External Review Draft No. 2
February 1981

Draft
Do Not Quote or Cite

Air Quality Criteria for Particulate Matter and Sulfur Oxides

Volume V

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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

NOTE TO READER

The Environmental Protection Agency is revising the existing criteria documents for particulate matter and sulfur oxides (PM/SO_x) under Sections 108 and 109 of the Clean Air Act, 42 U.S.C. §§ 7408, 7409. The first external review draft of a revised combined PM/SO_x criteria document was made available for public comment in April 1980.

The Environmental Criteria and Assessment Office (ECAO) filled more than 4,000 public requests for copies of the first external review draft. Because all those who received copies of the first draft from ECAO will be sent copies of the second external review draft, there is no need to resubmit a request.

To facilitate public review, the second external review draft will be released in five volumes on a staggered schedule as the volumes are completed. Volume I (containing Chapter 1), Volume II (containing Chapters 2, 3, 4, and 5), Volume III (containing Chapters 6, 7, and 8), Volume IV (containing Chapters 9 and 10), and Volume V (containing Chapters 11, 12, 13, and 14) will be released during January-February, 1981. As noted earlier, they will be released as volumes are completed, not in numerical order by volume.

The first external review draft was announced in the Federal Register of April 11, 1980 (45 FR 24913). ECAO received and reviewed 89 comments from the public, many of which were quite extensive. The Clean Air Scientific Advisory Committee (CASAC) of the Science Advisory Board also provided advice and comments on the first external review draft at a public meeting of August 20-22, 1980 (45 FR 51644, August 4, 1980).

As with the first external review draft, the second external review draft will be submitted to CASAC for its advice and comments. ECAO is also soliciting written comments from the public on the second external review draft and requests that an original and three copies of all comments be submitted to: Project Officer for PM/SO_x, Environmental Criteria and Assessment Office, MD-52, U.S. Environmental Protection Agency, Research Triangle Park, N. C. 27711. To facilitate ECAO's consideration of comments on this lengthy and complex document, commentators with extensive comments should index the major points which they intend ECAO to address, by providing a list of the major points and a cross-reference to the pages in the document. Comments should be submitted during the forthcoming comment period, which will be announced in the Federal Register once all volumes of the second external review draft are available.

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PREFACE

This document is a revision of External Review Draft No. 1, Air Quality Criteria for Particulate Matter and Sulfur Oxides, released in April 1980. Comments received during a public comment period from April 15, 1980 through July 31, 1980, and recommendations made by the Clean Air Scientific Advisory Committee in August have been addressed here.

Volume V contains Chapters 11, 12, 13, and 14 which cover the respiratory physiological, toxicological, clinical, and epidemiological aspects of exposure to sulfur oxides and particulate matter.

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11. RESPIRATORY TRACT DEPOSITION AND FATE OF INHALED AEROSOLS AND SO_2

11.1 INTRODUCTION

11.1.1 General Considerations

The respiratory system is the major route for exposure of people to airborne suspensions of particles (aerosols) and SO_2 gas. During inhalation (and exhalation) a portion of the inhaled aerosol and gas may be deposited by contact with airway surfaces or be transferred to unexhaled air. The remainder is exhaled. The portion transferred to unexhaled air may be either deposited by contact with airway surfaces or later exhaled. These phenomena are complicated by interactions that may occur between the particles, the SO_2 gas, other gases such as endogenous ammonia, and the water vapor present in the airways.

In inhalation toxicology, specific terminology is applied to these processes. The term deposition refers specifically to the removal of inhaled particles or gases by the respiratory tract and to the initial regional pattern of these deposited materials. The term clearance refers to the subsequent translocation (movement of material within the lung or to other organs), transformation, and removal of deposited substances from the respiratory tract or from the body. It can also refer to the removal of reaction products formed from SO_2 or particles. The temporal pattern of uncleared deposited particulate materials or gases and reaction products is called retention. At the end of a brief aerosol or gas exposure, these three concepts may be described by the relationship:

$$\text{RETENTION}(t) = \text{DEPOSITION}(t) - \text{CLEARANCE}(t) \qquad (1)$$

where (t) refers to a function of time after deposition occurs.

The mechanisms involved in the deposition of inhaled aerosols and gases are affected by physical and chemical properties, including aerosol particle size distribution, density, shape, surface area, electrostatic charge, hygroscopicity or deliquescence, chemical composition, gas diffusivity and solubility, and related reactions. The geometry of the respiratory airways from nose and mouth to the lung parenchyma also influences aerosol deposition; the important morphological parameters include the diameters, lengths, inclinations to vertical, and branching angles of airway segments. Physiological factors that affect deposition include breathing patterns, air flow dynamics in the respiratory tract, and variations of relative humidity and temperature within the airways. Clearance from the respiratory tract depends on many factors, including site of deposition, chemical composition and properties of the deposited particles, reaction products, mucociliary transport in the tracheobronchial tree, macrophage phagocytosis in the deep lung, and pulmonary lymph and blood flow. Paramount to the interpretation of the results of health effects studies described in Chapters 12-14 is an understanding of the regional deposition and clearance of particles and SO_2.

Translocation of sulfur compounds or other materials from the lung to other organs is also important, since the lung can be the portal of entry for toxic agents that have effects

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on other organs of the body. Hence, multicompartment models of clearance from the respiratory tract to other organs can provide predictive information about the potential for injury of those other organs. Mathematical representations of lung retention and translocation require data on the various factors that affect deposition and clearance.

Since many conclusions concerning the deposition, clearance, and health impact of inhaled aerosols and SO_2 are based upon data obtained from animal experiments, care must be taken to identify differences in physiological and anatomical factors between human beings and animals that may influence these phenomena. Emphasis in the following discussion will be on the regional deposition and clearance that occur in the human airways, but selected comparisons are made with other mammalian species to clarify differences that may affect health impact analyses of experimental data.

11.1.2 Aerosol and SO_2 Characteristics

An aerosol may be defined as a relatively stable suspension of liquid or solid particles in a gaseous medium. Airborne particulate materials in the environment are aerosols with a variety of physical and chemical properties. In particular, a given aerosol may include particles with a wide spectrum of physical sizes, even if all the particles have similar chemical composition. Also, the concentration of toxic components in particles may be different for different sized particles (Natusch et al., 1974) or morphologically identical particles may have totally different chemical compositions (Pawley and Fisher, 1977). Common assumptions that particles in a given aerosol have a relatively homogeneous chemical composition, toxic potential, and physical density may be seriously misleading, especially when particles are found in combination with SO_2 gas.

It is essential for evaluation of the possible health effects associated with their inhalation that the relevant physical and chemical properties of aerosols and gases be appropriately characterized. These properties then can provide predictive information concerning regional respiratory tract deposition and other important dosimetric factors that need to be considered if biological responses described in Chapters 12-14 are to be adequately understood.

If particles in an aerosol are smooth and spherical or nearly spherical, their physical sizes can be conveniently described in terms of their respective geometric diameters. However, unagglomerated aerosols of solids rarely contain smooth, spherical particles. Various conventions for describing physical diameters have been based upon available methods of observing and measuring particle size. For example, the size of a particle may be described in terms of its projected area diameter (D_p), defined as the diameter of a circle with an area equal to the apparent cross-sectional area of the particle when lying on a collection surface and viewed with an optical or electron microscope. Other conventions for describing physical size are based on measurements of scattered light, surface area, electrical mobility, diffusional mobility, or other physical or chemical phenomena (see Mercer, 1973; Stockham and Fochtman, 1979).

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Aerodynamic properties of aerosol particles depend upon a variety of physical properties, including the size and shape of the particles and their physical densities. Two important aerodynamic properties of aerosol particles are the inertial properties, which are most important for particles larger than 0.5 μm in diameter and are related to the settling speed in air under the influence of the earth's gravity, and the diffusional properties, which are most important for particles smaller than 0.5 μm in diameter and are related to the diffusion coefficient (Fuchs, 1964) (see Section 11.2.1). When particles are inhaled, their aerodynamic properties, combined with various anatomical and breathing characteristics, determine their fractional deposition in various regions in the respiratory tract.

To avoid the complications associated with the effects of particle shape, size, and physical density upon the inertial properties of inhaled airborne particles, "aerodynamic diameters" have been defined and used to describe particles with common inertial properties with the same "aerodynamic diameter." The aerodynamic diameter most generally used is the aerodynamic equivalent diameter (D_{ae}), defined by Hatch and Gross (1964) as "the diameter of a unit density sphere having the same settling speed (under gravity) as the particle in question of whatever shape and density." Raabe (1976) has recommended the use of an aerodynamic resistance diameter (D_{ar}), defined more directly with terms used in physics to describe the inertial properties of a particle. The difference between these two diameters is only 0.08 μm or less over all sizes under normal conditions at sea level. Hence, the term aerodynamic diameter can be used to refer to either or both of these two definitions.

Since not all particles in an aerosol are of the same physical or aerodynamic size, the distribution of sizes must be described. If either the physical diameter (D) or the aerodynamic diameter is used to characterize particles, the distribution of particle sizes in a mixed aerosol is most conveniently described as a probability density function. One such generally useful function, the lognormal function, involves two parameters, the geometric mean size (or median) and the geometric standard deviation (σ_g). Environmental aerosols have size distributions that are more complicated, reflecting the production of particles in atmospheric processes, emission sources or other anthropogenic activities, and the particle dynamics. They may have several modes (Whitby, 1978). Photochemical reactions and certain combustion processes create small particles that are generally smaller than 0.1 μm (the nuclei mode) while other combustion, condensation, and mechanical particle generation processes yield larger particles. Another mode, between 0.1 μm and 2 μm, is known as the accummulation mode and includes primary emissions plus aggregates and droplets formed by coagulation of the primary nuclei mode particles and the materials which condense on them from the vapor phase. The particle size distribution within each of the three modes (nuclei, accumulation, and coarse) is generally lognormal.

Since aerosols even from a single source, or in an atmospheric size mode, do not consist of particles of a single size, they must be described in terms of parameters of size distribution functions. It has become customary in the absence of detailed data and for the sake of

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generalization to describe aerosols in terms of their geometric mean or median diameter and the geometric standard deviation (σ_g) of the size distribution. Hence, if the particle number is being considered, the particle size may be reported as the count median (physical) diameter (CMD) and σ_g, or the count median aerodynamic diameter (CMAD) and σ_g if aerodynamic sizes have been measured. Numerically, half the particles in an aerosol have physical sizes less than the CMD and half have larger. Likewise, half the particles have aerodynamic diameters smaller than the CMAD and half have larger aerodynamic diameters. Since the mass of a material is usually more relevant to its potential toxicity, the mass median (geometrical) diameter (MMD) or mass median aerodynamic diameter (MMAD) and σ_g is usually preferred in describing aerosols in inhalation toxicology research. Half the mass of particles in an aerosol is associated with particles smaller than the MMD and half with larger particles. Likewise, half the mass of particles is associated with particles whose aerodynamic diameters are smaller than the MMAD and half with particles having larger aerodynamic diameters. If an aerosol is radioactive or radiolabeled, mass measurements may be replaced by activity measurements. Interrelationships among these various ways to express the diameter of the aerosol have been examined for the lognormal distribution by Raabe (1971).

In addition to particle characteristics, conditions of the gas medium influence the properties of aerosol dispersions. Such environmental conditions as relative humidity, temperature, barometric pressure, and fluid flow conditions (e.g., wind velocity or state of turbulence) affect the aerodynamics of aerosol particles.

The concentration of environmental aerosols or gases generally does not affect inhalation deposition and particle dynamics. The mass concentration (mg/m^3 or $\mu g/m^3$) or concentration of a specific potentially toxic species (mg of constituent/m^3) provides information needed to calculate inhalation exposure levels. For SO_2, the concentration may be expressed in parts per million (ppm) by volume or in mass concentrations (mg/m^3); each 1 ppm of SO_2 equals 2.62 mg/m^3 (2620 $\mu g/m^3$) at an air temperature of 25°C.

Sulfur dioxide gas is a rapidly diffusing reactive gas that is readily soluble in water and body fluids (Aharonson, 1976). These properties are responsible for the large removal of SO_2 in the extrathoracic region and in the upper generations of the tracheobronchial tree. Extraction of SO_2 during nose breathing is significantly greater than during mouth breathing, and over a four to six hour exposure to high levels of SO_2, no saturation effect for absorption can be seen (see Section 11.2.4). Through normal and catalyst mediated oxidation processes in air, SO_2 gas is slowly oxidized to SO_3 which rapidly hydrolyzes to form H_2SO_4, leading to sulfate salts. Since NH_3 is formed in natural biological processes including endogenously in the airways, $(NH_4)_2SO_4$ and NH_4HSO_4 are important products of H_2SO_4 neutralization.

11.1.3 The Respiratory Tract

The respiratory tract (Figure 11-1) includes the passages of the nose, mouth, nasal pharynx, oral pharynx, epiglottis, larynx, trachea, bronchi, bronchioles, and small ducts and alveoli of the pulmonary acini. With respect to respiratory tract deposition and clearance of

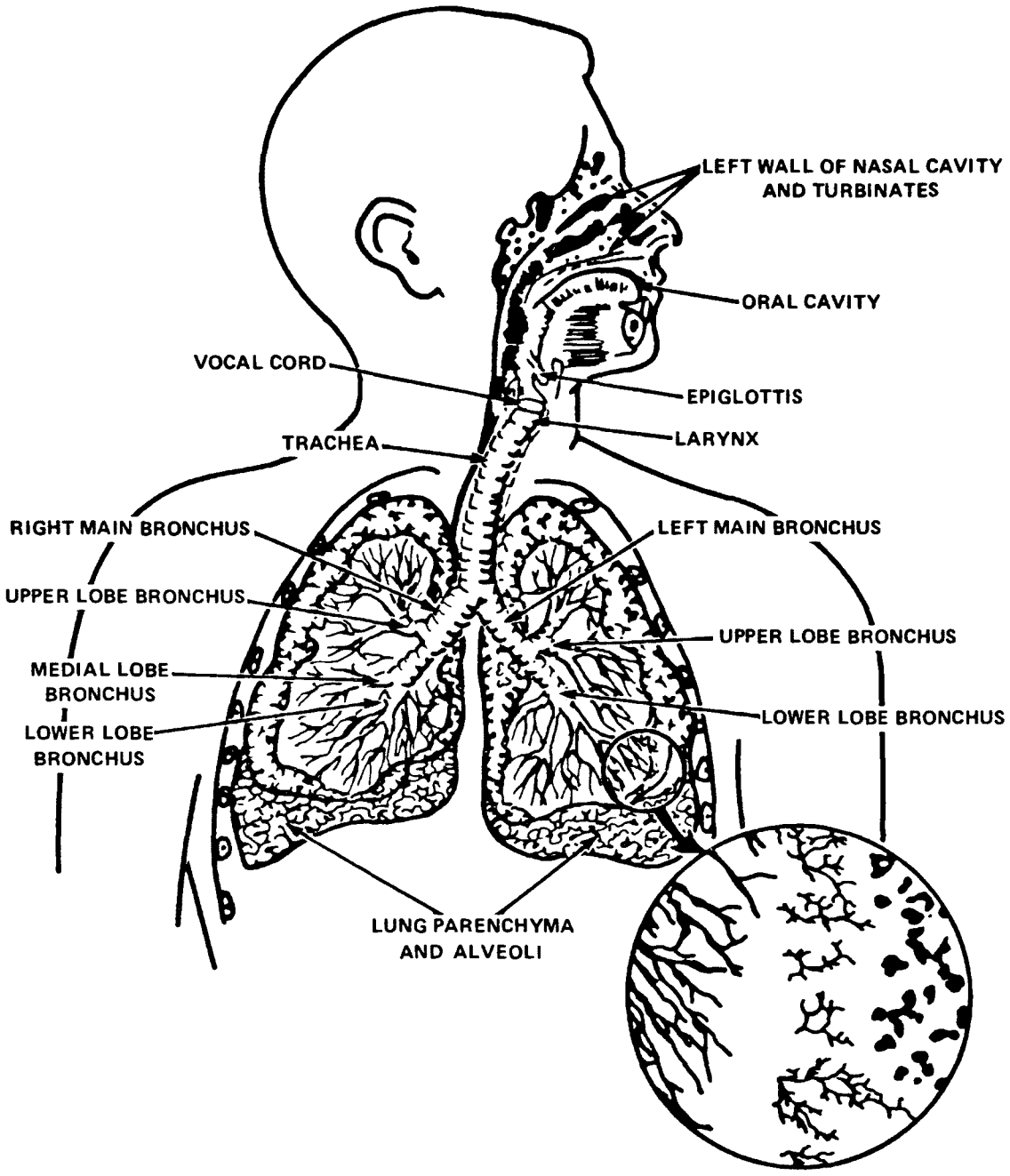

Figure 11-1. Features of the respiratory tract of man used in the description of the deposition of inhaled particles and gases with insert showing parts of a silicon rubber cast of a human lung showing some separated bronchioles to 3 mm diameter, some bronchioles from 3 mm diameter to terminal bronchioles, and some separated respiratory acinus bundles.

Source: Adapted from Hatch and Gross (1964) and Raabe (1979).

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inhaled aerosols, three regions can be considered: (1) extrathoracic (ET), the airways extending from the nares down to the epiglottis and larynx at the entrance to the trachea (the mouth is included in this region during mouth breathing); (2) tracheobronchial region (TB), the primary conducting airways of the lung from the trachea to the terminal bronchioles (i.e., that portion of the lung respiratory tract having a ciliated epithelium); and (3) pulmonary region (P), the parenchymal airspaces of the lung, including the respiratory bronchioles, alveolar ducts, alveolar sacs, atria, and alveoli (i.e., the gas-exchange region). The extrathoracic region, as defined above, corresponds exactly to the ICRP (Morrow et al., 1966) definition of the nasopharynx.

The nose is a complex structure of cartilage and muscle supported by bone and lined with mucosa (Holmes et al., 1950). The vestibule of the nares is unciliated but contains a low-resistance filter consisting of small hairs. The nasal volume is separated into two cavities by a 2- to 7-mm thick septum. The inner nasal fossae and turbinates are ciliated, with mucus flow in the direction of the pharynx. The turbinates are shelf-like projections of bone covered by ciliated mucous membranes with a high surface-to-volume ratio that facilitate humidification of the incoming air. The larynx consists of two pairs of mucosal folds that narrow the airway.

The trachea, an elastic tube supported by 16 to 20 cartilagenous rings that circle about 3/4 of its circumference, is the first and largest of a series of branching airway ducts (Tenney and Bartlett, 1967). The left and right lungs are entered by the two major bronchi of the trachea (Figure 11-1). The left lung consists of two clearly separated lobes, the upper and lower lobes; and the right lung consists of three lobes, the upper, middle, and lower lobes. The conductive airways in each lobe of the lung consist of up to 18 to 20 dichotomous branches from the bronchi to the terminal bronchiole (Pump, 1964; Raabe et al., 1976).

The pulmonary, gas-exchange region of the lung begins with the partially alveolated respiratory bronchioles. Pulmonary branching proceeds through a few levels of respiratory bronchioles to completely alveolated ducts (Smith and Boyden, 1949; Whimster, 1970; Krahl, 1963) and alveolar sacs (Tenney and Remmers, 1963; Pattle, 1961b; Machlin, 1950; Fraser and Pare, 1971). Alveoli are thin-walled polyhedron air pouches which cluster about the acinus through connections with respiratory bronchioles, alveolar ducts, or alveolar sacs.

The airway spaces in the pulmonary region are coated with a complex aqueous liquid containing several biochemically specialized substances (Green, 1974; Blank et al., 1969; Balis et al., 1971; Pattle, 1961b; Kott et al., 1974; Henderson et al., 1975; Kanapilly, 1977). An understanding of the chemical composition and dynamic nature of the acellular layer at the air-alveolar surface is needed to understand the general behavior of material deposited in the pulmonary region. This acellular layer consists of a surfactant film of < 0.01 μm thick and a hypophase of about 0.1 - 0.2 μm thick (Clements and Tierney, 1965). A mixture of phospholipids and neutral lipids are contained in the surfactant film (Scarpelli, 1968; Pfleger and Thomas, 1971; Pruitt et al., 1971; Reifenath, 1973). The major phospholipid is dipalmitoyl

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lecithin, and cholesterol and its esters are the major neutral lipids. Protein content in lung surfactant is less than 20 percent by weight (Pruitt et al., 1971; Klass, 1973). The composition of the hypophase is not well understood, with lung surfactant materials, mucopolysaccharides, lipoproteins, and possibly serum proteins such as albumin likely being present (Scarpelli, 1968; Reifenath, 1973; Tuttle and Westerberg, 1974). The pH of alveolar fluid may be similar to that of blood fluid. Various factors favoring and opposing transudation of fluid across the air-blood barrier result in the cyclic movement of fluid in and out of alveoli, thereby helping to maintain the very thin layer of alveolar fluid (Kanapilly, 1977). The concentrations of chelating and precipitating agents in the alveolar fluid influence the retention and transport of particles deposited in the alveolar region. However, the concentrations of chelating agents are not sufficiently high to prevent the transformation of polyvalent cations into an insoluble form (Kanapilly, 1977).

The deep lung parenchyma includes several types of tissue, circulating blood, lymphatic drainage pathways, and lymph nodes. In man, the weight of the lung, including circulating blood, is about 1.4 percent of the total body weight. Lung blood is equal to about 0.7 percent of total body weight (10 percent of total blood volume) (Snyder, 1975). Because a portion of lung is occupied by air, the average physical density of the parenchyma is about 0.26 g/cm^3 (Fowler and Young, 1959).

Models of the airways, which simplify the complex array of branching and dimensions into workable mathematical functions, are useful in comparing theoretical predictions of deposition with experimentally obtained deposition data, thereby leading to more refined models and increasing our understanding of the processes which affect respiratory tract deposition. An early idealized model of the airways of the human lung was developed by Findeisen (1935) for estimating the deposition of inhaled particles. Findeisen's model assumed branching symmetry within the lung, with each generation consisting of airways of identical size. Other models based on a symmetry assumption have been proposed by Landahl (1950), Davies (1961), Weibel (1963), and Horsfield and Cumming (1968). Asymmetric models which more closely approximate the human lung have been developed by Weibel (1963), Horsfield et al. (1971), and Horsefield and Cummings (1968). Yeh and Schum (1980) have proposed a typical pathway lung model and have made particle deposition calculations for each lobe of the lungs. Although currently available particle deposition models ignore the dynamic nature of the airways, future models should consider this aspect.

11.1.4 Respiration and Other Factors

Both the humidity and temperature of inhaled aerosols and gases, as well as the subsequent changes that occur as the aerosol-gas mixture passes through various parts of the airways, have important influences on the inhalation deposition of airborne particles. Deposition of hygroscopic aerosols will depend in part on the relative humidity in the airways, since the growth of such particles will directly affect both the site and extent of inhalation deposition.

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The complex anatomical structure of the nose is well suited for humidification, regulation of temperature, and removal of many particles and gases. The relative humidity of inhaled air probably reaches near saturation in the nose (Verzar et al., 1953). Since the human nose is a short passageway, tranquil diffusion alone cannot account for rapid humidification. Rather, convective mixing must play a role, suggesting a mechanism for enhancing SO_2 collection in the nose. The temperature of the inhaled air may not reach body temperature until relatively deep in the lung. Deal et al. (1979a, b, c) measured retrocardiac and retrotracheal temperatures under different ambient temperatures and found airway cooling associated with breathing cool air. Raabe et al. (1976) found that the temperature of the air at major bronchi in a nose-breathing dog averaged 35°C, 4°C less than the body temperature.

The air deflecting channels of the anterior nares cause impaction of large airborne particles and create turbulent air flow conditions. As the cross-sectional area expands beyond the entrance, flow separation occurs resulting in turbulence and eddies which continue as the air traverses the passages around the turbinates. Proctor and Swift (1971) studied the flow of water through a clear plastic model of the walls of the nasal passages and constructed charts of the direction and linear velocity of airflow in the model. With a steady inspiratory flow of 0.4 l/sec, they found that the linear inspiratory velocity at the nasal entrance reached at least 4.5 - 5 m/sec and at most 10 - 12 m/sec, values which are significantly greater than the 2 m/sec peak linear velocity in the tracheobronchial tree during quiet breathing.

The caliber of the trachea and major bronchi and their cross-sectional geometry is about 15 percent larger during inspiration than during expiration (Marshall and Holden, 1963; Fraser and Pare, 1971; Raabe et al., 1976). Bronchial caliber correlates with body size (Thurlbeck and Haines, 1975). The caliber of the smaller conductive bronchioles may be up to 40 percent greater during inspiration than during expiration (Marshall and Holden, 1963; Hughes et al., 1972).

Schroter and Sudlow (1969) studied a wide variety of flow patterns and rates in large scale symmetrical models of typical tracheobronchial tree junctions. For both inspiration and expiration and irrespective of entry profile form, they observed secondary flows at all flow rates in their single bifurcation model. When a second bifurcation was added a short distance downstream of the first, the entering flow profile was found to influence the resulting flow patterns. Also, different results were obtained depending upon the plane in which the second bifurcation was located relative to the first bifurcation.

Olson et al. (1973) studied convective airflow patterns in cast replicas of the human respiratory tract during steady inspiration. They showed that the effect of the larynx is such that flow patterns typical of smooth bifurcating tubes do not occur until the lobar bronchi are reached. Small eddies were observed as far down as the sublobar bronchi with 200 ml/s flows in the trachea. In man the glottis of the larynx acts as a variable orifice since the position of the vocal cords changes. During inspiration a jet of turbulent air enters the

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trachea and is directed against its ventral wall imparting additional turbulence over that associated with the corrugated walls and length of the trachea.

In the tracheobronchial tree with its many branches, changes in caliber and irregular wall surfaces, it is difficult to establish exactly where flow is laminar, turbulent, or transitional. Viscous forces predominate in laminar flow and streamlines persist for great distances, while with turbulent flow there is rapid and random mixing downstream. As the flow rate increases, unsteadiness develops and separation of the streamlines from the wall can occur leading to the formation of local eddies. This type of flow is termed transitional. The Reynolds number, the ratio of inertial to viscous forces, is useful in describing whether flow is laminar or turbulent. In smooth walled tubes values between approximately 2000 and 4000 are ascribed to transitional flow with smaller Reynolds numbers reflecting laminar flow and larger ones turbulent flow. Fully developed laminar flow probably only occurs in the very small airways; flow is transitional in most of the tracheobronchial tree, while true turbulence may occur in the trachea, especially during exercise when flow velocities are high (West, 1977).

Turbulence will gradually decay in any branch in which the Reynolds number is less than 3000 (Owen, 1969). Decays of 15 percent, 16 percent, and 10 percent are predicted to occur in the first three generations of bifurcation, respectively, using the theory of Batchelor (1953) for the change in turbulent energy at regions of rapid flow contraction. While these decay calculations neglect the possible effects of the strong secondary flows generated at the bifurcation, their validity is supported by the data of Pedley et al.(1971) which shows that the boundary layer remains laminar in the daughter-tube for Reynolds numbers in the parent-tube up to at least 10,000. Hence, the turbulent eddies are localized in the center.

Flow oscillations in the segmental bronchi attributed to beating of the heart are only detectable during breathholding or during pauses between inspiration and expiration (West, 1961). A peak oscillatory flow rate of 0.5 l/min was measured, which is about 20 percent of the peak flow rate in the segmental bronchi during quiet breathing. Gas mixing is improved by these oscillations.

Gas flow dynamics within the upper airways may be expected to be turbulent in humans and dogs but laminar everywhere in the airways of small rodents (Dekker, 1961; Fry, 1968; Schroter and Sudlow, 1969; Olson et al., 1973; Martin and Jacobi, 1972; West, 1961). The larynx introduces an important air flow disturbance that can influence tracheal deposition (Bartlett et al., 1973; Schlesinger and Lippmann, 1976). In the smaller human bronchi and bronchioles, where fluid flow is relatively tranquil, laminar flow prevails, but branching patterns, filling patterns (Grant et al., 1974), flow reversals with varying velocity profiles, and swirling complicate a description of flow in the small airways (Silverman and Billings, 1961; Cinkotai, 1974). Because actual flow in the respiratory airways is difficult to describe, simplifying assumptions, such as parabolic laminar or uniform velocity profiles, are usually incorporated into analytic descriptions.

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Inspiratory flow rate and depth of inhalation influence the deposition of inhaled particles. The air inspired in one breath is the tidal volume (TV). The average inspiratory flow rate, (Q), and tidal volume (Bake et al., 1974; Clement et al., 1973) affect both inertial and diffusional deposition processes (Altshuler et al., 1967). The total air remaining in the lungs at the end of normal expiration affects the relative mixing of inhaled particles and, when compared with total lung capacity, is indicative of the extent of aerosol penetration into the lung (West, 1974; Luft, 1958). Guyton (1947a, b) and Stahl (1967) have developed interspecies relationships describing respiratory volumes and patterns.

The inspiratory capacity, the maximum volume of air that can be inhaled after a given normal expiration, is contrasted to the vital capacity, which is the maximum volume of air that can be expelled from the lungs with effort after maximum forced inspiration. Air that remains in the conductive airways (from nose or mouth to terminal bronchioles) at end expiration is considered to occupy the anatomical dead space, since the conductive airways are not involved in gas exchange.

Representative values for normal human respiratory parameters, which can be used for deposition and dosimetric predictions, are available from various sources (Zenz, 1975; Higgs et al., 1967; American Heart Association, 1973; Jones et al., 1975; Intermountain Thoracic Society, 1975; Snyder, 1975). It should be noted that considerable variability in respiratory parameters may occur among individuals in the population, particularly when healthy adults are contrasted with children, aged, and ill individuals. Average tidal volume has a reasonably fixed relationship with body weight of 7-10 ml/kg from birth to adulthood (Doershuk et al., 1970, 1975). Gas-exchange area increases proportionally with age, and more or less with height, but not with body surface area. Average values for gas-exchange area are 6.5 m^2, 32 m^2, and 75 m^2 at 3 months, 8 years, and adulthood, respectively (Dunnill, 1962). Respiratory frequency decreases from about 35 breaths/min at birth to 12-16 breaths/min with normal respiration in adulthood (Polgar and Weng, 1979).

In some instances, the total and regional deposition data presented in Section 11.2 exhibit considerable scatter. Some of this variability might be expected given the range of breathing frequencies, tidal volumes, and average inspiratory flow rates used in the various deposition experiments. Previously, an interlaboratory comparison study of lung deposition data (Heyder et al., 1978), besides identifying possible sources of errors connected with the experimental technique, identified different deposition data among the subjects. Yu and coworkers (1979) used Monte Carlo techniques to determine the total and regional deposition of inhaled particles in a population of human lungs by taking into account variability in airway dimensions. Their results for particle sizes ranging from 0.1 μm to 8 μm D_{ae} suggest that observed subject deposition variability is caused primarily by differences in airway dimensions. When studying total respiratory tract deposition of particles between 0.3 μm and 1.5 μm D_{ae}, expressing the data as a function of the relative expiratory reserve volume to the normal expiratory reserve volume of a subject greatly reduces the intersubject variability (Tarroni et al., 1980).

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The vast majority of studies on the deposition of particles in man have been conducted using young healthy adults. Consequently, there is a paucity of data on deposition in other subpopulations, such as children, asthmatics, chronic bronchitics, etc. Significant pathologic changes in airways and parenchyma can markedly alter the deposition of particles. For example, Lippmann et al. (1971) found substantially increased bronchial deposition in chronic bronchitic and asthmatic subjects. These increases may vary with different phases of the disease (Goldberg and Lourenco, 1973). Tracheobronchial deposition appears to be enhanced at the expense of pulmonary deposition in most abnormal states. For example, the deposition of 2 μm particles in patients with bronchiostasis is frequently more central than that in normal subjects (Lourenco et al., 1972). Partial or complete airway obstruction in bronchitis, lung cancer, emphysema, fibrosis, and atelectasis may decrease or eliminate deposition of particles in some regions of the lungs (Taplin et al., 1970). The numerous and complex mechanisms responsible for alterations in the pattern of deposition in various disease states need to be studied.

Currently available human deposition data have been collected from volunteers inhaling aerosols through either mouthpieces or nose masks. Differences in mass burden of particles between these controlled inhalations and normal, spontaneous mouth breathing or nose breathing are possible. Studies in which the nose of the subject is completely occluded with a clip do not simulate oronasal breathing since no air passes through the nose and the oral airway is wider than usual. With partial nasal obstruction or in exercise, human beings resort to oronasal breathing. However, a significant number of healthy persons breathe through the mouth and nose even when at rest (Niinimaa, 1979). Also, with any of the common obstructive forms of nasal pathology such as allergic, viral, or vasomotor rhinitis or septal deviation, the proportion of ventilation passing through the mouth is higher at rest and at any level of exercise. Healthy young adults without nasal pathology, who breathe predominantly through the nose at rest, shift to breathing through the nose and mouth when minute ventilation is approximately 35 liters/min (Niinimaa, 1979; Saibene et al., 1978). Niinimaa (1979) found that during exercise requiring a rate of ventilation of 30-40 liters/min, 56 percent of the air passed nasally. Thus, studies on subjects breathing through a mouthpiece at rest (minute ventilation of 6-8 liters/min) provide conservative estimates of the mass burden of particles, since the total quantity of ventilation passing through the mouth is significantly less than that which would pass through the mouth in the same subjects breathing freely through the nose and mouth while performing enough exercise to require a minute ventilation of 35 liters/min. A minute ventilation of 35 liters/min corresponds anywhere from light to moderate exercise according to various sources (Zenz, 1975; Higgs et al., 1967; American Heart Association, 1973; Jones et al., 1975; Intermountain Thoracic Society, 1975; Snyder, 1975).

11.1.5 Mechanisms of Particle Deposition

The behavior of inhaled airborne particles in the respiratory airways and their alternative fate of either deposition or exhalation depend upon aerosol mechanics under the given

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physiological and anatomical condition (Yeh et al., 1976; DuBois and Rogers, 1968). It is usually described in terms of nonreactive stable spherical particles whose physical properties do not vary during the breathing cycle. Behavior of hygroscopic and deliquescent particles is more complex.

Figure 11-2 illustrates the five primary physical processes that lead to aerosol particle contact with the wall of the airways. Contact of particles with moist airway walls results in attachment and irreversible removal of the particle from the airstream. The contact process can occur during inspiration or expiration of a single breath or subsequently if a particle has been transferred to unexhaled lung air (Engel et al., 1973; Davies, 1972; Altshuler, 1961).

Electrostatic attraction of particles to the walls of the respiratory airways is probably a minor mechanism of deposition in most circumstances. Pavlik (1967) predicted that light air ions (which would include some atmospheric aerosol nuclei) would be deposited by electrostatic attraction in the mouth and throat and suggested that the tonsils were naturally charged for this purpose. Fraser (1966) found that an average of 1000 electronic units of charge per aerosol particle, a very large charge not normally occurring, doubled the inhalation deposition in experimental animals. Melandri et al. (1977) reported enhanced deposition of inhaled monodisperse aerosols by people when the particles were charged. Longley (1960) and Longley and Berry (1961) found the charge of the subject to have an influence on deposition. Similar observations have been made in in vitro studies (Chan et al., 1978). The airways are covered by a relatively conductive electrolytic liquid that probably precludes the buildup of forceful electric fields. Charged particles are therefore collected primarily by image charging as they near the wall of an airway or by mutual repulsion from a unipolarly charged cloud with a high concentration of particles (Yu, 1977). The role of this mechanism depends on particle source, concentration, age, and special electrical phenomena in the environment, as well as the residence time of the aerosol in the airways. It is reasonable to expect this mechanism to have a small role, if any, in the deposition of atmospheric environmental aerosols.

Interception consists of noninertial incidental meeting of a particle and the lining of the airway and thus depends on the physical size of the particle. It is important primarily for particles with large aspect ratios, such as long fibrous particles of asbestos (Harris and Fraser, 1976). Interception may be expected to play a minor role in the inhalation deposition of most environmental aerosols.

Impaction dominates deposition of particles larger than 3 μm D_{ae} in the nasopharyngeal and tracheobronchial regions (Pattle, 1961a; Bohning et al., 1975). In this process, changes in airstream direction or magnitude of air velocity streamlines or eddy components are not followed by airborne particles because of their inertia. For example, if air is directed toward an airway surface (such as a branch carina) but the forward velocity is suddenly reduced because of change in flow direction, inertial momentum may carry larger particles across the air streamlines and onto the surface of the airway. Impaction at an airway branch has been

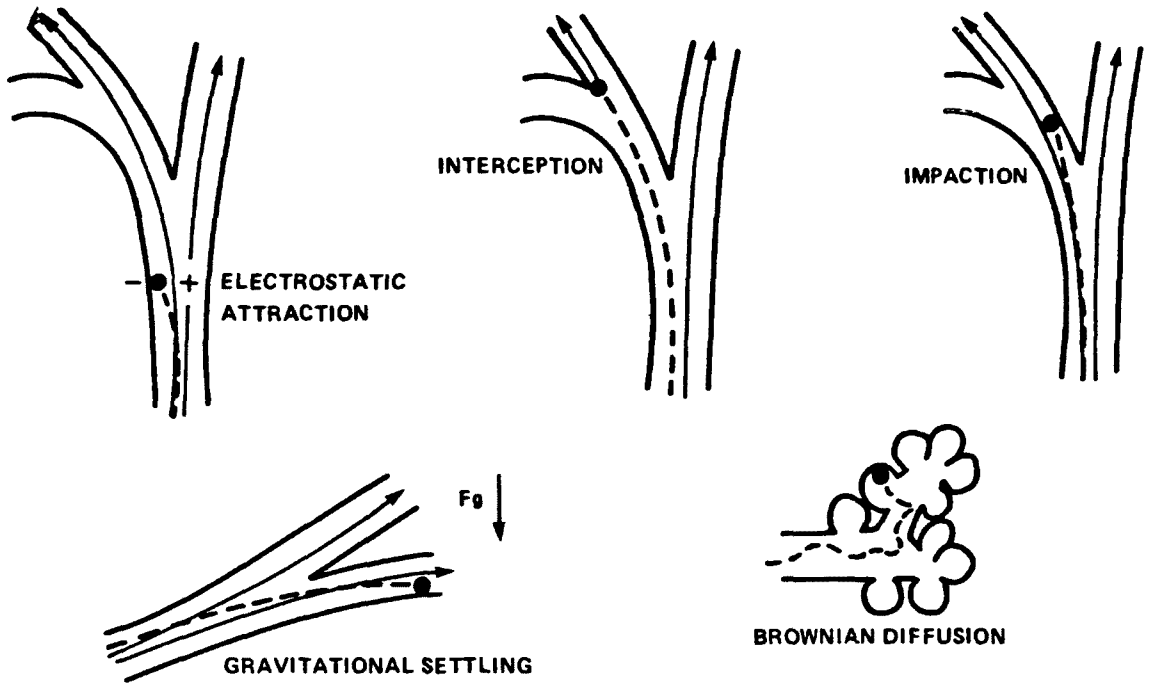

Figure 11-2. Representation of five major mechanisms of deposition of inhaled airborne particles in the respiratory tract.

Source: Raabe (1979).

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likened to impaction at the bend of a tube, providing theoretical estimates of the impaction probability (Johnston and Muir, 1973; Yeh, 1974; Cheng and Wang, 1975) and has been studied in a bifurcating tube model by Johnstone and Schroter (1979). Aerodynamic separation of this type is satisfactorily characterized in terms of the particle aerodynamic diameter. The airflow in the trachea and major bronchi in man is turbulent and disturbed by the larynx so that turbulent impaction plays a role in deposition in these larger airways (Schlesinger and Lippmann, 1976). Breathing patterns involving higher volumetric flow rates would tend to impact smaller particles. In contrast, the passages of the nose contain smaller airways, and the convective mixing spaces of the nasal turbinates would be expected to collect some particles as small as 1 or 2 μm D_{ae} by impaction. Hence, impaction is an important process affecting the inhalation deposition in the human airways of environmental aerosol particles greater than 1 μm in aerodynamic diameter.

Gravitational settling occurs because of the influence of the earth's gravity on airborne particles. Deposition of particles by this mechanism can occur in all airways except those very few that are vertical. The probability of gravitational deposition is usually estimated with equations describing gravitational settling of particles in an inclined cylindrical tube under laminar flow conditions (Wang, 1975; Heyder and Gebhart, 1977). This deposition depends on the residence time and particle concentration distribution in the airway segments, the incline angle with respect to gravity, and the aerodynamic diameter of the particle. Deposition by gravitational settling is therefore characterized in terms of the particle aerodynamic diameter. This mechanism has an important influence on the deposition of particles larger than 0.5 μm D_{ae}. Settling has an important role in the deposition of environmental aerosols in the distal region of the bronchial airways and in the alveolar region.

Deposition by diffusion results from the random (Brownian) motion of very small particles caused by bombardment of the gas molecules in air. The magnitude of this motion can be described by the diffusion coefficient for a given physical particle diameter. Since particles larger than 0.5 μm have relatively small diffusional mobility compared with sedimentation or inertia, diffusion primarily affects deposition of particles with physical diameters smaller than 0.5 μm. For particles of 0.5 μm with a physical density of about 1 g/cm^3, the influences of inertial properties and diffusional properties on lung deposition are about equal. Accurate calculation of the diffusional deposition of aerosols in the airways requires information concerning the three-dimensional velocity profile of air flow in each airway segment. If the flow of a given segment is laminar and approximately Poisueille, the probability of deposition by diffusion might be approximated using the Gormley-Kennedy (1949) equation for a cylindrical pipe. However, this assumes the aerosol is mixed at the entrance of the cylinder and that the flow is constant. It therefore overestimates deposition in lung segments where there is minimal mixing between tidal and residual air and reversible laminar flow between segments.

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It is important to note that the diffusivity and interception potential of a particle depend on its physical size, while the inertial properties of settling and impaction depend on its aerodynamic diameter. These two measures of size may be quite different, depending on particle shape and physical density. Because the main mechanism of deposition is diffusion for particles whose physical (geometric) size is less than 0.5 μm D and impaction and settling above 0.5 μm D_{ae}, it is convenient to use 0.5 μm as the boundary. Although this convention may lead to confusion in the case of very dense particles, most environmental aerosols have densities below 3 g/cm^3, and the deposition probability tends to have a minimum plateau between 0.2 μm and 1 μm D_{ae}.

It is possible to use information concerning breathing patterns and respiratory physiology, the anatomical and geometrical characteristics of the airways, and the physical behavior of insoluble spherical particles to develop theoretical models of regional deposition (Findeisen, 1935; Landahl et al., 1951; Landahl, 1963; Beeckmans, 1965). In these models, deposition of inhaled aerosols in a given region of the respiratory tract or in the entire tract is expressed as a fraction of inhaled particles. Deposition fraction is the ratio of the number or mass of particles deposited in the respiratory tract to the number or mass of particles inhaled. The undeposited fraction represents those particles that are exhaled after inhalation. For example, pulmonary (alveolar) deposition is the ratio of the number or mass of particles deposited in the unciliated small airways and gas exchange spaces of the parenchyma of the lung to the number or mass of particles entering the nose or mouth. The fraction not deposited in the pulmonary region is either deposited in some other region or exhaled. Similarly, deposition fractions can be defined for the other regions of the respiratory tract.

Most model calculations treat the various mechanisms of deposition as independently occurring phenomena. However, such processes as Brownian diffusion and gravitational settling will interfere with each other when their effects are of comparable magnitude, and that interference can reduce the combined deposition to less than the sum of the separate depositions (Goldberg et al., 1978). Taulbee and Yu (1975) have developed a theoretical deposition model which allows for the combined effects of the primary deposition mechanisms and features an imaginary expanding tube model of the airway system (Weibel, 1963) based on cross-sectional areas and airway lengths.

Historically, the most widely used models of regional deposition versus particle size were developed by the International Commission on Radiological Protection Task Group on Lung Dynamics under the chairmanship of P. E. Morrow (Morrow et al., 1966). These models were developed to determine radiation exposure from inhaled radioactive aerosols. Although the ICRP aerosol deposition and clearance models were not intended for broad application to environmental aerosols, they have been so applied by some scientists. The ICRP Task Group used the anatomical model and impaction and sedimentation equations of Findeisen (1935) and the general methods of Landahl (1950, 1963) for calculating deposition in the tracheobronchial and pulmonary regions. The Gormley-Kennedy (1949) equation for cylindrical tubes was used for

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calculating diffusional deposition. For head deposition, inhalation through the nose with a deposition efficiency given by the empirical equation of Pattle (1961a) was used. Particles were assumed to be insoluble, stable, and spherical with physical densities of 1 g/cm^3, and the aerosols were assumed to be log normally distributed with a σ_g as high as 4.5. When the results were expressed in terms of the mass median diameter (MMD) for these various sized distributions of unit density aerosols (equivalent to the MMAD), the range of the expected regional deposition values was relatively narrow.

At the time the ICRP Task Group models were developed, the available human data were primarily total deposition values for polydisperse and sometimes unstable aerosols (Landahl and Herrmann, 1948; Davies, 1964b; Van Wijk and Patterson, 1940; Brown et al., 1950; Dautrebande and Walkenhurst, 1966; Morrow et al., 1958; Landahl and Black, 1947). Since then, the deposition in humans of monodisperse insoluble, stable aerosols of different sizes has been measured under different breathing conditions. Extensive studies have been conducted by Lippmann (1977), Heyder et al. (1975, 1980), Stahlhofen et al. (1980), Chan and Lippmann (1980), and Giacomelli-Maltoni et al. (1972). Additional useful data are reported by Palmes and Wang (1971), Shanty (1974), George and Breslin (1967), Altshuler et al. (1967), Hounam et al. (1971a,b), Foord et al. (1976), Pavia et al. (1977), among others (Muir and Davies, 1967; Taulbee et al., 1978; Hounam, 1971; Heyder, 1971; Heyder and Davies, 1971; Fry and Black, 1973).

11.2 DEPOSITION IN MAN AND EXPERIMENTAL ANIMALS

11.2.1 Insoluble and Hydrophobic Solid Particles

11.2.1.1 Total Deposition--With the background information in Section 11.1, it is evident that understanding and interpreting the health effects associated with exposure to particles and SO_2 is critically influenced by knowing where particles of different sizes deposit in the respiratory tract and the extent of their deposition. As was seen, the respiratory tract can be divided into regions on the basis of structure, size, and function. Insoluble particles depositing in the various regions contact or affect different cell populations and have large differences in retention times and clearance pathways (see Section 11.3).

If the quantity of aerosol exhaled is compared with that inhaled, the data can be expressed as total deposition, but regional involvement cannot be distinguished. By tagging the test aerosols with radiolabels, investigators have been able to separate deposition by region, beginning with either nasal and nasopharyngeal deposition for nose breathing or oral and pharyngeal deposition for mouth breathing. The measurement of clearance of the radiolabeled aerosol from the thorax can be used to separate early clearance, indicative of tracheobronchial (TB) deposition, from more slowly cleared pulmonary (P) deposition.

Total respiratory tract deposition with nose breathing is given in Figure 11-3, and total deposition with mouth breathing is depicted in Figure 11-4. Analyses based on the difference between concentrations of inhaled and exhaled particles, as well as those based on external *in vivo* measurements of radiolabeled particles, are represented in the studies comprising these

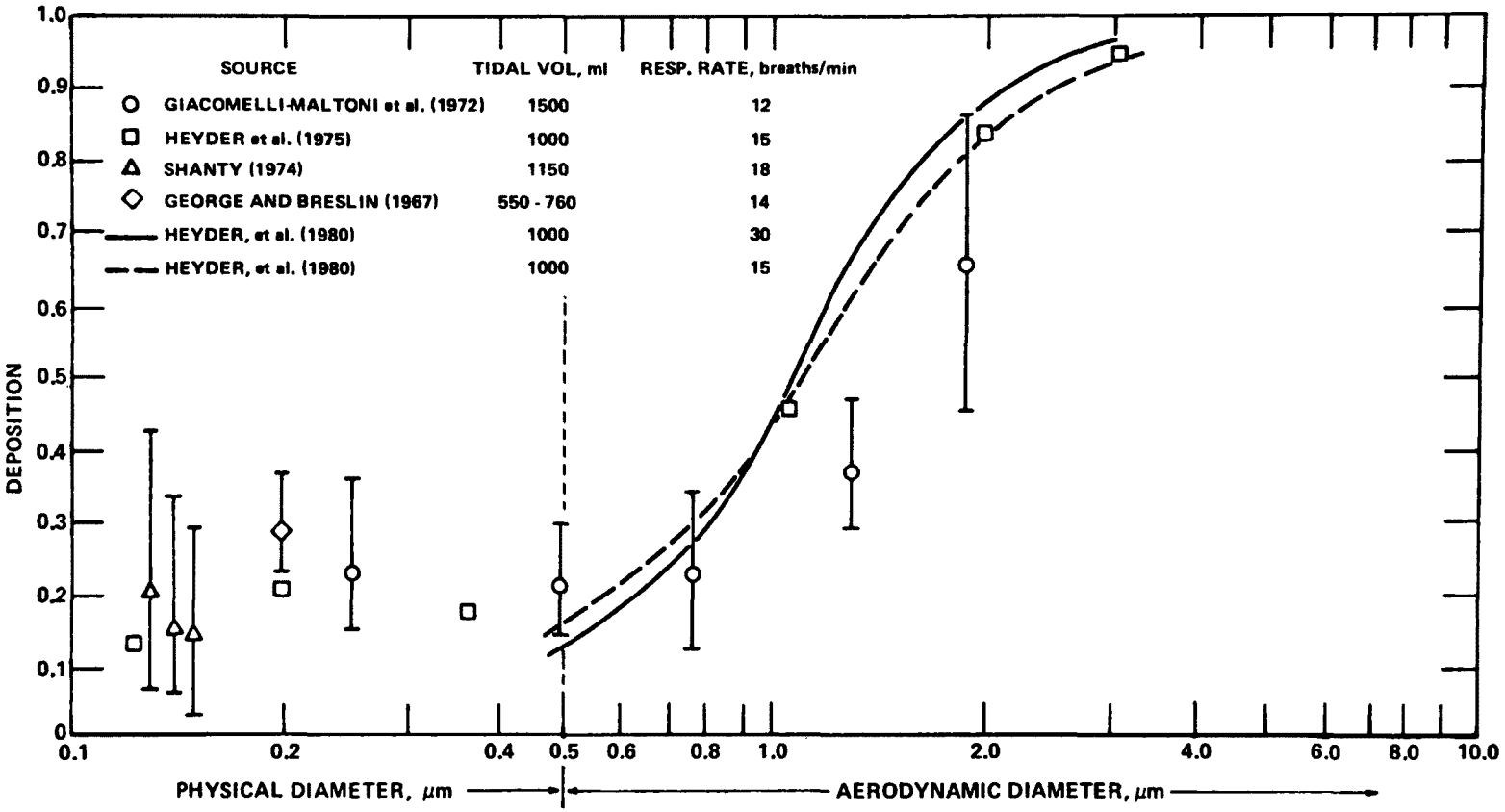

Figure 11-3. Deposition of monodisperse aerosols in the total respiratory tract for nasal breathing as a function of aerodynamic diameter except below 0.5 μm where deposition is plotted vs. physical diameter. The data are individual observations, averages, and ranges as cited by the various investigations.

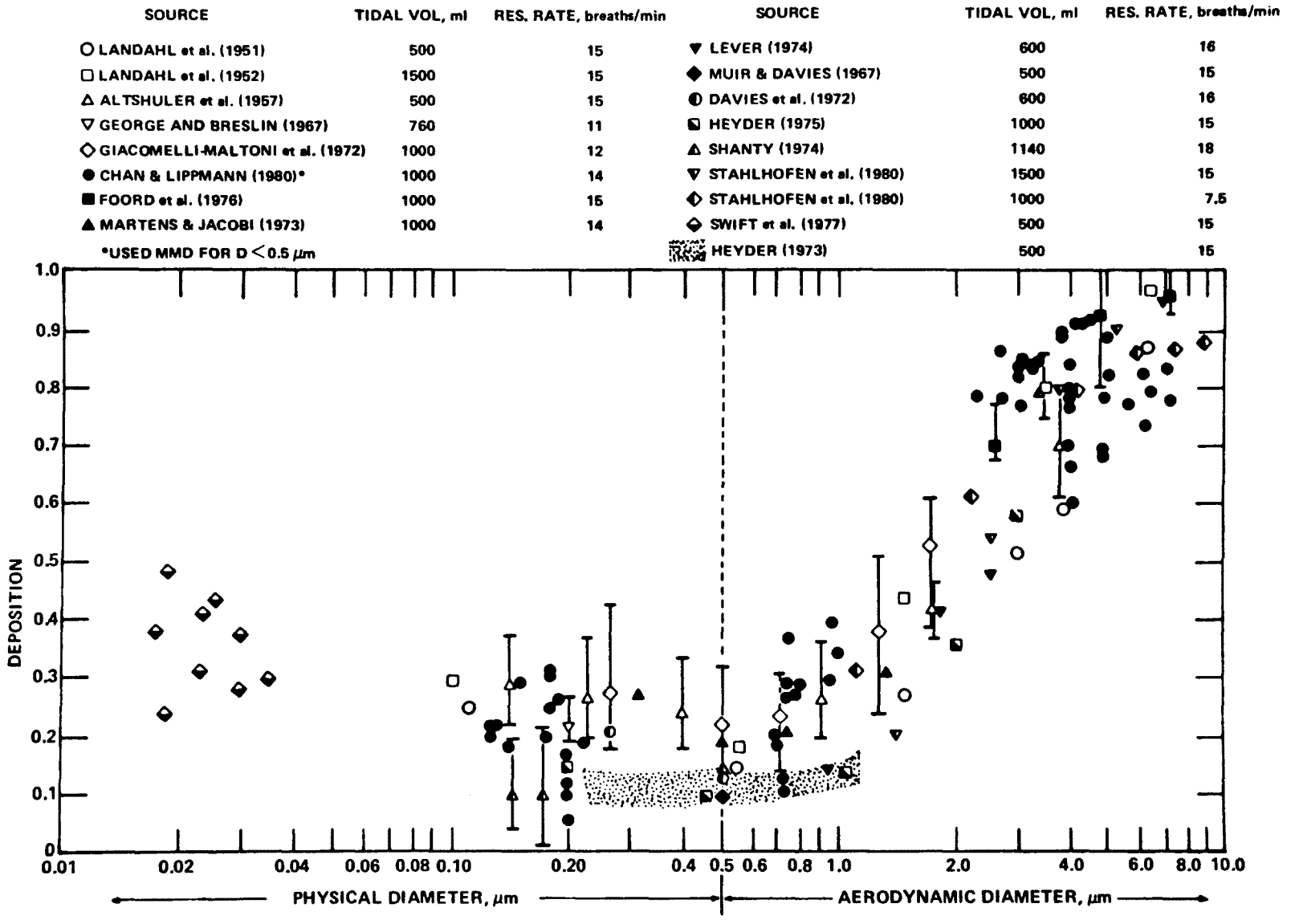

Figure 11-4. Deposition of monodisperse aerosols in the total respiratory tract for mouth breathing as a function of aerodynamic diameter except below 0.5 μm, where deposition is plotted vs. physical diameter. The data are individual observations, averages, and ranges as cited by the various investigators.

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figures. With nose breathing, complete deposition can be expected for particles larger than about 4 μm D_{ae}. Mouth breathing bypasses much of the filtration capabilities of the nasopharyngeal region, and there is a shift upward to around 10 μm D_{ae} before there is complete deposition of the inhaled particles.

The various studies all appear to show the same trend. The particle size for minimum deposition is less clear for nasal breathing as compared to mouth breathing, for which minimum deposition is at about 0.5 μm diameter. Heyder and coworkers (1973a, 1973b, 1975) carefully matched breathing patterns among subjects in studying the deposition of 0.5 μm D_{ae} particles upon which there were no electrical charges; their data are the deposition minima in Figure 11-4. Thus far, deposition of particles less than 0.1 μm diameter has only been studied in human subjects by Swift et al. (1977).

Comparison of the effects of respiratory parameters on aerosol deposition have been conducted by Heyder and co-workers (1975, 1980) in systematic experiments comparing deposition of different sized monodisperse aerosols in human volunteers at different tidal volumes, flow rates, and breathing frequencies. For particles between 0.1 μm and 4.0 μm in diameter, Heyder et al. (1975) measured total respiratory deposition during either nose or mouth breathing while sequentially maintaining a given tidal volume, breathing rate, or inspiratory flow rate and then varying the other two parameters. They demonstrated several important features of aerosol deposition in the human respiratory airways. Heyder and co-workers (1980) extended these studies to particles as large as 9 μm D_{ae}; in the mouth-breathing experiments they also determined alveolar deposition.

With volumetric flow rate held at 15 liter/minute while breathing through the mouth, the particle size yielding the lowest deposition changed from 0.66 μm at TV 250 ml to 0.46 μm at TV 2000 ml. Breathing at TV 1000 ml changed this minimum deposition size from 0.58 μm at 30 BPM to 0.46 μm at 3.75 BPM. Hence, the particle size of minimum deposition was reduced with increased residence time of particles in the lung and the net deposition for all particles was increased. In fact, as the breathing rate went from 3.75 BPM to 30 BPM, the deposition at 1 μm D_{ae} went from 0.08 to 0.4, an increase of a factor of 5. In contrast to mouth breathing, however, the particle size of minimum deposition with nose breathing was independent of the residence time of particles in the respiratory tract when 1000 ml of aerosol at different flow rates were inhaled.

When Heyder et al. (1975) kept the breathing frequency constant while changing the flow rate and having the subjects breathe through the mouth, the deposition for particles smaller than 1 μm remained essentially unchanged, indicating that inertial impaction was of little importance in the deposition of submicrometer aerosols. On the other hand, the deposition of particles larger than 1 μm D_{ae} was enhanced at high flow rates, indicating the influence of inertial impaction on the deposition of larger particles.

Sedimentation and impaction are competing deposition mechanisms, being governed by mean residence time and flow rate, respectively. Hence, impaction will be the dominant mechanism

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at high flowrates and short residence times, while most particles will be deposited by sedimentation at low flow rates and long residence times. Heyder et al. (1980) showed that for 1 μm D_{ae} particles, total deposition for mouth breathing at 1000 ml TV increased with increasing mean residence time, indicating these particles were mainly deposited by sedimentation. For 8 μm D_{ae}, increasing flow rate increased deposition so that these particles were mainly deposited by impaction. A transition region was observed for particles about 4 μm D_{ae}, while Heyder and co-workers (1980) noted the transition region was shifted towards smaller particles for nose breathing.

11.2.1.2 Deposition--The fraction of inhaled aerosol depositing in the extrathoracic region can be quite variable, depending upon particle size, flow rate, breathing frequency, and whether 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 tracheobronchial deposition. Nasopharyngeal deposition is shown for nose breathing in Figure 11-5 and for mouth breathing in Figure 11-6. Deposition in this region is usually plotted as a function of $D_{ae}^2 Q$ since this is a convenient parameter for normalizing impaction dominated deposition data when the actual flowrates are not identical (Pattle, 1961a; Stahlhofen et al., 1980; National Academy of Sciences, 1980; Hounam et al., 1969, 1971a). For reference, a scale showing aerodynamic diameter when Q = 30 liters/min is also shown since this flow rate approximates the average flow rate for the studies comprising these figures.

Particles entering the nose larger than about 10 μm D_{ae} are effectively deposited in the extrathoracic region (Figure 11-5). Also, deposition is slight (10 percent) for particles less than 1 μm D_{ae}. Similarly, for 10 μm and 1 μm D_{ae} particles under conditions of mouth breathing (Figure 11-6), extrathoracic deposition is about 65 percent and 2 percent, respectively. The regression curve shown in Figure 11-6 is from Chan and Lippmann (1980) who used their own data, as well as the data of Lippmann (1977) and Stahlhofen et al. (1980) for Q = 45 liters/min in their analysis. As indicated by Chan and Lippmann (1980), some of the lower values of extrathoracic deposition may be due to partial clearance to the stomach before the measurement of head deposition was obtained. Particles can be swallowed even when the subject consciously tries to avoid swallowing (Lippmann, 1977; Stahlhofen et al., 1980).

11.2.1.3 Tracheobronchial Deposition--As was seen earlier, when aerosols are inhaled through the nose, relatively efficient extrathoracic filtration eliminates the passage of most particles larger than about 10 μm D_{ae} to the tracheobronchial region. Mouth breathing markedly alters the deposition of inhaled particles in humans in that larger particles can enter both the tracheobronchial and pulmonary regions (Morrow et al., 1966; Lippmann, 1977; Heyder et al., 1980; Stahlhofen et al., 1980). For mouth-breathing tracheobronchial deposition expressed as a fraction of the particles entering the trachea is shown in Figure 11-7 plotted against particle size. Approximately 80-90 percent of 8-10 μm D_{ae} particles entering the trachea are deposited in the tracheobronchial region, as compared to less than 10 percent for particles

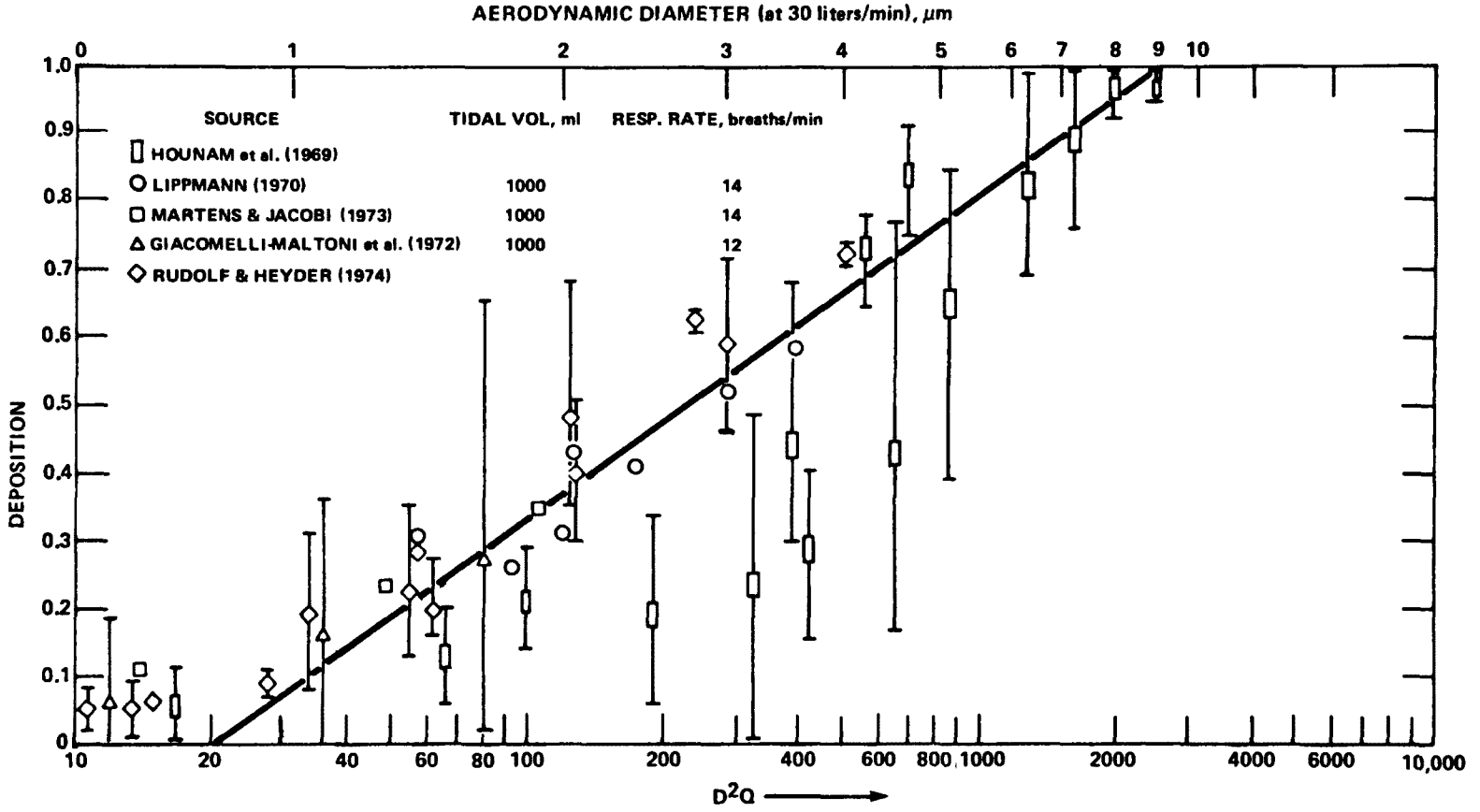

Figure 11-5. Deposition of monodisperse aerosols in extrathoracic region for nasal breathing as a function of D^2Q, where Q is the average inspiratory flow rate in liters/min. The solid line is ICRP deposition model based on the data of Pattle (1961a). Other data show the median and range of the observations as cited by the various investigators.

