range of pH values and mildly oxidizing to reducing conditions (Agency for Toxic Substances and Disease Registry, 1989; Elkin, 1982). Strong

oxidants convert selenium dioxide and its derivatives to the hexavalent state. Hydrogen selenide is highly reactive in air and is rapidly oxidized to elemental selenium and water; however, the gas may build up to hazardous levels in confined areas despite oxidative losses (Agency for Toxic Substances and Disease Registry, 1989). Elemental selenium is insoluble, but several selenium compounds are moderately to highly water soluble, including: selenium dioxide (SeO_2), hydrogen selenide (SeH_2), selenic acid (SeH_4O_4) and selenious acid (SeH_2O_3).

11.6.17.2 Pharmacokinetics

There is a lack of pharmacokinetic data following the inhalation of selenium and selenium compounds in humans and laboratory animals. Data presented in this section are based primarily from other routes of exposure.

Absorption and Distribution

Information on absorption of selenium following inhalation exposure is limited to occupational studies. Glover (1970) examined urinary selenium levels of workers employed in a selenium rectifier plant. Workers exposed to high levels of unspecified selenium compounds in the air excreted higher levels of selenium in their urine than workers employed in other areas of the plant with lower concentrations of selenium in the air. Although the study indicates that selenium compounds were absorbed from the lungs of the workers, the lack of exposure information does not permit an estimate of the extent or rate of absorption from the lungs.

Studies in dogs and rats indicate that absorption of selenium following inhalation exposure is extensive, although the rate of absorption was dependent on the administered selenium compound. In rats (Medinsky et al., 1981b) and dogs (Weissman et al., 1983), the absorption of selenious acid aerosol was approximately twice as rapid as the absorption of elemental selenium aerosol following inhalation exposure. Medinsky et al. (1981b) also found that, for both compounds, most of the selenium was absorbed after 4 days, and that the distribution of selenium in the body tissues was identical, suggesting that selenium entered the same body pool following absorption.

No studies were located concerning the distribution of selenium in humans following inhalation of elemental selenium or selenium compounds. The only laboratory animal distribution data were reported by Weissman et al. (1983) in which selenium concentrated in the liver, kidney, spleen, and lung of dogs following inhalation exposure to selenious acid or elemental selenium aerosols.

Once absorbed, selenium is transported throughout the body in the blood. Selenium in the blood is found in plasma and erythrocytes in a dose-related manner, with higher levels in the plasma (Cikrt et al., 1988).

There is no evidence that the tissue distribution of selenium was dependent on route of administration; however, tissue distribution differences appear to exist among the various selenium compounds (Agency for Toxic Substances and Disease Registry, 1989; Ben-Porath and Kaplan, 1969; Cantor et al., 1975). Selenium from selenomethionine has been observed to concentrate in the pancreas of humans and rats following intravenous administration and in the pancreas of chicks following oral administration (Ben-Porath and Kaplan, 1969; Cantor et al., 1975; Lathrop et al., 1972). Selenium from sodium selenite and sodium selenate, on the other hand, is found in the highest concentrations in the liver and kidney of humans and animals following oral administration or injection (Cikrt et al., 1988; Jereb et al., 1975; Sohn et al., 1991; Styblo et al., 1991). Selenium can also readily transfer into fetuses as shown by elevated selenium levels in fetal tissues following exposure to sodium selenite (Archimbaud et al., 1992).

Metabolism

Metabolic studies in humans are limited. Humans accidentally or occupationally exposed to selenium have been reported to have a noticeable garlic odor of the breath, probably due to excretion of dimethyl selenide in expired air (Bopp et al., 1982; Glover et al., 1970; Holness et al., 1989).

Medinsky et al. (1981b) reported that in rats exposed via ingestion or inhalation to elemental selenium or selenious acid aerosols, both selenium compounds were likely to enter the same metabolic pool once absorbed into the general circulation.

In rats, dimethyl selenide has been identified as the primary respiratory metabolite following injection of sodium selenite or sodium selenate (Hirooka and Galambos, 1966) and

appears to be produced in the liver (Nakamuro et al., 1977). In mice, dimethyl selenide and dimethyl diselenide have been detected in expired air following addition of unspecified amounts of sodium selenite, DL-selenomethionine, or DL-selenocystine to their drinking water (Jiang et al., 1983). A third unidentified volatile selenium compound was detected in expired air of the mice following DL-selenomethionine administration (Jiang et al., 1983).

In rats, the trimethylselenonium ion has been identified as the predominant urinary metabolite following intraperitoneal administration of sodium selenite (Byard and Baumann, 1967) or oral administration of sodium selenate, selenomethionine, selenocystine, selenium-methylselenocysteine, or seleniferous wheat (Palmer et al., 1970). Another major selenium metabolite that appeared in the urine more slowly than the trimethylselenonium ion was identified chromatographically but not structurally (Palmer et al., 1970).

The metabolic pathways for the conversion of selenite to dimethyl selenide has been studied in rodents. The reduction of selenite to dimethyl selenide requires glutathione and the methylating agent S-adenosylmethionine. NADPH, coenzyme A, ATP, and magnesium(II) salts are also required to provide optimal conditions for this reaction (Ganther, 1979). Ganther (1971) and Hsieh and Ganther (1975) found that selenite initially reacts nonenzymatically with glutathione to form a selenotrisulfide derivative. The selenotrisulfide derivative is then reduced nonenzymatically, in the presence of excess glutathione or by glutathione reductase in the presence of NADPH, to a selenopersulfide (GSSeH). GSSeH is unstable and decomposes to glutathione and selenium or is enzymatically reduced by glutathione reductase in the presence of NADPH to hydrogen selenide (Ganther, 1971; Hsieh and Ganther, 1975). Hydrogen selenide can then be methylated by S-adenosylmethionine in the presence of selenium methyltransferase.

Selenate apparently is not converted to dimethyl selenide as readily as is selenite. Studies of selenate metabolism are limited in mammals, but studies using bacteria indicate the selenate must be activated prior to conversion to selenite (Bopp et al., 1982; Dilworth and Bandurski, 1977). Dilworth and Bandurski (1977) demonstrated that in the presence of ATP, magnesium(II) salts, and ATP-sulfurylase, yeast could convert selenate to adenosine-5'-selenophosphate and proposed that the latter compound reacts with glutathione to eventually yield selenite.

No studies were located that indicate how the trimethylselenonium ion is derived, but injection of rats with trimethylselenonium chloride results in demethylation to dimethyl selenide (Obermeyer et al., 1971), indicating that trimethylselenonium is not a product of the methylation of dimethyl selenide.

Excretion

In humans and in laboratory animals, excretion of selenium occurs in the urine, feces, and expired air (Griffiths et al., 1976; Lathrop et al., 1972; McConnell and Roth, 1966; Medinsky et al., 1981a; Sohn et al., 1991; Styblo et al., 1991; Thomson, 1974). The initial rate of excretion appears to be dose-dependent (Griffiths et al., 1976; Lathrop et al., 1972; McConnell and Roth, 1966; Thomson and Stewart, 1974). Urinary and fecal excretion of selenium are similar, each representing approximately 50% of the total output (Stewart et al., 1978). At high selenium exposure levels, excretion of selenium in expired air becomes more important (McConnell and Roth, 1966).

Following acute exposures to selenium compounds, humans excrete some of the absorbed dose in the expired air as demonstrated by the odor of garlic in the breath (Glover, 1970). However, there were no studies located that quantified the rate of excretion or identified the selenium compounds in the exposure air of humans.

11.6.17.3 Health Effects

Human Data

The selenium compounds that are most likely to be encountered in occupational settings are dusts of elemental selenium, hydrogen selenide, and selenium dioxide, although other volatile selenium compounds (e.g., dimethyl selenide, dimethyl diselenide) might also be encountered in some situations. The largest number of reported human exposures has occurred in industries that extract, mine, treat, or process selenium-bearing minerals and in industries that use selenium or selenium compounds in manufacturing. In humans, the respiratory tract is the primary site of injury after inhalation of selenium dust or selenium compounds, but gastrointestinal and cardiovascular effects and irritation of the skin and eyes also occur. Little of the available information for humans, however, relates health effects to

measured concentrations of the selenium dust or compounds in the air. Toxicity data for humans are summarized in Table 11-45.

Hydrogen selenide, a highly poisonous selenium compound, is a gas at room temperature, with a density much higher than that of air. Irritation of mucous membranes, pulmonary edema, severe bronchitis, and bronchial pneumonia have been observed in humans following acute exposure to this gas (Buchan, 1947). Acute industrial inhalation exposure to elemental selenium dust, possibly including some selenium dioxide, has irritated mucous membranes in the nose and throat, produced coughing, nosebleed, and loss of olfaction and, in heavily exposed workers, dyspnea, bronchial spasms, bronchitis, and chemical pneumonia (Clinton, 1947; Hamilton, 1949).

Selenium dioxide is formed when selenium is heated in air. Selenium dioxide forms selenious acid on contact with water, including perspiration, and causes severe irritation. Acute inhalation of large quantities of selenium dioxide powder can produce pulmonary edema due to the local irritant effect on alveoli (Middleton, 1947; Pringle, 1942). Bronchial spasms, symptoms of asphyxiation, and persistent bronchitis have been noted in workers briefly exposed to high concentrations of selenium dioxide (Wilson, 1962). An abstract by Kinnigkeit (1962) reported that selenium dioxide concentrations of 7 to 50 μg selenium/m^3 in a selenium rectifier plant produced slight tracheobronchitis in 9 out of 62 exposed workers.

Gastrointestinal distress, including indigestion and nausea, were observed in humans following inhalation of selenium, selenium dioxide, or hydrogen selenide (Glover, 1967, 1970). Wilson (1962) reported that following an acute episode of exposure to selenium dioxide fumes, several workers had lower blood pressure but an elevated pulse rate, which normalized within 3 h. Brief exposure to clouds of elemental selenium dust ("red fumes") resulted in lacrimation, irritation, and redness of the eyes (Clinton, 1947) and acute exposure to selenium dioxide burned the eyes, conjunctiva, and skin upon contact (Middleton, 1947; Pringle, 1942). The dermal and ocular effects most likely are due to direct contact with selenium particles.

Information concerning possible neurological effects caused by inhalation of selenium or selenium compounds is limited. Headaches, dizziness, and malaise were reported by workers following acute occupational exposures to hydrogen selenide or to clouds of fine elemental selenium dust or selenium dioxide (Clinton, 1947; Glover, 1970).

TABLE 11-45. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR SELENIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Se/m^3$						
NA	40-3,600	8 h/d 5 d/wk NS (occup)	Elemental selenium, selenium dioxide dust (assumed)	NS	Human (<100) B	Clinical signs, urinalysis: No effects. Testing once every 3 months for 5 years.	Glover (1967)
NA	5-36	8 h/d 5 d/wk NS (occup)	Selenium dioxide NS	NS	Human (62) NS	Clinical signs: Slight tracheobronchitis reported in 9 workers.	Kinnigkeit (1962)
NA	0 >200	NS (occup)	NS	NS	Human (40) NS	Questionnaire, skin biopsy, biochemistry, pulmonary function, urinalysis: Clinical effects included nose and eye irritation, indigestion, stomach pain, fatigue, muscle joint pain, and sputum. Spirometry and ECG readings were normal. Anemia occurred, but iron levels were normal. Subjects also reported garlic-like breath odor. Note: Concurrent exposure to copper, nickel, silver, and trace levels of lead and arsenic.	Holness et al. (1989)

Abbreviations:

B = both males and females; d = day; ECG = electrocardiogram; h = hours; NA = not applicable; NS = not specified; occup = occupational; wk = week; wt = weight. occup = occupational; wk = week.

No studies were located regarding reproductive or developmental effects in humans following inhalation exposure to selenium or selenium compounds.

There are no epidemiological data that support a causal association between the inhalation of elemental selenium dusts or selenium compounds and the induction of cancer in humans (Gerhardsson et al., 1986; Wester et al., 1981). In a study by Gerhardsson et al. (1986), samples were collected postmortem from copper smelter workers who were exposed to several different airborne compounds, including selenium compounds. Samples from lung cancer cases had lower concentrations of selenium in lung tissue than samples from controls or from workers who had died from other causes. In another autopsy study of smelter workers, Wester et al. (1981) found that the selenium concentrations in kidney tissues from workers who had died of malignancies were lower than the selenium concentrations in kidney tissues from workers who died of other causes.

Laboratory Animal Data

Toxicity data for laboratory animals are available only for acute exposures and are summarized in Table 11-46. The respiratory tract is also the primary site of injury in experimental laboratory animals following inhalation exposure to selenium dust and hydrogen selenide. Hematological and hepatic effects have also been noted in animals.

Rats exposed to selenium dust at levels of 30,000 μg selenium/m^3 for 8 h experienced severe respiratory effects, including hemorrhage, edema, and chronic interstitial pneumonitis in the lungs (Hall et al., 1951). Rabbits and Guinea pigs inhaling selenium dust at similar concentrations for 8 days developed mild interstitial pneumonitis, vascular lymphocytic infiltration, increased number of alveolar macrophages, and slight emphysema (Hall et al., 1951).

Exposure to hydrogen selenide for 4 h produced respiratory irritation, diffuse bronchopneumonia, and pneumonitis in Guinea pigs (Dudley and Miller, 1941). Histologic examination of guinea pigs that had died following exposure to higher concentrations (21,450 μg/m^3) for 30 min revealed thickening of the alveolar walls and congestion of alveolar capillaries (Dudley and Miller, 1937).

Mild hepatic effects have been observed in animals following acute inhalation exposure to elemental selenium dust, hydrogen selenide, or dimethyl selenide vapor. One month after

TABLE 11-46. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR SELENIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Se/m^3$						
Acute Studies							
NA	30,000	8 h	Elemental selenium dust	MMAD = 1.2 μm	Rat, NS (20) F	Body wt, organ wt, gross and histopathology examination: Increased relative lung wt and pulmonary hemorrhage in two animals that died. After 3 wk postexposure, slight interstitial infiltration of lymphocytes and intraalveolar foci of large macrophages consistent with chronic interstitial pneumonitis. At 4 wk postexposure, slight liver congestion, with central atrophy. Note: No controls used.	Hall et al. (1951)
NA	31,000	4 h/2d 8 d	Elemental selenium dust	MMAD = 1.2 μm	Guinea pig, NS (10) M	Body wt, clinical signs, histopathology: After 1 or 3 wk postexposure, respiratory effects included mild chronic interstitial pneumonitis, pulmonary congestion, vascular lymphocytic infiltration, alveolar infiltration of large macrophages, and slight emphysema. Liver effects were congestion, central atrophy, and fatty metamorphosis. The spleen was congested, with fissuring of red pulp, and increased number of polymorphonuclear leukocytes. Note: No controls used.	Hall et al. (1951)

TABLE 11-46 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR SELENIUM AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Se/m^3						
NA	31,000	4 h/2d 8 d	Elemental selenium dust	MMAD = 1.2 μm	Rabbit, NS (6) F	Body wt, clinical signs, histopathology: After 1 or 3 wk postexposure, respiratory effects included mild chronic interstitial pneumonitis, pulmonary congestion, vascular lymphocytic infiltration, alveolar infiltration of large macrophages, and slight emphysema. No other effects were reported. Note: No controls used.	Hall et al. (1951)
0 1607 4499 8034	0 5,190,000 14,540,000 25,960,000	1 h (nose-only)	Dimethyl selenide vapor	NA	Rats, F344 (20) M	Body and organ wts, microscopic examination of lung, liver, kidney, spleen, thymus, lymph nodes, pancreas, and adrenal gland: Increased relative lung wt at low and high concentrations and increased liver wt at two highest concentrations.	Al-Bayati et al. (1992)
NA	7,800	4 h (1 h-60 d postexposure)	Hydrogen selenide	NS	Guinea pig, NS (16) NS	Histopathology: Fatty metamorphosis and increased weight in liver were reported. Respiratory effects included pneumonitis, diffuse bronchopneumonia, and irritation. Spleen effects included lymphoid hyperplasia and delayed increase in reticuloendothelial tissue. Note: No controls used.	Dudley and Miller (1941)
NA	21,450	30 min	Hydrogen selenide	NS	Guinea pig, NS (80) NS	Clinical signs, organ HP: Death in 47 of 80 animals. Examination of these animals indicated increased liver and spleen wts, fatty metamorphosis of kidney and liver, centrilobular atrophy of liver, and increased reticuloendothelial tissue in splenic pulp. Respiratory effects included thickening of alveolar wall and congestion of alveolar capillaries.	Dudley and Miller (1937)

TABLE 11-46 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR SELENIUM AND COMPOUNDS

Exposure Concentration		Exposure Protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Se/m^3$						
NA	0 6,000 7,000 12,000 15,000 44,000	4 h	Hydrogen selenide	NS	Guinea pig, NS (16) NS	Clinical signs and body wt: Slight nasal discharge occurred at <20 $\mu g/kg$, and nose and eye irritation and breathing difficulties at >20 $\mu g/kg$.	Dudley and Miller (1941)
NA	0 1,000 4,000 6,000 7,000 41,000	8 h	Hydrogen selenide	NS	Guinea pig, NS (16) NS	Clinical signs and body wt: Slight nasal discharge occurred at <20 $\mu g/kg$, and nose and eye irritation and breathing difficulties at >20 $\mu g/kg$.	Dudley and Miller (1941)
NA	0 6,000 12,000 13,000 20,000 33,000 35,000	2 h	Hydrogen selenide	NS	Guinea pig, NS (16) NS	Clinical signs and body wt: Slight nasal discharge occurred at <20 $\mu g/kg$, and nose and eye irritation and breathing difficulties at >20 $\mu g/kg$.	Dudley and Miller (1941)

Abbreviations:

B = males and females; d = day; h = hours; F = female; MMAD = mass median aerodynamic diameter; M = male; NA = not applicable; NS = not specified; occup = occupational; wk = week; wt = weight; wk = week; wt = weight.

an 8-h exposure to elemental selenium dust at a concentration of 30,000 μg selenium/m^3, rats exhibited slight liver congestion and a few exhibited mild central atrophy of the liver (Hall et al., 1951). Three weeks following acute exposure to higher concentration of elemental selenium dust for 8 days, guinea pigs had slight hepatic congestion with mild central atrophy and fatty metamorphosis (Dudley and Miller, 1941). Exposure to hydrogen selenide (7,800 μg selenium/m^3) for 4 h in guinea pigs produced mild fatty metamorphosis in the liver (Dudley and Miller, 1941). Al-Bayati et al. (1992) reported increased liver weight in rats exposed to high concentrations of dimethyl selenide vapor ($\geq$14,540,000 μg selenium/m^3) for an hour; however, no histopathological changes were exhibited in the liver.

In Guinea pigs, splenic effects (congestion, fissuring red pulp, and increased polymorphonuclear leukocytes) has been observed following acute exposure to elemental selenium dust (Hall et al., 1951).

There were no studies available on the reproductive or developmental effects of selenium in laboratory animals following inhalation exposure. Cancer data in laboratory animals are also lacking for selenium.

11.6.17.4 Factors Affecting Susceptibility

Data concerning human subpopulations with unusual susceptibility to the toxic effects of selenium were not located. It is likely that individuals with preexisting respiratory conditions would be more susceptible than the healthy individuals to the respiratory tract effects (e.g., irritation, bronchitis) of selenium (Middleton 1947; Pringle 1942; Wilson 1962). The developing respiratory tract of children may also be more susceptible.

Pregnant women and their fetuses might be at greater risk of adverse health effects from excess selenium exposure than the general population. Doses of 500 μg selenium/kg/day have been reported to reduce birthweight in mice (Schroeder and Mitchener 1971) without producing signs of maternal toxicity.

11.6.18 Tin

11.6.18.1 Chemical and Physical Properties

Tin, a metallic element, is a member of Group 4A of the periodic table. It exhibits three valence states, 0, +1, and +2 and readily forms compounds in both the stannous(+2)

and stannic(+4) states (Agency for Toxic Substances and Disease Registry, 1992). When metallic tin (oxidation state 0) is exposed to oxygen or dry air, a thin oxide film forms on its surface. This oxidation process is accelerated in the presence of heat (Gitlitz and Moran, 1983). In environmental waters, tin may exist as either Sn^{2+} or Sn^{4+}, with the stannous tin (Sn^{2+}) ion dominating in oxygen poor water (Agency for Toxic Substances and Disease Registry, 1992). Tin occurs naturally in the environment in both inorganic compounds, and in organotin compounds, the oxidation state of the tin species in the latter almost always being +4 (Gitlitz and Moran, 1983). Elemental tin is insoluble in water, as are both of its oxides: stannic oxide (SnO_2) and stannous oxide (SnO).

11.6.18.2 Pharmacokinetics

Inorganic Tin

Very little information was located regarding the absorption, distribution, metabolism, and excretion of inhaled tin in humans or animals. However, studies on the health effects of tin inhalation show that inhaled tin accumulates in the lungs. There was no clear evidence regarding whether tin is absorbed from the lungs into the bloodstream, but since tin and its oxides are insoluble, any absorption would be expected to be minimal. Teraoka (1981) observed that chromium refining and chromate refining workers had higher levels of tin in the lungs and hilar lymph nodes than did normal controls. Neither the source nor level of tin exposure were reported. In an early case study of stannosis (tin-associated pneumoconiosis), tin levels were highest in the lungs (Dundon and Hughes, 1950). Tin concentrations were higher in the spleen and liver than in the bone. Oral data indicate that tin is either poorly absorbed or rapidly excreted in the feces (Calloway and McMullen, 1966).

In a study of about 160 human maternal-fetal pairs, tin levels were slightly higher in the cord blood and placenta than in maternal blood, indicating that tin can cross the placenta (Creason et al., 1976). Levels in scalp and pubic hair (≈ 1 μg/g) were higher than in maternal and cord blood (≈ 5 μg/mL).

Organic Tin

Data are also limited regarding the pharmacokinetics of inhalation exposure to organotin compounds. Although no human or animal data were located regarding the rate or extent of

absorption of organotin compounds, the observation of urinary tin and nervous disorders in workers exposed to a mixture of di- and trimethyltin chloride (Rey et al., 1984) indicates that tin is absorbed from the lung to some degree. Similarly, the observation of systemic effects in animals following inhalation exposure to organotin compounds (Gohlke et al., 1969; Igarashi, 1959; Iwamoto, 1960) indicates that these compounds are absorbed from the lung. No other data regarding the distribution, metabolism, or excretion of absorbed organotin compounds were located. Data from other routes of exposure indicate that absorbed organotin compounds accumulate to some degree in the kidney, liver, and brain; metabolism may occur via oxidative mechanisms (Agency for Toxic Substances and Disease Registry, 1992; Iwai, 1981).

11.6.18.3 Health Effects

Inorganic Tin

Human Data. The primary health effect of inhalation exposure to tin or its oxide is stannosis, a rare pneumoconiosis characterized by dense mottling of the lungs. These effects are summarized in Table 11-47. Slightly more than 150 cases have been reported in the world literature, of which only five were in the United States (American Conference of Governmental Industrial Hygienists, 1991). Investigations of stannosis are limited to case studies, mostly from the 1940s and 1950s. Exposure levels were reported in only two studies (Cutter et al., 1949; Oyanguren et al., 1958). Because many studies reported the form of tin only as tin oxide, it is unclear whether stannosis results only from stannic oxide exposure or also from exposure to stannous oxide. Both fumes and dust of tin oxide can cause stannosis.

Most cases of stannosis are reported as asymptomatic, although dyspnea has been reported in a few cases (Cole et al., 1964; Spencer and Wycoff, 1954). Fibrosis has never been reported, and respiratory impairment is generally mild, so this disease is referred to in the literature as a "benign pneumoconiosis." However, mild adverse health effects as a result of employment were more acceptable at the time of these reports than in today's society. Therefore, while severe impairment clearly did not occur in the reported stannosis cases, any observed mild impairments might be given more weight today. In particular,

TABLE 11-47. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR TIN AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration μg Sn/m^3	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Inorganic Tin							
N/A	8,600, 14,900	<3 to >12 yr occup	Tin oxide fume, dust 58.4% metallic Sn, 0.07% soluble Sn, 9.7% Fe 2.0% S, 1.0% SiO_2, 28% unidentified	NS	Human (19) M	Case studies; x-ray, lung function, urinalysis, hematology, ECG: Based on x-ray findings, 8/9 subjects exposed <3 yr had suspected stannosis. Longer exposures led to stage 1 through stage 3 stannosis. No effect on resting ventilation, VC, maximum breath capacity, or ventilation reserve. No other findings. Note: Workers selected based on exposure to tin oxide fumes and dust.	Oyanguren et al. (1958); Schuler et al. (1958)
N/A	8- >50 mp/cf	20-24 yr occup	96-98% SnO_2, 0.4% SiO_2 dust	<2 μm, "but there was a strong tendency toward agglomeration, so some particle groups >10 μm" other area--99% <3 μm	Human (2) M	Case study; x-ray: No respiratory symptoms. Pulmonary nodulation. Expiratory rales in one subject. Note: Reported exposure on weighted average basis. Higher levels were at earlier periods. Concentration reported as dust counts.	Cutter et al. (1949)
N/A	NS	>3 yr occup	"Cassiterite, mainly tin oxide" dust; fume-- SnO_2	"EM shows a small size and denseness of particles"	Human (215) M	Physical exam, x-ray, chest expansion and VC measurement: Radiological changes found in 121/215 exposed workers. Changes range from faint mottling to gross dense modulation. Fewer opacities in those with shorter or lower exposure. No clinical signs referable to pneumoconiosis. Changes found in those exposed to only dust or only fume. Note: Sampling of particles in air $\leq$5 μm showed dust was >33% metallic tin.	Robertson and Whitaker (1954); Robertson (1960)

TABLE 11-47 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR TIN AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sn/m^3$						
N/A	NS	11-46 yr occup	Tin oxide dust, SnO_2 fume	NS	Human (7) M	Case studies; HP of lung, clinical signs of respiratory impairment: Radiological evidence of pneumoconiosis in all. Films of those exposed mostly to SnO_2 fume showed nodular appearance with opacities. Dust foci were dense aggregates of dust-laden macrophages surrounding the respiratory bronchioles or lying free in alveoli. No fibrous nodules. Note: Analysis of dust from ashed lungs showed particles of 0.1-0.5 μm, resembling furnace fume.	Robertson et al. (1961)
N/A	NS	18 yr occup	SnO_2 fume, dust	NS	Human (1) M	Case study; x-ray, physical exam, HP of lung: Mottling of lung fields, incident of epigastric pain and vomiting, sharp chest pain on deep inspiration, dec VC (85% normal). No evidence of enlarged hilar lymph nodes, no subjective respiratory complaints. Pigment-choked lymphatic channels. Note: 1,100 μg Sn/g wet lung tissue.	Dundon and Hughes (1950)
N/A	NS	15-26 yr occup	SnO_2 fumes	NS	Human (2) M	Case studies; x-ray, lung function, lung biopsy: Numerous small nodules in lung, no effect on FVC or FEV_1. Focal aggregations of macrophages containing dust particles in perivascular and peribronchiolar connective tissue.	Sluis-Cremer et al. (1989)
N/A	NS	15 yr occup	Tin oxide dust	NS	Human (1) M	Case study; x-ray: Discrete densities in both lungs, opaque material in hilar lymph nodes, no fibrous tissue.	Pendergrass and Pryde (1948)

TABLE 11-47 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR TIN AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Sn/m^3$						
N/A	NS	15-60 yr occup	"Tin oxide" form, valence NS	NS	Human (10) M	X-ray, clinical exam, HP of lung; case reports of stannosis victims: Micronodular opacities or other dense opacities in all cases. Honeycomb lung (in one case), dyspnea. HP of one case found dilation of the bronchia and bronchioles, black dust-pigmented interstitial fibrosis, and squamous hyperplasia and metaplasia of bronchial and bronchiolar epithelium. Carcinoma in one case. Note: Fibrosis was found in one man, but he may have been exposed to other types of dust.	Cole et al. (1964)
Organic Tin							
N/A	200	"short-term" occup	Organotin com-pounds (not further specified)	UK	Human (UK)	Headaches, upper respiratory tract irritation.	American Conference of Governmental Industrial Hygienists (1991)
N/A	190, 290	NS occup	Bis(tributyl tin) oxide	UK	Human (UK)	Irritation of the upper respiratory tract and eyes of 70% of exposed workers.	National Institute for Occupational Safety and Health (1976)

[1]Not identified; presumably million particles per cubic foot.
[2]Presumably reported as concentration of tin.

Abbreviations:

dec = decreased; ECG = electrocardiogram; EM = electron microscopy; Fe = iron; FEV_1 = forced expiratory flow in 1 second; FSH = follicle stimulating hormone; FVC = forced vital capacity; ; HP = histopathology; N/A = not applicable; NS = not specified; occup = occupational; S = sulfur; SiO_2 = silicon dioxide; Sn = tin; SnO_2 = stannous oxide; UK = unknown, not reported in available secondary source; VC = vital capacity; yr = year

choking of the lymphatic channels (Dundon and Hughes, 1950) might exacerbate infectious respiratory disease. Stannosis has not been reported to progress or to be reversible.

Stannosis is usually identified by chest x-rays performed on workers in tin foundries or other places where they work with tin or its dusts. Robertson and Whitaker (1954) reported asymptomatic radiological changes in the chests of 121 of 215 tin refinery workers and retirees. The physical examination included chest expansion and vital capacity measurements, and was conducted on >95% of the people who had worked at the refinery for at least 3 years. The radiological changes were characterized by small dense opacities. The degree of pneumoconiosis correlated with the dustiness of the job held and the duration of exposure, but no measurement was made of exposure level (Robertson, 1960). Analysis of the dust particles small enough to be inhaled into the alveoli (<5 microns) determined that they contained no silica and >33% metallic tin. In spite of the marked radiological changes, there was no increase in absences due to chest illness, sensitivity to tuberculosis, and no effect was observed in the clinical examination. The possibility of a delayed effect was also discounted but not eliminated, since the study group included workers with gross radiological changes who had been retired for >20 years. The study authors noted that the high atomic weight of tin (118.7) makes it very radio-opaque, so that inhalation of relatively small amounts is radiologically detectable. Histological analysis of the lungs of two tin workers who died of unspecified (but apparently unrelated) causes showed alveoli filled with dust cells, but no evidence of fibrosis. The results from the autopsies of seven workers suggested that the extent of radiological change in the lung correlated with the amount of tin dioxide in the lung (Robertson et al., 1961).

Schuler et al. (1958) observed pneumoconiosis in 10/19 workers exposed to tin oxide fumes or dust at a tin foundry. No adverse effects were observed on vital capacity, maximum breath capacity, ventilation reserve, or resting ventilation. The most severe cases of stannosis occurred in workers exposed to tin oxide fumes, but it is not clear if they were exposed for more years. No personal monitoring was done, but levels of tin fumes measured in two work areas were 14,900 and 8600 $\mu g/m^3$, respectively (Oyanguren et al., 1958). Small amount of lead, zinc, and iron fumes were also present.

Ten cases of stannosis in hearth tinners, who are exposed only to tin fumes, and not tin dust, were reported by Cole et al. (1964). The subjects had worked as tinners for 15–60

years. Although no respiratory disablement was reported for most of the cases, pulmonary lesions were reported in three cases. A man who had worked as a tinner for 19 years had honeycomb lung. Prior to death, he suffered from dyspnea. Post-mortem examination revealed dilation of the bronchia and bronchioles, black dust-pigmented interstitial fibrosis, and squamous hyperplasia and metaplasia of bronchial and bronchiolar epithelium. Fibrosis was found in a second man, but he may have been exposed to other types of dust. One man who worked for 50 years as a tinner developed carcinoma of the lung. Honeycomb lung is not commonly associated with stannosis, and was not observed by Robertson and Whitaker (1954) in 121 stannosis cases.

Pendergrass and Pryde (1948) reported one of the earliest cases of stannosis, in a man who had bagged tin oxide for 15 years. Although the study authors stated that there was no disability associated with the radiographic abnormalities, they also reported that the domes of the diaphragm scarcely moved. No silica was found in the tin oxide dust. Cutter et al. (1949) reported asymptomatic stannosis in both of the employees performing dusty work in a tin oxide recovery plant. Both workers had been exposed for about 20 years, but the subject with the heavier deposits had lower total exposure, although he may have been exposed to a higher percentage of tin as fumes. Time-weighted average exposure was estimated at 8 mp/cf (presumably million particles per cubic foot) per 8-h day for the previous few years, and >50 mp/cf in prior years.

Asymptomatic stannosis was reported in a worker exposed for 18 years to tin oxide fumes and dust (Dundon and Hughes, 1950). Dry lung tissue contained 1.15% tin, about 2500 times the normal level. X-ray diffraction analysis confirmed that tin was the only metal or mineral present. Lymphatic channels were choked with pigment. No recent reports of stannosis cases in the United States were located. However, a recent article reported two cases of radiologically-diagnosed stannosis in South Africa (Sluis-Cremer et al. 1989). One man was exposed to tin fumes and coal dust for 15 years, the other to tin fumes for 26 years. There was no effect on the forced vital capacity or the forced expiratory volume of the first second (FEV_1). Basal crackles on auscultation and a minor cough were present, although they may have resulted from the exposure to coal dust. Dust deposits in the air spaces of a biopsied lung sample were not associated with collagen deposition.

Extensive fibrosis (dense mottling) may occur together with only mild functional impairment. A worker who was exposed to tin oxide as a smelter and a bagger for 22 years developed slight dyspnea and slightly impaired vital capacity (70% of normal) (Spencer and Wycoff, 1954).

No data were located regarding reproductive, developmental, or carcinogenic effects of inorganic tin in humans.

Laboratory Animal Data. As a crude animal model of stannosis, 50,000 μg of tin dust in saline was injected into the trachea of an unspecified number of rats and "blown into their lungs" (Robertson, 1960). No other experimental details were provided. The dust was collected from the sampling room of a tin smelter, and sized to contain only particles ≤5 microns. The lungs of the rats resembled the lungs of the tin workers, with small, high-density foci. Histological examination revealed dust cells lining alveoli, and phagocytes containing tin particles. Tin particles were also found in the subpleural lymphatics and the mediastinal lymph glands. No other pathology or histopathology data were reported. Tin particles were found in the lungs, spleen, and liver of mice injected intravenously with 5000 μg/animal tin dust. Pendergrass and Pryde (1948) injected a branch artery to one lobe of a freshly excised dog lung with a saline suspension of tin oxide, and observed discrete opacities similar to those seen in a worker with tin pneumoconiosis. These experiments show that tin oxide alone can cause the radiographic abnormalities characteristic of stannosis.

No data were located regarding reproductive, developmental, or carcinogenic effects of inorganic tin in animals.

Organic Tin

Human Data. Limited data suggest that the nervous system, liver, and kidney are the major targets of organotin inhalation in humans; higher levels also affect the lungs. Data are limited to a few case reports. Nervous symptoms (headache, tinnitus, deafness, impaired memory, disorientation, "dreamy [epileptic equivalent] attacks," and loss of consciousness) were observed after a latent period of 1 to 3 days in a group of 6 chemical workers exposed to a 50 to 50 mixture in air of di- and trimethyltin chloride (Rey et al., 1984). Exposure levels were not determined, but the maximal exposure duration was reported as nine 10-min

exposures in 3 days. Respiratory depression was reported in the most severe cases. Elevated levels of serum transaminases, indicative of liver damage, were also reported in the more severe cases. Urinary tin correlated with the severity of symptoms. Anuria was reported in one patient who died; histological analysis revealed fatty degeneration and necrosis of liver cells, shock kidneys (i.e., proximal tubule degeneration), and cerebral edema. Nervous symptoms continued for at least 6 mo postexposure in the two highest-exposed workers who survived.