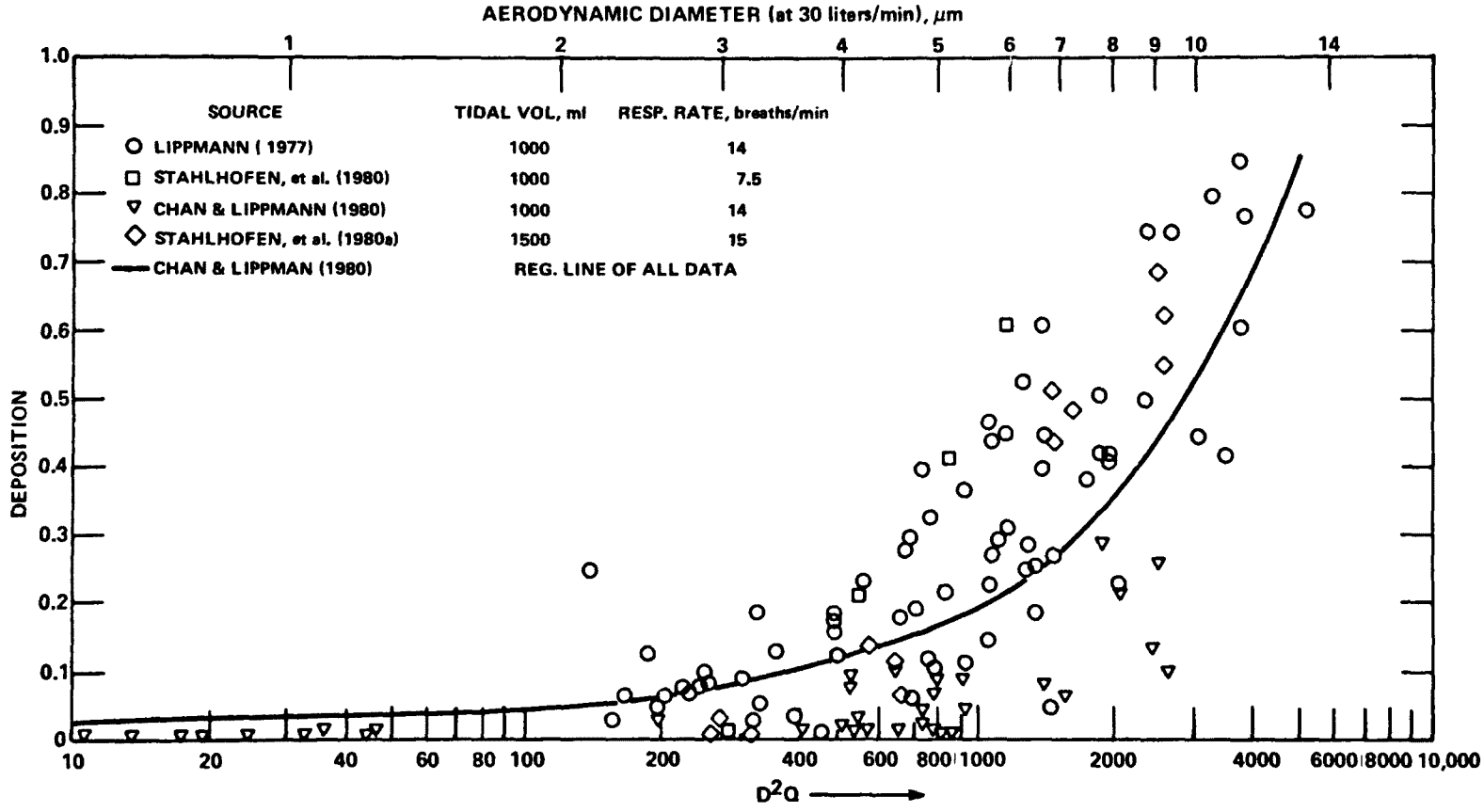

Figure 11-6. Deposition of monodisperse aerosols in extrathoracic region for mouth breathing as a function of D^2Q, where Q is the average inspiratory flow rate in liters/min. The data are the individual observations as cited by the various investigators. The solid line is the overall regression derived by Chan and Lippmann (1980).

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less than 1 μm D_{ae}. The increased penetration of large particles deeper into the respiratory tract when a person breathes through the mouth can be seen from the 20-30 percent experimental tracheobronchial deposition data for particles 8-10 μm D_{ae} (Stahlhofen et al., 1980). The solid curve in Figure 11-7 is from Chan and Lippmann (1980) depicting the experimental tracheobronchial deposition data from their investigations using the average value of a new anatomic parameter, the bronchial deposition size, for the average Q value measured in their study (Q = 39 liters/min). This parameter enables the classification of various individuals and populations according to their tracheobronchial deposition efficiencies.

Deposition in the tracheobronchial region is influenced by both impaction and sedimentation, with the relative contribution of these two mechanisms changing with particle size and air flow rate. Impaction predominates for deposition of particles larger than about 3 μm D_{ae} and flow rates greater than about 20 liters/min, while sedimentation deposition becomes a larger fraction of a diminishing tracheobronchial component for smaller particles and lower flows (Lippmann, 1977). Importance of impaction for tracheobronchial deposition is reflected by deposition often being plotted against the inertial parameter, D_{ae}^2Q (Stahlhofen et al., 1980 and Lippmann, 1977).

For a given particle size, tracheobronchial deposition varies greatly from subject to subject among nonsmokers, cigarette smokers, and patients with lung disease (Lippmann et al., 1971). On the average, tracheobronchial deposition is slightly elevated in smokers and greatly elevated in patients with lung-disease (Lippmann et al., 1977; Cohen, 1977). However, each subject exhibits a characteristic and reproducible relationship between particle size and deposition as indicated by the data of Stahlhofen et al. (1980), depicted in Figure 11-8. For the two breathing patterns shown, the steep increase of the nasopharyngeal deposition values with increasing particle size is accompanied by a corresponding decrease in tracheobronchial deposition, so that tracheobronchial deposition, as a function of particle aerodynamic diameter, may be described by a bell-shaped curve with a maximum (Stahlhofen et al., 1980). Although these investigators did not experimentally study particles larger than 9 μm D_{ae}, extension of their bell-shaped curves would support the conclusion of Miller et al. (1979) that about 10 percent of particles as large as 15 μm D_{ae} can enter the tracheo bronchial region during mouth breathing. Miller et al. (1979) had used the tracheobronchial deposition data of Lippmann (1977) and aerodynamic diameters computed at a mean flow rate of 30 liters/min. This flow rate is bracketed by the mean flow rates of 15 and 45 liters/min used by Stahlhofen et al. (1980).

The data of Stahlhofen et al. (1980) in Figure 11-7 on three subjects show lower values and less scatter than the other data contained in the figure. Chan and Lippmann (1980) cite two possible explanations for the differences. Stahlhofen and coworkers (1980) used constant respiratory flowrates in comparison to the variable flowrates used by Chan and Lippmann (1980). Also, the two laboratories used different bases to separate the initial thoracic burden into tracheobronchial and pulmonary components. Stahlhofen et al. (1980) extrapolated the thoracic

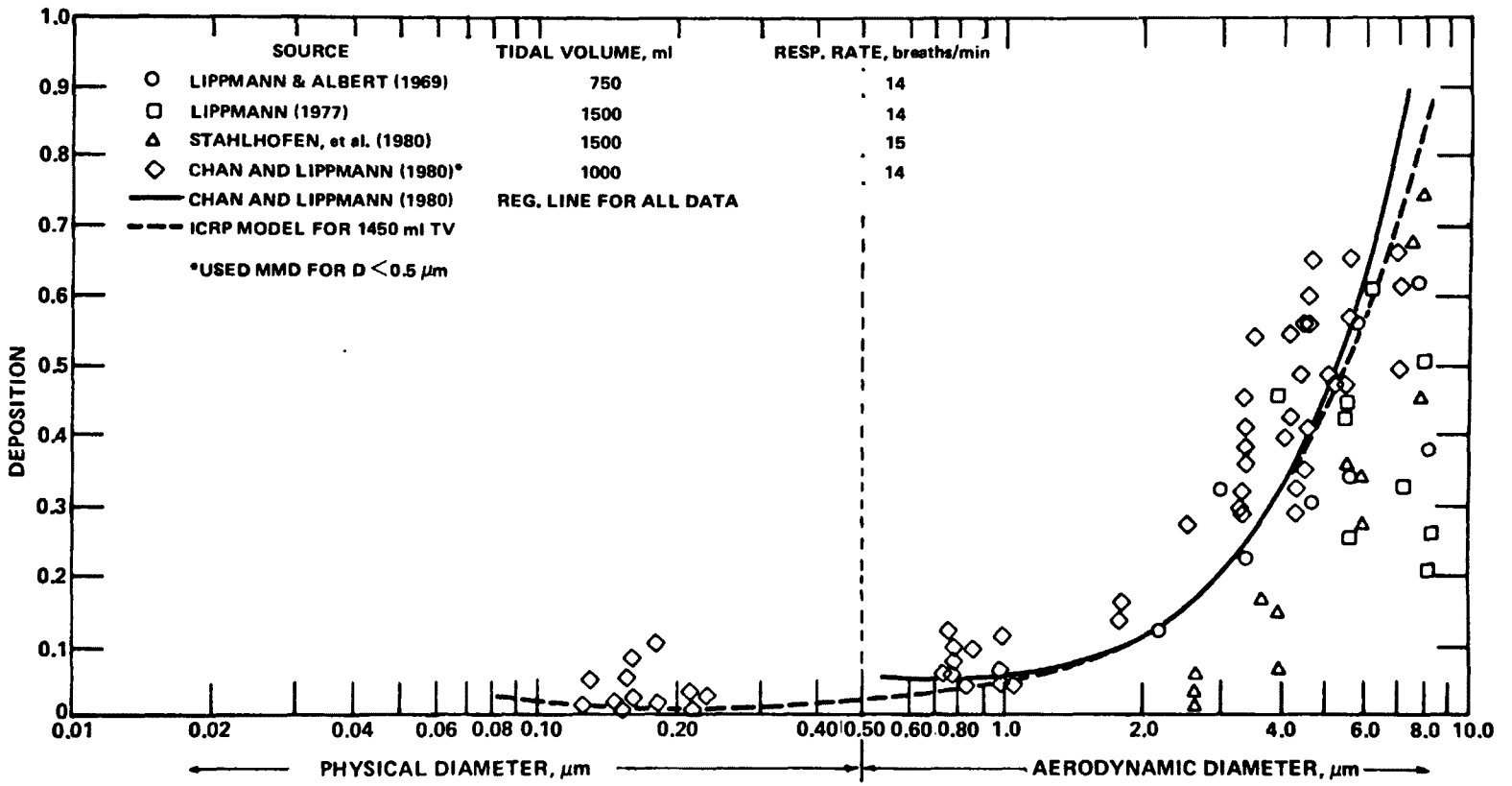

Figure 11-7. Deposition of monodisperse aerosols in the tracheobronchial region for mouth breathing in percent of the aerosols entering the trachea as a function of aerodynamic diameter except below 0.5 μm where deposition is plotted vs. physical diameter as cited by different investigators. Dashed line is ICRP model for 1450 ml tidal volume. The solid line is the overall regression derived by Chan and Lippmann (1980).

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retention values measured during the week after the end of bronchial clearance back to the time of inhalation; they considered pulmonary deposition to be the intercept at that time, with the remainder of the thoracic burden considered as tracheobronchial deposition. This approach yields results similar to, but not identical with those obtained by treating tracheobronchial deposition as equivalent to the particles cleared within the first day.

Deposition calculations usually group lung regions without regard to nonuniformity of the pattern of deposited particles within the regions. Schlesinger and Lippmann (1978) found that nonuniform deposition in the trachea could be caused by the air flow disturbance of the larynx. Bell and Friedlander (1973) and Bell (1978) observed and quantified particle deposition as it occurs at a single airway bifurcation and found it to be highly nonuniform and heaviest around the carinal arch. Raabe et al. (1977) observed that the relative lobar pulmonary deposition of monodisperse aerosols was up to 60 percent higher in the right apical lobes of small rodents (corresponding to the human right upper lobe) and that the difference was greater for 3.05 μm and 2.19 μm D_{ae} particles than for smaller particles. In addition, Raabe et al. (1977) showed that these differences in relative lobar deposition were related to the geometric mean number of airway bifurcations between trachea and terminal bronchioles in each lobe for rats and hamsters. Since similar morphologic differences occur in human lungs, nonuniform lobar deposition should also occur. Schlesinger and Lippman (1978) found nonuniform deposition in the lobar branches of a hollow model of the tracheobronchial airways with enhanced carinal deposition and were able to demonstrate a correlation of higher lobar deposition and the reported incidence of bronchogenic carcinoma in the different human lobar bronchi. Occupational lung diseases, such as silicosis and asbestosis, also show distinctive distributional features (Morgan and Seaton, 1975).

11.2.1.4 Pulmonary Deposition--Pulmonary deposition as a function of particle size is shown in Figure 11-9. All of the experimental points plotted were obtained in mouth-breathing studies on nonsmoking normal subjects who inhaled monodisperse aerosols.

The eye-fit band approximately encompasses the range of deposition values obtained in the studies cited; a variety of tidal volumes and breathing frequencies were used. Also shown in Figure 11-9 are the deposition curve from the predictive model of Yu (1978) and an estimate of the alveolar deposition that could be expected for nose breathing (Lippmann, 1977). Lippmann (1977) derived the estimate by analysis of the difference in head retention during nose breathing and mouth breathing.

The pulmonary deposition curve peaks at about 3.5 μm D_{ae} with the middle of the eye-fit band in Figure 11-9 being located at about 50 percent deposition. However, the data of Stahlhofen et al. (1980) for a tidal volume of 1000 ml and 7.5 breaths per minute (reflective of breathing very slowly and deeply) show that pulmonary deposition of 3.5 μm D_{ae} particles can be as high as 70 percent.

For nose breathing, the size associated with maximum deposition shifts downward to about 2.5 μm D_{ae}. Also, the deposition peak is much less pronounced (about 25 percent) with a nearly constant pulmonary deposition of about 20 percent for all sizes between 0.1 μm and 4 μm D_{ae}.

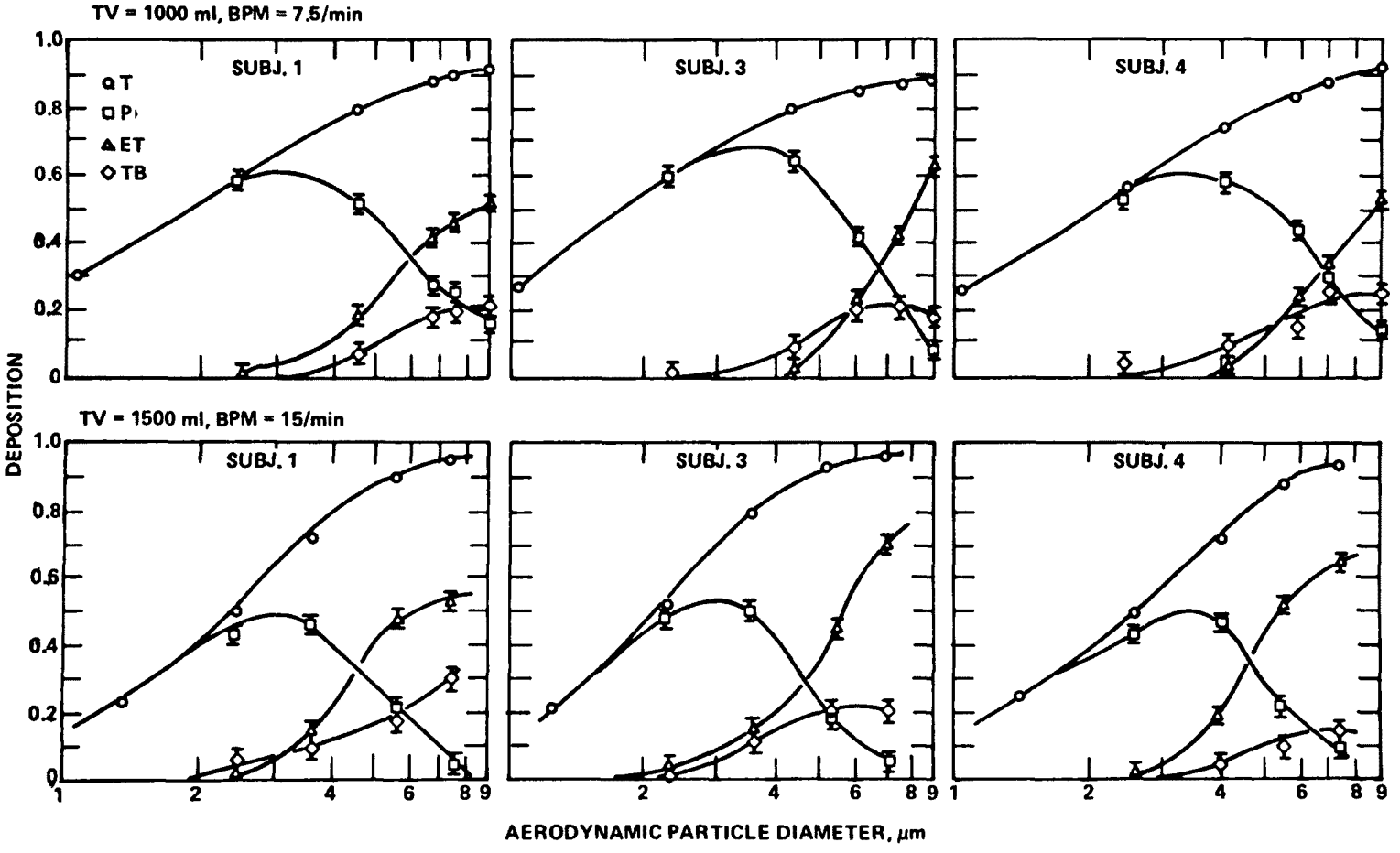

Figure 11-8. Total and regional depositions of monodisperse aerosols as a function of the aerodynamic diameter for three individual subjects as cited by Stahlhofen et al. (1980). (T = Total, TB = Tracheobronchial, P = Pulmonary, ET = Extrathoracic, TV = Tidal Volume, BPM = Breaths Per Minute)

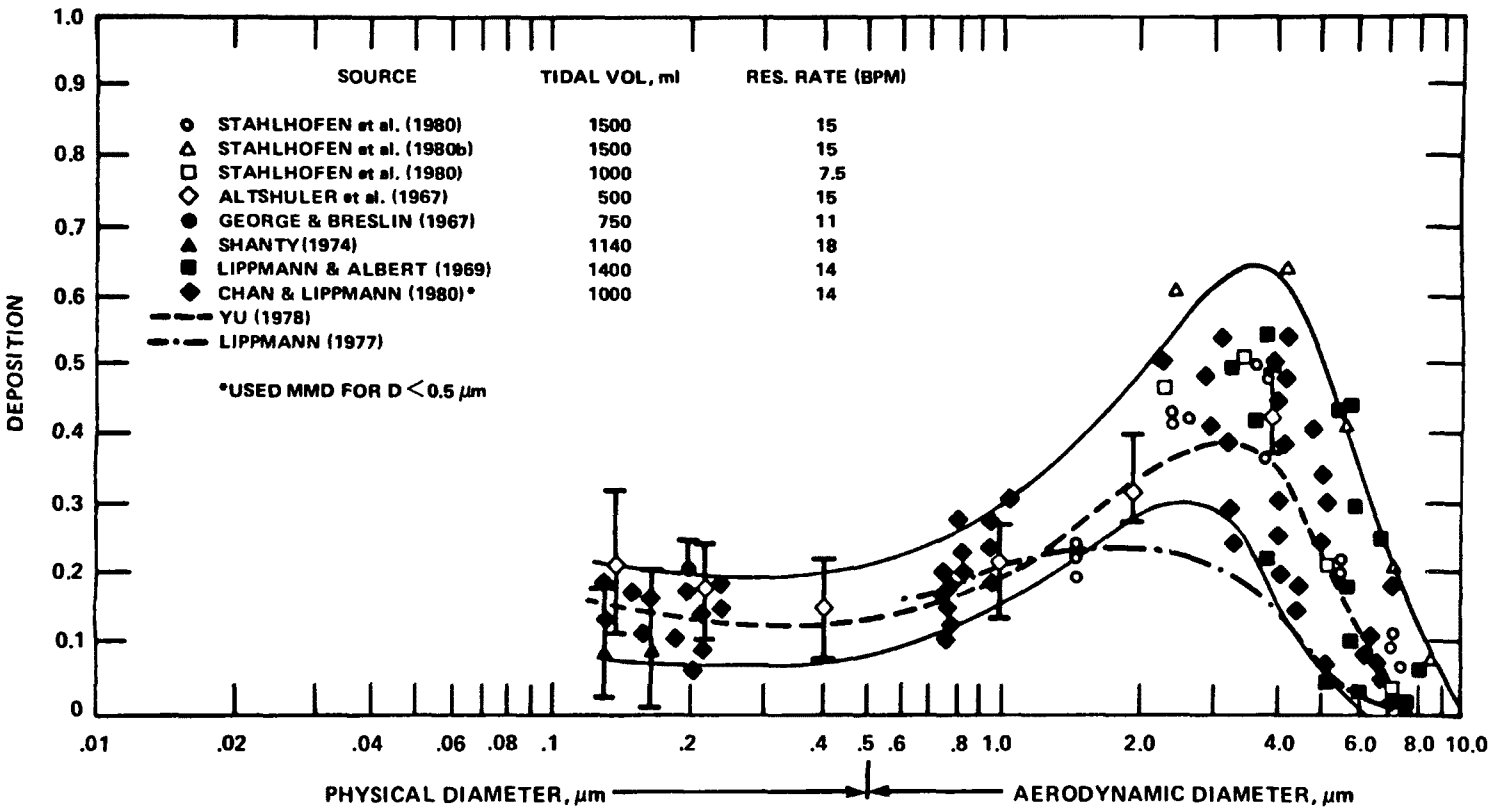

Figure 11-9. Deposition of monodisperse aerosols in the pulmonary region for mouth breathing as a function of aerodynamic diameter, except below 0.5 μm where deposition is plotted vs. physical diameter. The eye-fit band envelops deposition data cited by the different investigators. The dashed line is the theoretical deposition model of Yu (1978) and the broken line is an estimate of pulmonary deposition for nose breathing derived by Lippmann (1977).

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Pulmonary and total deposition of Fe_2O_3 (density 3.2 g/cm^3) particles and di-2-ethylhexyl sebacate droplets for mouth breathing was evaluated by Heyder et al. (1980) as a function of aerodynamic diameter for two breathing patterns. Some results with di-2-ethylhexyl sebacate particles were reported by Heyder et al. (1980) in terms of particle diameter. They are presented here for uniformity in terms of aerodynamic diameter since these particles were close to unit density. Keeping the mean volumetric flow rate constant at 250 ml/sec and allowing the mean residence time to vary between 2 and 8 sec, they observed that as the mean residence time increased, there was a decrease for the particle size having the greatest probability of deposition. With this mean flow rate, particles smaller than about 2.4 μm D_{ae} were exclusively deposited in the alveolar region, indicating their inertia was not sufficiently high for impaction loses. When the mean flow rate was increased to 750 ml/sec and the mean residence time was 2 sec, particles with an aerodynamic diameter smaller than about 1.5 μm were exclusively deposited in the alveolar region of the respiratory tract. From the data of Heyder et al. (1980) it can also be seen that the particle size associated with the peak of the deposition curve and the magnitude of the peak decrease as the mean flow rate increases. In the above studies, maximum pulmonary deposition was at 3.5 μm and 3 μm D_{ae} when Q was 15 liters/min and 45 liters/min, respectively.

11.2.1.5 Deposition in Experimental Animals--Since much information concerning inhalation toxicology is collected with beagles or rodents, it is important to consider the comparative regional deposition in these experimental animals to help interpret, from a dosimetric viewpoint, the possible implications for man of animal toxicological results.

The study by Holma (1967) on rabbits examined mucociliary clearance rates but Lippmann (1977) derived tracheobronchial deposition information by further analyzing the data. Lung retention curves indicated that the tracheobronchial deposition of 6 μm polystyrene spheres varied from 40 to 93 percent of the total lung deposition, with a median of 60 percent. A median of 29 percent was found for 3 μm particles. The above values are remarkably close to the available data for man. Cuddihy et al. (1973) measured the regional deposition of polydisperse aerosols in beagles with TV about 170 ml at about 15 BPM and expressed the results as mass deposition percentage versus mass median aerodynamic resistance diameter ($MMAD_{ar}$) that ranged from 0.42 μm to 6.6 μm with geometric standard deviation σ_g = 1.8. These results are summarized in Figure 11-10 and compared with the Task Group Values for man with TV 1450 ml, integrated to account for a σ_g = 1.8. In comparison to the tracheobronchial deposition of large particles in rabbits exposed to monodisperse aerosols for one test at 6.6 μm D_{ar}, the tracheobronchial deposition was about 44 percent of the total lung deposition. With sizes between 2.5 and 3 μm D_{ar}, the tracheobronchial deposition ranged from 5 to 39 percent, with a median deposition of 9 percent. The particle size for minimum pulmonary deposition was approximately 0.6 μm D_{ar}, with pulmonary deposition at this size ranging from about 12-35 percent and total deposition from about 18-55 percent.

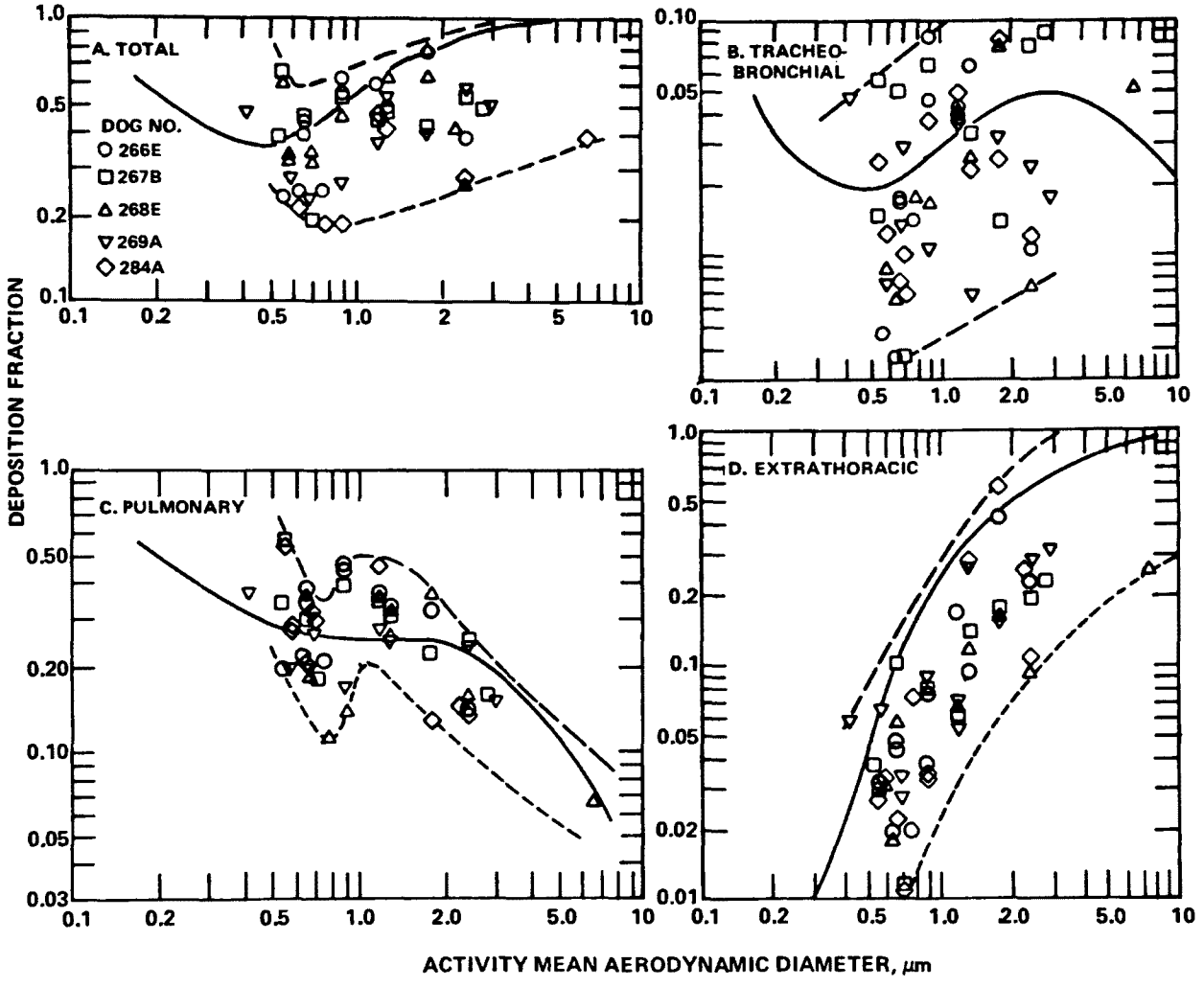

Figure 11-10. Deposition of inhaled polydisperse aerosols of lanthanum oxide (radio-labeled with ^{140}La) in beagle dogs exposed in a nose-only exposure apparatus showing the deposition fraction (A) total dog, (B) tracheobronchial region, (C) pulmonary aveolar region, and (D) extrathoracic region (adapted from Cuddihy et al. 1973). Dashed lines represent range of observed values.

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Somewhat different results were obtained by Phalen and Morrow (1973) in dogs exposed to a silver metal aerosol of 0.5 μm D_{ae} with a σ_g of 1.5 μm. Total deposition averaged 17 percent, with a range of 15-19 percent. In the Phalen and Morrow (1973) study, the dogs inhaled through a tracheal tube so that there was no head deposition, while head deposition varied from negligible to 5 percent for 0.5 μm particles in the study of Cuddihy et al. (1973). In experiments using donkeys (Albert el al., 1968, 1969; Spiegelman et al., 1968), eight animals were tested periodically with monodisperse 3-3.5 μm D_{ae} Fe_2O_3 aerosol. Tracheobronchial deposition averaged 50-70 percent of the total lung deposition, with a median of 54 percent.

Raabe et al. (1977) have measured the regional deposition of 0.1 μm to 3.15 μm D_{ae} monodisperse aerosols in rats (TV about 2 ml, 70 BPM) and Syrian hamsters (TV about 0.8 ml at about 40 BPM). Their results are summarized in Figure 11-11. The pulmonary deposition of 1-3 μm D_{ae} particles is about 6-9 percent in rats and hamsters, while in man deposition of these same size particles varies from 21-24 percent for nose breathing and from 20-50 percent for mouth breathing. For particles smaller than 1 μm D_{ae}, differences in pulmonary deposition between man and these species decrease. Tracheobronchial deposition of particles 5 μm D_{ae} is slight ($\sim$ 5 percent) in rodents due to very efficient removal of these particles in the head. In contrast, 50 percent of 5 μm D_{ae} particles inhaled via the mouth deposit in the tracheobronchial region of man (Figure 11-7), so that large differences can exist between man and rodents in the tracheobronchial deposition of large particles. In rodents, the relative distribution among the respiratory regions of particles less than 3 μm D_{ae} during nose breathing follows a pattern that is similar to human regional deposition during nose breathing. Thus, in this instance, the use of rodents or dogs in inhalation toxicology research for extrapolation to humans entails differences in regional deposition of insoluble particles less than 3 μm D_{ae} that can be reconciled from available data.

11.2.2 Soluble, Deliquescent, and Hygroscopic Particles

Most deposition studies and models tend to focus on insoluble and stable test aerosols whose properties do not change during the course of inhalation and deposition. However, environmental aerosols usually contain deliquescent or hygroscopic particles that may grow in the humid respiratory airways. That growth will affect deposition (Scherer et al., 1979). Although the ICRP Task Group on Lung Dynamics (Morrow et al., 1966) addressed this problem by considering the equilibrium diameter for deliquescent materials at relative humidities near, but less than, 100 percent, the residence times in the respiratory tract may be too short for large particles to reach their equilibrium size (Nair and Vohra, 1975; Charlson et al., 1978). Also, environmental aerosols may consist of a combination of components, including complex mixtures, that may not behave like pure substances. Since the temperature of the inspired aerosol will usually be less than that of the respiratory tract environment, supersaturation of water vapor, with respect to the aerosol particles, may exist.

Ferron (1977) has described the factors affecting soluble particle growth in the airways during breathing. His results suggest that particles 1 μm D_{ae} will increase by a factor of

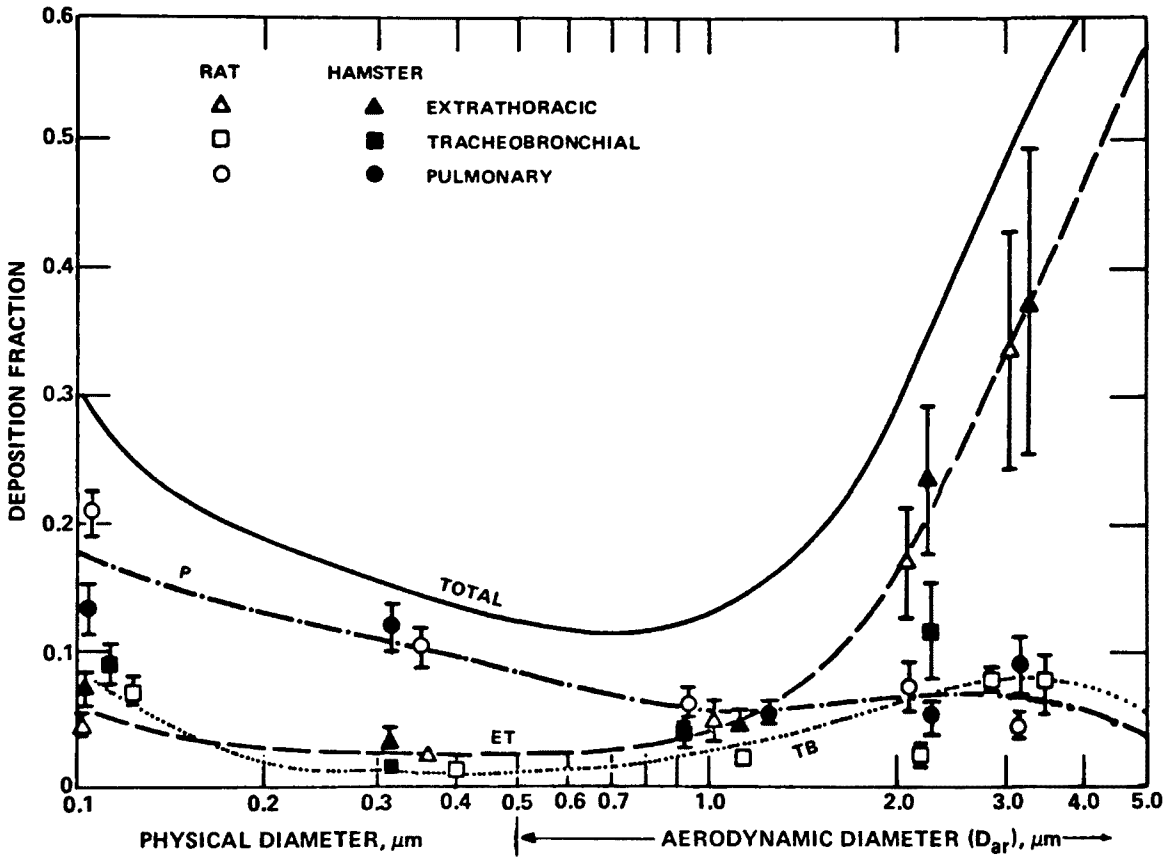

Figure 11-11. Deposition of inhaled monodisperse aerosols of fused aluminosilicate spheres in small rodents showing the deposition in the extrathoracic (ET) region, the tracheobronchial (TB) region, the pulmonary (P) region, and in the total respiratory tract based upon Raabe et al. (1977).

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three to four in aerodynamic diameter during passage through the airways. Extrathoracic, tracheobronchial, and pulmonary deposition of the enlarged particles would be greater than the deposition expected for the original particle size. Submicrometer particles, including those as small as 0.05 μm, will grow by a factor of two in physical diameter, with relatively little effect on deposition. However, the hygroscopic growth of particles in the diffusion size range (< 0.5 μm physical diameter) may alter their deposition pattern substantially as the diffusional displacement is related to the actual size and not the aerodynamic diameter. Pulmonary deposition of particles smaller than 0.3 μm may be reduced with growth because of reduced diffusivity.

Atmospheric sulfate aerosols can be described as sulfuric acid partially or completely neutralized by NH_3. Growth of these particles will occur in the respiratory airways during respiration. This growth involves chemical dilution of the electrolyte or acid with absorbed water. A particle growing a factor of three in physical diameter must absorb a volume of water equal to 26 times its original particle volume. Also, the increased size will enhance losses by inertial mechanisms, including impaction in the upper airways. A 1 μm D_{ae} particle of H_2SO_4 or $(NH_4)_2SO_4$ may grow to nearly 3 μm D_{ae} in the nasal region, increasing both nasal deposition and tracheobronchial deposition by a factor of 2 or more over the deposition expected for a 1 μm D_{ae} particle, with the net result that pulmonary deposition is reduced. Particle growth in the airways may in some cases be protective since the reduced electrolyte or acid concentration will probably reduce the level of local toxicity.

11.2.3 Surface Coated Particles

Some environmental particles may consist of a relatively insoluble core coated with various chemical species including metallic salts, $(NH_4)_2SO_4$, $(NH_4)HSO_4$, H_2SO_4, organic compounds including polynuclear aromatic hydrocarbons, and small particles of other sparingly soluble materials. Although some surface growth due to water adsorption may occur in the airways, growth will be limited by the availability of deliquescent or hygroscopic components on the particle surface. In general, the increase in aerodynamic diameter that may occur would be much less for coated particles than for more pure forms of insoluble materials.

Important examples of coated particles are the fly ash, soot, or other residual solid particulate aerosols released into the environment by combustion of fossil fuels. The exact chemical form of the relatively inert core of these particles will vary from nearly pure fused aluminosilicate particles produced during the combustion of coal to carbonaceous or metal oxide particles produced by internal combustion engines. Volatile trace metal compounds and organic compounds condense on these particles during the cooling of the effluent stream in the power plant smoke stack or engine exhaust line and during release to the atmosphere. In addition, gases such as SO_2 can adsorb to the particle surfaces or finer aerosols can aggregate onto the particle surfaces. If these processes are diffusion limited, the condensation and coagulation will be quantitatively proportional to particle diameter for particles larger than 0.5 μm D and to particle surface for smaller particles. In either case the fractional

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mass of the surface coating material will be greater on smaller particles than on larger ones. In other words, the condensed material coats the particles with a relative mass concentration that increases with decreasing particle size. Important elements such as Se, Cd, As, V, Zn, Sb, and Be have been found to exhibit this size dependence in coal fly ash aerosols (Davison et al., 1974; Natusch et al., 1974; Gladney et al., 1976). Therefore, the growth of such surface-coated particles in the airways should be expected to be much less than for pure deliquescent particles. Such growth should be only a minor influence on the deposition of large particles. On the other hand, small submicrometer coated particles may be principally composed of a deliquescent surface coating and subject to more extensive relative growth. (See also Chapters 3, 5, and 6.)

11.2.4 Gas Deposition

The major factors affecting the uptake of gases in the respiratory tract are the morphology of the respiratory tract, the physicochemical properties of the mucous and surfactant layers, the route of breathing and the depth and rate of airflow, physicochemical properties of the gas, and the physical processes which govern gas transport. A brief discussion of these factors serves to illustrate their general role in the deposition of gases and convey some aspects specific to the uptake of SO_2.

The complex morphological structure of the human respiratory tract has been discussed in section 11.1.3. The nature and structure of the respiratory tract in man and animals critically influences the deposition of gases since the relative contribution of gas transport processes varies as a result of this morphology. The human tracheobronchial tree is more symmetric, with respect to diameter ratios and branching angles, than that of dogs, rats, or hamsters, but is closest to that of the dog (Phalen et al., 1978). The structure of the tracheobronchial tree is variable from species to species, from lobe to lobe within a given lung, and from one depth to another in the lung.

Physicochemical properties of a gas relevant to respiratory tract deposition are its solubility and diffusivity in mucus, surfactant, and water and its reaction-rate constants in mucus, surfactant, water, and tissue. Henry's law relates the gas-phase and liquid-phase interfacial concentrations and is a function of temperature and pressure. In general, the more soluble a gas is in biological fluids the higher it is removed in the respiratory tract. The solubility of most gases in mucus and surfactant is not known. However, Henry's law constant for many gases in water is known, the value for SO_2 being 59.7 mole fraction in air per mole fraction in water at 37°C and one atmosphere of pressure (Washburn, 1928). The diffusivities of most gases in mucus, surfactant, tissue, and water are also unknown, thereby complicating efforts to model gas uptake in the respiratory tract. Diffusivity may be much smaller in a viscous mucous fluid than in water, but ciliary activity induces turbulence which effectively increases mass transfer. In the general case, transport rates of the gas across the mucus-tissue interface, tissue layer, and the tissue-blood interface are needed to fully understand the absorption and desorption of gases in the respiratory tract. However,

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information on biochemical reactions may enable one or more of these compartments to be ignored for a given gas.

The major processes affecting gas transport involve convection, diffusion, and chemical reactions. The bulk movement of inspired gas in the respiratory tract is induced by a pressure gradient and is termed convection. Molecular diffusion due to local concentration gradients is superimposed on this bulk flow at all times, with the transport of the gas being accomplished by the coupling of these two mechanisms. Convection can be decomposed into the processes of advection and eddy dispersion. Advection is the horizontal movement of a mass of air that causes changes in temperature or in other physical properties, while eddy dispersion occurs when air is mixed by turbulence so that individual fluid elements transport the gas and generate the flux. Due to the morphology of the respiratory tract and respiratory airflow patterns, the relative contribution of the various processes to transport and deposition is a function of location and point in the breathing cycle.

During the respiratory cycle, the volumetric flow rate of air varies from zero up to a maximum (dependent upon tidal volume, breathing frequency, and breathing pattern) and then back to zero. Usually expiration is longer than inspiration, and intervening pauses may occur. The net result of these variables is to impart complicated flow patterns and turbulence in some portions of the respiratory tract (see Section 11.1.4).

In studying the nature of gas mixing in the tracheobronchial tree and its effects on gas transport there have been numerous modeling efforts utilizing an approach in which all pathways from the mouth or trachea to the alveoli are combined into one effective pathway whose cross-sectional area is equal to the summed cross-sectional area of all bronchial tubes at a given distance from the mouth or trachea (Davidson and Fitz-Gerald, 1974; Paiva, 1973; Pedley, 1970; Yu, 1975; Scherer et al., 1972). In this formulation, the mechanical mixing imparted by tube bifurcations, turbulence, and secondary flows and the mixing due to molecular diffusion are represented by the functional form of the effective axial diffusion coefficient (Scherer et al., 1975). Thus, this coefficient of diffusion incorporates the effect of axial convection. The effective axial diffusion coefficient is a constant equal to the molecular diffusivity only in the alveolar region where gas velocity is very small. However, in other regions of the tracheobronchial tree, the local average gas velocity and the tube geometry will jointly determine the value. Various functional forms have been proposed in the studies cited above for an appropriate expression for the effective axial diffusion coefficient.

By constructing individual streamline pathways from the trachea to the alveoli, Yu (1975) derived an expression for the effective axial diffusion coefficient which equalled the algebraic sum of the molecular diffusion coefficient and an apparent diffusion coefficient. The apparent diffusion coefficient arises from two independent mechanisms: 1) the nonhomogeneous ventilation distribution in the lung, and 2) the interaction of nonuniform velocity and concentration profiles due to Taylor's mechanism in individual airways. Using an average standard deviation of airway lengths based upon the data of Weibel (1963) and various flow theory

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limiting values, Yu (1975) demonstrated that Taylor diffusion is everywhere in the tracheobronchial tree dominated by the apparent diffusion due to nonhomogeneous distribution of ventilation, rather than being a major mechanism for gas transport in some airways as claimed by Wilson and Lin (1970).

In all of the previously described studies the diffusivity expressions used assume fully developed flow in straight pipes to describe gas mixing, a condition not truly applicable over most of the tracheobronchial tree. Since flow patterns at tube bifurcations are different for inspiration and expiration (Schroter and Sudlow, 1969), the mixing process and hence the effective diffusivities are different. To obtain diffusivities applicable to the tracheobronchial tree, Scherer et al. (1975) used airway lengths and diameters from Weibel (1963) and branching angles from Horsfield and Cumming (1967) to construct a five-generation symmetrical branched tube model and to experimentally determine effective axial diffusivity for laminar flow of a gas as a function of mean axial velocities up to 100 cm/s in the zeroth generation tube. The relationship was approximately linear and diffusivities for expiration were about one-third those for inspiration. The values obtained by Scherer et al. (1975) for steady flow can be applied to oscillating flow in the tracheobronchial tree provided the oscillating flow can be considered quasi-steady, i.e., steady at any instant of time. This condition should hold in the first ten generations whenever flow rates are approximately greater than 0.1 l/s (Jaffrin and Kesic, 1974).

Additional experimental uptake data are needed to obtain a better understanding of the effects of various factors affecting the transport and removal in the lung of gases, such as SO_2. Also needed along with these experimental data are refined theoretical approaches, as well as more flexible computational models, such as that of Pack et al. (1977). The amount of SO_2 removed depends upon solubility, the velocity and turbulence of the air, the diffusing capacity across the air-tissue interface and through the tissue, the volume of tissue available for gas storage, and the rate of fluid exchange between these tissues and the storage reservoirs in the body for SO_2 (Aharonson, 1976). The rate controlling factor in the deposition of SO_2 is probably the vapor pressure of dissolved SO_2 in buffered body fluids.

The diffusion coefficient of SO_2 in air at body temperature is 0.144 cm^2/sec at sea level (Fish and Durham, 1971; Sherwood et al., 1975). The complicated flow patterns and turbulence in the upper respiratory tract and upper generations of the tracheobronchial tree in combination with high solubility in body fluids are responsible for the large removal of SO_2 in these regions. Frank et al. (1969) surgically isolated the upper respiratory tract of anesthetized dogs with separate connections for the nose and mouth. Sulfur dioxide labeled with ^{35}S was passed through this isolated nasopharyngeal region for 5 min, and nearly complete removal was observed for concentrations of 2.62 mg/m^3 to 131 mg/m^3 (1 to 50 ppm) at a flow rate through the nose of 3.5 liters/min. Uptake of the mouth averaged more than 95 percent at 3.5 liters/min with SO_2 levels of 2.62 mg/m^3 and 26.2 mg/m^3 (1 and 10 ppm). However, when flow was increased tenfold to 35 liters/min, uptake by the mouth fell to under 50 percent. Strandberg (1964) used

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a tracheal cannula with two outlets that allowed sampling of inspired and expired air to study the uptake of SO_2 in the respiratory tract of rabbits. He observed 95 percent absorption in the respiratory tract at 524 mg SO_2/m^3 (200 ppm) but at 0.13 mg SO_2/m^3 (0.05 ppm) absorption was lowered to about 40 percent during inspiration, demonstrating an apparent concentration effect. Absorption of SO_2 at expiration was 98% in the 524 mg/m^3 (200 ppm) studies compared to 80% for experiments using 0.13 mg/m^3 (0.05 ppm). Dalhamn and Strandberg (1961) found that rabbits exposed to 262-786 mg SO_2/m^3 (100 - 300 ppm) absorbed 90% - 95% of the SO_2. They noted that absorption was to some extent dependent upon the technique whereby tracheal air samples were obtained.

Corn et al. (1976) studied the upper respiratory tract deposition of SO_2 in cats and computed mass transfer coefficients which can be used with surface area data to calculate the amount of SO_2 removed in various parts of the respiratory tract. Utilizing a theoretical approach, their own empirical data, and information available from the literature, Aharonson et al. (1974) examined the effect of respiratory airflow rate on nasal removal of soluble vapors. The only assumption made regarding factors affecting local uptake was that there was no back pressure in the blood. Hence, whether the rate of uptake is limited by diffusion through the gas phase, diffusion through the tissue, chemical reactions in the tissue, or local blood flow in the tissues, the analytical approach is valid, as long as the rate of uptake is proportional to the gas phase pressure of the vapor. Their analysis for acetone, ether, ozone, and sulfur dioxide showed that the uptake coefficient, which defines the average flux of soluble vapors into the nasal mucosa per gas-phase unit partial pressure, increases with increasing airflow rate.

In experiments described by Brain (1970b) there was a 32-fold increase in the amount of SO_2 present in the trachea of dogs when the air flow-rate was increased 10-fold. However, had the uptake coefficient not changed with the flow rate, Aharonson et al. (1974) pointed out that penetration would have increased 500-fold. If the uptake coefficient for SO_2 is concentration dependent, as the data of Strandberg (1964) suggest, increasing airflow rate may increase uptake due to higher levels of SO_2 being present along the center of the airstream for the same inspired concentration.

The deposition and clearance of sulfur dioxide also has been studied in <u>in vitro</u> model systems. In a model of the tracheobronchial airways lined with a simulated airway fluid (bovine serum albumin dissolved in saline), it was observed that SO_2 was primarily absorbed in the upper third of the simulated airway with only a small fraction of the SO_2 reaching the simulated alveolar or bronchiolar regions (Kawecki, 1978).

Uptake and release of SO_2 in the nose of human subjects breathing 42.2 mg/m^3 (16.1 ppm) through a mask during a 30 minute exposure period was studied by Speizer and Frank (1966). During inspiration the concentration of SO_2 had dropped 14% at a distance 1-2 cm within the nose and was too small to detect at the pharynx with the analytical method used. Expired gas in the pharynx was also virtually free of SO_2, but in its transit through the nose the expired

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air acquired SO_2 from the nasal mucosa. The expired SO_2 concentration at the nose was 5.2 mg/m^3 (2.0 ppm), or about 12% of the original mask concentration. In most subjects the nasal mucosa continued to release small amounts of SO_2 during the first 15 minutes after cessation of the SO_2 exposure (see Section 11.3.2).

Melville (1970) exposed humans to SO_2 levels ranging from 4 mg/m^3 to 9 mg/m^3 (1.5 ppm to 3.4 ppm) for periods up to 10 min. Respiratory tract extraction of SO_2 during nose breathing was significantly greater ($p < 0.01$) than during mouth breathing (85% versus 70%, respectively) and was independent of the inspired concentration of SO_2. Andersen et al. (1974) found that at least 99% of 65.5 mg SO_2/m^3 (25.0 ppm) was absorbed in the nose of subjects during inspiration. Values obtained after one to three hours of exposure were not different from those obtained after four to six hours of exposure, thereby indicating there was no saturation effect during this period of time.

11.2.5 Aerosol-Gas Mixtures

Gases readily diffuse to the surface of particles and can participate in a variety of surface interactions. Surface adsorption related to temperature and gaseous vapor pressure occurs if adsorption sites for the gas molecules are present on the particles. Such physical adsorption can be described by the Langmuir isotherm or more complex isotherms (Gordieyeff, 1956). In addition chemical adsorption can occur involving chemical transformations and bonds that enhance transfer of gaseous materials to the particulate phase. Such transformations can include both inorganic and organic vapors. In addition, aerosols of liquid droplets can collect and carry volatile species that are dissolved in the droplets. In these cases, aerosols can serve as vectors carrying molecules of various substances deeper into the airways than would occur if the substances were in their gaseous forms.

Sulfuric acid in the environment may be reduced in acidity by naturally occurring ammonia (NH_3) to form ammonium sulfate $(NH_4)_2SO_4$ and ammonium bisulfate (NH_4HSO_4). Larson et al. (1977) made short-term measurements which suggest that endogenously generated ammonia (NH_3) gas in the human airways may rapidly and completely neutralize sulfuric acid aerosols in the concentrations that are normally encountered in the ambient environment. Also, ammonia is generated from food and excreta in inhalation chambers used to expose experimental animals to sulfuric acid (H_2SO_4) so that some neutralization of sulfuric acid in these test atmospheres probably occurs.

Since SO_2 is found in the gas phase in various environmental aerosols, the reactions that occur between SO_2 and aerosols, and the gas-to-particle conversions that may occur, can greatly influence the regional deposition of biologically active chemical species. Since SO_2 is highly soluble in water, droplet aerosols, including those formed by deliquescent particles, will collect dissolved SO_2 and can carry some of the resulting sulfurous acid not neutralized by NH_3 deep into the lung. The presence of certain sulfite species formed by such reactions in environmental aerosols has been suggested (Eatough et al., 1978). SO_2 is also known to be converted to sulfate by reactions catalyzed by some aerosols, including those containing iron

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or manganese. The simple adsorption of SO_2 to aerosol surfaces by chemical reaction may lead to the aerosol's acting as a vector for transporting SO_2 to the deep lung.

The deposition of the aerosol and gaseous fractions of the sulfur species can be predicted from the properties of these fractions. Hence, the problem of estimating deposition (and subsequent biological effects) requires an understanding of the proportion of sulfur species associated with the aerosol fraction and their chemical properties. Since these reactions are dynamic processes, the rate and mechanics of the gas-particle chemical reactions, especially as they may occur in the airways, must be understood, such as the potentiation of increased airway resistance in guinea pigs with SO_2 by some particles (Amdur and Underhill, 1968).

11.3 TRANSFORMATIONS AND CLEARANCE FROM THE RESPIRATORY TRACT

Particulate material deposited in the respiratory tract may eventually be cleared by the tracheobronchial mucociliary conveyor or nasal mucous flow to the throat and is either expectorated or swallowed. Other deposited material may be cleared by either the lymphatic system or transfer to the blood. SO_2 reacts rapidly with biological constituents to produce S-sulfonate (Gunnison and Denton, 1971). The role of clearance as a protective mechanism for the respiratory tract depends on the physicochemical characteristics of the particles (or gaseous species), the site of deposition, and respiratory physiology. If the particles dissolve rapidly in body fluids, their deposition in the nasal turbinates with subsequent absorption into the blood is important, and total deposition of soluble particles may be more critical than regional deposition. For relatively inert and insoluble particles, deposition in the pulmonary region, where they may be tenaciously retained, may be more hazardous, unless their action is mediated through nasal deposition. The deposition by dissolution of SO_2 in the extrathoracic region may be protective, since it may involve less serious biological effects than deposition in the bronchial or pulmonary airways. Mouth breathing would lessen the nasal absorption and increase the SO_2 levels entering the lung. If the particles or SO_2 chemically react with body fluids, transformations of the material can affect clearance. In all respiratory regions, the dissolution of particles competes with other clearance processes.

Since respiratory tract clearance may begin immediately after the initial deposition, the dynamics of retention can become quite complicated when additional deposition is superimposed on clearance phenomena, especially if the deposited material affected clearance mechanisms. Extended or chronic exposures are the general rule for environmental aerosols, and particulate material may accumulate in some portions of the lung (Davies, 1963, 1964a; Walkenhorst, 1967; Einbrodt, 1967).

11.3.1 Deposited Particulate Material

An understanding of regional deposition is requisite to an evaluation of respiratory clearance and a description of the retention of deposited particulate materials. In addition, there may be significant differences between the mechanisms of clearance in different mammalian

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species. Particle deposition in the extrathoracic region is limited primarily to larger particles deposited by inertial impaction. Deposition of various aerosol particles may lead to specific biological effects associated with this region. For particles that do not quickly dissolve or do not react with body fluids, clearance from this region is mechanical. The anterior third of the human nose (where most particles >5 μm may deposit) does not clear except by blowing, wiping, sneezing, or other extrinsic means, and particles may not be removed until 1 or more days after deposition (Proctor and Swift, 1971; Proctor et al., 1969, 1973; Proctor and Wagner, 1965, 1967).

The posterior portions of the human nose, including the nasal turbinates, have mucociliary clearance averaging 4 to 6 mm/min with considerable variation among individuals (Proctor and Wagner, 1965 and 1967; Ewert, 1965; van Ree and van Dishoeck, 1962). Particles are moved with this mucus to the throat and are swallowed or expectorated. Various reactions can occur in the gastrointestinal tract, and some assimilation into the blood is possible even for particles that were relatively insoluble in the nose. The ICRP Task Group (Morrow et al., 1966) adopted a 4-minute half-time for physical clearance from the human extrathoracic (nasopharyngeal) region by mucociliary transport to the throat and subsequent swallowing.

Soluble particles or droplets are readily assimilated by the mucous membranes of the nose directly into the blood. Solubility is graded from extremely insoluble to instantly soluble, and the dissolution rate constant for the particles must be considered for each aerosol.

Since the tracheobronchial region includes both very large and very small airways, particles of various sizes can be deposited. The retention of deposited materials in this region can differ markedly among individuals and can be affected by such factors as cigarette smoking, pathological abnormalities, or responses to inhaled air pollutants. Clearly, the more rapid the clearance, the less time available for untoward responses or latent injury at the site of original deposition. In mouth breathing of aerosols, such as during smoking or under physical exertion, the beneficial filtering of large particles in the nasal airways is lost, and a greater fraction of these large particles can be deposited in the TB region.

An important characteristic of the TB region is that it is both ciliated and equipped with mucus-secreting cells. Mucociliary clearance mechanisms have been reviewed by Schlesinger (1973). For relatively insoluble and inert particles, the primary clearance mechanism for the TB region is mucociliary transport to the glottis, with subsequent swallowing and passage into the gastrointestinal tract. Mucous flow influences the ciliary mucous conveyor (Van As and Webster, 1972; Besarab and Litt, 1970; Dadaian et al., 1971).

The rate of mucous movement is slowest in the finer, more distal airways and greatest in the major bronchi and trachea. In addition, coughing can accelerate tracheobronchial clearance by the mucociliary conveyor. The size distribution of particles affects their distribution in the tracheobronchial tree. The average clearance time for small particles that preferentially deposit deep in the lung is longer than for larger particles, which tend to deposit in the larger airways (Albert et al., 1967, 1973; Camner et al., 1971; Luchsinger et al., 1968).

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The clearance of material in the TB compartment cannot be described by a single rate. Data from experimental studies imply that the larger airways clear with a half-time of about 0.5 hours, intermediate airways with a half-time of 2.5 hours, and finer airways with a half-time of 5 hours (Morrow et al., 1967a; Morrow, 1973). There is also considerable variability among individuals (Camner et al., 1972, 1973a,b; Camner and Philipson, 1972; Albert et al., 1967). Material with slow dissolution rates in the TB compartment will usually not persist longer than about 24 hours in healthy humans. Cigarette smoking has been reported under various conditions to either increase, decrease, or have little effect on the efficiency and speed of TB clearance (Camner and Philipson, 1972; LaBelle et al., 1966; Bohning et al., 1975; Albert et al., 1974; Thomson and Pavia, 1973).

Particles smaller than about 10 μm D_{ae} are deposited to some extent in the pulmonary region of the lung upon inhalation, although the deposition of particles smaller than 0.01 μm may be quite limited because of the competing diffusional deposition in the NP and TB regions. Particles that deposit in the pulmonary region land on surfaces kept moist by a complex liquid containing pulmonary surfactants. Slowly dissolving materials that deposit in the human pulmonary region are usually retained for years. For example, McEuen and Abraham (1978) reported that birefringent particle counts were significantly higher in 37 cases of pulmonary alveolar proteinosis both in regions of alveolar proteinosis and perivascular and peribronchiolar regions (dust retention areas) than in 13 control subjects. Out of 8619 particles, 4817 were < 1 μm in physical diameter, 3771 were 1-10 μm in physical diameter, and 31 were > 10 μm in physical diameter, with 59 percent being round, 19 percent fibrous, and 22 percent irregular in shape.

Usually, relatively insoluble particles are rapidly phagocytized by pulmonary macrophages (LaBelle and Brieger, 1961; Sanders and Adee, 1968; Green, 1971, 1974; Ferin, 1967, 1976, 1977; Camner et al., 1973a,b, 1974; Chapman and Hibbs, 1977; Ferin et al., 1965; Brain and Corkery, 1977; Brain et al., 1977; Brain, 1970a). Some particles may enter the alveolar interstitium by pinocytosis (Strecker, 1967). Some particles may be cytotoxic to alveolar macrophages and thus influence this clearance mechanism (see Section 12.3.4.2). Migration and grouping of macrophages laden with particles can lead to redistribution of evenly dispersed particles into clumps and focal aggregations of particles in the deep lung. Such events have been described in the sequence of pathological changes observed in experimentally-induced silicosis (Heppleston, 1969). Silica particles ranging in size from less than 1 to 3 μm in physical diameter have been found post mortem in fibrotic lesions associated with deposits of crystalline silica (Craighead and Vallyatin, 1980). Sherwin and coworkers (1979) found an abnormal number of birefringent particles in the lungs of seven patients in association with early to late interstitial inflamation and fibrosis. Also, using scanning electron microscopy and energy dispersive X-ray analysis of particles < 5 μm in physical diameter, they found mostly silicates (especially aluminum, sodium, and potassium), with 5 to 10 percent silicon dioxide.

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Macrophages containing particles may enter the boundary region between the ciliated bronchioles and the respiratory ducts and then can be carried with the mucociliary flow of the TB region. Some insoluble particles deposited in the lung are eventually trapped in the pulmonary interstitium (Strecker, 1967), impeding mechanical redistribution or removal (Felicetti et al., 1975). Although protein molecules may pass across the airblood barrier intact with a clearance halftime of hours by pinocytotic vesicular transport (Bensch et al., 1967), there is conflicting evidence at best on the passage of very small particles (< 10 nm in physical diameter) across the airblood barrier. For example, the data of Kanapilly and Diel (1980) on the dissolution of ultrafine $^{239}PuO_2$ are in disagreement with the data and interpretations of Raabe et al. (1978).

Another possible clearance route for migrating particles and particle-laden macrophages is the pulmonary lymph drainage system with translocation first to the tracheobronchial lymph nodes (Thomas, 1968; Lauweryns and Baert, 1977; Leeds et al., 1971). Little information is available about the clearance rates for transfer from lung to lymph nodes in man, but halftimes of 1 to 2 years have been estimated from data on dogs and monkeys (Leach et al., 1970). Like transfer to the TB region with clearance by the mucociliary escalator, transfer to lymph nodes may affect only a portion of the material deposited in the lung.

Waligora (1971) reported the pulmonary clearance of extremely insoluble and inert particles of zirconium oxide radiolabeled with ^{95}Nb. Although his results were not precise, the biological clearance half-life in man was about 1 year, a value about the same as for beagles. By contrast, murine species have a more rapid pulmonary clearance (Morgan et al., 1977). Leach et al. (1970, 1973) exposed experimental animals to insoluble UO_2 (MMAD of about 3.5 μm) and observed lung retention half-times of 19.9 months for dogs and 15.5 months for monkeys. Ramsden et al. (1970) measured the retention of accidentally inhaled, relatively insoluble $^{239}PuO_2$ (plutonium dioxide) in a man's lungs and found the clearance half-time to be about 240 to 290 days; some of that material was dissolved into blood and excreted in the urine. Pulmonary clearance half-times as long as 1000 days have been reported for extremely insoluble particles of plutonium dioxide in dogs (Raabe and Goldman, 1979). Cohen et al. (1979) reported an apparent half-time of about 100 days for nonsmokers and about 1 year for smokers for pulmonary clearance of magnetite particles.

Because of the slow clearance by the various mechanical pathways, dissolution and associated physical and biochemical transformations are often the dominant mechanisms of clearance from the pulmonary region (Morrow, 1973). The term "dissolution" is taken in its broadest context to include whatever processes cause material in a discrete particle to be dispersed into the lung fluids and the blood (Green, 1975). Many chemical compounds deposited in the lung in particulate form are mobilized faster than can be explained by known chemical properties at the normal lung fluid pH of about 7.4 (Kanapilly, 1977). Raabe et al. (1978) suggested that the apparent dissolution of highly insoluble PuO_2 actually may be due to fragmentation into particles small enough to move readily into the blood, rather than to true dissolution.

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Mercer (1967) developed an analysis of pulmonary clearance based on particle dissolution under nonequilibrium conditions. If the dissolution rate constant (k) is known for a material, the time required to dissolve half the mass of (monodisperse) particles of initial physical diameter (D_o) is given by:

$$T_{1/2} = 0.618\ \alpha_v\ \rho D_o/\alpha_s k \qquad (2)$$

with ρ the physical density of the particles and α_v and α_s the volume and surface shape factors, respectively (for spherical particles $\alpha_s/\alpha_v = 6$).
The particles would be expected to be completely dissolved at a time, t_f, given by:

$$t_f = 3\alpha_v\ \rho\ D_o/\alpha_s k \qquad (3)$$

Mercer (1967) also calculated the expected dissolution half-time for polydisperse particles when their mass median (physical) diameter in the lung is known:

$$T_{1/2} = 0.6\ \alpha_v\ \rho(MMD)/\alpha_s k \qquad (4)$$

Further, he showed that the resulting apparent lung retention function R(t) could be described as the sum of two exponentials of the form:

$$R(t) = f_1 e^{-\lambda_1 \beta} + f_2 e^{-\lambda_2 \beta} \qquad (5)$$

where $f_1 = (1-f_2)$, $\beta = \alpha_s Kt/\alpha_v \rho(MMD)$ and f_1, f_2, λ_1, and λ_2 are functions of the geometric standard deviations as defined by Mercer (1967).

For dissolution-controlled pulmonary clearance, smaller particles will exhibit proportionately shorter clearance half-times. When the dissolution half-times are much shorter than the half-times associated with the translocations of particles to the TB region or to lymph nodes (i.e., much less than 1 year), dissolution will dominate retention characteristics. Materials usually thought to be relatively insoluble (such as glass) may have high dissolution rate constants and short dissolution half-times for the small particles found in the lung; the dissolution half-time for 1 μm D glass spheres is about 75 days (Raabe, 1979). Changes in structure or chemical properties, such as by heat treatment of aerosols (Raabe, 1971), can lead to important changes in dissolution rates and observed pulmonary retention.

Usually the retention time of material in the respiratory tract is measured (such as with radiolabeled aerosols) rather than the clearance rates (Sanchis et al., 1972; Camner et al., 1971; Edmunds et al., 1970; Luchsinger et al., 1968; Aldas et al., 1971; Ferin, 1967; Barclay et al., 1938; Morrow et al., 1967a,b; Friberg and Holma, 1961; Holma, 1967; Kaufman and Gamsus, 1974). The lung burden or respiratory tract burden can be represented by an appropriate retention function with time as the independent variable (Morrow, 1970a,b). For models

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based on simple first-order kinetics, the lung burden, y, at a given time during exposure is controlled by the instantaneous equation:

$$\frac{dy}{dt} = E - \lambda_1 y \qquad (6)$$

where E is the instantaneous deposition rate of particulate material deposited in the lung per unit time during an inhalation exposure and λ_1 is the fraction of material in the lung cleared from the lung per unit time (Raabe, 1967). For an exposure that lasts a time t_e, the lung burden from the exposure is given by:

$$y_e = (E - Ee^{-\lambda_1 t_e})/\lambda_1 \qquad (7)$$

where E is the average exposure rate. After the exposure ends, the clearance is governed by:

$$\frac{dy}{dt} = - \lambda_1 y \qquad (8)$$

and the lung burden is given by:

$$y = y_e e^{-\lambda_1 t} \qquad (9)$$

where y_e is the lung burden at the end of the exposure period (t_e). Hollinger et al. (1979) used this simple model to describe the deposition and clearance of inhaled submicronic ZnO in rats (Figure 11-12) where the concentration of zinc (as Zn) in the lungs (as described by Equations 7 and 9) is superimposed on the natural background concentration of zinc in lung tissue. The normally insoluble zinc has only a 4.8-hour dissolution half-time ($\lambda_1 = 0.21\ h^{-1}$) for this aerosol. Of course, environmental aerosol exposures are likely to continue so that a steady state lung burden may be expressed by:

$$y_{ss} = E/\lambda_1 \qquad (10)$$

If several deposition and clearance regions, subregions, or special pools are involved, a more complicated multicompartmental model may be required to describe lung or respiratory tract buildup and retention of inhaled aerosols. If each compartment can be described by first order kinetics, a general model can be specified by 1) subscripting E, λ, and Y with the subscript i whenever they appear on the right-hand side of Equations 7, 9, 10, and 2) performing a summation over i from one to the number of compartments. Each of the λ_i values translates to a clearance rate for each of the compartments given by half-time $T_{1/2} = \ln 2/\lambda_i$ (for example see Figure 11-13).

For chronic exposures where the several pools are in complex arrays of change, a simple power function may serve as a satisfactory model of pulmonary retention (Downs et al., 1967).

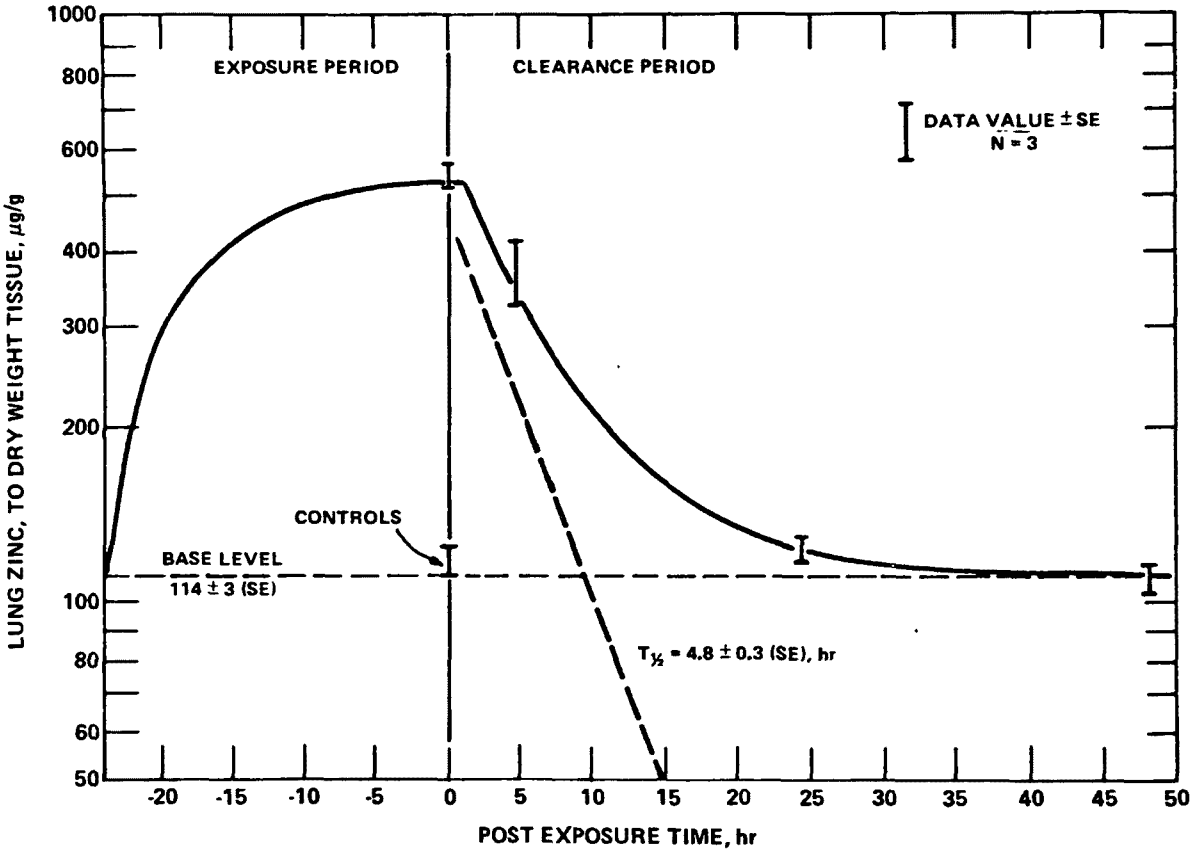

Figure 11-12. Single exponential model, fit by weighted least-squares of the buildup (based on text equation 7) and retention (based on text equation 9) of zinc in rat lungs.

Source: Hollinger et al. (1979).

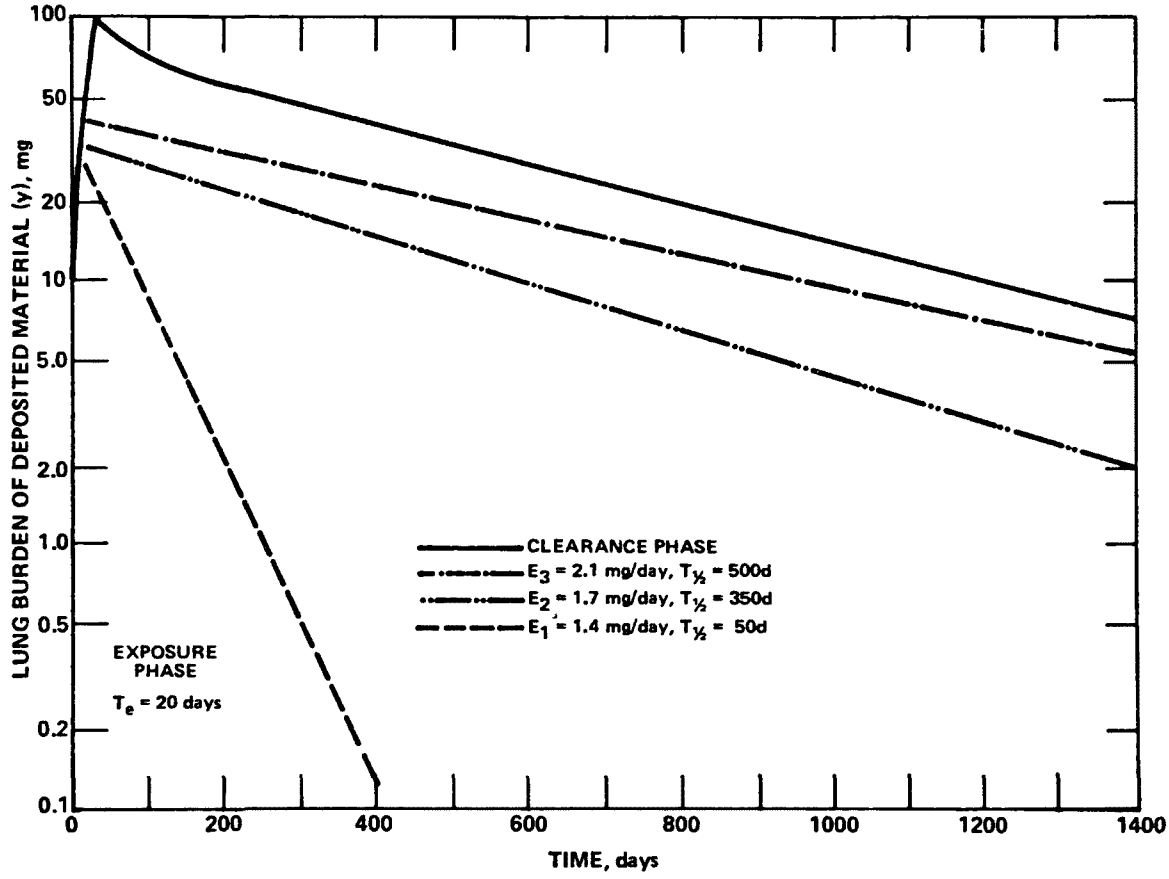

Figure 11-13. Example of the use of the sum of exponential models for describing lung uptake during inhalation exposure and retention (clearance phase) after exposure ends for three lung compartments with half-lives 50d, 350d, 500d, and 20-day exposure rates of 1.4 mg/day (E_1), 1.7 mg/day (E_2), and 2.1 mg/day (E_3), respectively.

Source: Raabe (1974).

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In such a model, the pulmonary region is treated as one complex, well-mixed pool into which material is added and removed during exposure, as given by the instantaneous equation:

$$\frac{dy}{dt} = E - \lambda_p y/t \quad [y = 0 \text{ at } t = 0] \tag{11}$$

where y is the total lung burden at a given time, t, E is the average deposition rate of inhaled particulate material in the lung, and λ_p is the fraction of available lung burden being cleared. Unlike the λ_i of the exponential retention models, λ_p is dimensionless. The time coordinate is not arbitrary; time is taken as zero only at the beginning of the inhalation exposure, when the lung burden is nil. Thus, during an exposure lasting until time (t_e), the pulmonary burden (y_e) is given by (Raabe, 1967):

$$y_e = Et_e/(\lambda_p + 1) \tag{12}$$

On this basis, no steady-state concentration is reached even though clearance is progressing and the lung concentration continues to increase during chronic exposures to environmental aerosols. This model is therefore not applicable to relatively soluble species. The lung burden, y, after the exposure has ended for a time, t_p, is given by (Raabe, 1967):

$$y = y_e\, t_e^{\lambda_p}\, t^{-\lambda_p} = At^{-\lambda_p} \quad [t = t_e + t_p] \tag{13}$$

This model is illustrated in Figure 11-14.

Deposited particulate material cleared from the lung is usually transformed chemically and transferred to other tissues of the body. The injurious properties of a toxic material translocated from the lung may therefore be expressed in other organs. Identification of the potential hazards associated with inhalation exposures to toxicants is compounded when the respiratory tract is not the only target for injury but still serves as the portal of entry into the body. The metabolic behavior and excretion of inhaled toxicants after deposition in the lung may define the probable target organs and indicate potential pathogenesis of resulting disease.

Multicompartmental models that describe biological behavior can become extremely complex. Each toxicant or component of aerosol particles deposited in the respiratory tract may need to be described by a separate rate constant and pool or compartment. A general model of the metabolic behavior of inhaled particles developed by Cuddihy (1969) identified 39 different places where rate constants may need to be determined. In this general model, the pulmonary region of the lung is visualized as consisting of three independent clearance compartments, and the particles are presumed to be converted from their original particulate state to some other physicochemical form or transformed state prior to clearance from the respiratory tract. Such a transformed state can be used to describe, for example, the behavior of hydrolytic aerosols in the respiratory tract.

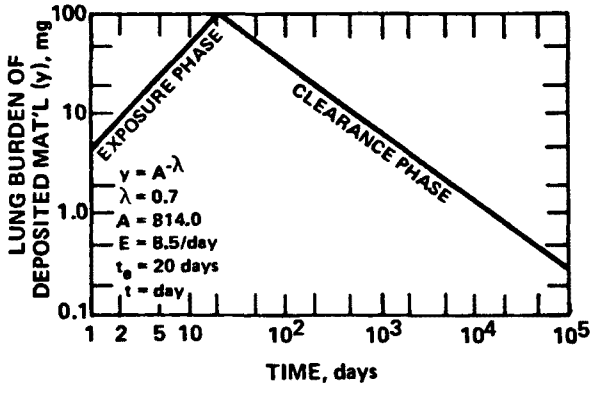

Figure 11-14. Example of the use of the power function model for describing lung uptake during inhalation exposure (text Equation 12) and retention (clearance phase) after exposure ends (text Equation 13) for a 20-day exposure at 8.5 mg/d (E).

Source: Adapted from Raabe (1967).

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To illustrate the potential complexity of models, a systemic metabolism model is shown in Figure 11-15 for cerium trichloride ($^{144}CeCl_3$) contained in particles of cesium chloride (CsCl) with a $MMAD_{ar}$ of about 2 μm (Boecker and Cuddihy, 1974). The resultant pattern of combined uptake and retention in various organs after inhalation exposure is illustrated in Figure 11-16. In this case, the exposure is short-term; the fate of relatively insoluble materials in chronically inhaled environmental aerosols may involve more complex relationships.

11.3.2 Absorbed SO_2

SO_2 coming in contact with the fluids lining the airways (pH 7.4) should dissolve into the aqueous fluid and form some bisulfite (HSO_3^-) and considerable sulfite (SO_3^{2-}) anions. Because of the chemical reactivity of these anions, various reactions are possible, leading to the oxidation of sulfite to sulfate (see Section 12.2.1).

Clearance of sulfite from the respiratory tract may involve several intermediate chemical reactions and transformations (see Section 12.2.1.2). Gunnison and Denton (1971) have identified S-sulfonate in blood as a reaction product of inhaled SO_2. The reaction rate is rapid, if not nearly instantaneous, so that there is no long-term clearance to characterize. However, intermediate and potentially toxic products may be formed. These products may have residence times that are long enough to demonstrate an elevation of the sulfur content of the lung.

Desorption from the upper respiratory tract may be expected whenever the partial pressure of SO_2 on mucosal surfaces exceeds that of the air flowing by. Desorption of SO_2 from mucosal surfaces was still evident after 30 minutes of flushing with ambient air the airways of dogs which had breathed 2.62 mg/m^3 (1.0 ppm) for 5 min. (Frank et al., 1969). Frank et al. (1967) reported SO_2 in the lungs of dogs that apparently was carried by the blood after nasal deposition. In human subjects breathing 42.2 mg/m^3 (16.1 ppm) through a mask for 30 minutes, 12% of the SO_2 taken up by the tissues in inspiration reentered the air stream in expiration and another 3% was desorbed during the first 15 minutes after the end of SO_2 exposure (Speizer and Frank, 1966). Thus, during expiration, SO_2 was desorbed from the nasal mucosa in quantities totaling approximately 15% of the original inspired concentration.

The effects of SO_2 on tracheobronchial clearance in 9 healthy, nonsmoking adults were studied by Wolff et al. (1975) (see Section 13.2.3.5). Technetium Tc 99m albumin aerosol (3 μm MMAD, σ_g = 1.6) was inhaled as a bolus under controlled conditions. A three hour exposure to 13.1 mg SO_2/m^3 (5.0 ppm) had no significant effect on mucociliary clearance in resting subjects, except for a small transient increase ($p < 0.05$) after 1 hour. A significant decrease in nasal mucus flow rates during a six hour exposure of 15 young men to 13.1 mg SO_2/m^3 (5.0 ppm) and 65.5 mg SO_2/m^3 (25.0 ppm), but not 2.62 mg SO_2/m^3 (1.0 ppm), was observed by Andersen et al. (1974). Decreases were greatest in the anterior nose and in subjects with initially slow mucus flow rates. Newhouse et al. (1978) assessed the effect of oral exposure to SO_2 on bronchial clearance of a radioactive aerosol (3 μm MMAD) in healthy nonsmoking males and

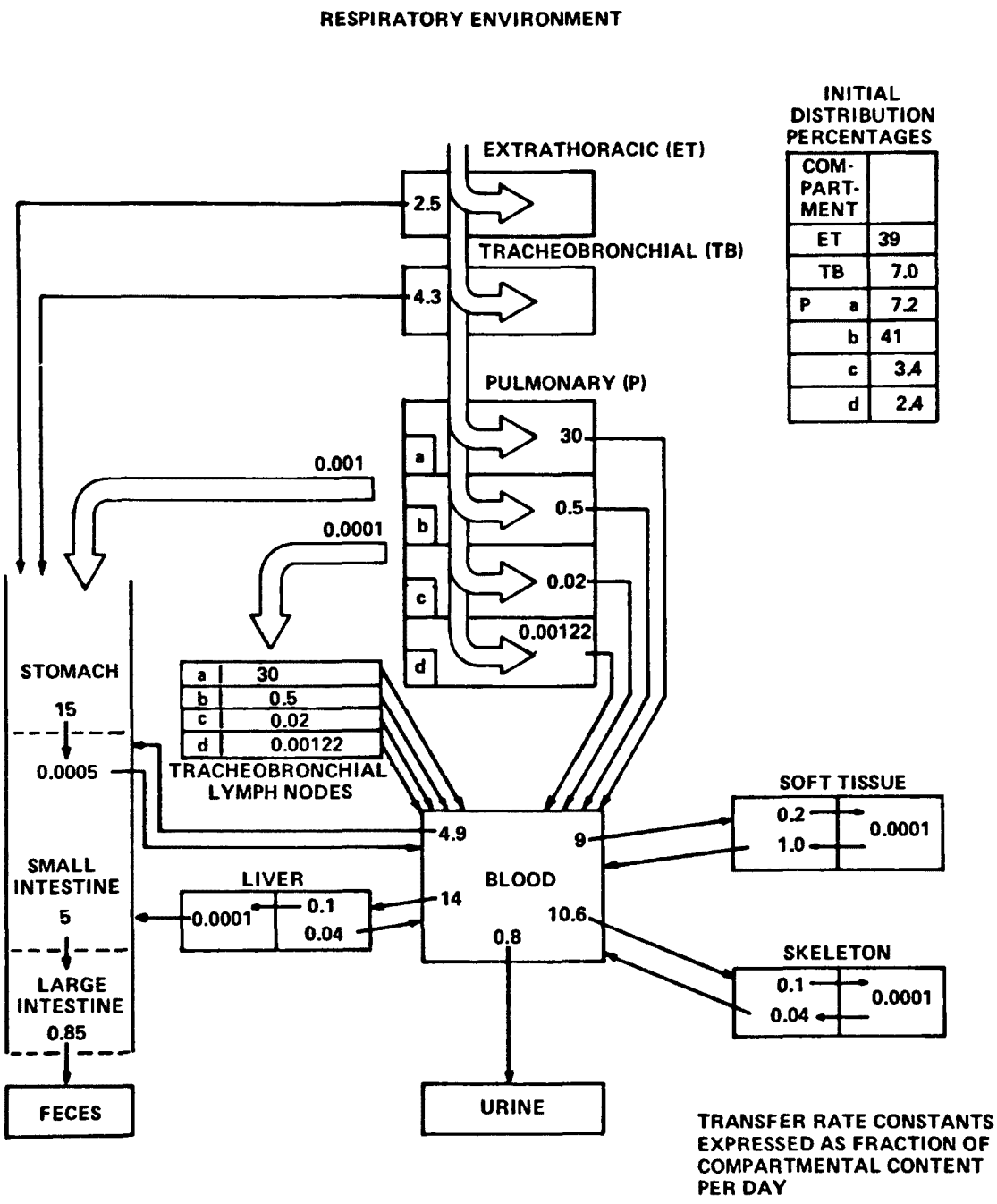

Figure 11-15. Multicomponent model of the deposition, clearance, retention, translocation and excretion of an example sparingly soluble metallic compound ($^{144}CeCl_3$ continued in CsCl particles) inhaled by man or experimental animals; the rate constants are based upon first order kinetics as in text Equation 8.

Source: Adapted from Boecker and Cuddihy (1974).

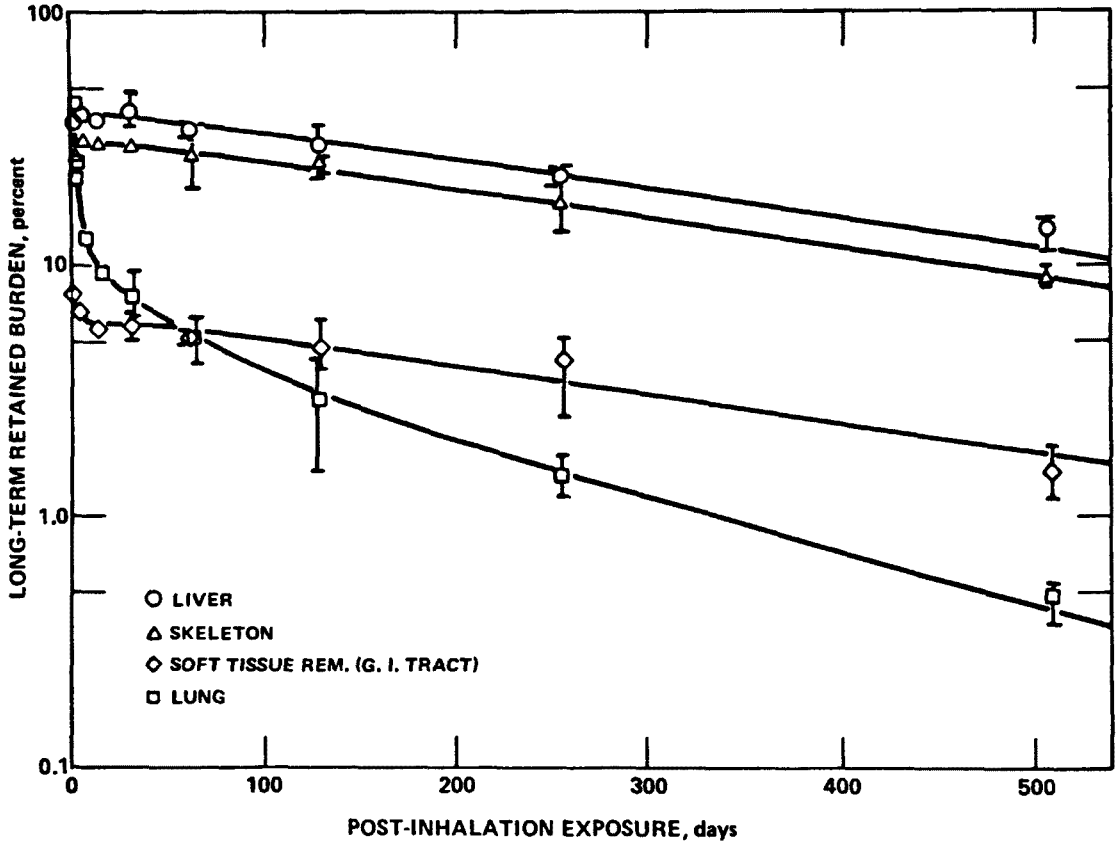

Figure 11-16. Example of the organ retention of an inhaled, sparingly soluble metallic compound assuming a single acute exposure demonstrating the translocation from lung and build-up and clearance from other organs.

Source: Boecker and Cuddihy (1974).

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females who exercised periodically during exposure at an exertion level sufficient to keep the heart rate at 70% - 75% of the predicted maximum. After a 2 hour exposure to 13.1 mg SO_2/m^3 (5.0 ppm), clearance was increased.

11.3.3 Particles and SO_2 Mixtures

The presence of adsorbed SO_2 or other sulfur compounds on aerosol surfaces may alter the clearance processes of both. Chemical reactions involving sulfur compounds on particle surfaces may enhance the apparent solubility of the aerosol particles. These aerosol particles may also undergo reaction with sulfite or other species upon contact with body fluids.

The formation of sulfate anions by oxidation of SO_2 to SO_3 may be catalyzed by manganese, iron, or other aerosol components. The SO_3 reacts immediately with water to form sulfuric acid that can react with other materials, such as metal oxides on fly ash aerosols, to produce sulfate compounds. Since sulfate is a normal constituent of body fluids (Kanapilly, 1977), the clearance of sulfate anions probably involves simple dissolution into body fluids.

11.4 AIR SAMPLING FOR HEALTH ASSESSMENT

The objective of air sampling in relation to health assessment is to obtain data on the nature and extent of potential health hazards resulting from the inhalation of airborne particles. To be effective the techniques used in air samplers must be based on a recognition of the size-selecting characteristics of the human respiratory tract (see Section 11.2). Of course the usual variables affecting the selection of methods, such as the physical limitations of the collection process and sensitivity and specificity properties of the analytical procedures, must still be addressed.

An increasing recognition of the importance of the selective sampling of "respirable" dusts has occurred in recent years. The commonly measured index of gross air concentration provides a crude and sometimes misleading indication of health hazard. Since most aerosols are polydisperse, with a σ_g >2, the mass median size approaches the diameter of the largest particles in the sample, resulting in a relatively few large particles strongly influencing the value reported for the mass concentration. The measured total mass concentration then will not relate to the inhalation hazard if these particles are not inhaled. Also, the true total airborne mass concentration may be underestimated when the aerosol contains very large particles since every sampler has its own characteristic upper size cut-off. This cut-off is dependent on its entry shape, dimensions and flowrate.

The best dose estimates for a substance whose toxicity is proportional to absorbed mass are obtained from information on the mass concentrations within various size ranges. Lippmann (1978) cites several ways such data can be obtained: (1) during the process of collection separate the aerosol into size fractions which correspond to anticipated regional deposition; (2) analyze the size distribution of the airborne aerosol; and (3) analyze the size distribution of the collected sample. The most reliable and useful information is obtained using methods of fractionation based upon aerodynamic diameters similar to the way fractionation occurs within the respiratory tract, thereby automatically compensating for differences in particle shape and density.

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There have been many recent advances in the technologies needed to develop samples that will separate particles during the process of collection into "respirable" and "nonrespirable" fractions. The absence of uniform criteria for "respirable" mass concentrations has been a major factor limiting the application of selective sampling concepts in the United States. Regulations established on the basis of only gross concentration limits do not promote field measurements of "respirable" mass.

The recommendations by Miller et al. (1979) on size considerations for establishing a standard for "inhalable" particles indicate a possible future departure from the current approach to the setting of a particulate standard in the United States. Also, the recent report on respirable dust by the International Standards Organization ad hoc Group to TC 146 (1980) contains recommendations for size definitions for particle sampling for the healthy normal segment of the population and high risk subpopulations. A perspective on these recent events can be obtained by examining the development of the field of respirable dust sampling.

In 1952, the British Medical Research Council (BMRC) adopted a definition of "respirable dust" which essentially considered respirable dust to be that dust reaching the alveoli, 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 cut-off was chosen to result in the best agreement with experimental lung deposition data. The Johannesburgh International Conference on Pneumoconiosis in 1959 adopted the same standard (Orenstein, 1960).

In January 1961 at a meeting in Los Alamos sponsored by the Atomic Energy Commistion (AEC) Office of Health and Safety a second standard was established, which defined "Respirable Dust" as that portion of the inhaled dust which penetrates to the non-ciliated portions of the lung (Hatch and Gross, 1964). This definition was not intended to be applicable to dusts which are readily soluble in body fluids or are primarily chemical intoxicants, but rather only for "insoluble" particles which exhibit prolonged retention in the lung. Criterion for respirability were such that all 2 μm D_{ae} particles were considered respirable, while particles 10 μm D_{ae} were considered to be nonrespirable.

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

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The sampler acceptance criteria of the BMRC and of the ACGIH and the pulmonary deposition curves from Figure 11-9 are shown in Figure 11-17. The cut-off characteristics of the pre-collectors 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. Recall that 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 AEC curve was designed mainly after 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 σ_g >2 μm, 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; Maguire and Barker, 1969; Lynch, 1970; Coenen, 1971; Moss and Ettinger, 1970).

The various definitions of respirable dust are somewhat arbitrary, with the BMRC and AEC definitions being based upon the "insoluble" particles which reach the pulmonary region. Since part of the aerosol which penetrates to the alveoli remains suspended in the exhaled air, respirable dust samples are not intended to be a measure of pulmonary deposition but only a measure of aerosol concentration for particles that are the primary candidates for pulmonary 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, multi-stage aerosol sampler data can provide estimates of the "respirable" fraction and deposition in other functional regions. Field sampling application of these samplers has been limited due to 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, have been reviewed by Lippmann (1978).

Size definitions for particle sampling which expand the area of concern beyond just "insoluble" dust penetrating to the pulmonary region have recently been advanced (Miller et al., 1979; International Standards Organization ad hoc Group to TC 146, 1980). As our knowledge of the regional deposition of particles increases through experimental studies, such as those discussed in Section 11.2, it is logical to envisage using samplers which broadly simulate the relative collection efficiencies of the major regions of the respiratory tract. These devices would first select from the total airborne material the inspirable fraction, and then sequentially divide this fraction into extrathoracic (nasopharyngeal), tracheobronchial, and pulmonary fractions.

Such a scheme has been recommended by the International Standards Organization ad hoc Group to TC 146 (1980) with various options depending upon the at risk population (healthy adults, children, sick and infirm) and upon the use of 10 μm D_{ae} or 15 μm D_{ae} as the 50 percent

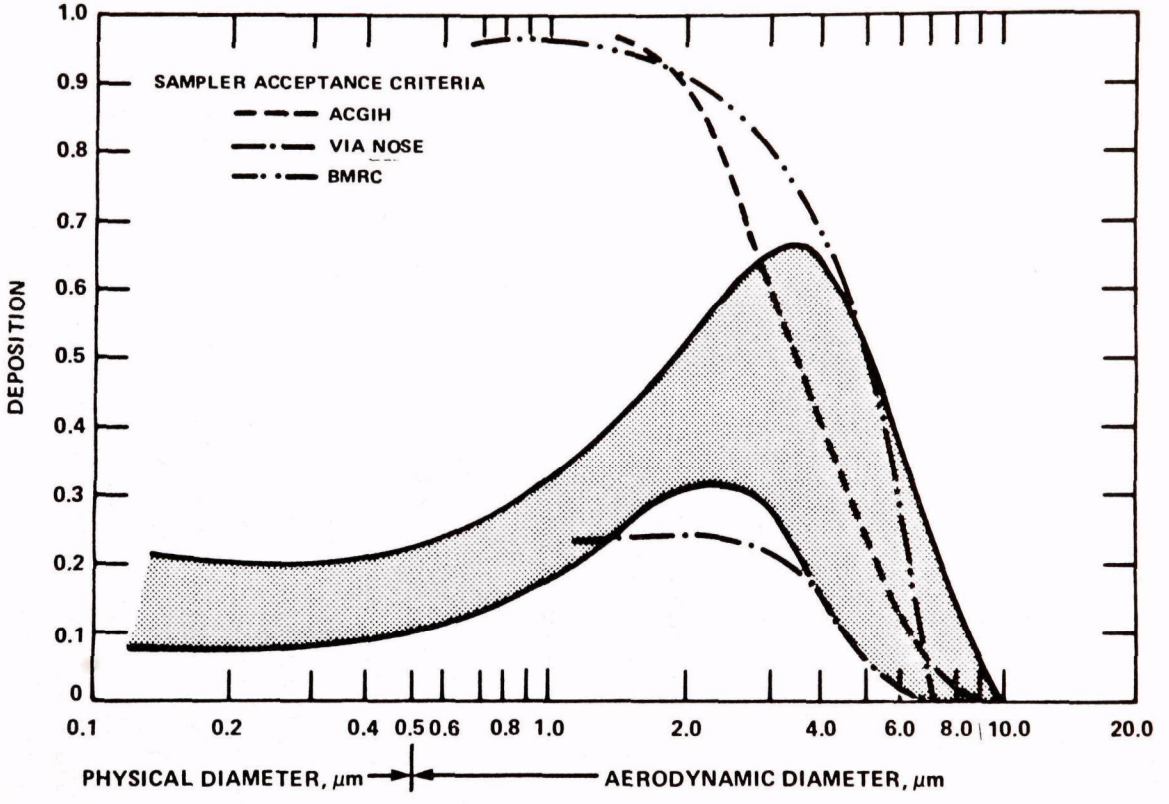

Figure 11-17. Comparison of sampler acceptance curves of BMRC and ACGIH conventions with the band for the experimental pulmonary deposition data of Figure 11-9.

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cut-point for material penetrating to the tracheobronchial region. Their division of the thoracic fraction into the pulmonary and tracheobronchial fractions, where the target population is healthy adults, is shown in Figure 11-18 using 15 μm D_{ae} as the 50 percent cut-point for the total thoracic fraction. The 50 percent cut-point refers to the aerodynamic diameter for which 50 percent of the particles that enter the mouth or nose are considered to pass the larynx. Thus, the material not passing the larynx forms the extrathoracic fraction, which includes the oral pharynx. Particles larger than 15 μm D_{ae} can enter and be deposited in the extrathoracic region. If any of these larger particles are readily soluble, they will be absorbed into the bloodstream just as quickly as smaller particles, with one 20 μm D_{ae} particle contributing as much to the systemic dose as a thousand 2 μm D_{ae} particles.

Also shown in the figure are the experimentally based pulmonary deposition curves from Figure 11-9 and the tracheobronchial deposition data from one of the subjects studied by Stahlhofen and coworkers (1980). The ad hoc group basically followed the BMRC and ACGIH conventions for pulmonary deposition in healthy adults, although their definition of the pulmonary fraction differs slightly because it is defined as a fraction of the inspirable material rather than the total aerosol. A "high-risk" selection curve for children or the sick and infirm used a 50 percent cut-point at 2.5 μm D_{ae} instead of 3.5 μm D_{ae} in recognition of the fact that a similar shift is seen in lung deposition in these groups (Lippmann, 1977); this strategy is surprising since a conservative approach for protection of these subpopulations would not lower the cut-point. Taken to its ultimate, by using size selective samplers that separate inspirable material into extrathoracic or nasopharyngeal, tracheobronchial, and pulmonary components, standards for airborne particles could specify which of these regional fractions should be measured, taking into account the biological effects of the material, and in the case of the tracheobronchial and pulmonary fractions, the population at risk.

11.5 SUMMARY

Besides being a target of inhaled particles and gases, the respiratory tract is also the portal of entry by which other organs may be affected. An understanding of the mechanisms and patterns of translocation to other organ systems is required for evaluation of the potential for injury or response in those organs. When aerosols or SO_2 are inhaled by man or experimental animals, different fractions of the inhaled materials deposit by a variety of mechanisms in various locations in the respiratory tract. Particle size distribution, particle chemical properties, physicochemical properties of SO_2, respiratory tract anatomy, and airflow patterns all influence the deposition. The three functional regions (extrathoracic or nasopharyngeal, tracheobronchial, and pulmonary) of the respiratory tract can each be characterized by major mechanisms of deposition and clearance.

Of the five mechanisms of deposition, impaction, gravitational settling, and diffusion predominate for the deposition of most types of particles in the respiratory tract, with electrostatic attraction and interception being of relatively minor importance. Diffusivity and interception potential of a particle depend on its geometrical size, while the inertial

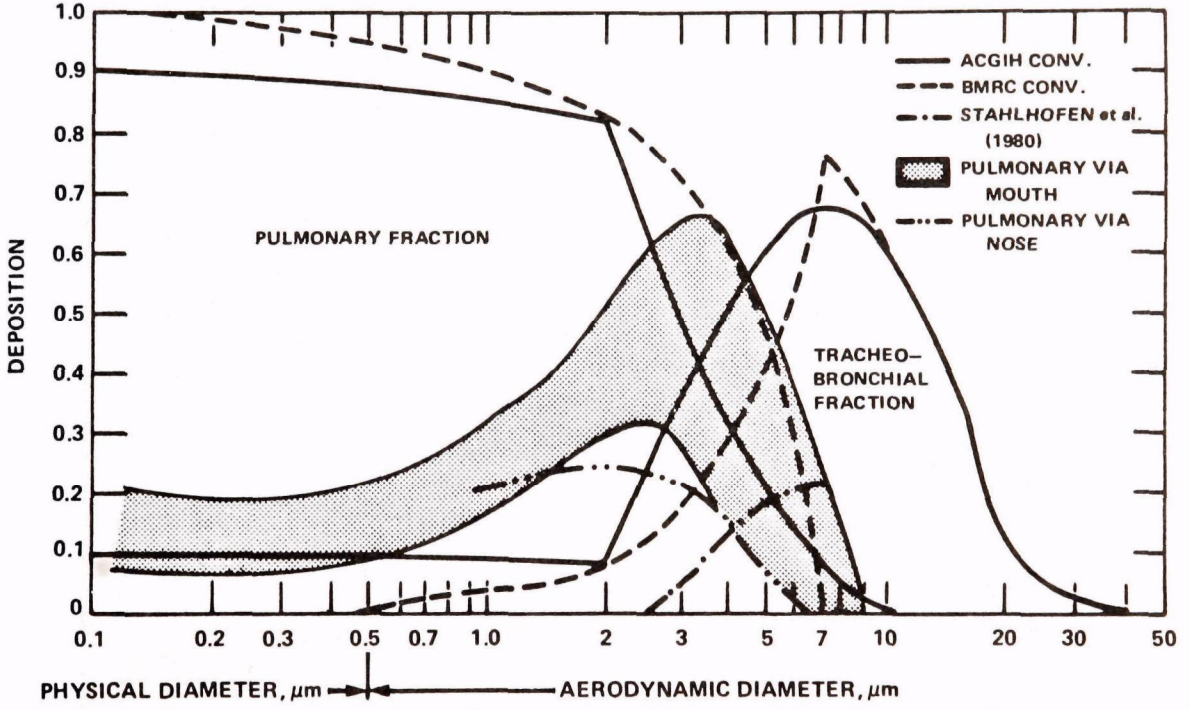

Figure 11-18. Division of the thoracic fraction into the pulmonary and tracheobronchial fractions for two sampling conventions (ACGIH and BMRC) as a function of aerodynamic diameter except below 0.5 μm where deposition is plotted vs. physical diameter, from International Standard Organization ad hoc group to TC-146, 1980. Also shown are the band for experimental pulmonary deposition data of Figure 11-9 and the tracheobronchial deposition data of one subject from Stahlhofen et al. (1980).

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properties of settling and impaction depend on its aerodynamic diameter. Gravitational settling is important for the deposition of particles in the tracheobronchial and pulmonary regions, while impaction contributes to deposition in the extrathoracic and tracheobronchial regions. Diffusion primarily affects respiratory tract deposition of particles with physical diameters smaller than 1 μm. The major processes affecting the transport of SO_2 in the respiratory tract are convection, diffusion, and chemical reactions. The rapid diffusivity of SO_2 in combination with its high solubility in body fluids is responsible for the large removal of SO_2 in the extrathoracic region and upper generations of the tracheobronchial tree.

After deposition, inhaled particles will be translocated by processes that depend on their character and site of deposition. The anterior third of the human nose does not clear except by blowing, wiping, sneezing, or other extrinsic means, and particles may not be removed until one or more days after deposition. If the particles are quite soluble in body fluids, they will readily enter the bloodstream. Relatively insoluble material that lands on ciliated epithelium, either in the extrathoracic region or tracheobronchial airways, will be translocated with mucus flow to the throat and will be swallowed or expectorated. Depending on particle size, relatively insoluble material that deposits on nonciliated surfaces in the pulmonary region may be phagocytized, may enter the interstitium and remain in the lung for an extended period, or may be translocated by phagocytic cells, blood, or lymphatic drainage. Some material from the pulmonary region may enter the tracheobronchial region and be cleared by the mucociliary conveyor. Dissolution can contribute to the clearance of particles in all regions of the respiratory tract.

Nose breathing and mouth breathing provide somewhat contrasting deposition patterns for some respiratory tract regions. With nose breathing nearly complete respiratory tract deposition can be expected for particles larger than about 4 μm D_{ae}. Since mouth breathing bypasses much of the filtration capabilities of the extrathoracic region, there is a shift upward to about 10 μm D_{ae} before there is complete deposition of inhaled particles. However, given the three general regions into which the respiratory tract can be divided on the basis of anatomical structure, function, particle retention times, and clearance pathways, regional deposition data for particles of various aerodynamic diameters are more useful than total respiratory tract deposition information.

Particles about 10 μm D_{ae} or larger are deposited in the extrathoracic region during nose breathing as compared to about 65 percent deposition of 10 μm D_{ae} particles under conditions of mouth breathing. On the other hand, for both routes of breathing, extrathoracic deposition of particles smaller than about 1 μm D_{ae} is slight. The increased penetration of larger particles deeper into the respiratory tract when a person breathes through the mouth is reflected by experimental deposition data showing that tracheobronchial deposition of 8-10 μm D_{ae} particles is on the order of 20-30 percent. Also, about 10 percent of particles as large as 15 μm D_{ae} are predicted to enter the tracheobronchial region during mouth breathing.

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For nose breathing, as compared to mouth breathing, the peak of the pulmonary deposition curve shifts downward from 3.5 μm D_{ae} to about 2.5 μm D_{ae}. Also, the peak is much less pronounced (about 25 percent compared to about 50 percent for mouth breathing) with a nearly constant pulmonary deposition of about 20 percent for all sizes between 0.1 μm and 4 μm D_{ae}.

It should be stressed that the deposition data cited above are based upon studies in which usually young healthy adult subjects were used. Although children are usually considered to be a subpopulation more susceptible to the effects of environmental pollutants, deposition data for children are not currently available, nor likely to be soon obtained. What little data is available on other subpopulations, such as asthmatics and chronic bronchitics, indicates that tracheobronchial deposition appears to be enhanced at the expense of pulmonary deposition in most abnormal states. Partial or complete airway obstruction in bronchitis, lung cancer, emphysema, fibrosis, and atelectasis may decrease or eliminate the deposition of particles in some regions of the lungs.

Regional deposition studies of particles less than 3 μm D_{ae} have been conducted using dogs and some rodents. In these species, the relative distribution among the respiratory regions of particles less than 3μm D_{ae} during nose breathing follows a pattern that is similar to regional deposition in man during nose breathing. Thus, in this instance, the use of rodents or dogs in toxicological research for extrapolation to humans entails differences in regional deposition of insoluble particles less than 3μm D_{ae} that can be reconciled from available data.

When breathing through the nose under resting conditions, SO_2 removal by nasal absorption is nearly complete in both man and laboratory animals. Expired air acquires SO_2 from nasal mucosa with small amounts of SO_2 continuing to be released after cessation of exposure. Extraction of SO_2 by the total respiratory tract during mouth breathing is significantly lower than during nose breathing, although regional uptake has not been studied in man during mouth or oronasal breathing. However, studies in which SO_2 was passed through the surgically isolated extrathoracic (nasopharyngeal) airways of dogs showed that SO_2 absorption in the extrathoracic region can be decreased to less than 50 percent by mouth breathing at elevated airflow rates. Sulfur dioxide may also enter into a variety of gas-to-particle conversions or gas-particle chemical reactions. As a consequence of these reactions with particles, SO_2 can be carried deeper into the respiratory tract, thereby increasing the potential for adverse effects.

Both deposition and retention play roles in determining the effects of inhaled particulate toxicants and SO_2. Everyone is environmentally exposed to a variety of dusts, fumes, sprays, mists, smoke, photochemical particles, and combustion aerosols, as well as SO_2 and other potentially toxic gases. The particle size distribution and chemical and physical composition of airborne particulate material require special attention in toxicological evaluations since a wide variety of physicochemical properties may be encountered in both experimental and ambient inhalation exposures. The need to characterize the aerosols to which individuals are exposed so that potential health hazards can be identified requires the development

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of appropriate air sampling techniques. For insoluble dusts whose site of action is the pulmonary region, inhalation hazard evaluations based on "respirable" mass are clearly superior to estimates based on gross air concentrations. Appropriate selective sampling procedures can and are being developed to provide more meaningful data on inhalation hazard potential for particles as a function of their regional deposition in the respiratory tract. Gross concentration sampling techniques are appropriate for highly soluble aerosols or where the particle size distribution is relatively constant. They can also be used if the particle size distribution is relatively constant and there is a known fixed ratio between the gross concentration and the concentration in the size range of interest.

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12. TOXICOLOGICAL STUDIES

12.1 INTRODUCTION

This chapter describes the toxicity of sulfur oxides and particulate matter in animals. The health effects of sulfur oxides and particles have also been reviewed recently by the National Academy of Sciences (Committee on Sulfur Oxides, 1978; National Academy of Sciences, Airborne Particles, 1979). The toxic effects of sulfur oxides and of atmospheric aerosols overlap because major components of atmospheric aerosols are salts of sulfuric acid (ammonium sulfate, sodium sulfate, and related compounds) (see Chapters 3 and 5). The toxicology of all forms of sulfur oxides must be considered as a whole. For example, in the ambient air, sulfur dioxide (SO_2) may interact with aerosols, may be absorbed on particles, or may be dissolved in liquid aerosols. To a lesser degree, similar interactions may occur in the air within the respiratory tract. Sulfuric acid aerosols may react with ammonia forming ammonium sulfate [$(NH_4)_2SO_4$] and ammonium bisulfate (NH_4HSO_4) in the ambient air, in the animal exposure chamber atmosphere before inhalation, or, to a lesser degree, in the respiratory tract simultaneously upon inhalation (see Section 12.3). Biological interaction can also occur, resulting in a situation where the effect of a mixture of pollutants has additive, synergistic, or antagonistic health effects compared to the effects of the single pollutants.

At the present time, it is clear that the major toxic effects of sulfur oxides are on the respiratory tract. Discussions of the deposition and clearance of sulfur oxides are limited here; the reader, therefore, should be familiar with the content of Chapter 11 which covers this subject in detail. The toxic effects of sulfur oxides, whether induced by SO_2, H_2SO_4, or sulfate salts, include immediate irritation of the respiratory tract. Most measurements of this irritation have been through studies of the respiratory mechanics of the experimental animal. Similar studies of respiratory mechanics have been undertaken with human subjects experimentally or environmentally exposed. The general effects of SO_2 on the respiratory mechanics of animals and man are the same. The animal studies reviewed here present some details of the metabolism of SO_2 and bisulfite, the effects of SO_2 on the biochemistry, physiology and morphology of the respiratory tract, and the potential effects on organs other than the lung.

A major problem area is the diversity of particulate matter in the atmosphere. Any organic compound whose local concentration exceeds its vapor pressure will condense and occur in the particulate fraction when sampled. Some may be sorbed on the surfaces of inorganic particles. Inorganic particles can be of a wide chemical variety. Unfortunately, our knowledge of the exact chemical nature and health effects of these materials is incomplete. Progress is being made toward a better understanding of the toxicity of these materials associated with particles, but at present inadequate data are available. There is no theoretical or practical reason why these data should not be attainable; rather, the present deficiency represents the sophistication of our knowledge. A more complete treatment of the health effects of

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polycyclic organic matter is found in a recent review (Environmental Criteria and Assessment Office, 1978). Overviews are provided for some of the heavy metals present in polluted air. More detail is found in documents dealing specifically with each heavy metal (Environmental Criteria and Assessment Office, 1979; Office of Research and Development, 1977; Committee on Biologic Effects of Atmospheric Pollutants, Vanadium, 1974; Committee on Medical and Biologic Effects of Environmental Pollutants, Nickel, 1975; Committee on Biologic Effects of Atmospheric Pollutants, Lead, 1972; Committee on Biologic Effects of Atmospheric Pollutants, Chromium, 1974; Committee on Medical and Biologic Effects of Environmental Pollutants, Arsenic, 1977; National Academy of Sciences, Iron, 1979; National Academy of Sciences, Zinc, 1979). This chapter deals primarily with sulfur oxide-derived aerosols, sulfuric acid, sulfate salts, and related compounds. It is not intended to represent all of the health effects associated with the complex mixture of materials present in atmospheric aerosols. The reader should supplement his knowledge through reference to the additional documents cited above.

Interactions between sulfur oxides and other pollutants are reviewed briefly because of the sparsity of the data available. Some of these studies are controversial and have not been duplicated. Especially controversial are those studies dealing with the potential mutagenic effects of SO_2 and the interaction of SO_2 and H_2SO_4 with known carcinogens.

Another difficulty with a current review of the toxicology of sulfur oxides is the sparsity of recent studies. A hiatus occurred approximately 10 years ago with few studies appearing subsequently. Work in progress is not included. As a consequence a certain degree of sophistication is lacking in some of the intrepretations, not through a lack of appreciation of the problem, but simply because insufficient information is available.

12.2 EFFECTS OF SULFUR DIOXIDE

12.2.1 Biochemistry of Sulfur Dioxide

Much of the discussion under Section 12.2.1 relates to *in vitro* experiments. *In vitro* studies are those in which the potential target (i.e., cells, enzymes, other molecules, etc.) is exposed to the toxicant outside the body. In such a system, some homeostatic or repair mechanisms are absent. In some cases, pollutants act by indirect mechanisms. For example, the pollutant affects target A which in turn alters target B. Thus, if only target B were present, the effect would not be observed. In addition, the dosimetric relationships of *in vitro* studies to *in vivo* studies are not defined. Therefore, effective concentrations cannot be extrapolated directly from *in vitro* to *in vivo* studies. For the above reasons, there is some controversy as to whether observed *in vitro* reactions can be extrapolated to *in vivo* mechanisms of toxicity. Nonetheless, sound *in vitro* investigations can show whether a given pollutant has the potential of affecting a given target. *In vitro* studies are best used to provide guidance for *in vivo* investigations or when *in vivo* results have been observed. In the latter case, the relatively simplified *in vitro* system can sometimes elucidate the potential mechanisms of toxicity. To these ends, they can be useful.

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Knowledge of the chemistry of sulfurous acid and SO_2 is necessary to understand the physiological and toxicological properties of SO_2. Sulfur dioxide is the gaseous anhydride of sulfurous acid. It dissolves readily in water; and at physiological pH near neutrality, hydrated SO_2 readily dissociates to form bisulfite and sulfite ions as illustrated by Equations 12-1 and 12-2. The rate of hydration of SO_2 is very rapid; the rate constant of hydration, k_1, is $3.4 \times 10^6\ M^{-1}\ sec^{-1}$, and the rate constant of the reverse reaction is $2 \times 10^8\ M^{-1}\ sec^{-1}$ at 20°C (Equation 12-1) (Tartar and Garetson, 1941). The dissociation constants of sulfurous acid are 1.37 and 6.25 (in dilute salt solutions) (Tartar and Garetson, 1941), so at pH 7.4 sulfite ions are present at about 14 times those of bisulfite, but in rapid equilibrium. Hence, SO_2 can be treated as bisulfite/sulfite and conversely.

$$SO_2 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} H_2SO_3 \qquad 12\text{-}1$$

$$H_2SO_3 \overset{pK_a = 1.37}{\rightleftharpoons} H^+ + HSO_3^- \overset{pK_a = 6.25}{\rightleftharpoons} H^+ + SO^{=}_3 \qquad 12\text{-}2$$

Sulfur dioxide reacts readily with all major classes of biomolecules. Reactions of SO_2 or bisulfite with nucleic acids, proteins, lipids, and other biological components have been repeatedly demonstrated *in vitro*.

12.2.1.1 Chemical Reactions of Bisulfite with Biological Molecules--There are three important reactions of bisulfite with biological molecules: sulfonation, autooxidation, and addition to cytosine.

Sulfonation (Gilbert, 1965) results from the nucleophilic attack of bisulfite on disulfides:

$$RSSR' + HSO_3^- \rightleftharpoons RSSO_3^- + R'SH \qquad 12\text{-}3$$

This reaction is also known as sulfitolysis. The products of the reaction are S-sulfonates ($RSSO_3^-$) and thiols (R'SH). Direct evidence for the formation of plasma S-sulfonates *in vivo* has been found (Gunnison and Benton, 1971; Gunnison and Palmes, 1973). Any plasma protein containing a disulfide group could react to form an S-sulfonate. Small molecular weight disulfides, such as oxidized glutathione, can also be reactants. Generally, analyses of plasma S-sulfonates have been restricted to diffusable (dialyzable or small molecular weight compounds) and nondiffusable (nondialyzable or protein) S-sulfonates. The exact molecular species has not been determined, and the results of such determinations represent pools of the two groups of compounds. S-sulfonates can react with thiols, either reduced glutathione or protein thiol groups, to form sulfite and disulfide. Since this reverse reaction is facile, S-sulfonates are hypothesized as being transportable forms of bisulfite within the body. Sulfitolysis represents a mechanism of toxicity, a means of detoxification and a means of redistribution of a reactive molecule, bisulfite.

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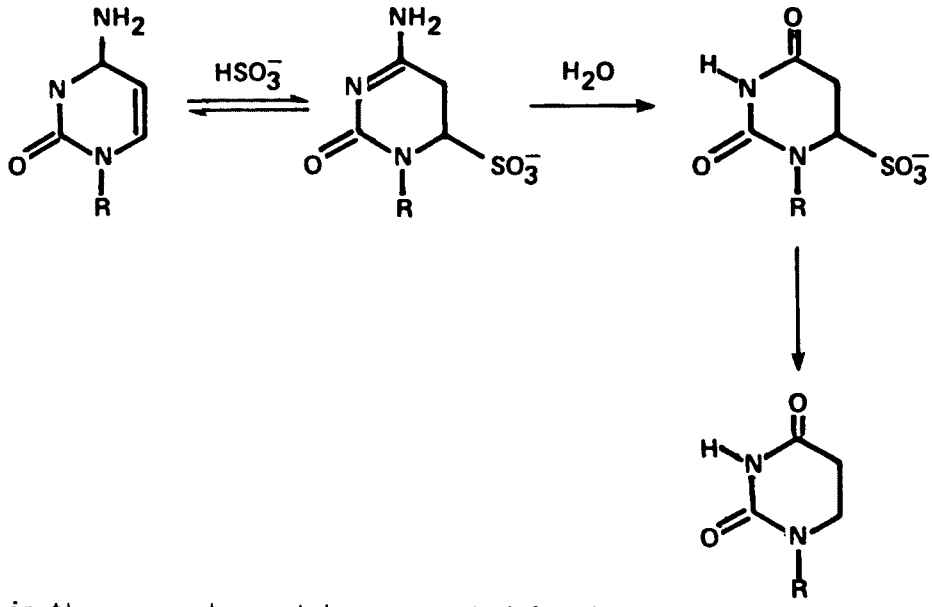
Similar reversible nucleophilic addition of bisulfite to a variety of biologically important molecules has been reported, but the toxicological importance of these chemical species is uncertain. It is not likely, for example, that the reactions of bisulfite with pyridine nucleotides (NAD or NADP), reducing sugars, or thiamine are important to the toxicity of bisulfite or SO_2.

Autooxidation of bisulfite occurs through a multistep chain reaction (Hayon et al., 1972; Backstrom, 1927; Fridovich and Handler, 1958, 1960; Asada and Kiso, 1973; Peiser and Yang, 1977; Yip and Hadley, 1966; Rotilio et al., 1970; Nakamura, 1970; Klebanoff, 1961; Yang, 1967, 1970; McCord and Fridovich, 1969a,b). These reactions may be important because they produce hydroxyl ($\cdot OH$) and superoxide ($\cdot O_2^-$) free radicals as well as singlet oxygen ($\cdot O_2$). These chemical species of oxygen are highly reactive and are also produced by ionizing radiation. Hydroxyl free radicals are theoretically responsible for the lethal effects of ionizing radiation. Autooxidation of bisulfite could lead to increased concentrations of these reactive chemical species within the cell and could hypothetically lead to similar adverse effects. The reactive forms of oxygen can also initiate peroxidation of the lipid bilayer of cells. Peroxidation of cellular lipids, especially plasma membrane lipids, is thought to be highly deleterious (Kaplan et al., 1975). No direct evidence has been presented to support peroxidation of cellular lipids as a mechanism of toxicity of SO_2.

Bisulfite addition to cytosine results in the formation of uracil. The reaction of bisulfite with nucleic acids is as follows (Shapiro and Weisgras, 1970; Shapiro et al., 1970a,b; Hayatsu, 1976):



Alteration of cytosine in the genome has not been reported *in vivo*.

Of these three reactions, sulfonation or sulfitolysis, is clearly the most important. The respiratory effects of SO_2 may be due to this reaction. Because all thiols in the respiratory tract will undergo sulfonation, no single protein or small molecular weight compound can presently be identified as the target or receptor for SO_2 in the toxic lesion.

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12.2.1.2 Metabolism of Sulfur Dioxide

12.2.1.2.1 Integrated metabolism. There are several studies of the metabolism of exogenously supplied SO_2, sulfite, or bisulfite. Quantitative differences exist between inhaled and ingested SO_2 with regard to the rate of clearance of the key intermediary in sulfite metabolism, plasma S-sulfonates (Gunnison and Palmes, 1973), but no qualitative differences exist in the metabolism of inhaled SO_2 and injected or ingested bisulfite or sulfite. The importance of the appearance of plasma S-sulfonates lies in their potential ability to serve as a circulating pool of sulfite molecules (Gunnison and Palmes, 1973) as evidenced by the presence of ^{35}S from $^{35}SO_2$ in non-pulmonary tissues such as ovaries, for example (Frank et al., 1967). Continuous inhalation of 26.2 mg/m^3 (10 ppm) SO_2 resulted in the attainment of 38 ± 15 nmole of plasma S-sulfonates/ml in rabbits after about 4 days (Gunnison and Palmes, 1973). The clearance of plasma S-sulfonates generated by either inhalation of SO_2 or ingestion of sulfite in the drinking water was exponential, exhibiting only a single compartment in most rabbits. The half-life was 4.1 days for S-sulfonates generated by inhalation vs. 1.3 days for those generated by ingestion (Gunnison and Palmes, 1973). The mechanism for this quantitative difference in clearance rates has not yet been found.

Inhaled SO_2 quickly penetrates the nasal mucosa and airways as shown by the rapid appearance of ^{35}S in the venous blood of dogs inhaling $^{35}SO_2$ (Yokoyama et al., 1971). A significant fraction of the blood ^{35}S was probably in the form of plasma S-sulfonates ($RSSO_3^-$). Most of the inhaled SO_2 is presumed to be detoxified by the sulfite oxidase pathway in the liver, forming sulfate which is excreted in the urine. The dominance of this reaction has been supported by studies of sulfite oxidase inhibition (Cohen, et al. 1972) which are discussed below and by the appearance of about 85 percent of the inhaled $^{35}SO_2$ as urinary sulfate in dogs (Yokoyama et al., 1971). Once oxidized by sulfite oxidase, most of the inhaled ^{35}S derived from $^{35}SO_2$ appears in the urine as ^{35}S-sulfate (Yokoyama et al., 1971). A small fraction (10 to 15 percent) of the urinary ^{35}S was in the form of sulfuric acid esters and ethers (Yokoyama, et al., 1971). Sulfate arising from the oxidation of sulfite can enter the sulfate pool and could be incorporated into sulfate macromolecules including glycosaminoglycans and glycoproteins. These macromolecules are actively synthesized by the respiratory mucosa and could account for the presence of radiolabeled sulfur in the respiratory tract following inhalation of $^{35}SO_2$ (Yokoyama et al., 1971). Most of the nondialyzable ^{35}S detected by Yokoyama et al. (1971) was bound to the α-globulin fraction of plasma. The chemical form of the ^{35}S was not determined. Yokoyama et al. (1971) speculated that the ^{35}S present in the α-globulin fraction was in the form of sulfonated carbohydrates. The problem is in need of further clarification. According to Gunnison and Palmes (1973), plasma S-sulfonated proteins may also have contained the ^{35}S. They have suggested that the slow clearance of plasma S-sulfonates is an important factor in determining toxicity. They have not reported, however, intracellular levels of S-sulfonates or sulfite.