In another case report, two chemists exposed to di- and trimethyltin chloride over a 3-mo period also reported nervous system symptoms, including seizures, headaches, memory defects, and loss of vigilance (Fortemps et al., 1978). Breathlessness and anorexia were also reported. Full recovery required approximately one year after exposure ceased.

American Conference of Governmental Industrial Hygienists, (1991) described two unpublished reports of organotin exposure concentrations resulting in symptoms. The first report was described by the National Institute for Occupational Safety and Health, (1976), and reported irritation of the upper respiratory tract and eyes in 70% of workers exposed to bis(tributyltin) oxide at 190 to 290 μg tin/m^3 at two buffing operation sites. A letter to ACGIH reported headaches and respiratory tract irritation following "short-term" exposures to organotin compounds at levels above 200 μg/m^3. In another case report, inhalation exposure to tributyltin oxide at undetermined levels resulted in asthma; a controlled challenge experiment confirmed the relationship to tin exposure (Shelton et al., 1992).

Laboratory Animal Data. Laboratory animal data, Table 11-48, support the hepatic, renal, and respiratory systems as targets of organotin toxicity. Data are too limited to make comparisons between the inhalation toxicity of different organotin compounds. However, oral data suggest that once organotin compounds are absorbed, toxicity within a class of compounds is higher for lower homologs, e.g., among trialkyltin compounds, trimethyltin and triethyltin are the most toxic (American Conference of Governmental Industrial Hygienists, 1991). Experimental details are also lacking for most organotin inhalation studies, because they were published in foreign languages, and only summaries from secondary sources are available.

TABLE 11-48. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR TIN AND COMPOUNDS

Exposure Concentration ppm	Exposure Concentration μg Sn/m^3	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Organic Tin							
0 0.44 1.2	0 2,120 5,650	7 h/d 6 d	Tributyltin bromide (1.1 ppm), dibutyltin bromide (0.06 ppm)	UK	Mouse, UK (UK)	HP of kidney, brain: Slight degenerative changes in the glomeruli, convoluted tubules, and collecting tubules, as well as extramedullary hematopoiesis. No brain histopathology.	Igarashi (1959)
0 0.41	0 2,000	5 h/d 10-80 d	Tributyltin dibromide (0.39 ppm), dibutyltin bromide (0.02 ppm)	UK	Rat, UK (UK)	HP of lungs, heart, liver, kidney, spleen, reproductive organs; reproductive function: At 80 d, severe bronchitis and vascular and alveolar edema of lungs observed in exposed animals. Also observed at this sacrifice time: mycardial atrophy, atrophy and necrosis of liver, extensive congestion and swelling of the renal tubular epithelium, and splenic hyperplasia and thickened sheaths. Pregnancy rate also reduced after 4 wk-3 mo of exposure (other measure of reproductive success not reported). Atrophy of glandular uterus at 14 d.	Iwamoto (1960)
0 0.30 0.45	0 1,460 2,190	6 h/d 95 d	Tributyltin chloride	UK	Rat, Albino (10) NS	HP of lung, liver: At low level, lung hyperemia, catarrhal bronchitis, minor fatty degeneration of the liver. Also inflamed eyes, and nostrils, probably due to direct contact.	Gohlke et al. (1969)
0 0.41	0 2,000	5 h/d 10 d	Tributyltin dibromide (0.39 ppm), dibutyltin bromide (0.02 ppm)	UK	Rat, UK (UK)	Reproductive function: 40% dec in "reproduction" (not further defined).	Iwamoto (1960)

Abbreviations:

d = day(s); dec = decrease; HP = histopathology; UK = unknown, not reported in available secondary source.

Inflammatory changes (hyperemia and bronchitis) were observed in the respiratory system of rats exposed to 1,460 to 2,190 μg tin/m^3 as tributyltin chloride for 95 days (Gohlke et al., 1969). In an experiment where rats were exposed for 80 days to 2,000 μg tin/m^3 (0.41 ppm) as a mixture of tributyltin dibromide (0.39 ppm), dibutyltin bromide (0.02 ppm), and hydrocarbon impurities, histopathological changes were reported as severe bronchitis and vascular and alveolar edema (Iwamoto, 1960).

Gohlke et al. (1969) also observed histological changes of the liver, consisting of fatty degeneration, in the experiment described above. Iwamoto (1960) reported atrophy and slight necrosis of the liver in rats exposed to 2,000 μg tin/m^3 as di- and tributyltin dibromide. Atrophy increased with exposure duration and some recovery occurred if exposure was stopped prior to sacrifice.

Mice exposed to 5,650 μg tin/m^3 as a mixture of tributyltin bromide (1.1 ppm), dibutyltin bromide (0.06 ppm), and hydrocarbon impurities for 7 h/day over 6 days had pathological changes in the kidney (Igarashi, 1959). The changes consisted of slight degenerative changes in the glomeruli, convoluted tubules, and collecting tubules, as well as extramedullary hematopoiesis. More extensive kidney damage (extensive congestion and swelling of the renal tubular epithelium) was observed in rats exposed to 2,000 μg tin/m^3 for 80 days, as described above (Iwamoto, 1960).

No studies that conducted standard neurological tests on animals exposed to organotin compounds were located. There was no evidence of histopathology in the brains of mice exposed for 6 days to 2,120 μg tin/m^3 as a mixture of di- and tributyltin bromide (Igarashi, 1959).

Reproductive data are limited to one study in which rats were exposed to 2000 μg tin/m^3 as a mixture of tributyltin bromide and dibutyltin dibromide (Iwamoto, 1960). A reversible decrease in pregnancy rates was observed after 4 weeks to 3 mo of exposure. Histologically, atrophy of the glandular uterus was observed as early as 14 days of exposure. No further reproductive data were provided. No studies were located that assessed developmental effects of the inhalation of organotin compounds in laboratory animals.

11.6.18.4 Factors Affecting Susceptibility

The limited inhalation data available on inorganic tin suggest that the respiratory tract is the target organ and therefore, individuals with respiratory system impairments may be at greater risk for toxicological effects. The developing respiratory tract of children may also pose an increased susceptibility. The limited data do not provide indications of any other susceptibility factors for inorganic tin.

The inhalation of organic tin may affect not only the respiratory tract, but also the nervous, hepatic, and renal systems, as well as causing teratogenic effects. Therefore, individuals with respiratory impairment, liver disease, kidney disease, or neurological disorders may be at greater risk for adverse health effects following the inhalation of organic tin compounds. The developing respiratory tract of children may also pose an increased susceptibility. In addition, limited animal data (Iwamoto, 1960) suggest that pregnant women and their fetuses may also be at greater risk for toxicological effects.

11.6.19 Titanium

11.6.19.1 Chemical and Physical Properties

Titanium, a dark gray lustrous metal, is the first member of Group IVB of the periodic system of elements. It has three valence states, +2, +3, and +4, of which titanium(+4) is the most stable (Hazardous Substances Data Bank [Data Base], 1995; Whitehead, 1983). The lower valence states of +2 and +3 are less common and are readily oxidized to the tetravalent state by air, water, and other oxidizing agents (Whitehead, 1983). Titanium forms organometallic compounds primarily in the tetravalent state. Trivalent titanium organic compounds and complexes are stable at room temperature, although most of them are attacked by oxygen and moisture (Rondestvedt, 1983). Titanium(+2) organic compounds are less common, and both titanium(+2) and titanium(0) organic compounds are potent reducing agents (Rondestvedt, 1983). Upon contact with moist air, titanium tetrachloride hydrolyzes with fuming to form a vapor of hydrochloric acid, titanium dioxide, and titanium oxychloride (Whitehead, 1983; Wilms et al., 1992). Elemental titanium is insoluble in water, as are the dioxide (TiO_2) and disulfate $Ti(SO_4)$ O_2 compounds. Titanium tetrachloride ($TiCl_4$) is soluble in cold water, but decomposes in hot water, whereas titanocene dichloride, $(C_5H_5)_2$

TiCl is sparingly soluble in water and tetrabutyl titanate, $Ti(C_4H_{10})$, reacts with water to form butanol and TiO_2.

11.6.19.2 Pharmacokinetics

Few studies were located regarding absorption, distribution, metabolism, or excretion of titanium or titanium compounds in humans or laboratory animals following inhalation exposure. The titanium compounds with the most toxicity data available are titanium dioxide and titanium tetrachloride. Titanium dioxide has low solubility and is deposited in the lung upon inhalation. Titanium tetrachloride hydrolyzes upon contact with moist air to form a vapor of hydrochloric acid, titanium dioxide, and titanium oxychloride (Whitehead, 1983; Wilms et al., 1992). The major route of exposure for titanium tetrachloride is by inhalation, and the major target organ is the lung. Particles of metallic titanium have been found in the lungs of occupationally exposed individuals (Elo et al., 1972; Ophus et al., 1979; Redline et al., 1986).

Titanium Dioxide

Titanium dioxide (as ultrafine particles of $\approx$20 nm) may enter the pulmonary interstitial space of the lungs and elicit an inflammatory response as a result of phagocytosis by alveolar macrophages. This in turn, may attract polymorphonuclear neutrophils to the interstitium. Within 24 h of titanium dioxide inhalation, the titanium particles are contained in the phagocytes and are transported by mucociliary action in the lungs; within 25 days after exposure, the phagocytes contain only a very few titanium particles and approximately 40% of the initial deposition is removed from the lungs via the airway (Ferin, 1976). Titanium dioxide deposited in the lungs is not translocated to other tissues even after 25 days (Ferin, 1976). Data from exposure of rats to 57,000 $\mu g/m^3$ titanium dioxide for 2 h showed that titanium dioxide concentrations increased in the lungs throughout the exposure period and slowly decreased thereafter (Ferin, 1970).

Following chronic inhalation exposure to titanium dioxide, metallic particulates have been found in lysosomes of phagocytes within the alveolar lumen (Elo et al., 1972). Rats exposed to titanium dioxide (concentration unspecified) for 2 h showed no titanium in the

blood, heart, liver, kidney or spleen; titanium found in the gastrointestinal tract was related to the titanium content of the food (Ferin, 1970).

Titanium Tetrachloride

The pharmacokinetics of titanium tetrachloride are largely determined by its chemical properties and by the pharmacokinetics of its hydrolysis products. Titanium tetrachloride is rapidly hydrolyzed upon contact with moisture because of its instability in the presence of water and heat. One hydrolysis product, hydrochloric acid, is largely responsible for the corrosive effects observed following exposure to titanium tetrachloride. Because the mechanism of action of titanium tetrachloride is so closely tied to its pharmacokinetics, both topics will be discussed in this section.

A study comparing the effects of titanium tetrachloride and hydrochloric acid in mice after acute inhalation exposure found that the active component in both cases was hydrochloric acid, and that effects were more severe following titanium tetrachloride exposure than following hydrochloric acid exposure (Mezentseva et al., 1967). The difference in severity is thought to be due to the high solubility of hydrochloric acid, which dissolves in the moisture of the nasopharynx and trachea and thus penetrates into the lungs to only a very limited extent. Because titanium tetrachloride is less soluble, it penetrates deeper into the lungs before being hydrolyzed. Titanium tetrachloride hydrolysis occurs via a two-stage exothermic reaction. First, titanium tetrachloride condenses into fine droplets that form a highly dispersed particulate smoke. This hygroscopic smoke then reacts with the moisture in the air to form secondary smoke, which contains various hydrolytic products of titanium tetrachloride (e.g., hydrochloric acid, titanium oxychloride, and titanium dioxide). One hydrolysis product, titanium oxide hydrate, is a particulate that adsorbs some of the hydrochloric acid vapors generated during hydrolysis and carries them into the deeper parts of the lungs. In the lungs, the hydrolysis process is repeated with the further release of hydrochloric acid, ultimately resulting in a larger amount of hydrochloric acid being carried deeper into the lungs and alveoli (Mezentseva et al., 1967). Titanium tetrachloride is not dermally absorbed; rather it hydrolyzes upon contact with the skin with the hydrochloric acid causing burns.

11.6.19.3 Health Effects

Studies regarding the effects on humans and animals following inhalation to titanium and titanium compounds were largely limited to exposure to titanium dioxide and titanium tetrachloride. The major toxicity endpoint for titanium exposure in humans and laboratory animals appears to be the respiratory system. Inhalation toxicity data for humans are summarized in Table 11-49. The laboratory animal data are summarized in Table 11-50.

Titanium Dioxide

Human Data. Occupational exposure to titanium dioxide has been linked to pneumoconiosis in workers. Of 197 workers in a titanium dioxide plant assessed spirometrically, 47% had some level of airway obstruction. Furthermore, 38% of those who had never smoked and had more than 20 years of exposure had airflow impairment. Of the 201 workers who were examined radiologically, 13% had irregular or nodular interstitial opacities. These data suggest that radiologic signs of pneumoconiosis from titanium are less sensitive than measures of pulmonary function (Daum et al., 1977).

An epidemiologic study of 1,576 active and terminated workers exposed to titanium dioxide for more than one year assessed the incidence of various types of cancer and of chronic respiratory disease. Exposure was estimated and subjects were grouped by cumulative exposure indices. Chest roentgenograms of 398 active workers showed that titanium dioxide exposure was not associated with pleural thickening or plaques; no pulmonary fibrosis was seen among the exposed workers. There was no correlation between incidence of chronic respiratory disease or pleural thickening and cumulative exposure index. There was also no relation between exposure and total cancer or lung cancer incidence, and no increase in cancer compared to the expected values for the general company cohort or for the general population (Chen and Fayerweather, 1988).

In a study of three workers who worked for 9 to 10 years in a titanium dioxide processing factory, electron microscopy and spectrometric and spectrographic analyses of lung tissue showed the presence of considerable amounts of titanium (Elo et al., 1972). Electron microscopy first identified 0.1 to 0.4 μm diameter black particles in the lysosomes of phagocytic cells filling the alveolar lumen. Large quantities of titanium were also present in the lymph nodes.

TABLE 11-49. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR TITANIUM AND TITANIUM COMPOUNDS[a]

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Ti/m^3$						
Acute Studies							
NS	NS	Single exposure accident	$TiCl_4$ vapor	NS	Human (1) M	CS: Case study of accidental spraying of $TiCl_4$ over head, chest, neck and back; CS: 25% second and third degree burns over chest, back, abdomen, arms, scalp due to dermal exposure. Erythema of tongue, pharynx, and conjunctivae; shallow breathing, agitation, confusion, upper airway stridor. Within 48 h of exposure, progressive hypoxia and diffuse pulmonary infiltrates characteristic of resp distress syndrome. Fiberoptic bronchoscopy revealed erythema of entire bronchial tree with 35–40 fleshy polypoid lesions.	Park et al. (1984)
Chronic Human							
NA	0-1,000 1,000-4,000 4,000-9,000 9,000-20,000 >20,000 (est)	>1 yr occup	TiO_2 dust	NS	Human (1,576) M	Medical history, chest x-ray, lung cancer incidence and mortality, incidence of total and other individual cancers: No association between exposure and increased cancer, chronic respiratory disease, or pleural thickening/plaques.	Chen and Fayerweather (1988)
NA	NS	9–10 yr	TiO_2 dust	NS	Human (3) M	HP of lung, CS: Recurrent bronchitis, dyspnea. HP showed carbon-like, birefractive pigment aggregations forming extensive patches under the pleura. Pigment-containing phagocytes filled some of the alveolar lumina; dense pigment accumulation present in perivascular and peribronchial sites; slight inc in connective tissue in pleura, subpleural, and alveolar septa. Lysosome-filled phagocytes within alveolar lumen containing black (0.1-0.4μm diameter) particles.	Elo et al. (1972)

TABLE 11-49 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR TITANIUM AND TITANIUM COMPOUNDS[a]

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Ti/m^3						
NS	NS	3 yr	TiO_2 dust	NS	Human (1) M	Case study: Death by lung metastases from undifferentiated tumor in right ileal bone. Large amounts of white, birefractive pigments in all parts of lungs without obvious fibrotic changes, accumulated Ti-rich material in the perivascular areas of lung, crystal modification of titanium in form of rutile (biologically inert crystalline modification of Ti/TiO_2).	Ophus et al. (1979)
NS	NS	NS occup	Mixture of Ti, $TiCl_4$, TiO_2, HCl, NaCl vapor and particulates	TiO_2 particulates 200–2,800 $\mu g/m^3$	Human (209) M	Cough, phlegm production, chronic bronchitis, wheezing with dyspnea. Reduced pulmonary capacity of 24 ml/yr of occupational exposure, pleural disease (pleural plaques and diffuse pleural thickening). Data suggest no clear association between pleural thickening and reduced ventilatory capacity.	Garabrant et al. (1987)

Abbreviations:

avg = average; BC = blood chemistry; BW = body weight; cardio = cardiovascular; CS = clinical signs; d = day; est = estimated; F = female; G6P = glucose-6-phosphate dehydrogenase; gastro = gastrointestinal; h = hour; hemat = hematological; HP = histopathology; inc = increase; M = male; MMAD = mass median aerodynamic diameter; mo = month; musc/skel = musculoskeletal; N/A = not applicable; NS = not specified in the literature reviewed; occup = occupational; PF = pulmonary function; PMN = polymorphonuclear neutrophils; resp = respiratory; SD = Sprague-Dawley; sig = significant; UA = urinalysis; Ti = titanium; TiO_2 = titanium oxide; $TiCl_4$ = titanium tetrachloride; TiH_2 = titanium hydride; wk = week; yr = years.

TABLE 11-50. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR TITANIUM AND TITANIUM COMPOUNDS[a]

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Ti/m^3$						
Acute Studies							
NS	370,000 1,290,000 1,900,000 2,900,000	10 min	$TiCl_4$ aerosol	NS	Rat, SD (NS) F	HP, CS: Nasal discharge, dyspnea, swollen eyelids at 370; discrete inflammatory residue in the lungs, coarsened alveolar septa at 1290. Signs disappeared with 48–72 h following exposure. HP of lungs was normal when examined 7 days post exposure.	Karlsson et al. (1986)
Chronic Studies							
NS	0 60 600 6,000	6 h/d 5 d/wk 2 yr	$TiCl_4$ vapor	"Fine, round particles $<1\ \mu m$ in diameter and large aggregated particles up to 400 μm in diameter"	Rat, CR (100) M, (100) F	HP, CS: No changes in CS, BW, or excess mortality. Tracheitis and rhinitis at 0.06; increased incidence of foamy lung macrophages with increased $TiCl_4$ dust deposition at 0.6. Squamous cell carcinoma in lungs of 2/69 males and 3/74 females at 6. Pneumocyte hyperplasia in alveoli adjacent to alveolar ducts. No reported abnormal HP (lungs, trachea, thyroid, adrenal glands, testes, kidneys and other organs — not specified).	Du Pont (1986); Lee et al. (1986)
NS	0 60 600 6,000	6 h/d 5 d/wk 2 yr	$TiCl_4$ vapor	NS	Rat, CR-CD (100) M, (100) F	HP of respiratory tract: Differentiated squamous cell carcinoma in lungs of 3/150, keratinized squamous cell carcinoma in lungs of 2/150 at 10. Alveolar cell hyperplasia and particulate dust deposition in the alveoli and tracheobronchial lymph nodes at 1 and 10.	Du Pont (1984)

TABLE 11-50 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR TITANIUM AND TITANIUM COMPOUNDS[a]

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Ti/m^3						
NS	0 60 6,000 30,000 150,000	6 h/d 5 d/wk 2 yr	TiO_2	Dust: 1.5–1.7 μm MMAD; 84% <13 μm	Rats, Crl:CD (400) M, (400)F	CS: No change in body weight, morbidity, mortality at any concentration. Lung weights increased at 30,000 at 6 mo and at 3 mo at 150,000 $\mu g/m^3$. Gross pathology: few white foci in lung at 6,000 $\mu g/m^3$, number increased with increasing concentration, tracheobronchial lymph nodes were white, chalky, dry. Microscopic: lungs contained dust laden macrophages in alveoli at 6,000 $\mu g/m^3$, hyperplasia. At 30,000 $\mu g/m^3$ foamy macrophages with cholesterol granuloma, thickened alveolar wall, fibrosis, and bronchiolarization and alveolar proteinosis. At 150,000 $\mu g/m^3$, bronchioloalveolar adenomas and cystic keratinizing squamous carcinomas, no metastasis was seen.	Lee et al. (1986a)
NS	31,100–38,500 (avg. 34,500 as Ti)	4 h/d 30 d	Titan dust (48.9% Ti)	Dust: <2 μm (5.7%), 2–4 μm (10.9%), 4–6 μm (26.7%), 6–8 μm (16.6%), 8–10 μm (12.4%), 10–12 μm (7.2%), 12–14 μm (7.2%), 14–16 μm (3.7%), 16–18 μm (3.6%), 18–20 μm (1.3%), >20 μm (4.5%)	Rat (10) M	HP of respiratory tract: Cell infiltration in alveoli with pigmentation. No other histopathological changes were seen. Dust also contained iron, silicon, magnesium and other elements.	Shirakawa (1985)

TABLE 11-50 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR TITANIUM AND TITANIUM COMPOUNDS[a]

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Ti/m^3						
NS	492,000-523,000 (507,000 avg)	4 h/d 286 d	TiH_2	Dust: <1 μm (37.4%), 1-2 m 44.6%), 2–3 μm (8.5%), 3–4 μm (3.4%), 4–6 μm (3.0%), 6–23 μm (3.1%)	Rabbits (4) M/(4) F	HP of respiratory tract: Changes in lung with accumulation of phagocytes and macrophages, proliferation of connective tissue in alveolar wall, deposition of dust in lymph nodes and formation of irreversible dust foci. Reticulonodular shadowing evident at 5 mo.	Shirakawa (1985)
NS	10,800 (avg)	2 h/d 7-10 mo	Titan dust (48% Ti)	Dust: <1 μm (17.3%), 1-2 m (26.7%), 2-3 μm (21.3%), 3-4 μm (10.1%), 4-5 μm (3.0%), 5-6 μm (2.4%), >6 μm (19.2%)	Rat (9) M Rabbit (8) M	HP of respiratory tract: Moderate punctiform opacities indicative of pneumoconiosis seen in rabbits at 4–5 mo and in rats at 6 mo. Histopathology: increased phagocytes and macrophages containing dust particles, epithelial cell proliferation, hyperplasia of alveolar connective tissue, and dust foci. Similar changes seen in rats but with less dust in cells.	Shirakawa (1985)
NS	228 (avg)	4 h/d 7 mo	Titan dust (48% Ti)	Fine dust, <325 mesh	Rat (9) M Rabbit (8) M	Radiography of respiratory tract: nodular shadows seen in rabbits at 1 mo and in rats at 3 mo. Retention of dust in alveoli and lymph nodes, proliferation of alveolar walls, hyperplasia of connective tissue, adsorption of dust particles by phagocytes and macrophages	Shirakawa (1985)

Abbreviations:

avg = average; BC = blood chemistry; BW = body weight; cardio = cardiovascular; CS = clinical signs; d = day; est = estimated; F = female; G6P = glucose-6-phosphate dehydrogenase; gastro = gastrointestinal; h = hour; hemat = hematological; HP = histopathology; inc = increase; M = male; MMAD = mass median aerodynamic diameter; mo = month; musc/skel = musculoskeletal; N/A = not applicable; NS = not specified in the literature reviewed; occup = occupational; PF = pulmonary function; PMN = polymorphonuclear neutrophils; resp = respiratory; SD = Sprague-Dawley; sig = significant; UA = urinalysis; Ti = titanium; TiO_2 = titanium oxide; $TiCl_4$ = titanium tetrachloride; TiH_2 = titanium hydride; wk = week; yr = years.

Similar findings were made in the case of a 55-year-old man who worked for three years in a titanium pigment processing factory and died of lung metastasis from an undifferentiated tumor in the right ileal bone (Ophus et al., 1979). Macroscopic and microscopic examinations revealed large amounts of white, birefractive pigment in all parts of the lungs without obvious fibrotic changes. Further analysis confirmed the presence of titanium and occasionally iron, and also showed that the crystal modification of titanium was in the form of rutile, a mineral of titanium dioxide that also contains iron. An increased concentration of titanium dust particulates was found in the right middle lobe (43.3–49%) and lower lobe (39.2 to 47%), compared to $<0.2\%$ in the controls.

Redline et al. (1986) reported a case study of a 45-year-old man with granulomatous lung disease, who worked for 13 years as a furnace feeder in an aluminum smelting company. Scanning electron microscopy and energy dispersive x-ray analysis showed that the lung tissue biopsy from the lower right lobe contained 1.39×10^9 exogenous particulates per cm^3 of tissue (including titanium). Lymphocyte proliferative response indicated a sensitivity to titanium. This finding confirms the possibility of titanium deposition in the lung tissue following titanium dioxide inhalation and, in this case, supports the association of granulomatous lung disease with metallic particle deposition.

These studies indicate that titanium dioxide can be deposited in the lungs of occupationally exposed workers, and that these deposits do not necessarily cause histopathological changes. However, these deposits may cause local pulmonary tissue irritation, which may progress to pneumonocoisis.

No studies were located regarding reproductive or developmental effects in humans of inhalation exposure to titanium compounds.

Laboratory Animal Data. A study of rats receiving a single intratracheal dose of ultrafine ($\approx$20 nm) titanium dioxide particles in saline indicated that these ultrafine particles enter the interstitial spaces of the lungs, whereas larger particles ($\approx$250 nm) do not. Inflammatory responses in the lung as evidenced by increased polymorphonuclear neutrophils and increased lavage proteins were greater for the fine particles, probably as a result of phagocytosis by alveolar macrophages (Oberdörster et al., 1992).

Rats exposed via inhalation to titanium dioxide dust for 2 years showed lesions only in the respiratory tract and thoracic lymph nodes. At a titanium dioxide dust concentration of 6,000 μg Ti/m^3, pathological and microscopic changes that occurred in the alveoli included the presence of white foci, alveolar macrophages and hyperplasia. At doses of 30,000 μg Ti/m^3 or greater, lung weights increased. At a maximum concentration of 150,000 μg Ti/m^3, lung adenomas were seen in alveoli showing hyperplasia of Type II pneumocytes, and cystic keratinizing squamous carcinomas were also observed. Dust particle retention increased progressively at the highest dose throughout the 2-year exposure period, indicating that the lung clearance capacity of the lung was overwhelmed (Lee et al., 1986b).

Rats receiving intratracheal instillations of 5 mg of titanium dioxide dust showed that although polymorphonuclear leucocytes counts were increased 24 h after administration, values had returned to control levels by 100 days post exposure (Sykes et al., 1982).

Titanium Tetrachloride

Human Data. Only epidemiological reports of occupational exposure and case reports of accidental exposure were found on effects on humans of inhaling titanium tetrachloride. In both types of studies, the exact exposure levels were not known, and inhalation exposure frequently occurred simultaneously with dermal exposure. Therefore, some of the effects reported below may be partially due to dermal exposure to titanium tetrachloride.

Case studies of humans acutely exposed by inhalation to titanium tetrachloride fumes indicate the irritant nature of chemical. Although the degree of pulmonary injury varies, inhalation exposure results in an intense chemical bronchitis or pneumonia (Lawson, 1961). Following an accidental acute exposure, three research workers experienced only mild irritant symptoms consisting of cough and chest tightness, both of which lasted only a couple of hours and left no abnormalities on the chest x-ray (Ross, 1985).

More severe pulmonary effects were reported in two other incidents of accidental exposure to titanium tetrachloride. One worker who was splashed with hot titanium tetrachloride suffered marked congestion of the mucous membranes of the pharynx, vocal cords, and trachea (Ross, 1985). This exposure had long-term effects that included stenosis of the larynx, trachea, and upper bronchi. In another accident, a worker who was sprayed with titanium tetrachloride developed cough and dyspnea 20 min after exposure (Park et al.,

1984). His symptoms progressed to severe upper airway distress that required intubation and ventilation. Additional symptoms included hypoxia and diffuse pulmonary infiltrates, suggestive of adult respiratory distress syndrome. Although he gradually improved, fiberoptic bronchoscopy five weeks later revealed erythema of the entire bronchial tree and the presence of 35–40 fleshy polypoid lesions. According to the authors, the presence of the polyps was a sign of an exaggerated but normal reparative process of the tracheobronchial injury. This delayed complication has been seen in thermal respiratory injuries, suggesting that the severe adverse respiratory effects seen in this case are in part due to the exothermic nature of the titanium tetrachloride hydrolysis reaction. His lungs appeared normal one year after the injury, although mild stenosis remained.

Two retrospective studies (Garabrant et al., 1987; Mosley et al., 1980) of the occupational exposure of 209 workers employed at a metals reduction facility indicate that inhalation of titanium tetrachloride causes respiratory irritation (cough, phlegm production, chronic bronchitis, and wheezing with dyspnea) and pulmonary impairment (pleural thickening and reduced pulmonary function). Further analysis of the workers, based on job and duration of employment, confirmed large decreases in forced vital capacity (FVC) in workers employed in titanium tetrachloride reduction for at least 10 years (Garabrant et al., 1987). A regression analysis of the data (adjusted for age, height, and smoking) revealed that the rate of FVC loss was 24 mL per year for the titanium tetrachloride workers. Garabrant et al. (1987) suggested that chronic exposure to titanium tetrachloride may result in restrictive pulmonary changes and that there is no clear association between pleural thickening and reduced ventilatory capacity. However, both studies were limited because of the lack of information on the duration, route, and exposure levels, the concomitant exposure to a mixture of chemicals, and the use of a control group consisting of maintenance workers exposed to multiple chemicals.

A few epidemiological studies have examined cancer mortality in workers employed in industries using titanium tetrachloride. No association between titanium tetrachloride and lung cancer mortality was found in 969 male workers occupationally exposed to <500 to $>$ 3,000 $\mu g/m^3$ titanium tetrachloride for up to five years or more (Fayerweather et al., 1992).

Laboratory Animal Data. Findings in laboratory animals support the observations made in humans. Rats exposed by inhalation to titanium tetrachloride (370,000, 1,290,000, 1,900,000, or 2,900,000 μg Ti/m^3) for 10 min had wet noses, nasal discharge, swollen eyelids, and dyspnea (Karlsson et al. 1986). The signs disappeared within three days following exposure, and lung histopathology conducted 7 days post exposure showed minor lesions. Rats chronically exposed to titanium tetrachloride (60 to 6,000 μg Ti/m^3 6 h/day, 5 days/week for 2 years) had concentration-related increased incidence of irregular respiration and abnormal lung noises, tracheitis, and rhinitis (Du Pont, 1986; Lee et al., 1986a). Gross pathology and histopathology revealed compound-related changes in the lungs and thoracic lymph nodes and increased relative and absolute lung weights in treated rats. Foci laden with yellow material (a titanium tetrachloride hydrolysis product) were found on the lung pleural surface and on the slightly enlarged tracheobronchial lymph nodes in the mid- and high-dose rats.

Although squamous cell carcinoma and keratinizing squamous cell carcinoma were observed in rats chronically exposed to titanium tetrachloride, it is difficult to estimate their relevance to lung tumors in humans (Du Pont, 1984; 1986; Lee et al., 1986a). Following a two-year exposure to 100 to 10,000 μg/m^3 hydrolyzed titanium tetrachloride vapors, two types of lung squamous carcinoma were found: well-differentiated squamous cell carcinoma and a keratinized, cystic squamous cell carcinoma. The carcinomas occurred in the alveoli with squamous metaplasia and next to the alveolar ducts with aggregated dust-laden macrophages, and were probably a result of chronic tissue irritation from dust-laden macrophages and cellular debris. According to the authors, these lung carcinomas are a unique type of experimentally induced tumors that are not usually seen in humans or other animals. Their etiology is also different from human squamous cell carcinoma. Therefore, it is difficult to estimate the relevance of these keratinizing carcinomas to humans.

Titanium Hydride/Titan Dust

Human Data. No toxicity data were located.

Laboratory Animal Data. Other forms of titanium have also been studied to determine their respiratory effects. Rats and rabbits were exposed by inhalation to titan dust (48%

titanium) and titanium hydride for periods of up to 1 year with a 1 year observation period. Titan dust, at concentrations up to 476,000 $\mu g/m^3$ (228,000 μg Ti/m^3), resulted in dust deposition in the alveoli and lymph nodes of the rabbits, as well as thickening of the alveolar wall, hyperplasia of the connective tissue, some fibrosis, and dust particles in the alveolar macrophages and phagocytes. Inhalation of titanium hydride (concentration 507,000 μg Ti/m^3) by rabbits for up to 286 days resulted in histopathologic changes in the lung similar to those seen with titan dust (Shirawaka, 1985).

No studies were located regarding reproductive or developmental effects in laboratory animals of inhalation exposure to titanium compounds.

11.6.19.4 Factors Affecting Susceptibility

Because the respiratory system is the major target of inhaled titanium (Chen and Fayerweather 1988; Daum et al. 1977; Elo et al. 1972; Fayerweather et al. 1992; Garabrant et al. 1987; NIOSH 1980), individuals with respiratory impairments or the developing respiratory tract of children may be at increased risk. Studies in humans and laboratory animals have shown that titanium compounds are not absorbed systemically or metabolized; therefore, it is unlikely that there are other susceptible populations at increased risk from the inhalation of titanium compounds.

11.6.20 Vanadium

11.6.20.1 Chemical and Physical Properties

Elemental vanadium is a light grey or white lustrous metal that may be found in a powder, crystal, or soft ductile solid form. Vanadium belongs to group V of the periodic system of elements. It has six oxidation states, -1, 0, +2, +3, +4, and +5, of which +3, +4, and +5 are the most common (Agency for Toxic Substances and Disease Registry, 1992; Rosenbaum, 1983). The element forms both anionic and cationic salts and is typically bound to oxygen. In the presence of oxygen, air, oxygenated blood, or oxidizing agents, vanadium compounds are found in the +4 oxidation state (World Health Organization, 1987). Divalent and trivalent vanadium compounds are oxidized in the presence of air (Rosenbaum, 1983). Vanadium forms organometallic compounds, although they are

generally unstable. Elemental vanadium is insoluble in water but vanadium pentoxide (V_2O_5) is slightly soluble at 25 °C and vanadyl sulfate ($VOSO_4 \cdot 5H_2O$) is highly soluble.

11.6.20.2 Pharmacokinetics

Most inhalation exposure to vanadium occurs in workers engaged in its industrial production and use. The most common vanadium compounds encountered occupationally are vanadium pentoxide (V_2O_5), elemental vanadium (V), vanadyl sulfate pentahydrate ($VOSO_4 \cdot 5H_2O$), and bismuth orthovanadate ($BiVO_4$). The pattern of absorption, distribution, metabolism, and excretion differs slightly for each vanadium species, depending on particle size and solubility. In general, vanadium compounds are primarily absorbed in the lung and transported by the blood throughout the body (kidney, liver, testicles, spleen, heart, teeth, breast milk). Retention occurs mainly in bone. Most inhaled vanadium is excreted in the urine, but some is found in the feces.

Absorption and Distribution

The respiratory tract is the most significant entry site for vanadium compounds. The extent to which various compounds are absorbed in the respiratory tract is not clear, but is estimated to be about 25% for the soluble compounds. As with all particles, deposition and rate of subsequent absorption are expected to depend on particle size and solubility (Lagerkvist et al., 1986), as well as on alveolar and mucociliary clearance. Vanadium accumulates in the lungs of the general population with increasing age, reaching approximately 6.5 μg/g (wet weight) in persons over age 65 (Tipton and Shafer, 1966). Accumulation was not observed in other tissues. Increased urinary vanadium levels in workers inhaling <1 ppm vanadium (Glyseth et al., 1979; Kiviluoto et al., 1981b; Lewis, 1959; Orris et al., 1983) and increased serum vanadium levels in workers inhaling vanadium pentoxide dusts (Kiviluoto et al., 1981b) have also been reported.

Data showing elevated vanadium levels in the tissues of rabbits exposed by inhalation to vanadium pentoxide dust provides indirect evidence that vanadium is absorbed by this route (Sjöberg 1950); no data on rate or extent of absorption were available. More data are available from intratracheal administration studies, which show that the absorption rate of vanadium from the respiratory tract depends on the solubility and chemical nature of the

vanadium species deposited. In rats administered $VOCl_2$ (a water-soluble vanadium compound) by intratracheal injection, 60% remained in the lungs after 15 min, and 33.5% remained after nine weeks. Absorption of vanadium in rats receiving radiolabeled vanadyl chloride intratracheally is rapid and complete (Conklin et al., 1982), with the greatest absorption of ^{48}V occurring 5 min after administration (Roshchin et al., 1980). Most of the vanadium, 80 and 85% of the tetravalent (V^{4+}) and pentavalent (V^{5+}) forms, respectively, cleared the lungs within 3 h of intratracheal exposure (Edel and Sabbioni, 1988). Greater than 50% of vanadyl oxychloride was cleared after 24 h from the lungs of male rats (Oberg et al., 1978), and 90% was cleared after 3 days from the lungs of female rats (Conklin et al., 1982). Rhoads and Sanders (1985) reported 50% clearance in 18 min and 100% clearance within several days.

Absorbed vanadium is transported mainly in the plasma, bound to transferrin. Vanadium is widely distributed in body tissues; principal organs of vanadium retention are kidney, liver, testicles, spleen, heart, bones, teeth, and breast milk (Byrne and Kosta, 1978). A major fraction of vanadium from cellular vanadium is found in nuclei (Sabbioni and Marafante, 1978).

No information was found regarding the distribution of inhaled vanadium in humans following acute exposure. Vanadium has been detected in the lungs and intestines at autopsy in humans with no known occupational exposure (Schroeder et al., 1963); lung vanadium levels were attributed to environmental exposure. Serum vanadium levels in occupationally exposed workers were highest within 24 h of exposure, and rapidly declined after exposure ceased (Gylseth et al., 1979; Kiviluoto et al., 1981b).

No information was found regarding the distribution of vanadium in laboratory animals following short- or long-term inhalation exposure. Vanadium administered intratracheally to rats is rapidly distributed. Within 15 min after acute intratracheal exposure to 360 μg/kg vanadium oxychloride, radiolabeled vanadium was detected in varying concentrations in all rat organs except the brain, with the highest concentrations in the lungs, followed by the heart and kidney. Maximum levels were obtained between 4 and 24 h (Oberg et al., 1978).

Vanadium has a two-phase lung clearance after a single intratracheal exposure in laboratory animals. In the first phase, a large percentage of the absorbed dose is rapidly distributed (within 24 h post-exposure) to most organs and blood. The second phase is a

slower clearance. Vanadium is transported mainly in the plasma; most is found initially in the blood, with only trace levels detected two days after exposure (Roshchin et al., 1980). The pentavalent and tetravalent forms appear to have similar distribution patterns; 3 h after exposure, 15 to 17% of the absorbed dose was found in the lung, 2.8% in the liver, and 2% in the kidney (Edel and Sabbioni, 1988).

Vanadium appears to be retained in the bones. Skeletal levels of vanadium peaked 1 to 3 days post-exposure (Conklin et al., 1982; Rhoads and Sanders, 1985; Roshchin et al., 1980) and have been detected as long as 63 days after exposure (Oberg et al., 1978). Orally administered vanadyl sulphate pentahydrate has been found to cross the placenta (Paternain et al., 1990).

Metabolism

Vanadium, in its elemental form, is not metabolized. In the body, vanadium interconverts between two oxidation states, tetravalent vanadyl (V^{+4}) and pentavalent vanadate (V^{+5}). In plasma, vanadium exists in either a bound or unbound form (Bruech et al., 1984). Vanadyl (Patterson et al., 1986) or vanadate (Harris and Carrano, 1984) reversibly binds to human serum transferrin at two metal-binding sites on the protein, and is then taken up by erythrocytes. The interconversion of oxidation states and the reversible binding to transferrin protein may affect the biphasic clearance of vanadium that occurs in the blood. With intravenous administration of vanadate or vanadyl, there is a short lag time for vanadate binding to transferrin, but at 30 h, the association is identical for the two vanadium forms (Harris et al., 1984). The vanadium-transferrin binding most likely occurs with vanadyl since this complex is more stable (Harris et al., 1984). In rats, the transferrin-bound vanadium is cleared from the blood at a slower rate than unbound vanadium, supporting the biphasic clearance pattern (Sabbioni and Marafante, 1978).

Vanadyl is taken up by erythrocytes more slowly than is vanadate. Five minutes after intravenous administration of radiolabeled vanadate or vanadyl in dogs, 30% of the vanadate and 12% of the vanadyl is found in erythrocytes (Harris et al., 1984). Five hours after administration, blood clearance of vanadyl and vanadate is essentially the same, although initially vanadyl leaves the blood more rapidly than does vanadate (Harris et al., 1984). Vanadate is considered more toxic than vanadyl because vanadate reacts with multiple

enzymes and is a potent inhibitor of plasma membrane Na^+K^+-ATPase (Harris et al., 1984; Patterson et al., 1986). Metabolism of the compound does not appear to be affected by the route of exposure (Edel and Sabbioni, 1988).

Excretion

Epidemiological and laboratory animal studies suggest that inhaled vanadium is eliminated primarily in the urine. Male and female workers occupationally exposed to 100 to 190 $\mu g/m^3$ vanadium had significantly higher urinary levels (20.6 $\mu g/L$) than did non-occupationally exposed controls (2.7 $\mu g/L$) (Orris et al., 1983). Although several occupational studies indicate significantly higher urinary vanadium levels in workers (Orris et al., 1983; Glyseth et al., 1979; Lewis, 1959; Zenz et al., 1962), the correlation between ambient levels and urinary levels is difficult to assess because most studies did not monitor other excretion routes (Kiviluoto et al., 1981b). Very low vanadium levels have been found in human breast milk (Byrne and Kosta 1978).

Although no laboratory animal studies were located assessing excretion after inhalation exposure, oral studies support the findings of the occupational data. Vanadium administered intratracheally to rats was excreted predominantly in the urine (Oberg et al., 1978) at levels twice that found in the feces (Rhoads and Sanders, 1985). Three days post-exposure to radiolabeled vanadium pentoxide, 40% of the recovered dose was cleared in the urine, 30% remained in the skeleton, and 2 to 7% was found in the lungs, liver, kidneys, or blood (Conklin et al., 1982).

11.6.20.3 Health Effects

Human Data

Acute and chronic inhalation studies in humans are generally limited to occupational case studies and epidemiology studies in workers engaged in the industrial production and use of vanadium. Based on these studies, the respiratory tract is the primary target of vanadium inhalation. Most of the reported exposures are to vanadium pentoxide dusts. Neurological symptoms have been reported following acute exposure at high vanadium concentrations. Gastrointestinal effects (nausea, vomiting), which may have occurred from swallowing

vanadium via mucociliary clearance, eye irritation, and conjunctivitis have also been reported. Human toxicity data are summarized in Table 11-51.

Acute and chronic respiratory effects were most commonly seen following exposure to vanadium pentoxide dusts. Mild respiratory distress (cough, wheezing, chest pain, runny nose, or sore throat) was observed in workers exposed to vanadium pentoxide dusts or vanadium in fuel oil smoke for as few as 5 h (Levy et al., 1984; Musk and Tees, 1982; Thomas and Stiebris, 1956; Zenz et al., 1962) or as long as 6 years (Lewis, 1959; Orris et al., 1983; Sjöberg, 1956; Vintinner et al., 1955; Wyers, 1946). Most clinical signs reflect the irritative effects of vanadium on the respiratory tract; only at concentrations $>1{,}000$ μg vanadium/m^3 were more serious effects on the lower respiratory tract observed (bronchitis, pneumonitis). Rhinitis, pharyngitis, bronchitis, chronic productive cough, wheezing, shortness of breath, and fatigue were reported by workers following chronic inhalation of vanadium pentoxide dusts (Sjöberg, 1956; Vintinner et al., 1955; Wyers, 1946). Two volunteers exposed to 60 μg vanadium/m^3 as vanadium pentoxide reported a delay of 7 to 24 h in the onset of mucus formation and coughing (Zenz and Berg, 1967).

Vanadium induced asthma in vanadium pentoxide refinery workers without previous history of asthma, with symptoms continuing for 8 weeks following cessation of exposure (Musk and Tees, 1982). Increased neutrophils in the nasal mucosa were reported in chronically exposed workers (Kiviluoto, 1980; Kiviluoto et al., 1979, 1981c).

Few studies were found that reported effects of vanadium compounds on organ systems other than the respiratory tract. However, nervous symptoms have been observed following chronic exposure (Sjöberg, 1950). Workers chronically exposed to vanadium dusts complained of nausea, vomiting (which may have resulted from ingesting dusts), slight to moderate eye irritation (Levy et al., 1984; Lewis, 1959; Sjöberg, 1950; Thomas and Stiebris, 1956; Vintinner et al., 1955), and conjunctivitis (Zenz et al., 1962). Chronic occupational exposure to vanadium dusts was also associated with some electrocardiographic changes (Sjöberg, 1950). Vanadium dusts had no effect on hematology following acute exposure (Zenz and Berg, 1967) or chronic exposure (Kiviluoto et al., 1981a; Sjöberg, 1950; Vintinner et al., 1955). Blood pressure and gross neurologic signs were not affected following chronic exposure to vanadium pentoxide dusts at levels up to 58,800 μg vanadium/m_3 (Vintinner et al., 1955), although other authors reported anemia or leukopenia

TABLE 11-51. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR VANADIUM COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ V/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
Acute Studies							
N/A	>500	1 d (occup)	V_2O_5 dust, fumes	UK	Human (18) M	Subjective symptoms, chest x-ray, spirometry (FVC, FEV, MEFR), UA V concentration; Mucosal irritation, conjunctivitis, cough, wheezing, bronchospasms. Chest x-rays, UA V concentration, pulmonary function normal. V found in urine. Note: Symptoms developed on Day 1 of exposure, and continued even when exposure was reduced.	Zenz et al. (1962)
N/A	NS	1 d (occup)	V_2O_5 dust	NS	Human (4) M	Case studies - history, prick skin test, chest x-ray, pulmonary function (FEV, FVC), total serum IgE: Wheezing, airflow obstruction, green tongue, asthma.	Musk and Tees (1982)
N/A	50-5,300	7 d (occup)	V_2O_5 fumes	NS	Human (100) M	Questionnaire, CS, PF, chest x-ray, UA V concentration: Bronchitis, productive cough, sore throat, dyspnea on exertion, chest pain, wheezing. Median latency of symptoms = 7 days. Exposure concentration not correlated with effects. Normal chest x-ray and blood work.	Levy et al. (1984)
N/A	60 100 600	8 h	V_2O_5 dust	98% < 5 μm in diameter	Human (2-5) NS	CS, spirometry, blood counts, V in blood: Bronchial irritation (cough, mucous formation) post-exposure at 60 $\mu g/m^3$. Cough at 100, 600 $\mu g/m^3$ lasted about 1 wk. No change in pulmonary function, blood counts, or hair or nail cystine levels.	Zenz and Berg (1967)
Chronic Studies							
N/A	0 100-300	2 yr (occup)	V_2O_5 dust	93-100% of particle < 5 μm; est 2-100% of part. mass < 5 μm	Human (24) M	Physical exam, history, electrocardiogram, UA V concentration, hematocrit, serum cholesterol: Productive cough, runny nose, sore throat, wheezing, green tongue.	Lewis (1959)

TABLE 11-51 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR VANADIUM COMPOUNDS

Exposure Concentration ppm	Exposure Concentration $\mu g\ V/m^3$	Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
N/A	0 130	6 yr (occup)	V_2O_5 dust	NS	Human (39) M, F	Questionnaire, physical exam, PF chest x-rays: Skin rash, green tongue, wheezing, nose bleeds. Normal pulmonary functions. X-rays-pleural thickening consistent with concurrent asbestos exposure.	Orris et al. (1983)
N/A	est ≤6,500	1-2 yr (occup)	Mixture of V_2O_5 (4.8-7.5% of dust); V_2O_3 (17%) FeV_2O_4	22% of dust < 8 μm; 17% 8-12 μm; 17% 12-18 μm; 44% > 18 μm	Human (36) M	Physical exam, bronchoscopy, ECG, hematology, urinalysis, serum bilirubin: Rhinitis, nasal discharge, irritated throat, bronchopneumonia, "asthmatic" bronchitis some changes on ECG, one case of tremor, neurasthenia, weakness. No effect on liver, kidney, blood.	Sjöberg (1950)
N/A	0-7 (control) 10-2, 120 (inactive ore area) 20-58,800 (active ore area)	<1->10 yrs (occup)	Vanadium ore (form NS, but included V_2O_5)	Inactive ore: 50% <1.5 μm diameter; 80% <2.5 μm; 100% <5 μm; Active ores: 75% <1.5 μm diameter; 80% <2.5 μm; 100% <5 μm	Human (37-39) NS	Med neuro exam, chest x-ray, spirometry: exposed workers had subjective respiratory complaints (cough, chest pain, and dyspnea) and eye and nose irritation. Incidences higher in active ore group than inactive ore group. No significant differences in vital capacity, tremor, coordination.	Vintinner et al. (1995)
N/A	0 200-500	5 yr (occup)	V_2O_5 dust	NS	Human (63) NS	Micro- and macroscopic examination of upper respiratory tract: No gross respiratory change, inc neutrophils/plasma cells in nasal mucosa.	Kiviluoto (1980); Kiviluoto et al. (1979, 1981)

Abbreviations:

BAL = bronchioalveolar lavage; CS = clinical signs; d = days; ECG = electrocardiogram; EM = electron microscopy; est = estimated; F = female; GI = gastrointestinal; h = hours; inc = increased; M = male; FEV = forced expiratory volume; FVC = forced vital capacity; mos = month; N/A = not applicable; NS = not specified; occup = occupational; PF = pulmonary function; UA = urinalysis; V = vanadium; V_2O_5 = vanadium pentoxide; wk = week; yr = years.

(Roschin, 1964; Watanabe et al., 1966). Based on serum biochemistry and urinalysis, there was no indication of kidney or liver toxicity in workers chronically exposed to 200 to 58,800 μg vanadium/m^3 vanadium dusts (Kiviluoto et al., 1981a,b; Sjöberg, 1950; Vintinner et al., 1955). Vanadium green discoloration of the tongue resulting from direct deposition of vanadium is often reported (Orris et al., 1983; Lewis, 1959; Musk and Tees, 1982).

No studies were located regarding developmental effects, reproductive effects, or cancer in humans after inhalation or oral exposure to vanadium.

Laboratory Animal Data

Acute and chronic laboratory animal studies support the respiratory tract as the main target of inhaled vanadium compounds. The animal data indicate that vanadium toxicity increases with increasing compound valency, and that vanadium is toxic both as a cation and as an anion (Venugopal and Luckey, 1978). The toxicity data for laboratory animals are summarized in Table 11-52.

The mechanism of vanadium's effect on the respiratory system is similar to that of other metals. *In vitro* tests show that vanadium damages alveolar macrophages (Castranova et al., 1984; Sheridan et al., 1978; Waters et al., 1974; Wei and Misra, 1982) by affecting the integrity of the alveolar membrane, thus impairing the cells' phagocytotic ability, viability, and resistance to bacterial infection. Cytotoxicity, tested on rabbit alveolar macrophages *in vitro*, was directly related to solubility in the order $V_2O_5 > V_2O_3 > VO_2$. Dissolved vanadium pentoxide (6 μg/ml) also reduces phagocytosis (Waters, 1977).

Respiratory effects in laboratory animals following acute inhalation of vanadium compounds include increased pulmonary resistance and significantly increased polymorphonuclear leukocytes in bronchioalveolar lavage fluid. These effects were observed in monkeys 24 h following a 6-h inhalation exposure to 2,800 μg/m^3 vanadium/m^3 as vanadium pentoxide (Knecht et al., 1985). In addition, increased lung weight and alveolar proteinosis were observed in rats after inhaling bismuth orthovanadate 6 h daily for two weeks (Lee and Gillies, 1986). Rabbits exposed to high concentrations of vanadium pentoxide dust for 1 to 3 days exhibited dyspnea and mucosal discharge from the nose and eyes (Sjöberg, 1950). In a follow-up experiment, rabbits had difficulty breathing following a daily 1-h exposure for 8 mo (Sjöberg, 1950).

TABLE 11-52. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR VANADIUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ V/m^3$						
Acute Studies							
N/A	0 17,000 190,000	6 h/d 5 d/wk 2 wk	Bismuth orthovanadate ($BiV0_4$) dust	0.05 - 0.3 μm	Rat, Charles River (20) M	CS, intrapulmonary lipids, dust-laden macrophage (dust cell) response with hyperplasia of type II pneumocytes: Alveolar proteinosis at 17,000 $\mu g/m^3$; dose-related increased lung weight, increased accumulation of macrophages, collagen deposition, lung lipid content, and Type II pneumocytes.	Lee and Gillies (1986)
N/A	0 340 2,500	6 h	V_2O_5 dust	Median area equivalent diameter = 0.59-0.61 μm σ_g = 2.09-1.85	Monkey, cynomolgus (16) M	PF, BAL: Reduced lung function at 2,500 $\mu g/m^3$, inc pulmonary resistance; inc leukocytes in bronchoalveolar lavage. Note: The same monkeys were exposed to both levels at a 2-week interval.	Knecht et al. (1985)
NA	5,600- 39,200	UK	V_2O_5 fume ("condensation-aerosol")	UK	Rat, UK (UK)	CS, BW, HP of major organs: Nasal discharge (sometimes containing blood), difficulty breathing, dec BW; hemorrhages in lung, heart, liver, kidney, brain. Fatty degeneration in liver and kidney; edema, bronchitis, focal interstitial pneumonia in lungs. Effects mainly in lungs at low concentration. Mild signs (not specified) of toxicity at 2,800. "Absolute lethal concentration" of 19,600. At high levels, dysentery, paralysis of hind limbs, and respiratory failure. Note: Concentration at which effects seen and form of V unclear from the available literature	Roshchin (1967a)

TABLE 11-52 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR VANADIUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ V/m^3$						
NA	44,800-392,000	UK	V_2O_5 dust ("grinding aerosol")	UK "large particles"	Rat, UK (UK)	CS, BW, HP of major organs: Nasal discharge (sometimes containing blood), difficulty breathing, dec BW; hemorrhages in lung, heart, liver, kidney, brain. Fatty degeneration in liver and kidney; edema, bronchitis, focal interstitial pneumonia in lungs. Effects mainly in lungs at low concentration. At high levels, dysentery, paralysis of hind limbs, and respiratory failure. Note: Concentration at which effects seen and form of V unclear from the available literature Note: Described as one-fifth as toxic as the fume	Roshchin (1967a)
NA	435,000	UK	Ammonium vanadate presumably as grinding aerosol (dust)	UK	Rat, UK (UK)	CS, BW, HP of major organs: Nasal discharge (sometimes containing blood), difficulty breathing, dec BW; hemorrhages in lung, heart, liver, kidney, brain. Fatty degeneration in liver and kidney; edema, bronchitis, focal interstitial pneumonia in lungs. Effects mainly in lungs at low concentration. Note: Concentration at which effects seen and form of V unclear from the available literature.	Roshchin (1967a)
Chronic Studies							
NA	0 11,000-22,000	1 h/d 8 mo	V_2O_5	30% by wt <5 μm; 33% by wt <10μm; 67% by wt >10 μm	Rabbit, NS (12) NS	CS, HP or major organs: Dyspnea, eye irritation at 800 $\mu g/m^3$. Nasal discharge, laryngeal irritation, bronchitis, emphysema. No fibrosis. No significant kidney, GI, heart, or bone marrow pathology. Some fatty degeneration of the liver, which the authors attributed to infectious hepatitis.	Sjöberg (1950)

TABLE 11-52 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR VANADIUM COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ V/m^3$						
Chronic Studies							
NA	0 1.2 15	"continuous" 70 d	V_2O_5 fume	UK	Rats, UK (UK)	BW, motor chronaxy of extensor and flexor muscles of tibla, serum biochemistry: No effect on BW. Decreased motor chronaxie (a measure of excitability) at 30 d and 7.6; no effect at 1.2. Decreased blood cholinesterase, serum protein at 15.	Pazynich (1966)
NA	1,700 2,800	2 h/every other day 3 mo	V_2O_5 fume	UK	Rat, UK (UK)	CS, HP or major organs: Capillary congestion, perivascular edema, hemorrhages in lungs. Also focal edema and desquantitative bronchitis in some cases, lymphocyte infiltration of interstitial spaces, constriction of small bronchi. Note: Concentration at which effects seen unclear from available literature.	Roshchin (1967a)
NA	5,600- 17,000	2 h/every other day 4 mo	V_2O_5 dust	UK	Rats, UK (UK)	CS, HP or major organs: Capillary congestion, perivascular edema, hemorrhages in lungs. Also focal edema and desquantitative bronchitis in some cases, lymphocyte infiltration of interstitial spaces, constriction of small bronchi. Note: Concentration at which effects seen unclear from available literature.	Roshchin (1967a)

Abbreviations:

BAL = bronchioalveolar lavage; BW = body weight; d = day; F = female; GI = gastrointestinal; h = hour; HP = histopathology; inc = increased; M = male; mos = month; N/A = not applicable; NS = not specified; occup = occupational; PF = pulmonary function; UA = urinalysis; V = vanadium; V_2O_5 = vanadium pentoxide; wk = week; WT = weight; yr = years.

The effects of acute exposure to 5,600-39,200 μg vanadium/m^3 as vanadium pentoxide fume or 44,800-392,000 μg vanadium/m^3 as vanadium pentoxide dust were investigated by Roshchin (1967a); the exposure duration was not described in the available literature. For vanadium pentoxide fume, "mild toxicity" occurred at 5,600 μg vanadium/m^3, and deaths were observed at the high level. The vanadium pentoxide dust was described as one-fifth as toxic as the fume. Effects at the lower levels were mostly observed in the lungs. These included irritation of respiratory mucosa, perivascular and focal edema, bronchitis, and interstitial pneumonia. Small hemorrhages were also observed in internal organs, along with fatty degeneration of the liver and kidneys. In a subchronic experiment, rats were exposed to vanadium pentoxide fume (1,700-2,800 μg vanadium/m^3) or vanadium pentoxide dust (5,600-17,000 μg vanadium/m^3) for 2 hours every other day for 3-4 months (Roshchin 1967a). Histopathological effects were limited to the lungs and were similar to those observed following acute exposure. The study author concluded that vanadium inhalation resulted in irritation of the respiratory mucosa, hemorrhagic inflammation, a spastic effect on smooth muscle of the bronchi, and vascular changes in internal organs (at higher levels). Similar effects were observed with the trivalent vanadium compounds vanadium trioxide and vanadium trichloride, although vanadium trichloride caused more severe histological changes in internal organs (Roshchin 1967b); further details were not available. This study also reported disturbances of the central nervous system (impaired conditioned reflexes and neuromuscular excitability) and electroencephalographic changes after inhalation exposure to vanadium oxides or salts.

Rats exposed to vanadium pentoxide condensation aerosol (15 μg vanadium/m^3) continuously for 70 days developed marked lung congestion, focal lung hemorrhages, and extensive bronchitis (Pazynich 1966). Hemorrhage of the liver, kidneys, and heart, and impaired neuromuscular excitability were also observed. There was no effect at 1.2 μg vanadium/m^3. Rabbits exposed to vanadium pentoxide dusts exhibited fatty degeneration of the liver (8-mo exposure), fatty degeneration of the kidney (acute or chronic exposure), and conjunctivitis (acute or chronic exposure) (Sjöberg, 1950). No pathological changes in the brain were observed in rabbits exposed to vanadium pentoxide for 8 mo (Sjöberg, 1950).

No studies were located regarding developmental effects, reproductive effects, or cancer in laboratory animals following inhalation exposure to vanadium. Oral exposure to

sodium metavanadate resulted in no or slight developmental effects (Paternain et al., 1987; Kowalska, 1988; Domingo et al., 1986). Oral studies using vanadium reported no significant effects on fertility, reproduction, or parturition in rats (Domingo et al., 1986) or were inadequate for evaluating carcinogenicity (Schroeder and Balassa, 1967; Schroeder and Mitchener, 1975; Schroeder et al., 1970).

11.6.20.4 Factors Affecting Susceptibility

No data were located that identified subpopulations with heightened susceptibility to vanadium. However, since the respiratory system is the main target of vanadium toxicity, individuals with respiratory diseases would be expected to be more susceptible. The developing respiratory tract of children may also increase susceptibility. There are also indications that exposure to high levels may result in sensitization to lower levels (Zenz et al. 1962).

Data on systemic effects of vanadium are too limited to determine whether other systems are also targets of vanadium toxicity. However, effects have been reported on the liver, kidney, heart, and nervous system. If these are targets of vanadium, people with impaired function may be more susceptible to vanadium toxicity.

11.6.21 Zinc

11.6.21.1 Chemical and Physical Properties

Zinc is a metallic element and belongs to Group 2B of the periodic system of elements. Zinc forms all of its compounds with a valence of +2. The compounds formed by zinc are all quite stable, and tend to be covalently bonded. However, compounds formed with highly electropositive elements such as chlorine tend to be ionic (Lloyd, 1984). The most important property of zinc is its high reduction potential toward other chemicals. Thus, oxidizing elements such as oxygen, sulfur, and halides react with zinc at room temperature if moisture is present, and at high temperatures in the absence of moisture. (Lloyd and Showak, 1984). In nature, zinc usually occurs as the sulfide, but the oxide, carbonate and silicate may also be mined (Lloyd, 1984). Evidence suggests that when zinc sulfide is exposed to the atmosphere, it is oxidized to a more water-soluble form, zinc sulfate. Zinc exists as the +2 form in aqueous solution and exhibits amphoteric properties; it dissolves in acids to form

hydrated Zn^{+2} cations and in strong bases to form zincate anions (probably $Zn[OH]_4^{-2}$). At the pH found in most natural waters, the formation of anionic zinc is not likely (Agency for Toxic Substances and Disease Registry, 1994). Zinc metal is insoluble in water, whereas zinc oxide (ZnO) and zinc sulfide (ZnS) are slightly soluble, zinc chloride ($ZnCl_2$) is moderatley soluble, and zinc sulfate ($ZnSO_4$) is highly soluble.

11.6.21.2 Pharmacokinetics

There is limited information on the toxicokinetic properties of zinc following inhalation exposure. Increased zinc levels in the blood and urine of humans and in the tissue of laboratory animals after inhalation exposure to zinc indicate that zinc is absorbed by this route. Once absorbed, zinc is widely distributed throughout the body. Zinc content is highest in muscle, bone, gastrointestinal tract, kidney, brain, skin, lung, heart, and pancreas. In plasma, two-thirds of the zinc is bound to albumin which represents the metabolically active pool of zinc. This pool of plasma zinc is frequently referred to as loosely bound zinc because albumin has the ability to give up bound zinc to tissues. Zinc is excreted in both urine and feces.

Humans

The absorption of inhaled zinc depends on the particle size and solubility. Data are limited to elevated levels of zinc found in the blood and urine of workers exposed to zinc oxide fumes (Hamdi, 1969). Occupational studies provide indirect evidence that zinc may distribute to tissues to produce systemic effects (Langham Brown, 1988; Drinker et al., 1927a; Malo et al., 1990; McCord et al., 1926; Rohrs, 1957; Sturgis et al., 1972).

Zinc is one of the most abundant trace metals in humans. It is found normally in all tissues and tissue fluids and is a cofactor in over 200 enzyme systems. Together, muscle and bone contain approximately 90% of the total amount of zinc in the body ($\approx$60% and 30%, respectively) (Wastney et al., 1986). Organs containing sizable concentrations of zinc are the liver, gastrointestinal tract, kidney, skin, lung, brain, heart, and pancreas (Drinker and Drinker, 1928; He et al., 1991).

Zinc is transported in the blood plasma, erythrocytes, leukocytes, and platelets, but is chiefly localized within erythrocytes (of which 87% is in carbonic anhydrase, the major

binding site) (Ohno et al., 1985). Zinc deficiency has been demonstrated to decrease the ability of erythrocytes to resist hemolysis *in vitro*. This finding suggests that zinc stabilizes the erythrocyte membrane.

In plasma, two-thirds of the zinc is bound to albumin; the remainder is bound primarily to α_2-macroglobulin (Wastney et al., 1986). Plasma provides a metabolically active transport compartment for zinc (Cousins, 1985), and zinc is most often complexed to organic ligands (existing in loosely or firmly bound fractions) rather than free in solution as metallic ion (Gordon et al., 1981). Zinc is found in diffusible or nondiffusible forms in the blood. In the diffusible form, approximately two-thirds of plasma zinc is freely exchangeable and loosely bound to albumin (Cousins, 1985); the zinc-albumin complex has an association constant of about 10^6 (National Research Council, 1979). The diffusible form of zinc also includes zinc bound to amino acids (primarily histidine and cysteine). The zinc-albumin complex is in equilibrium with the zinc-amino acid complex (Henkin, 1974). The zinc-amino acid complex can be transported passively across tissue membranes to bind to proteins. An important binding protein in the kidney and liver is metallothionein, although other tissue-binding proteins may be present.

In the nondiffusible form, a small amount of circulating zinc is tightly bound to α_2-macroglobulin in the plasma (Cousins, 1985). Zinc is incorporated into and dissociated from α_2-macroglobulin only in the liver (Henkin, 1974). This zinc-protein complex has an association constant of $>10^{10}$ (Henkin, 1974; National Research Council, 1979). The zinc bound to α_2-macroglobulin is not freely exchangeable with other zinc ligands (i.e., zinc-albumin and zinc-amino acid complexes) in serum.

The transfer of zinc across perfused placentas is slow; only $\approx 3\%$ of maternal zinc reached the fetal compartment in 2 hours (Beer et al., 1992). The *in vitro* transfer of zinc between mother and fetus is bidirectional, with binding in the placenta (Beer et al., 1992). Newborns may also be exposed to zinc from their mothers by milk transfer of zinc during lactation (Rossowska and Nakamoto, 1992).

Information was limited regarding zinc excretion following inhalation exposure in humans. Workers exposed to zinc oxide fumes had elevated levels of zinc in the urine (Hamdi, 1969) indicating that this is a route of excretion.

Laboratory Animals

The rates or percentages of absorption of inhaled zinc in laboratory animals are not available; however, studies provide data on zinc retention in the lungs. Zinc retention values were 19.8%, 11.5%, and 4.7% in the lungs of guinea pigs, rats, and rabbits, respectively, after inhalation exposure (nose-only) to 3,500 to 9,100 μg zinc/m^3 as zinc oxide aerosol for 2 to 3 h (Gordon et al., 1992). The retention of zinc in lungs was concentration-related in male Wistar rats administered a single intratracheal instillation of 70 to 3,700 μg zinc/m^3 as zinc oxide (Hirano et al., 1989). A half-life of 14 h was calculated for this experiment.

The absorption of zinc oxide fumes led to increased levels of zinc measured in the liver, kidney, and pancreas of cats exposed to zinc oxide fumes for durations ranging from 15 min to 3.25 h (Drinker and Drinker, 1928). The usefulness of the study is limited because reporting was inadequate and particle size of the zinc oxide aerosol was not determined. Some inhaled particles of zinc oxide are subject to ciliary clearance and swallowing. Thus, a portion of the inhaled zinc may ultimately be absorbed from the gastrointestinal tract. The presence of other trace metals (e.g., mercury, cadmium, copper) may also diminish zinc transport. Zinc levels in the lungs of cats peaked immediately after acute exposure to 12,000 to 61,000 μg zinc/kg/day as zinc oxide for approximately 3 h and remained high for 2 days postexposure, then dropped significantly thereafter (Drinker and Drinker, 1928). Levels in pancreas, liver, and kidneys increased slowly. No data were located regarding the excretion pattern or rate of zinc in animals.

11.6.21.3 Health Effects

The majority of data available on zinc toxicity are human occupational and acute laboratory animal studies. No chronic laboratory animal bioassays with zinc or its compounds have been performed. Two epidemiological studies have reported no increased incidence of cancers associated with occupational exposure to zinc (Logue et al., 1982; Neuberger and Hollowell, 1982); however, some of the workers were also concurrently exposed to copper.

Human Data

The major target organ of zinc toxicity appears to be the respiratory system as demonstrated in experimental and occupational studies with acute exposure to zinc oxide fumes or dust. Human toxicity data are summarized in Table 11-53. Heating zinc beyond its boiling point in an oxidizing atmosphere produces ultrafine zinc oxide particles (0.2 to 1.0 μm). Upon inhalation, these small particles (<1 μm) reach the alveoli and cause inflammation and tissue damage in the lung periphery (Langham Brown, 1988; Drinker et al., 1927b; Vogelmeier et al., 1987).

There is a large amount of information on metal fume fever, an acute disease induced by intense inhalation of metal oxides, especially zinc, that temporarily impairs pulmonary function but does not progress to chronic lung disease; however, quantitative data are limited (Langham Brown, 1988; Drinker et al., 1927b; Malo et al., 1990). Symptoms generally appear within a few hours after acute exposure, usually with dryness of the throat and coughing (Drinker and Drinker, 1927b). The most prominent respiratory effects of metal fume fever are substernal chest pain, cough, and dyspnea (Rohrs, 1957). The impairment of pulmonary function is characterized by reduced lung volumes and a decreased diffusing capacity of carbon monoxide (Malo et al., 1990; Vogelmeier et al., 1987). The respiratory effects have been shown to be accompanied by an increase in bronchiolar leukocytes (Vogelmeier et al., 1987). The respiratory symptoms generally disappear in the exposed individual within 1 to 4 days (Langham Brown, 1988; Drinker et al., 1927b; Sturgis et al., 1927). A fever appearing 3 to 10 h after exposure to zinc oxide fumes and lasting approximately 24 to 48 h is characteristic of metal fume fever caused by zinc (Mueller and Seger, 1985).