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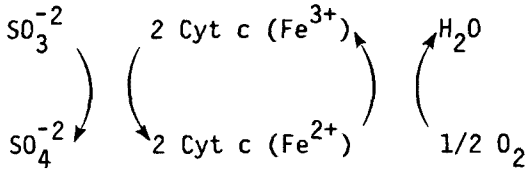
12.2.1.2.2 Sulfite oxidase. The biochemistry of sulfite oxidase will be discussed because of its importance as a mechanism of detoxification of sulfite. A very rare genetic deficiency of sulfite oxidase occurs in humans (Mudd et al., 1967; Irreverre et al., 1967; Shih et al., 1977). Dietary factors can, however, alter the enzymatic activity (Cohen et al., 1973). Sulfite oxidase (EC 1.8.3.1) is a metallo-hemo protein with molybdenum and protoheme as the prosthetic groups (Cohen et al., 1972). It exists in animals (Cohen et al., 1972,1974; Howell and Fridovich, 1968; Cohen and Fridovich, 1971a,b; Wattiaux-DeConinck and Wattiaux, 1974), bacteria (Lyric and Suzuki, 1970), and plants (Tager and Rautanen, 1955; Arrigoni, 1959; Fromageot et al., 1960). In both plants and animals, the enzyme is located in the mitochondria. Purified sulfite oxidase can utilize either cytochrome c or oxygen as the electron acceptor (Cohen and Fridovich, 1971a). When coupled with cytochrome c to the mitochondrial respiratory chain, sulfite oxidase reduces molecular oxygen to water (Equation 12-4), whereas during oxygen reduction, the product formed is hydrogen peroxide (Equation 12-5).



12-4

$$SO_3^{-2} + H_2O + O_2 \rightarrow SO_4^{-2} + H_2O_2 \qquad 12\text{-}5$$

Direct reduction of molecular oxygen by sulfite oxidase is prevented in the presence of ferric cytochrome c. In intact mitochondria, therefore, sulfite oxidation occurs through the interaction of sulfite oxidase with the respiratory chain of the mitochondria, producing 1 mole of ATP/mole of sulfite oxidase.

Sulfite oxidase is presumed to be necessary for the detoxification of sulfite. In three reported cases in humans, a genetic defect in this enzyme resulted in severe neurological problems (Mudd et al., 1967; Irreverre et al., 1967; Shih et al., 1977). Cohen et al. (1973) suggested that sulfite oxidase is the principal mechanism for detoxifying bisulfite and SO_2. This is supported by a study which showed that dogs exposed to $^{35}SO_2$ (Yokoyama et al., 1971) excreted 80 to 90 percent of the inhaled ^{35}S as sulfate in the urine. Because sulfite oxidase requires molybdenum, Cohen et al. (1973) were able to deplete rats of sulfite oxidase by feeding them a low molybdenum diet and treating them with 100 ppm of sodium tungstate in drinking water. Tungsten competes with molybdenum and essentially abolishes the activity of sulfite oxidase and xanthine oxidase (EC 1.2.3.2), the two major molybdo-proteins of rat liver. Similar decreases were observed in the lung and other organs. The LD50 for interperitoneally injected bisulfite was found to be 181 mg $NaHSO_3$/kg in the sulfite oxidase deficient rats compared to 473 mg/kg in the nondeficient animals.

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The effect of inhaled SO_2 on lethality was more complex (Cohen et al., 1973). High levels were used in all cases and two effects of inhaled SO_2 were observed. At 1,546 or 2,424 mg/m^3 (590 or 925 ppm) SO_2 or less, the principal effect in control rats was respiratory insufficiency resulting in death by asphyxiation. At 6,157 mg/m^3 (2,350 ppm) SO_2 or greater (up to 1.3×10^6 mg/m^3, 1,310,000 ppm), the principal effect appeared to be mediated by the central nervous system (CNS) resulting in seizures and prostration followed by death. A direct effect of bisulfite on the CNS has been suggested (Cohen et al., 1973). Mortality was observed in both the control and tungsten-treated animals exposed to greater than 1,554 mg/m^3 (593 ppm) SO_2 for 4 hr. Cohen et al. (1973) suggest that the shorter survival times and greater mortality of the tungsten-treated rats are due to an inability to detoxify inhaled SO_2 to sulfate.

Attempts to induce higher levels of sulfite oxidase through pretreatment of the rats with SO_2/bisulfite or phenobarbital failed (Cohen et al., 1973). Since sulfite oxidase is a mitochondrial enzyme with a long half-life, it is not likely that phenobarbital or chronic exposure to SO_2 would result in adaptation through induction of higher levels of sulfite oxidase.

12.2.1.3 Activation and Inhibition of Enzymes by Bisulfite--Both inhibition and activation of specific enzymes have been reported. This may be due to formation of S-thiosulfates, since disulfide bonds often stabilize the tertiary structure of proteins. Sulfite ions activated several phosphatases including ATP-ase (Marunouchi and Mori, 1967) and 2,3-diphosphoglyceric acid phosphatase (Harkness and Roth, 1969). The mechanism by which activation occurs is not known. Inhibition of several enzymes has been reported; these include aryl sulfatase (Harkness and Roth, 1969), choline sulfatase (Takebe, 1961), rhodanase (Lyric and Suzuki, 1970), and hydroxyl amine reductase (Zucker and Nason, 1955). Malic dehydrogenase was inhibited by micromolar concentrations of bisulfite (Ki = 5 μM) (Wilson, 1968; Ziegler, 1974). Other dehydrogenases (Oshino and Chance, 1975) and flavoprotein oxidases are inhibited by bisulfite.

Bisulfite effectively inhibits a number of other enzymes including potato and rabbit muscle phosphorylase (Kamogawa and Fukui, 1973). Bisulfite inhibition was competitive with respect to glucose-1-phosphate and inorganic phosphate, suggesting that the bisulfite inhibition was caused by competition of bisulfite with the phosphate binding site of phosphorylase. Several important coenzymes (such as pyrodoxylphosphate, NAD^+, $NADP^+$, FMN, FAD, and folic acid) may react with sulfite to form addition products as discussed above. As a result, these coenzymes could theoretically aid in inhibition of a wide variety of critical enzymic reactions. Pyridine coenzyme-bisulfite adduct (Tuazon and Johnson, 1977) and flavoenzyme-bisulfite adduct (Muller and Massey, 1969; Massey et al., 1969) have been studied in detail; these adducts have been shown to be biologically inactive.

Despite all of the data obtained using in vitro systems on the inhibition of enzymes by bisulfite/SO_2, no inhibition or activation has been determined in vivo with SO_2 exposure.

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Such inhibition may occur, but there has been no concerted effort to search for inhibition of specific enzymes during SO_2 exposure.

12.2.2 Mortality

The acute lethal effects of SO_2 have been examined mostly in the older literature and have been reviewed in the previous Air Quality Criteria Document for Sulfur Oxides (National Air Pollution Control Administration, 1970). In early studies, a number of different animal species was examined for susceptibility to SO_2. These data show that mortality was not observed at exposures of 65.5 mg/m^3 (25 ppm) for up to 45 days in either rats or mice; this conclusion has been confirmed by subsequent studies (Laskin et al., 1970). Mortality could be associated with long-term exposure to SO_2 at 134 mg/m^3 (51 ppm) or higher. The clinical signs of SO_2 intoxication appear to vary with the dose rate (Cohen et al., 1973). At concentrations below approximately 1,310 mg/m^3 (500 ppm), mortality is associated with respiratory insufficiency; above this concentration, mortality is ascribed to central nervous disturbances producing seizures and paralysis of the extremities. These clinical signs depend upon the presence and activity of sulfite oxidase as discussed in Section 12.2.1.2.2. Injections of histamine or adrenalectomy can increase the lethality of SO_2 (Leong et al., 1961).

Matsumura (1970a,b) examined the effect of a 30-min exposure to several air pollutants on mortality consequent to the anaphylactic response of guinea pigs to protein antigens. Sensitization to the antigen administered by aerosol was augmented by pretreatment with 786 mg/m^3 (300 ppm) SO_2, but not with 472 mg/m^3 (180 ppm).

On the basis of mortality due to acute exposure, SO_2 is far less toxic than ozone and is similar in toxicity to nitrogen dioxide. Concentrations required to produce mortality from SO_2 are far in excess of those which occur in the atmosphere due to pollution (Table 12-1).

12.2.3 Morphological Alterations

Because of the high solubility of SO_2 in water, morphological and physiological effects occur mostly in the upper airways. However, changes have also been detected in the lower airways (Table 12-2). At relatively high concentrations of >26.2 mg/m^3 (10 ppm) (used in most studies designed to detect morphological alterations), most of the inhaled SO_2 is removed by the nasopharyngeal cavity. (See Chapter 11, Section 11.2.4 for an expanded discussion of SO_2 absorption.) In rabbits, the concentration of inspired SO_2 determines how much is removed in the nasopharyngeal cavity as opposed to the bronchial and alveolar regions of the lung (Strandberg, 1964). At high SO_2 concentrations, greater than 26.2 mg/m^3 (10 ppm), 90 to 95 percent is removed in the nasopharyngeal cavity. A small part, 3 to 5 percent, is removed by the bronchiolar-alveolar region. So in this concentration range, most of the dose is delivered to the nasal turbinates with only a small percentage going to the lung parenchyma. At lower concentrations of inspired SO_2, [such as 0.13 mg/m^3 (0.05 ppm)] which are closer to ambient levels, only 40 percent of the dose is delivered to the nasopharyngeal cavity upon inspiration, while another 40 percent is removed by the respiratory tract upon expiration.

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TABLE 12-1. LETHAL EFFECTS OF SO_2

SO_2 Concentration mg/m^3	ppm	Duration	Species	Remarks	Reference
26.2	10	6 hr/day x 5 day/wk x 113 day	Rat	No mortality in excess of control	Laskin et al., 1970
134	51	113 days		No mortality in excess of control	
275	105	22 day		64% mortality (treated-control)	
(See Text)		5 min/day x 5 day/wk > x lifetime	Mice	No increased mortality; tumor formation found	Peacock and Spence, 1967
1,598	610	LT_{50} 285.6 min	Mice (Connaught Med. Res. Lab. Strain)	IP injection of 200 to 300 mg histamine/mouse increased toxicity	Leong et al. 1961
2,392	913	74.5 min			
3,086	1,178	38.7 min			
5,175	1,975	LT_{50} 197.6 min	Rat (Sprague-Dawley)	IP injection of 200 to 300 mg histamine/rat or adrenalectomy increased toxicity	Leong et al. 1961
9,165	3,498	71.7			
13,236	5,052	41.0			
5,782	2,207	LT_{50} 68.2 min	Guinea Pig		Leong et al. 1961
6,571	2,508	28.7			
7,205	2,750	35.5			
786	300	30 min	Guinea Pig	Increased mortality due to anaphylaxis from antigen challenge to sensitized animals	Matsumura, 1970a,b,

TABLE 12-2. EFFECTS OF SULFUR DIOXIDE ON LUNG MORPHOLOGY

Concentration	Duration	Species	Results	Reference
0.34, 2.65, or 15.0 mg/m^3 (0.13, 1.01, or 5.72 ppm) SO_2	1 yr, continuous	Guinea pig	Lungs of 15.0 mg/m^3 (5.72 ppm) group, killed after 13 or 52 wk of exposure, showed less spontaneous pulmonary disease than controls. Controls and 0.34 and 2.64 mg/m^3 (0.13 and 1.01 ppm) animals had evidence of lung disease. Tracheitis present in all but 15.0 mg/m^3 (5.72 ppm) group. Survival greater in the latter group	Alarie et al., 1970
0.37, 1.7 or 3.35 mg/m^3 (0.14, 0.64 or 1.28 ppm)	78 wk, continuous	Cynomolgus monkey	No remarkable morphologic alterations in the lung	Alarie et al., 1972, 1973c
12.3 mg/m^3 (4.69 ppm) then between 524 and 2620 mg/m^3 (200-1000 ppm) then 0 mg/m^3	30 wk then 1 hr then 48 wk	Cynomolgus monkey	Persistent changes in lung morphomology including: alterations in the respiratory bronchioles, alveolar ducts, and alveolar sacs; proteinaceous material within the alveoli; thicker alveolar walls infiltrated with histocytes and leucocytes; moderate hyperplasia of the epithelium of the respiratory bronchioles; bronchiectasis and bronchiolectasis; vacuolation of hepatocytes	Alarie et al., 1972, 1973c
13.4 mg/m^3 (5.12 ppm)	18 mo, continuous	Cynomolgus monkey	No alterations in lung morphology	Alarie et al., 1975
13.4 mg/m^3 (5.1 ppm)	21 hr/day, 620 days	Dog	No alterations in lung morphology	Lewis et al., 1973
26.2 mg/m^3 (10 ppm)	72 hr, continuous	Mouse	Pathological changes in the nasal mucosa appeared after 24 hr of exposure and increased in severity after 72 hr. Mice free of upper respiratory pathogens were significantly less affected than the conventionally raised animals. Morphological alterations were qualitatively identical in both groups.	Giddens and Fairchild, 1972
91.7 mg/m^3 (35 ppm) [rose on occasion to 262 mg/m^3(100 ppm)]	1 to 6 wk	Pig	Loss of cilia in nasal cavity, disappearance of goblet cells, metaplasia of the epithelium	Martin and Willoughby, 1971
1048 mg/m^3 (400 ppm)	3 hr/day, 5 day/wk, 6 wk	Rat	Tracheal goblet cells increased in number and size. Incorporation of $^{35}SO_4^{2-}$ into mucus increased. Sialidase resistant mucus secreting cells were found much more distally. Chemical composition of mucus altered	Reid, 1970
1048 mg/m^3 (400 ppm) SO_2	3 hr/day, 5 day/wk, 3 wk	Rat	Increased mitosis of goblet cells. Alteration not lost by 5 wk post-exposure	Lamb and Reid, 1968

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Thus, at lower concentrations, the actual percentage of SO_2 removed in specific regions of the respiratory tract is not known precisely. In the dog, over 95 percent was removed by the upper airways and nose at concentrations between 2.62 and 131 mg/m^3 (1 and 50 ppm) SO_2 (Frank et al., 1967, 1969). A more detailed consideration of SO_2 extraction by airways is given in Section 12.2.4 below.

Giddens and Fairchild (1972) pointed out that these differences in removal of inspired SO_2 could explain the apparent anomaly of little damage to the lower respiratory tract at high SO_2 concentrations. They undertook a study of the effects of inhaled SO_2 on the nasal mucosa of mice. Two groups of mice were used; one group that was free of specific upper respiratory pathogens, and an ordinary laboratory group that was presumed to be infected or to have a latent infection of upper respiratory pathogens. Mice were exposed continuously to 26.2 mg/m^3 (10 ppm) SO_2 for a maximum of 72 hr. Pathological changes in the nasal mucosa appeared after 24 hr of exposure and increased in severity after 72 hr of exposure. Mice free of upper respiratory pathogens had fewer pathological findings than the conventionally raised animals. Giddens and Fairchild (1972) concluded that resident or acquired pathogens exacerbated the morphological changes they had observed. Morphological alterations were, however, qualitatively identical in both groups of animals. Cilia were lost from the nasal mucosa; vacuolization appeared; the mucosa decreased to about one half the normal thickness, and a watery fluid accumulated. Desquamation of the respiratory and the olfactory epithelia was evident. Alveolar capillaries were slightly congested, but edema and inflammatory cells were absent. Martin and Willoughby (1971) reported loss of cilia, disappearance of goblet cells, and metaplasia of the epithelium of the nasal cavity of pigs exposed to 91.7 mg/m^3 (35 ppm) SO_2 for 1 to 6 wk. This study, however, was marred by difficulties with the control of the SO_2, rising on occasion to 262 mg/m^3 (100 ppm), and with high relative humidity occurring during cleaning of the pig pens.

Lamb and Reid (1968) and Reid (1970) attempted to use SO_2-exposed rats in a model of human chronic bronchitis. They presented favorable arguments that SO_2-induced bronchial hyperplasia is analogous to human chronic bronchitis. Most of their studies have been carried out at high concentrations of SO_2 (1,048 mg/m^3 or 400 ppm SO_2 for 3 hr/day, 5 days/wk) for up to 6 wk. Under these conditions, the tracheal glands clearly increased. The goblet cell density also increased in the proximal airways, main bronchi, trachea, and distal airways, with proximal airways and main bronchi showing the largest changes. The incorporation of ^{35}S-sulfate by goblet cells into mucus also increased with exposure, reaching a plateau at approximately 3 wk. The effects of SO_2 were concentrated in the central airways, again suggesting that the solubility of SO_2 in water limits its accessibility to the periphery. Mitosis reached a maximum after 2 or 3 exposures and declined rapidly as injured cells were replaced. On repeated exposure for periods up to 6 wk, mitosis remained elevated in the proximal airways compared to the distal airway in which the mitotic index returned to the control level. The magnitude was proportional to the SO_2 concentration up to 524 mg/m^3 (200 ppm) SO_2, but was

less at 786 mg/m^3 (300 ppm). An elevation of the mitotic index occurred at SO_2 concentrations as low as 131 mg/m^3 (50 ppm) when given for 3 hr/day, 5 days/wk. Major changes in the goblet cell type or substance produced by the goblet cells were also detected. Goblet cells which produced mucus resistant to digestion by sialidase increased in numbers, and their distribution extended distally from the upper bronchioles towards the respiratory bronchioles. Since each molecular type of mucin, sialidase resistant or susceptible, could be produced by one type of goblet cell, or each goblet cell could produce a different mucin, these results can be interpreted in two ways. The elaboration of a specific type of goblet cell could occur, or more goblet cells could be produced but with a change in their biochemical function towards sialidase resistant mucins. These studies present an interesting means of studying experimental bronchitis, but do not provide evidence that ambient SO_2 levels cause similar changes.

Alarie et al. (1970) examined the tissues of guinea pigs exposed continuously to 0, 0.34, 2.65, or 15.0 mg/m^3 (0, 0.13, 1.01, or 5.72 ppm) SO_2 for 1 yr. The lungs of the guinea pigs exposed to 15.0 mg/m^3 (5.72 ppm) and killed after 13 or 52 wk of exposure showed less spontaneous pulmonary disease than the control group. The prevalence of pulmonary disease in the control groups which was not observed prior to exposure suggests that they acquired pulmonary disease during the exposure period. These (Alarie et al., 1970) and other studies by Alarie and co-workers (1972, 1973c, 1975), were limited to light microscopic observations of conventional hematoxylin-eosin stained paraffin sections. The results are of limited value compared to more recent approaches using scanning electron microscopy of surfaces and transmission electron microscopy of organelles. The control group, as well as those exposed to 0.34 and 2.64 mg/m^3 (0.13 and 1.01 ppm) SO_2, had evidence of lung disease as shown by histocytic infiltration of the alveolar walls. Tracheitis was also present in the above three groups, but not in the 15.0 mg/m^3 (5.72 ppm) group. Hepatocyte vacuolation was observed in the latter group, but the pathological significance of this change needs further investigation. The survival was greater ($p < 0.05$) in the 15.0 mg/m^3 (5.72 ppm) group than in the other groups including the air-exposed control group. The authors do not address the significance of the hepatocyte vacuolation. The possible effects of SO_2 in this study cannot be accurately determined because of the disease in the control animals.

Subsequently these researchers (Alarie et al., 1972, 1973c) exposed cynomolgus monkeys continuously to 0.37, 1.7 or 3.35 mg/m^3 (0.14, 0.64 or 1.28 ppm) SO_2 for 78 wk but found no remarkable morphological alterations. Another group exposed to 12.3 mg/m^3 (4.69 ppm) SO_2 for 30 wk was accidentally exposed to concentrations of SO_2 not higher than 2,620 mg/m^3 (1,000 ppm) or lower than 524 mg/m^3 (200 ppm) for 1 hr, after which they were placed in a clean air chamber and held for 48 more wk. Persistent changes were noted in this group. Alterations in the respiratory bronchioles, alveolar ducts, and alveolar sacs were found. Proteinaceous material was found within the alveoli. The distribution of such lesions was focal, but was observed within all lobes of the lung. Alveoli containing proteinaceous material were generally those which arose directly from respiratory bronchioles. Alveolar walls were

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thicker and were infiltrated with histocytes and leukocytes. Macrophages were present within these foci. Moderate hyperplasia of the epithelia of the respiratory bronchioles was found, and frequently the lumina of the respiratory bronchioles were plugged with proteinaceous material, macrophages, and leukocytes. Bronchiectasis and bronchiolectasis were present in 8 of 9 monkeys. Vacuolation of hepatocytes was also observed, as with the guinea pig group exposed to 15.0 mg/m^3 (5.72 ppm) SO_2 in the prior study (Alarie et al., 1970).

In a replication of this study, cynomolgus monkeys were exposed to 13.4 mg/m^3 (5.12 ppm) SO_2 continuously for 18 mo. (Alarie et al., 1975). No alterations in lung morphology were reported to be due to SO_2. The morphological alterations reported in the control group included lung mite infections and associated "slight subacute bronchiolitis, alveolitis, and bronchitis." Pulmonary function measurements were made in the above mentioned studies (Alarie et al., 1970, 1972, 1973c, 1975) and are described in Section 12.2.4.

The absence of SO_2-induced morphological alterations as reported by Alarie et al. (1970, 1972, 1973c, 1975) and Lewis et al. (1973) who exposed dogs for 620 days (21 hr/day) to 13.4 mg/m^3 (5.1 ppm) SO_2 is not in conflict with the bronchoconstriction induced by acute SO_2 exposure reported by Amdur and co-workers (1973) at lower concentrations (see Section 12.2.4). Alarie et al. (1970) pointed out, "As recent literature attests, there is also an obvious lack of knowledge about the correlation between subtle microscopic alterations in the lung and concomitant changes in this physiological parameter (lung function)." Further, the transient nature of the pulmonary function effects observed during short-term exposures would be difficult to detect morphologically unless the lungs were fixed during the time of exposure. Even then, if the cause of the increased pulmonary resistance were a subtle alteration of smooth muscle tone as has been hypothesized, it might be morphologically undetectable.

Most of the studies in which the lungs of SO_2-exposed animals have been examined center around tracheitis, bronchitis, ulceration, and mucosal hyperplasia (Table 12-2). The lowest concentrations of SO_2 at which these alterations have been reported have been in the rat at 131 to 134 mg/m^3 (50 to 51 ppm) for 30 to 113 days. At higher concentrations (1,048 mg/m^3 or 400 ppm SO_2 for 3 hr/day, 5 days/wk for 3 wk), recovery to normal morphology did not occur after 5 wk post-exposure. The possibility of recovery from lower concentrations and shorter durations of exposure is not known (Lamb and Reid, 1968; Reid, 1970). Discounting their first study (Alarie, et al., 1970) where the control group of guinea pigs had a higher level of pulmonary infection than the exposed groups, Alarie et al. (1973c) reported no effect from SO_2 exposure up to 5 ppm. These observations were, however, restricted to light microscopy and did not include scanning or transmission electron microscopic observations. This group also reported no observable effects at 0.37, 1.7 or 3.35 mg/m^3 (0.14, 0.64, and 1.28 ppm) SO_2 (Alarie et al., 1975). The group of monkeys exposed to 12.3 mg/m^3 (4.69 ppm) must also be disregarded due to the accidental exposure to high levels of SO_2 (Alarie et al., 1975). No effects were reported for monkeys exposed to 13.5 or 13.7 mg/m^3 (5.15 or 5.23 ppm) SO_2 and sulfuric acid aerosols at 0.10 mg/m^3 or fly ash at 0.44 mg/m^3 (Alarie et al., 1975).

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12.2.4 Alterations in Pulmonary Function

Changes in breathing mechanics have been among the most sensitive parameters of SO_2 toxicity. They have likewise been useful in studying the effects of aerosols alone or in combination with SO_2 (Sections 12.3.3.1 and 12.4.1.1). A variety of methods have been used, some of which have been applied to human exposures. A method for measuring increases in flow resistance due to bronchoconstriction in guinea pigs has been developed by Amdur (Amdur and Mead, 1955, 1958). Animals are not anesthetized and breathe spontaneously, allowing sensitive measurements of pulmonary function. Another method by Alarie and co-workers (1973d) measures changes in respiratory rate. SO_2 also initiates bronchoconstriction in man, and is also more closely related to human health effects.

Several investigators (Nadel et al. 1965a; Corn et al., 1972; Frank and Speizer, 1965; Balchum et al., 1960; Nadel et al., 1965b) found that bronchoconstriction resulted from both head-only and lung-only exposures in cats and dogs. When corrected for the amount of SO_2 hypothesized to reach the lung, Amdur's study (1966) with guinea pigs has shown that SO_2 is highly effective in producing bronchoconstriction through direct exposure of the lung. Two sets of receptors are involved in the response of animals to SO_2. At high concentrations of SO_2 or following long durations of exposure, the nasopharyngeal receptors fatigue or become unresponsive, whereas the bronchial receptors do not. Widdicombe (1954a) originally described the receptors responsible for the SO_2-initiated bronchoconstriction. The bronchoconstriction is initiated through the activation of a bronchial epithelial chemoreceptor whose efferent and afferent pathways are through the vagus nerves (Nadel et al., 1965a,b; Grunstein et al., 1977; Tomori and Widdicombe, 1969). Chilling the vagus prevents conduction of nervous impulses produced on inhalation of SO_2. Other receptors located in the same regions of the lung respond to mechanical stimulation and particles such as talc (Widdicombe, 1954b; Widdicombe et al., 1962). Intravenous injection of atropine blocks the efferent impulses, presumably at the cholinergic preganglionic synapse (Grunstein et al., 1977). Sulfur dioxide-initiated bronchoconstriction involves smooth muscle contraction since β-adrenergic agonists, such as isoproterenol, reverse the SO_2-bronchoconstriction (Nadel et al., 1965a,b). Histamine may be involved in this response as implied by other studies of hyperreactive airways (Boushey, et al. 1980), but no definitive proof of histamine involvement is available. Release of acetylcholine could also cause increased mucus secretion as noted during SO_2 exposure. Chronic exposure to SO_2 could lead to mucus hypersecretion and altered airway caliber. Cholinomimetic drugs and histamine applied as aerosols mimic the SO_2-initiated bronchoconstriction (Islam et al., 1972). Cholinomimetic drugs act through either the same autonomic reflex arc or directly upon the cholinergic receptors on smooth muscles and mucus secreting cells and glands. As discussed in Chapter 13, SO_2 also produces bronchoconstriction in man through the same autonomic reflex arc.

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Exposure to SO_2 evokes an increased resistance to air flow in guinea pigs which can be repeated by several exposures over a period of hours and exhibits none of the tachyphylaxis found with other species (Corn et al., 1972; Frank and Speizer, 1965). However, different techniques were used for these different species. Amdur (1973), in a review of her data, reported that for a 1-hr exposure, a mean of 0.68 mg/m^3 or 0.26 ppm (range of 0.08 to 1.57 mg/m^3 or 0.03 to 0.6 ppm) was the lowest concentration of SO_2 that increased flow resistance in guinea pigs. The response, a 12.8 percent increase ($p < .001$) at these (Amdur, 1973) low levels of SO_2, was the average of 71 guinea pigs; the individual data points were reported in other publications (Amdur and Underhill, 1968, 1970; Amdur, 1974). For a 1 hr exposure, the lowest concentration these researchers tested which caused an increase ($p < 0.01$) in resistance was 0.42 mg/m^3 (0.16 ppm) SO_2 (Amdur and Underhill, 1970). In a more recent study, Amdur et al. (1978) showed that a 1 hr exposure of guinea pigs to 0.84 mg/m^3 (0.32 ppm) SO_2 caused a 12 percent increase in resistance ($p < 0.02$) and a non-statistically significant decrease in compliance. Investigations of the interaction of oil mists and SO_2 showed that 2.62 mg/m^3 (1 ppm) SO_2, the lowest concentration used, significantly increased resistance (Costa and Amdur, 1979a,b). At concentrations of SO_2 below 2.62 mg/m^3 (1 ppm), the response of individual animals varied considerably (Amdur, 1964, 1973, 1974). Of 1,028 guinea pigs, 135 were "susceptible", responding to low concentrations of SO_2 with greater changes in resistance than the predicted mean. Amdur cites comparative data for other species, including man, to suggest that a certain fraction of all subjects may exhibit this phenomenon (Amdur, 1973, 1974; Horvath and Folinsbee, 1977). On the other hand, Amdur et al. (1978) also point out that some groups of animals may by chance not have a "susceptible" individual. In this study, 3 groups of 10 animals each or a total of 30 guinea pigs exposed to 0.52, 1.05, or 2.1 mg/m^3 (0.2, 0.4, or 0.8 ppm) SO_2 had no significant increase in airway resistance above the control values. Based on data from earlier work (Amdur and Underhill, 1968), Amdur concluded that 10 to 13 percent of the guinea pig population is more responsive than the average (Amdur, 1974). In cats (Corn et al., 1972) and dogs (Frank and Speizer, 1965), on the other hand, few were found to be sensitive to short-term (< 1 hr) exposure to 52.4 mg/m^3 (20 ppm) SO_2 (cats) or 18.3 mg/m^3 (7 ppm) SO_2 (dogs). Even with the relatively small sample sizes used, some cats and dogs responded and others did not.

Some of the problem of "susceptible" vs. "non-susceptible" members of the experimental population can be understood by considering a simple hypothesis. If one assumes that the response to a given toxicant, such as SO_2, is the result of a number of different genes within the population and not just a single gene, then a single individual could have a number of recessive or dominant genes which could contribute to either the "susceptibility" or "non-susceptibility" of that individual. Since experimental animals and human subjects are drawn on as random a basis as is possible (in most experimental designs), there will be a maximum chance of getting some "susceptible" responders in each experiment. The total number of "susceptible" responders will be small and variable because of the low incidence of "susceptible" responders in the general animal population. A small, but variable, number of

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"susceptible" responders will tend to shift the dose- or concentration-response curve toward lower concentrations and to decrease the slope of the curve (e.g., when the data are expressed as the log-probit transformation). Such phenomena have been studied in detail for "resistant" insects which have different genomes responsible for increased detoxification mechanisms. In the case of SO_2, the matter is further complicated by comparisons between groups of animals and between different strains or species. Even with guinea pigs, the total number of animals examined to date (about 1,000 to 2,000) is too small to give more than a crude estimate of those animals having a "sensitive" genome. The incidence of "susceptibility" in the guinea pigs (about 13 percent) is too low to have been detected clearly in the 100 or so cats and dogs used in SO_2 experiments. Here only 1 or 2 "susceptible" animals would have been encountered in each experiment. Further, the small number of animals has been studied in different laboratories and at different times, and the animals have come from different genetic stocks. It is fortuitous that Amdur's laboratory has persisted in these studies with the same animal, the guinea pig, using the same general methodology so this low incidence of "susceptibility" could be detected. While the mechanism(s) responsible for "susceptibility" is not known, the question of "susceptibility" is an important aspect deserving further study. A similar incidence of some 10 percent "susceptible" individuals in man would present a major health problem. Adverse reactions might occur among "susceptible" individuals at exposures less than 2.62 mg/m^3 (1 ppm) (Amdur, 1964, 1973, 1974). These concentrations of less than 2.62 mg/m^3 (1 ppm) are encountered in ambient air. Neither the frequency of susceptibility to SO_2 in man, nor the physiological or biochemical basis, is known.

A broad dose-response curve has been noted also for histamine initiated bronchoconstriction in man (Habib et al., 1979), guinea pigs (Douglas et al., 1973, 1977; Brink et al., 1980), dogs (Loring et al., 1978; Snapper et al., 1978), and monkeys (Michoud, 1978). Among 12 normal human subjects a 38-fold range of inhaled histamine in both the threshold and median doses causing bronchoconstriction was observed (Habib et al., 1979). The dose required to produce a 50 percent change in dynamic lung compliance in 131 female guinea pigs varied over a 100-fold range of concentrations (Douglas et al., 1973). While the interindividual dose varied considerably, the values were log normally distributed indicating a single population (Douglas et al., 1973, 1977). Dogs showed a 40-fold variation in the histamine dose needed to initiate changes in airway diameter (Snapper et al., 1978). These values were also log normally distributed indicating a single population amongst the 102 mongrel dogs examined. A wide interindividual variation for histamine and methacholine initiated bronchoconstriction was found amongst 8 rhesus monkeys, some of which were sensitive to Ascaris suum allergen (Michoud, 1978). No differences in sensitivity to histamine or methacholine could be found with Ascaris sensitivity, however. While genetic differences in histamine sensitivity have been found in quinea pigs, naturally occurring or acquired allergic reactions are, thus, not likely to cause the large interindividual differences in sensitivity in either guinea pigs (Takino et al., 1971) or monkeys (Michoud et al., 1978). A further complicating factor is the age-dependence

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of histamine and other drug initiated bronchoconstriction (Brink et al., 1980). Younger guinea pigs were more sensitive to histamine than were older animals, for example. The decreasing bronchial reactivity to histamine with age in the guinea pig has been suggested as a model of human juvenile asthma. However, human bronchial hyperreactivity does not seem to decrease with age in the same manner (Boushey et al., 1980). While large interindividual differences apparently occur with a wide variety of chemical agents causing bronchial reactivity in both man and animals, the response of the same individual is quite reproducible regardless of species. The variability in the threshold dose of SO_2 needed to evoke a given bronchoconstriction (measured for example as an increased resistance to flow by the studies of Amdur) is apparently an inherent part of the bronchial response to a broad range of chemicals and is not an artifact of the method. Similar variations in threshold doses for SO_2 are likely to occur in man, judging from the variability to inhaled histamine. The general observation that asthmatic patients are hypersensitive to a broad range of chemical and physical agents initiating bronchoconstriction (Boushey et al., 1980) supports the contention that the most susceptible animal species should be used as a surrogate for man. A major difference in pharmacology may exist between the guinea pig and man. Autonomic mediators interact with histamine in bronchial reactivity in guinea pigs but not in man. Beta adrenergic blockade by propranolol causes no difference in bronchial reactivity in man (Habib et al., 1979) but potentiates histamine reactivity in the guinea pig (Douglas et al., 1973). Insufficient numbers of animals and subjects have been examined to predict the general shape of the dose-response curve for the human population, even excluding the hypersensitive asthmatic population. These variations in interindividual dose needed to evoke a specific amount of increased resistance to flow in guinea pigs by SO_2 likewise apply to the measurement of increased resistance to flow evoked by aerosols as discussed below in Section 12.3.3.

Using Strandberg's (1964) data from the rabbit to correct for the concentration of SO_2 hypothesized to reach the lung, Amdur (1966) was able to normalize the concentration-response curve for SO_2-induced bronchoconstriction in the guinea pig resulting from nose-only exposures. A break occurs in the concentration-response curve at about 52.4 mg/m^3 (20 ppm) SO_2, perhaps due to the poorer extraction of gaseous SO_2 by the upper airways at low concentrations. However, it should be recognized that SO_2 extraction data for rabbits (Strandberg, 1964) and dogs (Frank et al., 1967; Balchum et al., 1960; Frank et al., 1969) are in some conflict and that the data for rabbits are not clear with respect to the site of SO_2 removal. Thus, use of the rabbit data for guinea pig studies can be done only hypothetically. Sulfur dioxide introduced directly into the lung by a tracheal cannula was much more effective in producing bronchial constriction. Amdur (1966) suggests that at concentrations of 1.05 to 1.31 mg/m^3 (0.4 to 0.5 ppm) very little removal of SO_2 occurs in the upper airways. These data contrast with the radiotracer studies in dogs (Frank et al., 1967, 1969; Balchum et al., 1960). Others have required concentrations greater than 18.3 mg/m^3 (7 ppm) to evoke increases in flow resistance in anesthetized cats (Corn et al., 1972) and dogs (Frank and Speizer, 1965). Differences in

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the sensitivity of the two models may lie in the use of anesthesia, in the use of different species, or in a different incidence of "susceptible" individuals.

Using anesthetized, intubated, spontaneously breathing dogs exposed to 2.62, 5.24, 13.1, or 26.2 mg/m^3 (1, 2, 5, or 10 ppm) SO_2 for 1 hr, Islam et al. (1972) found an increased bronchial reactivity to aerosols of acetylcholine, a potent bronchoconstrictive agent. Acetylcholine is also the endogenous neuromuscular transmitter which causes bronchoconstriction. Greatest response occurred at 5.24 mg/m^3 (2 ppm), although 2.62 mg/m^3 (1 ppm) also caused an effect. The effect at 26.2 mg/m^3 (10 ppm) was less than that at 2.62, 5.24, and 13.1 mg/m^3 (1, 2, and 5 ppm). These results suggest that SO_2 may modify bronchial reactivity.

Animals chronically exposed to SO_2 have also been examined for alterations in pulmonary function. Guinea pigs exposed continuously to 0.34, 2.64, or 15 mg/m^3 (0.13, 1.01, or 5.72 ppm) SO_2 for up to 1 yr showed no changes in pulmonary function; however, spontaneous pulmonary disease was present in all animals (including controls) except those exposed to the highest concentration (Alarie et al., 1970). Dogs exposed for 21 hr/day to 13.4 mg/m^3 (5.1 ppm) SO_2 for up to 225 days demonstrated increased pulmonary flow resistance and decreased lung compliance (Lewis et al., 1969). After 620 days' exposure, the mean nitrogen washouts of dogs were increased (Lewis et al., 1969). Alarie and co-workers (Alarie et al., 1972, 1973c, 1975) exposed cynomologus monkeys continuously to 0.37, 1.7, 3.4, or 13.4 mg/m^3 (0.14, 0.64, 1.28, or 5.12 ppm) SO_2. The latter concentration was used in an 18-mo study, whereas the others were used for 78 wk exposures. Pulmonary function was unchanged in all of these groups. After 30 wk of exposure to 12.3 mg/m^3 (4.69 ppm) SO_2, monkeys were inadvertently exposed to concentrations between 524 and 2,620 mg/m^3 (200 and 1000 ppm) for 1 hr. This treatment resulted in pulmonary function alterations which persisted for the remaining 48 wk of the study during which the animals were exposed to clean air. Morphological alterations were also seen in this group (see Section 12.2.3).

In summary, there are at least two sets of receptors responsible for changes in respiratory function in animals acutely exposed to SO_2. Decreases in respiratory rate or increased resistance to flow are reproducible end points. Increased resistance to flow results from SO_2 concentrations as low as 0.42 mg/m^3 (0.16 ppm) using guinea pigs. Of the animals so far examined, guinea pigs are the most sensitive to SO_2. The reason for this is not known; potential factors include species, strains, and experimental technique used. Large interindividual differences in dose-response curves for changes in pulmonary resistance to air flow exist in all species. A single population of animals for this trait appears likely for guinea pigs, dogs, and cats. The exact number of animals responding to a given dose will depend upon the shape of the dose-response curve. The nature of the dose-response curve at low levels is poorly understood and has not been investigated directly. While pulmonary function measurements in guinea pigs appear to be highly sensitive to acute SO_2 exposures, chronic SO_2 exposure has not been proven to have a similar effect. Chronic studies with guinea pigs are unclear, however, because of disease in the control group. In other chronic studies, pulmonary

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function of monkeys was unchanged at SO_2 concentrations up to 13.4 mg/m^3 (5.12 ppm); dogs were affected by 225, but not 620, days of exposure to 13.4 mg/m^3 (5.1 ppm). High levels of SO_2 likely to initiate airway narrowing and hypersecretion of mucus do alter several parameters of pulmonary function. These results are not contradictory in view of the physiology of SO_2-initiated bronchoconstriction. Sulfur dioxide appears to cause bronchoconstriction through action on the smooth muscles surrounding the airways. Since smooth muscles fatigue or become adjusted to altered tone over time, chronic exposure to SO_2 is not likely to cause a permanent alteration in bronchial tone. Unfortunately, investigations of the reactivity of the airways after chronic exposure to SO_2 have not appeared. We do not know if chronic exposure to SO_2 causes an alteration in response to SO_2 itself, since only direct measurements of pulmonary function were made on the animals after chronic exposure. It would be very informative to learn if chronically exposed monkeys, for example, were more or less sensitive to SO_2 (Table 12-3).

The respiratory rate of mice has been used as an indication of sensory irritation by Alarie et al. (1973d). Mice were exposed for 10 min to 0, 44.5, 83.8, 162, 233, 322, 519, or 781 mg/m^3 (0, 17, 32, 62, 89, 123, 198, or 298 ppm) SO_2. About a 12 percent decrease in respiratory rate was observed at 44.5 mg/m^3 (17 ppm). The respiratory rate decreased inversely to the logarithm of the concentration of inspired SO_2. The decrease in respiratory rate, however, was transient, returning to nearly control levels within 10 min at all SO_2 concentrations. Complete recovery to control values occurred within 30 min following all exposures to SO_2. The time for maximum response was inversely related to the logarithm of the concentration of SO_2, being shortest at highest concentrations. Mice exposed to 262 mg/m^3 (100 ppm) SO_2 for 10 min were allowed to recover in clean air prior to a subsequent 10 min exposure to the same concentration. As the length of the recovery period was decreased (from 12 min to 3 min), the effect of the subsequent SO_2 exposure on respiratory rate was lessened. "Desensitization," thus, appeared to occur during the course of exposures. When another irritant, aerosols of chlorobenzilidene malononitrile (CBM), was used during the refractory period following SO_2 exposure, the respiratory rate decreased at a rate comparable to that following exposure to CBM alone. Thus, the refractory period associated with SO_2 exposures appeared specific to SO_2 and not to CBM. When 262 to 328 mg/m^3 (100 to 125 ppm) SO_2 was provided repeatedly for durations of 90 sec, with each exposure separated by a 60-sec recovery period, the refractory period was cumulative. Ten such exposures eventually abolished all respiratory rate responses to SO_2. Breathing clean air for 60 min resulted in a return of the response to initial levels. When mice were exposed to SO_2 by means of a tracheal cannula, no changes in the respiratory rate were observed, indicating that the decrease in respiratory rate was mediated by a reflex arc. This hypothesis has been developed in considerable detail in an extensive review by Alarie (1973) who suggests that stimulation and desensitization occur via cholinergic nerve endings of the afferent trigeminal nerve. Alarie et al. (1973d) also suggest that SO_2 is

TABLE 12-3. EFFECTS OF SULFUR DIOXIDE ON PULMONARY FUNCTION

Concentration	Duration	Species	Results	Reference
0.37, 1.7, 3.4, or 13.4 mg/m^3 (0.14, 0.64, 1.28, or 5.12 ppm) SO_2	72-78 wk, continuous	Cynomologus monkey	No change	Alarie et al., 1972, 1973c, 1975
0.42 or 0.84 mg/m^3 (0.16 or 0.32 ppm) SO_2	1 hr	Guinea pig	Increase in resistance	Amdur et al., 1970, 1978a
0.52, 1.04, or 2.1 mg/m^3 (0.2, 0.4, or 0.8 ppm) SO_2	1 hr	Guinea pig	No significant increase in airway resistance.	Amdur et al., 1978c
2.62, 5.24, 13.1, or 26.2 mg/m^3 (1, 2, 5, or 10 ppm) SO_2	1 hr	Dog	Increased bronchial reactivity to aerosols of acetylcholine, a potent bronchoconstrictive agent	Islam et al., 1972
13.4 mg/m^3 (5.1 ppm) SO_2	21 hr/day, 225 and 620 days	Dog	Increased pulmonary flow resistance and decreased lung compliance at 225 days; increased nitrogen washout at 620 days	Lewis et al., 1969
18 to 45 mg/m^3 (7 to 17 ppm) SO_2	1 hr	Guinea pig	General decrease in tidal volume and an increase in respiratory rate	Lee and Danner, 1966
0, 44.5, 83.8, 162, 233, 322, 519, or 781 mg/m^3 (0, 17, 32, 62, 89, 123, 198, or 298 ppm) SO_2	10 min	Mouse	Respiratory rate decreased proportionally to the log of the concentration; complete recovery within 30 min following all exposures. The time for maximum response was inversely related to the log of the concentration, being shortest at highest concentrations	Alarie et al., 1973d
>50 mg/m^3 (>19 ppm) SO_2	1 hr	Guinea pig	Increase in tidal volume and a decrease in respiratory rate	Lee and Danner, 1966

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hydrated to bisulfite and sulfite which react with a receptor protein to form an S-thiosulfate and a thiol, cleaving an existing disulfide bond. The receptor protein slowly regenerates to its original disulfide configuration by the oxidation of S-thiosulfide and free thiol moieties of the receptor protein to disulfide. No direct evidence for this hypothesis has been presented.

12.2.5 Effects on Host Defenses

Because alterations in the ability to remove particles from the lung could lead to increased susceptibility to airborne microorganisms or increased residence times of other non-viable particles, the effects of SO_2 on particle removal and engulfment, as well as on integrated defenses against respiratory infection, have been studied. Cilia function does not appear to be affected by exposure. No changes were observed in the cilia beat frequency or the relative number of alveolar macrophages laden with particles in rats exposed to 2.62 or 7.86 mg/m^3 (1 or 3 ppm) SO_2 and graphite dust (mean diameter 1.5 μm, 1 mg/m^3) for up to 119 consecutive days (Fraser et al., 1968). Donkeys (Spiegelman et al., 1968) were exposed by nasal catheters to 68.1 to 1,868 mg/m^3 (26 to 713 ppm) SO_2 for 30 min. Below 786 mg/m^3 (300 ppm) clearance was not affected, but at high concentrations (786 to 1,868 mg/m^3 or 376 to 713 ppm) clearance was depressed. Increased mucus flow and nasal irritation have been observed with as little as 26.2 mg/m^3 (10 ppm) SO_2 for 24 hr.

Ferin and Leach (1973) exposed rats to 0.26, 2.62, and 52.4 mg/m^3 (0.1, 1, or 20 ppm) SO_2 for 7 hr/day, 5 days/wk, for a total of 10 to 15 days and then measured the clearance of an aerosol of titanium oxide (TiO_2). The aerosol was generated at about 15 mg/m^3 (1.5 μm MMAD, σ_g 3.3). These investigators took the amount of TiO_2 retained at 10 to 25 days as a measure of the "integrated alveolar clearance". Low concentrations of SO_2 (0.26 mg/m^3 or 0.1 ppm) accelerated clearance after 10 and 23 days, as did 2.62 mg/m^3 (1 ppm) at 10 days but not afterwards until 25 days when clearance was decreased. Hirsch et al. (1975) found that the tracheal mucus flow was reduced in beagles exposed for 1 yr to 2.62 mg/m^3 (1 ppm) SO_2 for 1.5 hr/day, 5 days/wk. No differences in pulmonary function were reported. Confirmation of this study and determination of the persistence of the decreased mucus flow at this low level of SO_2 would be important to confirm in light of other data available.

SO_2 may have more of an effect on anti-viral than on anti-bacterial defense mechanisms. Bacterial clearance was not depressed or altered in guinea pigs exposed to 13.1 or 26.2 mg/m^3 (5 or 10 ppm) SO_2 for 6 hr/day for 20 days (Rylander, 1969; Rylander et al., 1970). Using the infectivity model (see Section 12.3.4.3), Ehrlich (1978) found that short (3 hr/day for 1 to 15 days) or long (24 hr/day for 1 to 3 mo) exposures to 13.1 mg/m^3 (5 ppm) SO_2 did not increase mortality subsequent to a pulmonary streptococcal infection. Virus infections, however, are augmented by simultaneous or subsequent SO_2 exposure. Mice were exposed to concentrations varying from 0 to 52.4 mg/m^3 (0 to 20 ppm) SO_2 continuously for 7 days (Fairchild et al., 1972). Mice breathing 18.3 to 26.2 mg/m^3 (7 to 10 ppm) SO_2 began to experience an increase in

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pneumonia. Lung consolidation was significant at 65.5 mg/m^3 (25 ppm), but not at 26.2 or 39.3 mg/m^3 (10 or 15 ppm). The rate of growth of the virus within the lung was unaffected by SO_2 exposure. Further analysis of the data (Lebowitz and Fairchild, 1973) indicated that SO_2 and virus exposure produced weight loss at concentrations as low as 9.43 mg/m^3 (3.6 ppm). Exposure to SO_2, whether alone or in combination with a viral agent, had more of an effect on weight reduction than on pneumonia. Since Giddens and Fairchild (1972) showed that mice with apparent respiratory infection were more susceptible to SO_2 (Section 12.2.3), a rebound effect may be possible in which SO_2 and microbial agents each potentiate the effect of the other.

Several studies of the effects of SO_2 on alveolar macrophages have been conducted, since these cells participate in clearance of viable and non-viable particles in the gaseous exchange regions of the lung. Alveolar macrophages from rats exposed for 24 hr to 2.62, 13.1, 26.2, and 52.4 mg/m^3 (1, 5, 10, and 20 ppm) SO_2 were investigated by Katz and Laskin (1976). Exposure to the 2 highest concentrations increased *in vitro* phagocytosis of latex spheres for up to 4 days in culture. At 13.1 mg/m^3 (5 ppm) SO_2, phagocytosis was increased after 3 or 4 days in culture, but not after 1 or 2 days. Histochemical studies of pulmonary macrophages from rats exposed to 786 mg/m^3 (300 ppm) SO_2 for 6 hr/day on 10 consecutive days showed no changes in the lysosomal enzymes, β-glucuronidase, β-galactosidase, and N-acetyl-β-glucosaminidase (Barry and Mawdesley-Thomas, 1970). Acid phosphatase activity was markedly increased. This is in agreement with Rylander's observation (Rylander, 1969) which suggests that SO_2 exposure (26.2 mg/m^3, 10 ppm, for 6 hr/day, 5 days/wk for 4 wk) does not affect the bactericidal activity of the lung. (Table 12-4)

12.3 EFFECTS OF PARTICULATE MATTER

Sulfur dioxide is oxidized to sulfuric acid in the atmosphere. Sulfuric acid can react with atmospheric ammonia to produce ammonium sulfate and bisulfate. Similar reactions can also occur in the animal exposure chamber and confound the experiment. Ambient particulate matter may be composed of sulfur compounds and definition of the effects of ambient aerosols independent of sulfur compounds may be impossible. Sulfur dioxide is often present in polluted atmospheres with complex mixtures of other compounds including heavy metals, which may be present as oxides or as sulfate or nitrate salts. In addition, organic compounds present in the atmosphere in the gaseous phase can be associated with the particulate fraction or become adsorbed on particles either *in situ* or during collection. The diversity of these organic compounds simply precludes any rational discussion of their toxicity at this time, since little or no inhalation data is available. The details of the composition of atmospheric aerosols are dealt with elsewhere (Chapter 5). The deposition and transport of particles are also discussed elsewhere (Chapter 11).

Since very few studies have appeared on the toxicity of complex atmospheric particles themselves, this section will deal primarily with the toxicity of the components of these particles and the toxicology of those compounds which have been identified as constituents of atmospheric particles. Therefore, these discussions, no matter how sophisticated for a single component, are inherently simplistic. For aerosols other than H_2SO_4, $(NH_4)_2SO_4$, and NH_4HSO_4,

TABLE 12-4. EFFECTS OF SULFUR DIOXIDE ON HOST DEFENSES

Concentration SO2	Duration	Species	Results	Reference
0.26, 2.62, or 52.4 mg/m^3 (0.1, 1, or 20 ppm)	7 hr/day, 5 day wk	Rat	Low concentrations (0.26 mg/m^3 or 0.1 ppm) accelerated clearance of TiO_2 aerosol after 10 and 23 days, as did 2.62 mg/m^3 (1 ppm) at 10 days but not afterwards until 25 days when clearance was decreased.	Ferin and Leach, 1973
2.62, 13.1, 26.2, and 52.4 mg/m^3 (1, 5, 10, and 20 ppm)	24 hr	Rat	Exposure to the 2 higher concentrations increased *in vitro* phagocytosis of latex spheres for up to 4 days in culture. At 13.1 mg/m^3 (5 ppm) phagocytosis was increased after 3 or 4 days in culture, but not 1 or 2 days.	Katz and Laskin, 1976
2.62 mg/m^3 (1 ppm)	1.5 hr/day, 5 day/wk	Dog	Tracheal mucous flow was reduced.	Hirsch et al., 1975
2.62 or 7.86 mg/m^3 (1 or 3 ppm) SO_2 + graphite dust (mean diameter 1.5 μm, 1 mg/m^3)	Up to 119 days	Rat	No changes in the cilia beat frequency or the relative number of alveolar macrophages laden with particles.	Fraser et al., 1968
9.43 to 52.4 mg/m^3 (3.6 to 20 ppm)	7 days continuous	Mouse	Exposure to SO_2 and a virus produced weight loss.	Lebowitz and Fairchild, 1973
13.1 or 26.2 mg/m^3 (5 or 10 ppm)	6 hr/day, 20 day	Guinea pig	Bacterial clearance was not altered.	Rylander, 1969, 1970
13.1 mg/m^3 (5 ppm)	3 hr/day, 1-15 days and 24 hr/day, 1-3 mo	Mouse	Did not increase mortality subsequent to a pulmonary streptococcal infection.	Ehrlich, 1979
Varying from 0 to 52.4 mg/m^3 (0 to 20 ppm)	7 days, continuous	Mouse	Increase in viral pneumonia at 18.3 to 26.2 mg/m^3 (7 to 10 ppm). Rate of growth of virus unaffected.	Fairchild et al., 1972
26.2 mg/m^3 (10 ppm)	6 hr/day for 20 days	Rat	Did not affect the bactericidal activity of the lung.	Rylander, 1969
65.5 to 1868 mg/m^3 (25 to 713 ppm)	30 min	Donkey	Below 786 mg/m^3 (300 ppm) clearance was not affected, but at high concentrations (786 to 1868 mg/m^3 or 376 to 713 ppm) clearance was depressed.	Spiegelman et al., 1968
786 mg/m^3 (300 ppm)	6 hr/day, 10 days continuous	Rat	No changes in selected lysosomal enzymes.	Barry et al., 1970

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no attempt will be made to be as inclusive as separate documents would be for some of the individual components. Rather, an attempt will be made to integrate this information in the perspective of the potential biological effects of atmospheric particles.

As will be apparent from the discussion of the toxicity of sulfate aerosols in this section, the chemical composition of the atmospheric particulates will determine the toxicity of the aerosol. Atmospheric particles are likely to have direct toxic effects in themselves, indirect toxic effects through interactions with other pollutants, and chronic effects through cell transformation or chronic alteration in cell function. Direct toxic effects are best substantiated by studies of cytotoxicity. Those reviewed here are for some specific compounds which are known to occur in the particulate fraction. The studies cited are by no means complete and could be expanded by including a number of other investigations carried out in vitro or by exposures other than inhalation. The review was purposefully restricted to those most applicable to the inhalation route of exposure. Major exceptions to this policy have been made for silica and the limited data on compounds in the so-called "coarse-mode" particles fraction. Most of the effects through interaction with other pollutants have previously been discussed for SO_2. Some additional data implicating interactions between SO_2 and particulate material, between SO_2 and ozone, and between H_2SO_4 and ozone are included here. One should recall that a large fraction of the mass of atmospheric particles is composed of sulfate and nitrate compounds.

Almost all of the studies (and all of the inhalation studies) discussed in this section involve the health effects of particles in the "fine mode" size range and composition. Within the category of fine mode particles, several investigators examined the influence of particle size for a given chemical. For coarse mode particles, only a few in vitro and intratracheal instillation studies could be found. This work is discussed separately.

12.3.1 Mortality

The susceptibility of laboratory animals to sulfuric acid aerosols varies considerably. Amdur (1971) has reviewed the toxicity of sulfuric acid aerosols and pointed out that, of the commonly used experimental animals, guinea pigs are the most sensitive and most similar to man in their bronchoconstrictive response to sulfuric acid. The lethal concentration (LC) of sulfuric acid depends upon the age of the animal (18 mg/m^3 for 1 to 2 mo-old versus 50 mg/m^3 for 18 mo-old animals), the particle size (those near 2 μm being more toxic), and the temperature (extreme cold increasing toxicity). In a recent study (Wolff et al., 1979b), the LC50 (the concentration at which 50 percent of the animals die) in guinea pigs for an 0.8 μm (MMAD) aerosol was 30 mg/m^3, whereas for a 0.4 μm (MMAD) aerosol, the LC50 was above 109 mg/m^3. In determining acute toxicity, the concentration of the aerosol appears to be more important than the length of exposure (Amdur et al., 1952). The animals that died did so within 4 hr. Chronic studies have only recently been undertaken, and they support this conclusion that mortality rarely occurs at moderate concentrations of sulfuric acid.

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Sulfuric acid aerosol appears to have two actions. Laryngeal and/or bronchial spasm are the predominant causes of death at high concentrations. When lower concentrations are used, bronchostenosis and laryngeal spasm can still occur. Pathological lesions in the latter case include capillary engorgement and hemorrhage. Such findings are in accord with anoxia as the prime cause of death.

12.3.2 Morphological Alterations

Alarie et al. (1973a) investigated the effects of chronic H_2SO_4 exposure. Guinea pigs were exposed continuously for 52 wk to 0.1 mg/m^3 H_2SO_4 (2.78 μm, MMD) or to 0.08 mg/m^3 H_2SO_4 (0.84 μm, MMD). Monkeys were exposed continuously for 78 wk to 4.79 mg/m^3 (0.73 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD), 0.48 mg/m^3 (0.54 μm, MMD), or 0.38 mg/m^3 H_2SO_4, (1.15 μm, MMD). Sulfuric acid had no significant hematological effects in either species. No light microscopic lung alterations resulting from H_2SO_4 exposure were observed in guinea pigs after 12 or 52 wk of exposure in this study (Alarie et al., 1973a) or in a later study (Alarie et al., 1975). Morphological changes were evident in the lungs of monkeys. At the two highest concentrations, there were changes (more prevalent in the 4.79 mg/m^3 H_2SO_4 group) regardless of the particle size. Major findings included bronchiolar epithelial hyperplasia and thickening of the walls of the respiratory bronchioles. Alveolar walls were thickened in monkeys exposed to 2.43 mg/m^3, but not to 4.79 mg/m^3, H_2SO_4. However, particle size had an impact at lower H_2SO_4 concentrations. No significant alterations were seen after exposure to 0.48 mg/m^3 of the smaller particle size (0.54 μm). However, bronchiolar epithelial hyperplasia and thickening of the walls of the respiratory bronchioles were seen after exposure to the larger size (1.15 μm) and lower concentration (0.38 mg/m^3). These results are not those predicted from strict considerations of particle deposition within the lung. The larger particles should have been deposited mostly in the upper airways, with less deposition in the lower airways (See Chapter 11). Pulmonary function changes followed a slightly different pattern (See Section 12.3.4.2). In these studies, the cynomolgus monkey was much more sensitive than the guinea pig. Dogs also appear to be relatively insensitive to H_2SO_4 alone as judged by morphological changes. Lewis et al. (1973) found no morphological changes after the dogs had been exposed for 21 hr/day for 620 days to 0.89 mg/m^3 H_2SO_4 aerosol (90 percent of the particles were <0.5 μm in diameter)

Recently, Cockrell and Busey (1978) and Ketels et al. (1977) studied the morphological changes resulting from sulfuric acid aerosols. Cockrell and Busey (1978) examined the effects of 25 mg/m^3 H_2SO_4 (1 μm, MMD, σ_g 1.6) for 6 hr/day for 2 days in guinea pigs. Segmented alveolar hemorrhage, type 1 pneumocyte hyperplasia, and proliferation of pulmonary macrophages were reported. Ketels et al. (1977) examined the response of mice to 100 mg/m^3 sulfuric acid; these exposures produced injury to the top and middle of the trachea, but none to the lower trachea and distal airways. In an attempt to investigate the dose-response relationship for sulfuric acid, mice received either 5 daily 3 hr exposures to 200 mg/m^3, 10 daily exposures to 100 mg/m^3, 20 daily exposures to 50 mg/m^3, or any one of these doses combined with 5 mg/m^3 carbon particles. The damage was judged to be proportional to the concentration (C) of H_2SO_4,

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but not to the integrated dose (C x T) or to the time of exposure (T). (All of the exposures had the same C x T and therefore their equivalence might have been hypothesized.)

A number of other studies of the morphological effects of H_2SO_4 when combined with other pollutants have been conducted. (See Section 12.4.1.2. and Table 12-5)

Inhalation of Si results in silicosis which is characterized by morphological changes of the lungs. Because the extensive information on the health effects of Si has been reviewed elsewhere (Ziskind et al., 1976; NIOSH, 1974; Reiser and Last, 1979; Singh, 1978), it will not be discussed in detail in this document. Due to the toxicity of Si a Threshold Limit Value (American Conference of Governmental Hygenists, 1979) has been set. Because of the involvement of alveolar macrophages in its toxicity and its presence in ambient particles, however, some of the effects of Si will be summarized briefly here. All the information given below for silicon is derived from reviews by Ziskind et al. (1976) and NIOSH (1974).

Silicon is ubiquitous in the earth's crust. Silicon dioxide (SiO_2), which is responsible for the disease silicosis, is found in 3 crystalline forms (quartz, cristobalite, and tridymite) As a generalization, the ranking of toxicity is tridymite >cristobalite > quartz. These uncombined forms of SiO_2 are generally called "free silica." SiO_2 is also found combined with cations, in which case the term silicates is applied. Very few animal toxicological studies of silicates exist. Several hypotheses of the etiology of silicosis have been developed, but no single one has been proven definitively. One widely accepted hypothesis was developed from both animal and human studies. According to this theory, alveolar macrophages ingest the particles, die, and release their intracellular contents, including lysosomal enzymes and SiO_2. This is followed by a recycling of particle ingestion by macrophages and their death, slow accumulation of other macrophage cells, increased collagen synthesis in response to macrophage lysosomal enzymes, hyalinization, and perhaps complicating factors. Since the alveolar macrophage hypothesis does not explain completely the etiology and pathogenesis of the disease, it is likely that additional factors contribute to the disease. These might include autoimmunity, co-existing tuberculosis or other infections, and/or alterations of lung lipid content and metabolism.

Many animal toxicological studies of SiO_2 exist. Unfortunately, comparisons are difficult because of the species and strain of animal used, accidental infections, the size of SiO_2 particle used, and the crystalline form of SiO_2 used.

Silicosis, similar to that observed in man, has been produced in animals exposed to high concentrations of quartz and other SiO_2 dusts via intratracheal instillation (30-50 mg) or chronic inhalation. Chronic exposures (2.5 yr) of dogs to earth containing 61 percent cristobalite produced fibrotic nodules in hilar lymph nodes, but not the lungs.