The exact pathogenesis of metal fume fever from zinc exposures is not known. It is believed to be an immune response to the inhaled zinc oxide (Mueller and Seger, 1985). It has been suggested that the zinc oxide causes inflammation of the respiratory tract and the release of histamine or histamine-like substances. In response, an allergic reaction may occur upon subsequent exposure to the allergen. In response to the allergen-antibody complex, an anti-antibody is formed. The anti-antibody dominates with continued exposure to the zinc oxide, thereby producing tolerance. When the exposure is interrupted and

TABLE 11-53. HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ZINC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	$\mu g\ Zn/m^3$						
Acute Studies							
NA	0 3,900	2 h/d 1 d (face mask)	ZnO	MMAD = 0.17 μm σ_g = 1.8	Human (4) NS	Subjective symptoms, pulmonary function tests (airway resistance, FVC, FEV1), peak expiratory flow rates: Symptoms (fever, chills, chest tightness, muscle/joint pain, sore throat, headache at 4-8 hours postexposure); inc airway resistance of 16%.	Gordon et al. (1992)
NA	0, 4.1 19 34 (range NS) dust	6-8 h (a work-shift) (occup)	Zn	Based on wind tunnel experiments, 50% cutoff diameter of sampling device was approximately 18 μm	Human (10-17) NS	Pulmonary function tests (FEV1, FEV1/FVC): No occurrence of metal fume fever. Significant correlation between change in peak expiratory flow rate and dust concentration. Note: 8.5 yr avg as welders exposed to steel	Marquart et al. (1989)
NA	600,000	10.5-12 min (occup)	ZnO fumes*	NS	human (2M)	Clinical signs, leukocyte count, vital capacity, blood pressure, x-ray of lungs, urinalysis: dec vital capacity, substernal irritation, nausea, mucoid sputum, rales, inc leukocytes, clinical symptoms (headaches, lethargy, vague pains). Note: Impurities in test material; subjects experienced metal fume fever in the previous 2 years.	Sturgis et al. (1927)
NA	77,000-153,000	15-30 min (occup)	Zn	NS	human (11) M, (3) F	Bronchoalveolar lavage (BAL) fluid for differential cell types at 6 or 20 h postexposure: inc number of leukocytes, T cells, T suppressor cells, and NK cells in BAL fluid; inc PMN leukocytes.	Blanc et al. (1991)

TABLE 11-53 (cont'd). HUMAN EXPOSURE CONDITIONS AND EFFECTS FOR ZINC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Zn/m^3						
NA	3.6	2 h	$ZnSO_4 \cdot (NH_4)_2SO_4$ aerosol	MMAD = 1.1 μm σ_g = 2.6	Human (21) NS	Pulmonary function tests, symptoms: Minimal substernal irritation and throat irritation during exposure.	Linn et al. (1981)
NA	8,000-12,000 320,000-580,000	1-3 h (occup)	ZnO fumes*	NS	Human NS	Symptoms: Nausea, chills, shortness of breath and chest pains at 320,000-580,000 μg/m^3. Note: Inadequate information on exposure conditions.	Hammond (1944)
NA	53,000-610,000	3-5 h/d 2 d (occup & experim)	ZnO fumes*	NS	Human (1) M	Subjective symptoms and clinical tests: Mild pain when breathing deeply and inc WBC count at 430,000 μg/m^3.	Drinker et al. (1927a)

Abbreviations:
CO = carbon monoxide; d = days; dec = decreased; hr = hours; inc = increased; LDH = lactate dehydrogenase; MMAD = mass median aerodynamic diameter; NS = not specified; σ_g = geometric standard deviation of distribution; $ZnSO_4 \cdot (NH_4)_2SO_4$ = zinc ammonium sulfate (ambient metallic sulfate aerosol); wk = week; wt = weight; ZnO = zinc oxide; ZnCl = zinc chloride.

*Fumes refer to ultrafine zinc oxide particles originate from heating zinc beyond its boiling point in an oxidizing atmosphere.
**ZnCl produced from ZnO and hexachloroethane smoke.

re-exposure occurs, the response of the initial antibody dominates, producing an allergic reaction and symptoms of metal fume fever (McCord, 1960).

Acute experimental exposures to low concentrations of zinc oxide (45,000 μg zinc/m^3 for 20 min) and occupational exposures to similar concentrations (8,000 to 12,000 μg zinc/m^3 for 1 to 3 h and 34 μg zinc/m^3 for 6 to 8 h) have not produced symptoms of metal fume fever (Drinker et al., 1927b; Hammond, 1944; Marquart et al., 1989).

Exposure of subjects to 3,900 μg zinc/m^3 as zinc oxide resulted in sore throat and chest tightness but no impairment of pulmonary function (Gordon et al., 1992). Nasal passage irritation, cough, substernal chest pain, persistent rales of the lung base, and a decreased vital capacity were observed in two volunteers $\approx$3 to 49 h following a 10 to 12 min exposure to high levels of zinc oxide (Sturgis et al., 1927). Shortness of breath and chest pains were also observed in individuals exposed to high acute concentrations of zinc oxide fumes (Drinker et al., 1927a; Hammond, 1944). Minimal changes in forced expiratory flow were observed 1 h after a 15 to 30-min exposure to 77,000 μg zinc/m^3 as zinc oxide (Blanc et al., 1991). It is speculated that workers develop a tolerance to zinc following long-term exposure to zinc oxide (Gordon et al., 1992), which may explain the lack of observation of similar findings in chronic studies.

Zinc chloride, a corrosive inorganic salt, is more damaging than zinc oxide to the mucous membranes of the nasopharynx and respiratory tract upon contact. Zinc chloride is a primary ingredient in smoke bombs used by the military for screening purposes, crowd dispersal, and occasionally in military and civilian fire-fighting exercises. Reports of serious respiratory injury have been reported to result from accidental inhalation of smoke from these bombs. These reports are of limited use in assessing the toxicity of zinc chloride because exposure to other compounds, usually hexachloroethane, zinc oxide, and calcium silicides, also occur. Furthermore, the specific concentrations inhaled are usually unknown. Despite these limitations, several case studies have described similar respiratory effects in humans following acute inhalation exposures. These effects include dyspnea, cough, pleuritic chest pain, bilateral diffuse infiltrations, pneumothorax, and acute pneumonitis from respiratory tract irritation (Johnson and Stonehill, 1961; Matarese and Matthews, 1966; Schenker et al., 1981). In other studies, more severe effects have occurred, including ulcerative and edematous changes in mucous membranes, fibrosis, subpleural hemorrhage,

advanced pulmonary fibrosis, and fatal respiratory distress syndrome (Evans, 1945; Hjortso et al., 1988; Homma et al., 1992).

Zinc ammonium sulfate is a compound emitted during combustion of fossil fuels and is, therefore, found in the ambient air. Humans acutely exposed to a concentration of 3.6 μg zinc/m^3 as zinc ammonium sulfate for 2 hours exhibited minimal or no short-term respiratory effects (Linn et al., 1981). However, no information was available about the health effects associated with chronic exposures.

Hematological and immunological effects have also been associated with exposure to zinc oxide. One of the hallmarks of metal fume fever is leukocytosis persisting for approximately 12 hours after fever dissipates (Mueller and Seger, 1985). Such effects have been observed in a number of case reports of occupational and experimental exposure of humans to zinc oxide fumes (Langham Brown, 1988; Drinker et al., 1927a; Malo et al., 1990; Rohrs, 1957; Sturgis et al., 1927). Increased leukocyte counts were observed following acute experimental exposures to zinc oxide (Drinker et al., 1927a; Sturgis et al. 1927). These studies are limited because there was an inadequate number of subjects tested, a lack of controls, and impurities in the zinc oxide.

Immunological effects following occupational exposure were reported in a group of 14 welders acutely exposed to 77,000 to 153,000 μg zinc/m^3 as zinc oxide. Significant correlations were observed between the concentration of airborne zinc and the proportion of activated T cells, T helper cells, T inducer cells, T suppressor cells, and activated killer T cells (Blanc et al., 1991). In addition, significant increases in levels of polymorphonuclear leukocytes, macrophages, and all types of lymphocytes were observed in the bronchoalveolar lavage (BAL) fluid. Increased levels of lymphocytes, with a predominance of CD8 cells, in the BAL fluid were reported in a case study of a smelter exposed to unspecified levels of zinc fumes (Ameille et al., 1992). Hives and angioedema developed in a man exposed to zinc fumes at a zinc smelting plant (Farrell, 1987). The author suggested that the patient had an immediate or delayed immunoglobulin E (IgE) response (or both) after a low dose of zinc fumes. Metal fume fever also resulted when the exposure was increased. The signs and symptoms of toxicity were repeated in a challenge test.

There is no indication that zinc produces any reproductive or developmental effects in humans following inhalation and oral exposures.

Laboratory Animal Data

As with human exposure, the respiratory system is the primary site of injury following inhalation exposure. The toxicity data for laboratory animals are summarized in Table 11-54. Acute administration of zinc oxide to rats and rabbits resulted in the pulmonary changes including congestion, various degrees of peribronchial leukocytic infiltration, and exudate composed almost entirely of polymorphonuclear leukocytes in bronchi (Drinker and Drinker, 1928). Cats similarly exposed exhibited more severe effects including bronchopneumonia, leukocyte infiltration into alveoli, and grayish areas with congestion, as well as labored breathing and evidence of upper respiratory tract obstruction.

Pulmonary function tests have been performed in Guinea pigs; results have been mixed. A progressive decrease in lung compliance but no change in air flow resistance was observed in guinea pigs following a 1-h exposure to low concentration of zinc oxide (730 μg zinc/m^3) (Amdur et al., 1982). These observations reflect a response in the lung periphery where submicrometer aerosols are likely to deposit (Amdur et al., 1982). In contrast to the results of Amdur et al. (1982), no effects on ventilation, lung mechanics (respiratory frequency, tidal volume, pulmonary resistance, and pulmonary compliance), diffusing capacity of carbon monoxide, or most lung volume parameters were observed by Lam et al. (1982) following the exposure of guinea pigs to higher concentration of zinc oxide (6,300 μg zinc/m^3) for 3 h. However, functional residual capacity was significantly decreased. The discrepancy between the results may be attributable to the use of anesthetized animals by Lam et al. (1982). Lam et al. (1985) observed functional changes (increased flow resistance, vital capacity, decreased lung compliance, and decreased diffusing capacity) in guinea pigs exposed to 3,700 to 5,600 μg zinc/m^3 as zinc oxide for 5 to 6 days (Lam et al., 1985; 1988); however, no effects were observed in guinea pigs exposed to 2,200 μg zinc/m^3. These effects have been seen in the guinea pig at exposure levels lower than in humans, probably due to structural differences in the lungs. The bronchi and peripheral airways of guinea pigs have a thicker smooth muscle layer and only a small surface area covered by alveolar sacs compared to the bronchi and peripheral airways of other laboratory animals and humans. This makes the guinea pig more susceptible than other laboratory animals to functional impairment of the peripheral airways (Lam et al., 1982).

TABLE 11-54. LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ZINC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Zn/m^3						
Acute Studies							
NA	0 2,200 5,400	3 h/d 1 d	ZnO (nose-only)	MMAD = 0.17 μm σ_g = 1.8	Rat, NS (NS) M	BAL fluid: Inc protein, LDH, and B-glucuronidase, inflammation at 2,200 μg/m^3.	Gordon et al. (1992)
NA	0 4,600	2 h/d 1 d	ZnO (nose-only)	MMAD = 0.17 μm σ_g = 1.8	Rabbit, NS (NS) M	BAL fluid: No effect.	Gordon et al. (1992)
NA	0 2,200 4,500	3 h/d 1 d	ZnO (nose-only)	MMAD = 0.17 μm σ_g = 1.8	Guinea pig (NS) M	BAL fluid: Inc protein, LDH, and B-glucuronidase (suggesting altered macrophage function), inflammation (2,200 μg/m^3).	Gordon et al. (1992)
NA	0 1,800 4,700 9,700	3 h/d 1-3 d	ZnO (nose-only)	Area diam = 0.05 μm (estimated) σ_g = 2	Guinea pig, Hartley (3-6) M	BAL fluid, LM of lungs: Inc protein, neutrophils, and activities of B-glucuronidase, acid phosphatase, alkaline phosphatase, LDH, and angiotensin-converting enzyme and inflammatory foci in lungs at 4,700 μg/m^3.	Conner et al. (1988)
NA	0 2,200 5,600	3 h/d 5 d	ZnO (nose-only)	Area diam = 0.05 μm (estimated) σ_g = 2	Guinea pig, Hartley (8) M	Pulmonary function test: Impaired lung function (gradual decreases in total lung capacity and vital capacity, dec in CO diffusing capacity), inc lung weight at 5,600 μg/m^3.	Lam et al. (1988)

TABLE 11-54 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ZINC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex	Assays performed: Effect(s)	Reference
ppm	μg Zn/m^3						
NA	0 3,700 4,300	3 h/d 6 d	ZnO (nose-only)	Area diam = 0.05 μm (estimated) σ_g = 2	Guinea pig, Hartley (18-38) M	Pulmonary function tests (3,700 μg/m^3 only): Impaired lung function (dec compliance and lung volume, inc pulmonary resistance, dec CO diffusing capacity). Respiratory epithelial permeability, morphologic examination of respiratory tract, and DNA synthesis in epithelial cells of bronchi and terminal bronchioles (4,300 μg/m^3 only): Inc lung weight; inflammation, and increased interstitial thickening, fibroblasts, and interstitial infiltrates.	Lam et al. (1985)
NA	0 6,300	3 h	ZnO	Area diam = 0.05 μm (estimated) σ_g = 2	Guinea pig, Hartley (10-16) M	Pulmonary function tests (anesthetized animals): Dec functional residual capacity.	Lam et al. (1982)
NA	730	1 h	ZnO (head-only)	Mean geom. size = 0.0056-1 μm	Guinea pig, Hartley (7) M	Pulmonary mechanics (e.g., intrapleural pressure, tidal volume, compliance): Dec pulmonary compliance, followed by inc during 2-h postexposure.	Amdur et al. (1982)
Subchronic Studies							
NA	0 1,300 12,800 121,700	1 h/d 5 d/wk 20 wk (13 mo postexp.)	ZnCl[**]	MMAD = 2 μm (1.92-2.04 μm) Zn content of impact material was 20% (w)	Rat, Porton-Wistar (50) F	Body and organ wt, clinical signs, histopathology: Inc macrophages in lungs at 121,700 μg/m^3.	Marrs et al. (1988)

TABLE 11-54 (cont'd). LABORATORY ANIMAL EXPOSURE CONDITIONS AND EFFECTS FOR ZINC AND COMPOUNDS

Exposure Concentration		Exposure protocol	Chemical form	Particle size and distribution	Species, Strain, (Number) Sex,	Assays performed: Effect(s)	Reference
ppm	μg Zn/m^3						
NA	0 1,300 12,800 121,700	1 h/d 5 d/wk 20 wk (13 mo postexp.)	ZnCl**	MMAD = 2 μm (1.92-2.04 μm) Zn content of impact material was 20% (w)	Mouse, Porton (98-100)F	Body and organ wt, clinical signs, histopathology: inc incidence of fatty change in liver at 12,800 μg/m^3 (not clear conc-related), macrophage infiltration in lungs (0/78, 2/74, 2/76, 5/50) and alveogenic carcinoma (6/78, 7/74, 8/76, 15/50) at 121,700 μg/m^3.	Marrs et al. (1988)
NA	0 1,300 12,800 119,300	1 h/d 5 d/wk $\leq$20 wk (13 mo postexp.)	ZnCl**	MMAD = 2 μm (1.92-2.04 μm) Zn content of impact material was 20% (w)	Guinea pig, Dunkin-Hartley (49-50) F	Body and organ wt, clinical signs, histopathology: No effects in survivors. Emphysema, alveolitis, congestion, minimal fibrosis in respiratory system of high-concentration animals that died during exposure.	Marrs et al. (1988)

Abbreviations:
CO = carbon monoxide; d = days; dec = decreased; h = hours; inc = increased; LDH = lactate dehydrogenase; MMAD = mass median aerodynamic diameter; NS = not specified; σ_g = geometric standard deviation of distribution; wk = week; wt = weight; ZnO = zinc oxide; ZnCl = zinc chloride.

*Fumes refer to ultrafine zinc oxide particles originate from heating zinc beyond its boiling point in an oxidizing atmosphere.
**ZnCl produced from ZnO and hexachloroethane smoke.

The BAL fluid of rats or guinea pigs exposed acutely to zinc contained increased levels of lactate dehydrogenase and protein, suggesting effects on cell viability or membrane permeability (Gordon et al., 1992), and elevated angiotensin converting enzyme and neutrophils (Conner et al., 1988). Increased levels of β-glucuronidase, suggesting a change in macrophage function, was also evident in BAL fluid (Gordon et al., 1992). In rabbits treated with similar acute exposure conditions, no effects were observed.

Morphological changes in the lungs were observed in Guinea pigs exposed to $\approx$4,000 μg zinc/m^3 as zinc oxide for an acute duration (Conner et al., 1988; Lam et al., 1985). Effects included increased lung weight, inflammation involving the proximal portion of alveolar ducts and adjacent alveoli, interstitial thickening, inflammation, and increased pulmonary macrophages and neutrophils in adjacent air spaces. In Guinea pigs with evidence of an inflammatory reaction involving the peripheral airways, DNA synthesis increased in bronchiolar cells.

In longer duration studies, focal alveolitis, consolidation, emphysema, infiltration with macrophages, and fibrosis were observed in Guinea pigs that died following exposure to high concentrations of zinc chloride smoke for 3 weeks (Marrs et al., 1988). In rats and mice, increased macrophages in the lungs occurred 13 months after a 20-week inhalation exposure to similar levels of zinc chloride smoke (Marrs et al., 1988). The smoke also contained zinc oxide, hexachloroethane, and other compounds.

An increased incidence of alveologenic carcinoma was reported in female mice 13 weeks after intermittent exposure to 121,700 μg zinc/m^3 as zinc chloride for 20 weeks (Marrs et al., 1988). Guinea pigs and rats were also tested with similar dose levels, but no significant carcinogenic response was observed. A number of factors limits the usefulness of this study, including the presence of several compounds in the smoke that may have carcinogenic potential, the use of only female animals, and the short duration of the exposure period.

In mice, significant increases in the incidence of fatty liver were observed with exposure to zinc chloride smoke for 20 weeks; however, the incidence did not increase with concentration (Marrs et al., 1988). The smoke contained other compounds in addition to zinc chloride. No adverse effects were observed in rats and guinea pigs at similar concentrations of zinc chloride smoke.

No adverse effects were seen in the mammary glands, ovaries, fallopian tubes, or uteri of rats, mice, and guinea pigs following inhalation of zinc chloride smoke for 20 weeks (Marrs et al., 1988). Although no inhalation developmental studies were available, oral studies report increased fetal resorptions, reduced fetal weights, and reduced growth in offspring following high level exposure to zinc in the diet prior to and/or during gestation (Agency for Toxic Substances and Disease Registry, 1994).

11.6.21.4 Factors Affecting Susceptibility

No specific data regarding human subpopulations that are unusually susceptible to the toxic effects of zinc were located. Because the respiratory tract is the major target organ of zinc, individuals with respiratory difficulties or the developing respiratory of children may be more susceptible to the toxic effects of zinc (Gordon et al. 1992; Hammond 1944). Data from laboratory animal studies indicate that certain human subpopulations may be more susceptible to excess zinc because of zinc's depleting effect on copper (Underwood 1977). People who are malnourished or have a marginal copper status may be more susceptible to the effects of excessive zinc than people who are adequately nourished (Underwood 1977).

Hepatic zinc levels are elevated in patients with hemochromatosis, a genetic disease associated with increased iron absorption from the intestine (Adams et al. 1991). The chronic iron loading that occurs could result in hepatic metallothionein induction leading to the accumulation of zinc because metallothionein has a greater affinity for zinc than iron. These individuals may, therefore, have a greater likelihood of developing toxicity with zinc exposure levels that do not normally result in any symptoms in the general population.

11.7 SILICA

This section on silica particle toxicity as well as the section on asbestos fibers is designed to give an overview of current concepts regarding the pulmonary toxicity of these environmental pollutants as they relate to different species, different polymorphs (crystalline vs. amorphous), and biological mechanisms of action. No attempt has been made to review all of the relevant toxicity data, which is voluminous. Silica is well established as a

fibrogenic pollutant which also causes lung tumors following chronic exposures in experimental animals. An review of the literature on the non-cancer effects of silica can be found elsewhere (U.S. Environmental Protection Agency, 1995).

The pulmonary response to occupational concentrations of inhaled silica has long been considered to be a major occupational hazard, causing disability and deaths among workers in a variety of industries. Some of the processes and work environments which are frequently associated with silica exposure include mining, sandblasting using abrasive materials, quarrying and tunneling, stonecutting, glass and pottery manufacturing, metal casting, boiler scaling, and vitreous enameling (Ziskind et al., 1976).

11.7.1 Physical and Chemical Properties

Silica particle emissions in the environment can arise from natural, industrial, and farming activities. There is only limited data on ambient air concentrations of either crystalline or amorphous silica particles, due in part, to the limits in accurately quantifying crystalline silica and to the inability, under existing measurement methods, of separating the identity of crystalline silica from other particulate matter. Davis et al. (1984) used X ray fluorescence and mass calibration methods of X ray diffraction to determine the inhalable composition and concentration of quartz in ambient aerosols collected on dichotomous filters at 25 U.S. metropolitan areas. They reported the average weight percent of quartz in the coarse and fine particle mass to be 4.9 ($\pm$ 2.3) and 0.4 ($\pm$ 0.7), respectively. Combining the weight percent data for the coarse fraction and 7 year average annual arithmetic mean PM_{10} information available for 17 of the 25 areas, annual average and high U.S. ambient metropolitan quartz levels of 3 and 8 $\mu g/m^3$, respectively, have been estimated (U.S. Environmental Protection Agency, 1995). The actual fraction of quartz in the PM coarse samples may be slightly lower than that which was estimated by Davis et al. (1984) in the coarse fraction, however, due to the large number of sources and widespread emissions, there is some potential for some silica particles to be in the fine mode (U.S. Environmental Protection Agency, 1995).

Silica is one of the most common substances to which workers are exposed. There are two physical forms of silica (i.e., crystalline and amorphous), with at least four polymorphs or forms of crystalline silica. These include quartz, cristobalite, tridymite, and tripoli.

Although identical chemically, they differ from quartz in their crystal parameters. The basic structural units of the silica minerals are silicon tetrahedra, arranged in such a manner so that each oxygen atom is common to two tetrahedra. However, there are considerable differences in the arrangements of the silicon tetrahedra among the various crystalline forms of silica (Coyle, 1982). Naturally occurring rocks that contain amorphous forms of silica include diatomite or diatomaceous earth, a hydrated form such as opal, and an unhydrated form, flint (Stokinger, 1981). Silica is also a component of many naturally occurring silicate minerals in which various cations and anions are substituted into a crystalline silica matrix. Examples of such silicates are kaolin, talc, vermiculite, micas, bentonite, feldspar, and Fuller's earth (Silicosis and Silicate Disease Committee, 1988). Commonly encountered synthetic amorphous silicas, according to their method of preparation, are SiO_2 gel (silica G), precipitated SiO_2 (silica P), and fumed SiO_2 (silica F). The most outstanding characteristics of synthetic amorphous silicas are their particle size and high specific surface area, which determine their numerous applications (Stokinger, 1981).

11.7.2 Health Effects

The causal relationship between inhalation of occupational levels of dust containing crystalline silica and pulmonary inflammation and the consequent development of silica-induced pulmonary fibrosis (i.e., silicosis) is well established (Spencer, 1977; Morgan et al., 1980; Bowden and Adamson, 1984). During the acute phase of exposure, a pulmonary inflammatory response develops and may progress to alveolar proteinosis and a granulomatous-type pattern of disease in rats and other rodent species. A pattern of nodular fibrosis occurs in chronically exposed laboratory animals and humans (Ziskind et al., 1976; Spencer, 1977; Morgan et al., 1980; Bowden and Adamson, 1984). Although there is experimental and some human evidence that quartz can also cause lung cancer, a clear correlation between pulmonary fibrosis and neoplasia has been suggested but has not been definitively established. Acute high occupational exposures can elicit a rapid onset of lung inflammation, lead to serious, if not fatal, lung dysfunction.

The pulmonary morphological effects of inhaled crystalline silica are well established, however, there is a paucity of information on the respiratory tract effects of inhaled amorphous forms of silica. The limited information available suggests that the respiratory

tract effects following exposures to amorphous silicates may be reversible in the absence of continuing exposures (Groth et al., 1981; Schepers, 1981; Gosicki et al., 1978; Pratt, 1983). Thus, current evidence infers that amorphous silica is not as severe a hazard as the various polymorphs of crystalline silica.

Parameters which have been commonly used to assess the respiratory effects of silica exposure in experimental animals include lung weight, development of pulmonary fibrosis, or biomarkers for fibrosis, such as collagen content, cytotoxicity, respiratory inflammation, biochemical indices of homogenized lung samples or BAL samples, and immunologic responses. Few studies have provided exposure-response data from which definitive effect levels could be derived, thus necessitating comparisons among studies in which experimental conditions may vary considerably. A review of the published laboratory animal toxicology studies is available (U.S. Environmental Protection Agency, 1995).

11.7.2.1 Differences Between Chemical Forms of Silica

A few studies have been carried out to compare the effects of inhaled crystalline and amorphous silica particles. Pratt (1983) exposed guinea pigs to atmospheric suspensions of either crystalline silica in the form of cristobalite, to amorphous diatomaceous earth, or to amorphous volcanic glass for 21 to 24 mo. The index of lung effects was substantially higher for the cristobalite-exposed animals when compared to guinea pigs exposed to the other two polymorphs of amorphous silica particles (Pratt, 1983). Hemenway et al. (1986) exposed rats for 8 days to aerosols of one of three silicon dioxide species, α-cristobalite, α-quartz, and amorphous silica particles. The greatest measure of lung injury was produced with cristobalite, which caused substantial inflammation and fibrosis. Exposures to α-quartz produced intermediate effects, while amorphous silica produced only minimal pulmonary effects. The authors concluded that amorphous silica particles were less toxic than the two different species of crystalline silica polymorphs. In support of the results of Hemenway et al., Warheit and coworkers (1991a) carried out a number of short-term inhalation studies using cristabolite, quartz, Ludox colloidal silica, a form of precipitated amorphous silica, and amorphous silica particles in the form of Zeofree 80. Rats were exposed to silica aerosols for periods ranging from 3 days to 4 weeks and evaluated by bronchoalveolar lavage and cellular proliferation indices at several postexposure time periods. Brief exposures to

2 different forms of crystalline silica particles at 100,000 $\mu g/m^3$ produced persistent pulmonary inflammatory responses, characterized by PMN recruitment and consistent elevated biomarkers of cytotoxicity in BAL fluids. Progressive histopathologic lesions previously were observed within 1 mo after a 3-day exposure (Warheit et al., 1991a). In contrast, a 3-day exposure to amorphous silica, Zeofree 80 particles produced a transient pulmonary inflammatory response, and 2 or 4-week exposures to Ludox elicited pulmonary inflammation at 50 or 150 mg/m^3 but not at 10 mg/m^3. Most biochemical parameters returned to control values following a 3-mo recovery period. These results demonstrated that the crystalline forms of silica dust were much more potent in producing pulmonary toxicity in comparison to amorphous or colloidal forms of silica, which generally produced transient pulmonary effects (Warheit et al., 1991a, 1991b, 1995).

11.7.2.2 Species Differences

It seems clear that the fibrogenic effects of crystalline silica exposure may vary depending on the species used in experimental studies. Rats appear to be more sensitive to the development of silica-induced lung injury when compared to other mice and hamsters. For example, Uber and McReynolds (1982) reported that hamsters were more resistant to the effects of silica when compared to other rodent species. In addition, Warheit et al., (1994) reported that inhalation exposure to silica in complement-normal and complement-deficient mice produced an acute pulmonary inflammatory response which was mild and transient, compared to the pulmonary effects observed in rats wherein silica produced a sustained and progressive pulmonary inflammatory response. In support of these results, mice intratracheally injected with silica particles had a milder fibrogenic response when compared with rats (Hatch et al., 1984). It seems clear, however, that the silica-induced response in mice depends upon the strain, as there appear to be low and high responding strains of mice to silica (Callis et al., 1985; Hubbard, 1989).

Differences are not only apparent across and within rodent species, but also between rodents and humans. Unlike the nodules observed in human X rays, silicosis is manifested in rat X rays as a diffuse "haziness," described as a ground-glass appearance with some peripheral striation (Drew and Kutzman, 1984). In a chronic study by Muhle et al. (1989), the principal nonneoplastic finding in the silica-exposed rats, extensive subpleural and

peribronchiolar fibrosis, was described as being unlike the nodular fibrosis seen in human silicosis. Such interspecies differences and the fact that most of the available laboratory animal studies only examined one dose level may limit the use of laboratory animal data for extrapolation of the silicosis risk observed in higher exposure conditions of human occupational studies. Fortunately, recent documentation of several well conducted human studies obviates the need to rely exclusively on extrapolation from laboratory animal data.

Table 11-55 summarizes the four epidemiologic studies reviewed. A more complete review of these and other relevant human studies is available elsewhere (U.S. Environmental Protection Agency, 1995). Because of the size of the cohorts, the use of similar longitudinal retrospective study designs, and the use of a similar, high quality statistical approach to the representation of silicosis risk from silica exposure, the studies of white South African gold miners and Canadian hardrock miners are considered the most reliable basis for an assessment of silicosis risk at low exposure levels. A 70-year continuous exposure to the average and high estimates of ambient U.S. quartz levels (3 and 8 $\mu g/m^3$) would result in approximate occupational equivalent cumulative silica exposures of 0.6 and 1.6 μg silica/m^3 $\times$ years, respectively (U.S. Environmental Protection Agency, 1995). Both the South African and Canadian studies predict a silicosis risk of 0% for a cumulative silica exposure of 0.6 mg/m^3 $\times$ years.

The estimates of cumulative risk from these two studies quickly diverge at higher cumulative exposures. At 1.6 mg/m^3 $\times$ years, the South African study predicts a 2% and the Canadian study predicts a 0.4% cumulative silicosis risk. Even greater divergence occurs at higher exposure levels. An indication that the South African results may be more representative of the true shape of the dose-response curve is given by the results of other studies in the United States and Hong Kong. Muir et al. (1989b) suggest that the data from studies of Vermont granite miners (Theriault et al., 1974) suggest that "...the true probability of developing category 1 [on the ILO, 1972 scale] pneumoconiosis after 46 years of exposure to 0.05 mg/m^3 of respirable silica [a 2.3 mg/m^3 $\times$ years cumulative exposure] might be about 30%." Ng and Chan (1994) reported that 24% of the X rays of Hong Kong granite workers that received an average cumulative silica exposure of 1.9 mg/m^3 $\times$ years contained rounded opacities indicative of silicosis. These estimates of risk are well above the $< 1\%$ cumulative risk of silicosis predicted by Muir et al. (1989b) for a cumulative exposure of

TABLE 11-55. SUMMARY OF OCCUPATIONAL STUDIES OF SILICOSIS RISK

Study Type	Study Population	Health Effect	% Silica (Quartz)	3 μg Q/M^3 Risk (%)[a]	8 μg Q/M^3 Risk (%)[a]	Reference
LRC	2235 South African miners; started after 1938 & worked $\geq$ 10 yrs; followed to 1991	313 cases of Silicosis (ILO $\geq$ 1/1)	30%	0%	2%	Hnizdo & Sluis-Cremer (1993)
LRC	2109 Canadian miners; started 1940-1959; followed to 1982 or end of exposure	32 cases of silicosis (ILO $\geq$ 1/1)	6-8.4%	0%	0.4%	Muir et al. (1989a,b); Verma et al. (1989)
XRC	338 Hong Kong granite workers; 132 past workers (1967-1985) and 206 current workers (1985); only most recent X rays examined	36 radiographical abnormalities, rounded opacities (ILO $\geq$ 1/1)	27%	6%	10%	Ng and Chan (1994)
CC	U.S. (North Carolina) dust trade workers diagnosed with silicosis 1935-1980	216 cases of silicosis; 672 controls	1-50%	b	b	Rice et al. (1986)

CC - Case-Control L - Longitudinal RC - Retrospective Cohort X - Cross-Sectional Q - Quartz

[a]To obtain risk estimates for continuous lifetime exposures of 3 and 8 μg Q/m^3 from occupational studies, these ambient levels were converted to equivalent cumulative occupational exposure levels of 0.6 and 1.6 mg/m^3 $\times$ years (U.S. Environmental Protection Agency, 1995).

[b]A dose-response curve was not reported. The no measureable effect level of 80-100 μg/m^3 reported by Rice et al. (1986) represents number of cases in the group exposed to this amount did not significantly differ relative to number of cases observed in the reference group. However, risk among the reference group was not 0.

Source: Adopted from Rice et al. (1993).

2 mg/m^3 × years, but are consistent with the 10% risk and the shape of the dose-response curve reported by Hnizdo and Sluis-Cremer (1993) for South African gold miners (U.S. Environmental Protection Agency, 1995). Also, a recently completed Italian study of male workers employed in the ceramics industry (Cavariani et al., 1995) reports a 48% cumulative risk of silicosis (95% confidence interval 41.5 to 54.9) after 30 years of employment (past exposure levels not given, but estimated to be 3 to 5 times higher then the current 0.1 mg/m^3 standard). The authors reported that their risk estimates were higher than those predicted by Muir et al. (1989b), but "...consistent with the findings among South African gold miners."

Rice et al. (1993) have suggested that the differences in the South African and Canadian studies at higher cumulative exposures are likely the combined result of several factors, including differences in the definition of radiographic silicosis used in the two studies, possible errors in exposure estimates, possible underestimation of the quartz content of the dust in the Canadian study, inhalation of aluminum dust as a protective measure by Canadian miners, reader variability, and the use of cumulative exposures to estimate risk. These and other issues, such as the importance of tracking worker health beyond employment, the quality of radiographs and the importance of surface properties, particle size, distribution, and percentage of silica in the respirable dust fraction are discussed elsewhere (U.S. Environmental Protection Agency, 1995).

11.7.3 Recent Concepts in the Mechanisms of Silica-related Lung Disease

Exposures to crystalline silica are associated with the development of chronic inflammation and pulmonary fibrosis (i.e., silicosis) in humans (Ziskind et al., 1976; Spencer, 1977; Sargent and Morgan, 1980) and in experimental animals (Allison et al., 1966; Ziskind et al., 1976; Burns et al., 1980; Morgan et al., 1980; Lugano et al., 1982; Donaldson et al., 1988). The pathogenetic mechanisms of silica-induced lung injury have not been fully elucidated, however, it is generally considered that both alveolar and interstitial macrophages play important roles in the development of this disease (Bowden, 1987). In this regard, the fibrogenic stimulus of crystalline silica particles has been attributed, in part, to the rupture of macrophage plasma and lysosomal membranes followed by the subsequent synthesis and secretion of fibroblast proliferating factors (Allison et al., 1966; Reiser and Last, 1986; Bowden, 1987; Brown et al., 1988). However, the continuous recruitment of

fibroblasts, PMNs, lymphocytes, and plasma cells to alveolar and interstitial sites, as well as the multifocal distribution of lesions, suggests that the development of silica-related pulmonary lesions is a complex process. The Type 1 epithelial injury and consequent hypertrophic and hyperplastic responses of Type 2 epithelial cells is probably an important component of the fibrogenic process. Alternatively, the sequestration of silica-containing lipid-filled, foamy AMs within alveoli is an example of an effect that may be independent of the fibrogenic process (Warheit and Gavett, 1993).

The role of growth factor regulation of pulmonary cells in the development of particle-related pulmonary fibrosis has been described in numerous reviews (Crouch, 1990; Goldstein and Fine, 1986; King et al., 1989, Kovacs, 1991; Reiser and Last, 1986; Rom et al., 1991). Briefly, it is generally considered that competence factors and progression factors play important roles in facilitating the movement of cells through the cell cycle. Competence factors, such as platelet-derived growth factor (PDGF) and fibronectin, prime cells to respond to additional factors such as progression factors (e.g. interleukin-(IL)-1, and insulin-like growth factor (IGF), which initiate DNA synthesis and mitosis. Pulmonary macrophages synthesize and secrete numerous growth factors for fibroblasts, including PDGF, transforming growth factor-β (TGF-β), IL-1, tumor necrosis factor-α (TNF-α), IL-6, fibroblast growth factor (FGF) (Kovacs, 1991). Proliferation of interstitial fibroblasts and consequent synthesis and secretion of collagen is thought to play a significant role in the fibrogenic process (Warheit and Gavett, 1993).

Inhalation of high concentrations of crystalline silica particles in rats is known to cause a sustained pulmonary inflammatory response. It appears that the development of pulmonary inflammation and the corresponding release of inflammatory mediators are necessary, but not always sufficient for the development of fibrosis (Crouch, 1990). This conclusion is based upon the observation that the temporal onset of inflammatory cells in the lung always precedes the development of pulmonary fibrosis.

The role of PMNs, which form a major component of the acute inflammatory response to silica, in the development of silica-related lung injury has not been established. A short-term inhalation bioassay (Warheit et al., 1991a) was used to assess the contribution of PMNs to lung injury induced by the inhalation of silica particles (Gavett et al., 1992). In this study male CD rats were depleted of PMNs by intraperitoneal administration of

anti-PMN serum immediately prior to the first and third days of a 3-day exposure to silica (100,000 $\mu g/m^3$). There were no significant differences in biomarkers of lung injury between normal and PMN-depleted, silica-exposed groups, measured in BAL fluids immediately or 1 day following the 3-day exposure. These results were in contrast with the data reported by Henderson and coworkers (1991) who studied the effects of PMN depletion on silica-induced lung injury in female Fischer rats. These investigators found that depletion of blood leukocytes one day prior to instillation of quartz particles caused a reduction in BAL fluid markers of permeability and cytotoxicity. In this study, administration of anti-PMN serum reduced numbers of AMs to one-third of their normal numbers. This reduction of AM numbers was not however observed in the study of Gavett et al. (1992), and this may indicate that AM release of cytotoxic proteases contributes significantly to lung injury following exposure to crystalline silica particles.

11.8 ASBESTOS

This section on asbestos fibers is designed to give an overview of current concepts regarding the pulmonary toxicity of this environmental pollutant and underlying mechanisms of action. No attempt has been made to review all of the relevant toxicity data, which is voluminous. Asbestos is well established as a fibrogenic pollutant and causes tumors following chronic exposures in experimental animals. Reviews on the effects of asbestos can be found elsewhere (U.S. Environmental Protection Agency, 1986; Mossman and Gee, 1989) (Rom, Travis and Brody, 1991; Health Effects Institute - Asbestos Research, 1991).

11.8.1 General Characteristics

Asbestos fibers are ubiquitous atmospheric pollutants in the environment which have been present in airborne concentrations for centuries. Evidence for the widespread nature of asbestos can be found by the confirmation of fiber deposition recovered from Antarctic ice samples (Kohyania, 1989). According to NIOSH and WHO counting rules, only fibers greater than 5 μm in length qualify for measurement. Using these criteria, mean fiber concentrations of 0.0005 fibers/cc of air (f/cc) have been measured in rural areas. In urban areas, total fiber concentrations of 0.002 f/cc greater than 5 μm in length have been

reported (Health Effects Institute - Asbestos Research, 1991). Fiber concentrations in suburban areas are roughly an order of magnitude lower than in urban areas. As might be expected, industrial sites or sites in close proximity to asbestos sources have higher fiber counts than normal urban areas (Corn, 1994). The vast majority of asbestos fibers in outdoor air are less than 5 μm in length (Health Effects Institute - Asbestos Research, 1991). To summarize, the presence of asbestos fibers in the air is universal and all humans have a significant numbers of fibers in their respiratory system.

11.8.1.1 Types of Asbestos

Asbestos fibers are usually identified as a family of crystalline hydrated silicates that have a diameter of $\leq$ 3.5 μm and an aspect ratio of more than 3:1 (ratio of length to diameter) which confers them with a fibrous geometry. The term asbestos does not refer to a common mineralogical designation, but to a commercial one, as the six different asbestos minerals are physically distinct types of minerals. There are two major groups of asbestos materials, 1) the serpentine group, which contains curly chrysotile fibers, accounting for 95% of the world's production of asbestos; and the amphibole group which is generally needlelike in shape and contains the five other types of asbestos fibers, namely crocidolite, amosite, anthophyllite, tremolite, and actinolite (Mossman and Gee, 1989).

Long-term exposure to asbestos fibers in humans and experimental animals clearly has been associated with the development of pulmonary disease (Selikoff and Lee, 1978). Pleural mesothelioma, bronchogenic carcinoma, and asbestosis are likely to occur far more frequently in asbestos workers when compared to the normal population. Asbestosis is a restrictive lung disease manifested by diffuse and progressive interstitial fibrosis (Selikoff and Lee, 1978). Several reviews have emphasized that the pathogenetic mechanisms of this disease have not been well elucidated (Becklake, 1982; Craighead *et al.*, 1982; Rom *et al.*, 1991). Similar to the effects of silica, alveolar and interstitial macrophages are postulated to play a central role between the initial inflammatory process and the subsequent synthesis and deposition of connective tissue, which is a characteristic feature of the fibrogenic response (Warheit and Hesterberg, 1994).

11.8.2 Biophysical Factors and their Roles in the Development of Fiber Toxicity

The underlying mechanisms through which fibers cause lung disease have unique biophysical elements which are related to the development of fiber-induced lung disease. Two important factors, namely dimension and durability, will be briefly discussed here because they are additional key factors which separate the biological effects of fibers from those of simple low solubility particles. In addition, they play a significant role in the toxicity of asbestos fibers.

Fiber dimension plays an important role in influencing the pathogenesis of asbestos-related lung disease (Stanton *et al.*, 1981). In support of this concept, Davis and coworkers (1986) exposed rats by inhalation for one year to aerosols of specially prepared "short" (< 5 μm in length) amosite asbestos fibers or a preparation of long (> 20 μm) amosite fibers. Both preparations were derived from the same source. The respirable dust mass concentration was identical for each sample preparation, (10,000 $\mu g/m^3$); however the long fiber amosite preparation contained 2060 fibers/cc > 5 μm in length, while the short fiber amosite preparation contained only 70 fibers/cc > 5 μm in length. Thus, the short fiber amosite sample contained greater numbers of fibers compared to the long fiber sample. After a one year exposure, no histopathological effects were reported in rats exposed to the short fiber amosite preparation, while one-third of the rats exposed to the long fiber amosite preparation developed lung tumors. Moreover, virtually all of the rats exposed to the long fibers developed diffuse interstitial lung fibrosis, while no fibrosis was observed in animals treated with the short fiber amosite preparation (Davis *et al.*, 1986). Similar effects were observed when Davis and Jones (1988) compared the pathogenicity of long and short chrysotile asbestos fibers in rats. One year inhalation studies were undertaken with rats exposed to a specially prepared short-fiber sample of Canadian chrysotile asbestos. This was compared, at equal gravimetric concentrations (10 mg/m^3) to fibers generated from the same chrysotile batch, but size-selected to contain the highest possible numbers of long fibers. The short-fiber chrysotile sample contained 1170 fibers/cc > 5 μm in length while the longer-fiber sample contained 5510 fibers/cc > 5 μm in length. Rats exposed to the long-fiber chrysotile sample developed substantially more pulmonary fibrosis than animals treated with the short fiber chrysotile and three times the number of pulmonary tumors (Davis and

Jones, 1988). Based on the results of these studies and other reports, its seems likely that fiber dimension and in particular, fiber length, plays an important role in the development of lung pathological responses.

Fiber durability or biopersistence refers to the retention of inhaled or instilled fibers in the lung over time with regard to number, dimension, surface chemistry, chemical composition, surface area, or other characteristics (Warheit, 1994). The biological activity of fibers can be affected by any alterations in these parameters. Elimination of inhaled fibers from the lung occurs by bulk clearance, generally involving AM uptake and transport to the mucociliary escalator, translocation of fibers to other sites (e.g., lymph nodes) or by dissolution and/or fiber breakage.

Studies have been performed to evaluate the biopersistence/durability of various asbestos fiber types. Two short-term inhalation studies were utilized by Roggli and colleagues to investigate fiber clearance of either inhaled chrysotile or crocidolite asbestos fibers in rats (Roggli *et al.*, 1987; Roggli and Brody, 1984). Asbestos fibers were recovered from digested lung tissue and assessed for dimensional changes at several postexposure time points. After a short exposure to crocidolite asbestos fibers, there was a progressive increase in mean fiber lengths with time, but no change in the mean diameters of fibers recovered from the lung, indicating that the shorter fibers were cleared while the longer fibers were retained (Roggli *et al.*, 1987). In the rats exposed to chrysotile asbestos fibers, there was a similar progressive enhancement of mean fiber lengths with increasing time, but also a reduction in mean fiber diameter, suggesting longitudinal splitting of fibers (Roggli and Brody, 1984). It was concluded that the long chrysotile and crocidolite fibers were selectively retained in the lungs of exposed rats, but only the chrysotile asbestos fibers underwent longitudinal splitting. These results have been corroborated in studies by Bellmann and colleagues who instilled chrysotile and crocidolite fibers into the lungs of rats and evaluated fiber clearance parameters over a 2-year post-instillation period. These investigators reported that lung clearance of short crocidolite fibers was slow and the number of crocidolite fiber longer than 5 μm were not decreased over time suggesting that these fibers were not cleared from the lung. In contrast, the number of retained chrysotile fibers longer than 5 μm was continuously increased over a 2-year period, again principally due to longitudinal splitting of the fibers (Bellmann *et al.*, 1987). In summary, the results of these

studies indicate that asbestos fibers which are long and biopersistent such as amosite, crocidolite, and to a lesser extent, chrysotile asbestos have a greater tendency to produce pulmonary pathological effects relative to shorter fibers or fibers of low durability.

11.8.2.1 Studies on the Mechanisms of Asbestos-Induced Lung Injury

Laboratory animal models of asbestos-related pulmonary fibrosis (i.e., asbestosis) have been developed in rats (Pinkerton *et al.*, 1984; Wagner *et al.*, 1974), mice (Bozelka *et al.*, 1983) guinea pigs (Holt *et al.*, 1966) and sheep (Begin *et al.*, 1981, 1983) exposed chronically to fibers. The experimental models are important for evaluating the anatomic patterns of disease. A major shortcoming of the chronic exposure models, however, is the difficulty in identifying the early pathogenetic events. One example of this problem stems from the fact that the connecting link between initial fiber deposition patterns and the subsequent cellular events that lead to asbestos-related lung injury have not been addressed. Similarly, the role of the macrophage in the early development of asbestos-induced lung injury has not been elucidated. In an effort to address these questions, a rat model of asbestos-induced lung disease was developed wherein animals were exposed for 1 h to an aerosol of chrysotile asbestos fibers and the early physiologic as well as pathological cellular events were evaluated at 48 h and 1 mo postexposure (Warheit *et al.*, 1984; Chang *et al.*, 1988).

Following a 1-h inhalation exposure to chrysotile asbestos, fibers were observed to have deposited selectively on alveolar duct bifurcations (Brody *et al.*, 1981; Brody and Roe, 1983) and were cleared from epithelial surfaces by macrophage-mediated clearance or fiber translocation. The translocated fibers migrated from airspace, through Type 1 epithelial cells, into pulmonary interstitial sites, where they were phagocytized primarily by fibroblasts or interstitial macrophages (Brody *et al.*, 1981, Brody and Hill, 1982). The interactions of these fibers with fibroblasts induced the formation of intracellular microcalcifications, a form of nonspecific cellular injury (Brody and Hill, 1982). On the alveolar side, AMs rapidly were recruited to sites of fiber deposition and phagocytized chrysotile fibers (Warheit *et al.*, 1984). The mechanisms for AM recruitment to alveolar duct bifurcations is associated with complement activation by the inhaled fibers and consequent generation of chemotactic factors (Warheit *et al.*, 1985). Histologic examination of exposed lung tissue indicated that proximal

alveolar duct bifurcations were prominent in asbestos-exposed animals sacrificed 48 h after exposure (Warheit *et al.,* 1984). Using ultrastructural morphometric methods, Chang *et al.* (1988) demonstrated that the influx of recruited alveolar and interstitial macrophages formed a component of an early lesion, which was characterized by enhanced volumes of the epithelial and interstitial compartments of the alveolar duct bifurcation. Additionally, the numbers of alveolar and interstitial macrophages, as well as Type 1 and Type 2 epithelial cells were significantly increased over sham exposed controls. One month postexposure, the numbers of alveolar macrophages on bifurcation surfaces were no longer elevated over the normal level but the volume of the interstitium was still significantly increased by 67% over sham controls. This was due to an increase in the volume of noncellular interstitial matrix, along with an accumulation of interstitial cells, including macrophages, myofibroblasts, fibroblasts, and smooth muscle cells (Chang *et al.*, 1988). The authors concluded that acute structural alteration measured at 2 days after a 1-h exposure were followed by a progressive response, as evidenced by elevated numbers of interstitial cells and localized interstitial fibrosis measured at 1 mo postexposure (Chang *et al.*, 1988).

The measurement of an early asbestos-induced lesion at 48 h and 1 mo after a 1-h exposure and identification of the target cell types have been useful for studying the mechanisms underlying the acute pathologic response to asbestos exposure in rats. The finding of changes in the cellular and noncellular interstitial compartments which precede the consequent development of fibrosis implicates the involvement of fibroblasts in proliferating and synthesizing matrix components such as collagen, elastin, and glycosaminoglycans. The rate of collagen buildup is likely to be a function of both the number of fibroblasts (i.e., fibroblast proliferation) as well as the rate of collagen synthesis by individual cells, balanced by the degradation of collagen by protease-secreting cells. It seems likely that fibroblast proliferation and connective tissue formation are complex processes and may be independently regulated (Goldstein and Fine, 1986; King *et al.,* 1989). Moreover, although fibroblasts are usually considered to be cells which respond passively to the products of effector cells, it seems clear that these cell types play a more active role in facilitating the development of fibrosis (Rom *et al.*, 1991). Notwithstanding our lack of knowledge regarding the complexity of cellular responses in the interstitial microenvironment, it is still attractive to postulate that asbestos-exposed alveolar or interstitial macrophages synthesize

and secrete mitogenic factors that stimulate interstitial cells to increase in number and generate enhanced amounts of connective tissue proteins (Warheit and Hesterberg, 1994).

11.8.2.2 Fiber-Induced Inflammation

Similar to the responses associated with silica exposure, inhalation of asbestos fibers is likely to cause a respiratory tract inflammatory response. Among the many responses that can occur, reactive oxygen species are released by activated macrophages and neutrophils causing tissue damage and may be linked to inflammation, fibrosis, and possibly genotoxic effects. The production of reactive oxygen species by cells may result in their own death. In this regard, *in vitro* exposure of macrophages to crocidolite asbestos fibers resulted in cell death as well as a release of oxygen metabolites (Goodglick and Kane, 1990). This toxicity was scavenged by administration of superoxide dismutase, catalase, or deferoxamine. The role of oxidants in the development of asbestos-induced inflammation and pulmonary fibrosis has also been evaluated by administering a chronic regimen of antioxidants to asbestos-exposed rats (Mossman *et al.*, 1990). The results of these studies demonstrated that the antioxidants mitigated the inflammatory effects of asbestos exposure, and this finding suggests that oxygen radicals (probably derived from inflammatory cells or AMs) may play a role in asbestos-induced lung injury. In previous studies, it had been reported that asbestos fibers induced the production of oxygen radicals by AMs *in vitro* as well as in cell-free reaction mixtures (Hansen and Mossman, 1987; Weitzman and Graceffa, 1984).

11.8.2.3 Growth Factors

Growth factors have been implicated in mediating the progression of fiber-induced pulmonary fibrosis. Many of the studies linking growth factors and the development of fibrosis have been investigated in association with asbestos exposure. Chrysotile asbestos fibers were shown to stimulate lavaged AMs to produce a platelet-derived growth factor (PDGF) homolog that is mitogenic for rat lung fibroblasts *in vitro* (Kumar *et al.*, 1988). PDGF along with fibronectin is one of the classical competence factors for fibroblasts (Goldstein and Fine, 1986). In addition, PDGF derived from AMs was shown to be chemotactic for fibroblasts *in vitro* (Osornio-Vargas *et al.*, 1990).

Cells recovered by pulmonary lavage from asbestos-exposed rats are also capable of releasing progression factors for fibroblasts. Asbestos-exposed macrophages secreted a fibroblast growth factor (FGF), also referred to as macrophage-derived growth factor (MDGF), over a period of 24 weeks following exposure (Lemaire *et al.*, 1986). This secretion of MDGF coincided with the development of histopathological changes in the lungs of exposed animals. However, other studies have failed to demonstrate a correlation between *in vitro* fibroblast proliferation and pathological responses *in vivo*. In one study, AMs exposed to both long and short crocidolite asbestos fibers *in vivo* were evaluated for fibroblast proliferation factors *in vitro* (Adamson and Bowden, 1990). It was surprising to find, that no fibroblast activity could be measured in the culture supernatant of cells lavaged from rats instilled with long fibers, despite significant pathological effects in the lungs of instilled animals (Adamson and Bowden, 1990). In contrast, short fibers produced no significant pathological effects, but significant fibroblast proliferation activity was measured in cell culture supernatants from rats exposed to these fibers. This finding does not correlate with the results of previous inhalation studies (described earlier in this section) which have shown that long asbestos fibers are significantly more pathogenic than short fibers (Davis *et al.*, 1986).

The development of interstitial fibrosis depends upon production of connective tissue proteins as well as increased mesenchymal cell proliferation. TGF-β which is secreted by AMs and induces fibroblast proliferation, also has been shown to increase elastin production by neonatal rat lung fibroblasts (McGowan and McNamer, 1990). In this regard, it will be important to more fully ascertain the functions of the different forms of TGF-β and TGF-β receptors on fibroblasts, in order to better understand the fibrogenic process (Kalter and Brody, 1991; Segarini, 1991).

11.9 TOXICOLOGY OF OTHER PARTICULATE MATTER

11.9.1 Introduction

This section reviews the toxicology of other PM within the framework described in the introduction to the chapter. The particle classes chosen for inclusion here are those which may actually occur in ambient air or may be surrogates for these. For example, some

of the particles discussed are considered to be models of "nuisance" or "inert" dusts (i.e., those having low intrinsic toxicity) and, as such, are likely to be representative of similar ambient PM. In many instances, there are only a few studies examining the response on specific biological endpoints following inhalation exposure. In these cases, and where available, intratracheal instillation studies (injection of a bolus of material into the lungs) have been used to compare the toxicity of different particle types. While instillation may produce more severe pulmonary damage than would inhalation (largely due to differences in delivered doses and dose rates), the relative toxicities of different particles seem to be similar when given by either method (Driscoll et al., 1991). Thus, intracheal instillation studies can be used for comparative potency purposes, but it is not possible to quantitatively extrapolate the resulting exposure-response data to inhalation exposure-responses. In a number of cases, particles with low intrinsic toxicity have been used in instillation studies to delineate nonspecific particle effects from effects of known toxicants. Some of these studies are discussed herein, as they are often the only database for such materials.

11.9.2 Mortality

Table 11-56 shows results of mortality assays using particles >1 μm in diameter; all of these involved repeated or chronic exposures to high concentrations of various PM, some of which are considered to be of low toxicity. Essentially no treatment-related mortality was observed in any of these studies.

Recent interest has been focused on the inherent toxicity of a smaller size class of particles, namely the ultrafine particles which are discussed in section 11.5. While the mass concentration of ultrafine particles in ambient air may be low, their number concentration may be quite high, as discussed previously in terms of acidic sulfate aerosols.

11.9.3 Pulmonary Mechanical Function

Assessments of pulmonary mechanical function have generally been carried out with particles having some inherent toxicity, but there have been some studies examining effects due to other, low intrinsic toxicity particles for comparison.

TABLE 11-56. EFFECTS OF PM (≥1 μm) ON MORTALITY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect[a]	Reference
Raw shale oil	Rat, M/F, F344, 11 weeks	Whole body	56,000-492,000	6-8 (MMAD); 1.7-2	13 weeks	33-50%, only at 492,000 $\mu g/m^3$	Gordon et al. (1987)
TiO_2	Rat, M/F, F-344, 8 weeks	Whole body	5,000	1.1 (MMAD); 1.5	6 h/day, 5 days/week, 2 years	None	Muhle et al. (1991)
Toner	Rat, M/F, F-344, 8 weeks	Whole body	16,000	4 (MMAD)	6 h/days, 5 days/week, 2 years	None	Muhle et al. (1991)
Coal dust	Rat, M, Wistar, 18 weeks	Whole body	6,600, 14,900	2.1 (MMAD); 2.7	6 h/day, 5 days/week, 20 mo	None	Karagianes et al. (1981)
Petroleum coke (micronized)	Rat, M, SD	Whole body	10,000, 30,000	3.1 (AED); 1.9	6 h/day, 5 days/week, 2 years	None	Klonne et al. (1987)
Petroleum coke (micronized)	Monkey, adult, cynomologous	Whole body	10,000, 30,000	3.1 (AED); 1.9	6 h/day, 5 days/week, 2 years	None	Klonne et al. (1987)
Volcanic ash	Rat, M/F, F-344, 3 mo	Whole body	5,000, 50,000	respirable (unspecified size)	6 h/day, 5 days/week, 2 years	None	Wehner et al. (1983)
TiO_2	Rat, M/F, CD	Whole body	10,000, 50,000, 250,000	1.5-1.7 (MMD)	6 h/day, 5 days/week, 2 years	None	Lee et al. (1985)
Fly ash (coal)	Rat, M, Wistar, 3 mo	Whole body	270,000	47% ≤ 3.75 μm	6 h/day, 15 days	None	Chauhan et al. (1987)
California road dust	Rat, F344	Nose-only	300, 900	4 (MMAD); 2.2	4 h/day, 4 days/week, 8 weeks	None	Kleinman et al. (1995)

[a]Effect indicates "treatment related" mortality.

Wright et al. (1988) instilled rats (Sprague-Dawley; F; 200g) with 10,000 μg iron oxide (0.1 μm GMD, σg = 1.7) or silica (quartz) (1.3 μm, σg = 2.5). At 1 mo after exposure, they noted no changes in various indices of pulmonary mechanics (total lung capacity [TLC]; functional residual capacity [FRC]; nitrogen [N_2] washout; FEV1; or peak expiratory flow [PEF]) in animals exposed to iron oxide, but silica exposure resulted in changes in the N_2 washout curve and decreased compliance. Bégin et al. (1985) instilled into sheep (Male; 25 to 45 kg BW) 100,000 μg latex beads (0.1 μm) or asbestos fibers. The latex produced no change in pulmonary function (TLC, residual volume [RV]; vital capacity [VC]; expiratory reserve volume [ERV]; pulmonary compliance [Cpulm]; pulmonary resistance [Rpulm]; FRC), while the asbestos produced a reduction in compliance, abnormalities in the N_2 washout curve, and changes in forced expiratory flow measurements.

There are a few studies of pulmonary function responses following inhalation exposures to PM. Wehner et al. (1983) exposed rats (F-344; M/F, 3mo) to 5,000 or 50,000 $\mu g/m^3$ volcanic ash (Mt. St. Helens) for 6 h/day, 5 days/week for up to 24 mo (Table 11-57). By 12 mo of exposure, no changes in lung volume were noted. By 8 mo of exposure, there was an increase in respiratory frequency in animals exposed at the higher concentration, but no change at the lower concentration.

Heinrich et al. (1989) exposed rats for 6 h/day, 5 days/week up to 24 mo to titanium dioxide (TiO_2) at 5,000 $\mu g/m^3$ and silica at 1,000 $\mu g/m^3$. Exposure to silica produced a reduction in quasistatic lung compliance, tidal volume, (V_T), inspiratory capacity (IC), VC, RV, and TLC. Diffusion capacity for carbon monoxide (DLco) was also reduced, and the N_2 washout curve was altered; these changes indicate a functionally restrictive lung, a finding often noted in humans occupationally exposed to silicates. None of these variables were altered by exposure to TiO_2.

Acidic sulfates have been associated with alterations in bronchial responsiveness, but there are few studies with other particles which examined this response. Fedan et al. (1985) exposed rats (F344, whole body) for 7 h/day, 5 days/week for 2 years to coal dust (size described as respirable, but not specifically stated) at 2,000 $\mu g/m^3$, and examined the pharmacological response of isolated tracheal preparations to various agonists. The coal dust

TABLE 11-57. EFFECTS OF INHALED PM ON PULMONARY MECHANICAL FUNCTION

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect[a]	Reference
Volcanic ash	Rat, Sprague-Dawley, 40 days	Whole body	9,400	0.65 (MMAD); 1.78	2 h/days, 5 days	No changes (F, V_T, V_{insp}, V_{exp})	Raub et al. (1985)
Fly ash (coal) (Illinois # 6)	Guinea pig, Hartley, 250-320 g	Nose-only	5,800	0.21 (MMAD); 4.14	1 or 2 h	2 h: ↓TLC, VC, DL_{co} up to 96 h PE 1 h: no effect	Chen et al. (1990)
Fly ash (coal) (Montana lignite)	Guinea pig, Hartley, 250-320 g	Nose-only	5,800	0.21 (MMAD); 4.14	1 or 2 h	2 h: ↓TLC, VC; no change in DL_{co}	Chen et al. (1990)
Volcanic ash	Rat, M/F, F-344, 3 mo	Whole body	5,000, 50,000	Respirable	6 h/day, 5 days/week, 24 mo	↑f for 50,000 $\mu g/m^3$ by 8 mo; no change for 5,000 $\mu g/m^3$	Wehner et al. (1983)
Volcanic ash	Guinea pig, Hartley, 300-425 g	Head	9,400	0.65 (MMAD); 1.78	2 h	No change in R_{aw}, C_{dyn}, f, V_I, $\dot{V}_E$	Wiester et al. (1985)
Coal dust	Rat, Wistar, 200-300 g Conventional and germ free	Whole body	10,000	geometric mean <5 μm	8 h/day, 120 days	↓ FEV_1, $\dot{V}_{max}$ (10%) (Germfree); only ↓ $\dot{V}_{max}$ (10%) conv.	Moorman et al. (1977)
TiO_2	Rat, F, F-344, 8 weeks	Whole body	5,000	—	6 h/day, 5 days/week, 24 mo	No changes (C, V_T, IC, VC, RV, TLC, DL_{co}, N_2 washout)	Heinrich et al. (1989)

Key to abbreviations:
f: breathing frequency
V_T: tidal volume
V_{insp}: inspiratory flow
V_{exp}: expiratory flow
TLC: total lung capacity
VC: vital capacity
DL_{co}: carbon monoxide diffusing capacity
PE: post exposure
IC: inspiratory capacity
RV: residual volume
R_{aw}: airway resistance
C_{dyn}: dynamic compliance
$\dot{V}_I$ = max inspiratory flow
$\dot{V}_E$ = expiratory minute volume
$FEV_{1.0}$ = forced expiratory volume (1 sec)
$\dot{V}_{max}$ (10%) = maximal flow at 10% FVC
FVC = forced vital capacity

exposure increased the maximal contractile response of the tracheal smooth muscle to acetylcholine (a bronchoconstrictor), compared to air exposed control tissue, but did not alter the slope of the acetylcholine concentration-response curve nor sensitivity (i.e., EC50). No change in response to isoproterenol (a bronchodilator) was noted. Wiester et al. (1985) exposed guinea pigs for 2 h to 9,400 $\mu g/m^3$ of Mt. St. Helens volcanic ash (0.65 μm). No changes in pulmonary mechanics measured during exposure (airway resistance, dynamic compliance, breathing frequency, maximum inspiratory flow or expiratory minute volume) were noted. However, following exposure, airway hyporesponsiveness to histamine challenge was observed.

It should be noted that, as with acidic sulfates, changes in pulmonary function may not be the most sensitive marker of response to other PM. For example, inflammatory changes in sheep following the instillation of latex particles (100,000 μg in 100 ml fluid) were not associated with any changes in lung volumes, resistance, or compliance (Bégin et al., 1985).

11.9.4 Pulmonary Morphology and Biochemistry

The vast majority of the information concerning morphologic alterations from inhaled particles involve diesel exhaust, and this is discussed in this chapter and reviewed in another document (U.S. Environmental Protection Agency, 1994). In addition, and as previously mentioned with acidic sulfate particles, markers in lung BAL have been used to assess damage following PM exposure.

The ability of ambient particles to affect lung morphology was strongly suggested by Böhm et al. (1989). They exposed rats (Wistar, F, 2.5 mo) for 6 mo to the ambient air of two cities in Brazil, namely São Paulo and Cubatao. Although characterization of air pollution levels was vague, pollution in the former appeared to be dominated by automobile exhaust gases, while that in the latter by industrially derived particulate matter. Rats exposed in Cubatao showed various responses, such as mucus hypersecretion and epithelial hyperplasia, in both the upper and lower bronchial tree, while those exposed in São Paulo showed effects generally limited to the upper bronchial tree. Particle concentrations (PM_{10}) were as high as 164 $\mu g/m^3$ in Cubatao. Thus, high PM levels were suggested to be

responsible for the observed effects, although the contribution of other components of the pollutant mix could not be discounted.

Some intratracheal instillation studies have compared morphological effects resulting from exposure to different particles. Wright et al. (1988) instilled 10,000 μg iron oxide (Fe_2O_3; 0.1 μm GMD, σg = 1.7) or 10,000 μg quartz (1.3 μm GMD, σg = 2.5) into rats, and examined the lungs 30 days following each exposure. The iron oxide did not produce any histological or morphometric changes, while the quartz exposure resulted in aggregations of PMNs and AMs around small airways, alveolar proteinosis, increased alveolar distances, airspace enlargement, and increased thickness of respiratory bronchiolar walls.

Another example of an instillation study which may be used to compare effects from different types of particles is that of Sanders et al. (1982), who instilled rats (F-344, female, young adult) with 40,000 μg of either soil (sandy loam, 1.6 μm CMD), volcanic ash (Mt. St. Helens, 0.5 to 1.5 μm CMD), or crystalline quartz (1.5 μm CMD). Mononuclear cell infiltration was noted with both the soil and ash particles in regions of high particle aggregation. There was also some Type 2 epithelial cell hyperplasia 7 to 37 days following ash or soil instillation. However, the ash produced a fibrotic response to a greater extent than did the soil, with indications from the former of a simple pneumoconiosis and moderate lipoproteinosis. Some foci of particle-laden macrophages were noted in the mediastinal lymph nodes of soil exposed animals, but the ash-exposed animals showed reactive lymphoid hyperplasia. Quartz resulted in production of granulomas, deposition of collagen, widespread lipoproproteinosis, and fibrosis in regional lymph nodes.

The comparative fibrogenic potential of a number of particle types was examined by Schreider et al. (1985). Rats (M, SD, 300g) were exposed by intratracheal instillation to 5,000, 15,000, or 45,000 μg of Montmorillonite clay (0.84 μm CMD), quartz (1.1 μm), Mt. St. Helens volcanic ash (1.2 μm), stack-collected coal fly ash (1.5 μm) or hopper-collected fly ash (1.9 μm), or to 5 or 15 mg of a coal-oil ash mixture (3.9 μm). Lung histology was assessed at 90 days post instillation. Neutrophils were noted in alveoli only with quartz (all concentrations), stack ash (at high concentration), and volcanic ash (low and mid concentrations). Some fibrosis was produced by all of the particles, although there were qualitative and quantitative differences among the different exposure groups. The order of

fibrosis potential, from greatest to least, was as follows: quartz > clay > volcanic ash > hopper coal ash > stack coal ash > oil-coal ash mixture.

Bégin et al. (1985) instilled 100,000 μg of 0.1 μm latex beads or asbestos fibers into the lungs of sheep (25 to 45 kg), and examined lavage at 1 to 60 days post instillation. The latex produced only transient alveolitis and transient increases in the number of AMs and PMNs in lavage beginning at day 1, while the asbestos-exposed animals had a persistent inflammatory response and more severe damage. Callis et al. (1985) instilled silica or latex particles (0.9 μm) into the lungs of mice. While the latter produced some increase in protein and cell number in lavage, the response to the former was much greater. Finally, Lindenschmidt et al. (1990) instilled rats with either of two inert dusts, (Al_2O_3; 5.3 μm) and TiO_2 (2.2 μm) at 1,000 or 5,000 μg/100g body weight and examined the lungs up to 63 days post instillation. Both particle types produced similar increases in N-acetylglucosamine and total recovered cells in lavage, while a minimal Type 2 cell hyperplasia noted with Al_2O_3 was even less severe with TiO_2. However, when results were compared with those for instilled silica, any responses seen with the inert particles decreased towards control level during the 2-mo study period, while changes with silica progressed. This highlights the difference between the inert and fibrogenic materials. Thus, the instillation studies suggest that there may be some nonspecific particle effect, but clearly the chemical characteristics of the particle affects the ultimate biological response. In any case, levels of particles with low intrinsic toxicity are not associated with major nonspecific effects.

The effects of inhaled PM on pulmonary morphology are outlined in Table 11-58. Most of the studies used fly ash and volcanic ash; TiO_2 has also been used to assess effects of a "nuisance" (low intrinsic toxicity) type of particle. However, with the exception of the study of road dust by Kleinman et al. (1995), exposure concentrations ranged from very high to extremely high and likely caused overload with long-term exposures. Responses, when they did occur, were quite similar for the various particles, characterized by focal aggregates of particle-laden macrophages with evidence of an inflammatory response; the intensity of both effects was related to exposure duration and concentration. On the other hand, the Kleinman et al. (1995) study at relatively low particle concentrations showed a more diffuse pattern of morphological change and no inflammatory loci.