Several studies of the hemolysis of red blood cell by particles have been reported. This model may correlate with the ability of mineral dusts to cause lung fibrosis in vivo and thus is used for screening. Ottery and Gormley (1978) studied the influence of particle size of quartz (Min-u-sil) and other materials on red cell hemolysis. The particle size of the quartz

TABLE 12-5. EFFECTS OF PARTICULATE MATTER ON LUNG MORPHOLOGY

Concentration	Duration	Species	Results	Reference
0.08 mg/m^3 H_2SO_4 (0.84 μm, MMD), or 0.1 mg/m^3 H_2SO_4 (2.78 μm, MMD)	52 wk, continuous	Guinea pig	No significant hematological effect. No microscopic lung alterations after 12 or 52 weeks exposure.	Alarie et al., 1973a, 1975
0.38 mg/m^3 (1.15 μm, MMD), 0.48 mg/m^3 (0.54 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD), or 4.79 mg/m^3 (0.73 μm, MMD)	78 wk, continuous	Monkey	No significant hematological effect. Morphological changes in the lungs. At the two highest concentrations there were changes, regardless of the particle size. Major findings included bronchiolar epithelia hyperplasia and thickening of the respiratory bronchioles. Alveolar walls were thickened with 2.43 mg/m^3, but not 4.79 mg/m^3. No alterations with 0.48 mg/m^3 (0.54 μm), but with larger size (1.15 μm, 0.38 mg/m^3) hyperplasia and bronchiole thickening.	Alarie et al., 1973a
0.89 mg/m^3 (90% <0.5 μm in diameter) H_2SO_4 aerosol	21 hr/day, 620 days	Dog	No morphological changes.	Lewis et al., 1973
25 mg/m^3 (1 μm, MMD, σ_g 1.6) H_2SO_4 aerosol	6 hr/day, 2 days	Guinea pig	Segmented alveolar hemorrhage, type 1 pneumocyte hyperplasia, and proliferation of pulmonary macrophages.	Cockrell et al., 1978
50 mg/m^3 H_2SO_4, or 100 mg/m^3 H_2SO_4, or 200 mg/m^3 H_2SO_4, or any of of these doses combined with 5 mg/m^3 carbon particles (at all three duration schedules)	3 hr/day, 20 days; or 3 hr/day, 10 days; or 3 hr/day, 5 days	Mouse	Damage was proportional to the concentration.	Ketels et al., 1977

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was from 2.7 to 6.8 μm (mean volume diameter, MVD). At lower concentrations (0.025 to about 0.15 mg/ml), there was a linear dose-response increase in hemolysis for quartz (1.35 and 3.55 μm, MVD), kaolin (4.7 μm, MVD), cristobalite (3.05 μm, MVD), and bentonite (5 μm MVD). In this experiment, the effectiveness for increasing hemolysis was ranked as bentonite >kaolin > quartz > cristobalite. Even though this test is typically used to predict fibrotic potential, it should be noted that usually cristobalite is more fibrogenic than quartz. In another experiment, kaolin and quartz were additive when mixed. Linear increases in hemolysis were also observed with increasing numbers of particles. When the various sizes of Min-u-sil were directly compared, as particle size decreased from 6.8 μm to 2.7 μm, a smaller concentration was required to produce 5% hemolysis. For example, at the largest size tested, 2.7 mg/ml was required, whereas at the smallest size tested, 0.21 mg/ml was needed.

12.3.3 Alterations in Pulmonary Function

12.3.3.1 Acute Exposure Effects--On short-term exposure, respiratory mechanics are very sensitiv to inhaled H_2SO_4 and some other compounds. Amdur (1971) has cautioned that her method for measuring airway resistance (Amdur and Mead, 1955, 1958) should not be used as an indication of chronic toxicity and should be considered only for very short-term toxicity. As pointed out above, the Mead-Amdur method uses unanesthetized guinea pigs in which a transpleural catheter has been implanted. Amdur suggests (1971) that, if anything, this procedure increases rather than decreases the sensitivity of the guinea pigs to inhaled irritants.

Using this method, Amdur and co-workers (Amdur and Underhill, 1968, 1970; Amdur, 1954; 1958, 1959, 1961; Amdur and Corn, 1963; Amdur et al., 1978a,b,c,) have studied the effects of aerosols alone (see Table 12-6) or in combination with SO_2. The combination studies are described in Section 12.4.1.1. In all of their studies, exposures were for 1 hr. The method records resistance to air flow in and out of the lungs and airways, compliance (a measure of lung distensibility), tidal volume (the volume of air moved during normal breathing), respiratory frequency, and minute volume. While increased flow resistance is often the most striking feature of the response to aerosols, calculations of the elastic, resistive, and total work of breathing can also be made. The method is, therefore, nearly as elaborate and inclusive an evaluation of pulmonary mechanics as could be made in small laboratory animals until very recently (Drazen, 1976).

The importance of particle size on the site of pulmonary deposition is described in Chapter 11. The impact of these factors on the effects on human health is clear from an early study (Amdur, 1958). Sulfuric acid aerosols of concentrations ranging from 1.9 to 43.6 mg/m^3 were generated in three particle sizes: 0.8 μm (σ_g, 1.32 μm), 2.5 μm (σ_g, 1.38 μm), or 7 μm (σ_g, 2.03 μm) MMD. Particles of the largest size (7 μm, at 30 mg/m^3) produced a significant increase in flow resistance but no other detectable changes in respiration. At the lowest concentration tested, 1.9 mg/m^3, the 0.8 μm particles produced an increase in resistance to flow and in elastic, resistive, and total work of breathing; but they produced a decrease in compliance. The 2.5 μm particles also increased the resistance to flow at concentrations from 2.3 to 43.6 mg/m^3. The relative efficacy of the 0.8 and 2.5 μm particles differed. At

TABLE 12-6. RESPIRATORY RESPONSE OF GUINEA PIGS EXPOSED FOR 1 HR TO PARTICLES IN THE AMDUR et al. STUDIES

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm H_2O/ml/sec % difference from control	Compliance ml/cm H_2O % difference from control	Reference
H_2SO_4	0.10	0.3	+41*	-27*	Amdur et al., 1978b; Amdur, 1975
	0.51	0.3	+60*	-33*	Amdur et al., 1978b
	1.00	0.3	+78*	-40*	Amdur et al., 1978b
	1.90	0.8	+51*	-35*	Amdur, 1969; Amdur, 1958
	5.30	0.8	+54*	-40*	Amdur, 1958
	15.40	0.8	+69*	-24*	Amdur, 1958
	26.1	0.8	+89*	-38*	Amdur, 1958
	42.00	0.8	+120*	-26*	Amdur, 1958
	0.11	1.0	+14*	-13	Amdur et al., 1978b
	0.40	1.0	+30*	-8	Amdur et al., 1978b
	0.69	1.0	+47*	-25*	Amdur et al., 1978b
	0.85	1.0	+60*	-28*	Amdur et al., 1978b
	2.30	2.5	+39*	-16	Amdur, 1958
	8.90	2.5	+61*	-26*	Amdur, 1958
	15.40	2.5	+96*	-43*	Amdur, 1958
	43.60	2.5	+317*	-76*	Amdur, 1958
	30.50	7.0	+42*	-17	Amdur, 1958
$(NH_4)_2SO_4$	0.50	0.13	+23*	-27*	Amdur et al., 1978a
	2.14	0.20	-4	-13*	Amdur et al., 1978a
	1.02	0.30	+29*	-23*	Amdur and Corn, 1963; Amdur et al., 1978a; Amdur, 1974
	9.54	0.81	0	-12*	Amdur et al., 1978a
NH_4HSO_4	0.93	0.13	+15*	-15*	Amdur et al., 1978a
	2.60	0.52	+28*	-30*	Amdur et al., 1978a
	10.98	0.77	+23*	-19*	Amdur et al., 1978a

TABLE 12-6. (continued).

Compound	Concentration mg/m^3	Particle size, μm, MMD**	Resistance cm H_2O/ml/sec % difference from control	Compliance ml/cm H_2O % difference from control	Reference
Na_2SO_4	0.90	0.11	+2	-7	Amdur et al., 1978a
$ZnSO_4$	0.91	1.4	+41*		Amdur and Corn, 1963; Amdur, 1974
$ZnSO_4 \cdot$	0.25	0.29	+22*		Amdur and Corn, 1963; Amdur, 1975
$(NH_4)_2SO_4$	0.50	0.29	+40*		Amdur and Corn, 1963
	1.10	0.29	+81*		Amdur and Corn, 1963; Amdur, 1974
	1.80	0.29	+129*		Amdur, 1969; Amdur and Corn, 1963
	1.50	0.51	+43*		Amdur and Corn, 1963; Amdur, 1975
	2.48	0.51	+68*		Amdur and Corn, 1963
	1.40	0.74	+29*		Amdur, 1969; Amdur and Corn, 1963; Amdur, 1975
	1.10	1.4	+6		Amdur and Corn, 1963; Amdur, 1975
	3.60	1.4	+32*		Amdur and Corn, 1963
$CuSO_4$	0.43	0.11	+9	-11*	Amdur et al., 1978a
	2.05	0.13	+25*	-15*	Amdur et al., 1978a
	2.41	0.33	+14*	-11*	Amdur et al., 1978a
$NaVO_4$	0.70		+7		Amdur and Underhill, 1968
$FeSO_4$	1.00		+2		Amdur and Underhill, 1968

TABLE 12-6. (continued)

Compound	Concentration mg/m^3	Particle size, μm, MMD	Resistance cm H_2O/ml/sec % difference from control	Compliance ml/cm H_2O % difference from control	Reference
Fe_2O_3 (2hr)	11.70	0.076 (GMD)	-9	5	Amdur and Underhill, 1968; 1970
(Fumes)	21.00	0.076 (GMD)	0	0	Amdur and Underhill, 1968; 1970
$MnCl_2$	1.00		+4		Amdur and Underhill, 1968
MnO_2	9.70		-6		Amdur and Underhill, 1968
$MnSO_4$	4.00		-1		Amdur, 1974
Open hearth	0.16	0.037 (GMD)	+9	0	Amdur and Underhill, 1968; 1970
dust	7.00	0.037 (GMD)	+6	-16	Amdur and Underhill, 1968; 1970
Activated carbon	8.70		-3		Amdur and Underhill, 1968
Spectographic	2.00		+7		Amdur and Underhill, 1968
carbon	8.00		+17		Amdur and Underhill, 1968

*$p < 0.05$

**Diameters are provided as mass median diameter (MMD) unless specified as geometric median diameter by count (GMD).

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concentrations of 2 mg/m^3, the 0.8 μm particles were more effective than the 2.5 μm particles. The time course of the response also varied with the particle size, since the 2.5 μm particles did not evoke their major effects until the last 15 to 20 min of the 1 hr exposure. These differences in response were probably associated with the degree and site of obstruction within the bronchi. The 2.5 μm particles affected the larger bronchi producing obstruction, whereas the 0.8 μm particles caused narrowing of the smaller bronchi. While the results of the experiments are reported in a straightforward concentration-response curve, the physiological mechanisms producing the measurable effects are obviously highly complex. Detailed understanding is lacking.

In a more recent investigation, Amdur et al. (1978b) exposed guinea pigs for 1 hr to either 0.3 or 1 μm (MMD) H_2SO_4 in concentrations ranging from 0.1 to 1 mg/m^3. The concentration-response for percent change in resistance was linear for both particle sizes. However, the smaller particle caused a greater response, particularly at 0.1 mg/m^3 where a 26 percent increase in airway resistance was observed. Except for exposure to 0.11 mg/m^3 H_2SO_4 (1 μm), all increases in resistance were statistically significant. The smaller particle size also decreased compliance at all concentrations tested. However, for the 1 μm particle the lowest effective concentration tested was 0.69 mg/m^3. For equivalent concentrations, the 0.3 μm particle decreased compliance more than the 1 μm particle. Animals were also examined 30 min after exposure ceased. At this time, after exposure to 0.1 mg/m^3 H_2SO_4 (0.3 μm) resistance was still elevated above control in guinea pigs; but for the 1 μm particle, recovery had occurred. These exposures caused no alterations of tidal volume, respiratory frequency, or minute volume. In comparing these results to earlier work with SO_2 (Amdur, 1966), Amdur et al. (1978b) describe how the same amount of sulfur when given as H_2SO_4 produces 6 to 8 times the response observed than when given as SO_2.

Silbaugh et al. (1980) exposed Hartley guinea pigs for 1 hr to 1 μm (MMAD) sulfuric acid aerosols at concentrations and relative humidities of 0 mg/m^3 (control group) (40 or 80 percent RH), 1.2 mg/m^3 (40 percent RH), 1.3 mg/m^3 (80 percent RH), 14.6 mg/m^3 (80 percent RH), 24.3 mg/m^3 (80 percent RH), or 48.3 mg/m^3 (80 percent RH). Ten animals were exposed at each concentration except for the 24.3 and 48.3 mg/m^3 groups, which consisted of 9 and 8 animals, respectively. Measurements of tidal volume, breathing frequency, minute volume, peak inspiratory and expiratory flow, tidal transpulmonary pressure excursions, total pulmonary resistance and dynamic lung compliance were obtained every 15 min during (1) a 30 min baseline period, (2) the 60 min exposure period, and (3) a 30 min recovery period. Pulmonary function changes in sulfuric acid-exposed guinea pigs did not differ from controls, except for 1 animal exposed to 14.6 mg/m^3, 3 animals exposed to 24.3 mg/m^3, and 4 animals exposed to 48.3 mg/m^3. Pulmonary function changes in these 8 responsive animals included marked increases in total pulmonary resistance and marked decreases in dynamic compliance. Four of these 8 guinea pigs died during exposure. The proportion of responsive to non-responsive animals increased with exposure concentration, but the magnitude of pulmonary function change was similar for all responsive animals. Compared to non-responders, responsive animals tended to have higher pre-exposure

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values of total pulmonary resistance and lower pre-exposure values of dynamic compliance. Authors suggested that guinea pigs react to acute sulfuric acid exposure with an essentially all-or-none airway constrictive response. The finding that resistance and compliance changes are important components of the guinea pig's airway response to sulfuric acid aerosols is consistent with results published by Amdur et al. (1978b). The presence of high pre-exposure pulmonary resistance values in responsive animals is similar to the finding by Amdur (1964) that guinea pigs with high pre-exposure resistance values were those most severely affected during irritant aerosol exposure. However, the lack of effects at lower concentrations and the essentially all-or-none airway constrictive response observed in these studies differs markedly from the graded response observed by Amdur et al. (1958, 1978b) during similar exposures. The bifurcating and declining airway diameter of the lung make all-or-none responses as measured by changes in airflow unlikely. The graded response observed by Amdur et al. (1958, 1978b) seems more reasonable. The reasons for the differences in experimental results are unclear, but may be at least partially related to differences in animal strains and techniques. These results indicate that changes in respiratory function do not occur at environmental concentrations of sulfuric acid in most animals, but suggest that susceptible subpopulations might exist. (See discussion above about susceptible individuals.)

Sackner et al. (1978) evaluated pulmonary function in anesthetized dogs immediately after or 2 hr after exposure to approximately 18 mg/m^3 H_2SO_4 for 7.5 min or to 4 mg/m^3 H_2SO_4 for 4 hr. The MMAD was < 0.2 μm. There were no significant changes in respiratory resistance, specific respiratory conductance, specific lung compliance, or functional residual capacity. At the higher concentration, cardiovascular parameters (e.g., blood pressure, cardiac output, heart rate, and stroke volume) and arterial blood gas tensions were also studied, but no significant changes were observed. The pulmonary function (pulmonary resistance and dynamic compliance) of donkeys was not affected by H_2SO_4 exposure (1.51 mg/m^3, 0.3 to 0.6 MMAD, 1 hr) (Schlesinger et al., 1979).

Studies of the irritant potential of sulfate salts have shown that these aerosols are not innocuous but evoke increased flow resistance similar to sulfuric acid aerosols. The influence of particle size on the effects of zinc ammonium sulfate has also been investigated by Amdur and Corn (1963). They showed, in guinea pigs exposed for 1 hr, that zinc sulfate had about half the potency of zinc ammonium sulfate, with ammonium sulfate being one-third to one-fourth as potent as zinc ammonium sulfate. Zinc ammonium sulfate was chosen for study because it had been reported as a major component of the aerosol from the Donora, PA episode of 1948 (Hemeon, 1955). Zinc ammonium sulfate is not a common species found in urban air. Four sizes of aerosols were administered: 0.29, 0.51, 0.74, and 1.4 μm (particle mean size by weight). When the aerosol concentration was held constant at 1 mg/m^3, the smaller particles produced greater increased resistance to flow. This response was thought to be the result of the number of particles rather than of differential sites of deposition. The dose-response curve also became steeper with decreasing particle size. These data should be carefully compared with those from similar human exposures (Chapter 13, pp. 26-29) where no response occurred.

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Amdur et al. (1978a) recently compared the effects of $(NH_4)_2SO_4$, NH_4HSO_4, $CuSO_4$, and Na_2SO_4. Although particle sizes and concentrations were not precisely matched throughout the study, statistical analyses for ranking were not applied, and the degree of response increased with decreased size (size range, 0.1 to 0.8 μm, MMD), the authors suggest that the order of irritant potency was $(NH_4)_2SO_4$ > NH_4HSO_4 > $CuSO_4$. Sodium sulfate (0.11 mg/m^3, 0.11 MMD) caused no significant effects on either resistance or compliance. At the lowest concentrations used, $(NH_4)_2SO_4$ (0.5 mg/m^3, 0.13 μm MMD), NH_4HSO_4 (9.93 mg/m^3, 0.13 μm MMD), and $CuSO_4$ (0.43 mg/m^3, 0.11 μm MMD) decreased compliance. These concentrations of $(NH_4)_2SO_4$ and NH_4HSO_4 also increased resistance. For $CuSO_4$, the lowest concentration tested which caused an increase in resistance was 2.05 mg/m^3 (0.13 μm MMD). All of these compounds are less potent than H_2SO_4 in the Amdur studies.

Comparisons between sulfuric acid and sulfate salt aerosols are difficult to make because of the marked dependence of the efficacy on the aerosol size. If the particles are of identical size, sulfuric acid is more efficacious than zinc ammonium sulfate; but if the zinc ammonium sulfate were present as a submicron aerosol and the sulfuric acid as a large aerosol, then zinc ammonium sulfate would be more efficacious at the same concentration (Amdur, 1971). Regardless of the particle size, the equivalent amount of sulfur present as SO_2 is much less efficacious than if it were present as a sulfate salt or sulfuric acid. When present as SO_2, 2.62 mg/m^3 (1 ppm) SO_2 is equivalent to 1.3 mg/m^3 S and produces a 15 percent increase in flow resistance. If this amount of sulfur were present as a 0.7 μm aerosol of sulfuric acid, it would evoke a 60 percent increase in flow resistance or be about 4 times more efficacious. If the sulfur were present as zinc ammonium sulfate as a 0.3 μm aerosol, the increase in flow resistance would be about 300 percent or a 20-fold increase in efficacy. Some sulfate salt aerosols are not irritating. For example, though ferrous sulfate and manganous sulfate do not cause an increase in flow resistance, ferric sulfate does cause this response. A summary of irritant potency is presented below.

Relative Irritant Potency of Sulfates In Guinea Pigs Exposed for One Hour[a] (Amdur et al., 1978a)

Sulfuric acid	100
Zinc ammonium sulfate	33
Ferric sulfate	26
Zinc sulfate	19
Ammonium sulfate	10
Ammonium bisulfate	3
Cupric sulfate	2
Ferrous sulfate	0.7
Sodium sulfate (at 0.1 μm)	0.7
Manganous sulfate	-0.9

[a]Data are for 0.3 μm (MMD) particles. Increases in airway resistance were related to sulfuric acid (0.41% increase in resistance per μg of sulfate as sulfuric acid) which was assigned a value of 100.

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Nadel et al. (1967) found that zinc ammonium sulfate (no concentration given) and histamine aerosols produced similar increases in resistance to flow and decreases in pulmonary compliance in the cat. Histamine was more potent than zinc ammonium sulfate. The increase in flow resistance could not be blocked by intravenous administration of atropine sulfate, but was blocked by either intravenous or inhaled isoproterenol. The increased flow resistance was suggested to be due to an increase in bronchial smooth muscle tone. Histamine appears to be a likely mediator of the bronchoconstriction following inhalation of sulfate salt aerosols. Charles and Menzel (1975a) investigated the release of histamine from guinea pig lung fragments incubated with varying concentrations of sulfate salts. Almost complete release of tissue histamine occurred with 100 mM ammonium sulfate. Intratracheal injection of ammonium sulfate also released all of the histamine from perfused and ventilated rat lungs (Charles et al., 1977a). The potency ranking of different sulfate salts in the release of histamine from lung fragments (Charles and Menzel, 1975a; Charles et al., 1977a) was equivalent to that causing increased resistance to flow (Amdur et al., 1978a). Bronchoconstriction of the perfused lung occurred on intratracheal injection of sulfate salts or histamine (Charles et al., 1977a). About 80 percent of the constriction could be blocked by prior treatment of the isolated lungs with an H-1 antihistamine. These experiments, as well as the original observations of Nadel et al. (1967) and Amdur et al. (1978a), support the concept that an intermediary release of histamine or some other vasoactive hormone is involved in the irritant response of sulfate aerosols. An ammonium sulfate particle is calculated to reach a concentration of about 275 mM at equilibration with the 99.5 percent relative humidity of the respiratory tract (Committee on Sulfur Oxides, NAS, 1978). Thus, the concentration of the hydrated particle on striking the mucosa would be within the range found to cause release of histamine in guinea pig and rat lung fragments (Charles and Menzel, 1975a; Charles et al., 1977a). A recently published estimate of the dose of inhaled ammonium sulfate needed to release histamine in the lung is in error (Committee on Sulfur Oxides, NAS, 1978). Complete release of histamine (100 percent) occurred with 1 μmole of ammonium sulfate/lung and not 1 μM solution for the entire lung (Charles et al., 1977a). Further, total release of all histamine stores of a tissue rarely, if ever, occurs under physiological conditions. Only about 10 percent of the total histamine is released during degranulation reactions in vivo, producing anaphylactic shock and death. Therefore, even if the calculations were correct, only a small fraction of the ammonium sulfate dose would be required to produce the far less violent increases in flow resistance reported by Amdur et al. (1978a) for ammonium bisulfate and ammonium sulfate. Assuming the calculation of ammonium sulfate to be correct, a 4 hr, not a 2 day, inhalation would produce a marked increase in resistance to flow. Additionally, Charles et al. (1977b) found the rate of removal of $^{35}SO_4^{-2}$ from the rat lung both in vivo and in vitro to be a function of the cation associated with the salt and to follow the same order of potency as reported by Amdur and co-workers (1978a) in the guinea pig irritancy test. Especially noteworthy is the fact that manganous sulfate was removed at essentially the same rate as sodium sulfate, both of which did not produce increased resistance to flow in the guinea pig.

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Hackney (1978) has presented a preliminary summary of the effects of aerosols of H_2SO_4 and nitrate and sulfate salts on squirrel monkeys (Saimiri sciurens). Monkeys were exposed (head-only) to aerosols at 2.5 mg/m^3 of the respective salts or sulfuric acid, 40 or 85 percent RH at 25°C. The exposure system was designed to reduce stress on the unanesthetized monkey. A non-invasive method of pulmonary function measurement was used in which total respiratory resistance was measured by the forced pressure oscillation technique at sine wave frequencies of either 10 or 20 Hz. The measurement of pulmonary resistance included the resistance of the chest wall which was assumed to be irrelevant to pollutant response and to be constant throughout the experiments. To correct for stress, control values were taken as those for a given monkey exposed on the previous day to an aerosol of distilled water (for aerosol experiments).

Hackney (1978) reports that the measurement of respiratory resistance was frequency-dependent, with changes in resistance appearing greater in the 10 Hz than the 20 Hz measurement frequency. (The measurement frequency is not to be confused with the breathing frequency.) The exposure period in the experiments was either 1 or 2 hr. Some aerosols were studied at only 40 percent RH. No attempt was made at a dose-response curve for aerosols and all exposures were at or near 2.5 mg/m^3. At low relative humidity (40 percent RH; MMAD 0.3 μm, σ_g 2.0), there were no differences between $(NH_4)_2SO_4$-exposed and control values, while at high relative humidity (85 percent RH, MMAD 0.6 μm, σ_g 2.3), 3 of 5 monkeys had increased airway resistance by 1 hr. Zinc ammonium sulfate aerosols produced increased resistance at low humidity (40 percent RH; MMAD 0.3 μm, σ_g 2.5) but no consistent increases over control values at high humidity (85 percent RH; MMAD 0.6 μm, σ_g 1.6). Ammonium bisulfate (40 percent RH; MMAD 0.4 μm, σ_g 1.8) also produced increased resistance at 2.7 mg/m^3.

Data (Hackney, 1978) from exposures to sulfuric acid and NH_4NO_3 aerosols were analyzed by computer and differed quantitatively from the data reported above for those exposures which were reduced by hand. Differences were probably due to a systematic error in the hand reduced data which required a judgement in selection of raw data points. The biological interpretation does not appear to be altered by these two approaches, but it does point out the experimental difficulties in interpretation of pulmonary function data from experimental animals. While H_2SO_4 aerosols (40 percent RH; MMAD 0.4 μm, σ_g 2.0) caused no statistically significant increases, there was a trend toward increased resistance after 60 min which then tended to decline. Ammonium nitrate exposures produced no changes.

Multiple contrast analysis of the above data (Hackney, 1978) showed that no significant differences between baseline or control values could be found for any exposure using data collected at the 20 Hz measurement frequency. At the 10 Hz measurement frequency, the data were more variable, but significant differences indicative of increased airway resistance could be found for animals exposed to $ZnSO_4$, $(NH_4)_2SO_4$ and H_2SO_4 at 40 percent relative humidity. Several procedural aspects should be recognized. First, data were analyzed on a group mean basis, even though large differences between individual monkeys existed in both variability

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and absolute magnitude. Second, the time course of exposure to the aerosols illustrated a trend indicative of a transient response on the part of monkeys to sulfate, nitrate, or sulfuric acid aerosols. The use of group means tended to reduce the magnitude of the response and flatten the response-time curve. This is certainly true for the SO_2 exposures. Third, there were major differences in the response measured at either 10 or 20 Hz. Fourth, the response estimated by both manual and computer reduction differed by as much as 40 percent. However, compared to the data reported for guinea pigs, these experiments support the general trends originally proposed from the guinea pig data.

Sackner and co-workers (1976, 1977a,b,c, 1978b) have noted that neither ammonium sulfate or sulfuric acid aerosols alters cardiovascular and pulmonary function in dogs or tracheal mucus velocity in sheep. Some of these reports are at variance with the previously cited published experiments. No significant alterations in pulmonary resistance and dynamic compliance were observed in donkeys exposed to 0.4 to 2.1 mg/m^3 $(NH_4)_2SO_4$ (0.3 to 0.6 μm MMAD) for 1 hr (Schlesinger et al., 1978). The small size of the particles may be responsible for the lack of an effect. Larger particles in other studies may be more potent.

Larson and co-workers (1977) have proposed that breath ammonia is important in neutralizing inhaled sulfuric acid. Ammonia is released in the breath from blood ammonia and bacterial decay products in the buccal cavity. Ammonia in the breath could react with sulfuric acid to produce ammonium bisulfate or ammonium sulfate, depending upon the amount of ammonia and sulfuric acid present in the aerosol droplet. Complete neutralization of sulfuric acid would produce ammonium sulfate. This theory has been discussed at some length (Committee on Sulfur Oxides, NAS, 1978). Much of the data has not yet been published, so a critical review of the model given for the neutralization of sulfuric acid aerosol droplets by gaseous ammonia is not available. Calculation of the relationship between inhaled sulfuric acid aerosol and neutralization by breath ammonia is not simple, and the model needs to be validated.

The biological effects of sulfuric acid aerosols could be due to a combination of several factors. First, the pH of the particle could be very important. Larson et al. (1977) have calculated the neutralization capacity of the breath ammonia. Once the neutralization capacity of the ammonia present in the breath is exceeded, the pH of the aerosol reaching the lung may fall rapidly. Under low pH, the physical properties of the mucous layer lining the upper airways may be altered (Holma et al., 1977) or the permeability of the lung may be increased (Charles, 1976). Second, the chemical composition of the sulfate aerosol, if other than sulfuric acid, may also alter the permeability of the lung to sulfate (Charles et al., 1977b; Charles, 1976; Charles and Menzel, 1975b). Third, the cation associated with the sulfate compound may have pharmacological properties in itself. The permeability of the lung to sulfate ion presented as various sulfate salts (Charles et al., 1977b) is in the same relative order as the irritant potential found for aerosols of the same sulfate salts (Amdur et al., 1978a).

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It is likely that ammonia functions within pulmonary tissue as a source of protons to increase the flux of sulfate to the site of action. Ammonia can diffuse readily across cell membranes as unionized ammonia to react with protons forming ammonium ion. Intracellular transport of negatively charged sulfate would result in the concomitant accumulation of positively charged protons to preserve electrochemical neutrality. At physiological pH values, a significant fraction of ammonium salts is present as ammonia. Ammonium salts could augment the local ammonia concentration and thus increase the uptake of sulfate ions and result in release of histamine. Ammonia increased the uptake of sulfate by the lung (Charles et al., 1977a; Charles, 1976), possibly by this mechanism.

In relation to sulfuric acid, ammonium sulfate and bisulfate are less irritating to the lung because of their higher pH values once dissolved in the milieu of the lung. Thus, neutralization of sulfuric acid aerosols by breath ammonia could be an important detoxification step. The concept of breath ammonia does not negate the histamine release hypothesis since ammonium sulfate is active in the release of histamine in guinea pig lung fragments (Charles, 1976) and in rat lungs (Charles and Menzel, 1975b).

An important problem is the relation of these observations to human effects. Unfortunately, histamine release by non-immune mediate reactions, such as the apparent ion exchange process due to sulfate interaction with mast cell granules (Charles, 1976), is poorly understood. Metabolism of histamine by man and rodents could have important differences. Also, not all of the pharmacological action of ammonium sulfate instilled intratracheally in the perfused rat lung could be blocked by an H-1 antihistamine (Charles et al., 1977a). A number of other inflammatory hormones, aside from histamine, mediate bronchial tone in man. Slow reacting substance of anaphylaxis (SRS-A or leukotrienes), prostaglandins, and kinins would not be blocked by an H-1 antihistamine. Thus, species differences are not unanticipated, but should be clarified so the potential applicability of these data to man is understood.

The biological effect of sulfate compounds is highly dependent upon the chemical composition of the compound. For example, for pulmonary function sulfuric acid is much more potent than any sulfate salt, but the sulfate salts also are of differing potency. The cations associated with the sulfate ion may promote the transport of the sulfate ion and, thereby, increase the biological response. The cation has biological effects by itself as discussed here. It is not possible, then, to predict the potential toxicity of a sulfate aerosol based solely on the sulfate content. Clearly, the acidity of the aerosol plays an important role in the toxicity as do particle size and other physical properties.

An important experimental problem is raised by the ammonia neutralization of sulfuric acid. Ammonia is produced in all animal experimental exposure systems through the accumulation of urine and feces. This is particularly so in whole-body chronic exposures. Few exposure systems provide a rapid turnover of the chamber air, e.g., 1 chamber volume/min, and given the technological problems in monitoring NH_3, even this rate of air flow may be insufficient. The

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usual turnover rate is 10 to 15 chamber volumes of air/hr or less. Under these conditions, animals exposed to sulfuric acid aerosols may, in fact, be inhaling ammonium sulfate and ammonium bisulfate aerosols as well. The high concentrations of sulfuric acid aerosols needed to produce significant pathological effects on chronic exposure may be due to these chemical conversions. Since human exposure chambers would not be expected to have comparably high levels of ammonia, there could be difficulty in comparing results of human and animal studies of H_2SO_4. The level of ammonia in the breath of animals is also unknown and is sure to vary with the diet of the animals. Some commercial animal diets are low in protein, while others are high. The blood ammonia will depend, in part, on the total amount of protein and quality of the protein as well as on the kidney function of the animal. What effects, if any, the buccal flora have on the exhalation of ammonia in animals is totally unknown. Certainly, the propensity of SO_2- and sulfuric acid-exposed animals to develop nasal infections raises disturbing questions. The buccal flora of animals may be very different from that of man in its ability to produce ammonia. This technical problem of ammonia in the exposure atmosphere should be addressed and solved before further reliance can be placed on these data for sulfuric acid (Table 12-7).

12.3.3.2 Chronic Exposure Effects--The influence of chronic exposure to H_2SO_4 on pulmonary function was investigated by Alarie et al. (1973a, 1975). Guinea pigs exposed continuously to either 0.9 mg/m^3 (0.49 μm, MMD) (Alarie et al., 1975), 0.1 mg/m^3 (2.78 μm, MMD) (Alarie et al., 1973a), or 0.08 mg/m^3 (0.84 μm, MMD) (Alarie et al., 1973a) for 52 wk had no significant changes of pulmonary mechanics (including measurements of flow resistance, respiratory rate, lung volumes, and work of breathing) that could be attributed to H_2SO_4. However, cynomolgus monkeys exposed continuously and tested periodically during 78 wk were affected by some treatment regimens (Alarie et al., 1973a). Monkeys exposed to 0.48 mg/m^3 (0.54 μm, MMD) experienced an altered distribution of ventilation (increased N_2 washout) early in the exposure period, but recovery occurred during exposure. Animals exposed to a similar concentration (0.38 mg/m^3) but a larger particle size (2.15 μm, MMD) had no change in this parameter. Higher concentrations altered distribution of ventilation, with the lesser concentration (2.43 mg/m^3) and larger particle size (3.6 μm, MMD) causing an onset sooner (at 17 wk compared to 49 wk) in monkeys exposed to 4.79 mg/m^3 H_2SO_4 (0.73 μm, MMD). Beginning at approximatey 8 to 12 wk of exposure, 0.38 mg/m^3 (2.15 μm, MMD), 2.43 mg/m^3 (3.6 μm, MMD) and 4.79 mg/m^3 (0.73 μm, MMD) H_2SO_4 increased respiratory rate. The only alteration in arterial partial pressure of O_2 was a decrease observed in monkeys exposed to 2.43 mg/m^3. Except for respiratory rate as described above, mechanical properties (including resistance, compliance, tidal volume, minute volume, and work of breathing) were not significantly altered by the chronic H_2SO_4 exposures. Morphological studies of these animals are described in Section 12.3.2.

Chronic studies of dogs were performed by Lewis et al. (1969, 1973). The animals were exposed for 21 hr/day for 225 or 620 days to 0.89 mg/m^3 H_2SO_4 (90 percent < 0.5 μm in

TABLE 12-7. EFFECTS OF ACUTE EXPOSURE TO PARTICULATE MATTER ON PULMONARY FUNCTION*

Concentration	Duration	Species	Results	Reference
0 mg/m^3 (40 or 80% RH) 1.2 mg/m^3 (40% RH), 1.3 mg/m^3 (80% RH), 14.6 mg/m^3 (80% RH), 24.3 mg/m^3 (80% RH), and 48.3 mg/m^3 (80% RH) 1 μm (MMAD) H_2SO_4 aerosol	1 hr	Guinea pig	Pulmonary function changes observed in one animal (out of 10) exposed to 14.6 mg/m^3, three animals (out of 9) exposed to 24.3 mg/m^3, and four animals (out of 8) exposed to 48.3 mg/m^3	Silbaugh et al., 1980
0.8 - 1.51 mg/m^3 H_2SO_4 (0.3 - 0.6 μm, MMAD) or 0.4 - 2.1 mg/m^3 $(NH_4)_2SO_4$ (0.3 - 0.6 μm, MMAD)	1 hr	Donkey	No significant alterations in pulmonary resistance and dynamic compliance	Schlesinger et al., 1978
2.5 mg/m^3 $(NH_4)_2SO_4$, $ZnSO_4$, $(NH_4)_2SO_4$, H_2SO_4, and NH_4NO_3; 2.7 mg/m^3 NH_4HSO_4	1 hr	Monkey	Increased airway resistance at high relative humidity for $(NH_4)_2SO_4$, and low relative humidity for $ZnSO_4$ $(NH_4)_2SO_4$. NH_4HSO_4 also increased resistance. No significant effects with H_2SO_4 or NH_4NO_3	Hackney, 1978

*See Table 12-6 for the Amdur et al. studies on pulmonary function effects in guinea pigs.

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diameter) alone and in combination with SO_2 (see Section 12.4.1.2 for expanded discussion). After 225 days (Lewis et al., 1969), dogs receiving H_2SO_4 had a significantly lower diffusing capacity for CO than animals that did not receive H_2SO_4. After 620 days of exposure, CO diffusing capacity was still decreased ($p < 0.05$) (Lewis et al., 1973). In addition, residual volume and net lung volume (inflated) were decreased ($p < 0.05$), and total expiratory resistance was increased ($p < 0.05$). Total lung capacity, inspiratory capacity, and functional residual capacity were also decreased ($p = 0.1$). Other pulmonary function measurements were not significantly affected (see Table 12-8).

12.3.4 Alteration in Host Defenses

To protect itself against inhaled microorganisms and inanimate particles, the host has several mechanisms of defense. Microbes reaching the gaseous exchange regions of the lung can be phagocytized and killed by alveolar macrophages. Later these macrophages can move to the ciliated airways where they are cleared from the lung, along with other particles that are deposited on the airways, by the mucociliary escalator. Inanimate particles can also be engulfed and removed from the lung by this means (See Chapter 11). Mucociliary clearance is an important defense against both microorganisms and inanimate particles. It is likely then that an impairment of mucociliary clearance might not be expressed as increased infections. These and other means of defense against microbes are discussed here.

12.3.4.1 Mucociliary Clearance--Fairchild et al. (1975b) investigated the influence of a 1 hr exposure to H_2SO_4 on deposition of inhaled nonviable bacteria (Streptococcus pyogenes, 2.6 μm MMAD) in guinea pigs. All exposure regimens used caused no significant alterations of breathing frequency, tidal volume, or minute ventilation. After exposure to 3.02 mg/m^3(1.8 μm CMD), a 60 percent increase ($p < 0.01$) in total pulmonary bacterial deposition and a proximal shift in the deposition pattern to the nasopharynx were observed. No alteration in deposition was observed in the trachea or lung. After exposure to 0.32 mg/m^3 (0.6 μm CMD), no significant effect on total or regional deposition was seen. However, at a lower concentration and particle size (0.03 mg/m^3, 0.25 μm CMD), the deposition pattern did shift ($p < .05$) to the trachea but without a significant change in total pulmonary deposition.

After studying effects of H_2SO_4 on deposition of bacteria, these investigators (Fairchild et al., 1975a) turned their attention to effects on clearance of bacteria. They showed that 4 hr exposures to 15 mg/m^3 H_2SO_4 (3.2 μm, CMD) after exposure to a nonviable radiolabeled streptococcal aerosol reduced the rate of ciliary clearance of the bacteria from the lungs and noses of mice. When mice received a 90 min exposure to 15 mg/m^3 H_2SO_4 (3.2 μm, CMD) 4 days prior to the bacterial aerosol, clearance of nonviable bacteria was reduced in the nose but not in the lungs. Neither regimen affected clearance of viable streptococci. No significant effects were seen at concentrations of 1.5 mg/m^3 H_2SO_4 (0.6 μm, CMD).

Schlesinger et al. (1978) demonstrated that 1 hr exposures to 0.3 to 0.6 μm H_2SO_4 mist at concentrations in the range of 0.19 to 1.36 mg/m^3 produced transient slowing of bronchial mucociliary particle clearance in 3 of 4 donkeys tested. In addition, 2 of the 4 donkeys

TABLE 12-8. EFFECTS OF CHRONIC EXPOSURE TO PARTICULATE MATTER ON PULMONARY FUNCTION

Concentration	Duration	Species	Results	Reference
0.08 mg/m^3 H_2SO_4 (0.84 μm, MMD) or 0.1 mg/m^3 H_2SO_4 (2.78 μm, MMD)	52 wk, continuous	Guinea pig	No effects on pulmonary function.	Alarie et al., 1975, 1973
0.38 mg/m^3 (1.15 μm, MMD) 0.48 mg/m^3 (0.54 μm, MMD) 2.43 mg/m^3 (3.6 μm, MMD) 4.79 mg/m^3 (0.73 μm, MMD) H_2SO_4	78 wk, continuous	Monkey	Exposure to 0.48 mg/m^3 altered distribution of ventilation early in the exposure period, but not later. Exposure to 2.43 or 4.79 mg/m^3 altered distribution of ventilation. Exposure to 0.38, 2.43, or 4.79 mg/m^3 increased respiratory rate. Other pulmonary function parameters were not affected.	Alarie et al., 1973
0.89 mg/m^3 H_2SO_4 (90% <0.5 μm in diameter)	21 hr/day, 225 or 620 days	Dog	After 225 days lower CO diffusing capacity. After 620 days capacity was still decreased, residual volume and net lung volume were decreased, and total expiratory resistance was increased; total lung capacity, inspiratory capacity, and functional residual capacity were also decreased. Other pulmonary function parameters were not affected.	Lewis et al., 1969, 1973

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developed persistently slowed clearance after about 6 exposures. Similar exposures had no effects on regional particle deposition or respiratory mechanics, and corresponding exposures to $(NH_4)_2SO_4$ up to 2 mg/m^3 had no measurable effects. In subsequent experiments (Schlesinger et al., 1979), the 2 animals showing only transient responses and 2 previously unexposed animals were given daily 1 hr exposures, 5 days/wk, to H_2SO_4 at 0.1 mg/m^3. Within the first few wk of exposure, all 4 donkeys developed erratic clearance rates, i.e., rates which, on specific test days, were either significantly slower than or significantly faster than those in their pre-exposure period. However, the degree and the direction of change in rate differed to some extent in the different animals. These changes may herald subsequent alterations and, like many other toxicant effects, may represent important low level signals at the detection limit of the method. The 2 previously unexposed animals developed persistently slowed bronchial clearance during the second 3 mo of exposure and during 4 mo of follow-up clearance measurements, while the 2 previously exposed animals adapted to the exposures in the sense that their clearance times consistently fell within the normal range after the first few wk of exposure. The sustained, progressive slowing of clearance observed in 2 initially healthy and previously unexposed animals is a significant observation, since any persistent alteration of normal mucociliary clearance can have important implications. Lippmann et al. (1980) have conducted similar experiments in human subjects which are reviewed in Chapter 13.

Tracheal mucociliary transport rates have been measured in several other animal studies. Sackner et al. (1978a) failed to find significant changes in tracheal mucus velocity following short-term exposures to 14 mg/m^3 (0.12 μm) H_2SO_4 in sheep. Similarly, Schlesinger et al. (1978) saw no effect on tracheal transport in donkeys after 1-hr exposures to concentrations up to 1.4 mg/m^3 (0.3 to 0.6 μm MMAD) H_2SO_4. On the other hand, Wolff et al. (1979a) reported a depression in tracheal transport rate in anesthesized dogs exposed for 1 hr to 1.0 mg/m^3 (0.9 μm, MMAD, σ_g 1.4) which persisted at 1 wk postexposure. Recovery had occurred when the animals were examined again at 5 wk post exposure. Following a 1 hr exposure to 0.5 mg/m^3 H_2SO_4, there were slight increases ($p > 0.05$) in tracheal mucous velocities immediately and 1 day after exposure. However, 1 wk after exposure, clearance was significantly decreased. The latter results are quite similar to those observed in the bronchi of individual humans in the Lippmann et al. (1980) study (see Chapter 13), although they recorded no significant change in the mean tracheal mucociliary transport rates.

Clearly, the results of the donkey studies support the human experiments (Chapter 13) which indicate that H_2SO_4 aerosol affects mucociliary clearance in the distal conductive airways. Mucociliary clearance is dependent upon both the physicochemical properties of the mucus and the coordinated beat of the underlying cilia. Mucus is excreted into the airway lumen in an alkaline form which is then acidified by CO_2 (Holma et al., 1977). In vitro studies have shown that mucus is a sol in high pH solutions, while at lower pH it becomes viscous (Breuninger, 1964). The H^+ supplied by the H_2SO_4 may stiffen the mucus and increase

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the efficiency of removal. This is consistent with the increase in bronchial clearance rate observed in humans following exposure to 0.1 mg/m^3. Major changes in mucous viscosity could also impair clearance by making the mucus so stiff that ciliary movement is not possible. Other studies (Grose et al., 1980; Schiff et al., 1979) have shown that exposures to 0.9 to 1.1 mg/m^3 H_2SO_4 can cause a depression of tracheal ciliary beat frequency in hamsters which may lead to a depression in overall bronchial clearance. See Sections 12.4.1.1 and 12.4.2 for more details on these latter studies (Grose et al., 1980; Schiff et al., 1979) which were conducted with pollutant mixtures.

Based on the results summarized above, it is possible that chronic H_2SO_4 exposures at concentrations of about 0.1 mg/m^3 could produce persistent changes in mucociliary clearance and exacerbate preexisting respiratory disease (see Table 12-9).

Cadmium and nickel chlorides also disrupt the activity of the ciliated epithelium (Adalis et al., 1977, 1978). Tracheal rings have been isolated from hamsters and the beat frequency and morphology of the ciliated epithelium have been observed. Concentrations of $CdCl_2$ as low as 6 μM in vitro resulted in decreased beat frequency and degradation of the ciliated epithelium architecture (Adalis et al., 1977). A prior 2-hr exposure in vivo to 2 μm aerosols of $CdCl_2$ at 0.05 to 1.42 mg/m^3 caused a significant decrease in cilia beat frequency proportional to the aerosol concentration. When hamsters were exposed to 1.33 mg/m^3 Cd for 2 hr/day for 2 days, the beat frequency did not return to control values until 6 wk after exposure. Nickel chloride aerosols or solutions had similar, but less marked, effects (Adalis et al., 1978). The beat frequency decreased by 60 beats/min on exposure to 0.1 mg/m^3 Ni for 2 hr. The decrement in beat frequency was proportional to the concentration of Ni aerosol or solution. A single 2 hr exposure to 0.1 mg/m^3 Ni depressed cilia beat frequency 24 hr after exposure, but the frequency returned to near normal values after 72 hr. After exposure to 0.1 mg/m^3, Cd was about 20 percent more effective than Ni in slowing cilia beat (Table 12-10).

12.3.4.2 Alveolar Macrophages--Cytotoxicity of components of atmospheric aerosols has been studied with alveolar macrophages (AM). The physiological role of AM in the prevention of infection and in the defense of the lung through removal of inhaled particles has been amply demonstrated (Green, 1970).

The viability of guinea pig alveolar macrophages was decreased by Min-u-sil silica (6.8, 4.5, and 2.7 μm MVD), with the effect increasing as particle size decreased (Ottery and Gormley, 1978).

Aranyi et al. (1979) reported cytotoxic effects to AM with fly ash particles coated with PbO, NiO, or MnO_2. The percentage of metal adsorbed on the fly ash was fairly similar across particle size for a given metal. The fly ash particles were of three size ranges: <2, 2 to 5, or 5 to 8 μm in diameter. All of the particles, regardless of the coating or particle size, decreased cell viability and were phagocytized by the AM. Within a given chemical series of coated particles, the effects were both concentration and size related, with smaller particles and greater concentrations producing greater effects. The greater surface area of

TABLE 12-9. EFFECTS OF SULFURIC ACID ON MUCOCILIARY CLEARANCE

Concentration	Duration	Species	Results	Reference
0.1 mg/m^3 H_2SO_4	1 hr/day, 5 day wk, several mo	Donkey	Within the first few wk, all 4 animals developed erratic bronchial mucociliary clearance rates, either slower than or faster than those before exposure. Those animals never pre-exposed before the 0.1 mg/m^3 H_2SO_4 had slowed clearance during the second 3 mo of exposure.	Schlesinger et al., 1979
0.19 to 1.4 mg/m^3 H_2SO_4 (0.3 to 0.6 μm, MMAD)	1 hr	Donkey	Bronchial mucociliary clearance was slowed.	Schlesinger et al., 1978
0.5 mg/m^3 H_2SO_4	1 hr	Dog	Slight increases in tracheal mucociliary transport velocities immediately and 1 day after exposure. One wk later clearance was significantly decreased.	Wolff et al., 1979a
1.0 mg/m^3 H_2SO_4 (0.9 μm, MMAD, σ_g 1.4)	1 hr	Dog	Depression in tracheal mucociliary transport rate persisted at 1 wk post-exposure.	Wolff et al., 1979a
1.4 mg/m^3 H_2SO_4 (0.3 to 0.6 μm, MMAD)	1 hr	Donkey	No effect on tracheal transport.	Schlesinger et al., 1978
1.5 mg/m^3 H_2SO_4 (0.6 μm, CMD)	90 min	Mouse	No significant effects.	Fairchild et al., 1975a
14 mg/m^3 H_2SO_4 (0.12 μm MMAD)	Short-term	Sheep	No significant changes in tracheal mucociliary transport rate.	Sackner et al., 1978a
15 mg/m^3 H_2SO_4 (3.2 μm, CMD)	4 hr	Mouse	Exposure to H_2SO_4 after exposure to a nonviable streptococcal aerosol reduced the rate of ciliary clearance of the bacteria from the lungs and nose.	Fairchild et al., 1975a
15 mg/m^3 H_2SO_4 (3.2 μm, CMD)	90 min	Mouse	Exposure to H_2SO_4 4 days prior to bacterial aerosol. Clearance of nonviable bacteria reduced in nose, but not lungs.	Fairchild et al., 1975a

TABLE 12-10. EFFECTS OF METALS AND OTHER PARTICLES ON HOST DEFENSE MECHANISMS

Concentration	Duration	Species	Results	Reference
0.01 or 0.15 mg/m^3 Pb_2O_3 (0.18 μm, MMAD)	3 mo	Rat	Decreased the number of alveolar macrophages/lung.	Bingham et al., 1968
0.01 mg/m^3 (0.17 μm, MMAD) $PbCl_2$ or 0.11 mg/m^3 (0.32 μm, MMAD) $NiCl_2$ or 0.15 mg/m^3 (0.15 μm, MMAD) Pb_2O_3 or 0.12 mg/m^3 (0.17 μm, MMAD) NiO	12 hr/day, 6 day/wk, 2 mo with $PbCl_2$, $NiCl_2$, or NiO; continuously for 2 mo with Pb_2O_3	Rat	Exposure to Pb_2O_3, but not $PbCl_2$, resulted in a depression of the number of alveolar macrophages (AM) for up to 3 mo but returned to control levels within 3 days after discontinuation. NiO produced a marked AM elevation, while $NiCl_2$ did not. $NiCl_2$ resulted in marked increases in mucus secretion and bronchial hyperplasia. No morphological alterations with $PbCl_2$ or Pb_2O_3.	Bingham et al., 1972
0.05 to 1.42 mg/m^3 $CdCl_2$	2 hr	Hamster	Decreased ciliary beating frequency in trachea.	Adalis et al., 1977
0.1 mg/^{3} $NiCl_2$	2 hr	Hamster	Decreased ciliary beating frequency in trachea.	Adalis et al., 1978
Graded concentrations: 0.075 to 1.94 mg/m^3 $CdCl_2$ 0.1 to 0.67 mg/m^3 $NiCl_2$, or 0.5 to 5 mg/m^3 Mn_3O_4; all aerosols (94-99%) <1.4 μm in diameter	2 hr	Mouse	The aerosols increased the mortality from the subsequent standard airborne streptococcal infection: $CdCl_2$ affect the response at 0.1 mg/m^3 Cd, $NiCl_2$ at 0.5 mg/m^3 Ni, and Mn_3O_4 at 1.55 mg/m^3 Mn.	Gardner et al., 1977b Adkins et al., 1979, 1980c
109 mg/m^3 MnO_2 (0.70 μm, mean diameter)	3 hr/day	Mouse	Increased mortality after 3 or 4 days exposure when mice received bacterial aerosol immediately after exposure. When the bacteria were administered 5 hr post pollutant exposure, a single 3 hr exposure increased mortality. In mice exposed to aerosols of virus 1 or 2 days prior to MnO_2, there were also increased mortality and pulmonary viral lesions.	Maigetter et al., 1976
0.2 mg/m^3 $CdSO_4$, 0.6 mg/m^3 $CuSO_4$, 1.5 mg/m^3 $ZnSO_4$, 2.2 mg/m^3 $Al_2(SO_4)_3$, or 3.6 mg/m^3 $MgSO_4$	3 hr	Mouse	Estimated concentrations which caused a 20% enhancement of bacterial-induced mortality over controls.	Ehrlich et al., 1978, 1979
Ammonium sulfate at 5.3 mg/m^3 SO_4, NH_4HSO_4, at 6.7 mg/m^3 SO_4, NO_2SO_4 at 4 mg/m^3 SO_4, $Fe_2(SO_4)_2$ at 2.9 mg/m^3 SO_4, or $Fe(NH_4)_2SO_4$ at 2.5 mg/m^3 SO_4	3 hr	Mouse	No significant alterations of host defense mechanisms.	Ehrlich et al., 1978, 1979
5.0 mg/m^3 carbon black or 2.5 mg/m^3 iron oxide	2 hr	Mouse	No significant increases in mortality resulted on subsequent exposure to airborne infection.	Gardner, 1981
0.19 mg/m^3 $CdCl_2$ 0.25 mg/m^3 $NiCl_2$	2 hr	Mouse	Decreased number of antibody-producing spleen cells.	Graham et al., 1978

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the smaller particles was suggested as being responsible for the greater toxicity of the small particles. Total cellular protein and lactic acid dehydrogenase also decreased after treatment, probably as a non-specific result of the death of the cultured AM. For each particle size, Pb-coated particles were most toxic, NiO- and MnO_2-coated particles had intermediate effects, and the untreated fly ash was least toxic. The toxicity did not appear related to the solubility of the metal oxide coating, since no soluble metal could be found using the AM themselves as a bioassay. The toxicity appeared to be associated with the uptake of the intact particle. No changes were observed in the total lysosomal enzyme content, but the latency or intactness of the lysosomal membrane was not examined. Toxicity could have resulted from the disruption of the intracellular lysosomal membrane, which in turn could have released intracellular lysosomal enzymes. Lysosomal enzyme release has been proposed as one potential mechanism for the toxicity of asbestos and silica particles (Heppleston, 1962). These results support the concept that the surface activity of particles determines the toxicity of the particle (Allison and Morgan, 1979).

Camner et al. (1974) exposed rabbit alveolar macrophages in vitro to 5 μm Teflon particles coated with Al, Be, C, Pb, Mn, Ag, and U. All particles were phagocytized by the cells, but only Be caused a decrease in viability.

Although White and Kohn (1980) did not consider particle size in their investigation, they did conduct in vitro alveolar macrophage studies with iron carbonyl (0.5-5 μm, diameter), SiO_2 (size not given), crocidolite and crysotile asbestos (size not given), kaolinite (size not given), and polystyrene latex beads (1.1 μm, diameter). Although particle to cell ratios were roughly equivalent (10-15 particles/cell), the particle concentration differed markedly for each chemical. Enzyme release was measured. Compared to a no particle control group, iron carbonyl, SiO_2, both forms of asbestos and latex beads, but not kaolinite, increased ($p < 0.02$) the percent of extracellular β-glucuronidase (a lysosomal enzyme). Similar results were obtained for % extracellular LDH, except for this parameter, latex beads had no significant effect. All particles, except crocidile asbestos and latex beads increased elastase secretion.

Allison and Morgan (1979) have summarized the evidence that AM ingest both toxic and non-toxic particles in the same manner. In the case of fibers, ingestion appears more dependent upon the length of the fiber (Allison, 1973). Short fibers of >5 μm are almost always ingested, while fibers >30 μm are seldom ingested completely and remain in contact with the plasma as well as with the lysosomal surface. Intermediate sized particles (5 to 20 μm) are sometimes completely ingested and sometimes not. Once ingested, particles have two effects. An immediate cytotoxicity appears which is apparently due to the interaction of the particle with the plasma membrane (Allison and Morgan, 1979). This interaction is similar to the hemolytic effects described for silica particles. The second effect results in delayed cytotoxicity and occurs after the particle has been ingested into a primary phagocytic vacuole which then combines with a primary lysosome to yield a secondary lysosome containing the

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particle (Allison and Morgan, 1979). Here toxic particles exert an effect upon the permeability of the lysosomal membrane, resulting in the release of lysosomal enzymes into the cell and into the external medium. These proteolytic enzymes have the potential of causing tissue damage.

Hatch et al. (1980) examined the influence of in vitro exposure to a variety of particles on AM oxidant production (O_2^- and H_2O_2) and found the response to be chemical specific. All the particles studied stimulated the chemiluminescence, with amphibole asbestos being the most active. Silica, chrysotile asbestos, and metal oxide (Pb, Ni, Mn)-coated fly ash had intermediate activity. Fugitive dusts and fly ash had the lowest activity.

Waters et al. (1974) found that AM cultured with particulate forms of vanadium had decreased cell viability, indicating a direct cytotoxicity. Alveolar macrophages were cultured in medium containing vanadium pentoxide (V_2O_5), vanadium trixoide (V_2O_3), or vanadium dioxide (VO_2). Cytotoxicity was directly proportional to the solubility of the vanadium compound: $V_2O_5 > V_2O_3 > VO_2$. The concentration of V required to produce a 50 percent decrease in viability after 20 hr of culture was found to be: 13 μg V/ml as V_2O_5, 21 μg V/ml as V_2O_3, and 33 μg V/ml as VO_2. When V_2O_5 was dissolved in the medium prior to incubation with the AM, only about 9 μg V/ml were required to reduce viability by 50 percent, thus indicating that the soluble V was responsible for toxicity. Phagocytosis, an essential function for the defense of the lung, was decreased by 50 percent with 6 μg V/ml as dissolved V_2O_5. Acid phosphatase, a lysosomal degradation enzyme necessary for digestion of phagocytized bacteria, was inhibited by 1 μg V/ml as V_2O_5, while the lysosomal enzymes, lysozyme and β-glucuronidase, were not inhibited by concentrations as high as 50 μg V/ml.

The effects of Fe_2O_3 on AM have also been investigated. Rabbits were exposed for 3 hr to 186-222 mg/m^3 Fe_2O_3 (0.17-0.31 μm, MMAD), and AM were removed 0, 12, 18, and 24 hr later (Grant et al., 1979). When selected lysosomal enzyme activites were determined for the first three post-exposure times, there were no significant differences from control. However, since an increased ($p < 0.02$) number of cells were recovered 12, 18, and 24 hr post-exposure, the total amount of some of the lysosomal enzymes in the lung was increased. It appears that the increased number of cells was due to the influx of smaller cells into the lung.

Alveolar macrophages exposed in vitro for 20 hr to metallic salts were also studied by Graham et al. (1975b) using a technique to determine phagocytosis of viable cells only. The chlorides of Cd (2.2×10^{-5}M), Cr (3.1×10^{-3}M), Mn (1.8×10^{-3}M), and Ni (5.1×10^{-4}M) significantly inhibited phagocytosis. Ammonium vanadate (6.9×10^{-4}M) had no effect on phagocytosis, but did lyse and kill cells. Nickel, which caused the greatest reduction in phagocytosis, had very little effect on viability or cell lysis. Antibody-mediated rosette formation of AM was also inhibited in vitro by low concentrations of $CdCl_2$ (2.2×10^{-5}M) or $NiCl_2$ (10^{-4}M) (Hadley et al., 1977). Inhibition was proportional to the Ni^{++} or Cd^{++} concentration and reached its maximum within 20 min. These studies showed that the antibody dependent recognition system of AM was inhibited by trace concentrations of Ni^{++} and Cd^{++}

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almost immediately after contact with the metal. Such an effect implies that these metals may affect receptors for phagocytosis of the opsonized bacteria. Depression of AM viability, phagocytosis, and receptors for phagocytosis may be a mechanism by which these heavy metal salts increase the susceptibility to airborne infections as discussed later (Section 12.3.4.3).

Bingham and co-workers (1968, 1972) have examined the effects of Pb and Ni inhalation on the number and type of AM present in the lungs of rats. In a preliminary report, Bingham et al. (1968) showed that a 3 mo exposure to 0.01 or 0.15 mg/m^3 Pb_2O_3 (0.18 μm, MMAD) decreased the number of AM/lung. The specificity of this response was investigated in a subsequent study (Bingham et al. 1972) using soluble $PbCl_2$ (0.1 mg/m^3, 0.17 μm MMD) and $NiCl_2$ (0.11 mg/m^3, 0.32 μm MMD) and insoluble Pb_2O_3 (0.15 mg/m^3, 0.15 μm MMD) and NiO (0.12 mg/m^3, 0.25 μm MMD) aerosols. Rats were exposed for 12 hr/day, 6 days/wk for 2 mo. The only exceptions were those exposed to Pb_2O_3 continuously. Exposure to Pb_2O_3, but not $PbCl_2$, aerosols resulted in a depression of the number of AM which persisted throughout the experiment. The number of AM was depressed on inhalation of 0.15 mg/m^3 Pb_2O_3 for up to 3 mo, but returned to control levels within 3 days after discontinuation of the exposure. The solubility of the Ni compound also had marked effects on the biological response. Nickel oxide produced a marked elevation in the number of AM/lung, while $NiCl_2$ did not. The most significant effects in $NiCl_2$-exposed rats were marked increases in mucus secretion and bronchial hyperplasia. No morphological alterations were observed in those rats exposed to $PbCl_2$ or Pb_2O_3. Isolated AM also varied in diameter with the exposure, but the biological significance of this size variation is not known at present. Perhaps different cell populations were recruited into the lung with the differing exposure conditions.

Cadmium chloride aerosols also altered the number and kind of cells recoverable by lavage following exposure (Gardner, 1977b, 1981). The total number of AM isolated from exposed rats decreased following exposure to 1.5 mg/m^3 Cd (99 percent <3 μm in diameter) but returned to normal values within 24 hr. The viability of the isolated cells decreased by 11.2 percent immediately after exposure and was still depressed 24 hr later. There was an influx of polymorphonuclear leukocytes, especially 24 hr post-exposure, but no increase in lymphocytes. These effects were not observed at 0.5 mg/m^3 Cd, indicating that the minimum effective dose may lie somewhere between these two concentrations.

Nickel chloride aerosols (Adkins et al., 1979; Gardner 1981) produced neither an effect on the number of AM isolated by lavage of rats the day following a 2 hr exposure to 0.65 mg/m^3 Ni nor an influx of polymorphonuclear leukocytes. The phagocytic capacity of the isolated AM was, however, depressed. A 2-hr exposure of mice to 0.9 mg/m^3 Mn_3O_4 reduced the number of AM which could be recovered by lavage, but did not result in an influx of other cell types (Adkins et al., 1980a). The AM had a reduced concentration of ATP and total protein and acid phosphatase activity. Viability and phagocytic activity of AM were normal.

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The number, function and kind of cells isolated from the lung by lavage are influenced by the prior exposure to heavy metal aerosols. Not all metals produced the same effect but Cd, Ni, and Mn also enhanced the susceptibility of mice to subsequent airborne infections (Gardner, 1981). The observations of two independent laboratories (Bingham et al., 1968, 1972; Adkins et al., 1979) on $NiCl_2$ aerosols are essentially in agreement (Table 12-10).