TABLE 11-58. EFFECTS OF PM ON RESPIRATORY TRACT MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Coal dust (micronized bituminous)	Rat, M, Wistar, 18 weeks	Whole body	6,600, 14,900	2.1 (MMAD); 2.7	6 h/day, 5 days/week, 20 mo	Accumulation of aggregates of particles in alveolar macrophages immed. after exposure; alveolar histocytosis, interstitial fibrosis and emphysema, indication of simple pneumoconiosis; no lesions in upper respiratory tract.	Karagianes et al. (1981)
Petroleum coke (micronized raw)	Rat, M/F, Sprague-Dawley; cynomologus monkey (mature)	Whole body	10,000, 30,000	3.1 (AED); 1.9	6 h/day, 5 days/week, 2 years	Rat: chronic pulmonary inflammation at 3, 6, 12, and 18 mo observation times at both conc; focal fibrosis; sclerosis; squamous alveolar metaplasia. Monkey: accumulation of particle-laden macrophages; no inflammation	Klonne et al. (1987)
Fly ash (coal)	Rat, M/F, F-344, 10-13 mo	Whole body	36,000	3.6 (MMAD); 2	7 h/day for 3 days on week 1, 5 days/week next 3 weeks, 2 days on week 5	No exposure-related histopathology in large or small airways; but increased cell division; slight increase in number of hypertrophic Type 2 cells by 2 weeks; small areas of thickened alveolar walls and some perivenous inflammatory cell infiltration; by 4 weeks, aggregation of macrophages with particles and greater alveolar wall thickening and inflammation; some resolution by 42 weeks in pathology.	Shami et al. (1984)
Volcanic ash (Mt. St. Helens)	Rat, M/F, F-344, 3 mo	Whole body	5,000, 50,000	Respirable (no size given)	6 h/day, 5 days/week, up to 24 mo	At 5,000 $\mu g/m^3$: small aggregations of particle-laden macrophages at 4 mo and some thickening of alveolar septa. Aggregates of dust deposits at 8 mo, and some peribronchiolar lymphoid hyperplasia which increased by 12 mo. Enlargement of mediastinal nodes by 12 mo. At 50,000 $\mu g/m^3$: more severe lesions; low to moderate macrophage accumulation by 4 mo which increased by 8 mo and stabilized by 12 mo. Prominent peribronchial and mediastinal node reaction by 4 mo, which increased by 8 mo and stabilized by 12 mo; alveolar proteinosis by 8 mo.	Wehner et al. (1983)

TABLE 11-58 (cont'd). EFFECTS OF PM ON RESPIRATORY TRACT MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
TiO_2	Rat, F, F-344, 8 weeks	Whole body	5,000		6 h/day, 5 days/week, up to 24 mo	No fibrosis; no bronchiolar hyperplasia; no accumulation of macrophages in lung tissue.	Heinrich et al. (1989)
Fly ash (coal)	Mmice, M, C57BL/6, 12 weeks	Nose-only	200,000	1.6-1.7 (MMAD); 1.4-1.5	100 min	Increased no. of macrophages; no other lesions evident by light microscopy.	Fisher and Wilson (1980)
TiO_2	Guinea pig, F, Dunkin-Hartley, 300-350 g	Whole body	23,000	95% < 1.98 (MMAD)	20 h/day, 14 days	At 1 day PE: dust laden cells in bronchial lymph nodes and BALT; some thickening of alveolar septa in areas of high dust conc.; some degenerative changes in macrophages; no PMN. At 6 d PE: increased number of dust laden macrophages.	Baskerville et al. (1988)
Volcanic ash	Rat, Sprague-Dawley, 40 days	Whole body	9,400	0.65 (MMAD); 1.78	2 h/day, 5 days	Slight peribronchial and perivascular mononuclear cell infiltration.	Raub et al. (1985)
California road dust	Rat, F-344	Nose Only	900	4 (MMAD); 2.2	4 h/day, 4 days/week, 8 weeks	↑ Alveolar septal wall thickness; ↓ Alveolar diameter	Kleinman et al. (1995)
TiO_2	Rat, M/F, CD	Whole body	10,000, 50,000, 250,000	1.5-1.7 (MMAD)	6 h/day, 5 days/week, 2 years	At 10,000 $\mu g/m^3$: slight alveolar epithelial hyperplasia. At 50,000 $\mu g/m^3$: marked alveolar epithelial hyperplasia; bronchiolarization of alveoli adjacent to terminal bronchioles; alveolar proteinosis. At 250,000 $\mu g/m^3$: increased alveolar hyperplasia and bronchiolarization; deposition of collagen fibers.	Lee et al. (1985)
Fly ash (fluidized bed coal combustion)	Rat, M/F, F-344, 12-16 weeks	Whole body	142,000	3 (MMAD); 2.6	6 h	No pathology, except accumulation of particles.	Hackett (1983)
Fly ash (coal)	Hamster, golden, 8 weeks	Whole body	2,000, 1,000, 2,000 20,000	2.3-2.4 (MMAD); 1.5	20 h/day, 7 days/week, 6 mo	Accumulation of particle laden macrophages in proximal alveoli in a concentration/duration dependent fashion; ↑ PMN at 20,000 $\mu g/m^3$ in peripheral alveoli.	Negishi (1994)
Fly ash (fluidized bed coal combustion)	Rat, M/F, F-344, 12 weeks	Whole body	36,000	3.6 (MMAD); 2.0	7 h/day, 5 days/week, 4 weeks	Slight enlargement of lung associated lymph nodes due to increased no. of lymphoid cells (persistent up to 48 weeks PE); small cluster of particle laden macrophages in alveoli.	Bice et al. (1987)

TABLE 11-58 (cont'd). EFFECTS OF PM ON PULMONARY MORPHOLOGY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Fly ash (pulverized coal combustion)	Rat, M/F, F-344, 12 weeks	Whole body	37,000	2.7 (MMAD); 2.1	7 h/day, 5 days/week, 4 weeks	Moderate enlargement of lung associated lymph nodes due to hyperplasia and cell accumulation (persistent up to 48 weeks PE); small granulomas in lungs.	Bice et al. (1987)
Carbon black	Rat, M, F-344, 14-15 weeks	Whole body	10,000	2.0/0.12 (MMAD) (bimodal distr. with 70% in smaller mode) 2.5/2.3	7 h/day, 5 days/week, 12 weeks	Mild hyperplasia of Type 2 cells; particle laden macrophages in distal terminal bronchioles and proximal alveolar ducts.	Wolff et al. (1990)
Carbon black	Rat, F, Wistar 6 weeks		6,000	n/s	18 h/day, 5 days/week, 10 mo	Moderate to severe hyperplasia in bronchio-alveolar region; some inflammation; alveolar lipoproteinosis	Nolte et al. (1994)
Fly ash (coal)	Rat, M, Wistar, 160-175 g	Whole body	270,000	47% <3.75 μm	6 h/day, 15 days	Mild infiltration of mononuclear cells and mild pneumonitis 45 days PE; numerous particle-laden macrophages outside alveoli up to 105 days PE; ↑ lung weight by 30 days PE.	Chauhan et al. (1987)
Shale dust (raw or spent)	Monkey, cynomolgus, M/F, 2-4.5 kg rat, M/F, F344, 90-95 g	Whole body	10,000, 30,000	3.9-4.5; (1.8-2.2)	6 h/day, 5 days/week, 2 years	Concentration-related accumulation of macrophages; subacute bronchiolotis and alveolitis Concentration-related proliferative bronchiolitis and alveolitis, chronic inflammtion with spent shale; no lymph node inflammation; accumulation of macrophages	MacFarland et al. (1982)

Key to abbreviations:

NS: Not specified
PE: Post-exposure

There is some evidence for interspecies differences in response to comparable exposure atmospheres (Klonne et al., 1987). In the study of Shami et al. (1984), increased proliferation of large and small airway epithelial cells occurred in the absence of overt histopathology following exposure to fly ash. The authors suggested that this may indicate some potential for the interaction of fly ash with carcinogens.

Table 11-59 outlines studies in which lavage fluid was analyzed following inhalation exposure to PM. As with morphology, most exposure concentrations were very high, but effects, when they occurred, indicated inflammation.

As mentioned earlier, eicosanoids are potent mediators of various biological functions, and alterations in arachidonic acid metabolism, which may be involved in lung pathology, can be assessed in lavage fluid. Exposure to coal dust (25,000 $\mu g/m^3$) produced decreases in prostaglandin E_2, and increases in thromboxane A_2 and leukotriene B_4, perhaps suggesting smooth muscle constriction, vasoconstriction and increased chemotactic activity of macrophages (Kuhn et al., 1990).

Table 11-60 outlines studies examining lung biochemistry following particle inhalation, mostly to fly ash. In some cases, effects on the xenobiotic metabolizing system of the lungs were examined. For example, van Bree et al. (1990) exposed rats to coal fly ash (10,000, 30,000, 100,000 $\mu g/m^3$) and examined cytosolic antioxidant enzymes and the microsomal P-450 linked mixed function oxidase system involved in lung metabolic defense against reactive oxygen species and xenobiotic compounds. They noted both exposure-related increases and decreases in different components of this system, which they ascribed to differential effects of organic and trace metal components of the ash. Srivastava et al. (1985) also found that the effects of fly ash were likely due to chemicals adsorbed onto, or that were part of, the fly ash particle, rather than to some nonspecific particle effect. This was because the activity of the lung mixed function oxidase system was induced in rats by instillation of coal fly ash (<0.5 μm), but not by instillation of glass beads.

There is some evidence that fly ash exposure can initiate cell division and DNA synthesis in the lungs (Hackett, 1983; Shami et al., 1984), but exposure levels were very high ($>30,000$ $\mu g/m^3$).

TABLE 11-59. EFFECTS OF PM ON MARKERS IN LAVAGE FLUID

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Carbon black	Mouse, F, Swiss, 20-23 days	Nose-only	10,000	2.45 (MMAD); 2.54	4 h/day, 4 days	No change in total cell no. or differential counts; no change in albumin levels.	Jakab (1992, 1993)
Volcanic ash	Mouse, F, CD-1, 4-8 weeks	Whole body	9,400	0.65 (MMAD); 1.8	2 h	Increase in PMN.	Grose et al. (1985)
TiO_2	Rat, M, F-344 180-200 g	Whole body	50,000	1 (MMAD); 2.6	6 h/day, 5 days	No change in: AMs, PMNs, lymphocytes; LDH; protein; to 63 days PE.	Driscoll et al. (1991)
TiO_2	Rat, HAN	Whole body	50,000		8 h/day, 5 days/week (up to 15 weeks)	Slight increase in PMN at 15 weeks.	Brown et al. (1992)
Coal dust	Rat, HAN	Whole body	10,000, 50,000		8 h/day, 5 days/week (up to 15 weeks)	Increased PMN (persistent).	Brown et al. (1992)
California road dust	Rat, F-344	Nose-only	300, 900	4 (MMAD); 2.2	4 h/day, 4 days/week, 8 weeks	↑ Albumin at 900 $\mu g/m^3$; no change in total cells or differential counts	Kleinman et al. (1995)
TiO_2	Rat, M/F, F-344, 8 weeks	Whole body	5,000	1.1 (MMAD); 1.6	6 h/day, 5 days/week, 24 mo	No change in total cell no. in lavage but ↑ AMs and ↓ PMNs some time points; no change in LDH, protein, ß-glucuronidase in lavage.	Muhle et al. (1991)
Fe_2O_3	Rat, M, Long-Evans, 225-250 g	Nose-only	18,000-24,000	1.45-1.7 (MMAD); 2.9-3	2 h	No change total cell no. or differential counts.	Lehnert and Morrow (1985)
Carbon black	Rat, M, F-344, 14-15 weeks	Whole body	10,000	2.0/0.12 (MMAD) (bimodal distr. with 70% in smaller mode); 2.5/2.3	7 h/day, 5 days/week, 12 weeks	↑ PMN in lavage; ↑ acid proteinase in lavage.	Wolff et al. (1990)
Carbonyl iron	Rat, M Crl:CDBR, 8 weeks	Nose-only	100,000	3.6 (MMAD); 1.7	6 h; 6 h/day, 3 days	No change in total cell no, protein, or LDH.	Warheit et al. (1991)
Carbon black	Mouse, F, Swiss 20-23 g	Nose-only	10,000	2.4 (MMD); 2.75	4 h	No change in total cell no. or differential count at 20 h PE.	Jakab and Hemenway (1993)

TABLE 11-59 (cont'd). EFFECTS OF PM ON MARKERS IN LAVAGE FLUID

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
TiO_2	Guinea pig, M/F, 400 g	Whole body	24,000	85% < 2 μm	8 h/day, 5 days/week, 3 weeks	No change in LDH, AP, AG, Cathepsin D at 4-24 h PE.	Sjöstrand and Rylander (1984)
Coal dust	Rat, F, F-344, 180 g	Whole body	25,000	4-5	16 h/day, 7 days/week, 2 weeks	↑ TxA_2, LTB_4, protein; ↓ PGE_2 at 1 day PE; TxA_2, and LTB_4 change persistent for 2 weeks.	Kuhn et al. (1990)
TiO_2	Guinea pig, M/F, 400 g	Whole body	24,000	most between 0.5-2 (GMD)	8 h/day, 5 days/week, 3 week	No change PMN; ↑ no. AM, eosinophils by 16 weeks PE.	Fogelmark et al. (1983)

Key to abbreviations:
LDH: lactate dehydrogenase
AP: acid phosphatase
AG: N-acetyl-ß-d-glucosaminidase
TxA_2: thromboxane A_2
LTB_4: Leukotrine B_4
PGE_2: Prostaglandin E_2
AM: alveolar macrophage
PE: post-exposure
PMN: polymorphonuclear leukocyte
↑: increase
↓: decrease

TABLE 11-60. EFFECTS OF PM ON LUNG BIOCHEMISTRY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Fly ash (coal)	Rat, M, Wistar, 5 weeks	Whole body	10,000, 30,000, 100,000	80-95% mass was ≤42 μm (AED) —	6 h/day, 5 days/week, 4 weeks	↑ Cytosolic $GSHP_x$, protein at 30,000 100,000; ↑ G6PDH at 100,000; ↑ lung microsomal protein, ↓ microsomal BROD at 30,000/100,000; no change microsomal P-450 content; induction of EROD activity at all conc. (all in lung tissue).	van Bree et al. (1990)
Carbon black	Rat, M, F-344, 200-250 g	Whole body	6,000	0.22 (MMAD)	20 h/day, 1-14 days	No change in synthesis of lung total DNA; no change in DNA synthesis of Type 2 cells.	Wright (1986)
Fly ash (fluidized bed coal)	Rat, M/F, F-344	Whole body	142,000	3 (MMAD); 2.6	6 h	↑ Labeling of Type 2 cells; ↑ incorporation of thymidine in AM DNA, persisting 4 days PE; ↑ labeling airway epithelial cells, persistent up to 4 days PE.	Hackett (1983)
Carbonyl iron	Rat, M, Crl:CD BR, 8 weeks	Nose-only	100,000	3.6 (MMAD); 2.6	6 h/day, 3 days	No effect on labeling index of lung parenchymal or airway cells.	Warheit et al. (1991)
Fly ash (fluidized bed coal combustion)	Rat, M/F, F-344, 10-13 weeks	Whole body	36,000	3.6 (MMAD); 2	7 h/day, 3 days week 1; 5 days/week week 2-4; 2 days week 5	↑ Labeling index of large airway basal cells and bronchiolar Clara cells at 2 weeks, resolved by 2 weeks PE; ↑ labeling index of Type 2 cells by 4 weeks, resolved by 2 weeks PE.	Shami et al. (1984)
Fly ash (coal)	Rat, M, Wistar, 160-175 g	Whole body	270,000	47% < 3.75 μm	6 h/day, 15 days	↑ P-450 content; ↑ activity of aryl hydrocarbon hydroxylase, glutathione S-transferase, δ-amino levulinic acid synthetase; inhibition of hemeoxygenase.	Chauhan et al. (1989)
Fly ash (coal)	Rat, M, Wistar, 160-170 g	Whole body	270,000	47% <3.75 μm	6 h/day, 15 days	↑ Total lung phospholipids; ↑ phosphatidylcholine up to 45 days PE.	Chauhan and Misra (1991)

Key to abbreviations:
$GSHP_x$ = glutathione peroxidase
G6PDH = glucose 6 phosphate dehydrogenase
BROD = benzoxyresorufin 0-dearylase
EROD = NADPH-mediated ethoxyresorufin 0-deethylase
↑: increase
↓: decrease
PE = post exposure
AM = alveolar macrophage

11.9.5 Pulmonary Defenses

11.9.5.1 Clearance Function

Mucociliary Transport

Grose et al. (1985) exposed (whole-body) rats (Sprague-Dawley CD, M, 60 to 70 days) to volcanic ash from Mt. St. Helens (0.65 μm, $\sigma g = 1.8$) at 9,400 $\mu g/m^3$ for 2 h. At 24 h post exposure, a depression in ciliary beat frequency in excised tracheas was noted. Whether this would contribute to any change in mucociliary transport function in the intact animal is unknown.

Pulmonary Region Clearance and Alveolar Macrophage Function

A number of studies have examined particle retention following exposure to high concentrations of inhaled particles, some of which have low intrinsic toxicity. Such exposures resulted in a phenomenon known as overload, in which the effectiveness of lung clearance mechanisms is significantly reduced. This response, which is nonspecific to a wide range of particles, is discussed in detail in Chapter 10.

While there are no studies of effects of exposure to nonacidic sulfate particles on alveolar region clearance, there have been several studies examining AM function following inhalation exposures (Table 11-61) or with in vitro exposure. High exposure concentrations of various particles can depress the phagocytic activity of AMs following inhalation.

To examine the effects of different fly ashes, Garrett et al. (1981b) incubated rabbit AMs with $\leq 1{,}000$ μg of either conventional coal combustion fly ash or fluidized bed combustion fly ash at >3 and <3 μm, for 20 h. While all exposures caused reductions in cell viability and cell ATP levels, conventional coal fly ash $<3\mu$m produced the greatest effect. These results suggest toxicity somewhat dependent on size, as observed previously with other endpoints.

To examine for a nonspecific particle effect on phagocytosis, Finch et al. (1987) exposed bovine AMs in vitro to TiO_2 (1.57 μm MMD, $\sigma g = 2.3$) or to glass beads (2.1 μm, $\sigma g = 1.8$), the former at 2.3 or 5 $\mu g/ml$, and the latter at 5 or 8.4 $\mu g/ml$. Neither exposure altered phagocytic activity, but TiO_2 did produce some decrease in cell viability.

TABLE 11-61. EFFECTS OF PM ON ALVEOLAR MACROPHAGE FUNCTION

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect[a]	Reference
Carbon black	Mouse, F, Swiss, 20-23 g	Nose-only	10,000	2.45 (MMAD); 2.54	4 h/day, 4 days	No change in F_c-mediated AM phagocytic activity up to 40 days PE.	Jakab (1992, 1993); Jakab and Hemenway (1993)
Volcanic ash	Mouse, F, CD-1, 4-8 weeks	Whole body	9,400	0.65 (MMAD); 1.8	2 h	No change in viability of recovered cells; no effect on AM phagocytosis at 0 or 24 h PE.	Grose et al. (1985)
TiO_2	Rat, M, F-344 180-200 g	Whole body	50,000	1 (MMAD); 2.6	6 h/day, 5 days	No change in spontaneous/ stimulated release of IL-1 by AMs up to 63 days PE.	Driscoll et al. (1991)
Fly ash (coal)	Mouse, F, BALB/C; C57BL; 6-8 weeks	Whole body	535 (fine particle fraction < 2.1 μm)	32 % < 2.1 μm (by wt)	148 days	↓ AM phagocytic activity by 21 days of exposure.	Zarkower et al. (1982)
TiO_2	Rat, HAN	Whole body	50,000		8 h/day, 5 days/week	No change in chemotactic activity of AM.	Brown et al. (1992)
Coal dust	Rat, HAN	Whole body	10,000, 50,000		8 h/day, 5 days/week	Decreased AM chemotactic activity.	Brown et al. (1992)
California road dust	Rat, F-344	Nose-only	300, 900	4 (MMAD)	4 h/day, 4 days/week, 8 weeks	↓ Production of superoxide at high concentration; no change in F_c receptor mediated phagocytic activity.	Kleinman et al. (1995)
Iron oxide (Fe_2O_3)	Rat, M, Long-Evans, 225-250 g	Nose-only	18,000-24,000	1.45-1.7 (MMAD); 2.9-3	2 h	No change in AM adherence; ↑ phagocytic activity of AM (F_c-mediated) up to 20 days PE.	Lehnert and Morrow (1985)
Carbonyl iron	Rat, M, Crl:CDBR, 8 weeks	Nose-only	100,000	3.6 (MMAD); 1.7	6 h; 6 h/day, 3 days	No change in AM chemotactic activity; cell viability ; slight ↑ AM phagocytic activity for single exp.	Warheit et al. (1991)
Carbon black	Mouse, F, Swiss, 20-23 g	Nose only	10,000	2.4 (MMD); 2.75	4 h	No change in F_c-receptor mediated AM phagocytic activity.	Jakab and Hemenway (1993)
TiO_2	Guinea pig, M/F 400g	Whole body	24,000	Most between 0.5-2 (GMD)	8 h/d, 5 days/week, 3 weeks	No change in AM phagocytic activity.	Fogelmark et al. (1983)

Macrophages may contact particles via chemotactic-directed movement. Constituents of lung fluid having high chemotactic activity are components of complement, and particles which activate complement tend to show greater chemoattractant activity for macrophage accumulation at sites of particle deposition (Warheit et al., 1988). For example, in an in vitro study, iron-coated asbestos and carbonyl iron particles activated chemotactic activity in rat serum and concentrated rat lavage proteins, while volcanic ash did not. When the rats were exposed by inhalation to 10,000 to 20,000 $\mu g/m^3$ of these particles, only the volcanic ash failed to produce an increased number of macrophages on the first alveolar duct bifurcations, the primary deposition site for these particles and fibers. Complement proteins on alveolar surfaces are likely to be derived primarily from normal transudation of serum components from the pulmonary vasculature (Warheit et al., 1986). The generation of chemotactic factors at particle deposition sites may facilitate clearance for some particle types, but not for others, such as silica (Warheit et al., 1988, 1991).

In a somewhat related study, Hill et al. (1982) examined the interaction with complement of coal combustion fly ash particles (2 to 3 μm MMAD) from different sites, using serum from dogs. In addition to releasing peptides that are chemotactic for macrophages and other inflammatory cells, fly ash also induced release of lysosomal enzymes and increased vascular permeability, all processes involved in inflammation. While the authors noted that some fly ash samples activated complement, while others did not, they were not able to determine which component on or in the ash was responsible for this action. A possibility was suggested to be some metals, such as Mn, which are potent activators of the complement cascade (Lew et al., 1975).

Thorén (1992) examined the metabolic activity of AMs by measuring heat exchange rates after exposing cell monolayers to TiO_2 or manganese dioxide (MnO_2) at $0.6 - 4 \times 10^6$ particles/ml. The former affected metabolism only at the highest concentration used, while the latter caused changes at lower concentrations as well.

The response of AMs to PM is influenced by both physical and chemical characteristics of the particles with which they come into contact. Shanbhag et al. (1994) exposed a macrophage cell line (P388D1) to particles of two different composition (TiO_2 or latex) at comparable sizes, 0.15 and 0.45 μm for the former, and 0.11 and 0.49 for the latter. They also used pure titanium at 1.76 μm for comparison to latex at 1.61 μm.

Titanium dioxide decreased cellular proliferation, depending upon both size and concentration. Similar sizes and concentrations of latex produced lesser responses. In addition, cells incubated with latex released factors, into the medium, which produced fibroblast proliferation to a greater extent than did cells incubated with TiO_2 of a similar size and concentration.

11.9.5.2 Resistance to Infectious Disease

Susceptibility of mice to challenge with several infectious agents has been used to assess effects of various inhaled particles on microbial defense of the lungs (Table 11-62). The study of Jakab (1993) is of particular interest because the infectious agents used were selected based upon differences in the antimicrobial defense mechanism most effective in eliminating each organism. Thus, *Staphylococcus aureus* defense depends primarily upon the integrity of AMs, while that for *Proteus mirabilis* involves both AMs and PMNs. *Listeria monocytogenes* defenses involve specific acquired immunity, namely the integrity of the lymphokine-mediated components of the cell- mediated immune response (e.g., AMs and lymphocytes). A number of host defenses play a role in defense against influenza, including specific cytotoxic lymphocytes. However, repeated exposure to 10,000 $\mu g/m^3$ carbon black did not alter any of these antimicrobial defense systems.

Particles of low intrinsic toxicity may impair mechanisms involved in the clearance of bacteria, perhaps increasing their persistence and resulting in increased infectivity. To examine this possibility, a study was aimed at determining whether animals (guinea pigs) in which phagocytic activity was impaired by exposure to a high concentration (23,000 $\mu g/m^3$) of an "inert" dust (TiO_2) were more susceptible to bacterial infection, in this case due to *Legionella pneumophila* (Baskerville et al., 1988). While those AMs having heavy burdens of TiO_2 particles did not phagocytize the bacteria, there was no increase in infectivity in particle-exposed compared to air-exposed control animals; this was suggested to be due to the recruitment of monocytes into the lungs of the TiO_2-exposed animals, and these cells were able to phagocytize the bacteria.

The studies presented in Table 11-62 indicate that particles inhaled even at high concentrations did not reduce resistance to microbial infections. However, some changes were noted in an instillation study. Hatch et al. (1985) examined various particles

TABLE 11-62. EFFECTS OF PM ON MICROBIAL INFECTIVITY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Carbon black	Mouse, F, Swiss, 20-23 g	Nose-only	4,700-6,100	2.45 (MMAD); 2.54	4 h/day, 4 days	No effect on susceptibility to infection from *S. aureus* administered 1 day PE; no effect on intrapulmonary killing of bacteria by AM.	Jakab (1992)
Carbon black	Mouse, F, Swiss, 20-23 g	Nose-only	10,000	2.4 (MMAD); 2.75	4 h/day, 4 days	No change in no. of *S. aureus* or *P. mirabilis* recovered in lung after bacterial challenge or on intrapulmonary killing of bacteria administered 1 d PE; no effect on proliferation of *L. monocytogenes*; no effect on proliferation or elimination of influenza A virus; no change in albumin level in lavage 4 h after bacterial challenge; no change in PMN in lavage 4 h after challenge.	Jakab (1993)
TiO_2	Guinea pig, F, Dunkin-Hartley 300-350 g	Whole body	23,000	95% < 1.98 μm (MMAD)	20 h/day, 14 days	No change in susceptibility to *Legionella pneumophila* administered 1-6 days PE but AM with heavy particle burden did not ingest bacteria.	Baskerville et al. (1988)
Coal dust	Mouse, F, Swiss CD-1, 20-24 g	Whole body	2,000	80% <10 μm; 50% <5 μm	7 h/day, 5 days/week, 6 mo	No change in susceptibility to influenza virus administered after 1, 3 and 6 mo exposure; decrease in interferon level in lung at 3 mo; no change in inflammatory response to virus.	Hahon et al. (1985)
Volcanic ash	Mouse, F, CD-1, 4-8 weeks	Whole body	9,400	0.65 (MMAD); 1.8	2 h	No change in susceptibility to bacteria (*Streptococcus*) or virus administered 0 or 24 h PE; no change in lymphocyte response to mitogens.	Grose et al. (1985)
TiO_2	Mouse, Harlan-Olac, 8 weeks	Whole body	2,000, 20,000	95% <1.98 μm (UDS)	20 h/day, 2 or 4 weeks	↓ Clearance of *P. haemolytica* administered after exposure in proportion to exposure duration at 20,000 $\mu g/m^3$ only.	Gilmour et al. (1989a)

TABLE 11-62 (cont'd). EFFECTS OF PM ON MICROBIAL INFECTIVITY

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
TiO_2	Mouse, Harlan-Olac, 8 weeks	Whole body	20,000	95% <1.98 μm (UDS)	20 h/day, 10 days	↓ Clearance of *P. haemolytica*, persistent up to 10 days PE.	Gilmour et al. (1989a)
TiO_2	Mouse, Harlan-Olac, 8 weeks	Whole body	20,000	95% <1.98 μm (UDS)	20 h/day, 7 days	↓ Response to bacterial antigens of mediastinal lymph node lymphocytes from mice inoculated with *P. haemolytica* after exposure.	Gilmour et al. (1989b)

Key to abbreviations:
↓: decrease
PE: post-exposure

administered by intratracheal instillation for their ability to alter infectivity in mice subsequently exposed to a bacterium *(Streptococcus sp)*. The specific particle types and their sizes (VMD) were as follows: conventional coal combustion fly ash from various sources (0.5 μm); various samples of fluidized bed combustion coal fly ash (0.4 to 1.3 μm); various samples of oil combustion fly ash (0.8-1.3μm); volcanic ash (1.4 and 2.3μm); latex (0.5 and 5 μm); and urban air particles (0.4 μm) from Dusseldorf, Germany, Washington, DC, and St. Louis, MO. The instillation dose was 100 μg particles/mouse. An increase in infectivity was found with all oil fly ash samples, some of the combustion and fluidized bed coal fly ash samples, ambient air particles from Dusseldorf and Washington, latex, and also from carbon and ferric oxide particles of unstated size. Exposure to volcanic ash, St. Louis ambient particles, and other coal fly ash samples did not have an effect. It was postulated that the activity of the fly ash reflected either the speculated presence of metals or the ability of the ash to alter the pH of airway fluid. In a corollary to the above study, rabbit AMs were incubated for 20 h with the various particles and cell viability assessed. Viability was reduced by all oil fly ash samples, coal fly ash, ambient particles from all three sites, volcanic ash and latex. These results did not totally correlate with the response following in vivo exposures.

To examine effects of particles on nonimmunological antiviral defense, Hahon et al. (1983) exposed monolayers of mammalian cells (rhesus monkey kidney cell line) to coal combustion fly ash (2.5 μm) at 500 to 5,000 μg/10 ml medium and assessed effects on interferon. Induction of interferon due to infection with influenza and parainfluenza virus was reduced when the cells were pretreated with the fly ash. This was suggested to be due to either the matrix itself, or to some surface component which was not extractable with either polar or nonpolar solvents.

For some endpoints, there may be a particle size dependence of effect, with ultrafine particles having greater inherent toxicity than larger particles. One study examined the effect of two larger particles on infectivity. Grose et al. (1985) instilled (42 μg/animal) mice (CD-1, F, 4 to 8 weeks) with two sizes of volcanic ash from Mt. St. Helens, namely coarse mode (12.1 μm MMAD, σg=2.3) and fine mode (2.2 μm MMAD, σg=1.9), followed by challenge with bacteria (*Streptococcus sp.*) immediately or 24 h postexposure. No particle size related difference was noted in susceptibility to bacterial infection, with both sizes

producing a similar increase in infection following bacterial challenge at 24 h, but not immediately, after pollutant exposure. However, inhalation exposure to 9,400 $\mu g/m^3$ volcanic ash (0.65 μm) produced no change in infectivity (Table 11-62).

11.9.5.3 Immunologic Defense

The few studies on effects of inhaled particles on respiratory tract immune function are shown in Table 11-63. Particles may affect some aspects of immune defense and not others. For example, fly ash did not produce any change in the cellular immune response, namely delayed hypersensitivity, but did depress the ability of macrophages to enhance T-cell mitogenesis (Zarkower et al., 1982).

11.9.6 Systemic Effects

A few studies have examined systemic effects of inhaled particles. One assessed the ability of particles to affect systemic immune responses (Eskew et al., 1982). Mice (F, BALB/C) were continuously exposed for various times to coal combustion fly ash (32% by wt <2.1 μm), and the antigenic response of spleen cells to protein derivatives after sensitization with BCG (delayed hypersensitivity reaction) was examined, as was the mitogenic response of spleen cells to concanavalin A or lypopolysaccharide (LPS). Exposure for 1 to 8 weeks to 1,150 $\mu g/m^3$ reduced the mitogenic response of spleen cells after 3 weeks of exposure, but not after 5 or 8 weeks and only for concanavalin A. Exposure for 5 mo to 2,220 $\mu g/m^3$ increased thymidine incorporation into spleen cells from BCG-sensitized mice. Finally, exposure for 5 weeks to 871 $\mu g/m^3$ reduced the number of antibody plaque forming cells in the spleen and the hemagglutinin titer. These results suggest that fly ash has little effect on the cellular immune response, but depresses the humoral response. The implications of the increase in thymidine incorporation into the spleen of BCG-sensitized mice was not clear, but may indicate an increase in resistance to infection.

In another study of systemic immunity, Mentnech et al. (1984) exposed rats (F344, M, whole body) to 2,000 $\mu g/m^3$ coal dust (40% $<7\mu m$) for 7 h/day, 5 days/week for 12 or 24 mo. The number of antibody-producing cells in the spleen 4 days after immunization with sheep red blood cells was used as a test of effects on humoral immunity, while the

TABLE 11-63. EFFECTS OF PM ON RESPIRATORY TRACT IMMUNE FUNCTION

Particle	Species, Gender, Strain, Age, or Body Weight	Exposure Technique	Particle Characteristics: Mass Concentration ($\mu g/m^3$)	Particle Characteristics: Size (μm); σ_g	Exposure Duration	Observed Effect	Reference
Fly ash (fluidized bed coal combustion)	Rat, M/F, F-344, 12 weeks	Whole body	36,000	3.6 (MMAD); 2.0	7 h/day, 5 days/week, 4 weeks	No effect on humoral immune function.	Bice et al. (1987)
Fly ash (pulverized coal combustion)	Rat, M/F, F-344, 12 weeks	Whole body	37,000	2.7 (MMAD); 2.1	7 h/day, 5 days/week, 4 weeks	↓ Antibody response at 48 weeks PE.	Bice et al. (1987)
Fly ash (coal)	Mouse, F BALB/C; C57BL 6-8 weeks	Whole body	760 (fine particle fraction, <2.1 μm)	32% < 2.1 μm (by wt)	28 days (continuous)	↓ Ability of AMs to stimulate PHA-induced T-lymphocyte mitogenesis.	Zarkower et al. (1982)
			2,200 (fine particle fraction, <2.1 μm)		160 days (continuous)	No change in ability of animals sensitized with BCG during exposure to respond to purified protein derivative challenge (delayed hypersensitivity cellular immune response).	

Key to abbreviations:
AM: macrophage
PE: post-exposure
IL = interleukin
↑: increase
↓: decrease

proliferative response of splenic T-lymphocytes to the mitogens concanavalin A and phytohemagglutin was used to assess cellular immunity. No changes were found.

11.10 MECHANISMS OF TOXICOLOGICAL INTERACTIONS

Toxicological interactions with PM may be antagonistic, additive, or synergistic. The presence and nature of any interaction seems to depend upon the concentration of pollutants in the mixture, the exposure duration, and the endpoint being examined, and it is not possible to predict a priori from the presence of certain pollutants whether there will be any interaction.

Mechanisms responsible for the various forms of interaction are generally not known. The greatest hazard in terms of potential health effects from pollutant interaction is the possibility of synergism, especially if effects occur at all with mixtures which do not occur at all when the individual constituents are inhaled. Various mechanisms may underly synergism. One is physical, the result of adsorption or absorption of one material on a particle and subsequent transport to more sensitive sites, or sites where this material would not normally deposit in toxic amounts. This may explain the interaction found in studies of mixtures of carbon black and formaldehyde, or carbon black and acrolein (Jakab, 1992, 1993), especially since formaldehye has been shown to be absorbed onto particles (Rothenberg et al., 1989).

Somewhat related to this hypothesis is the possibility of reactions on particle surfaces, forming some secondary products which may be more toxicologically active than the primary material and which is then carried to some sensitive site. This may explain the results of the Jakab and Hemenway (1993) study, wherein mice were exposed to carbon black either prior to or after exposure to O_3, and then to both materials simultaneously. Simultaneous exposure produced evidence of interaction, while exposure to carbon black either before or after O_3 did not produce responses which were different from that due to exposure to O_3 alone. The authors' suggested that this was due to a reaction of O_3 on the surface of the carbon black particles in the presence of adsorbed water, producing surface bound, highly toxicologically active reactive oxygen species. Production of these species would not occur when the exposures were sequential.

Another mechanism may involve a pollutant-induced change in the local microenvironment of the lung, enhancing the effects of the co-inhalant. Thus, the observed synergism in rats between O_3 and acidic sulfates was suggested to be due to a shift in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of O_3 by producing a change in the reactivity or residence time of reactants, such as radicals, involved in O_3-induced tissue injury (Last et al., 1984). This hypothesis was examined in a series of studies (Last et al., 1983, 1984, 1986; Last and Cross, 1978; Warren and Last, 1987; Warren et al., 1986) in which rats were exposed to various sulfur oxide aerosols [H_2SO_4, $(NH_4)_2SO_4$, Na_2SO_4] with and without oxidant gases (O_3 or NO_2), and various biochemical endpoints examined. Acidic sulfate aerosols alone did not produce any response at concentrations that caused a response in conjunction with O_3 or NO_2. Further evidence that the synergism was due to H^+ was the finding that neither Na_2SO_4 nor NaCl was synergistic with O_3 (Last et al., 1986). But if this was the only explanation for acid/O_3 interaction, then the effects of ozone should be consistently enhanced by the presence of acid in an exposure atmosphere regardless of endpoint examined. However, in the study of Schlesinger et al. (1992b), in which rabbits were exposed for 3 h to combinations of 0.1, 0.3, and 0.6 ppm O_3 with 50, 75, and 125 $\mu g/m^3$ H_2SO_4 (0.3 μm), antagonism was noted when evaluating stimulated production of superoxide anion by AMs harvested by lavage immediately after exposure to 0.1 or 0.3 ppm ozone in combination with 75 or 125 $\mu g/m^3$ H_2SO_4, and also for AM phagocytic activity at all of the ozone/acid combinations; there was no change in cell viability compared to air control.

11.11 TOXICOLOGY OF PM IN COMPROMISED HOST ANIMAL MODELS

Epidemiological studies suggest there may be subsegments of the population that are especially susceptible to effects from inhaled particles (see Chapter 12). One particular group may be those having lungs compromised by respiratory disease. However, most toxicology studies have used healthy adult animals, and there are very few data to allow examination of the effects of different disease states upon the biological response to PM. A number of studies have examined the effects of lung disease on deposition and/or clearance

of inhaled aerosols, and these are discussed in Chapter 10. Alterations in deposition sites and clearance rates/pathways due to concurrent disease may impact upon dose delivered from inhaled particles and ultimate toxicity.

Some work has been performed with acidic sulfate aerosols using models of compromised hosts. Rats and guinea pigs with elastase-induced emphysema were examined to assess whether repeated exposures (6 h/day, 5 days/week, 20 days) to $(NH_4)_2SO_4$ (1,000 $\mu g/m^3$, 0.4 μm MMAD) or NH_4NO_3 (1,000 $\mu g/m^3$, 0.6 μm MMAD) would alter pulmonary function compared to saline-treated controls (Loscutoff et al., 1985). Similarly, dogs having lungs impaired by exposure to NO_2 were treated with H_2SO_4 (889 $\mu g/m^3$, 21 h/day, 620 days) (Lewis et al., 1973). Results of both of these studies indicated that the specific induced disease state did not enhance the effect of acidic sulfate aerosols in altering pulmonary function; in some cases, there were actually fewer functional changes in the diseased lungs than in the unimpaired animals. It is possible, however, that other types of disease states could result in enhanced response to inhaled acidic aerosols; as mentioned, asthma is a likely one, but there are no data to evaluate whether effects are enhanced in animal models of human asthma.

Few studies have examined effects of other particles in health compromised host models. Mauderly et al. (1990) exposed young rats having elastase-induced emphysema to whole diesel exhaust (3,500 μg soot/m^3) for 24 mo (7 h/day, 5 days/week). Various endpoints were examined after exposure, including pulmonary function (e.g., respiratory pattern, lung compliance, DLco), biochemical components of BAL (e.g., enzymes, protein, collagen), and histopathology and morphometry. There was no evidence that the diseased lungs were more susceptible to the diesel exhaust than were normal lungs. In fact, in some cases, there seemed to be a reduced effect of the diesel exhaust in the emphysematous lungs. But this could be due to a reduced lung burden in the diseased lungs, resulting from differences in deposition and/or clearance compared to normal lungs.

Rats having elastase-induced emphysema were exposed to 9,400 $\mu g/m^3$ (0.65 μm) Mt. St. Helens volcanic ash for 2 h/day for 5 days (Raub et al., 1985; Table 11-78), with and without 2,700 $\mu g/m^3$ SO_2. Effects on pulmonary mechanics in these rats were similar to those noted in normal animals exposed to the same atmosphere.

Raabe et al. (1994) exposed rats with elastase-induced emphysema to two particle atmospheres, a California-type aerosol and an London-type aerosol. The former consisted of 1.1 to 1.5 μm (MMAD; σg = 1.7 to 2.4) particles of graphitic carbon, natural clay, NH_4HSO_4, $(NH_4)_2SO_4$, NH_4NO_3, $PbSO_4$, $VOSO_4$, $MnSO_4$, and $NiSO_4$. The latter consisted of 0.8 to 0.9 μm particles (σg = 1.7 to 1.8) of NH_4HSO_4, $(NH_4)_2SO_4$, coal fly ash, and lamp black carbon. While the elastase treated rats showed increased lung DNA and RNA, exposure for 3 days (23 h/day) to the London aerosol produced a further increase not seen in exposed normal rats. There were no changes in tracheobronchial clearance or lung permeability compared to normals. A 30-day exposure to the California aerosol enhanced small airway lesions in the elastase-treated animals, but did not alter lung hydroxyproline, tracheobronchial clearance, or small airway fibrosis.

Thus, the available toxicological database is yet unable to provide a conclusion as to any enhanced susceptibility to PM of "compromised" hosts with concurrent lung disease.

One potential inherent host factor affecting susceptibility to particles is age. In an early study, Amdur et al. (1952) determined that the H_2SO_4 (1 μm, MMD) concentration needed to produce 50% mortality (LC_{50}) for an 8-h exposure in guinea pigs was 18,000 $\mu g/m^3$ for 1-to 2-mo old animals, and 50,000 $\mu g/m^3$ for 18-mo old animals.

11.12 FACTORS INFLUENCING PM TOXICITY

The factors modulating biological responses to PM are not always clear. However, the available toxicological database does allow for some speculation as to which factors may influence biological responses to diverse types of PM. For example, the toxic potency of inorganic particles may be related to certain physicochemical characteristics. While the bulk chemical makeup of a particle would clearly influence its toxicity, responses may also be driven by chemical species adsorbed onto the particle surface, even for those particles considered to have low intrinsic toxicity. Furthermore, certain physical properties of particles, such as size or surface area, and of aerosols, such as number concentration, may be factors in determining reponses from PM. This section provides an overview of current hypotheses concerning characteristics of particles which may relate to their toxicity.

11.12.1 Particle Acidity

It should be clear from discussions in Section 11.2 that the deposition of acidic particles in the respiratory tract can result in various biological effects. The bulk of the toxicologic database on acidic PM involves sulfate particles, primarily H_2SO_4, but the available evidence indicates that the observed responses to these are likely due to the H^+, rather than to the $SO_4^=$. Thus, effects observed for this pollutant likely apply to other inorganic acidic particles having similar deposition patterns in the respiratory tract, although the specific chemical composition of different acids may be a factor mediating the quantitative response (Fine et al., 1987). In terms of H^+, the irritant potency of an acid aerosol may be related more to the total available H^+ concentration (i.e., titratable acidity in lung fluids following deposition) rather than to the free H^+ concentration as measured by pH (Fine et al., 1987). In any case, the response to acidic particles appears to be due to a direct irritant action and/or the subsequent release of humoral mediators.

Acidic particles exert their action throughout the respiratory tract, with the response and location of effect dependent upon particle size and mass concentration. They have been shown to alter bronchial responsiveness, mucociliary transport, clearance from the pulmonary region, regulation of internal cellular pH, production of cytokines and reactive oxygen species, pulmonary mechanical function, and airway morphology.

Particles do not have to be pure acid droplets to elicit health effects. The acid may be associated with another particle type. For example, in the study of Chen et al. (1990), guinea pigs were exposed to two different fly ashes, one derived from a low sulfur coal and one from a high sulfur coal (Table 11-52). Levels of acidic sulfates associated with the fly ash were found to be proportional to the coal sulfur content, and greater effects on pulmonary functional endpoints were noted for the high sulfur fly ash than for the low sulfur fly ash.

11.12.2 Particle Surface Coatings

The presence of surface coatings may make certain particles more toxic than expected based solely upon particle core composition. This was noted in studies of acid-coated metal oxides (Section 11.4). Certain surface metals may be especially important in this regard, and because trace metal species vary geographically, this may account to some extent for

particles in different areas having different toxic potentials. Garrett et al. (1981a) exposed rabbit AMs in vitro to fly ash, with and without surface coatings of various metal oxides. Reductions in cell viability and cellular ATP content were found only with the metal-coated ash particles. To determine potencies of specific metals, Berg et al. (1993) examined different fractions of fly ash, all of which were <4 μm in diameter, for their ability to stimulate bovine AMs to secrete reactive oxygen species, namely superoxide anion and hydrogen peroxide. They noted that production of these species was often associated with the metal content of the fly ash particle, with the order of greatest association as follows: iron > manganese > chromium > vanadium > arsenic. The positioning of iron as first in this scheme is consistent with results of some other studies examining the biological effect of iron present as a particle surface coating.

Ghio et al. (1992) and Ghio and Hatch (1993) examined surface components which may be responsible for the biological effects of silica. Functional groups on the surface of mineral oxides coordinate ferric ion, and such complexes can result in an increased capacity to catalyze an electron exchange, producing hydroxyl radicals. This could then expose lung tissues to oxidant stress, which can result in an increase in the products of lipid peroxidation and induction of gene expression. They noted that an extracellular accumulation of surfactant following silica exposure was associated with the concentration of ferric ion (Fe^{+3}) complexed to the surface of the particles, and that surfactant-enriched material was a target for oxidants, the production of which was catalyzed by ferric ion. In addition, they noted that the ability of silicates to catalyze the generation of reactive oxygen species, to trigger respiratory bursts, and to elicit release of leukotriene B_4 by AMs increased with increasing surface-complexed ferric ion content.

A role of iron-induced oxidative stress in PM-related lung injury is further supported by a study demonstrating that surface available iron and the oxidizing power of mineral particles were both correlated with cytotoxicity, expression of cytokeratin-13, and formation of cross-linked envelopes of rabbit tracheal epithelial cells (Guilianelli et al., 1993), and that deferoxamine treatment blocked these effects. Thus, it is possible that reactive oxygen species produced through chemical reactions involving iron could initiate lipid peroxidation of the cell membrane, resulting in cell death and subsequent lung injury.

Recently, surface complexed iron has been implicated in pulmonary injury due to a variety of environmental particles (Costa et al., 1994a,b; Tepper et al., 1994). Three particle types (Mt. St. Helen's volcanic ash, ambient particles of Dusseldorf, Germany, and residual oil fly ash), which represented a range of inflammatory potential, were intratracheally instilled into rats. Both the degree of acute inflammation (as measured by assessing PMNs, eosinophils, LDH and protein in lavage) and nonspecific bronchial responsiveness correlated with the iron (specifically Fe^{+3}) loading of the particles. An interesting observation was that surface iron was correlated with particle acidity, yet when instillation of H_2SO_4 at comparable pH was performed, the lavage analysis indicated much less inflammation with the pure acid compared to the high surface iron particles. In fact, neutralization of the fly ash instillate (which could occur if similar particles were inhaled, due to endogeneous respiratory tract ammonia) actually enhanced particle toxicity, while the pulmonary response diminished when iron was removed from the fly ash by acid washing. These preliminary results generally support the notion that oxidant generation by iron present on the surface of particles may increase lung injury; but clearly other factors are likely to contribute to this response. For example, some metals can catalyze conversion of SO_2 to acidic sulfate on some particles, increasing their acidity (Kleinman et al., 1984).

11.12.3 Particle Size

Studies which have examined PM-induced mortality seem to suggest some inherent potential toxicity of ultrafine particles (Section 11.5), and other endpoints appear to show this as well. This is especially important when considering particles which may have low inherent toxicity at one size, yet greater potency at another. However, the mechanism which underlies a size-related difference in toxicity is not known at this time.

To compare toxic potency of particles of different sizes, intratracheal instillation has often been used. This technique allows the delivery of equivalent doses of different materials and avoids differences in deposition which would occur if particles of different sizes were inhaled. While this approach may highlight inherent similarities and differences in responses to particles of various sizes, in reality, there would be greater deposition of singlet ultrafine particles (in the size range used in the toxicology studies described) in the lungs, especially within the alveolar region, than for the larger fine or coarse mode particles.

The release of proinflammatory mediators may be involved in lung disease, and their levels may be increased with exposure to ultrafine particles. For example, Driscoll and Maurer (1991) compared effects of instilled fine (0.3 μm) or ultrafine (0.02 μm) TiO_2, in rat (F344) lungs. Concentrations were 10,000 μg particles/kg BW. Lavage was performed up to 28 days post-exposure, and pathology was assessed at this 28-day time point. While both size modes produced an increase in the number of AMs and PMNs in lavage, the increase was greater and more persistent with the ultrafine particles. The release of another monokine, tumor necrosis factor (TNF), by AMs was stimulated with both sizes, but again the response was greater and more persistent for the ultrafines. A similar response was noted for fibronectin produced by AMs. Finally, fine particle exposure resulted in a minimally increased prominence of particle-laden macrophages associated with alveolar ducts, while ultrafine particle exposures produced somewhat of a greater prominence of macrophages, some necrosis of macrophages and slight interstitial inflammation associated with the alveolar duct region. In addition, increased collagen occurred only with ultrafine particle exposure.

Oberdörster et al. (1992) instilled rats with 500 μg TiO_2 in either fine (0.25 μm) or ultrafine (0.02 μm) sizes, and performed lavage 24 h later. Various indicators of acute inflammation were altered with the ultrafine particles; this included an increase in the number of total cells recovered, a decrease in percentage of AMs and increase in percentage of PMNs, and an increase in protein. On the other hand, instillation of the fine particles did not cause statistically significant effects. Thus, the ultrafine particles had greater pulmonary inflammatory potency than did the larger size particles of this material. The investigators attributed enhanced toxicity to greater interaction of the ultrafine particles, with their large surface area, with alveolar and interstitial macrophages, resulting in enhanced release of inflammatory mediators. They suggested that ultrafine particles of materials of low in vivo solubility appear to enter the interstitium more readily than do larger size particles of the same material, which accounted for the increased contact with macrophages in this compartment of the lung. In support of these results, Driscoll and Maurer (1991) noted that the pulmonary retention of ultrafine TiO_2 particles instilled into rat lungs was greater than for the same mass of fine mode TiO_2 particles.

Not all ultrafine particles will enter the interstitium to the same extent, and this may influence toxicity. For example, both TiO_2 and carbon black elicit an inflammatory response, yet much less of the latter appears to enter the interstitium after exposure (Oberdörster et al., 1992). Since different particles may induce chemotactic factors to different extents, it is possible that a lower generation with TiO_2 results in less contact with and phagocytosis by macrophages, a longer residence time at the area of initial deposition, and a resultant greater translocation into the interstitium. Similarly, Brown et al. (1992; Table 11-24) noted following inhalation exposure of rats to TiO_2 or coal mine dust that the former did not affect macrophage chemotaxis, while the latter reduced it; the coal dust also produced a greater inflammatory response than did the TiO_2. This is consistent with less interaction of coal dust with AMs and greater movement into the interstitium.

The above studies appear to support the concept of some inherent toxicity of ultrafine particles compared to larger ones. Both particle size and the resultant surface area of a unit mass of particles likely influences toxic potential. Surface area is important because, as noted above, adsorption of certain chemical species on particles may enhance their toxicity, and this could be an even greater factor for ultrafine particles with their larger surface area per unit mass.

Other studies have compared effects following exposures to larger than ultrafine particle sizes, and the results ranged from none detectable to some particle size-related differences. Raub et al. (1985) instilled into rats coarse mode (12.2 μm) and fine mode (2.2 μm) volcanic ash at two dose levels, 50,000 or 300 μg particles/animal. The coarse mode produced a change in end expiratory volume, but no changes in other pulmonary function endpoints (i.e., frequency, V_T, peak inspiratory and expiratory flows, VC, RV, TLC). When lungs were examined 6 mo after instillation, animals exposed to the low dose of either size fraction showed no changes in lung weight or hydroxyproline content compared to control, while those exposed to the high concentration of coarse mode ash showed increased lung weight. In terms of histopathology, both size modes produced some focal alveolitis. Thus, there were essentially no differences in responses between the two size modes, especially at the low exposure dose. In a similar study, Grose et al. (1985) instilled mice with 42 μg/animal of volcanic ash in the same two size fractions as above, coarse and fine,

24 h prior to challenge with bacteria *(Streptococcus sp.)*. A small, but similar, increase in susceptibility to infection was noted with both particle sizes.

Shanbhag et al. (1994) exposed a mouse macrophage cell line (P388D1) to particles of two different composition (TiO_2 or latex) at comparable sizes, 0.15 and 0.45 μm for the former, and 0.11 and 0.49 for the latter. They also used pure titanium at 1.76 μm for comparison to latex at 1.61 μm. In order to examine effects of particle surface area, the cells were exposed to a constant surface area of particles, expressed in terms of mm^2 per unit number of cells. This was obtained based upon particle size and density and, therefore, the weight percentage was greater for larger particles than for smaller ones for the same surface area. Furthermore, because of particle density differences, the weight percentage for similarly sized particles of different materials to obtain the same surface area also differed. The authors noted that at a constant total particle surface area to cell ratio, the 0.15 and 0.45 μm particles were less inflammatory than were the 1.76 μm particles, in that the smaller particles produced lower elicited levels of interleukin-1 and less cell proliferation. These results indicate that the larger particles had greater toxicity than the smaller ones in this experimental system. Thus, the exact relationship between particle size and toxicity is not resolved, but may differ for different size modes.

11.12.4 Particle Number Concentration

The number concentration of particles within an aerosol will increase as the size of the constituent particles decrease. Thus, for a given mass concentration of a material, there would be greater particle numbers in an ultrafine aerosol than in a fine aerosol.
As previously discussed (Section 11.3.1), studies have shown various biological responses, such as reductions in lung volumes and diffusion capacity, alterations in biochemical markers, and changes in lung tissue morphology, in guinea pigs following exposure to ultrafine ZnO having a surface layer of H_2SO_4. These responses were much greater than were found following exposure to H_2SO_4 aerosols in pure droplet form yet having a similar mass concentration.

A possible contribution to this differential response is that the number concentration of particles in the exposure atmospheres were different, resulting in different numbers of particles deposited at target sites. At an equal total sulfate mass concentration, H_2SO_4

existed on many more particles when layered on the ZnO carrier particles than when dissolved into aqueous droplets (i.e., pure acid aerosol); this was because the particle size distribution of the former aerosol was smaller than that of the latter. Therefore, it is possible that the greater the number of particles containing H_2SO_4, the greater will be the number of cells affected after these particles deposit in the lungs, and the more severe will be the overall biological response. While differences in particle size distributions between the coated and pure acid particles may have influenced the results to some extent, a recent in vitro study confirmed that the number of particles in the exposure atmosphere, not just total mass concentration, is an important factor in biological responses following acidic sulfate particle inhalation (Chen et al., 1995) when aerosols having the same size distribution were compared.

11.14 SUMMARY

11.14.1 Summary of Acid Aerosols

The results of human studies indicate that healthy subjects do not experience decrements in lung function following single exposures to H_2SO_4 at levels up to 2,000 $\mu g/m^3$ for 1 h, even with exercise and use of acidic gargles to minimize neutralization by oral ammonia. Mild lower respiratory symptoms occur at exposure concentrations in the mg/m^3 range, particularly with larger particle sizes. Acid aerosols alter mucociliary clearance in healthy subjects, with effects dependent on exposure concentration and the region of the lung being studied.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels. Although the reasons for the inconsistency among studies remain largely unclear, subject selection and acid neutralization by NH_3 may be important factors. Even in studies reporting an overall absence of effects on lung function, occasional asthmatic subjects appear to demonstrate clinically important effects. Two studies from different laboratories have suggested that responsiveness to acid aerosols may correlate with degree of baseline

airway hyperresponsiveness. There is a need to identify determinants of responsiveness to H_2SO_4 exposure in asthmatic subjects. In very limited studies, elderly and individuals with chronic obstructive pulmonary disease do not appear to be particularly susceptible to the effects of acid aerosols on lung function.

Two recent studies have examined the effects of exposure to both H_2SO_4 and ozone on lung function in health and asthmatic subjects. Both studies found evidence that 100 $\mu g/m^3$ H_2SO_4 may potentiate the response to ozone, in contrast with previous studies.

Human studies of particles other than acid aerosols provide insufficient data to draw conclusions regarding health effects. However, available data suggest that inhalation of inert particles in the respirable range, including three studies of carbon particles, have little of no effect on symptoms or lung function in healthy subjects at levels above peak ambient concentrations.

The bulk of the toxicologic data base on PM involves sulfur oxide particles, primarily H_2SO_4, and the available evidence indicates that the observed responses to these are likely due to H^+ rather than to $SO_4^=$.

Acidic sulfates exert their action throughout the respiratory tract, with the response and location of effect dependent upon particle size and mass and number concentration. At very high concentrations that are not environmentally realistic, mortality will occur following acute exposure, due primarily to laryngeal or bronchoconstriction; larger particles are more effective in this regard than are smaller ones. Extensive pulmonary damage, including edema, hemorrhage, epithelial desquamation, and atelectasis can also cause mortality, but even in the most sensitive animal species, concentrations causing mortality are quite high.

Both acute and chronic exposure to H_2SO_4 at levels well below lethal ones will produce functional changes in the respiratory tract. The pathological significance of some of these are greater than for others. Acute exposure will alter pulmonary function, largely due to bronchoconstrictive action. However, attempts to produce changes in airway resistance in healthy animals at levels below 1,000 $\mu g/m^3$ have been largely unsuccessful, except when the guinea pig has been used. The lowest effective level of H_2SO_4 producing bronchoconstriction to date in the guinea pig is 100 $\mu g/m^3$ (1-h exposure). In general, the smaller size droplets were more effective in altering pulmonary function, especially at low

concentrations. Yet even in the guinea pig, there are inconsistencies in the type of response exhibited towards acid aerosols. Chronic exposure to H_2SO_4 is also associated with alterations in pulmonary function (e.g., changes in the distribution of ventilation and in respiratory rate in monkeys). But, in these cases, the effective concentrations are $\geq$500 $\mu g/m^3$. Hyperresponsive airways have been induced with repeated exposures to 250 $\mu g/m^3$ H_2SO_4 in rabbits, and have been suggested to occur following single exposures at 75 $\mu g/m^3$.

Severe morphologic alterations in the respiratory tract will occur at high acid levels. At low levels and with chronic exposure, the main response seems to be hypertrophy and/or hyperplasia of mucus secretory cells in the epithelium; these alterations may extend to the small bronchi and bronchioles, where secretory cells are normally rare or absent.

The lungs have an array of defense mechanisms to detoxify and physically remove inhaled material, and available evidence indicates that certain of these defenses may be altered by exposure to H_2SO_4 levels $<$1,000 $\mu g/m^3$. Defenses such as resistance to bacterial infection may be altered even by acute exposure to concentrations of H_2SO_4 around 1,000 $\mu g/m^3$. However, the bronchial mucociliary clearance system is very sensitive to inhaled acids; fairly low levels of H_2SO_4 produce alterations in mucociliary transport rates in healthy animals. The lowest level shown to have such an effect, 100 $\mu g/m^3$ with repeated exposures, is well below that which results in other physiological changes in most experimental animals. Furthermore, exposures to somewhat higher levels that also alter clearance have been associated with various morphometric changes in the bronchial tree indicative of mucus hypersecretion.

Limited data also suggest that exposure to acid aerosols may affect the functioning of AMs. The lowest level examined in this regard to date is 500 $\mu g/m^3$ H_2SO_4. Alveolar region particle clearance is affected by repeated H_2SO_4 exposures to as low as 250 $\mu g/m^3$.

The assessment of the toxicology of acid aerosols requires some examination of potential interactions with other air pollutants. Although such interactions may be antagonistic, additive, or synergistic, the exact mechanism by which they occur is not well defined, and evidence for them may depend upon the sequence of exposure as well as on the endpoint examined. Low levels of H_2SO_4 (100 $\mu g/m^3$) have been shown to react synergistically with O_3 in simultaneous exposures using biochemical endpoints. In this case,

the H_2SO_4 enhanced the damage due to the O_3. This is common in studies with O_3, while H_2SO_4 effects themselves may be more manifest with other, less potent, co-inhalants. The most realistic exposures are to multicomponent atmospheres, but the results of these are often difficult to assess due to chemical interactions of components and a resultant lack of precise control over the composition of the exposure environment.

11.14.2 Summary of Complex Mixtures

11.14.2.1 Summary of Carcinogenicity of Atmospheric Particulate Matter

The 1982 Air Quality Criteria Document for Particulate Matter and Sulfur Dioxide concluded from its review of studies on the genotoxicity and carcinogenicity of atmospheric particles that "all the major types of airborne particulate matter may contain adsorbed compounds that are mutagenic and/or carcinogenic to animals and may contribute in some degree to the human cancer associated with exposure to urban air pollution." Recent research activity has added data that support this conclusion, but do not warrant that it be changed significantly. Recent research activity has included:

(1) extensive in vitro mutagenicity testing and limited in vivo animal tumorigenicity testing or organic-solvent extracts of ambient air particulate matter showing predominately positive responses;

(2) mutagenicity and tumorigenicity testing of condensates or organic-solvent extracts of particulate emissions from specific combustion sources (e.g., diesel engines, gasoline engines and burning of cooking and heating fuels) showing predominately positive responses;

(3) and fractionation studies showing that significant portions of the genotoxic or carcinogenic activity of whole extracts of particulate matter emitted from specific combustion sources are accounted for by fractions containing complex mixtures of neutral organic molecules including polycyclic aromatic hydrocarbons.

The direct relevance of the evidence for the mutagenicity and tumorigenicity of extracts of particulate matter in experimental systems to exposure scenarios experienced by humans is uncertain at this time. Recent analytical epidemiological studies, that adjusted for tobacco smoking and other major potential risk factors, have found a weak to non-existent association between human lung cancer and indices of exposure to air pollution including particulate matter. Most investigators believe that the epidemiological evidence obtained thus far does not substantiate causality, although the hypothesis remains credible.

11.14.2.2 Summary of Diesel Emissions

Noncancer effects of diesel emissions

Acute toxic effects caused by exposure to diesel exhaust are mainly attributable to the gaseous components (i.e., mortality from carbon monoxide intoxication and lung injury from respiratory irritants). When the exhaust is diluted to limit the concentrations of these gases, acute effects are not seen.

A total of 10 different long-term (> 1 year) animal inhalation studies of diesel engine emissions have been conducted. The focus of these studies has been on the respiratory tract effects in the alveolar region. Effects in the upper respiratory tract and in other organs were not found consistently in chronic animal exposures. Several of these studies are derived from research programs on the toxicology of diesel emissions that consisted of large-scale chronic exposures, which are represented by multiple published accounts of results from various aspects of the overall research program. The respiratory system response has been well characterized in terms of histopathology, biochemistry, cytology, pulmonary function, and respiratory tract clearance. The pathogenic sequence following the inhalation of diesel exhaust as determined histopathologically and biochemically begins with the phagocytosis of diesel particles by AMs. These activated macrophages release chemotactic factors that attract neutrophils and additional AMs. As the lung burden of diesel particles increases, there is an aggregation of particle-laden AMs in alveoli adjacent to terminal bronchioles, increases in the number of Type 2 cells lining particle-laden alveoli, and the presence of particles within alveolar and peribronchial interstitial tissues and associated lymph nodes. The PMNs and macrophages release mediators of inflammation and oxygen radicals and particle-laden macrophages are functionally altered resulting in decreased viability and impaired

phagocytosis and clearance of particles. There is a substantial body of evidence for an impairment of particulate clearance from the bronchio-alveolar region of rats following exposure to diesel exhaust. The latter series of events may result in the presence of pulmonary inflammatory, fibrotic, or emphysematous lesions. The noncancer toxicity of diesel emissions is considered to be due to the particle rather than the gas phase, since the long-term effects seen with whole diesel are not found or are found to a much lesser extent in animals exposed to similar dilutions of diesel exhaust filtered to remove most of the particles. Chronic studies in rodents have demonstrated pulmonary effects at 200 to 700 $\mu g/m^3$ (expressed as equivalent continuous exposure to adjust for protocol differences). No-effect level have been reported ranging from 60 to 260 $\mu g/m^3$.

Several epidemiologic studies have evaluated the effects of chronic exposure to diesel exhaust on occupationally exposed workers. None of these studies are useful for a quantitative evaluation of noncancer toxicity because of inadequate exposure characterization, either because exposures were not well defined or because the possible confounding effects of concurrent exposures could not be evaluated.

Carcinogenic effects of diesel emissions

The U.S. Environmental Protection Agency (1994) has developed a draft qualitative and quantitative cancer assessment for diesel emissions. The summary to follow was drawn from that document. This draft is currently undergoing external review by the public and the Clean Air Scientific Advisory Committee. As a result of limited evidence from epidemiological data, supported by adequate evidence for carcinogenicity of diesel engine emissions in animal studies, as well as positive evidence for mutagenicity, it was concluded that diesel engine emissions best fit into cancer weight-of-evidence Category B1. Diesel engine emissions are thus considered to be probable human carcinogens. This is in agreement with a 2A classification by the International Agency for Research on Cancer.

Using a dosimetry model that accounted for animal-to-human differences in lung deposition efficiency, lung particle clearance rates, lung surface area, ventilation, metabolic rate, as well as elution rates of organic chemicals from the particle surface, equivalent human doses were calculated on the basis of particle concentration per unit lung surface area. Following dosimetric adjustment, risk estimates were derived using a linearized

multistage model. A unit risk estimate of 3.4×10^{-5} (the upper 95% bound of the cancer risk from lifetime exposure to 1 $\mu g/m^3$ diesel particulate matter) is recommended. This estimate is based on the geometric mean of estimates derived from three separate animal bioassays using Fischer 344 rats.

This unit risk estimate should not be used to evaluate the cancer risk of other types of particulate matter present in the ambient air. These particles may have differing solubilities, surface areas, presence of free radicals, or other properties which may greatly affect cancer potency.

11.14.3 Summary of Metals

11.14.3.1 Aluminum

Although pharmacokinetic data following inhalation exposure are somewhat limited, the existing data indicate that there are no major differences between the pharmacokinetics of aluminum in humans and laboratory animals. Differences in deposition are anticipated however.

Human occupational and epidemiological studies and animal studies support the respiratory tract as the primary target of inhaled aluminum compounds. Common reported symptoms include asthma, cough, and decreased pulmonary function (Abramson et al., 1989; Chan-Yeung et al., 1983; Simonsson et al., 1985); fibrosis has also been reported (Chen et al., 1978; De Vuyst et al., 1986; Gaffuri et al., 1985; McLaughlin et al., 1962; Musk et al., 1980; Shaver and Riddel, 1947). However, the occupational studies report concomitant exposure to known carcinogens and other respiratory irritants (PAHs, carbon monoxide, sulfur dioxide, hydrogen fluoride), and many of the workers were chronic smokers. Therefore, it is not clear whether effects reported in workers with occupational inhalation of aluminum can be attributed to the metal itself since the studies were confounded by co-exposure to other agents with known respiratory tract effects.

For these reasons, short- and long-term studies in laboratory animals may more accurately reflect the effects of inhaling aluminum. These studies have generally found that effects are limited to macrophage proliferation (Christie et al., 1963; Drew et al., 1974; Steinhagen et al., 19781 Thomson et al., 1986), pulmonary alveolar macrophage damage, and effects on Type II alveolar cells (Finelli and Que Hee, 1981). These studies support

the findings from human studies that aluminum acts via an irritant, rather than an allergic, mechanism (Abramson et al., 1989).

11.14.3.2 Antimony

Although kinetic data are limited, no major differences in the pharmacokinetics of antimony in humans and laboratory animals are evident. There is limited information on antimony toxicity, with human data primarily from chronic occupational exposures. Both human and laboratory animal data do demonstrate that the respiratory system is the primary target organ for antimony (trioxide) following inhalation exposure. However, the differences in toxicity for different particle sizes or valence states of antimony have not been well studied. In humans, respiratory effects (irritation, inflammation, pneumoconiosis, pulmonary dysfunction) have been reported in workers chronically exposed to mg levels of antimony dust (Cooper et al., 1968; Potkonjak and Pavlovich, 1983; Renes, 1953). Similar effects have been reported in several laboratory animal species (Bio/dynamics Incorporated, 1990; Gross et al., 1952, 1955; Groth et al., 1986; Watt, 1980, 1983; Wong et al., 1979). In addition, rats had increased number of alveolar macrophages following antimony exposure (Bio/dynamics Incorporated, 1985, 1990).

Altered ECG records is a cardiovascular effect observed in both workers (Brieger et al., 1954; Renes, 1953) and laboratory animals exposed to antimony trisulfide (Brieger et al., 1954). Gastrointestinal symptoms have also been reported in exposed workers, but may be due to mucociliary clearance from the lungs resulting in oral ingestion. Ocular and dermal effects are probably due to direct contact with antimony particles.

A Russian study (Belyaeva, 1967) reported reproductive effects on female workers; however, the study lacked quantitative exposure information. An animal study conducted by the same author suggested reproductive effects with mg level antimony exposure. A decreased number of offspring occurred in rats exposed to high concentrations of antimony prior to conception and during gestation. In those animals that failed to conceive, effects on the uterus and ovum-maturing process were observed.

Although increased tumor incidences have not been seen in workers exposed to antimony oxides (Potkonjak and Pavlovich, 1983), lung tumors developed in rats exposed to antimony trioxide or antimony trisulfide aerosols for a year (Groth et al., 1986). Therefore,

antimony may possibly be carcinogenic in humans but there are insufficient data for a definitive conclusion.

11.14.3.3 Arsenic

The toxicity data on inhalation exposures arsenic are limited in humans and laboratory animals. Acute data are largely lacking for this route of exposure. In humans, inhalation exposure data are primarily limited to long-term occupational exposure of smelter workers, which have indicated that chronic exposure leads to lung cancer. In laboratory animals, intratracheal administration of arsenic compounds in the lungs have not indicated tumor development in rats and mice (Berteau et al., 1978; Ishinishi et al., 1977), but insufficient exposure duration may have been used in these studies. However, respiratory tract tumors occurred in hamsters exposed to intratracheal doses of arsenic when a charcoal carbon carrier dust was used to increase arsenic retention in the lungs.

Chronic inhalation exposure has also been shown to cause skin changes (hyperpigmentation, hyperkeratosis) (Perry et al., 1948) and peripheral nerve damage (Feldman et al., 1979) in workers; however, the available inhalation studies in laboratory animals have not evaluated these endpoints. The laboratory animal inhalation data are limited and thus do not allow a thorough comparison of the toxicological and carcinogenic potential of arsenic with the human data. Oral data may be considered; however, it does not seem prudent to compare data from oral exposure to inhalation exposure since a portal-of-entry effect occurs for inhaled arsenic trioxide. Species differences in dosimetry, absorption, clearance, and elimination of arsenic (i.e., strong affinity to rat hemoglobin) exist between rats and other animal species, including humans, which complicate comparisons of quantitative toxicity (Mast et al., 1990; Vahter et al., 1982).

11.14.3.4 Barium

Both human and laboratory animal data are extremely limited, with no epidemiological data available, and no standard inhalation toxicity studies in animals. Occupational case studies are available for only the insoluble barium sulfate and barium carbonate salts, with no difference between effects of these compounds being apparent (Doig, 1976; Essing et al., 1976). The respiratory tract appears to be a target of these

barium compounds, based on subjective symptoms, physical examinations, chest radiography, spirometry and lung function tests; but, very few subjects were studied. Histopathological changes in rats exposed to barium carbonate for 1 or 4 months support the human data (Tarasenko et al., 1977). Guinea pigs exposed intratracheally exhibited bronchoconstriction (Hicks et al., 1986); there are no data on corresponding effects in humans, such as whether inhalation of barium compounds causes asthma or is immunogenic.

Cardiovascular effects were also reported in both human and laboratory animal studies, but the data are too limited by lack of controls and poor reporting to determine if these observations were related to barium exposure. Gastrointestinal, neurological and renal effects reported in one human by Shankle and Keane (1988) were not observed in the available animal studies, but no high quality animal studies of sufficient sensitivity assessed these endpoints. The general deficiencies in the Tarasenko et al. (1977) study preclude its use for predicting reproductive, developmental, or systemic endpoints in humans.