12.3.4.3 Interaction with Infectious Agents--Gardner (1981) and Ehrlich (1978) have reviewed their groups' studies and presented new data on the effects of aerosols on host defense mechanisms against infectious pulmonary disease in mice. In all of the Gardner studies, 94 to 99 percent of the aerosols was less than 1.4 μm in diameter (Gardner et al., 1977b; Gardner, 1981). Animals were placed in a head-only exposure system for 2 hr and were given graded concentrations ranging from 0.075 to 1.94 mg/m^3 Cd (Gardner et al., 1977b), from 0.1 to 0.67 mg/m^3 Ni (Adkins et al., 1979), or from 0.5 to 5 mg/m^3 Mn (Adkins et al., 1980c). In mice, these exposures to Cd and Ni chlorides and Mn_3O_4 resulted in the deposition of 0.002 to 0.026 mg Cd (Gardner et al., 1977b), 0.001 to 0.012 mg Ni (Adkins et al., 1979), or 0.005 to 0.042 mg Mn (Adkins et al., 1980b) per g dry weight of lung respectively. Nickel clearance (Graham et al., 1978) from the lungs of mice had a half-life of 3.4 days; while Mn (Adkins et al., 1980b) clearance was rapid, with a half-life of only 4.6 hr. None of the exposures appeared to be edematogenic as judged by the ratio of dry weight to wet weight of the lung. After metal exposure, mice were challenged with an aerosol of Streptococcus pyogenes (S. pyogenes). The aerosols of $CdCl_2$ (Gardner et al., 1977b), $NiCl_2$ (Adkins et al., 1979), or $MnCl_2$ (Gardner, 1981) increased the mortality from the subsequent standard airborne infection. Cadmium was more toxic than Ni, which was more toxic than Mn. Exposure to Cd and Mn resulted in a significant linear concentration response. The lowest concentration tested at which a significant increase in mortality was detected was 0.1 mg/m^3 Cd or 0.5 mg/m^3 Ni. Manganese, as Mn_3O_4 (Adkins et al., 1980c), was statistically estimated to produce a 10 percent increase in mortality at 1.55 mg/m^3 Mn, while $MnCl_2$ (Gardner, 1981) required a higher concentration to produce a measurable increase in mortality. Using a different infectivity model (Maigetter et al., 1976), 3 or 4 days (3 hr/day) of exposure to 109 mg/m^3 MnO_2 (0.70 μm, mean diameter) were required to increase mortality consequent to Klebsiella pneumoniae infection when the mice received the bacterial aerosol immediately after exposure.

The toxicity of $NiCl_2$ was complex (Adkins et al., 1979). Nickel exposure had no effect on the S. pyogenes infection if the bacteria was given immediately after Ni aerosol exposure. When the bacterial exposure was delayed by 24 hr, Ni aerosols increased the mortality in a concentration-related fashion. In contrast, effects of $CdCl_2$ (Gardner et al., 1977b) and Mn (Gardner, 1981) were observed when the bacterial challenge immediately followed exposure. The concentration-response curve of Ni was very steep compared to those of Cd and Mn exposures (Gardner, 1981). No explanation has been offered for the delay in effect of Ni. Perhaps the delayed effects represent either redistribution of Ni to the site of action or some major change in the lung such as death of a specific cell type. The delayed toxicity does raise the possibility of carry-over of effects from a single exposure to a second.

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The influence of a variety of sulfate species on host defense mechanisms against infectious respiratory disease has been investigated by Ehrlich (1979) and Ehrlich et al. (1978) using the infectivity model with S. pyogenes. Mice were exposed for 3 hr. The estimated concentrations of the compounds which caused a 20 percent enhancement of bacterial-induced mortality over controls were 0.2 mg/m^3 $CdSO_4$, 0.6 mg/m^3 $CuSO_4$, 1.5 mg/m^3 $ZnSO_4$, 2.2 mg/m^3 $Al_2(SO_4)_3$, 2.5 mg/m^3 $Zn(NH_4)_2(SO_4)_2$, and 3.6 mg/m^3 $MgSO_4$. Ammonium sulfate at 5.3 mg/m^3 SO_4, NH_4HSO_4 at 6.7 mg/m^3 SO_4, Na_2SO_4 at 4 mg/m^3 SO_4, $Fe_2(SO_4)_3$ at 2.9 mg/m^3 SO_4, and $Fe(NH_4)_2SO_4$ at 2.5 mg/m^3 SO_4 did not cause significant alterations. The nitrates of Pb, Ca, Na, K, and NH_4 did not cause an effect at concentrations of 2 mg/m^3 or higher. However, $Zn(NO_3)_2$ caused effects similar to $ZnSO_4$. From this body of work, it appears that the NH_4 ion rendered the compound less toxic, and that the toxicity is primarily due to the cation. With the infectivity model, $ZnSO_4$ and $Zn(NH_4)_2(SO_4)_2$ ranked differently than with airway resistance experiments (Amdur et al., 1978a). This is not unexpected as airway resistance primarily detects alterations of the medium to large conducting airways, while the infectivity model (Gardner and Graham, 1977) is hypothesized to reflect alveolar level changes.

When mice were exposed for 2 hr to 5.0 mg/m^3 carbon black or 2.5 mg/m^3 iron oxide, no significant increases in mortality resulted on subsequent exposure to airborne infection (Gardner, 1981).

Death from S. pyogenes exposure in this infectivity model is due to septicemia (Gardner et al., 1977b). Septicemia occurs when the bacteria have grown to 10^5 organisms per lung. Removal and killing of the inhaled organisms will reduce the growth of the bacteria within the host and prevent the occurrence of septicemia. For these reasons, the infectivity model is an integrative assessment of toxicity for host defense systems against infectious pulmonary disease. As reported above, the number, kind, function and viability of the cells isolated by lavage from the lungs of animals exposed to heavy metal aerosols are different from those of control animals. Studies of tracheal rings isolated from aerosol-exposed hamsters also indicate depression of mucociliary clearance. Both mucocilary and AM clearance of bacteria are depressed by aerosols of these heavy metals (Gardner, 1981) (Table 12-10).

12.3.4.4 Immune Suppression--Antibodies play a significant role in the ability of macrophages to recognize and engulf pathogenic bacteria. The functioning of the immune system interlocks with the macrophage system in other ways also. In mice, intramuscular injections of $NiCl_2$ depressed the number of antibody-producing cells in the spleen (Graham et al., 1975a). Using the Jerne plaque assay, a negative linear dose-response curve was found with injections ranging from 9.26 to 12.34 μg Ni/g body weight. No effect was observed with a dose of 3.09 μg Ni/g body weight. The inhalation of $NiCl_2$ aerosols (99 percent less than 3 μm in diameter) was more effective in suppressing the primary immune response. Graham et al. (1978) calculated that exposure to an aerosol of 0.25 mg/m^3 Ni for 2 hr would result in a maximum deposition of 0.98 μg Ni, assuming complete retention and a minute volume of 1.45 ml/g body weight. This concentration was found to be the lowest tested which produced a significant

depression in the immune response. The lowest dose found to produce a similar effect by injection was 208 μg Ni/mouse (Graham et al., 1975a). The inhalation dose was, therefore, approximately 200 times more potent. Ni was found to follow first order removal kinetics from the lung, but measurable elevations remained in the lung up to 4 days after exposure. Similar kinetics of removal have been found using the isolated, ventilated, and perfused rat lung (Williams et al., 1980) and human, rat, and cat type II pneumocytes in culture (Saito and Menzel, 1978).

Inhaled Cd also depresses the number of antibody producing cells and is more potent than intramuscularly injected Cd. The highest intramuscular dose of $CdCl_2$ examined by Graham et al. (1978) was 11.81 μg Cd/g body weight (about 266 μg Cd/mouse), and it produced no immunosuppression. When mice were exposed to 0.19 mg/m^3 Cd for 2 hr, a significant suppression was observed. In both cases the Cd was administered as $CdCl_2$, a highly soluble salt. The inhalation dose can be calculated on the same basis as that given above for Ni to be at a maximum at 0.74 μg Cd/mouse. The inhaled dose was, therefore, at least 350-fold more potent. Inhalation also appeared to be more potent than ingestion or interperitoneal injection (Exon et al., 1975; Koller et al., 1975). Koller et al. (1975) found that 150 μg Cd given orally was required to produce immunosuppression.

For comparative purposes, the lowest inhalation exposure of $CdCl_2$ found to be immunosuppressive was 0.19 mg/m^3; 0.2 mg/m^3 was the 1971 Threshold Limit Value (TLV). The current TLV is 0.05 mg/m^3. The human intake from air has been estimated to be 7.4 μg/day and from water to be 160 μg/day (Schroeder, 1970). $NiCl_2$ was found to be immunosuppressive at an inhalation exposure of 0.25 mg/m^3 while its TLV is 1 mg/m^3. The human exposure is estimated to be 2.36 μg/day from inhalation and 600 μg/day from ingestion (Schroeder, 1970). Should the effectiveness of inhaled aerosols be equivalent in mice and men, then the inhaled doses are biologically almost equivalent to those ingested.

Inhaled Cd or Ni aerosols impair the bacterial defenses of the lung through direct cytotoxicity to AM, depression of antibody production, and inhibition of antibody dependent aggregation reactions. All of these mechanisms can help to explain the increased susceptibility of mice to airborne pathogens following inhalation of Ni or Cd aerosols. The rapidity of clearance of Ni and Cd from the lung may allow rapid recovery (see Table 12-10).

Mouse splenic lymphocytes have also been exposed in vitro to 500 μg of various sizes of silica (Wirth et al., 1980) and mitogen-induced transformation measured (a reflection of immune function). Four silica samples were tested unfractionated, or size-fractionated into 2 categories (0.3 and 5.3 μm). All the unfractionated samples depressed the blastogenic response to Conconavalin A (a measure of T cell function) and LPS (a measure of B cell function). The T cell response was decreased by the 0.3 μm size fraction of all samples. However, the 5.3 μm particles of 2 samples increased the response, while one sample caused no change and another caused a small decrease. When B cell function was examined, it was more depressed by the 0.3 μm silca than the 5.3 μm particles, although 3 of the 4 larger-sized samples did cause a decrease.

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Kysela et al. (1973) administered high concentrations (50 mg) of 9 sizes of quartz dust (0.7 to 35 μm) to rats by intratracheal instillation. A variety of biochemical determinations as well as a histological examination of the lungs were made 3 mo after dosing. As particle size decreased, there was a trend towards increased wet weight of the lung, hydroxyproline content, total lipids, esterified fatty acids and phospholipids. Only cholesterol showed a slight increase. For hydroxyproline in total lung, the increase was stepwise, with increments occurring at about 0.9, 5, 7, and 10 μm. Between 0.7 and 14 μm, the increase was significant ($p < 0.05$). Lipid changes, based on gram of tissue, exhibited a trend towards linearity with particle size decrease. The larger particles (14-35 μm) caused a stationary granulamatous response. With the intermediate particles (5-10 μm), the lungs had cellular nodules with a few collagenous fibers and an increased tissue cellularity and endoalveolar foam cells. With the smaller particles, the nodules were more numerous and collagenous.

Goldstein and Webster (1966) also investigated the effects of size graded quartz particles in rats exposed by intratracheal instillation and examined 4 months later. The sizes and concentrations used (< 1 μm, 13.99 mg; 1-3 μm, 46.1 mg; and 2-5 μm, 92.7 μg) were such that the rats were exposed to an equivalent surface area (600 sq. cm.) for each of the size ranges. The < 1 μm particles caused more numerous nodules. The two other size ranges produced an equivalent number of lungs with nodules, but there were many more lungs with confluent nodules, compared to the smallest size quartz. The degree of fibrosis was similar in the 1-3 μm and 2-5 μm groups and was more severe than that observed in the < 1 μm group. The weight of collagen in lungs increased as particle size increased. However, it should be recalled that the concentration of particles was increased as particle size increased.

Particle size also has an influence on the immunological effects of silica (Wirth et al., 1980). Average particle sizes of the silica preparations were 0.012, 0.8, 1.5, and 1.9 μm. The silica particles were from different suppliers; the crystalline structures could have differed also. Mice were injected intravenously. The smaller particles tended to depress the humoral immune response to a greater extent.

12.4 INTERACTION OF SULFUR DIOXIDE AND OTHER POLLUTANTS

12.4.1 Sulfur Dioxide and Particulate Matter

Although man breathes a multitide of chemicals in various mixtures at various dose-rates, most animal toxicological and controlled human exposures are conducted with single chemicals. This simplifies the research and permits an improved estimate of cause-effect relationships, but it prohibits evaluation of the effects of pollutant mixtures which may be additive, synergistic, or antagonistic with respect to the individual pollutants. However, some interaction studies which elucidate the complexity of toxicological interrelationships have been conducted. Some of this work utilized pollutant combinations that would favor the conversion of the primary pollutant to a secondary pollutant (i.e., SO_2 altered to H_2SO_4, etc.). Other research was directed at evaluating the influence of several pollutants when delivered in combination or in sequence.

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12.4.1.1 Acute Exposure Effects--The question of the possible effect of aerosols on the response to SO_2 is a critical problem in air pollution toxicology (Amdur, 1975). The phenomenon has been investigated in simple model systems of SO_2 alone or in combination with an aerosol of a single chemical. The typical bioassay system has been the comparison of the increase in pulmonary flow resistance in guinea pigs produced by a given concentration of SO_2 alone with that produced in the presence of the aerosol. The aerosols used in many of these studies were "inert" in the sense that they did not produce an alteration in flow resistance when they were given alone.

The initial simple prototype aerosol used was sodium chloride (NaCl) at concentrations of 10 mg/m^3 and 4 mg/m^3 (Amdur, 1961). These experiments with guinea pigs indicated that the response to a given concentration of SO_2 was potentiated by 10 mg/m^3 sodium chloride. For example, a concentration of 5.24 mg/m^3 (2 ppm) SO_2 alone produced an increase of 20 percent in pulmonary flow resistance; when the sodium chloride was present, the increase was 55 percent. The potentiation did not occur until the latter part of a 1 hr exposure. When the concentration of sodium chloride was reduced to 4 mg/m^3, the potentiation was greatly reduced. Examination of post-exposure data indicated that the response to the combination resembled the response to a more irritant aerosol. The length of recovery was related to the concentration of SO_2, and the presence of the aerosol delayed recovery to control values. The chamber relative humidities were below 70 percent; but on entering the high humidity of the respiratory tract, the sodium chloride would absorb water to become a droplet capable of dissolving SO_2, thus favoring the production of H_2SO_4. Sodium chloride does not catalyze the oxidation of SO_2 to sulfuric acid.

Experiments by McJilton et al. (1973) indicate the importance of ambient relative humidity and the solubility of SO_2 in the sodium chloride droplet. They examined the effect of 1 mg/m^3 NaCl on the response to 2.62 mg/m^3 (1 ppm) SO_2 at low (<40 percent) and high (>80 percent) relative humidity. An increase in pulmonary flow resistance in guinea pigs was the criterion of response. As would have been predicted from the earlier work, no increase was observed with this sodium chloride concentration at low relative humidity. At high relative humidity, the potentiation was marked and was evident during both the early and late parts of the 1 hr exposure. The rapid onset indicates the formation of an irritant aerosol in the exposure chamber under conditions of high humidity. As would have been predicted, no conversion to sulfate was found, but the droplets were acid with an estimated pH of 4. Presumably, this was sulfurous acid. (See the discussion of the effect of relative humidity on sulfate and nitrate aerosols above and on human exposure experiments in Chapter 13).

Amdur and Underhill (1968) studied the effect of aerosols of soluble salts of metals shown to convert SO_2 to sulfuric acid using the Mead-Amdur method. Manganous chloride, ferrous sulfate, and sodium orthovanadate caused a three-fold increase in the resistance to flow over that of 2.62 mg/m^3 (1 ppm) SO_2 alone. The potentiation was evident during the first 10 min as well as during the remainder of the 1 hr exposure. Chamber relative humidity was 50

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percent, indicating that high humidity was not necessary for the formation of an irritant aerosol in the chamber when the catalyzing metals were present. Analysis of the collected aerosol indicated the presence of sulfate, presumably as sulfuric acid (Amdur, 1973). These analyses indicated that at an SO_2 concentration of 0.52 mg/m^3 (0.2 ppm) about 0.08 mg sulfuric acid was formed. When this amount of sulfuric acid was administered with 0.52 mg/m^3 (0.2 ppm) SO_2, the increase in flow resistance duplicated the increase observed with the iron and vanadium aerosols (Amdur, 1974). This suggests that sulfuric acid formation is the most likely mechanism of potentiation for the aerosols of these metals. Amdur et al. (1978a) have reported that a 1 hr exposure to 0.4 mg/m^3 copper sulfate also potentiated the response to 0.94 mg/m^3 (0.36 ppm) SO_2. It is not certain whether this is mediated through the formation of sulfuric acid or through the formation of a sulfite complex. The increased resistance to flow from exposure to 0.79 to 0.84 mg/m^3 (0.3 to 0.32 ppm) SO_2 with ammonium sulfate (0.9 mg/m^3), ammonium bisulfate (0.9 mg/m^3), or sodium sulfate (0.9 mg/m^3) was purely additive. It should be pointed out that these salts have not been tested under conditions of high relative humidity.

Amdur and Underhill (1968) also examined the effect of a variety of solid aerosols (carbon, iron oxide, manganese dioxide, and fly ash) which do not catalyze the conversion of SO_2 to H_2SO_4. None of these potentiated the increased resistance to flow when compared to SO_2 (Table 12-11).

12.4.1.2 Chronic Exposure Effects--Animals were exposed continuously to various combinations of SO_2, sulfuric acid (0.5 to 3.4 μm, MMD), and fly ash (3.5 to 5.9 μm, MMD). The fly ash had been collected downstream from electrostatic precipitators of coal-burning electric generating plants (Alarie et al., 1975). Monkeys were exposed for 18 mo and guinea pigs for 12 mo. For monkeys, exposures were to SO_2, H_2SO_4 + fly ash, SO_2 + H_2SO_4, or SO_2 + H_2SO_4 + fly ash. Guinea pigs received either 0.9 mg/m^3 H_2SO_4 (0.49 μm MMD) or 0.08 mg/m^3 H_2SO_4 (0.54 or 2.23 μm MMD) + 0.45 mg/m^3 fly ash (3.5 or 5.31 μm MMD). In monkeys, a battery of hematological and pulmonary function (tidal volume, respiratory rate, minute volume, dynamic compliance, pulmonary flow resistance, work of breathing, distribution of ventilation, CO diffusing capacity, and arterial blood gases) tests were applied at various times during exposure, but no significant effects were attributed to the exposures. Similar methods (except for distribution of ventilation and CO diffusing capacity) were used with guinea pigs, and again no significant effects were observed. At the end of the exposure to 2.59 mg/m^3 (0.99 ppm) SO_2 + 0.93 mg/m^3 H_2SO_4 (0.5 μm MMD, σ_g 1.5 to 3.8), the lungs of monkeys had morphological alterations in the bronchial mucosa (focal goblet cell hypertrophy and occasional hyperplasia and focal squamous metaplasia). Monkeys exposed to 2.65 mg/m^3 (1.01 ppm) SO_2 + 0.88 mg/m^3 H_2SO_4 (0.54 μm MMD, σ_g 1.5 to 3.8) + 0.41 mg/m^3 fly ash (4.1 μm MMD, σ_g 1.8 to 2.8) had similar alterations. Thus, fly ash did not enhance the effect. Monkeys which received 0.99 mg/m^3 H_2SO_4 (0.64 μm MMD, σ_g 1.5 to 3.0) + 0.55 mg/m^3 fly ash (5.34 μm MMD, σ_g 1.8 to 2.2) had slight alterations in the mucosa of the bronchi and respiratory bronchioles. Focal areas of erosion and epithelial

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TABLE 12-11. EFFECTS OF ACUTE EXPOSURE TO SULFUR DIOXIDE IN COMBINATION WITH PARTICULATE MATTER

Concentration	Duration	Species	Results	Reference
5.24 mg/m^3 (2 ppm) SO_2, 10 mg/m^3 and 4 mg/m^3 NaCl	1 hr	Guinea pig	5.24 mg/m^3 (2 ppm) SO_2 alone produced an increase of 20% in pulmonary flow resistance; with NaCl at 10 mg/m^3 the increase was 55% and the potentiation did not occur until the latter part of the exposure. At 4 mg/m^3 NaCl, the potentiation was greatly reduced.	Amdur, 1961
2.62 mg/m^3 (1 ppm) SO_2, 1 mg/m^3 NaCl at low (40 %) and high (80%) relative humidity (RH)	1 hr	Guinea pig	No increase in pulmonary flow resistance at low RH. At high RH, the potentiation was marked and evident during both early and late parts of the exposure.	McJilton et al., 1973
2.62 mg/m^3 (1 ppm) SO_2, an aerosol of soluble salts (manganous chloride, ferrous sulfate, and sodium orthovanadate) 50% RH	1 hr	Guinea pig	Presence of soluble salt increased pulmonary flow resistance about 3-fold. The potentiation was evident early in the exposure.	Amdur and Underhill, 1968
0.94 mg/m^3 (0.36 ppm) SO_2, 0.4 mg/m^3 copper sulfate	1 hr	Guinea pig	Potentiated pulmonary flow resistance.	Amdur et al., 1978a
0.79 to 0.84 mg/m^3 (0.3 to 0.32 ppm) SO_2 and 0.9 mg/m^3 ammonium bisulfate, or 0.9 mg/m^3 sodium sulfate	1 hr	Guinea pig	The effect on pulmonary flow resistance was additive.	Amdur et al., 1978a

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hypertrophy and hyperplasia were observed. The other groups of monkeys had no remarkable morphological changes. All monkeys exposed to fly ash displayed no morphological alterations, although presence of the fly ash was easily observed. Guinea pigs experienced no morphological effects which could be attributed to pollutant exposure.

In a previous study, Alarie et al. (1973bc) found no effects on pulmonary function, hematology, or morphology of monkeys or guinea pigs exposed to approximately 0.56 mg/m^3 fly ash in combination with 3 concentrations of SO_2 (0.28, 2.62, or 13.1 mg/m^3; 0.11, 1, or 5 ppm). Monkeys were exposed continuously for 78 wk and guinea pigs continuously for 52 wk.

Lewis et al. (1969, 1973) investigated the effects of SO_2 and H_2SO_4 in normal dogs and in dogs which had been previously exposed for 191 days to 48.9 mg/m^3 (26 ppm) NO_2. Dogs identically treated with NO_2 had morphological changes in the lung, and one of the animals had striking bullous emphysema. Sulfur oxide exposures were for 21 hr/day for a maximum of 620 days to 13.4 mg/m^3 (5.1 ppm) SO_2, to 0.89 mg/m^3 H_2SO_4 (90 percent < 0.5 μm in diameter), or to a combination of the two. These concentrations were averaged over time, and when the animals were examined at 225 days, the concentration of H_2SO_4 was lower (0.76 mg/m^3 H_2SO_4 in the H_2SO_4 group and 0.84 mg/m^3 H_2SO_4 in the H_2SO_4 + SO_2 group). After 225 days of exposure (Lewis et al., 1969), dogs receiving H_2SO_4 had a significantly lower diffusing capacity for CO than those that did not receive H_2SO_4. In the SO_2-exposed animals, pulmonary compliance was reduced ($p < 0.05$), and pulmonary resistance was increased ($p < 0.05$) compared to animals that did not receive SO_2. Dogs not pre-exposed to NO_2 which received SO_2 + H_2SO_4 had a smaller residual volume ($p < 0.01$) than all other dogs.

These dogs were also examined after 620 days of exposure (Lewis et al., 1973). At 3, 7, 19 or 20.5 mo of exposure, sulfur oxides did not markedly affect hematological indices (number of erythrocytes and leukocytes, hemoglobin concentration, hematocrit, mean corpuscular hemoglobulin value, mean corpuscular volume, and mean corpuscular hemoglobin concentration). There were no morphological changes that could be clearly identified as resulting from sulfur oxide exposure. However, pulmonary function was altered. Generally, the animals pre-exposed to NO_2 were more resistant to the sulfur oxides. Sulfur dioxide did not produce any significant effects except for an increase in mean nitrogen washouts. Sulfuric acid caused a significant ($p < 0.05$) decrease in diffusing capacity for CO, residual volume, and net lung volume (inflated) with an increase in total expiratory resistance. There was also a significant ($p = 0.1$) decrease in total lung capacity, inspiratory capacity, and functional residual capacity. Total lung weight and heart weight were also decreased. Other measurements (other lung volumes, dynamic and static compliance, and N_2 washout) were not significantly affected. These alterations of diffusing capacity for CO and lung volumes are interpreted as a loss of functional parenchyma, and, along with the increase in total pulmonary resistance, are in the direction expected for animals that develop obstructive pulmonary effects. Although the standard histological techniques used did not detect morphological effects, it is conceivable that the pulmonary function effects preceeded measurable structural alterations.

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Female beagle dogs were exposed 16 hr/day for 68 mo to raw or photochemically reacted auto exhaust, oxides of sulfur or nitrogen, or their combinations. A description of the exposure groups is given in Table 12-12. More than 90 percent of the particles were <0.5 μm in diameter. They were examined after 18 (Vaughn et al., 1969), 36 (Lewis et al., 1973), and 61 mo (Lewis et al., 1974) of exposure and 32 to 36 mo (Hyde et al., 1978; Orthoefer et al., 1976) after the 68 mo exposure ceased. A monograph describing the entire study and results is available (Stara et al., 1980). Only those results pertaining to sulfur oxides will be described here.

Typical hematological examinations (except for differential counts) were made approximately every 6 mo (Stara et al., 1980). The SO_x group had no major differences from control. However, in the presence of auto exhaust (with or without irradiation), SO_x did cause some significant elevations in hematocrit and hemoglobin concentration. Clinical chemistries were unchanged during or approximately 1 1/2 yr after exposure (Stara et al., 1980). Although cardiovascular function was also assessed after 4 yr of exposure and 3 yr after exposure ceased, no significant changes which could be attributed to SO_x were found (Stara et al., 1980).

A variety of other parameters were examined during or immediately after exposure (Stara et al., 1980). SO_x caused no significant effect on visual evoked brain potentials.

After 18 (Vaughn et al., 1969) or 36 mo (Lewis et al., 1974) of exposure, no significant changes in pulmonary function were observed. A variety of alterations were found using analysis of variance after 61 mo (Lewis et al., 1974) of exposure, but only those significant results related to sulfur oxides will be discussed in detail here. Residual volumes were increased in dogs receiving R + SO_x (see Table 12-12 for abbreviations) compared to those receiving I + SO_x, SO_x, and CA. Residual volumes of the SO_x group were lower than those of the CA group. When χ^2 analyses were applied to the data of the number of dogs/group having alterations as judged by clinical criteria, additional significant differences were found. More dogs of the I + SO_x group had higher total expiratory resistance than their controls (CA and SO_x). The ratio of residual volume to total lung capacity was higher in animals exposed to R + SO_x, compared to those receiving clean air (CA). This change was interpreted as pulmonary hyperinflation. Although other lung volumes, compliance, resistance, diffusing capacity for CO, N_2 washout, peak expiratory flow, and maximum breathing capacity were also measured, sulfur oxides had no effects.

Two years after exposure ceased, pulmonary function measurements were made again (Stara et al., 1980). These measurements were made in a different laboratory than those made during exposure, but consistency among measurements of the control group and another set of dogs of similar age at the new laboratory indicated that this difference did not cause a major impact of the findings. Animals in the R, R + SO_x, and I + SO_x groups had an increased $PaCO_2$ ($p < 0.05$) compared to controls. These groups and the SO_x group had a greater dead space volume compared to controls. Respiratory frequency was increased in the SO_x group. Although

TABLE 12-12. POLLUTANT CONCENTRATIONS FOR CHRONIC EXPOSURE OF DOGS (Hyde et al., 1978)

Atmosphere	Pollutant Concentration, mg/m^3						
	CO	HC (as CH_4)	NO_2	NO	OX (as O_3)	SO_2	H_2SO_4
Control Air (CA)[a]							
Nonirradiated auto exhaust (R)	112.1	18.0	0.09	1.78			
Irradiated auto exhaust (I)	108.6	15.6	1.77	0.23	0.39		
SO_2 + H_2SO_4(SO_x)[b]						1.10	0.09
Nonirradiated auto exhaust + SO_2 + H_2SO_4 (R + SO_x)	113.1	17.9	0.09	1.86		1.27	0.09
Irradiated auto exhaust + SO_2 + H_2SO_4 (I + SO_x)	109.0	15.6	1.68	0.23	0.39	1.10	0.11
Nitrogen oxides, 1 (NO_2 high)			1.21	0.31			
Nitrogen oxides, 2 (NO high)			0.27	2.05			

[a]Abbreviations in parentheses
[b]>90% of H_2SO_4 particles were < 0.5 μm in diameter (optical sizing)

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DL_{CO} was unchanged, the ratio of DL_{CO} to total lung capacity was decreased in all pollutant-exposed dogs. Vital capacity was not changed. For the SO_x group compared to control, total lung capacity and residual volume were significantly increased. But, there was no change in functional residual volume; respiratory, pulmonary, and chest wall resistance were not affected; and quasistatic chest wall compliance was decreased. There was a greater change in dynamic compliance with increasing breathing frequency in dogs exposed to SO_x. When the pulmonary function values at the end of exposure were compared directly to those values 2 yr after exposure ceased, the following observations were made in the SO_x group: residual volume, total lung capacity, vital capacity, inspiratory capacity, and functional residual capacity, DL_{CO} and the ratio of DL_{CO} to total lung capacity increased. The magnitudes of these changes were greater than changes in controls, in most cases. From evaluation of all the data, the authors state that functional loss continues following termination of the exposure and the damage caused by SO_x was primarily to the parenchyma. They also state that the combination of auto exhaust and SO_x "did not appear to augment specific functional losses caused by single species of pollutants."

Thirty-two to 36 mo (Hyde et al., 1978) after exposure ceased, the lungs of the beagles were examined using morphologic (light, scanning electron and transmission electron microscopy) and morphometric techniques. Only the results for sulfur oxide combinations will be described in detail. In the SO_x group, lung weight, total lung capacity, and the displaced volume of the processed right lung were significantly increased over the controls (CA). In the most severely affected SO_x dogs, the air spaces enlarged and the number and size of interalveolar pores increased. Only the high NO_2 dogs had a greater degree of air space enlargement. The SO_x animals had a loss of cilia in the conducting airways without squamous cell metaplasia; nonciliated bronchiolar cell hyperplasia; and loss of interalveolar septa in alveolar ducts. When SO_x was combined with R, cilia were also lost, but squamous cell metaplasia occurred. Exposure to R + SO_x and I + SO_x produced nonciliated bronchiolar cell hyperplasia and an increase in interalveolar pores and alveolar air space enlargement. The enlargement of the distal air spaces was centered on respiratory bronchioles and alveolar ducts and was associated with an apparent loss of interalveolar septa in all animals receiving SO_2 and H_2SO_4. The authors consider these changes to be analogous to an incipient stage of human proximal acinar (centrilobular) emphysema. The important observation from these experiments is that mixtures of SO_2 and H_2SO_4, representing an interacting gas-aerosol system similar to that in urban atmospheres, produced anatomic alterations at concentrations lower than either SO_2 or H_2SO_4 aerosols alone.

In a monograph (Stara et al., 1980) describing all the dog studies, the morphological and functional changes are compared. In the SO_x group the changes in pulmonary function correlated well with the morphological effects. Since the changes in pulmonary function were progressive over the post-exposure period, it is likely that morphological changes were also progressive.

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Biochemical analyses were performed on these dogs at the time of sacrifice, 2.5 to 3 yr after exposure ceased. Hydroxyproline concentration (used as an index of collagen content) and prolyl hydroxylase activity (the rate-limiting enzyme in collagen synthesis) were measured (Orthoefer et al., 1976). No significant changes in hydroxyproline were found. The SO_x and I + SO_x groups had significantly elevated prolyl hydroxylase activity compared to the R, R + SO_x, and CA groups. While it is remarkable that effects on prolyl hydroxylase remained 2.5 - 3 yr post-exposure, it is not possible to interpret further these results. No significant alterations were observed in brain, heart, lung or liver lipids amongst the experimental groups (Stara et al., 1980).

Zarkower (1972) reported mixed effects on the immune system of mice exposed to 5.24 mg/m^3 (2 ppm) SO_2 and 0.56 mg/m^3 carbon (1.8 to 2.2 μm, MMD), alone and in combination for 100 hr/wk for up to 192 days. Animals were immunized with aerosols of bacteria (Escherichia coli) at various times during exposure. After 102 days of exposure, there were no statistically significant changes. Sulfur dioxide exposure caused an increase ($p < 0.05$) in serum antibody titer at 135 days and a decrease ($p < 0.01$) at 192 days. Carbon and carbon + SO_2 produced an equivalent decrease ($p < 0.01$) in antibody titer at 192 days (but not at 135 days) which appeared to be a greater decrease than that found in the SO_2-exposed mice. In the spleen, exposure to SO_2 caused an increase ($p < 0.01$) in the number of antibody-producing cells at 135 days and a decrease ($p < 0.01$) in number at 192 days. In the mediastinal lymph nodes (which drain the lung), SO_2 caused no such changes. Carbon + SO_2, but not carbon alone, caused an increase ($p < 0.01$) in the number of antibody-producing cells in the mediastinal lymph nodes and a decrease ($p > 0.05$) in the spleen at 135 days. After 192 days of exposure to carbon or carbon + SO_2, the number of antibody producing spleen cells decreased ($p < 0.01$). The immunosuppression in these 2 groups was roughly equivalent and appeared to be more severe than that in the SO_2 alone group. In the mediastinal lymph nodes, only carbon + SO_2 caused immunoenhancement ($p < 0.05$). Thus, for the pulmonary immune system, only exposure to the combination of SO_2 and carbon caused significant effects. After 192 days, the systemic immune system was affected in all 3 exposure groups. It appeared that carbon and carbon + SO_2 caused equivalent effects and that both regimens were more effective than SO_2.

Fenters et al. (1979) showed that exposure for 3 hr/day, 5 days/wk for up to 20 wk to a mixture of 1.4 mg/m^3 H_2SO_4 plus 1.5 mg/m^3 carbon (0.4 μm, mean particle diameter) or to 1.5 mg/m^3 carbon only (0.3 μm, mean particle diameter) also altered the immune system of mice. Serum immunoglobulins (Ig) decreased, with the exception of IgM which was increased after 1 wk of exposure to either carbon or H_2SO_4 + carbon. After 1 wk, some Ig classes decreased in both exposure groups, but after 4 or 12 wk of exposure, alterations were observed only in the H_2SO_4 + carbon group. Results for Ig were mixed at 20 wk. In the carbon group, the number of specific antibody-producing spleen cells was increased at 4 wk, unchanged at 12 wk, and decreased at 20 wk. A similar trend was observed in the H_2SO_4 + carbon group, but only the immunosuppression at 20 wk was significant. In examining other host defense systems, no

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alterations of alveolar macrophage viability or cell numbers were observed. After 4 and 12 wk of exposure, pulmonary bactericidal activity was increased in both exposure groups. By 20 wk of exposure, values were not significantly different from controls. Using the infectivity model with influenza A_2/Taiwan virus, a 20-, but not a 4-, wk exposure to H_2SO_4 + carbon increased mortality.

Morphological changes were observed in these mice (Fenters et al., 1979) using scanning electron microscopy after 12 wk of carbon exposure. In the external nares, there was excess sloughing of squamous cells. In the trachea, the number of mucous cells appeared to increase; dying cells were present, and microvilli were lost. No alterations of the bronchi were seen. The alveoli had some areas of congestion with thickening, loss of interalveolar septa, and enlarged pores. After 20 wk of exposure, damage was similar, but to a lesser degree. Mice exposed to the mixture of H_2SO_4 and carbon showed equivalent effects, but the damage was somewhat more severe than that seen in the carbon only group.

The influence of H_2SO_4 and carbon on the trachea of hamsters was investigated by Schiff et al. (1979). Animals were exposed for 3 hr to 1.1 mg/m^3 H_2SO_4 (0.12 μm, mean size) and/or 1.5 mg/m^3 carbon (0.3 μm, mean size) and were examined either immediately, or 24, 48, or 72 hr later. Carbon caused no change in ciliary beat frequency. Sulfuric acid exposure, however, caused depression in this frequency at all time periods. The combination of H_2SO_4 and carbon produced similar effects, but recovery had occurred by 48 hr post-exposure. Using light microscopy, the percentage of normal tracheal epithelium was determined. Up to 48 hr after exposure, the combination of H_2SO_4 and carbon resulted in more tissue destruction than either pollutant alone, although the single pollutants did cause some damage. Morphological alterations of all pollutant exposure groups were observed using light and scanning electron microscopy (see Table 12-13).

12.4.2 Interaction with Ozone

Cavender et al. (1977) exposed rats and guinea pigs to sulfuric acid aerosols (10 mg/m^3, 1 μm MMD), 3.9 mg/m^3 (2 ppm) ozone, or a combination of the two for 6 hr/day for 2 or 7 days; they then measured the ratio of lung to body weight and examined the lungs histologically. No synergism was observed between the ozone and sulfuric acid treatments. The histological lesions were those ascribed to ozone alone. This same group (Cavender, 1978) exposed rats and guinea pigs to sulfuric acid aerosols (10 mg/m^3, 50 percent equivalent aerodynamic diameter, 0.83 μm, σ_g = 1.66), 1.02 mg/m^3 (0.52 ppm) ozone, or a combination of the two for 6 hr/day, 5 days/wk for 6 mo. The histological alterations were those due to ozone alone.

Last and Cross (1978) found synergistic effects of a continuous exposure of sulfuric acid aerosol (1 mg/m^3) and ozone (0.78 to 0.98 mg/m^3 or 0.4 to 0.5 ppm) when administered simultaneously to rats for 3 days. Glycoprotein synthesis was stimulated in tracheal ring explants measured ex vivo. Ozone alone caused a decreased glycoprotein secretion; sulfuric acid was relatively inactive, requiring concentrations in excess of 100 mg/m^3 to produce changes in

TABLE 12-13. EFFECTS OF CHRONIC EXPOSURE TO SULFUR OXIDES AND PARTICULATE MATTER

Concentration	Duration	Species	Results	Reference
Various combinations of SO_2, H_2SO_4 (0.5 to 3.4 μm, MMD), and fly ash (3.5 to 5.9 μm, MMD): SO_2, H_2SO_4 + fly ash, SO_2 + H_2SO_4, SO_2 + H_2SO_4 + fly ash	18 mo, continuous	Monkey	No significant effects on hematology or pulmonary function tests during exposure. At end of exposure to 0.99 ppm SO_2 + 0.93 mg/m^3 H_2SO_4 (0.5 μm, MMD) lungs had morphological alterations in the bronchial mucosa. Exposure to 1.01 ppm SO_2 + 0.88 mg/m^3 H_2SO_4 (0.54 μm, MMD) + 0.41 mg/m^3 fly ash (4,1 μm, MMD) had similar alterations, thus fly ash did not enhance effect. Exposure to 0.99 mg/m^3 H_2SO_4 (0.64 μm, MMD) + 0.55 mg/m^3 fly as (5.34 μm, MMD) had slight alterations.	Alarie et al., 1975
0.9 mg/m^3 H_2SO_4 (0.49 μm, MMD); 0.08 mg/m^3 H_2SO_4 (0.54 or 2.23 μm, MMD) + 0.45 mg/m^3 fly ash (3.5 or 5.31 μm, MMD)	12 mo, continuous	Guinea pig	No significant effects on hematology, pulmonary function, or morphology.	Alarie et al., 1975
Approximately 0.56 mg/m^3 fly ash in combination with SO_2 at 0.28, 2.62, or 13.1 mg/m^3 (0.11, 1, or 5 ppm).	78 wk, continuous	Monkey	No effects on pulmonary function, hematology, or morphology.	Alarie et al., 1973b
Approximately 0.56 mg/m^3 fly ash in combination with SO_2 at 0.28, 2.62, or 13.1 mg/m^3 (0.11, 1, or 5 ppm)	52 wk, continuous	Guinea pig	No effects on pulmonary function, hematology, or morphology.	Alarie et al., 1973b
13.4 mg/m^3 (5.1 ppm) SO_2, or 0.89 mg/m^3 H_2SO_4 (90% <0.5 μm in diameter), or to a combination of the two	21 hr/day, 620 days	Dog	After 225 days, dogs receiving H_2SO_4 had a lower diffusing capacity for CO than those that did not receive H_2SO_4. In the SO_2-exposed group, pulmonary compliance was reduced and pulmonary resistance was increased compared to dogs that did not receive SO_2. Dogs not pre-exposed to NO_2 who received SO_2 + H_2SO_4 had a smaller residual volume than all other dogs. After 620 days, pulmonary function was altered from sulfur oxide exposure but no hematological or morphological changes occurred. SO_2 did not produce any effects except for an increase in mean nitrogen washout. H_2SO_4 decreased diffusing capacity for CO, residual volume, and net lung volume and increase in total expiratory resistance. Total lung capacity, inspiratory capacity functional residual capacity were decreased. Total lung weight and heart rate were also decreased.	Lewis et al., 1969, 1973

TABLE 12-13 (continued).

Concentration	Duration	Species	Results	Reference
(see Table 12-12)	16 hr/day, 68 mo	Dog	After 18 or 36 mo exposure no changes in pulmonary function. Residual volumes increased in dogs receiving R + SO_x compared to I + SO_x, SO_x, and CA. Residual volumes of the SO_x group were lower than of the CA group. More dogs of the I + SO_x had higher total expiratory resistance than their controls (CA and SO_x). The ratio of residual volume to total lung capacity was higher in R + SO_x than CA. 32 to 36 mo after exposure ceased, the SO_x group had lung weight, total lung capacity, and displaced volume of the processed right lung increased over controls (CA). SO_x dogs had loss of cilia in the conducting airways. SO_x + R had loss of cilia and squamous metaplasia. Exposure to R + SO_x and I + SO_x produced nonciliated bronchiolar cell hyperplasia and an increase in interalveolar pores and alveolar air space enlargement.	Lewis et al., 1969, 1973
5.24 mg/m^3 (2 ppm) SO_2, or 0.56 mg/m^3 carbon (1.8 to 2.2 µm, MMD), or in combination	100 hr/wk, 192 days	Mouse	For the pulmonary immune system, only exposure to the combination caused significant effects. After 192 days, the systemic immune system was affected in all 3 exposure groups; carbon and carbon + SO_2 were more effective than SO_2, although SO_2 did cause significant effects.	Zarkower, 1972
1.4 mg/m^3 H_2SO_4 plus 1.5 mg/m^3 carbon (0.4 µm, mean particle diameter), or 1.5 mg/m^3 carbon only (0.3 µm, mean particle diameter)	3 hr/day, 5 day/wk, 20 wk	Mouse	Altered the immune system. Morphological changes observed; more severe with carbon only exposure.	Fenters et al., 1979
1.1 mg/m^3 H_2SO_4 (0.12 µm, mean size), or 1.5 mg/m^3 carbon (0.3 µm, mean size), or in combination	3 hr	Hamster	Carbon caused no change in ciliary beat frequency. Ciliary beat frequency was depressed after H_2SO_4 exposure. The combination produced similar effects, but recovery had occurred by 48 hr post-exposure. Up to 48 hr after exposure H_2SO_4 + carbon resulted in more tissue destruction than either pollutant alone.	Schiff et al., 1979

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glycoprotein secretion. The lμng DNA, RNA, and protein content increased in the group exposed to ozone and sulfuric acid aerosols, while the ozone-exposed group had only a small increase and the sulfuric acid group had none.

Grose et al. (1980) investigated the interaction of H_2SO_4 and O_3 on ciliary beat frequency in the trachea of hamsters. A 2 hr exposure to 0.88 mg/m^3 H_2SO_4 (0.23 μm, VMD) significantly depressed ciliary beat frequency. By 72 hr after exposure, recovery had occurred. Hamsters exposed to 0.196 mg/m^3 (0.1 ppm) O_3 for 3 hr were not significantly affected. However, when animals were exposed in sequence, first to O_3 and then to H_2SO_4, ciliary beat frequency was decreased significantly, but to a lesser extent than that caused by H_2SO_4 alone. Analysis showed that antagonism ($p < 0.05$) occurred in this sequential exposure.

Gardner et al. (1977a) found that the sequence of exposure to sulfuric acid aerosols and ozone altered the response of mice to airborne infections. Mice were exposed alone or in sequence to 0.196 mg/m^3 (0.1 ppm) ozone for 3 hr and to 0.9 mg/m^3 sulfuric acid aerosol (VMC 0.23 μm ± 2.4 SD, geometric) for 2 hr. When given alone, neither pollutant caused a statistically significant increase in the mortality to a subsequent infection with S. pyogenes. When the pollutants were given sequentially, a significant increase in mortality occurred only when ozone was given immediately before exposure to sulfuric acid, and the response was additive. The reverse procedure had no effect on mortality due to S. pyogenes infections. Because photochemical oxidants and sulfur oxides often co-exist in polluted air, these studies are of very practical importance. The question of the temporal sequence has been poorly investigated. Simple mechanisms to predict this additive response sequence are not apparent. Thus, the results are opposite those of the Grose et al. (1980) study described above with the tracheal model which showed that sequential exposure to O_3 and H_2SO_4 had an antagonisitic effect. The reasons for this difference are not known. However, the infectivity model is thought to reflect alveolar level effects (Gardner and Graham, 1977), whereas the ciliary beat frequency model is a measure of effects at the level of the trachea. In addition different animal species were used. These findings also indicate the complexity of interaction effects and the need to exercise care in extrapolating the effects of pollutants from one parameter to another (see Table 12-14).

12.5 CARCINOGENESIS AND MUTAGENESIS OF SULFUR COMPOUNDS AND ATMOSPHERIC PARTICLES

Attempts have been made for several decades to correlate various indices of particulate air pollution with the development of cancer in man. In many cases a positive association has been found between increased community air pollution and cancer of the lungs and/or gastrointestinal tract. This knowledge has led to suspicions concerning the chemical nature of that portion or portions of airborne particulate matter which may be contributing to an excess of human cancer. At least three classes of potential etiologic agents have been studied in this regard: organic matter (including polycyclic hydrocarbons) which is adsorbed to suspended particles; sulfur oxides; and trace metals.

TABLE 12-14. EFFECTS OF INTERACTION OF SULFUR OXIDES AND OZONE

Concentration	Duration	Species	Results	Reference
10 mg/m^3 (1 μm, MMD) H_2SO_4 aerosol, or 3.9 mg/m^3 (2 ppm) O_3, or combination of the two	6 hr/day, 2 or 7 days	Rat and Guinea pig	No synergism in effect on ratio of lung to body weight. Histological lesions were those ascribed to O_3 alone.	Cavender et al., 1977
10 mg/m^3 (50% equivalent aerodynamic diameter, 0.83 μm, σ_g = 1.66) H_2SO_4 aerosol, or 1.02 mg/m^3 (0.52 ppm) O_3, or combination of the two	6 hr/day, 5 day/wk, 6 mo	Rat and Guinea pig	Morphological alterations due to O_3 alone.	Cavender et al., 1978
1 mg/m^3 H_2SO_4 aerosol and 0.78 to 0.98 mg/m^3 (0.4 to 0.5 ppm) O_3	3 days, continuous	Rat	Synergistic effects. Glycoprotein synthesis was stimulated in tracheal ring explants; lung DNA, RNA, and protein content increased.	Last and Cross, 1978
0.196 mg/m^3 (0.1 ppm) O_3; 0.9 mg/m^3 H_2SO_4 aerosol (VMC 0.23 μm ± 2.4 SD, geometric) exposed alone or in sequence	3 hr, O_3; 2 hr, H_2SO_4	Mouse	In response to airborne infections a significant increase in mortality only when O_3 was given immediately before exposure to H_2SO_4, and the response was additive.	Gardner et al., 1977a
0.196 mg/m^3 (0.1 ppm) O_3; 0.88 mg/m^3 H_2SO_4 aerosol (0.23 μm, VMD) exposed alone or in sequence	3 hr, O_3; 2 hr, H_2SO_4	Hamster	H_2SO_4 depressed ciliary beat frequency. By 72 hr after exposure, recovery had occurred. O_3 exposure had no effect. Sequential O_3 then H_2SO_4 exposure decreased ciliary beat frequency significantly but to a lesser extent than that caused by H_2SO_4 alone.	Grose et al., 1980

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Test systems for the bioassay of potential mutagens and carcinogens are diverse, ranging from the measurement of chemically-induced reverse mutations in bacteria to the frank production of carcinomas by administration to mammals. However, it is commonly believed that fundamental similarities exist between the molecular mechanisms of both mutagenesis and carcinogenesis. This assumption is based on the theory that chemical interaction with DNA and/or other critical cellular macromolecules initiates a mutagenic or carcinogenic transformation.

Because of the relationship between molecular events involved in mutagenesis and carcinogenesis (Miller, 1978), the demonstration of mutagenic activity for a substance is generally taken as strong presumptive evidence for the existence of carcinogenic activity. Therefore, it is believed that an investigation of the mutagenicity of a substance may be predictive of its carcinogenic potential, and may serve as an early warning of a possible threat to human health in cases where positive results are obtained.

12.5.1 Airborne Particulate Matter

12.5.1.1 In Vitro Mutagenesis Assays of Particulate Matter--Organic material associated with airborne particles has been investigated to a limited extent for mutagenic and carcinogenic potential. In these studies, particulate material is experimentally limited to that which is retained by the filter medium used (glass fiber, paper...etc.). Organic compounds associated with aqueous particles cannot effectively be trapped, and thus there is no information on the biological effect or nature of these compounds. The particles that have created most interest are those with a carbonaceous core. These particles, because of their large surface area, adsorb many organic compounds some of which are known to be mutagenic and carcinogenic, such as benzo(a)pyrene. Because of the small size (0.2-0.3 μm mean diameter) of many of the particles, they can be deposited in the respiratory regions of the lung where the adsorbed organic material can desorb into the alveolar fluid and enter the associated tissue. The ability of soluble proteins to leach mutagens off particulates has been demonstrated using horse serum and coal fly ash (Crisp et al., 1978).

A number of studies were conducted with fractionated extracts of particulate matter from urban air in order to obtain information on the chemical nature of the mutagens present (Dehnen et al., 1977; Teranishi et al., 1978; Møller and Alefheim, 1980; Tokiwa et al., 1980). Estimates have been made as to the relative mutagenicity of each extract; however, due to the possible interaction among the many compounds present in any fraction of the extracts the only conclusion that can be drawn is that both the polar and neutral fraction contain significant portions of the total mutagenic activity. The polar fraction contained direct acting mutagens. Some could be chemical derivatives of polycyclic aromatic hydrocarbon (PAH) compounds. At present the identity of compounds which are acting as direct mutagens is uncertain.

In a similar manner as in studies with airborne particulate matter, mutagens were extracted from particles emitted from a coal powered electric plant (Crisp et al., 1978;

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Kubitschek et al., 1979), gasoline engines (Wang et al., 1978), and light-duty and heavy-duty diesel engines (Huisingh et al., 1977). The extracts obtained from all sources were direct acting frame-shift mutagens. Only in the heavy duty diesel engine study was fractionation carried out on the crude extract. A review of diesel engine particulate matter is available (Santodonato, 1978).

The Salmonella assay has been used in an attempt to define air quality by measuring the mutagenic potential of airborne particulates. Tokiwa et al. (1977) compared the number of revertants per μg of particulate matter collected in the industrial area of Ohmata with that collected in the residential area of Fukuoka, Japan. In a similar manner Pitts et al. (1978) compared eight urban samples in the California South Coast Basin with one collected in a rural area of the San Bernadino mountains. In both cases the mutagenic activity was less in the residential and rural areas compared to that observed in the urban areas. Also, mutagenic potential was determined in a quantitative manner for a variety of air samples collected in Chicago (Commoner et al., 1978). In order to rank samples, the inverse of the minimum quantity of particulate matter needed to obtain a significant Ames assay result was calculated. Again, mutagenic potential was correlated with urban pollution and prevailing concentration gradients from sources of pollution.

Caution must be exercised when comparing in a quantitative manner results of Ames assays on complex environmental mixtures. Indirect mutagenesis is extremely difficult to quantitate, since microsomal oxidation to non-reactive as well as reactive compounds occurs. Mixtures of direct and indirect mutagens may not produce an additive result. For any valid comparison there has to be nearly complete separation of these two types of mutagens (Commoner et al., 1978). Also, the effects on mutagenesis of synergism and antagonism among compounds in complex mixtures has not been adequately investigated. In the case of complex mixtures obtained from tar-sand, the mutagenic activity of the known mutagen, 2-aminoanthracene, was greatly inhibited by interaction with the mixture (Shahin and Fournier, 1978). For these reasons a quantitative assessment of air quality is not readily obtainable with the use of the Ames Salmonella mutagenicity assay.

The data obtained with mammalian cell transformation assays support the conclusions derived from the Ames Salmonella assays. There appears to be a variety of biologically active agents present in the extracts of airborne particulate matter, and these agents are of both a polar and nonpolar nature. The identity of these compounds is unknown; however, the activity present is greater than that which could be accounted for by the PAH present in the samples. Even though the cells transformed by extracts of particulate matter formed tumors when injected into newborn mice, it is presently unclear how the process of transformation in virus-infected cells relates to the process of chemical carcinogenesis. Hence, cell transformation assays should be considered in the same way as Ames assays; that is, as only an indicator of the presence of biologically active compounds.

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The dominant lethal assay of Epstein et al. (1972) is the only short term in vivo assay performed on airborne particulate extracts. The water soluble and benzene soluble fractions produced no fetal deaths or preimplantation losses beyond control limits. On the other hand, the oxygenated fraction showed significant fetal deaths and decreased total implants.

12.5.1.2. Tumorigenesis of Particulate Extracts--It was realized as early as the 1930's that increasing amounts of particulate matter in the air may correlate with the increasing rate of human lung cancer. Some of the earliest in vivo experiments dealt with the repeated exposure of mice to clouds of soot, followed by autopsy examination for tumors at the end of their natural lifespan. A number of different kinds of soot have been chosen for these studies due to their significant contribution to airborne particulate matter. Upon bioassay of soot from chimneys (Campbell, 1939; Seelig and Benignus, 1938), motor exhaust (Campbell, 1939), and airborne particulate matter collected in the vicinity of a factory and roadway (McDonald and Woodhouse, 1942), a slight increase over control in the number of lung tumors was observed. Only in the case where road dust from a freshly tarred road was used were there significant increases, with 57 percent of the experimental and 8 percent of the control group having lung tumors (Campbell, 1934). However, when five years later dust from the same road, which had not been retarred, was again tested only 8 percent of the experimental group and 1.4 percent of the control group developed lung tumors (Campbell, 1942). In a recent study with lifetime exposure of rats to automotive exhaust, no tumors were detected in the lungs of the treated animals. Although these studies have all attempted to demonstrate the potential of airborne particulate matter to cause lung tumors, the results obtained are ambiguous due to the low tumor incidence and the small size of the animal groups.

Among the various compounds associated with airborne particles, PAH have received the greatest attention with regard to carcinogenic potential. PAH were the first compounds ever shown to be associated with carcinogenesis. To this day, carcinogenic PAH are still distinguished by several unique features: (a) several compounds of this class are among the most potent animal carcinogens known to exist, producing tumors by single exposures to microgram quantities; (b) they act both at the site of application and at organs distant from the site of absorption; and (c) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration. The most widely studied PAH, benzo(a)-pyrene, is ubiquitous in the environment and produces in animals tumors which closely resemble human carcinomas.

The production of lung tumors with airborne particulates has been extremely difficult. However, organic extracts of airborne particulates readily cause tumors when injected subcutaneously into mice. As early as 1942 sarcomas were produced in mice using the benzene extracts of particulate matter collected from an urban area (Leiter and Shear, 1942; Leiter and Shimkin, 1942). In these initial studies the tumor incidence was low, with only 8 percent of the mice developing tumors by the end of the study; however, none of the control mice had sarcomas. In one later study, the tumor incidence was as high as 61 percent when particles

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were collected in the vicinity of a petrochemical plant (Rigdon and Neal, 1971). Even in this case of high tumor production, no increase in the incidence of tumors over the spontaneous rate was observed in any organ of the animal distant to the site of injection. Only when neonatal mice were injected subcutaneously with particulate extracts did tumors appear distant from the injection site (Epstein et al., 1966), with a very high incidence of hepatomas (83 percent) and multiple pulmonary adenomas (67 percent). Remote tumor formation after subcutaneous injection of neonatal mice was confirmed with both the crude extract of particles collected in New York City and subfractions of this extract; the predominant tumors were again hepatomas (Asahina et al., 1972).

The carcinogenic nature of extracts of particulate matter has also been demonstrated by studies involving skin painting on the backs of mice. With repeated application (three times per week for the life of the animal) of the benzene extract of particulates collected in the Los Angeles area, papillomas were formed which subsequently progressed to carcinomas (Kotin et al., 1954). Papillomas first appeared after 465 days, and at the time the data were presented 42 percent of the mice had developed tumors. Although papillomas and carcinomas of the skin were the most commonly observed tumors, lung tumors have also been noted after skin application (Clemo et al., 1955). Among the different methods of administering particulate extracts to the mouse for bioassay, skin painting yields the highest tumor incidence, with greater than 90 percent of the surviving animals in some cases developing tumors.

In subsequent studies, the phenomenon of two-stage tumorigenesis was used to characterize further the biological activity in airborne particulates. In two-stage tumorigenesis an initiator is an agent (usually a carcinogen) which, when applied in a single dose to the skin of a mouse does not produce tumors at the applied concentration, but predisposes the skin so that later repeated application of a promoter (an agent that by itself will not produce tumors) will cause the formation of tumors. A complete carcinogen is one which, if applied in sufficient concentration, can produce tumors by itself. Extracts of airborne particles from Detroit were fractionated, and the fractions examined for complete carcinogenicity and tumor initiating and promoting activity (Stern, 1968; Wynder and Hoffman, 1962). Only the whole extract and the aromatic fraction proved to be a complete carcinogen, while the insoluble, acidic, aliphatic and oxygenated fractions produced no tumors (there was insufficient basic fraction to perform the assay).

In order to examine the aromatic fraction for initiating activity, this fraction was applied to the backs of mice in a sub-tumorigenic dose followed by repeated application of the known promoter croton oil. Tumor initiating activity corresponded in a general way to the benzo(a)pyrene content of the fraction. The other fractions of the particulate extract were not tested for initiating activity. It should be noted that an initiator does not necessarily have to be a complete carcinogen, although most if not all complete carcinogens will initiate if applied at a low dose where their complete carcinogenic action is not apparent. For this reason it is possible that some of the fractions could have initiating activity even though

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they did not act as complete carcinogens when first tested. However, the relevance of two-stage carcinogenesis to environmentally-caused cancer is not known.

Several contributing sources of airborne particulate matter, gasoline and diesel engines and the soot from coal and oil burning furnaces, have been examined individually and shown to produce tumors. Extracts of particulates from gasoline engines show carcinogenic activity when painted on the backs of mice (Brune, 1977; Wynder and Hoffman, 1965) and when injected subcutaneously (Pott et al., 1977). Extracts from diesel engines have shown tumorigenic activity in some studies but not in others; the same holds true for extracts of chimney soot where activity was shown in some instances (Campbell, 1939) while not in others (Mittler and Nicholson, 1957). The discrepancies among these results could be due to qualitative and/or quantitative differences in the nature of the organic compounds adsorbed to the particles or difference in assay systems. Differences may have existed in the operating parameters of the generating source, or variations in particulate collection procedures. With diesel engines the mode of operation (the load under which the engine was run), the type of fuel and the temperature at which the particles were collected all affect the biological activity of the sample. With soot collected from chimneys, an important consideration is the temperature at which the particulate matter is collected. The organic material on particulates is generated in the gaseous phase while condensation on nuclei occurs at lower temperatures. Unless particles are collected under similar conditions, disparities will exist in their chemical composition and biological activity. Taken together, it is nevertheless apparent that all the major types of airborne particulate matter contain adsorbed compounds which are carcinogenic to animals and may contribute in some degree to the incidence of human cancer associated with exposure to urban particulate matter.

12.5.2 Potential Mutagenic Effects of Sulfite and SO_2

Bisulfite addition to cytosine can result in deamination to form uracil (Shapiro, 1977; Fishbein, 1976). The result would be a DNA conversion of GC to AT sites and could be mutagenic. Transamination of cytosine can occur through reaction of an amine with cytosine-sulfite adduct. Since the nucleus is rich in polyamines, transamination is a likely event. Deamination of cytosine occurs most readily in high (1 M) concentrations of sulfite; transamination also requires high sulfite and amine concentrations. The decomposition of the cytosine-sulfite adduct is the rate limiting step in both reactions. At the present time, no clear evidence exists for mutagenicity caused by SO_2 or sulfite. However, because of the reactivity of sulfite with cytosine, the potential mutagenic properties of sulfite and SO_2 have been examined. Such experiments have recently been reviewed (Shapiro, 1977; Fishbein, 1976). To date, microbial experiments with high concentrations of sulfite in acid solutions in vitro have produced mutations. These conditions would be similar to those favoring deamination of cytosine. Experiments conducted at low concentrations ($> 10^{-3}$m sulfite) and neutral pH (7-7.4) have not provided clear-cut evidence of mutagenesis. The microbial assays were not done with strains of Salmonella known to be sensitive to mutagens (Ames Assays). Background

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mutation rates, mechanisms of error-prone repair, and corrections for cytotoxicity were not studied. Negative experiments have been reported when insects (Drosophila) (Valencia et al., 1973) and mammals (mice) were exposed. Cytotoxicity, rather than mutagenicity, appears when cultured animal and human cells (Thompson and Pace, 1962; Nulsen et al., 1974; Kikigawa and Iizuka, 1972; Schneider and Calkins, 1971; Timson, 1973) are exposed to sulfite. (See Table 12-15 for summary.)

12.5.3 Tumorigenesis in Animals Exposed to SO_2 or SO_2 and Benzo(a)pyrene

Tumorigenesis after exposure to SO_2 alone or to SO_2 and an aerosol of benzo(a)pyrene has been examined. Mice were exposed over their lifetimes in a 180 liter chamber into which 500 ppm SO_2 was introduced at a rate of 20 ml/min for 5 minutes, 5 days/week (Peacock and Spence, 1967). The concentration used cannot be calculated accurately from the paper. Thus, no concentration-related effects can be deduced from this study. Examinations for tumors of the lung and other organs were undertaken only in mice that survived longer than 300 days, since no primary lung tumors had been seen in younger mice. Only tumors greater than 1 mm were recorded. Primary pulmonary neoplasias increased in the males (n = 35) from 31 percent in the control group to 54 percent in the SO_2-exposed group and in the females (n = 30) from 17 to 43 percent. The incidence of the next most common tumors in this strain of mice, hepatomas and lymphomatoses, was not affected. The authors classified only tumors which invaded blood vessels as carcinoma. In males, SO_2 did not affect the incidence of malignant tumors (2/35, 6 percent in air group; 2/28, 7 percent in SO_2 group). However, in females, the incidence of primary lung carcinoma increased from 0/30 in the controls to 4/30 (18 percent) in the SO_2-exposed mice. These were early studies and the statistical analysis reported in the paper is vague. Therefore, Hasselblad and Stead (1980) analyzed the data reported in the Peacock and Spence (1967) study. A one-sided Fisher's exact test was used. In the males, the incidence of primary lung carcinoma was not significantly affected by SO_2 ($p = 0.604$). However, for females SO_2 increased the incidence of primary lung carcinoma ($p = 0.056$). The incidence of lung adenomas was marginally increased in males ($p = 0.065$) and significantly increased in females ($p = 0.011$). It, thus, appears that female mice of this strain were more susceptible. The significance of these increases (Peacock and Spence, 1967), therefore, is questionable. Peacock and Spence concluded that the increased incidence of primary lung tumors was due to the initial inflammatory reaction to SO_2, followed by tolerance, which accelerated spontaneous tumor development. They further state that this study does not "justify the classification of SO_2 as a chemical carcinogen as generally understood."

Lung tumors or other significant pathological effects were not observed in hamsters exposed for 98 wk to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day, 5 days/wk for 534 exposure days or to 9.17 mg/m^3 (3.5 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene for 1 hr/day, 5 days/wk for 494 exposure days or to a combination of the 2 regimens (Laskin et al., 1970). When rats (Laskin et al., 1970) were exposed to the same regimen, however, lung squamous cell carcinoma was found in 5/21 (23.8 percent) animals receiving the combined exposure of 26.2 mg/m^3 (10 ppm)

TABLE 12-15. POTENTIAL MUTAGENIC EFFECTS OF SO_2/BISULFITE

Concentration SO_2	Bisulfite	Organism	End Point	Response	Comments	Reference
	0.9 M HSO_3^- pH 5.0	Phage T4-R11 System	GC→AT or deamination of cysocine	+		Summers and Drake, 1971
	3 M HSO_3^- pH 5-6	Phage T4-R11 System	deamination of cytosine	±	Poor dose response	Hayatsu and Miura, 1970, Iida et al., 1974
	1 M HSO_3^- pH 5.2	E. coli K12 & K15	GC→AT or deamination of cytosine	+		Mukai et al., 1970
	5×10^{-3} M HSO_3^- pH 3.6	S. cerevisiae	Point Mutation	+		Dorange and Dupuy, 1972
	0.04 or 0.08 M	D. melanogaster	Point Mutation	-	May not be bioavailable	Valencia et al., 1973
1310 mg/m^3 (500 ppm)		Hela cells (Human)	Cytotoxicity	+		Thompson and Pace, 1962
13.1 - 105 mg/m^3 (5 - 40 ppm x 3 min)		Mouse fibroblasts & Peritoneal macrophages				Nulsen et al., 1974
14.9 mg/m^3		Human lymphocytes	Point Mutation Chromosomal aberrations Cytotoxicity	- - +		Kikigawa and Iizuka, 1972
	0.0001M 0.01M	Human lymphocytes	Inhibition of mitosis	+	Dose related response	Harman et al., 1970
	0.0001M	Mouse oocytes	Inhibition of meiosis	+	Observed fuzziness of chromosomes may be due to cytotoxicity	Jagiello et al., 1975
	0.0040M	Ewe oocytes	Inhibition of meiosis	+		
	0.0025M	Cow oocytes	Inhibition of meiosis	+		

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SO_2 for 6 hr/day and 9.17 mg/m^3 (3.5 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene for 1 hr/day and in 2/21 (9.5 percent) animals exposed to the benzo(a)pyrene plus SO_2 for 1 hr/day. Renal metastasis also occurred. Control rats exposed to air (n = 3) or to 26.2 mg/m^3 (10 ppm) SO_2 (n = 3) had no tumors.

This study was subsequently extended to lifetime (exact time not specified) exposures (5 days/wk) of rats (Laskin et al., 1976). Exposure to air alone (n = 15) or to 26.2 mg/m^3 (10 ppm) SO_2 (n = 15) for 6 hr/day caused no cancers (squamous cell carcinoma). A 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene caused cancer in 1/30 (3.3 percent) rats. A 6 hr/day exposure to 26.2 mg/m^3 (10 ppm) SO_2 plus a 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene resulted in a cancer incidence of 6.7 percent (2/30). When animals received a combination of 10 mg/m^3 benzo-(a) pyrene and 10.48 mg/m^3 (4 ppm) SO_2, 4/45 (8.9 percent) of the rats had cancer. The highest incidence (19.6 percent, 9/46) was found in animals exposed for 6 hr/day to 26.2 mg/m^3 (10 ppm) SO_2 plus a combination of 10 mg/m^3 benzo(a)pyrene and 10.48 mg/m^3 (4 ppm) SO_2 for 1 hr/day.

The biological significance of these studies (Table 12-16) is complex and difficult to interpret, particularly since statistical analyses were not reported in the publications. Hasselblad and Stead (1980) analyzed the tumor incidence data of the later study (Laskin et al., 1976) using a multiple probit approach. The cancer incidence increases due to SO_2 alone and BaP alone were not statistically significant ($p = 0.116$ and $p = 0.113$, respectively). However, the increase due to the combination of BaP and SO_2 was significant ($p = 0.005$). Few SO_2 exposure experiments have been carried out for the near lifetime of the animal as in the early mouse study (Peacock and Spence, 1967) and the subsequent rat study (Laskin et al., 1976). Most work has centered around short-term acute studies in which the experimental design and other aspects of the study would be inadequate to detect a low incidence of tumors. The incidence of lung tumors increases as the animals age; but no historical control data are available for the colony of rats used (Laskin et al., 1970; 1976), making the increased incidence by the combined SO_2-benzo(a)pyrene treatment difficult to interpret. Tumor formation may be a multistep process, requiring more than just the initiation for expression. In order to assure the biological and statistical validity of such tumorigenicity studies a careful control of the diet is needed, along with detailed records of the incidence of tumors throughout the life span of the animals. The absolute incidence of tumors, as well as the rate of occurrence should be determined for a large number of control animals. Given the lack of experimental details in the non-peer reviewed publication (Laskin et al., 1976) and the difficulty of performing statistical analyses not done by the author, especially with the experimental design used, it is not possible to come to a definitive conclusion about the results of this study.

12.5.4 Effects of Trace Metals Found In Atmospheric Particles

Among the numerous trace metals found in the atmosphere, evidence of carcinogenicity in experimental animals has been shown for at least nine (beryllium, cadmium, cobalt, chromium, iron, nickel, lead, zinc, titanium). Limited evidence also points to compounds of molybdenum

TABLE 12-16. TUMOROGENESIS IN ANIMALS EXPOSED TO SO_2 OR SO_2 AND BENZO(a)PYRENE

Concentration	Duration	Species	Results	Reference
(See Text for details)	5 min/days, 5 day/wk, lifetime	Mice	Primary pulmonary neoplasias increased in the males from 31 to 54% and in the females from 17 to 43%. Incidence of hepatomas and lymphomatoses were not affected. Carcinoma incidence increased in females from 0 to 18%; no change in carcinomas in males	Peacock and Spence, 1967
26.2 mg/m^3 (10 ppm) SO_2 for 534 exposure days, or 1 hr exposure (5 day/wk) to 9.17 mg/m^3 (3.5 ppm) SO_2 + 10 mg/m^3 benzo(a)-pyrene for 494 exposure days, or a combination of the 2 regimens	6 hr/days, 5 day/wk, 98 wk	Hamster	No lung tumors or other pathological effects	Laskin et al., 1970
26.2 mg/m^3 (10 ppm) SO_2 for 534 exposure days, or 1 hr exposure (5 day/wk) to 9.17 mg/m^3 (3.5 ppm) SO_2 + 10 mg/m^3 benzo(a)pyrene for 494 exposure days, or a combination of the 2 regimens	6 hr/day, 5 days/wk, 98 wk	Rat	Lung squamous cell carcinoma: 5/21 (23.8%) animals exposed to combined regimen of 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day and 9.17 mg/m^3 (3.5 ppm) SO_2 + 10 mg/m^3 benzo(a)pyrene for 1 hr/day; 2/21 (9.5%) animals exposed to benzo(a)pyrene + SO_2 for 1 hr/day; 0/3 in animals exposed to 26.2 mg/m^3 (10 ppm) SO_2; and 0/3 in animals exposed to air	Laskin et al., 1970
26.2 mg/m^3 (10 ppm) SO_2, or 10.5 mg/m^3 (4 ppm) SO_2 + 10 mg/m^3 benzo(a)pyrene, or a combination of the 2 regimes	Lifetime (5 days/wk)	Rat	A 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene caused cancer in 1/30 (3.3%). A 6 hr/day exposure to 26.2 mg/m^3 (10 ppm) SO_2 + a 1 hr/day exposure to 10 mg/m^3 benzo(a)pyrene resulted in squamous cell carcinoma incidence of 6.7% (2/30). A combination of 10 mg/m^3 benzo(a)pyrene and 10.5 mg/m^3 (4 ppm) caused cancer in 4/45 (8.9%). Highest incidence (19.6%, 9/46) found in exposure for 6 hr/day to 26.2 mg/m^3 (10 ppm) SO_2 + 10 mg/m^3 benzo(a)-pyrene and 10.5 mg/m^3 (4 ppm) SO_2 for 1 hr/day. The air control had an incidence of 0/15 and the 26.2 mg/m^3 (10 ppm) SO_2 exposure caused an incidence of 0/15.	Laskin et al., 1976

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and manganese as possible tumorigens (Clemo and Miller, 1960). Moreover, three of these metals (cadmium, chromium, nickel), in addition to arsenic, are implicated as human carcinogens.

Although trace metals are ubiquitous in the environment, their levels are generally so low that it is difficult to predict the magnitude of carcinogenic risk in community settings. This problem is compounded by the fact that clear dose-response relationships have not been well-defined for most carcinogenic metals. For the present it is likely that the possible role of trace metals in the production of cancer due to particulate air pollution will be limited to qualitative judgments.

The topic of metal carcinogenesis has been extensively reviewed in recent years from various perspectives (Furst, 1978; Furst and Haro, 1969; Sunderman, 1978; 1979). These surveys generally conclude that with certain compounds tumors can be induced via a mechanism which is apparently distinct from the phenomenon of so-called solid-state or foreign-body carcinogenesis. However, it is still debatable in many cases whether metal-induced tumors which are associated with a particular route of administration (e.g., local sarcoma by subcutaneous implantation) are indicative of true chemical carcinogenesis. While most carcinogenic metals are active only in the form of organic and inorganic salts, for nickel and cadmium it appears that both the pure elemental form as well as several of their salts are carcinogenic.

One of the most widely recognized and well-studied carcinogenic metals is nickel [International Agency for Research on Cancer (IARC), 1973b; 1976b]. Sunderman (1979, 1978) indicated that nickel subsulfide (Ni_3S_2) is probably the most potent carcinogenic metal studied to date. Single intramuscular injections of 5 μmol (1.2 mg) or 10 μmol (2.5 mg) to Fischer rats produced rhabdomyosarcomas in 77 percent and 93 percent of the treated animals, respectively. Numerous investigators have confirmed that Ni_3S_2 produces local sarcomas following injection, and one group has indicated that chronic inhalation of Ni_3S_2 in rats caused lung cancer (IARC, 1973b; 1976b). Several other forms of nickel have shown both positive and negative carcinogenic activity. The chronic inhalation of nickel carbonyl ($Ni(CO)_4$) by rats at levels as low as 0.03 mg/l has produced pulmonary carcinomas (IARC, 1976b). In addition, Lau et al. (1972) induced carcinomas and sarcomas in various organs, including liver and kidney, by multiple intravenous injections of $Ni(CO)_4$ to rats. Inhalation of elemental nickel powder has produced equivocal results in mice, rats, and guinea pigs, and negative results in hamsters (IARC, 1976b). Single and repeated intramuscular injections of nickel powder induced local tumors in rats and hamsters, although intravenous injections were either marginally effective (rat) or ineffective (mouse, rabbit) (IARC, 1976b). A single intrapleural injection of nickel powder (0.02 ml of a 0.06 percent suspension) did not produce neoplasms in mice; multiple intrapleural injections at high doses in rats were effective in the induction of local tumors (IARC, 1976b).

The toxicology and carcinogenic potential of cadmium have been the subject of extensive reviews in the past several years (IARC, 1976a; U.S. EPA, 1979; Towill et al., 1978). Cadmium

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is similar to nickel in that both the elemental form and several salts are carcinogenic, and that oral administration is ineffective in producing tumors. The ability of cadmium to induce tumors by inhalation exposure has not been adequately studied. However, single or repeated injections (intramuscular, subcutaneous) of cadmium powder, cadmium chloride ($CdCl_2$), cadmium oxide (CdO), cadmium sulfate ($CdSO_4$), or cadmium sulfide (CdS) to rodents frequently produces local sarcomas (Furst and Haro, 1969; IARC, 1976b; Sunderman, 1979). A unique feature of the action of cadmium is that single subcutaneous injections of $CdCl_2$ to rodents (3.7 - 5.5 mg/kg body weight) leads to a high incidence of interstitial cell (Leydig cell) tumors of the testis. Stoner et al. (1976) recently reported that cadmium acetate did not cause a significant increase in pulmonary tumor response in the strain A mouse bioassay system.

Chromium in the hexavalent (but not trivalent) state has produced tumors following inhalation, implantation, and injection (IARC, 1973a; Towill et al., 1978). The inhalation of mixed chromate dust failed to induce lung tumors in mice, rats, and rabbits, although pulmonary adenomas developed in mice exposed by inhalation to calcium chromate ($CaCrO_4$) dust (IARC, 1973a). Local sarcomas in rats, mice, and rabbits have resulted from the intramuscular, subcutaneous, intrapleural, intraosseous, and intraperitoneal injection of chromium powder and hexavalent chromium compounds (IARC, 1973a; Sunderman, 1979). Several groups of investigators, however, have failed to induce tumors by the parenteral administration of chromium compounds.

Although arsenic is recognized as a human carcinogen based upon epidemiological data, there is little evidence to indicate carcinogenic activity in experimental animals (Furst and Haro, 1969; Sunderman, 1979). In particular, the chromic administration of arsenous trioxide (As_2O_3) in drinking water (34 mg/l) to rats failed to induce tumors (Furst and Haro, 1969). However, others have reported that the subcutaneous injection of a sodium arsenite compound led to an increase in the incidence of lymphocytic leukemias and malignant lymphomas in pregnant Swiss mice and their offspring (Sunderman, 1979).

Although not generally recognized as a human carcinogen, lead compounds have shown considerable carcinogenic activity in rodents [IARC, 1972; U.S. Environmental Protection Agency (U.S. EPA), 1977]. Several studies confirmed that renal carcinomas result from the oral and parenteral administration of lead phosphate, lead acetate, or basic lead acetate to rats and mice, but not to hamsters. In addition, tumors of the testis (Leydig cell), adrenals, thyroid, pituitary and prostate have been found among rats fed lead acetate (3-4 mg/day for 18 months) (U.S. EPA, 1977). In a recent study using the strain A mouse pulmonary tumor bioassay system, Stoner et al. (1976) reported that lead subacetate caused a statistically significant increase in tumor formation. However, a dose-response relationship could not be demonstrated.

Beryllium salts have induced pulmonary cancers upon inhalation and osteosarcomas upon intravenous injection in a variety of animal species (IARC, 1972). Aerosols of beryllium sulfate ($BeSO_4$) induced pulmonary carcinomas in all of a group of 43 rats (34 mg/m^3 for 56 weeks), and in 2 of 10 Rhesus monkeys inhaling the compound at 35 mg/m^3 for 8 years (IARC,

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1972). In addition, 3 of 20 monkeys developed pulmonary cancers after the intrabronchial and/or bronchomural implantation of beryllium oxide (5 percent suspension in saline). Numerous investigators found that the intravenous injection of zinc beryllium silicate or beryllium oxide caused malignant bone tumors (osteosarcoma) in rabbits (IARC, 1972; Sunderman, 1979).

Evidence to support the carcinogenic potential of zinc and iron is limited. Zinc compounds ($ZnCl_2$, $ZnSO_4$, $ZnNO_3$) are carcinogenic only by intratesticular injection (Furst and Haro, 1969; Sunderman, 1979). When evaluated in the strain A mouse pulmonary tumor bioassay system, zinc acetate was found to be negative (Stoner et al., 1976). Iron-polysaccharide complexes (e.g., iron-dextran) have commonly produced local sarcomas upon injection in mice, rats, and rabbits (Furst and Haro, 1969; IARC, 1973c). In contrast to the sarcomagenic properties of iron-dextran, ferric oxide (Fe_2O_3, hematite) produced no tumors in hamsters (intratracheal instillation), guinea pigs (inhalation) or rats (subcutaneous implantation).

The carcinogenicity of titanium has not been fully investigated. Chronic studies with mice involving the ingestion of a titanium salt in the drinking water gave negative results (Furst and Haro, 1969). However, Furst and Haro (1969) succeeded in producing local sarcomas and neoplasms in distant organs by the intramuscular injection of titanocene to rats and mice. In addition, local fibrosarcomas developed in three out of 50 rats injected with titanium dioxide.

Several groups of investigators have indicated that sarcomas can be produced by the subcutaneous, intramuscular, or intraosseous injection of cobalt powder, to rabbits and rats (Sunderman, 1979). Little additional data are available regarding the carcinogenic potential of cobalt. Stoner et al. (1976) recently found that cobalt acetate had no effect on tumor incidence in the strain A mouse pulmonary tumor bioassay system.

Selenium has recently received considerable attention as a potential carcinogen, and is found in ambient air (IARC, 1975). Oral administration of sodium selenite and sodium selenate to mice and rats has resulted in a wide range of neoplasmas including sarcomas, "lymphoma-leukemias," mammary carcinomas, lung adenocarcinomas, and hepatic tumors (IARC, 1975). Because selenium is an essential trace element, its role in the etiology of environmentally-induced cancers remains unclear.

In an attempt to understand the fundamental biological activity of metals and its relationship to carcinogenesis, numerous in vitro experiments have been conducted. Many of these studies attempt to exploit the strong formal relationships between molecular events involved in mutagenesis and carcinogenesis. In particular, the interaction of xenobiotics with nucleic acids is believed to be a critical event in mutagenesis and/or cell transformation. Cultures of mammalian cells and bacteria, as well as cell-free systems, have been used to explore the potential mutagenicity/carcinogenicity of various metals.

Several biochemical studies have been completed which point to a possible direct action on nucleic acids by metal cations as the basis for metal carcinogenesis. Murray and Feisel

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(1976) prepared mixtures of synthetic polynucleotides and measured the changes in the melting curves induced by the addition of carcinogenic and non-carcinogenic metal salts at a 10^{-3}M concentration. Both cadmium chloride ($CdCl_2$) and manganese chloride ($MnCl_2$) induced alterations in spectrophotometric measurements which were indicative of mispairing of nucleotide bases.

More extensive studies have been conducted on the ability of metal salts to affect the fidelity of DNA synthesis in a cell-free system (Loeb et al., 1977; Sirover and Loeb, 1976). These investigators found a high correlation between metals which were mutagenic/carcinogenic and the ability to increase the error frequency of deoxynucleotide incorporation. Nine metals were scored as positive in this system at concentrations between 20 μM and 150 μM; silver, beryllium, copper, cadmium, cobalt, chromium, manganese, nickel, and lead. Negative results were obtained with barium, calcium, aluminum, iron, potassium, magnesium, sodium, rubidium, strontium, and zinc. The authors concluded that the fidelity of DNA synthesis may have potential application as a screening technique for mutagenic/carcinogenic metals.

The recent proliferation of in vitro cell transformation assays has resulted in further confirmation of the carcinogenic/mutagenic action of several metals. The most noteworthy cell transformation studies thus far with metals have been those employing primary cultures of Syrian hamster embryo cells (Costa, 1979; DiPaolo and Casto, 1979; DiPaolo et al., 1978). Morphological transformation has been obtained with salts of nickel, lead, cadmium, chromium, beryllium, and arsenic. Salts of iron, titanium, tungstate, zinc, and aluminum displayed no transforming properties. Unfortunately, there has not yet been an extensive validation of any single test system for screening of potential metal carcinogens. Moreover, techniques are not yet available to elucidate the molecular mechanism of metal-induced transformation, or to explain how the physicochemical state of the metal affects its carcinogenic potential.

12.6 CONCLUSIONS

12.6.1 Sulfur Dioxide

Once inhaled, SO_2 appears to be converted to its hydrated forms, sulfurous acid, bisulfite, and sulfite. The rate of absorption and removal of inhaled SO_2 varies with species, but it is at least 80 percent of the inhaled amount.

The metabolism of SO_2 is predominantly to sulfate and is mediated by the enzyme sulfite oxidase. Since sulfite oxidase is a molybdenum containing enzyme, dietary factors could influence the function of the enzyme. No conclusive evidence has yet been reported. The reaction of bisulfite with serum proteins to form S-thiosulfates is rapid. The S-thiosulfates are remarkably long-lived (t 1/2 = 4.1 days in rabbits), supplying a circulating pool of bisulfite which can reach all tissues. Since some circulating S-thiosulfates decompose to SO_2 which is exhaled, S-thiosulfates can donate their bisulfite content to distal tissues.

An immediate effect of acute ($\leq$ 1 hr) SO_2 inhalation is either a decrease in respiratory rate or an increase in resistance to flow within the lung. The decrease in respiratory rate depends on afferent conduction through the Vth or IXth cranial nerve following activation of

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receptors in the nose and upper airways. Nasal air flow is decreased. The response is transient in nature and occurs at 44.5 mg/m^3 (17 ppm) SO_2. Lower concentrations were not tested.

The increased resistance to flow on inhalation of SO_2 is mediated through receptors in the bronchial tree and persists during continued exposure. With this physiological parameter, lower concentrations of SO_2 have been observed to cause reproducible changes in respiration. The increased resistance to flow of air in the lung on SO_2 inhalation represents the activation of an autonomic reflex arc through the vagus nerves. The same reflex arc occurs in man. The reflex is cholinergic since atropine blocks the reflex, presumably at preganglionic synapses. The guinea pig is the most sensitive animal for measuring airway resistance, with significant changes in pulmonary resistance to air flow occurring on the inhalation of concentrations as low as 0.42 mg/m^3 (0.16 ppm) SO_2 for 1 hr. Chronic exposures have produced alterations in pulmonary function in cynomolgus monkeys, but only at concentrations greater than 13.1 mg/m^3 (5 ppm). Dogs exposed to 13.4 mg/m^3 (5.1 ppm) SO_2 for 21 hr/day for 225 days had increased pulmonary flow resistance and decreased compliance. Lower concentrations were not examined. It should be remembered that SO_2 appears to cause its immediate bronchoconstrictive effect through action on airway smooth muscles, as evidenced by the antagonism of the SO_2-initiated bronchoconstriction by isoproterenol in man and animals. Since smooth muscles adapt or fatigue during long-term stimulation, chronic exposure to SO_2 is not likely to evidence bronchoconstriction equivalent to that occurring on short-term exposure. Alterations in pulmonary function after chronic exposure to SO_2 are likely to occur through other mechanisms, such as morphological changes in the airways or hypersecretion of mucus, which will result in narrowing the airway. Concentration, rather than duration of exposure, seems to be the most important parameter in determining responses to SO_2, whether the response is measured as a histopathological lesion or as a permanent alteration in respiration. There is no theoretical hypothesis available at present to integrate the short-term effects observed with 1 hr exposures and the effects of long-term exposures of several months.

In rats, histopathological effects of SO_2 alone are confined to the bronchial epithelium, with most of the effects occurring on the mucus secreting goblet cells. Goblet cell hypertrophy occurs on chronic exposure of rats, leading to the suggestion that SO_2 produces a chronic bronchitis similar in many respects to that in man. Repeated exposure to a critical concentration of SO_2 (not less than 131 mg/m^3 or 50 ppm) may be needed to produce the chronic bronchitis. While SO_2-produced chronic bronchitis in rats is similar to that in man and is a useful model for the study of bronchitis, no evidence exists that chronic bronchitis is produced in man from ambient concentrations of SO_2.

The nasal mucosa of mice (particularly those with upper respiratory pathogens) was altered by 72 hr exposure to 26.2 mg/m^3 (10 ppm) SO_2. Continous exposure to 0.37 to 3.35 mg/m^3 (0.14 to 1.28 ppm) SO_2 for 78 wk did not cause any significant lung morphological alterations in monkeys. The effects of near ambient concentrations of SO_2 on the morphology and function of the nasal mucosa are not known.

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Some pulmonary host defense mechanisms are also affected by SO_2 exposure. After 10 and 23 days of exposure (7 hr/day, 5 days/wk) to 0.26 mg/m^3 (0.1 ppm), clearance of particles from the lower respiratory tract was accelerated in rats. At a higher concentration of SO_2 (2.62 mg/m^3, 1 ppm) there was an initial acceleration (at 10 days), followed by a slowing at 25 days. A 5 day (1.5 hr/day) exposure to 2.62 mg/m^3 (1 ppm) reduced tracheal mucus flow in dogs, but a longer exposure to this concentration caused no changes in ciliary beat frequency of rats. These aberrations in tracheal clearance and mucus flow in several species are consistent with the profound effects of higher concentrations of SO_2 on mucus glands in rats.

Antiviral defenses were altered by a 7 day continous exposure to 18.3 to 26.2 mg/m^3 (7 to 10 ppm) SO_2 as evidenced by an increase in viral pneumonia. In this study, the combined exposure to SO_2 and virus produced weight loss on exposure to concentrations as low as 9.43 mg/m^3 (3.6 ppm) SO_2. Mice exposed to 13.1 mg/m^3 (5 ppm) SO_2 for 3 hr/day for 1 to 15 days or for 24 hr/day for 1 to 3 mo did not have increased susceptibility to bacterial lung disease. A variety of changes in the humoral immune response of mice exposed for up to 196 days to 5.24 mg/m^3 (2 ppm) have been reported.

Sulfur dioxide and bisulfite are mutagenic in microbial test systems (E. coli and yeast systems). The concentration of bisulfite was high (1m) and the pH low. The relevancy to inhaled SO_2 as a mutagen is not clear. A mechanism for the mutagenesis of SO_2 could be the deamination of cytosine at high concentrations. Free radical reactions breaking glycosidic bonds in DNA may be responsible at low concentrations. The potency of bisulfite in these in vitro systems is moderate to weak when compared to agents such as nitrosamines or polycyclic aromatic compounds. To date, experiments testing for mutagenicity or carcinogenicity by bisulfite in mammals have been equivocal. On the basis of present evidence, one can not decide whether or not bisulfite, and hence SO_2, is a mutagen in mammals.

The influence of SO_2 on tumorigenesis has also been examined. Unfortunately, the two key studies on tumorigenesis have not been replicated. Rats exposed (5 days/wk for 98 wk to a lifetime) to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day in combination with 9.2 or 10.5 mg/m^3 (3.5 or 4 ppm) SO_2 plus 10 mg/m^3 benzo(a)pyrene had an increased incidence of lung squamous cell carcinoma. Hamsters were not affected. A reanalysis of the data shows that the increase in tumors in rats due to SO_2 and benzo(a)pyrene is statistically significant. As a result of these studies, the possibility exists that SO_2 may be a co-carcinogen in rats. The question of carcinogenicity of SO_2 alone cannot be resolved at present. For the rat studies described above, a total of 15 rats were exposed to 26.2 mg/m^3 (10 ppm) SO_2 for 6 hr/day, 5 days/wk for lifetimes, and none developed cancer. However, this sample size is small and would have a very small probability of detecting a low cancer incidence. In a different study, mice were exposed over their lifetimes to an indeterminable SO_2 concentration for 5 min/day, 5 days/wk. This exposure increased the incidence of carcinoma in female, but not male, mice. Reanalysis of the data showed the increased incidence of carcinoma in females was statistically significant. The incidence of primary pulmonary neoplasias increased in both sexes. The investigators for this mouse study state that although SO_2 increased lung tumors, the results do "not

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justify the classification of SO_2 as a chemical carcinogen as generally understood." Other chronic SO_2 experiments have been conducted with several other animal species which included lung morphology as an endpoint, but no lung tumors were reported. This does not negate the positive studies, since they showed a species susceptibility to tumor development and were conducted either at very high concentrations or in the presence of benzo(a)pyrene. The general conclusion to be drawn from these studies is that SO_2 has not been proven to be a carcinogen or co-carcinogen, but remains suspect.

12.6.2 Particulate Matter

The chemical and physical diversity of the particulate matter in the atmosphere presents a severe limitation on the scope of the conclusions presented here. Most of the evidence for adverse health effects of inhaled particles presented in this chapter relates to compounds arising from sulfur oxides, e.g., sulfuric acid, ammonium sulfate, metal sulfates, and related compounds. A brief treatment is presented for heavy metals and their compounds. A summary of data related to organic material associated with particles is also presented, focusing primarily on polycyclic organic compounds. Due to limitations of space, details dealt with in other criteria documents or recent major reviews on specific elements and the broader aspects of polycyclic organic compounds are presented by reference only. This chapter, then, should not be taken as a summary of all of the data available on the health effects of atmospheric particles, but rather as a selected summary related mostly to sulfur oxides. The reader should refer to, and study, the more detailed reports before attempting to integrate the present limited material into the generic problem of the effects of atmospheric particles. Similarly, the subsequent section on the interactions between sulfur dioxide and particles relates to a limited scope of the atmospheric particles.

All inhalation studies of particles available for review in this document were conducted with particles which could be expected to be within the size range alveolar envelope of deposition (>5 μm MMAD, depending upon the species exposed). Although particle deposition is related to MMAD, the majority of studies did not report particle sizes as MMAD. A few *in vitro* or intratracheal instillation studies have been performed which compared the effects of a wide range of particles including those which occur in the atmospheric coarse mode particle sizes (>2.5 μm D_{ae}).

Reports disagree as to the potency of acute exposure to sulfate aerosols. Some investigators contend that sulfuric acid is highly irritating, producing increases in pulmonary flow resistance at low concentrations. The increased resistance to air flow in the lung was directly proportional to the sulfate aerosol concentration inhaled. The bronchoconstriction produced by zinc ammonium sulfate was similar in many properties to that produced by histamine aerosols. Unlike SO_2-initiated bronchoconstriction, intravenous atropine had no effect. Inhaled or intravenous isoproterenol, however, blocked the zinc ammonium sulfate aerosol bronchoconstriction. These data suggest that the zinc ammonium sulfate aerosol receptor and presumably other sulfate receptors are not identical to the SO_2 receptor. The two agents

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accordingly could act at separate sites in the lung. Histamine is implicated in the sulfate aerosol action more clearly than in the bronchoconstricting action of SO_2.

The lowest effective concentration producing bronchoconstriction so far reported was 0.1 mg/m^3 H_2SO_4 (1 hr) in the guinea pig. Particle size influenced the results in several ways but the smaller sizes were generally more effective. Another study has observed an "all or none" response (increased airway resistance) in guinea pigs exposed for 1 hr to 14.6, 24.3, or 48.3 mg/m^3 H_2SO_4. Exposure to lower concentrations (1.2 or 1.3 mg/m^3 H_2SO_4) caused no effects. Some of these conflicts may be due to differences in technique or in age or strain of guinea pig. Large interindividual differences in dose-response curves are characteristic for inhaled histamine. In man, dogs, cats, and guinea pigs, 100-fold differences in the bronchoconstrictive response to histamine have been observed. The individual dose-response curves are remarkably reproducible. In dogs and guinea pigs the bronchoconstrictive response to histamine fell within a single log-normal distribution, despite the large interindividual differences in the dose of histamine required to elicit a specific response. These large interindividual differences could represent differences in "susceptibility" of different individuals, suggesting a small fraction of "susceptible" individuals; or they could represent a very flat dose-response curve for a single population. Currently, the data favor a single population hypothesis for histamine. The dose-response relationship for sulfate and sulfuric acid aerosols is not adequate to differentiate between these two hypotheses. It is clear that large interindividual differences in response to inhaled aerosols are a characteristic of the biological response as measured by increased resistance to flow, regardless of the species used, and are not an artifact of the exposure or measurement system.

Age may also play in important part in this response, since young guinea pigs are more susceptible than older ones. For histamine sensitivity, age-dependence has been suggested as an analog of juvenile asthma, but human airway sensitivity does not seem to follow the same developmental pattern. Further research is needed to settle the question of special susceptibility of young animals and children.

For the effects of 1 hr exposure of guinea pigs to sulfur oxides from one laboratory, an apparent ranking of potency (for increased flow resistence) is as follows: H_2SO_4 > $ZnSO_4(NH_4)_2SO_4$ > $Fe_2(SO_4)_3$ > $ZnSO_4$ > $(NH_4)_2SO_4$ > NH_4HSO_4, $CuSO_4$ > $FeSO_4$, Na_2SO_4, $MnSO_4$. The latter three caused no effects.

The toxicology of H_2SO_4 is complicated by its partial concentration-dependent conversion to $(NH_4)_2SO_4$ and NH_4HSO_4 by ammonia in the breath or in the air of animal exposure chambers. While this chemical reaction is stoichiometric, the actual concentrations of $(NH_4)_2SO_4$ and NH_4HSO_4 in the airways or chambers have not been measured definitively. Thus, comparing results of H_2SO_4 studies using animals to those using humans is confounded, particularly since extensive neutralization would not be expected in the atmosphere of human exposure chambers. One theory for the irritating action of sulfuric acid contends that sulfate salts can act to promote release of histamine or other mediators of bronchoconstriction and is supported by

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biochemical and pharmacological evidence in 2 species. Anionic release of histamine may play a role in the bronchial constriction as evidenced by the blockade with H-1 antihistamines. The effects of adrenergic agonists and antagonists suggest the involvement of tracheal smooth muscle. Certainly, the clearance of sulfurous acid, bisulfite, sulfite, and sulfate from the lung is influenced by the cations present in the aerosols inhaled simultaneously. Since polluted air is such a complex mixture of these aerosols, the question of the toxicity of ambient aerosols can not be approached on a simplistic basis by estimating toxicity from the acidity or sulfate content alone.

Chronic exposure to H_2SO_4 also produces changes in pulmonary function. Monkeys exposed to 0.48 mg/m^3 H_2SO_4 continously for 78 wk had altered distribution of ventilation early in the exposure period. Higher concentrations (2.43 and 4.79 mg/m^3 H_2SO_4) changed the distribution of ventilation and increased respiratory rate, but caused no effects on other pulmonary function measurements. A lower concentration (0.38 mg/m^3 H_2SO_4) caused no effects. Morphological changes occurred at the lowest concentration tested (0.38 mg/m^3 H_2SO_4). The effects appeared to be related to size of the particle as well as to concentration. Major findings at 2.43 mg/m^3 H_2SO_4 included bronchiolar epithelial hyperplasia and thickening of the respiratory bronchioles and alveolar walls. Guinea pigs exposed continously for 52 wk to 0.08 or 0.1 mg/m^3 H_2SO_4 had no effects on pulmonary function or morphology. Dogs which inhaled 0.89 mg/m^3 H_2SO_4 for 620 days (21 hr/day) also had no morphological alterations. However, CO diffusing capacity, residual volume, and net lung volume were decreased. Several other changes were noted, including an increase in total expiratory resistance.

Sulfuric acid also alters mucociliary clearance which is responsible for clearing the lung of viable or inanimate particles. These particles impact on the ciliated airways during inhalation or reach this region as a result of alveolar clearance. A 1 hr exposure of dogs to 0.5 mg/m^3 H_2SO_4 increased tracheal mucocilary transport, whereas 1 mg/m^3 H_2SO_4 depressed this rate. A 2 to 3 hr exposure to 0.9 to 1 mg/m^3 H_2SO_4 also decreased tracheal ciliary beat frequency in hamsters. Lower concentrations (0.1 mg/m^3 H_2SO_4, 1 hr/day, 5 days/wk) caused erratic bronchial mucociliary clearance rates in donkeys after several wk of exposure. Continued exposure of the donkeys which had not received pre-exposures caused a persistent slowing of bronchial clearance after about 3 mo of exposure. From these and other studies, it appears that repeated exposures to low concentrations of H_2SO_4 can slow mucociliary clearance. This might imply increased lung residence times of materials that would ordinarily be cleared.

Other host defense parameters, e.g., resistance to bacterial infection, are not altered by low concentrations of H_2SO_4, but are affected by metal sulfates. The apparent relative potency of various particles for increasing susceptibility to infectious (bacterial) respiratory disease has been determined in mice exposed for 3 hr: $CdSO_4$ > $CuSO_4$ > $ZnNO_3$, $ZnSO_4$ > $Al_2(SO_4)_3$ > $Zn(NH_4)_2(SO_4)_2$. At concentrations > 2.5 mg/m^3 the following particles had no significant effects in this model system: H_2SO_4, $(NH_4)_2SO_4$, NH_4HSO_4, Na_2SO_4, $Fe_2(SO_4)_3$, $Fe(NH_4)_2SO_4$, $NaNO_3$, KNO_3, and NH_4NO_3.

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It is evident that accurate estimates of the toxicity of complex aerosols occurring in urban air based solely on their sulfate contents are inappropriate. The chemical composition of the sulfate aerosols determines their relative toxicities. For pulmonary irritance, the potency of a sulfate salt aerosol can be correlated with the permeability of the lung to that specific sulfate salt. The metallic ions are also toxic. Since urban air contains sulfuric acid, ammonium sulfate, and metallic sulfates in varying proportions, it is not possible to extrapolate from the currently inadequate toxicological data on single compounds in animals to man as he exists in a complex environment.

No data are available on the toxicity of secondary or complex atmospheric aerosols, since only a very few published reports of animal studies have appeared. The problem is highly complex because of the variability of aerosols from different urban localities and the compositional changes on collection. Toxicity can be approached, at present, only from estimates of composition and toxicity of individual components. Using in vitro tests, metal oxide-coated fly ash has measurable toxicity which can be ascribed to the insoluble oxides when alveolar macrophages are exposed. The effects of soluble salts of Ni and Cd have major differences. Nickel and Cd are removed from the lung with relative rapidity but may be stored or bound to intracellular proteins to an extent which is sufficient for accumulation on repeated short-term exposures. Two-hr exposures to both Ni (0.5 mg/m^3) and Cd (0.1 mg/m^3) aerosols impair the anti-bacterial defenses of the lung, leading to an increased sensitivity to airborne pathogens in mice. Ciliary beat frequency in the trachea can be decreased by Cd and Ni also. Humoral immunosuppression in mice has been reported after a 2-hr exposure to 0.19 mg/m^3 $CdCl_2$ or 0.25 mg/m^3 $NiCl_2$.

12.6.3 Combinations of Gases and Particles

Although man is exposed to a complex mixture of gases and particles, few animal studies have been conducted with mixtures. The dissolution of SO_2 into liquid aerosols or the sorption onto solid aerosols tends to increase the potency of SO_2. The exact mechanism by which potentiation occurs is still controversial. Sodium chloride and soluble salts (manganous chloride, ferrous sulfate, or sodium orthovanadate) potentiated the effect (increased flow resistance) of a 1-hr SO_2 exposure of guinea pigs. Hypothetically, these particles favored the conversion of SO_2 to H_2SO_4, thus increasing the response.

The effects of chronic exposure to a variety of mixtures of SO_2, H_2SO_4, and fly ash were examined in guinea pigs and monkeys. None of these studies showed effects on pulmonary function. Morphological changes were observed in monkeys after an 18 mo continuous exposure to 2.6 mg/m^3 (0.99 ppm) SO_2 plus 0.88 mg/m^3 H_2SO_4; but the addition of fly ash did not potentiate the response.

When dogs were exposed to SO_2 (13.4 mg/m^3, 5.1 ppm) and H_2SO_4 (0.89 mg/m^3) alone and in combination for 21 hr/day for 620 days, no morphological changes were observed. Sulfur dioxide did not cause any significant changes in pulmonary function except for an increase in N_2 washout, but H_2SO_4 caused a variety of changes which were interpreted as the development of obstructive pulmonary disease.

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In another series of studies, dogs were exposed for 16 hr/day for 68 mo to raw or photochemically reacted auto exhaust, oxides of sulfur or nitrogen, or their combinations. The animals were examined periodically during exposure and at 32 to 36 mo after exposure ceased. After 18 or 36 mo of exposure, no significant changes in pulmonary function were observed. After 61 mo, a few functional alterations were observed in dogs exposed to SO_x (1.1 mg/m^3, 0.42 ppm SO_2, and 0.09 mg/m^3 H_2SO_4) alone and in combination with other pollutants. The animals had been placed in clean air for 32 to 36 mo after exposure ceased, at which time the SO_x group had a variety of pulmonary functional and morphological alterations. These structural changes included a loss of cilia without squamous cell metaplasia, nonciliated bronchiolar hyperplasia, and a loss of interalveolar septa in alveolar ducts. The authors hypothesized that these changes are analogous to an incipient stage of human proximal acinar (centrilobular) emphysema. Since the pulmonary function changes were progressive during the post-exposure period and they were correlated with the pathology, it can be hypothesized that the morphological alterations were also progressive.

Combinations of carbon and H_2SO_4 or SO_2 were investigated also. In mice exposed for 3 hr/day, 5 days/wk for up to 20 wk to a mixture of 1.4 mg/m^3 H_2SO_4 and 1.5 mg/m^3 carbon or to carbon only, morphological and immunological alterations were seen. In hamsters, a 3 hr exposure to 1.1 mg/m^3 + 1.5 mg/m^3 carbon depressed ciliary beat frequency, as did H_2SO_4 alone. Alterations of both the pulmonary and systemic immune systems were found in mice at various lengths of exposure (100 hr/wk up to 192 days) to 5.2 mg/m^3 (2 ppm) SO_2 and 0.56 mg/m^3 carbon, alone or in combination. Generally, carbon and carbon + SO_2 caused more extensive effects than SO_2 alone.

When the interaction of O_3 and H_2SO_4 was studied, the morphological effects of a 6 mo intermittent exposure of rats and guinea pigs to the mixture [10 mg/m^3 H_2SO_4 + 1.02 mg/m^3 (0.52 ppm) O_3] were attributed to O_3 alone. However, combined exposure to 1 mg/m^3 H_2SO_4 and 0.78 to 0.98 (0.4 to 0.5 ppm) O_3 resulted in synergistic effects on glycoprotein synthesis in the tracheal and certain indices of lung biochemistry. Acute sequential exposure to first 0.196 mg/m^3 (0.1 ppm) O_3 and then 0.9 mg/m^3 H_2SO_4 caused additive effects on increased susceptibility to infectious pulmonary disease and antagonistic effects on depression of trachea ciliary beat frequency. From these studies, the interaction of O_3 and H_2SO_4 is quite complex and appears to be dependent on the sequence of exposure as well as on the parameter examined.

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13. CONTROLLED HUMAN STUDIES

13.1 INTRODUCTION

Evaluation of health effects induced by exposure to air pollutants requires that studies be conducted under rigorously controlled conditions. Controlled studies provide a necessary bridge between epidemiology and animal toxicology data. In general, such studies should provide situations which realistically simulate the exposures experienced by man in his normal environment. However, the complexity and variability of the ambient environment is such that most controlled studies initially have been designed to evaluate the effects of exposure to single pollutants, and then later have been extended to the more complex mixtures of pollutants actually present in the environment.

The high cost and minimal number of subjects who can be studied under controlled conditions make it imperative that studies be conducted under stringent conditions in order to be relevant to larger populations. Ideally the design of such controlled trials should include normal individuals of both sexes and all age groups, subjects especially sensitive to some particular pollutant, and individuals from populations suspected to be at special risk. Consideration must also be given to the activity levels of the subjects, ambient environmental conditions prevailing prior to the subjects' testing, and exposure variables that realistically simulate ambient conditions, including such factors as temperature, humidity, duration of exposure, and mode of exposure. Controlled studies also require proper experimental design which should include purified air conditions, double blind exposure procedures (this cannot be complied with when certain pollutants and some levels of these pollutants are being evaluated), several concentrations of these pollutants should be employed in order to develop dose response relationships, as well as comprehensive statistical treatment of the data obtained. In addition, adequate (even duplicate) pollutant monitoring equipment with documentation of quality control are needed. Proper attention must also be given to the presence of potentially interfering pollutants inadvertently present or developing under certain conditions. Ideally not only should physiological and biochemical evidence be obtained, but subjective symptoms and/or changes in performance capability should also be assessed. Since the respiratory tract is the initial target of many air pollutants, proper and sensitive respiratory function measurements are a primary requirement. Since diurnal patterns are known to occur in physiological systems, experiments should be controlled as to time of day that they are conducted. However, various biochemical systems may be affected if pollutants (or their reaction products or substances absorbed on particulates) pass into the circulatory and other, systems.

The above criteria need to be applied to any evaluation of clinically controlled studies. However, due to particular restraints placed on investigators, no studies meet all of these ideal requirements. Nonetheless, certain basic information may be derived from a number of studies. This chapter provides an overview of controlled air pollutant exposure studies of

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certain human health effects of sulfur compounds. It should be noted that laboratory studies utilizing man have been limited to the evaluation of acute effects; thus the potential for chronic health effects cannot be predicted from such exposures.

13.2 SULFUR DIOXIDE

Exposure of man to sulfur dioxide has been shown to induce a number of physiological responses. Alterations in sensory system responses such as irritation of eyes and nose, changes in odor perception, and dark adaptation have been reported. Various changes in function of the respiratory system have also been reported. The following sections address these various functional changes in greater detail. (See Chapter 11 for more detailed discussion of SO_2 deposition).

13.2.1 Subjective Reports

The perception of odor and the sensation of irritation in the eyes, nose, throat, or other parts of the body are difficult to measure precisely. Thus subjects may be observed for qualitative changes (coughing, rhinorrhea, lacrimation) or asked to report whether they detect something in the air they are breathing. Several studies have used such subjective reports as an indication of the effects of SO_2 on human subjects.

A number of early investigators exposed themselves to high concentrations of SO_2 (>500 ppm) and experienced coughing, irritation of the eyes and nose, and difficulty in breathing (e.g., Ogata, 1884; Yamada, 1905; Kisskalt, 1904). In the course of investigating the effects of SO_2 on industrial workers, Lehman (1893) and his associates experienced nasal irritation during exposures of 10 to 15 minutes to 6.5 ppm SO_2. Holmes et al. (1915 -- cited by Greenwald, 1954) carried out an extensive study of 60 subjects, 28 of whom were unaccustomed to breathing SO_2, and 32 of whom were familiar with it. All of the subjects already familiar with the gas seemed to detect it (either as SO_2 or as "something foreign") at 3 ppm. But only 10 of 28 unaccustomed subjects detected something in the air at 3 ppm SO_2. Few subjects found momentary whiffs of 5 ppm disagreeable, although "Long-continued breathing of air containing slightly more than 5 parts per million would probably cause discomfort to most people..." (Holmes et al., 1915). Amdur et al. (1953) noted that during exposure to 1 to 2 ppm their subjects could not usually detect the odor of SO_2; even at 5 ppm most subjects could not smell the gas, although they did complain of dryness in the throat. One subject, however, objected so strongly to 5 ppm SO_2 odor that exposure was terminated. Above 5 ppm the odor was definitely detected by all subjects.

A number of more recent studies have asked subjects to report their subjective experiences (e.g., Greenwald, 1954; Tomono, 1961; Frank et al., 1962; Toyama and Nakamura, 1964; Speizer and Frank, 1966a,b; Melville, 1970; Weir and Bromberg, 1972, 1973; Lawther et al., 1975; Horvath and Folinsbee, 1977), but the results seem to be quite variable at exposures less than 5 ppm SO_2. Also, Frank et al. (1962) have shown that subjective reports are in some situations an unreliable indicator of physiological responses, since coughing and a sense of throat

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irritation tended to subside in their subjects after a few minutes while other changes in respiratory effects were still maximal.

13.2.2 Sensory Effects

Among the physiological functions that may reflect the effects of exposure to SO_2 are certain sensory processes. These studies have investigated not only odor threshold but also sensitivity of the dark-adapted eye to light and interruption of the alpha (α) rhythm in electroencephalograms (see Table 13-1). Most of these investigations have been summarized by Ryazanov (1962).

13.2.2.1 Odor Perception Threshold--In the Russian studies odor threshold is typically determined in a well-ventilated chamber containing 2 orifices from which emerge 2 small streams of gas, one being very pure air and the other other being a stream of the test gas. The subject sits in front of the apparatus, sniffs both orifices, and points out the odorous one. This experiment is repeated with the same concentration of test gas over a period of several days. The experiment is performed with increasingly reduced concentrations until the subject, in the majority of instances, denies the presence of an odor or gives erroneous answers. The threshold concentration for the most sensitive subject in a group of volunteers is defined as the threshold for odor perception.

Using the 2-orifice apparatus described above, Dubrovskaya (1957) conducted sulfur dioxide odor perception threshold tests on 12 subjects. Sulfur dioxide concentrations of 0.5 mg/m^3 to 13 mg/m^3 (0.17 ppm to 4.6 ppm) were used in 530 threshold determinations. Six test subjects sensed the odor of sulfur dioxide in the range 2.6 mg/m^3 to 3.0 mg/m^3; four subjects sensed the odor in the range 1.6 mg/m^3 to 2.0 mg/m^3; one sensed the odor in the range 2.1 mg/m^3 to 2.5 mg/m^3; and one sensed the odor in the range 3.1 mg/m^3 to 3.6 mg/m^3. Thus, the average sulfur dioxide odor threshold concentration was 0.8 ppm to 1 ppm (~2.3 mg/m^3 to ~2.9 mg/m^3), and for the more sensitive of these persons it was 0.5 ppm to 0.7 ppm (~1.5 mg/m^3 to ~2.0 mg/m^3). It should be noted, however, that most of the subjects were of an age at which odor perception was presumed to be most sensitive.

Determination of sulfur dioxide odor thresholds (1968) conducted for the Manufacturing Chemists' Association in the United States gave somewhat lower values than those cited above (Arthur D. Little, Inc., 1968). The concentrations at which first one-half and then all of the panel members could positively recognize the odor were reported to both be 0.47 ppm (1.3 mg/m^3). The details of the test procedure are thoroughly discussed in the report, but one important aspect is reiterated as a reminder that odor thresholds usually represent values derived under ideally suited conditions and with trained individuals. The investigators, who were highly qualified to judge on the basis of substantial experience with consumer evaluation of known flavor and odor situations, derived threshold values under ideal conditions lower than those which would be recognized by the majority of a population under ordinary atmospheric conditions. This does not mean that normal individuals exposed to sulfur dioxide under ideal

* XD13A/B-1

TABLE 13-1. SENSORY EFFECTS OF SO_2

Concentration SO_2 (ppm)	Exposure mins.	Effects	Reference
400	120	Dyspnea	Ogata, 1884
6.5	10 - 15	Nasal irritation	Lehman, 1893
140, 210, 240	30	Marked nasal irritation, sneezing	Yamada, 1905
210, 240	30	Eye irritation, lacrimation	Yamada, 1905
1, 2, 5	--	All subjects detect odor above 5 ppm	Amdur et al., 1953
3, 5, plus	--	Discomfort to all subjects exposed to 5 plus. Some noted disagreeable odor at 5 ppm.	Holmes, 1915 (see Greenwald, 1954)
0.17 - 4.6	--	Average SO_2 odor threshold was 0.8 - 1.0 ppm	Dubrovskaya, 1957
	--	Positive recognition of SO_2 was 0.47 ppm	Arthur D. Little, Inc., 1968
0.34 - 6.9	15	Light sensitivity increased at 0.34 - 0.63 ppm and above.	Dubrovskaya, 1957
0.23	--	Ocular sensitivity to light increased at SO_2 levels of 0.23 ppm and above	Shalamberidze, 1967
0.2 - 1.7	0.33	Attenuation of α-waves at levels above 0.2 ppm	Bushtueva, 1962
1 - 10	--	Organoleptic effects at levels 2 ppm and above	Greenwald, 1954

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test conditions could not perceive the 0.47 ppm level indicated. However, because of background odor and lack of awareness or concern with ambient odor conditions, such individuals in an everyday situation would probably be less responsive to this low concentration.

13.2.2.2 Sensitivity of the Dark-Adapted Eye--The sensitivity of the eye to light while a subject is in darkness increases with time. Several investigations have been made of the effects of inhalation of sulfur oxides on this sensitivity. Typically, measurements of a subject's normal sensitivity are taken in a dark, well-ventilated chamber in complete silence (sudden stimuli, including noise, may affect the subject's response). Each subject is tested once daily following preliminary stimulation at a high light level. Light sensitivity is measured at 5-minute or 10-minute intervals, and a curve of increasing sensitivity to light is established from measurements taken over a period of 7 to 10 days.

Dubrovskaya (1957) studied the effect of inhaling sulfur dioxide in concentrations from 0.96 mg/m^3 to 19.2 mg/m^3 for 15 minutes before measuring light sensitivity during dark adaptation. She reported that light sensitivity was increased by sulfur dioxide concentrations of 0.96 mg/m^3 to 1.8 mg/m^3 (0.34 ppm to 0.63 ppm), that the increase in sensitivity reached a maximum at concentrations of 3.6 mg/m^3 to 4.8 mg/m^3 (1.3 ppm to 1.7 ppm), and that further increases in the sulfur dioxide concentration resulted in progressive lowering of eye sensitivity to light until at 19.2 mg/m^3 the sensitivity was identical with that of the unexposed subject.

In exposures during light adaptation, sulfur dioxide concentrations of 0.6 mg/m^3 to 7.2 mg/m^3 (0.21 ppm to 2.5 ppm) caused slight increases in eye sensitivity. Maximum sensitivity was attained at 1.5 mg/m^3 (0.52 ppm); at higher concentrations the increased sensitivity began to abate. Two human subjects were used in these experiments. The odor threshold was between 2.5 mg/m^3 and 3.0 mg/m^3 for one subject and between 3.0 mg/m^3 and 3.6 mg/m^3 for the other, so that changes in sensitivity to light during dark adaptations were caused by sulfur dioxide concentrations below the odor threshold.

Shalamberidze (1967) investigated the effects of SO_2 and NO_2, singly and in combination, on visual light sensitivity as determined by measures of dark adaptation. According to this report, SO_2 concentrations of 0.6 mg/m^3 (0.23 ppm) and higher caused "a considerable increase in the ocular sensitivity to light" (Shalamberidze, 1967, p. 11). So few details on methods or results were presented, however, that this report cannot be accepted without reservations.

13.2.2.3 Interruption of Alpha Rhythm--The electroencephalogram is a composite record of the electrical activity of the brain recorded as the difference in electrical potential between two points on the head. In the adult, the electroencephalogram characteristically shows a fairly uniform frequency from 8 cycles to 12 cycles per second in the posterior head regions (alpha). Variations occur with age, the state of wakefulness and attentiveness, or as a result of incoming sensory stimuli from exteroceptive or interoceptive receptors. The dominant frequency (α) is inhibited or attenuated by eye opening and by mental activity.

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Subjects with well defined α-rhythms studied in a silent and electrically shielded chamber show a temporary attenuation of the α-rhythm each time they are given a light signal. When the light is excluded, the α-rhythm returns to normal. A concentration of test gas is determined which is so low that by itself it does not cause attenuation of the α-rhythm. A subject breathes the gas at this concentration, and then he receives the light signal. After exposure to this sequence (gas then light) several times (5 to 30 times in 1 day), a subject will show attenuation before he receives the light signal; that is, he responds to the unperceived odor. The unperceived odor thus becomes the conditioning stimulus and brings about the so-called conditioned electrocortical reflex.

Bushtueva (1962) reported that 20-second exposures of six human subjects to sulfur dioxide concentrations from 0.9 mg/m^3 to 3 mg/m^3 (~0.3 ppm to ~1.0 ppm) produced attenuation of the α-wave lasting 2 to 6 seconds; at concentrations of 3.0 mg/m^3 to 5.0 mg/m^3 (~1.0 ppm to 1.7 ppm) attenuation lasted throughout the 20-second exposure. Exposures to 0.6 mg/m^3 (~0.2 ppm) did not cause attenuation of the α-wave. The threshold for attenuation of the α-wave was the same as the odor theshold or the threshold of irritation of the respiratory tract. Bushtueva further demonstrated that electrocortical conditioned reflexes could be developed with sulfur dioxide at 0.6 mg/m^3 (~0.2 ppm) but not with lesser concentrations of the mixture.

13.2.3 Respiratory and Related Effects

13.2.3.1 Respiratory Function--A number of studies have documented the various respiratory and cardiovascular effects deriving from exposure to SO_2 (see Table 13-2). (See Chapters 11 and 12 for further discussion of respiratory effects of SO_2.) One of the first clinical studies of the effects of inhaling SO_2 was reported by Amdur et al. (1953). They had 14 resting subjects breathing SO_2 for 10 minutes through a face mask in concentrations ranging from 1 to 8 ppm. Pulse rate and respiration rate increased and tidal volume decreased during exposure to as little as 1 ppm SO_2. Several investigators attempted to replicate Amdur et al.'s (1953) findings, including McIlroy et al. (1954), Lawther (1955), and Frank et al. (1962). None was able to find consistent respiratory or cardiovascular effects of SO_2 below 5 ppm. Nevertheless, these and other studies have documented a variety of subjective and physiological effects under various conditions of exposure to SO_2. Sim and Pattle (1957) performed extensive clinical studies over a 10-month period on an unspecified number (8 to 12) of "healthy males aged 18 to 45." SO_2 was administered either by face mask at concentrations ranging from 1.34 to 80 ppm for 10 minutes or in an inhalation chamber at concentrations of 1.0 to 23.1 ppm for 60 minutes. Regardless of exposure route, the only notable effects of SO_2 were stated to be bronchoconstric tion (increased resistance to air flow) and high-pitched chest rales at 49 ppm and greater concentrations. They also reported that when ammonia (no value given) was also present in the chamber (9.9 ppm SO_2) the subjective impressions of bronchoconstriction disappeared.

Frank et al. (1962) examined the effects of acute (10 to 30 minute) exposures to SO_2 via mouth in 11 subjects. Each subject received approximately 1, 5, and 13 ppm of the gas in

* XD13A/B-2

13-2. RESPIRATORY EFFECTS OF SO_2

Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)*	Effects	Reference
1.0 3.0 5.0	3 3 3	8 - 10 8 - 9 10	O O O	R + E R + E R	Light exercise potentiates effect of SO_2 $MEF_{40\%}$ decreased	Kreisman et al., 1976
9 - 60	5	25	N - O	R	Airway resistance increased	Nakamura, 1964
1 - 8	10	14	Face mask	R	Pulse rate, respiratory increased; tidal volume rate decreased	Amdur et al., 1953
--	10	--	N	R	Could not duplicate Amdur's results	McIlroy et al., 1954
5, 10 20	10 10	18 6	O - N O	R R	No changes in pulse rate, respiratory rate or tidal volume (5, 10 ppm) 2 subjects had bronchospasm	Lawther, 1955
1, 5, 13	10	12	O	R	No changes in pulse rate, respiratory rate. Pulmonary flow resistance increased at 5 and 13 ppm	Frank et al., 1962
1.3 - 80	10	8 - 12	Face Mask	R	Bronchoconstriction at the higher concentrations	Sim and Pattle, 1957
1 - 45	10	46	Face Mask	R	Decreased peak flow, decreased expiratory capacity above 1.6 ppm	Tomono, 1961
2.5, 5.0, 10.0	10	15	O, N	R	SG_{aw} decreased less with nasal breathing	Melville, 1970
4 - 6	10	7	O	R	Airway conductance decreased reflex effect	Nadel et al., 1965

*Intermittent Exercise

13-7

13-2. (continued)

Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
15, 28	10	8	O N	R	Pulmonary flow resistance increased less with nasal breathing	Speizer and Frank, 1966[a]
5	10	5	O M	R	$MEF_{50\%}$ decreased less with nasal inhalation	Snell and Luchsinger, 1969
2,5 - 50	10	5	O	R	Increased respiratory and inspiratory resistance	Abe, 1967
1.3 - 80	10	8 - 12	Face mask	R	Bronchoconstriction	Sim and Pattle, 1957
0.5, 1.0, 5.0	15	9		R	$MEF_{50\%}$ decreased at 1 and 5 ppm	Snell and Luchsinger, 1969
1, 3, 5	10	7, 7, 7 (21)	O	R	SR_{aw} increased significantly at all conc for asthmatics; only at 5 ppm for normals and atopic subjects	Sheppard, et al., 1980
0.1, 0.25, 0.5	10	7, 6	O	E	SR_{aw} significantly increased in the asthmatic group at 0.5 and 0.25 ppm SO_2 and even at 0.1 in the two most responsive subjects	Sheppard, et al., 1981
1, 5, 13	10 - 30	11	O N	R	Pulmonary flow resistance increased at 5 and 13 ppm but less during nasal breathing; at 1 ppm, one subject experienced 7% increase in flow resistance, another a 23% decrease	Frank et al., 1962
16.1	25	7	Face mask O - N	R	SO_2 almost completely removal by nasal breathing	Speizer and Frank, 1966b
1, 5, 15	30	12	O	R	Increased in Rl at SO_2 levels above 5 ppm	Frank et al., 1964
1.1 - 3.6	30	10	O	R	Deep breathing produced no effects	Burton et al., 1969
5	30	10	O	E	MMFR decreased	Newhouse et al., 1978

13-8

13-2. (continued)

Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
1 - 23	60	8 - 12	Mask, chamber N	R	Bronchoconstriction	Sim and Pattle, 1957
1	60	-	N	R	No effects observed	McJilton, 1976
5	60	9	O	R	No effect or mucus transport	Wolff et al., 1975a
5 - 30	10	10	CO_2 stimulus	(O) R	Deep breathing significantly increased SR_{aw}	Lawther, 1975
1	50	13	Chamber (N)	R		
3	-	17	O	R		
10, 15, 25, 50	60 *Intermittent Exercise				At higher conc. of SO_2 mucociliary activity decreased	Cralley, 1942
0.37	120	8	Chamber	E	No pulmonary effects	Bates and Hazucha, 1973; Hazucha and Bates, 1975
0.37	120	4 - 12	Chamber	E	No pulmonary effects	Bell et al., 1977
0.40	120	9	Chamber	E	No pulmonary effects	Horvath and Folinsbee, 1977; Bedi et al., 1979
0.75	120	4 - 8	Chamber	E	Significant decrease in MEFR; FVC, $FEV_{1.0}$, MMFR also decreased	Bates and Hazucha, 1973;
1.0, 5.0	120	15	N	R	Increase in nasal air flow resistance; decrease in nasal mucus flow	Andersen et al., 1974
5.0	120	11	Chamber	E	Insignificant changes in R_e and $P_{A_{O_2}}$	von Neiding et al., 1979
5.0	120	10	Chamber (oral)	E	MMFR decreased 8.5% increased tracheobronchial clearance	Newhouse et al., 1978
25.0	120	15	N	R	Increased nasal airfow resistance; decreased nasal mucus flow	Andersen et al., 1974

* XD13A/B-5

13-2. (continued)

Concentration SO_2 (ppm)	Duration of exposure (mins)	Number of subjects	Oral or nasal exposure	Rest (R) or exercise (E)	Effects	Reference
0.50	180	40 (normal subjects)	Oral	R	No pulmonary effects	Jaeger et al., 1979
0.50	180	40 (asthmatics)	Oral	R	MMFR decreased 2.7%; recovery within 30 minutes; 3 subjects incurred delayed effects and required medication.	Jaeger et al., 1979
5	180+	10	0	E	Increased tracheobronchial clearance	Wolff et al., 1975b
0.3, 1.0 and 3.0	96 - 120 Hours	12 (normal) 7 (COPD)	Chamber	R	No difference in response between groups. Slight decrease in pulmonary compliance but of questionable significance	Weir and Bromberg, 1972
1.0, 5.0 and 25.0	Up to 6 hrs/day	15	Chamber (N)	R	Significant decreases in expiratory flow and $FEV_{1.0}$ decreased mucus flow	Andersen et al., 1974
5	4.5 hours	32 (16 exposed)	Chamber	R	Number of colds similar in both groups but severity less in SO_2 exposed subjects	Andersen et al., 1977

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separate exposures at least 1 month apart. The only significant effects were a 39 percent increase ($p < 0.01$) in pulmonary flow resistance at 5 ppm and a 72 percent increase ($p < 0.001$) at 13 ppm. Only one subject showed a significant increase with 1 ppm SO_2 concentration, his control resistance was the highest encountered. The recovery of some subjects was complete within a few minutes. As in Sim and Pattle's study (1957), other cardiovascular or pulmonary measures did not show any significant effects.