11.14.3.5 Cadmium

The kidney is clearly the primary target of chronic inhalation exposure to cadmium in the human; toxicity is dependent on cumulative exposure (Chia et al., 1989; Elinder et al., 1985a,b; Falck et al., 1983; Kjellstrom et al., 1977; Mason et al., 1988; Smith et al., 1980; Thun et al., 1989). Tubular proteinuria occurs after kidney levels of cadmium accumulate to a certain level, estimated at 200 μg/g (Ellis et al., 1985; Roels et al., 1983). An early 7 to 9 mo animal study found proteinuria in rabbits (Friberg, 1950), but this finding has not been replicated in more recent 90-day studies (Glaser et al., 1986; Prigge, 1978a). Because the threshold for renal cadmium toxicity is determined by the cadmium levels accumulated in the kidney, these differences are likely to be due to an insufficient exposure duration, rather than metabolic or mechanistic differences between humans and rodents.

The respiratory system is also a target of inhaled cadmium in humans and animals. Intense irritation occurs following high-level exposure in humans (Beton et al., 1966), and more mild effects on pulmonary function (dyspnea, decreased forced vital capacity) occur following chronic low-level exposure (Chan et al., 1988; Davison et al., 1988; Smith et al.,

1976). These effects and their mechanism have been investigated to a greater degree in animals, although spirometry has not been conducted in animals. The observed effects (increased lung weight, inhibition of macrophages and edema) (Boudreau et al., 1989; Buckley and Bassett, 1987; Bus et al., 1978; Grose et al., 1987; Henderson et al., 1979; Palmer et al., 1989) are consistent with the irritation observed in human studies. In humans (Chan et al., 1988), symptoms reverse with cessation or lessening of exposure; animal studies have reported no progression or slight reversal with continued exposure (Hart, 1986; Hart et al., 1989a).

Developmental toxicity has been reported in animals (Baranski, 1985); but no corresponding studies of developmental or reproductive toxicity have been conducted with humans.

Rat studies show that several forms of cadmium (cadmium chloride, cadmium oxide dust or fume, cadmium sulfide, or cadmium sulfate) can cause lung cancer (Oldiges et al., 1989; Takenaka et al., 1983). There is some evidence that lung cancer has been observed in humans following high occupational exposure (Elinder et al., 1985c; Sorahan, 1987; Thun et al., 1985), although confounding exposures were present. Because animal cancer studies only examined the lung, they did not address the suggestive evidence of cadmium-related prostate cancer found in several occupational studies (Elinder et al., 1985c; Sorahan, 1987).

11.14.3.6 Chromium

Human and laboratory animal data are in agreement that the respiratory system is the primary target of chromium compounds, and Cr(VI) is more toxic than Cr(III). This difference in toxicity is attributed to the greater solubility of Cr(VI) compared to Cr(III). Because acute data are limited to a single study showing that Cr(III) causes macrophage accumulation in the lungs of hamsters, this discussion is limited to subchronic and chronic studies. Human and animal data are in agreement regarding the specific nature of nasal effects (irritation, perforation of nasal septum). Lung lesions (e.g., abscesses) have been reported only in animals (Adachi, 1987; Adachi, et al. 1986; Steffee and Baetjer, 1965), but studies in humans have not been conducted in a manner that would detect such lesions. Similarly, several animal studies have reported evidence of inflammation, such as alveolar

macrophage accumulation and increased lymphocytes in BAL fluid (Glaser et al., 1985; 1986; 1990; Johansson et al., 1980; 1986a,b; 1987; Steffee and Baetjer, 1965), but no human BAL studies have been performed that would detect such changes. The reports of altered pulmonary function characteristic of obstructive lung disease (Langard, 1980; Lindberg and Hedenstierna, 1983) indicate that the lung is a target of chromium toxicity in humans. Human and animal data are also in agreement that Cr(VI) compounds cause lung cancer. In most human studies, the type of cancer was not identified. However, Langard and Norseth (1975) reported bronchial carcinomas in pigment workers, and Langard and Vigander (1983) reported epithelial cell carcinoma and adenocarcinoma in a followup of the same cohort. In animal studies, lung cancers were adenomas and adenocarcinomas (Glaser et al., 1986; Nettesheim et al., 1971). Due to the lack of human data, it is unlikely that these differences reflect actual differences in target cells.

Human studies have also reported early signs of renal damage (increased urinary levels of the proteins ß-2-microglobulin, retinol binding protein, and renal tubular antigen) with exposure to Cr(VI) compounds (Franchini and Mutti, 1988; Lindberg and Vesterberg, 1983b). Although such effects were not seen in animals, it is not clear if the analyses in animals were sufficiently sensitive to detect a subtle effect. Only two animal studies (Glaser et al., 1986; 1990) used histological examinations of the kidney, and small changes may have been missed because chronic nephrosis was common in both experimental and control groups. Also, urinalyses only measured total protein, so changes in individual proteins may have been missed.

11.14.3.7 Cobalt

Human and laboratory animal studies agree that the respiratory tract is the major target of the inhalation of cobalt compounds. In humans, two major types of effects are observed, interstitial lung disease (fibrosis) and asthma. Cobalt-related asthma is related to the induction of an immune response to inhaled cobalt (Roto, 1980; Shirakawa et al., 1988; 1989). The applicability of an laboratory animal model could not be evaluated because no studies were located that assessed the immunogenic potential of cobalt inhalation in animals. Several epidemiological and case studies of workers exposed to cobalt metal alone or in combination with tungsten carbide have shown that interstitial lung disease is

manifested as small opacities on radiographs, reduced lung function, and respiratory symptoms, such as dyspnea (Gennart and Lauwerys, 1990; Mosconi et al., 1991; Roto, 1980; Sprince et al., 1984; 1988). Evidence of inflammation (accumulation of macrophages, infiltration of macrophages into alveolar spaces) (Johannson and Camner, 1986; Bucher, 1991) and decreased lung function (Kerfoot et al., 1975) have been observed in laboratory animals.

Effects on the upper respiratory tract (nose, trachea, and larynx) were observed in the Bucher (1991) study, but were not reported in human studies. The cobalt sulfate used in the Bucher (1991) study is more soluble than the cobalt dusts evaluated in human studies, the differences in observed effects could also be due to differences in dosimetry in the URT region between rodents and humans, to the greater sensitivity of URT evaluation (e.g., histopathology) in laboratory animal studies, or the higher exposure levels used in the animal study. Alternatively, it could be due to differences between humans and rats or mice in species sensitivity.

Cardiomyopathy has been observed following occupational exposure to cobalt (Barborik and Dusek 1972; Kennedy et al., 1981). Although the data are limited to case studies, they are supported by oral evidence for cardiovascular effects of cobalt (Morin et al., 1971) and a report of elevated cobalt levels in the hearts of exposed workers (Kennedy et al., 1981). No effects on heart histology or on biochemical measures of cardiac damage were found in the one study that assessed these effects (Bucher, 1991), but high background levels in the controls may have obscured any effect. However, ECG findings consistent with cardiomyopathy were observed in miniature swine (Kerfoot et al., 1975).

Effects on the thymus and testes were observed at near-fatal exposure levels in acute and subchronic studies of rats and mice (Bucher, 1991). These effects have not been observed in humans, but they were observed at levels higher than those to which humans are exposed for more than brief periods. In addition, no studies were located that specifically assessed these endpoints in people. Finally, such systemic effects may be more likely to occur following exposure to soluble cobalt sulfate, as in the Bucher (1991) study, than following exposure to cobalt or hard-metal dust.

No standard neurotoxicity studies have been conducted with laboratory animals to evaluate the suggestion of deficits following cobalt inhalation reported by Jordan et al. (1990) and Meecham and Humphrey (1991).

Data on carcinogenic effects are limited to single studies in humans and laboratory animals. Although increased lung cancer was observed in a study of workers in an electrochemical plant, the small study size and concomitant exposure to other chemicals mean that the effect cannot be strongly attributed to cobalt (Mur et al., 1987). No effect on lung cancer was seen in hamsters exposed to cobalt oxide for 14 mo, but few study details were available (Wehner and Craig, 1972). Thus, no conclusion can be reached regarding the carcinogenic potential of inhaled cobalt compounds in humans or laboratory animals.

11.14.3.8 Copper

Although both human and laboratory animal data are limited, both data bases support the respiratory system as a major target of inhaled copper and copper compounds, including copper sulfate and copper chloride. In humans, the data are limited primarily to subjective reporting of respiratory symptoms following acute and chronic inhalation exposures to copper fumes or dust. Suciu et al. (1981) supported the respiratory symptoms with radiographic evidence of pulmonary involvement. The human data do not include pulmonary function tests or histopathology of the respiratory tract. In laboratory animal studies, supporting evidence exists for the involvement of the respiratory system after copper inhalation exposure. Respiratory tract abnormalities in mice repeatedly exposed to copper sulfate aerosols, and decreased tracheal cilia beating frequency in singly exposed hamsters have been reported (Drummond et al., 1986). Respiratory effects, although minor, have also been observed in rabbits (Johansson et al., 1983, 1984); these included a slight increase in amount of lamellated cytoplasmic inclusions in alveolar macrophages, and a slight increase in volume density of alveolar Type 2 cells. Although respiratory effects were observed in both human and laboratory animal studies, direct comparisons are not possible since different parameters were examined in the different species for which limited data exist. Immunological effects have been investigated in only one animal study (Drummond et al., 1986). In the one study addressing the issue, immunotoxic effects observed included: decreased survival time after simultaneous *S. zooepidemicus* aerosol

challenge, and decreased bactericidal activity after simultaneous *K. pneumonia* aerosol exposure. No laboratory animal studies have addressed whether the gastrointestinal, hepatic, neurological and reproductive effects observed in humans by Suciu et al. (1981) are reproducibly attributable to copper inhalation. This study is also possibly tainted with concomitant oral exposure to the copper dust.

11.14.3.9 Iron

There is limited information on iron toxicity, with human data primarily from chronic occupational exposures. Both human and laboratory animal data, mostly qualitative information, do demonstrate that the respiratory system is the primary target organ for iron oxides following inhalation exposure. However, the differences in toxicity (if any) for different particle sizes or valence states of iron have not been well studied. In humans, respiratory effects (coughing, siderosis) have been reported in workers chronically exposed to iron dust (Buckell et al., 1946; Charr, 1956; Friede and Rachow, 1961; Morgan, 1978; Schuler et al., 1962; Sentz and Rakow, 1969; Teculescu and Albu, 1973). In laboratory animals, hyperplasia and alveolar fibrosis have been reported after inhalation or intratracheal administration of iron oxide (Creasia and Nettesheim, 1974; Port et al., 1973). The lack of information on the histopathological changes in the lungs of exposed workers precludes direct comparison with animal data.

The available human and laboratory animal studies are limited and do not provide conclusive evidence regarding the respiratory carcinogenicity of iron oxide exposures (Boyd et al., 1970; Campbell, 1940; Creasia and Nettesheim, 1974; Faulds, 1957).

11.14.3.10 Mercury

Both human and animal data demonstrate that the neurological system is the most sensitive target organ for elemental mercury following inhalation exposure for acute or chronic durations. Effects range from reversible neurological symptoms to psychomotor and neurobehavioral changes and peripheral nerve dysfunction (Hallee, 1969; Jaffe et al., 1983; Albers et al., 1988; Piikivi et al., 1984; Ellingson et al., 1993). In animals, neurological and behavioral findings have been reported, but some studies have serious limitations (Ashe et al., 1953). It is clear that mercury can produce significant neurological

damage to humans; however, direct comparisons on the neurological dysfunction and symptoms are not possible because histopathology of the brain has been only performed in animal species.

Respiratory, gastrointestinal, and cardiovascular symptoms have also been reported in case reports and occupational studies (Fagala and Wigg, 1992; Hallee, 1969; Jaffe et al., 1983; Kanluen and Gottlieb, 1991); these effects appear with exposure to higher concentrations of mercury. Animal data on elemental mercury exposure are limited. Respiratory, cardiovascular, and liver effects have been reported, but information is inadequate (Ashe et al., 1953). The kidney is a sensitive target organ of toxicity following elemental mercury exposure in humans, due to the high accumulation of mercury in the kidneys (Barregard et al., 1988; Cardenas et al., 1993; Ehrenberg et al., 1991; Stewart et al., 1977). In animals, data on renal effects were limited to one study that reported proteinuria in Brown-Norway rats exposed to mercuric chloride aerosol (Bernaudin et al., 1981). Clearly, the database for inhalation mercury exposure is more extensive for humans than for laboratory animals, and therefore, available data for comparison between species is inadequate.

Inhalation exposure to elemental mercury does not appear to produce fertility effects in exposed workers (Alcser et al., 1989; Cordier et al., 1991; Lauwerys et al., 1985; Mishonova et al., 1980; Sikorski et al., 1987); however, exposure data are lacking for these studies. A developmental study in rats suggest that inhalation of mercury vapors during gestation may also lead to developmental effects in the offspring (Baranski and Szymczyk, 1973).

11.14.3.11 Manganese

As Roels et al. (1992) and other investigators have noted, a threshold for the neurotoxic effects of manganese has not been reported in the epidemiological literature. However, a LOAEL may be obtained from the study by Roels et al. (1992) by dividing the geometric mean integrated respirable dust concentration (793 μg Mn/m^3 $\times$ years) by the average period of worker exposure (5.3 years) to eliminate time (in years) from the

time-weighted average,[1] thereby yielding a LOAEL of 150 μg Mn/m^3. The workplace-based LOAEL of 150 μg Mn/m^3 could be adjusted for nonoccupational lifetime exposure by multiplying it by (1) the quotient of 10 m^3/day divided by 20 m^3/day (for worker versus nonworker ventilation rates) and (2) the quotient of 5 days divided by 7 days (for work week versus full week). The resulting adjusted LOAEL is 50 μg Mn/m^3.

The U.S. Environmental Protection Agency (IRIS, 1993) used the above approach in deriving an inhalation reference concentration[2] (RfC) for manganese. More recently, the U.S. Environmental Protection Agency (1994) considered various alternative approaches to deriving a quasi NOAEL from the data of Roels et al. (1992), as part of its evaluation of the manganese gasoline additive methylcyclopentadienyl manganese tribcarbonyl (MMT). In particular, a benchmark dose (BMD) approach was used to estimate the concentration that would produce a specified effect (e.g., a 10% increase in the prevalence of abnormal scores on the eye-hand coordination test of Roels et al. [1992]). The BMD was calculated by fitting a mathematical model to the data from Roels et al. (1992) and additional data supplied by Roels (1993). A maximum likelihood estimate of the dose associated with a 10, 5, or 1% increase in response is denoted as the BMD_{10}, BMD_5, or BMD_1, respectively. The 95th percentile lower confidence limit on the BMD is denoted as the benchmark dose level (BMDL), as in $BMDL_{10}$, $BMDL_5$, or $BMDL_1$. Of six mathematical models considered, the U.S. EPA concluded that the quantal linear model was the most suitable choice for the data available in this case. Focusing primarily on 10 and 5% effect levels, the U.S. EPA calculated $BMDL_{10}$ and $BMDL_5$ values of 26 and 13 μg/m^3, respectively, after adjusting for the non-occupational exposure scenario.

Additional analyses by the U.S. EPA using a Bayesian statistical approach essentially duplicated the results of the benchmark analyses. In essence, the Bayesian approach yields a distribution of concentrations (rather than a point estimate) associated with a specified effect. In addition, the Bayesian approach made it possible to estimate the

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[2]The geometric mean concentration was used to represent the average exposure because the workers' exposure measurements were log-normally distributed, and the arithmetic mean exposure period was used because it was the only value reported by Roels et al. (1992).

[3]The reference concentration is defined as an estimate (with uncertainty spanning about an order of magnitude) of a continuous inhalation exposure level for the human population (including sensitive subpopulations) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime.

concentrations associated with specified increases of errors on the eye-hand coordination test of Roels et al. (1992) (e.g., 32 $\mu g/m^3$ for a 10% increase; 19 $\mu g/m^3$ for a 5% increase; and 17 $\mu g/m^3$ for a 4% increase, which was the minimum difference achieving statistical significance [all concentrations adjusted to nonoccupational exposure conditions]).

In evaluating the potential health risks associated with inhalation exposure to manganese, various uncertainties must be taken into consideration. Virtually all of the human health evidence is based on healthy, adult male workers. However, certain populations, such as children, pregnant women, elderly persons, iron- or calcium-deficient individuals, and individuals with liver impairment, may have an increased potential for excessive manganese body burdens due to increased absorption or altered clearance mechanisms. In addition, the potential reproductive toxicity of inhaled manganese has not been adequately investigated in females or males. Limited available information concerning the developmental toxicity of inhaled manganese suggests the possibility that prenatal and/or postnatal exposure of laboratory rodents to MnO_2 (via the air supplied to the pregnant mother) may depress neurobehavioral activity. The concentrations and durations of exposure sufficient to induce such effects are not known.

Another uncertainty is due to the lack of adequate human or laboratory animal studies involving chronic exposures and effects. As noted above, it may be that longer exposure and/or testing later in life would result in the detection of effects at lower concentrations than is possible after shorter periods of exposure and/or in younger workers. On the other hand, it is also evident from these studies that a much shorter period than a full lifetime of occupational manganese exposure may be sufficient to induce manganese neurotoxicity. Another uncertainty owes to the fact that different forms of metals may have different toxic properties (due to different oxidation states, different solubilities, and possibly other factors). Sufficient data are not available to judge the comparative toxicity of different compounds of manganese.

11.14.3.12 Magnesium

Data on the inhalation toxicity of magnesium and its compounds in humans and laboratory animals are very limited, but they do support the respiratory tract as a target. Acute exposure of humans (Drinker et al., 1927) or laboratory animals (Drinker and

Drinker, 1928) to magnesium oxide fume results in a reaction described as similar to zinc oxide metal fume fever. Fever was observed in humans, and dyspnea and hypothermia in animals. The reason for the opposite effects on body temperature is unclear. There are no acute data on humans or laboratory animals exposed to magnesium carbonate.

There is suggestive evidence in humans and laboratory animals that chronic exposure to magnesium carbonate or magnesium oxide dusts may produce pneumoconiosis; the evidence is stronger for an association with magnesium oxide dust. Pneumoconiosis has been reported in workers exposed to magnesium carbonate dust, but the effect may have been due to concomitant exposure to silicon dioxide and/or asbestos (Tokmurzina and Dzangosina, 1970; Zeleneva, 1970). However, a correlation with exposure to magnesium oxide (roasted magnesite) has been observed (Zeleneva, 1970). It is unclear if fibrosis was assessed in these studies. Irritation of the eyes and nose has also been reported in humans exposed to magnesium oxide dust (Pleschitzer, 1936). In laboratory animals, fibrosis was observed following chronic exposure to high levels of magnesium oxide or magnesium carbonate dusts, although magnesium oxide was more fibrogenic (Katsnel'son et al., 1964; Zeleneva, 1970). No more sensitive measures of inflammation appear to have been assessed. No data were available on chronic inhalation exposure of humans or laboratory animals to magnesium oxide fume.

Nonrespiratory effects of inhalation exposure to magnesium have not been reported, but the degree to which such effects have been assessed is unclear. Indirect evidence indicates that magnesium is absorbed following inhalation of magnesium oxide (Pleschitzer, 1936), and the solubility of magnesium carbonate in aqueous solutions would suggest that it is also absorbed from the respiratory tract. Due to the large amounts of magnesium stored in the body, one would expect that relatively large amounts of inhaled magnesium would need to be absorbed before any systemic effects occur. However, toxic effects resulting from hypermagnesemia have been reported following oral dosing with large amounts of magnesium sulfate (Garrelts et al., 1989; Gren and Woolf, 1987; Ratzan et al., 1980).

11.14.3.13 Molybdenum

The respiratory tract appears to be the main target in humans and animals of inhalation exposure to molybdenum compounds; however, inhalation exposure to

molybdenum has also been associated with nonspecific effects in humans. These nonspecific complaints from occupationally exposed workers in Russia include general weakness and dizziness (Mogilevskaya, 1963). Studies on U.S. molybdenum workers have failed to show specific complaints other than increased serum ceruloplasmin and serum uric acid concentrations (Walravens et al., 1979). However, high employee turnover may have resulted in the elimination of sensitive employees from the study population.

Data from inhalation experiments in animals indicate that molybdenum toxicity varies with the molybdenum compound. Subchronic exposure to molybdenum trioxide or ammonium molybdate resulted in greater toxicity than did exposure to molybdenum dioxide or metallic molybdenum (Mogilevskaya, 1963). Similarly, subchronic exposure to molybdenum trioxide dust was more toxic to guinea pigs than was exposure to comparable levels of molybdenum disulfide dust; molybdenum trioxide fumes were less toxic than molybdenum trioxide dust, but the exposure levels were also lower, so a direct comparison is difficult (Fairhall et al., 1945). Data from acute exposure studies also suggest that ammonium dimolybdate is more toxic than molybdenum trioxide or ammonium dimolybdate, but differing exposure levels make comparisons difficult (Barltrop, 1991). Animal studies did not address the complaints of weakness and dizziness reported in an occupational study (Mogilevskaya, 1963).

Pharmacokinetic data are insufficient to provide meaningful data on comparative toxicity. However, indirect data indicate that inhaled molybdenum compounds are absorbed, so the possibility of systemic effects (most likely gout-like symptoms) is of interest.

11.14.3.14 Nickel

Both human and laboratory animal data demonstrate that the respiratory tract is the primary target organ for nickel compounds following inhalation exposure. In humans, respiratory effects include asthma and altered pulmonary function (reduced vital capacity and expiratory flows) (Dolovich et al., 1984; Kilbam et al., 1990; McConnell et al., 1973; Novey et al., 1983). In laboratory animals, inflammatory response (morphological and enzyme changes in alveolar macrophages, interstitial infiltrates) were observed in rabbits, rats, and mice (Benson et al., 1987, 1988, 1989, 1990; Bergham et al., 1987, Dunnick

et al., 1988, 1989; Horie et al., 1985; Jarstrand et al., 1978; Johansson and Camner, 1980, 1986; Murthy et al., 1983). These animal data do suggest an immunological response in the lungs. Occupational studies have not evaluated these lung parameters in exposed workers; therefore, it is not known whether nickel can produce similar immunological changes in the respiratory tract of humans. Bencko et al. (1983, 1986) did report immunological changes (altered serum levels of IgG, IgA, IgM, and IgE levels, α2-macroglobulin) occurring in refinery workers exposed to nickel. In animals, immunosuppression was also observed following acute exposure to nickel chloride aerosols in rats (Graham et al., 1978) and for up to 6 mo with various nickel compounds in rats, mice, and rabbits (Benson et al., 1987, 1988; Dunnick et al., 1988; Haley et al., 1990; Spiegelberg et al., 1984). Although human and laboratory animal studies indicate immunological effects associated with nickel, the studies measured different immunological endpoints.

In humans, the potential of lung and nasal cancer (primarily squamous cell carcinomas) was evident in occupational settings; nickel refinery workers are exposed to both soluble and insoluble nickel compounds (Chovil et al., 1981; Doll et al., 1970). Quantitative data on acute exposures in humans were not available. Animal data demonstrated increased tumor incidences in the respiratory system following longer duration exposures to insoluble nickel compound (nickel subsulfide); tumors included adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcomas (Ottolenghi et al., 1974).

An occupational study of exposed nickel refinery workers reported increased incidence of abortions and structural malformations (Chashschin et al., 1994). Laboratory animal studies also suggest reproductive effects (decreased fetal body weight, testicular degeneration) associated with nickel exposure (Benson et al., 1987, 1988; Weischer et al., 1980).

11.14.3.15 Potassium

The available data on the toxicity or pharmacokinetics of inhaled potassium compounds are insufficient to assess the comparative toxicity in humans and laboratory animals. Data on the response to inhaled potassium are limited to one abstract assessing

the effects in atopic subjects (Dixon et al., 1989); some other data may be available from the Russian literature, but cannot be assessed currently.

Other inhalation data are available from studies in which potassium was used as the counterion for the study of the ion of interest; such studies are discussed in the sections on bromine and chromium. Other studies on compounds such as potassium ferricyanide were not discussed here because the potassium ion would not be expected to contribute significantly to the compound's overall toxicity.

No data were located on the pharmacokinetics of potassium following the inhalation of potassium compounds. Although many of these compounds are water-soluble and the potassium could be distributed systemically, systemic toxicity would not be expected to result, since large amounts would need to be absorbed in order to disturb potassium homeostasis. The pharmacokinetics of potassium absorbed from the gastrointestinal tract are well-characterized and do not differ qualitatively between humans and laboratory animals.

11.14.3.16 Selenium

There is limited information on selenium toxicity, with human data primarily from chronic occupational exposures. Both human and laboratory animal data demonstrate that the respiratory system is the primary target organ for selenium following inhalation exposure. In humans, respiratory effects (irritation, edema, bronchitis, pneumonia) have been reported in workers chronically exposed to selenium (Buchan, 1974; Clinton, 1947; Glover, 1970; Hamilton, 1949). Similar effects have been reported in several animal species (Dudley and Miller, 1941; Hall et al., 1951). Gastrointestinal effects and irritation of the skin and eyes have also been reported in humans following exposure to elemental selenium, selenium dioxide, or hydrogen selenide (Clinton, 1947; Glover, 1970; Middleton, 1947; Pringle, 1942); however, these effects may be attributed to ingestion of or direct contact with selenium particles. Laboratory animal data suggest that mild hepatic effects may occur in humans with exposure to selenium. However, the effects of selenium on the liver has not been investigated in exposed workers, although selenium has been detected in human liver (Jereb et al., 1975).

Reproductive and developmental endpoints have not been evaluated in humans or laboratory animals following inhalation exposure to selenium. However, Archimbaud et al. (1992) has demonstrated that selenium can readily cross the placenta to reach the fetus, suggesting that developmental or reproductive effects may be possible. Occupational studies have not reported any increased incidence of tumors in exposed workers. No chronic carcinogenicity bioassays have been conducted in laboratory animals so that comparative evaluation of this endpoint is precluded.

11.14.3.17 Tin

Inorganic Tin

Human (Cutter et al., 1949; Dundon and Hughes, 1950; Robertson and Whitaker, 1954; Robertson et al., 1961; Schuler et al., 1958) and animal (Pendergrass and Pryde, 1948; Robertson, 1960) studies agree that inorganic tin is relatively toxicologically inert, and that effects are limited to mild respiratory effects, along with the formation of radio-opaque nodules in the lungs. Fibrosis is not observed. No other target systems for inhalation exposure to inorganic tin have been reported.

Organic Tin

Limited data indicate that the nervous, hepatic, renal, and respiratory systems are targets of inhalation exposure to organotin compounds. Nervous system toxicity symptoms are the most slowly reversible effects of organotin compounds in humans (Rey et al., 1984). Neurotoxicity effects could not be confirmed in laboratory animals, since no standard neurological testing has been conducted. Limited animal data, including histopathological data, confirm that organotin compounds adversely affect the lungs, liver, and kidney (Gohlke et al., 1969; Igarashi, 1959; Iwamoto, 1960). Organotin compounds may also decrease reproductive success (Igarashi, 1959).

11.14.3.18 Titanium

Both human and laboratory animal data demonstrate that the respiratory system is the primary target organ for titanium following inhalation exposure. Although few studies have assessed titanium toxicity outside the respiratory tract, no histopathology of other

organs was found in rats chronically exposed to titanium tetrachloride at up to 6,000 μg Ti/m^3 (Du Pont, 1986; Lee et al., 1986a). In addition, occupational studies in humans and experimental data from animals indicate that titanium is not translocated in the body, as titanium has not been found body organs other than the respiratory tract, even with chronic exposure and with high concentrations. The toxic compounds most studied are titanium dioxide and titanium tetrachloride. In humans and animals, exposure to titanium dioxide has resulted in deposition of the titanium particles in the alveoli of the lungs. This results in pneumoconiosis in humans (Daum et al., 1977) and signs of inflammation in animals (Oberdörster et al., 1992). However, data do not suggest that titanium dioxide causes lung cancer in humans (Chen and Fayerweather, 1988). In rats, very high levels (150,000 μg Ti/m^3) did result in lung cancers that are believed to be unique to rats and are not suggestive of similar cancers in humans or other laboratory animals. These high exposure levels also overwhelmed the clearance capacity of the lung.

Because titanium tetrachloride degrades to highly corrosive hydrochloric acid, it is a much stronger irritant that titanium dioxide. This has been illustrated in studies of acute and chronic occupational exposure. Symptoms in humans include stenosis of the upper respiratory tract (Park et al., 1984) and decreased lung capacity (Garabrant et al., 1987); deposits of titanium metal were also found in the lungs (Elo et al., 1972; Ophus et al., 1979; Redline et al., 1986). In rats with acute exposure to titanium tetrachloride, respiratory tract irritation was also seen, chronic exposure resulted in more severe symptoms such as tracheitis and abnormal lung noises with accompanying histopathological changes (Du Pont, 1986; Lee et al., 1986a). In humans, exposure to titanium tetrachloride has not been associated with cancer. As with titanium dioxide, chronic exposure of rats to titanium tetrachloride has led to squamous cell carcinoma and keratinizing squamous cell carcinoma (Du Pont, 1986; Lee et al., 1986a). The relevance of these unique cancers to humans is unknown, as these tumors are not usually seen in humans.

11.14.3.19 Vanadium

Human and laboratory animal data confirm the respiratory tract as the primary target of inhaled vanadium compounds. Laboratory animal data suggest that vanadium

compounds damage alveolar macrophages, and that toxicity is related to compound solubility and valence.

Because of the difficulty in obtaining clinical signs of respiratory distress in laboratory animals, most reported animal data consisted of histological findings (increased leukocytes and lung weights, perivascular edema, alveolar proteinosis, and capillary congestion) (Knecht et al., 1985; Lee and Gillies, 1986; Roscin, 1967; Paynich, 1966). Human occupational case studies and epidemiological studies generally emphasize clinical symptoms of respiratory distress, including wheezing, chest pain, bronchitis, rhinitis, productive cough, and fatigue (Levy et al., 1984; Musk and Tees, 1982; Sjöberg 1956; Thomas and Stiebris, 1956; Zenz et al., 1962). No human data were found describing histopathology following oral or inhalation exposure.

There are insufficient data to definitively determine whether vanadium inhalation causes extrarespiratory (systemic) effects. However, symptoms of the nervous and cardiovascular systems have been observed following chronic occupation exposure (Roschin, 1964 Sjöberg, 1950; Watanaze et al., 1966), and laboratory animal studies have observed effects on the liver, kidneys, gonads, nervous, hematological and cardiovascular systems (Pazynich, 1966; Roshchin, 1967a,b; Sjöberg, 1950).

There was a lack of information on developmental effects, reproductive effects, or cancer in both humans and in animals following inhalation exposure. However, following oral exposure to sodium metavanadate, no or very slight developmental effects were reported in rats (Paternain et al., 1987; Kowalska, 1988; Domingo et al., 1986).

11.14.3.20 Zinc

No major differences in the pharmacokinetics of zinc in humans and laboratory animals were evident. Both human and laboratory animal data demonstrate that the respiratory system is the primary target organ for zinc following inhalation exposure; the toxic compounds most studied are zinc chloride and zinc oxide. In humans, the development of metal fume fever, characterized by respiratory symptoms and pulmonary dysfunction, was observed in workers and experimental subjects during acute exposures to zinc oxide (Gordon et al., 1992; Hammond, 1944). An immunological component is believed to be responsible for these respiratory responses (Sturgis et al., 1927).

Quantitative data on chronic exposures in humans are not available. In Guinea pigs, BAL fluid and pulmonary function were assessed after zinc oxide exposures for less than a day (Conner et al., 1988; Gordon et al., 1992). Inflammation with altered macrophage function (as suggested by biochemical and morphological changes in the lungs) and impaired pulmonary function (decreased compliance, total lung capacity, decreased carbon monoxide diffusing capacity) were observed in guinea pigs. Rats also showed altered macrophage function in the lungs (Gordon et al., 1992). At subchronic durations, histopathological changes in the lungs (increased macrophages) were observed in rats, mice, and Guinea pigs exposed to zinc chloride (Marrs et al. 1988). It is clear that zinc can produce inflammatory response in both human and animal species, however, direct comparisons on the respiratory etiology are not possible because pulmonary function tests and BAL fluid analyses for humans examine different parameters than those for animals, and immunological evaluations in BAL fluid were performed only on humans. Alveologenic carcinomas have been observed in mice exposed to zinc chloride for 20 weeks (Marrs et al., 1988); however, human studies have shown no evidence of increased tumor incidences at exposure levels found in occupational settings (Logue et al., 1982; Neuberger and Hollowell, 1982).

11.14.4 Silica

Emissions of silica into the environment can arise from natural, industrial, and farming activities. There are only limited data on ambient air concentrations of amorphous or crystalline silica, principally because existing measurement methods are not well suited for distinguishing silica from other particulate matter. Using available data on the quartz fraction of coarse dust (Davis et al., 1984) and average annual arithmetic mean PM_{10} measurements for 17 U.S. metropolitan areas, annual average and high U.S. ambient quartz levels of 3 and 8 $\mu g/m^3$, respectively, have been estimated (U.S. Environmental Protection Agency, 1995). Davis et al. (1984) found that most of the quartz was in the fraction between 2.5 to 15 μm MMAD.

Silica can occur in two chemical forms, amorphous and crystalline. Crystalline forms include quartz, which is the most prevalent; cristobalite; tridymite; and a few other rare forms. Freshly fractured crystalline silica is more toxicologically reactive than aged forms of crystalline silica or forms that may be coated with other chemical compounds.

Amorphous silica is less well studied and may have similar toxic endpoints but is less potent than crystalline silica. With sufficient exposure, crystalline silica is toxic to the respiratory system. Acute high exposure in both humans and animals causes lung inflammation and, if the exposure is high enough, rapid onset of a fibrotic lung disease which can be fatal. Occupational studies show that chronic exposure to crystalline silica causes inflammation of the lung which is followed by fibrosis and a human fibrotic disease called silicosis which can lead to early mortality. Some occupational studies also show a concurrent incidence of lung cancer. The role, if any, of silica-induced lung inflammation, fibrosis, and silicosis in the development of lung cancer is hypothesized but not adequately demonstrated. Crystalline silica interaction with DNA has been shown. Chronic exposure animal studies in rats also show a similar pattern of lung inflammation, fibrosis, and lung cancer. In 1987, the International Agency for Research on Cancer classified crystalline silica as a "possible" human carcinogen owing to a sufficient level of evidence in animal studies with inadequate evidence in human studies. While surveillance of the U.S. population for fibrosis and silicosis is not standard practice, the health statistics of the U.S. do not reveal a population increase of these crystalline silica diseases. However, there is an increase in these diseases within segments of the occupational work force.

An assessment of the occupational risk of silicosis was made using recent studies from South Africa (Hnizdo and Sluis-Cremer, 1993) and Canada (Muir et al., 1989b), both of which examined medical histories of over 2000 miners. Both predicted zero risk for cumulative silica exposures of 0.6 $mg/m^3 \cdot$years (equivalent to a 20-year workplace exposure to an average concentration of 30 $\mu g/m^3$). At higher exposures, excess risk was observed in these workers (e.g., 2% risk at 1.6 $mg/m^3 \cdot$ years). These effective occupational exposures are greater and the particle sizes smaller (Verma et al., 1994) than those likely to be experienced by the public; however, the public would be expected to include susceptible subpopulations. Information gaps still exist for both the exposure-response relationship (especially in potentially susceptible subgroups) for levels of exposure within the general population.

11.4.5 Asbestos

The mechanisms underlying the development of asbestos-induced pulmonary fibrosis in rats is complex. While the acute response to asbestos results in pulmonary inflammation and cell proliferation, the pattern of fibrosis following chronic exposures becomes more complex. It is likely that the retention of inhaled fibers and consequent accumulation of interstitial fibers concomitant with prolonged inflammation will contribute to the development of a diffuse and progressive pattern of pulmonary fibrosis. The pathogenesis of asbestos-related lung tumors clearly is a complex process and requires further investigation.

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