Tomono (1961) tested 46 men for the effects of SO_2 on their pulmonary physiology. The subjects inhaled 1 to 45 ppm SO_2 through a face mask for 10 minutes. Decreases in expiratory capacity and peak flow rate were proportional to the concentration of SO_2. Such effects were detected at a concentration as low as 1.6 ppm. Slight increases in pulse and respiration rates were observed in about 10 percent of the subjects but were not proportional to SO_2 exposures. Nakamura (1964) exposed 10 subjects each to a different concentration of SO_2 (9 to 60 ppm) for 5 minutes. Airway resistance increased an average of 27 percent. Since each subject was exposed to only one concentration of SO_2 and there was considerable variability in response to the different concentrations, the significance of those isolated findings may be questioned. No significant correlation between dosage and response was discovered. For example, a subject had a 17 percent increase after exposure to 9 ppm, another 9 percent after exposure to 16 ppm, another 75 percent after exposure to 4 ppm and another 22 percent after exposure to 57 ppm.

Snell and Luchsinger (1969) also found significant decreases in pulmonary function consequent to SO_2 exposure. Nine subjects inhaled through a mouth piece SO_2 at concentrations of 0.5, 1.0, and 5 ppm for 15 minutes each, with 15-minute control periods interspersed. Maximum expiratory flow ($MEF_{50\%\ VC}$) was significantly lower after exposure to 1 ppm SO_2 ($p < 0.02$) as well as 5 ppm ($p < 0.01$). Reichel (1972) exposed 32 normal subjects continuously in a chamber to 7.7 ppm SO_2 for 6 days. Intrathoracic gas volume and intrabronchial flow resistance was not altered consequent to any of the 6 days of exposure. Airway resistance was measured in 16 of these subjects by inhalation of 3% acetylcholine chloride solution. The sensitivity response to this challenge was not altered as a consequence of the exposure of SO_2. Jaeger et al. (1979) exposed 40 normal non-smokers and 40 asthmatics (mild to moderate but with no recent exacerbations) subjects for 3 hours to 0.5 ppm SO_2. Oral inhalation was forced by having the subjects wear a nose clip. These resting subjects were also studied during exposure to ambient air having an average SO_2 content of 0.005 ppm. Three pulmonary function tests (VC, FEV_1 and MMFR) were performed at intervals during the exposure and a more intensive series of tests were made prior to and after the exposure. The only significant ($p < 0.04$) effect observed was a 2.7 percent decrease in MMFR in the asthmatic subjects. This minimal change was stated to have little physiological importance. One normal and two asthmatic subjects exhibited adverse reactions--the asthmatics requiring standard asthma medication.

Nadel et al. (1965) have helped elucidate the mechanism of bronchoconstriction resulting from SO_2 exposure. They exposed seven subjects to 4 to 6 ppm SO_2 for 10 minutes via mouth in a closed plethysmograph. The mean decrease in specific airway conductance was 39 percent

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($p < 0.001$). Injecting the subjects with 1.2 to 1.8 mg atropine sulfate 20 minutes before SO_2 inhalation resulted in only a 3 percent ($p > 0.20$) decrement in specific airway conductance/thoracic gas volume. However, atropine did not affect the coughing or sensation of irritation in the pharynx or substernal area. From this and other evidence, Nadel et al. concluded that the bronchoconstriction induced by SO_2 depends on changes in smooth muscle tone mediated by parasympathetic motor pathways. Thus, when sensory receptors in the tracheobronchial region are irritated by a substance such as SO_2, a reflexive bronchospasm may be triggered.

Apart from fairly consistent bronchoconstriction effects, a common element in these and other reports of the effects of SO_2 has been the notable variability among subjects in their responses to such exposures. In Frank et al.'s study (1962), for example, 9 of 11 subjects showed no effects at 1 ppm, but 1 subject showed a significant ($p < 0.01$) decrease in pulmonary flow resistance, whereas the remaining subject showed a significant ($p < 0.01$) increase. Sim and Pattle (1957) reported that they themselves appeared to be exceptionally sensitive to SO_2 encountered in the course of their research. They experienced persistent and uncomfortable spells of coughing and wheezing upon contact with the gas. Other investigators (e.g., Burton et al., 1969; Frank, 1964; Nadel et al, 1965; Lawther, 1955; Lawther et al., 1975; Jaeger et al., 1979) have reported "hyper-reactors" among their subjects. Indeed, some investigators have suggested that about 10 percent of the total population is made up of especially sensitive persons (Amdur, 1973, 1974; Horvath and Folinsbee, 1977). However, in at least one instance (Andersen et al., 1974), a subject's response was exaggerated even under control conditions, which raises the possibility of psychological factors contributing to this observed sensitivity.

13.2.3.2 Water Solubility--One of the first points to note is that because of its high solubility in water, SO_2 is readily absorbed when it comes in contact with the moist surfaces of the nose and upper respiratory passages (Frank et al., 1973). This has a number of important implications for the analysis of the effects of SO_2 on respiratory functions. These considerations will be illustrated in the following sections (see Chapter 11).

13.2.3.3 Nasal Versus Oral Exposure--A number of studies have demonstrated significant response differences between the nose and mouth as routes of exposure to SO_2. Speizer and Frank (1966a), for example, compared the effects of SO_2 (10-minute exposures at 15 and 28 ppm) in eight subjects breathing the gas either by nose or by mouth. The subjects coughed less and reported less irritation of the throat and chest when breathing through their noses. Also, pulmonary flow resistance increased less during nasal exposure than during oral exposure.

A second study by the same investigators (Speizer and Frank, 1966b) refined their analysis of these effects, using seven subjects and a specially designed face mask. Air was sampled at various points, including: (1) within the face mask before being inspired, (2) within the subject's nose, and (3) within the subject's oropharynx. Exposures lasted 25 to 30 minutes. The average concentration of SO_2 within the mask was 16.1 ppm; within the oropharynx the concentration was too low for the investigators' equipment to measure. Thus, essentially all of the SO_2 (90 to 99 percent) in the inspired air was removed by the nose. Similar

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results were obtained by Andersen et al. (1974) in a study that will be described in detail later.

Melville (1970) also compared oral and nasal routes of administration. He used 15 subjects and exposed them (for 10 minutes) sequentially to 2.5, 5, and 10 ppm SO_2. More SO_2 was cleared per minute with nose breathing than with mouth breathing. There was a clear dose-dependent response reflected in measures of the subjects' specific airway conductance (SG_{aw}): as the SO_2 concentration increased, SG_{aw} decreased ($p < 0.05$). This was true regardless of administration route (for 2.5 ppm SO_2), but the average decrease under oral administration was greater (in 80 percent of subjects), than the decrease under nasal administration ($p < 0.05$). During a 1-hour exposure to 5 ppm SO_2 no significant difference was observed in SG_{aw} regardless of whether the 49 subjects breathed through mouth or nose.

Snell and Luchsinger (1969) also examined the differences between nasal and oral exposure using SO_2 at 5 ppm. Five subjects' average maximum expiratory flow ($MEF_{50\% VC}$) was 10 percent lower following oral exposure than following nasal exposure. This difference, however, was not statistically significant. See Chapter 11 for further discussion of SO_2 deposition.

13.2.3.4 Subject Activity Level--One of the practical implications of the above findings is that vigorous activity, such as heavy exercise or work, may significantly affect the actual dose received by a person during exposure to SO_2. At some level of ventilation, inhalation of air shifts from nasal to mouth breathing. Studies under way (Horvath, Ph.D. theses, personal communication) suggest that subjects who are nasal breathers at rest move to oral-nasal breathers when ventilatory exchange is approximately 30 L/min. However, it should be remembered that many individuals are always mouth breathers. Saiben et al. (1978) studied 63 subjects while they exercised at increasing work loads. Incomplete information was obtained on 13 subjects. Ten subjects breathed through the mouth at all work loads while five never opened their mouths. In the remaining 35 subjects, the highest ventilation volume attained with nasal breathing was 40.2 liters per minute. Determination of the shift to oral breathing was obtained by a subjective observation by an observer. In a second study using 10 subjects, ventilation was more precisely (but still not a completely adequate technique) determined by movements of the rib cage. The mean value of ventilation at the point of shift to oral breathing was 44.2 liters/min. It should be noted that there remains the possibility that some air continues to enter the lungs through the nose, but the volume definitely is reduced (Horvath, personal communication).

Kreisman et al. (1976), for example, reported that exercise may potentiate the effect of SO_2 on respiratory function. In their study, subjects inhaled a mixture of SO_2 in air for 3 minutes while exercising on a bicycle ergometer at a pace sufficient to double their resting minute ventilation rate. Eight subjects recieved 1 ppm SO_2 and nine subjects received 3 ppm. Those receiving 3 ppm showed a significant ($p < 0.05$) decrease in maximal expiratory flow ($MEF_{40\% (P)}$) compared to a control (untreated air) exposure. However, it is not clear that this change differed significantly from the change in $MEF_{40\% (P)}$ occurring in resting subjects.

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Bates and Hazucha (1973) reported significant decreases in FVC (10 percent), $FEV_{1.0}$ (10%), MMFR (10%), and MEFR (23%) in 4 subjects (who exercised intermittently during the exposure) exposed in a chamber containing 0.75 ppm SO_2. At 0.37 ppm SO_2, Hazucha and Bates (1975) observed no significant pulmonary function changes. Horvath and Folinsbee (1977) and Bedi et al. (1979) exposed nine intermittently exercised subjects in a chamber to 0.4 ppm SO_2 and found no pulmonary function changes.

Lawther et al. (1975) have demonstrated that simply instructing 12 subjects to take 25 deep breaths by mouth resulted in a significant ($p < 0.001$) increase in specific airway resistance (SR_{aw}) during exposure to SO_2 at 1 ppm. While sitting quietly in an inhalation chamber, the same subjects had previously shown no such increase after breathing concentrations of 1 to 3 ppm SO_2 for an hour. As part of a series of experiments in this study, 17 subjects also received 3 ppm SO_2 by a mouthpiece and were instructed to take 2, 4, 8, 16, and 32 deep breaths at 5-minute intervals. Increases in SR_{aw} due to SO_2 were significantly greater after 16 ($p < 0.01$) or 32 ($p < 0.001$) deep breaths.

Burton et al. (1969), however, found no consistent effects in 10 subjects exposed to SO_2 at 1.1 to 3.6 ppm for 30 minutes, regardless of whether the subjects breathed normally or at a forced hyperventilation rate of up to 2.5 L/sec. One (other) difference between these two studies was the duration of exposure. Burton et al. (1969) exposed their subjects for 30 minutes, whereas, Lawther et al. (1975) maintained exposures for an hour. This raises another important consideration in reviewing the effects of SO_2 on human subjects, namely, temporal parameters.

Sheppard et al. (1981), using 13 non-smoking mild asthmatic volunteers (10 men, 3 women, 20 to 30 years of age), demonstrated that moderate exercise increases the bronchomotor effect of SO_2 at concentrations of 0.5, 0.25, and 0.1 ppm. In seven subjects with mild asthma, inhalation of 0.50 and 0.25 ppm of SO_2 during the performance of moderate exercise significantly increased SRaw, whereas neither inhalation of 0.50 ppm of SO_2 at rest nor inhalation of humidified, filtered air during exercise had any effect on SRaw. Inhalation of 0.50 ppm during exercise significantly increased SRaw in all seven subjects ($p < 0.05$), and three developed wheezing and shortness of breath. During the corresponding period of exercise alone and during inhalation of 0.50 ppm at rest, SRaw did not increase in any subject. After inhalation of 0.50 ppm of SO_2 during exercise, SRaw was significantly greater than after exersise alone or inhalation of 0.50 ppm of SO_2 at rest ($p < 0.05$). Inhalation of 0.25 ppm during exercise significantly increased SRaw in three of the seven subjects, and the increase in SRaw for the group was significant ($p < 0.05$). No subject developed wheezing or shortness of breath. During the corresponding period of exercise alone, SRaw did not increase in any subject. In the two most responsive subjects, inhalation of 0.10 ppm of SO_2 as well as 0.25 and 0.50 ppm significantly increased SRaw, and there appeared to be a dose-response relationship.

In the second set of studies, in all six subjects, inhalation of 1 ppm of SO_2 dramatically increased SRaw, both when it was delivered during exercise and during eucapnic hyperventilation.

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In every case, the increase in SRaw was accompanied by dyspnea and audible wheezing. The magnitude of the increase in SRaw was the same when the subjects inhaled SO_2 while they exercised or while they performed eucapnic hyperventilation at the same minute ventilation.

The bronchoconstriction produced by inhalation of 0.50 ppm of SO_2 during exercise was gradual in onset. Immediately after exercise, SRaw did not differ significantly from baseline values. It then increased over the first 3.5 min, reached a plateau, and gradually returned to baseline values by 30 min after exposure. A similar time course was seen in those subjects who developed bronchoconstriction after exposure to 0.25 and 0.10 ppm of SO_2.

13.2.3.5 Temporal Parameters--Early studies (e.g., Lehman, 1893) suggested that workers chronically exposed to relatively high concentrations of SO_2 were less conscious of its presence in the atmosphere than persons not as familiar with the gas. However, Holmes et al.'s data (1915) indicated that subjects already accustomed to SO_2 could detect its odor at lower concentrations than could persons unaccustomed to it. Nevertheless, it would seem plausible that "self-selection" would tend to reduce the number of relatively sensitive persons among the population of workers chronically in contact with supra-threshold levels of SO_2.

As previously noted, a study by Frank et al. (1962) has indicated that subjective reports are not a reliable indicator of physiological responses in any event. After 5 to 10 minutes of exposure to either 5 or 13 ppm SO_2 their subjects' pulmonary resistance measures were just reaching their peaks, while subjective reports of an odor of SO_2 had already subsided.

In a later study by Frank et al. (1964) the increase in pulmonary resistance induced by SO_2 peaked at about 10 minutes and then gradually decreased over the next 15 minutes. This finding corresponds closely to Sim and Pattle's (1957) report that, if lung resistance increased at all in individual subjects, the increase occurred within the first 10 minutes.

Similar short-term responses (within 5 to 10 minutes after the start of exposure) have been recorded by other investigators. Melville (1970) found in 49 subjects that percentage decreases in specific airway conductance (SG_{aw}) were greatest during the first 5 minutes of up to 60 minutes of exposure to SO_2 by mouth/nasal breathing. At 5 ppm, for example, he noted that SG_{aw} decreased significantly ($p < 0.05$) within 5 minutes of exposure and stabilized slightly above the values recorded under control conditions of no SO_2.

Similar results were obtained by Lawther et al. (1975), who noted that SR_{aw} increased most during the first 5 minutes of exposure. Recovery to baseline levels generally required about 5 minutes, although 3 "SO_2 sensitive" subjects out of a total of 14 took 10 to 65 minutes to recover from higher exposure levels (up to 30 ppm SO_2). In this last regard, similar findings were reported by Gökenmeijer et al. (1973) for bronchitic patients exposed to 10 ppm SO_2. Respiratory effects were maximal at the end of a 3-minute inhalation period, and recovery following removal to clean environment required 45 to 60 minutes.

Abe (1967) compared the temporal course of SO_2 exposures. His five mouth-breathing subjects were given 2.5 or 5.0 ppm SO_2. He reported immediate significant ($p < 0.05$) increases in expiratory resistance (42 percent) and inspiratory resistance (25 percent).

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Longer term effects (over a period of hours) have been reported by Andersen et al. (1974), who investigated nasal mucus flow rates as well as airway resistance and subjective responses. Nasal mucociliary flow was measured by placing a radioactivity labeled resin particle on the superior surface of the inferior turbinate and tracking its position with a slit-collimator detector. A total of 15 subjects were exposed via an inhalation chamber to increasing concentrations (1, 5, and 25 ppm) of SO_2 for approximately 6 hours per day over 3 consecutive days. Baseline measurements were made under conditions of filtered air on a day prior to experimental exposures. This study found a number of effects reaching their maximum after 1 to 6 hours of exposure. Nasal cross-sectional airway area generally decreased throughout the 6-hour daily trials, but the decreases were only significant ($p < 0.05$) at 1 ppm and 5 ppm, since there was an overall drop in this measure (approaching a "floor level") by the time 25 ppm was administered on the third day of the study. Nasal airflow resistance increased significantly ($P < 0.05$) with the 6-hour exposure to each concentration (1, 5, 25 ppm SO_2). Significant ($p < 0.05$ or less) decreases in forced expiratory flow ($FEF_{25-75\%}$) and forced expiratory volume ($FEV_{1.0}$) also occurred both within daily exposures and across days (i.e., increasing concentrations), although the within-day decrease in $FEV_{1.0}$ was only significant on day 3 (at 25 ppm) (see Andersen et al., 1974, Figure 7).

13.2.3.6 Mucociliary Transport--Cralley (1942) investigated mucociliary clearance when sophisticated radioactive measurement techniques were not available. A drop of red dye was placed in the active ciliary region of the inferior meatus of a volunteer subject. The rate of mucus clearance was reflected in the time between the dye's introduction and its appearance in the expelled mucus. Exposure to SO_2 at 10 to 15 ppm for 60 minutes produced only a small decrease in the rate of mucus removal. A 30- to 60-minute exposure to 25 ppm SO_2 resulted in a 50 percent reduction in mucociliary transport and a 65 to 70 percent reduction at 50 to 55 ppm. Mucositis in the anterior region of the nose was observed in 14 of 15 subjects after 4 to 5 hours of exposure on successive days to 1, 5, and 25 ppm SO_2 (Andersen et al., 1974). There appeared to be no carry-over effect from the previous days exposure. Mucous flow rates on the first day of exposure (to 1 ppm) tended to be lower but were not significantly lower than those observed on the control day (0 ppm). Mucus flow rates were significantly lower on the second day (5 ppm) and were further decreased on the third day (25 ppm) of exposure. The subjects noted discomfort only on the second and third day exposures. At these concentrations some subjects also had sporadic mucostasis, although there were pronounced individual differences in these measures even at baseline. Andersen et al. (1974) calculated the cross-sectional area of the nasal airways. A significant decrease ($0.02 < P < 0.05$) was observed during the 1 ppm exposure. The reduction in area during the longer SO_2 exposures amounted to 11, 24, and 29 percent at 1, 5, and 25 ppm SO_2 respectively.

Wolff and his co-workers (Wolff et al., 1975a,b; Newhouse et al., 1978) have also measured the rate of mucociliary transport. In Wolff et al.'s (1975a) first study, nine subjects were

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exposed to 5 ppm SO_2 for 1 hour while sitting quietly in an inhalation chamber and breathing through their mouths. Mucociliary clearance was assessed by having the subjects first inhale a radioactively tagged aerosol and then monitoring its subsequent tracheobronchial deposition and retention during SO_2 exposure. No significant effects were found in mucociliary clearance, except for a small transient change ($p < 0.05$) after 1 hour of exposure.

In their second study, Wolff et al. (1975b) used similar methods to compare subjects while resting or exercising. Exercise was performed on a bicycle ergometer for 0.5 hour at a pace to yield heart rates 70 to 75 percent of estimated maximum values. Exposure in this study lasted for 2.5 to 3 hours. The combination of exercise and exposure (via mouth) to 5 ppm SO_2 resulted in a significantly ($p < 0.05$) greater rate of tracheobronchial mucociliary clearance. This result contrasts with Andersen et al.'s findings (1974) that nasal clearance rates were reduced by exposure to 5 ppm SO_2. However, the difference between the two studies can probably be explained on the basis of dose. Dose to the lung will be much lower than to the nose because of the absorption of SO_2 onto upper airway mucosal surfaces. Therefore, lung effects could be typical of lower concentrations and increases might be anticipated as seen for low levels of H_2SO_4. Of course, the two studies focused on different regions of the respiratory tract (tracheobronchial versus nasal), but this in itself provides no cogent account for these contrasting effects. Both of these investigators replicated their findings in later studies [Andersen et al., (1977) and Newhouse et al., (1978)]. Extension of these studies was made by Newhouse et al. (1978) whose 10 subjects breathed either SO_2 (5 ppm) or H_2SO_4 mist (1 mg/m^3) delivered as an aerosol of 0.58 μm MMAD. An aerosol containing a 0.025 percent solution of ^{99m}Tc-albumen was inhaled prior to pollutant exposure. The bolus technique (exposure to short-term peak concentrations) employed achieved deposition of the aerosol, primarily in the large airways. One-half hour later the subjects were exposed to the pollutants. They immediately exercised for the next 0.5 hour. A total of 20 minutes of exercise at approximately 70 to 75 percent of predicted maximum heart rate was performed, followed by an additional 1.5 hours of rest exposure. The subjects breathed through the mouth to eliminate nasal ventilation and absorption of pollutants. Pulmonary function tests conducted at the end of 2 hours' exposure to SO_2 indicated no changes in FVC or $FEV_{1.0}$ but maximum mid-expiratory flow rate (MMFR) decreased 8.5 percent, possibly due to a reflex bronchoconstriction. No pulmonary changes were found consequent to the H_2SO_4 mist exposures. Tracheobronchial clearance increased in both SO_2 (6 of 10 subjects) and H_2SO_4 (5 of 10 subjects) exposures. The investigators did not present their data in a manner which would provide information as to the relationship between clearance rates and MMFR. It should be noted that even these data are in contrast to the replicated observations by Andersen et al. (1977), who showed a slowing of nasal clearance on exposure to 5 ppm SO_2.

Mucociliary transport is a significant aspect of the respiratory system's defense against airborne agents. A disturbance in this function might have important implications for a number of health effects, such as susceptibility to cold-virus infections. Andersen et al. (1974),

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for example, noticed that 4 of 17 subjects caught colds within a week of their participation in a study where mucostasis generally occurred during SO_2 exposure. Andersen et al. (1977) followed up this observation by inoculating volunteers with a strain of rhinovirus (RV3). The basic design of the study and reactions of the subjects are shown in a table (Andersen et al., 1977, p. 121). Although there was no difference in the number of colds that developed in the two groups of subjects (all nose breathers), cold symptoms were judged (under a double-blind procedure) to be less severe ($p < 0.05$) in the group exposed to SO_2. It was unknown, however, whether this result reflected a direct effect of SO_2 on the host, the rhinovirus, or both. In addition, the average incubation period was somewhat shorter for the group exposed to SO_2 ($p < 0.06$). Virus shedding (a measure of infection determined from nasal washings) also seemed to be somewhat decreased in the SO_2 exposed group, but not significantly.

13.2.3.7 Health Status--Some studies have considered the preexisting health status of subjects as a variable in assessing the physiological effects of SO_2. Weir and Bromberg, for example, conducted separate studies on 12 healthy subjects (Weir and Bromberg, 1972) and on 7 smokers who showed early signs of chronic obstructive pulmonary disease (Weir and Bromberg, 1973). The subjects were exposed to 0, 0.3, 1, and 3 ppm SO_2 in an inhalation chamber for 96 or 120 hours (smokers or nonsmokers, respectively), with several days separating each trial. The individual variablity among the smokers in their daily lung functions was so great that no effects could be attributed to SO_2 exposure. Also, subjective complaints also appeared to be randomly distributed throughout the course of the study and could not be related to SO_2 exposure levels.

Gunnison and Palmes (1974) compared heavy smokers (7) and non-smokers (13) with respect to blood plasma levels of S-sulfonate after exposure to 0.3, 1.0, 3.0, 4.2, and 6.0 ppm SO_2. Both groups showed highly significant correlations ($p < 0.001$) between SO_2 concentrations and S-sulfonate levels. But there was no significant differentiation between the two groups of subjects in this regard.

Several other studies of SO_2 (e.g., Snell and Luchsinger, 1969; Andersen et al., 1974; Gokenmeijer et al., 1973; Burton et al., 1968, 1969) have included asthmatic patients or smokers, but have not provided even qualitative ratings of their health status. This alone would make it difficult to compare the results of different studies using "healthy" or "impaired" subjects. Morever, the great individual variability among both normal and impaired persons in these studies makes it difficult to reach any conclusions about the relative importance of an individual's health status in determining his physiological response to SO_2.

13.3. PARTICULATE MATTER

One of the significant factors influencing physiological responses to SO_2 is the presence of particulate matter in the atmosphere (Amdur, 1969) (see Table 13-3). Particulate matter interacts with SO_2 in at least two distinct ways: as a carrier of SO_2 and as a factor in chemical reactions resulting in the conversion of SO_2 to other forms. In their carrier role, particles may adsorb SO_2 and, depending on their size, solubility, and other characteristics,

13-3. PULMONARY EFFECTS OF AEROSOLS

Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
SO_2 (1.6 - 5 ppm) NaCl 0.22 μm MMD	5	13	Mask	Synergistic increases in airway resistance with aerosol	Toyama, 1962
SO_2 (9-60 ppm) NaCl (CMD = 0.95 μm)	5	10	Mask	Airway resistance greater after exposure to aerosol than to exposure to SO_2 alone	Nakamura, 1964
SO_2 (0.5, 1.0 and 5.0 ppm) Saline particles 7.0 μm	15	9	Oral	$MEF_{50\%}$ significantly greater decreases in aerosol (NaCl) condition	Snell and Luchsinger, 1969
High conc. aerosol ($1 \mu m/m^3$ each) Low conc. aerosol ($0.1 mg/m^3$ each) $NaHSO_4$ NH_4HSO_4 $(NH_4)_2SO_4$ H_2SO_4	16*	16 normals 17 asthmatics	Oral	SG_{aw} induced by carbachol was significantly potentiated in asthmatics breathing H_2SO_4 and NH_4HSO_4 at $1 mg/m^3$ each. Low sulfate exposure ($0.1 mg/m^3$) produced no changes in SG_{aw}; however, the two most responsive asthmatics to high H_2SO_4 dose via inhalation exhibited a potential effect to the lower acid exposure	Utell et al., 1981
SO_2 (1 ppm) NaCl $1 mg/m^3$ MMD 0.9 μ σg = 2.0 μm	30	8 (asthmatics)	Mask (exercise for 10 minutes)	$\dot{V}_{max\ 50\%}$, $\dot{V}_{max\ 75\%}$, $FEV_{1.0}$ and R_T decrease significantly in aerosol condition	Koenig et al., 1981
SO_2 (1.1 - 3.6 ppm) NaCl 2.0 - 2.7 $\mu g/m^3$ MMD = 0.25 μm	30	10	Oral	No effect on pulmonary functions	Burton et al., 1969
SO_2 (1-2, 4-7, 14-17 ppm) NaCl 10-30 mg/m^3 MMD 0.15 μm	30	12	Oral	Changes in pulmonary function similar to changes due to SO_2 alone not influenced by aerosol	Frank et al., 1964
SO_2 (1 ppm) NaCl $1 mg/m^3$ MMD 0.9 μ σg = 2.0 μm	60	9 (asthmatics)	Oral	Significant decreases in $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$	Koenig et al., 1980
SO_2 (1ppm) NaCl $1 mg/m^3$ MMD 0.9 μ σg = 2.0 μm	120	(normals)	Mask	No pulmonary effects demonstrated	Morgan et al., 1977
Mixture of: SO_2 (0.37 ppm); O_3 (0.37 ppm) and H_2SO_4 ($100 \mu g/m^3$) MMD 0.5 μm, σg = 3.0	120	19 (normal)	Chamber (exercise)	Small but statistically significant decrements in FEV_1 and slight increases in the incidence of clinical symptoms	Kleinman et al., 1981
Ammonium sulfate $100 \mu g/m^3$	150	5 (*normal*) 4 (ozone sensitive) 6 (asthmatics)	*Chamber* (exercise)	*No changes in pulmonary functions*	*Bell and Hackney, 1977*
Ammonium bisulfate $85 \mu g/m^3$ aerosol size distribution 0.4 μm (MMAD)	150	16	Chamber (exercise)	No changes in pulmonary functions	Kleinman and Hackney, 1978; Avol et al., 1979

*Rest

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transport it deep into the respiratory system (see Chapter 11, Section 11.2 for more detailed discussion of deposition.)

This point is illustrated by the results of studies by Nakamura (1964) and Toyama (1962), who reported that sodium chloride (NaCl) aerosol potentiated the response of human subjects to SO_2. In Nakamura's (1964) study, 10 subjects were first exposed to NaCl aerosol (CMD = 0.95 μm; Horvath's estimate MMAD = 5.6 μm) alone for 5 minutes, allowed to recover for 10 to 15 minutes, exposed to SO_2 alone at 9 to 60 ppm for 5 minutes, allowed 20 to 30 minutes to recover, and then exposed to SO_2 and the NaCl aerosol together for 5 minutes. Airway resistance was greater after the combination exposure than after exposure to SO_2 alone (see Table 1 and Figure 4a, Nakamura, 1964). As noted, the combination condition always followed exposure to SO_2 alone, thus raising the possibility that the effects of the latter exposure were confounded. However, on average, the subjects' airway resistance measures returned to only 4 percent above their pre-exposure control levels, thus making it more likely that the reported effects were independent of preceding conditions.

Toyama (1962) also reported that 5 minutes' exposure SO_2 in combination with submicronic (0.22 μm MMD; Horvath's estimate MMAD = 0.36 μm) particles of NaCl aerosol produced synergistic increases in airway resistance in 13 subjects, even at levels as low as 1.6 to 5 ppm SO_2. There was also a linear relationship between SO_2 concentration and percentage increase in airway resistance.

On the other hand, Burton et al. (1969) were unable to demonstrate comparable effects in 10 subjects exposed to SO_2 (1.1 to 3.6 ppm) in combination with NaCl aerosol (2.0 to 2.7 mg/m^3; 0.25 μm MMD; Horvath's estimate MMAD = 0.4 μm). There was, however, a great deal of variability within and between subjects in this study, including one or two possible "hyperreactors" who did show effects below 3 ppm. Frank et al. (1964) studied 12 subjects who were exposed to three conditions of SO_2 and NaCl aerosols. There were six subjects in each group, but the same subjects were not evaluated under each of the three conditions. The purpose of this study was to determine whether acute changes in respiratory dynamics R_1 (pulmonary flow resistance) noted to occur during SO_2 exposure were intensified by the presence of sodium chloride particles. The NaCl aerosols had a mean geometric diameter of 0.15 μm (Horvath's estimate MMAD = 0.3 μm) and a concentration of 10 to 30 mg/m^3; SO_2 concentrations were 1 to 2, 4 to 7, and 14 to 17 ppm. The subjects' response to the SO_2 exposures were as previously noted in that R1 was not affected by the lower levels of SO_2 and progressively increased at the higher levels. The only statistically significant difference ($p < 0.05$) between the effects of the gas alone and the gas-aerosol mixture was a slightly greater average increase in pulmonary flow resistance at 4 to 7 ppm SO_2 than under the combination condition. Addition of the NaCl aerosol resulted in similar changes as observed to SO_2 alone. This effect was interesting in that earlier work was cited suggesting that H_2SO_4 may have been formed in the droplets. (See discussion of similar animal studies in Chapter 12).

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Snell and Luchsinger (1969) also compared the effects SO_2 alone and in mixture with aerosols of either NaCl or distilled water. Nine subjects inhaled SO_2 at 0.5, 1, and 5 ppm alone and in combination with aerosols for 15-minute periods separated by 15-minute control periods. For the SO_2 - saline aerosol exposure, decreases in maximum expiratory flow rate ($MEF_{50\%\ \dot{V}C}$) were significant ($p < 0.01$) only at 5 ppm SO_2; whereas, the SO_2 - distilled water aerosol exposure produced significant decreases ($p < 0.01$) at all exposure levels (0.5, 1, and 5 ppm SO_2). (See Figures 3 and 4, Snell and Luchsinger, 1969.) The authors noted that the size of the aerosol particles differed considerably, saline particles averaging around 7 μm in diameter and water aerosols averaging less than 0.3 μm in diameter (see Figure 5, Snell and Luchsinger, 1969). (See also Ulmer, 1974.) Koenig et al. (1980) exposed nine adolescent resting subjects (extrinsic asthmatics) for 60 minutes to either filtered air, 1 ppm SO_2 and 1 mg/m^3 of sodium chloride droplet aerosol or 1 mg/m^3 of NaCl droplet aerosol (MMD 0.9 μm, unable to estimate MMAD, and σ_g of 2.0 μm). Exposure to SO_2 alone was not performed. Oral breathing was forced on all subjects. Total respiratory resistance (R_T), maximal flow at 50 and 75 percent of expired vital capacity (partial flow volume), $FEV_{1.0}$, and functional residual capacity were measured before, during (30 minutes), and after exposures. No significant changes were found during exposures to filtered air or NaCl aerosol. Significant decreases ($p < 0.025$) were observed in $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$, suggesting that the effect of the SO_2-NaCl droplet aerosol occurred in the airways. It should be noted that $\dot{V}_{max\ 50\%}$ was significantly depressed (8 percent) only at the midpoint of exposure. However, since possible chemical reactions can occur between dissolved SO_2 and the NaCl droplets (producing sulfite, bisulfite, and hydrogen ions), the pulmonary effects observed cannot be directly attributed to gaseous SO_2 or to the chemical substances produced. Morgan et al. (1977) also exposed an unstated number of healthy non-smoking adults to the SO_2-NaCl mixture for 120 minutes at rest. No changes were observed in $\dot{V}_{max\ 75\%}$. Sheppard et al. (1980) exposed three groups of seven subjects (normal, atopic and mild asthmatic) for 10 minutes to 0, 1, 3 and 5 ppm SO_2. The subjects breathed these gases orally while their specific airway resistance (SR_{aw}) was measured in a body plethysmograph. Despite large inter-and intra-subject variability in these subjects breathing clean air, it was found that asthmatic subjects SR_{aw} increased significantly (0.05-0.025) at all concentrations of SO_2. Normal and atopic subjects had significant increases in SR_{aw} only while breathing 5 ppm SO_2. Some asthmatic subjects exhibited marked dyspnea requiring bronchodilator therapy. The increased SR_{aw} seen in either normal or mild asthmatic subjects were prevented by treatment with atropine confirming the involvement of parasympathetic pathways in this response. Reichel (1972) exposed two groups of subjects with obstructive bronchial disease to varying concentrations of SO_2 in his chamber. Patients with minor obstructive disease were exposed continuously for 4 days to 10 mg/m^3 SO_2 ($n = 8$), for 4 days to 4.7 mg/m^3 ($n = 4$) and 5 subjects for 6 days to 0.75 mg/m^3 ($n = 5$). Patients with serious obstructive bronchial disease were also exposed--4 to 4.7 mg/m^3 for 4 days and 4 to 2.6 mg/m^3 for 6 days. Airway resistance was not influenced by such exposure. The details of

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the measuring procedures were not adequately presented in his report. Koenig et al. (1981) exposed 8 adolescent extrinsic asthmatics to the same conditions as in her above study but had them also undergo a 10-minute period of moderate exercise during the exposures. $\dot{V}_{max\ 50\%}$ and $\dot{V}_{max\ 75\%}$ decreased 44 and 50 percent respectively from the baseline mean after the exercise. Significant changes in $FEV_{1.0}$ and R_T were observed, suggesting that exercise and SO_2-NaCl exposure resulted in effects on both large as well as small airways. The functional changes seen after exercise with exposure to filtered air or NaCl droplet aerosol alone were not statistically significant. Although $\dot{V}_{max\ 50\%}$ was depressed in resting subjects (extrinsic asthmatics) 8 percent ($t = 2.83$ $p < 0.025$) and 6 percent ($t = 0.38$, $p = N.S$), respectively, in the 1980 and 1981 studies by Koenig et al., it should be mentioned that the latter change was not significant after 30 minutes of exposure. In the 1980 study, all subjects ($N = 9$) decreased in $\dot{V}_{max\ 50\%}$; however, in the 1981 study some of the eight subjects increased and some decreased.

As chemical interactants, particles such as aerosols of certain soluble salts (e.g., ferrous iron, manganese, vanadium) may act as catalysts to convert SO_2 to H_2SO_4. H_2O from atmospheric humidity or from physiological sources figures prominently in these reactions. The following sections deal with common compounds of sulfur oxides and point up the influence of a number of variables that affect human physiological response to these compounds.

13.4 SULFUR DIOXIDE AND OZONE

Sulfur dioxide and ozone (O_3) may combine to form sulfuric acid on the warm, moist surfaces of the respiratory tract. Studies have not yet demonstrated, however, that a true synergistic bond exists between SO_2 and O_3 (see Chapters 6, 7, and 11).

Bates and Hazucha (1973) and Hazucha and Bates (1975) exposed eight volunteer male subjects to a mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 for 2 hours. Temperature, humidity, concentrations and particle sizes of ambient aerosols (if any) were not measured. Sulfur dioxide alone had no detectable effect on lung function, while exposure to ozone alone resulted in decrements in pulmonary function. The combination of gases resulted in more severe (10 to 20% decrement) respiratory symptoms and pulmonary function changes than did ozone alone. Using the maximal expiratory flow rate at 50 percent vital capacity as the most sensitive indicator, it was evident that after 2 hours exposure to 0.37 ppm SO_2 no change occurred. However, during exposure to 0.37 ppm O_3 a 13 percent reduction was observed, while exposure to the mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 resulted in a reduction of 37 percent in this measure of pulmonary function. The effects resulting from O_3 and SO_2 in combination were apparent in 0.5 hours, in contrast to a 2-hour time lag for exposure to O_3 alone.

Bell et al. (1977) attempted to replicate these studies alone with four normal and four ozone-sensitive subjects. They showed that $O_3 + SO_2$ mixture had greater detrimental effect on all pulmonary function measured than did O_3 alone. However, only some of these parameters showed statistical significants decrement when compared to O_3. Four of Hazucha and Bates' subjects were also studied by Bell et al. (1977). Two of these subjects had unusually large

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decrements in FVC (40 percent) and FEV_1 (44 percent) in the first study (Bates and Hazucha, 1973), while the other two had small but statistically significant decrements. None of the subjects responded in a similar manner in the Bell study. Restrospective sampling of the ambient air conditions utilizing particle samplers and chemical analysis in the chamber showed that acid sulfate particles could have been 10- to 100-fold higher in Hazucha and Bates' chamber and thus might have been responsible for the synergistic effects observed. In the Montreal chamber, concentrated streams of SO_2 and O_3 exited from tubes separated by 8 inches (20 cm) under a fan which forced 167 ft^3/min (4.7 m^3/min) of air conditioned laboratory air with SO_2 and O_3 through the chamber and out an exhaust line on the opposite wall. The concentrated streams of SO_2 and O_3 could have reacted rapidly with each other and with ambient impurities like olefins, to form a large number of H_2SO_4 nuclei which grew by homogenous condensation, coagulation, and absorption of NH_3 during their 2-minute average residence time in the chamber.

Horvath's group (Horvath and Folinsbee, 1977; Bedi et al., 1979) exposed nine young men (18 to 27 years old) to 0.4 ppm O_3 and 0.4 ppm SO_2 singly and in combination for 2 hours in an inhalation chamber at 25°C and 45 percent RH. The subjects exercised intermittently for one-half of the exposure period. A large number of pulmonary function tests were conducted before, during, and after the exposure. Subjects exposed to filtered air or to 0.4 ppm SO_2 showed no significant changes in pulmonary function. When exposed to either O_3 or O_3 plus SO_2, the subjects showed significant decreases in maximum expiratory flow, forced vital capacity, and inspiratory capacity. There were no significant differences between the effects of O_3 alone and the combination of O_3 + SO_2; thus, no synergistic effects were discernible in their subjects. Although particulate matter was not present in the inlet air, it is not known whether particles developed in the chamber at a later point.

The question of potential synergistic interaction between SO_2 and O_3 remains unresolved. Chamber studies were conducted by Kagawa and Tsuru (1979) exposing six subjects for 2 hours with intermittent exercise (50 watts i.e. ventillation of 25 l/min) for periods of 15 minutes exercise separated by periods of 15 minutes rest. The exposures were performed weekly in the following sequence: filtered air, 0.15 ppm O_3; filtered air, 0.15 ppm SO_2; filtered air and finally 0.15 ppm O_3 - 0.15 ppm SO_2. Pulmonary function measurements were obtained prior to exposure after 1 hour in the chamber and after leaving the chamber. Although a number of pulmonary function tests were performed, they utilized change in specific airway conductance (SG_{aw}) as the most sensitive test of change in function. They found a significant decrease in five of the six subjects (5/6) exposed to O_3 alone. In three of the six young male subjects, they found a significant enhanced decrease in SG_{aw} after exposure to the combination pollutants compared to the decrease in SG_{aw} in these subjects in O_3 exposure. Two other subjects had similar decreases in either O_3 or O_3-SO_2 exposure. They further suggest that the effect of the two gases on SG_{aw} is more than simply additive and results from a combined pollutant exposure. Subjective symptoms of cough and bronchial irritation were reported to occur in subjects exposed to O_3 or O_3-SO_2.

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Von Nieding et al. (1979) exposed 11 subjects to O_3, NO_2 and SO_2 singly and in various combinations. The subjects were exposed for 2 hours with 1 hour devoted to exercise which doubled their ventilation. The work periods were of 15 minute duration interspersed with 15-minute periods at rest. In the actual exposure experiments, no significant alterations were observed for $P_{A_{O_2}}$, $P_{A_{CO_2}}$, pH_a, and thoracic gas volume (Vtg). Airway resistance total (R_t) and $P_{A_{O_2}}$ were altered in certain studies. $P_{A_{O_2}}$ was decreased (7-8 torr) by exposure to 5.0 ppm NO_2 but was not further decreased following exposures to 5.0 ppm NO_2 and 5.0 ppm SO_2 or 5.0 ppm NO_2, 5.0 ppm SO_2 and 0.1 ppm O_3 or 5.0 ppm NO_2 and 0.1 ppm O_3. Airway resistance increased significantly [0.5 to 1.5 cm $H_2O/(L/s)$] in the combination experiments to the same extent as in the exposures to NO_2 alone. In the 1-hour post exposure period of the NO_2, SO_2, and O_3 experiment, R_t continued to increase. Subjects were also exposed to 0.06 NO_2, 0.12 SO_2, and 0.025 O_3 (all in ppm). No changes in any of the measured parameters were observed. These same subjects were challenged with a 1, 2, and 3 percent solution of acetylcholine following control (filtered air) exposure and to the 5.0 NO_2, 5.0 SO_2, and 0.1 O_3 (ppm) as well as after the 0.06 NO_2, 0.12 SO_2, and 0.025 O_3 (ppm) exposures. The expected increase in airway resistance was observed in the control study. Specific airway resistance (R_{aw} x Vtg) was significantly greater than in the control study following the combined pollutant exposures. (See Table 13-4 for a summary of the pulmonary effects of SO_2 and other air pollutants.)

Three groups of eight subjects, each of different ages (>30, >49 and between 30-40 years) were exposed for 2 hours in a chamber on three successive days (Islam and Ulmer, 1979a). On the first day, subjects breathed air and exercised intermittently (levels not given); on the second day they were exposed at rest to 5.0 ppm SO_2, 5.0 ppm NO_2 and 0.1 ppm O_3; on the third day the environment was again 5.0 ppm SO_2, 5.0 ppm NO_2 and 0.1 ppm O_3 but the subjects exercised intermittently during the exposure. Statistical evaluation of the data on the 11 lung functions and the two blood parameters ($P_{A_{O_2}}$ and $P_{A_{CO_2}}$) was not adequately performed. These measurements were made before, immediately and 3 hours post exposure. Individual variability was quite marked. The investigators concluded that in their healthy subjects no synergistic effects occurred. However, since they did not systematically expose these subjects to the individual components of their mixed pollutant environment, the conclusion can only be justified in that they apparently saw no consistent changes. There were some apparent changes in certain indiviuals related to exercise (unknown level) and age but the data were not adequately analyzed nor could they be from the information presented.

Islam and Ulmer (1979b) studied 15 young healthy males during chamber exposures to 0.9 mg/m^3 SO_2, 0.3 mg/m^3 NO_2 and 0.15 mg/m^3 O_3. Ten subjects were exposed to 1 day of filtered air and 4 successive days to the above gas mixture. Another group of 5 subjects were exposed for 4 days to the pollutant mixture followed by 1 day to filtered air. Each exposure was 8 hours in duration. Following each exposure the subjects were challenged by an acetylcholine aerosol. Nine pulmonary function tests and four blood tests ($P_{A_{O_2}}$, P_{ACO_2}, Hb and lactate

13-4. PULMONARY EFFECTS OF SO_2 AND OTHER AIR POLLUTANTS

Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
SO_2 (0.15 ppm) and O_3 (0.15 ppm)	120	6	E*	Significant enhanced decrease in SG_{aw} after exposure to SO_2 - O_3 in comparison to O_3 alone	Kagawa et al., 1979
SO_2 (0.37 ppm) and O_3 (0.37 ppm)	120	8	Chamber (exercise)	Decrease pulmonary functions (in synergistic effect of SO_2 on O_3) FRC, $FEV_{1.0}$, MMFR, $MEFR_{50\%}$	Hazucha and Bates, 1975 Bates and Hazucha, 1973
SO_2 (0.37 ppm) and O_3 (0.37 ppm)	120	4 (normal) 4 (ozone sensitive) 4 (from Bates)	Chamber (exercise)	Unable to confirm synergistic effects pulmonary decrement due to O_3 alone	Bell et al., 1977
SO_2 (0.40 ppm) and O_3 (0.40 ppm	120	9	Chamber (exercise)	Unable to confirm synergistic effects changes due to ozone alone	Horvath and Folinsbee 1977; Bedi et al., 1979
SO_2 (5 ppm) and NO_2 (5 ppm)	120	11	Chamber (exercise)	No changes in P_A , P_{ACO_2}, pHa or TGr $\cdot R_{aw}^{O2}$ increased	von Nieding et al., 1979
SO_2 (5 ppm) NO_2 (5 ppm) and O_3 (0.1 ppm)	120	11	Chamber (exercise)	No changes in P_{AO_2}, P_{ACO2}, pHa or TGr $\cdot R_{aw}$ increased	von Nieding et al., 1979
SO_2 (0.12 ppm) NO_2 (0.06 ppm) and O_3 (0.025 ppm)	120	11	Chamber (exercise)	No changes in pulmonary functions	von Nieding et al., 1979
Mixture of: SO_2 (5 ppm) NO_2 (5 ppm) O_3 (0.1 ppm)	120	8	Chamber (exercise)	Data not adequately analyzed and could not be from the data presented.	Islam and Ulmer, 1979a
Mixture of: SO_2 (0.33 ppm) NO_2 (0.16 ppm) O_3 (0.075 ppm)	8 hr/da for 4 successive days	15	Chamber (rest)	Statistical analysis of the data not adequate	Islam and Ulmer, 1979b

*Exercise.

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dehydrogenase) were performed before and after the exposure. The study suffers from a deficiency in statistical analysis of the data. No impairments of lung functions, blood gases or blood chemistry were found. However, some of the subjects were said to have unusual reponses.

13.5 SULFURIC ACID AND SULFATES

13.5.1 Sensory Effects

A number of studies have been directed toward determining threshold concentrations of H_2SO_4 for various sensory response (see Table 13-5). In a study with 10 test subjects, Bushtueva (1957) found that the minimum concentration of sulfuric acid aerosol (particle size not given) which was sensed by odor ranged from 0.6 mg/m^3 to 0.85 mg/m^3 (average 0.75 mg/m^3). In tests with five subjects (Bushtueva, 1961), a combination of sulfur dioxide at 1 mg/m^3 (0.35 ppm) and sulfuric acid mist at 0.4 mg/m^3 was below the odor threshold. Amdur et al. (1952) reported on 15 subjects (males and females) exposed for 5 to 15 minutes to various concentrations of sulfuric acid mist the subjects breathed via a face mask. It was found that 1 mg/m^3 was usually not detected, while 3 mg/m^3 was detected by all subjects.

Bushtueva (1957) studied the effect of sulfuric acid mist on the light sensitivity of two test subjects. Sensitivity was measured every 5 minutes during the first half-hour of each test, then at 10-minute intervals thereafter. A control curve was established for each subject by seven repeated tests, and then sulfuric acid aerosol was administered for 4 minutes and for 9 minutes at the 15th and 60th minutes, respectively. With sulfuric acid mist of undetermined particle size at a concentration of 0.6 mg/m^3, a just detectable increase in light sensitivity occurred with the first exposure but not with the second. Concentrations in the range of 0.7 mg/m^3 to 0.96 mg/m^3 brought about a well-defined increase in light sensitivity. With 2.4 mg/m^3, increased sensitivity to light was elicited by the exposures at both the 15th and 60th minutes of the test; normal sensitivity was restored in 40 to 50 minutes.

Bushtueva (1961) studied the effect of sulfur dioxide, sulfuric acid mist and combinations of the two on sensitivity of the eye to light in three subjects. The combination of sulfur dioxide at 0.65 mg/m^3 (0.23 ppm) with sulfuric acid mist at 0.3 mg/m^3 resulted in no change in sensitivity of the eye to light. An increase of approximately 25 percent in light sensitivity resulted from exposure to either sulfur dioxide at 3 mg/m^3 (~1.0 ppm) or sulfuric acid mist at 0.7 mg/m^3. The combination of sulfur dioxide at 3 mg/m^3 with sulfuric acid mist at 0.7 mg/m^3 resulted in an increase of approximately 60 percent in light sensitivity. Exposures lasted for 4 1/2 minutes.

Bushtueva (1962) demonstrated that combinations of sulfur dioxide at 0.50 mg/m^3 (0.17 ppm) with sulfuric acid mist at 0.15 mg/m^3 or sulfur dioxide at 0.25 mg/m^3 (0.087 ppm) with sulfuric acid mist at 0.30 mg/m^3 could produce electrocortical conditioned reflexes. There are some uncertainties regarding this study.

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13-5. SENSORY EFFECTS OF SULFURIC ACID AND SULFATES

Concentration	Subjects	Effects	References
0.75 mg/m^3	5	Threshold detected by odor - increase in light sensitivity - increase in optical chronaxie	Bushtueva, 1957, 1961
1-3 mg/m^3	15 (exposed 5-15 min)	3 mg/m^3 detected by all subjects	Amdur et al., 1952

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Bushtueva (1961) studied the effects of different concentrations of sulfur dioxide, sulfuric acid mist, and combinations of the two on the optical chronaxie of three subjects. Optical chronaxie was determined in each test subject at 3-minute intervals as follows: at the start and on the 3rd, 6th, 9th, 12th and 15th minutes. Between the 6th and 9th minutes the subjects inhaled sulfur dioxide, sulfuric acid mist, or their combination for 2 minutes. In each subject, the threshold concentrations of sulfur dioxide and sulfuric acid mist were first determined independently, and then threshold concentrations for combinations of the two were determined. Sulfuric acid mist (0.75 $\mu g/m^3$) increased optical chronaxie.

13.5.2 Respiratory and Related Effects

Amdur et al. (1952) found respiratory changes in all subjects exposed for 15 minutes to H_2SO_4 aerosol at concentrations of 0.35 mg/m^3 to 5 mg/m^3. Vapors from an electrically heated flask containing concentrated sulfuric acid were carried by compressed air into the main air stream and then into a lucite mixing chamber, delivering a mist of MMD 1 μm. The subjects breathed through a pneumotachograph, permitting measurement of inspiratory and expiratory flow rate. In 15 subjects, exposed to 0.35, 0.4, or 0.5 mg/m^3, the respiration rate increased about 35 percent above control values, while the maximum inspiratory and expiratory flow rates decreased about 20 percent. Tidal volume decreased about 28 percent in subjects exposed to 0.4 mg/m^3. These changes occurred within the first 3 minutes of exposure and were maintained throughout the 15-minute exposure period. Lung function returned rapidly to baseline levels after the exposure ended. The tidal volume rose above control values during the first minute after termination of the exposure and then returned to preexposure levels. Breathing through the same apparatus without the acid mist was done as a control, and no such changes were observed. Some subjects showed a marked reaction to 5 mg/m^3, a level of acid mist perceptible to all. Individual responses were much more varied at this level, the main effect being a decrease in minute volume. The investigators suggest that bronchoconstriction may have been the response to sulfuric acid.

The effect of breathing sulfuric acid mist at different relative humidities (RH) was studied by Sim and Pattle (1957). Healthy males (variable number of subjects), 18 to 46 years of age, breathed 3 to 39 mg/m^3 concentrations of H_2SO_4 at 62 percent RH either via mask or exposure chamber. Subjects were also exposed in the chamber to 11.5 to 38 mg/m^3 concentrations at 91 percent RH. At the lower RH, particles were 1 μm in size. The addition of water vapor to raise RH increased the mean particle size to 1.5 μm and intensified irritant effects of exposure. For example, the irritancy of wet mist at 20.8 mg/m^3 was much more severe ("almost intolerable at the onset") than that of the dry mist at 39.4 mg/m^3 ("well tolerated by all"). Air flow resistance ranged from 43 to 150 percent above normal in response to the wet mist, compared to increases ranging from 35.5 to 100 percent above normal in response to the dry mist. Two subjects exposed to sulfuric acid mist developed bronchitic symptoms but may have been previously exposed to other substances. Adding ammonia (quantity

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not given) to the acid mist annulled its irritant properties. There was no consistent evidence that the acid mist caused changes in respiratory functions or blood pressure, pulse rate, or other cardiovascular functions.

Toyama and Nakamura (1964) investigated the synergistic effects of SO_2 in combination with hydrogen peroxide (H_2O_2) aerosol mixtures, the latter of which oxidizes SO_2 to form H_2SO_4. SO_2 concentrations ranged from 1 to 60 ppm; the H_2O_2 concentrations were 0.29 mg/m^3 for particles of 4.6 μm CMD (Horvath estimated MMAD = 13) and 0.33 mg/m^3 for particles of 1.8 μm CMD (Horvath estimated MMAD = 5). Airway resistance increased significantly in the combination (H_2O_2 + SO_2) exposure, particularly for the group of 15 subjects inhaling the larger particles ($p < 0.01$). Toyama and Nakamura (1964) exposed subjects to a mixture of SO_2 and H_2SO_4 aerosols. They used an inadequate method to measure airway resistance. They described the aerosols as having a 4.5 μm diameter. They found a strong constricting effect on the upper airways.

Sackner et al. (1978) studied normal resting young adults and seven asthmatic middle-aged subjects who breathed, by mouth, either sodium chloride or sulfuric acid aerosols for 10 minutes at concentrations of 10, 100, and 1000 μg/m^3 (0.1-0.2 MMAD). Measurements on these individuals continued for up to 3 hours after exposure. The asthmatic patients represented a wide range of clinical status and treatment. Neither normal nor asthmatic individuals showed significant alterations of lung volumes, distribution of ventilation, earoximetry, dynamic mechanics of breathing, oscillation mechanics of the chest-lung system, pulmonary capillary blood flow, diffusing capacity, arterial oxygen saturation, oxygen uptake, or pulmonary tissue volume. No delayed effects were observed during a follow-up period of a few weeks.

Kleinman and Hackney (1978) and Avol et al. (1979) reported on the pulmonary responses of six normal and six asthmatic subjects exposed in an ambient environment of 88°F dry bulb and 40 percent relative humidity, and 94 μg/m^3 H_2SO_4. The asthmatics had pulmonary function test results which ranged widely from normal to abnormal. A sham exposure was followed by 2 consecutive days of acid exposure. Sufficient excess acid aerosol to neutralize the NH_3 present (about 56 μg/m^3 ammonia neutralization product) was added to the air to provide for the desired acid concentration (75 μg/m^3). The aerosol MMAD was approximately 0.48 to 0.81 μm. The effective exposure time was 2 hours, with the first 15 minutes of each half-hour devoted to exercise which increased ventilation to twice the resting level. Only one subject was exposed at a time to minimize the effects of ammonia neutralization. The normal subjects showed no exposure-related changes. The lung functions of the asthmatics showed no significant changes. Two asthmatics, the extent of their disease state not given, exhibited increases in respiratory resistance on both exposure days. Nonetheless, it was concluded that there were no convincing adverse short-term health effects of sulfuric acid. However, they also noted the small size of their subject pool and recommended additional studies.

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Utell et al. (1981) exposed 16 normal subjects and 17 asymptomatic asthmatics (all subjects non-smokers) to acidic aerosols (MMAD = 0.5-1.0 μm, σ_g 1.5-2.2) for periods of 16 minutes. Several aerosol exposures were given each day in a double-blind random pattern. At the beginning of each study, an approximate dose-response curve to inhaled carbachol was obtained. All aerosols [$NaHSO_4$, $(NH_4)_2SO_4$; NH_4HSO_4, H_2SO_4, NaCl] were given orally. The data presented in the manuscript is incomplete, but what is available suggests that specific airway conductance (SGaw) induced by carbachol was significantly potentiated ($p < 0.01$) in asthmatics breathing H_2SO_4 and NH_4HSO_4 (each 1 mg/m^3). Low sulfate exposure (0.1 mg/m^3) produced no changes in SGaw, however; the two asthmatics most responsive to the high H_2SO_4 dose via inhalation exhibited a potential effect to the lower sulfuric acid exposure. No effects were noted in the normal subjects. A more extensive presentation of the data obtained by these investigators will be required before final decision of the effects of sulfates on asthmatics can be determined.

Lippmann et al. (1980) had 10 non-smokers inhale via nasal mask 0.5 μm (σ_g = 1.9) H_2SO_4 at 0 and approximately, 100, 300, and 1,000 μg/m^3 for 1 hour. The exposures were random over the 4 days of testing. Pulmonary functions (assessed by body plethysmograph, partial forced expiratory maneuver, and nitrogen washout) were measured before, and at 0.5, 2, and 4 hours post exposure. ^{99m}Tc-tagged monodispersed Fe_2O_3 aerosol (7.5 μm MMAD, σ_g = 1.1) was inhaled 10 minutes before exposure for the determinations of lung retention of these particles. Tracheal mucus transport rates (TMTR) and bronchial mucociliary clearance were determined. No significant changes in respiratory mechanics or TMTR were observed following H_2SO_4 exposure at any level. However, bronchial mucociliary clearance halftime ($TB_{\frac{1}{2}}$) was on the average markedly altered at all concentrations of H_2SO_4 inhaled. Bronchial clearance was increased ($p < 0.02$) following exposure to 100 μg/m^3 H_2SO_4, while following exposure to 1,000 μg/m^3, it was significantly ($p < 0.03$) reduced. Mucociliary transport in the airways distal to the trachea was affected more by H_2SO_4 exposure than was transport in the trachea. Out of ten subjects four did not respond. "The alterations in bronchial clearance half-time were all transient, which was consistent with the results seen earlier in similar inhalation tests on donkeys (Schlesinger et al., 1978). However, when donkeys were repeatedly exposed to sulfuric acid at comparable concentrations, four of six animals developed persistently slowed clearance, which remained abnormal for at least several months (Schlesinger et al., 1978, 1979). Taken together, these results suggest that at the concentrations employed persistent changes could occur in mucociliary clearance in previously healthy individuals and exacerbate preexisting respiratory disease.

Kleinman and Hackney (1978) and Avol et al. (1979) presented in greater detail the preliminary findings reported by Bell and Hackney (1977). They evaluated the effects of various sulfate compounds on normal subjects, ozone-sensitive subjects, and asthmatic subjects (requiring medical treatment). The exposures were approximately 2.5 hours in duration, with

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the subjects exercising the first 15 minutes of each half hour at a pace sufficient to double their ventilation rates. Measurements of pulmonary functions, which included FVC, FEV_1, MEFR, $FEF_{50\%}$, $FEF_{75\%}$, TLC, RV, delta nitrogen (ΔN_2), closing volume, and total respiratory resistance (R_t) were made before and 2 hours after the work-rest regimen began. The ambient conditions were 88°F dry bulb and either 40 or 85 percent relative humidity. Most of the exposure studies were made on five to seven subjects. Four to five sensitive subjects and six asthmatics completed the subject pool. Subjects were first exposed to a control (no pollutant) environment and then to 2 or 3 consecutive days of the pollutants. The asthmatics were not studied in the high humidity conditions, but were exposed to a higher concentration (up to 372 $\mu g/m^3$) of $(NH_4)_2SO_4$. Nominal exposure concentrations were 100 $\mu g/m^3$ for ammonium bisulfate (NH_4HSO_4) and 85 $\mu g/m^3$ for ammonium sulfate [$(NH_4)_2SO_4$]. The sulfate aerosol size distribution was nominally 0.4 μm MMAD (σ_g 2.5 to 3). There was some ammonia (NH_3) in the exposure chamber. Pulmonary functions were unaffected by exposure to the two types of aerosol.

An interesting side observation was made on the asthmatics. On their first day of exposure to NH_4HSO_4 aerosol, they exhibited worse lung functions in the pre-exposure measurements than they had on a control day. Their functions improved consequent to the pollutant exposure. Subsequent analysis of local ambient conditions showed that these subjects arrived for their aerosol testing after a 3-day period of increased SO_2 and ozone levels during a "mild air pollution episode." (See Table 13-6 for a summary of the pulmonary effects of sulfuric acid.)

Kleinman et al. (1981) conducted studies in which 19 volunteers with normal pulmonary function and no history of asthma were exposed on two separate days to clean air and to an atmosphere mixture containing O_3 (0.37 ppm), SO_2 (0.37 ppm), and H_2SO_4 aerosol (100 $\mu g/m^3$, MMAD 0.5 μm; σg = 3.0). During this 2-hour period, the subjects alternatly exercised for 15 minutes, at a level calibrated to double minute ventillation, and rested for 15 minutes. Statistical analysis of the group average data suggested that the mixture may have been slightly more irritating to the subjects than O_3 alone. A large percentage (13 of 19) of the subjects exhibited small decrements in pulmonary function. The groups averaged $FEV_{1.0}$ on the exposure day was significantly depressed, 3.7 percent of the control value. One might expect O_3 alone to depress $FEV_{1.0}$ by approximately 2.8 percent under similar exposure conditions.

Kerr et al. (1981) investigated the respiratory effects associated with exposure to low levels of sulfuric acid (H_2SO_4) aerosol. Twenty eight normal subjects were exposed for 4 hours to 100 $\mu g/m^3$ H_2SO_4 aerosol of particle size 0.1 to 0.3 μm (MMD = 0.14 μm; σg = 2.9) in an environmentally controlled exposure chamber. At one and three hours into the study on each day, bicycle ergometer exercise was performed at a workload at 100 watts at 60 RPM for 15 minutes. Of the 28 subjects, 14 were nonsmokers and 14 were cigarette smokers. None of the subjects complained of symptoms attributable to the exposure. Measurements of pulmonary

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13-6. PULMONARY EFFECTS OF SULFURIC ACID

Concentration	Duration of exposure (mins)	Number of subjects	Source	Effects	Reference
0.35 - 5.0 mg/m^3 H_2SO_4 MMD 1 μm	15	15	Mask (rest)	Respiratory rates increased, max. insp. and expiratory flow rates and tidal decreased volumes	Amdur et al., 1952
3-39 mg/m^3 H_2SO_4 MMD 1-1.5 μm	10 - 60	Variable	Mask (rest) Chamber (rest)	Longer particles due to "wet mist" resulted in increased flow resistance cough, rales bronchoconstriction	Sim and Pattle, 1957
SO_2 (1-60 ppm) plus H_2O_2 to form H_2SO_4 aerosol CMD 1.8 and 4.6 μm	Variable	24	(Rest)	Airway resistance increased especially with larger particles	Toyama and Nakamura, 1964
H_2SO_4 mist (1000 μg/m^3 MMD 0.5 μm (σg = 2.59)	120	10	Chamber (exercise)	No pulmonary function changes but increased tracheobronchial clearance	Newhouse et al., 1978
H_2SO_4 aerosol 10, 100, 1000 μg/m^3 MMD 0.1 μm	10	6 normal 6 asthmatics	Oral	No pulmonary function changes, no alterations in gas transport	Sachner et al., 1978
H_2SO_4 (75 μg/m^3) MMAD 0.48 - 0.81 μm	120	6 normal 6 asthmatics	Chamber (exercise)	No pulmonary effects in either group	Kleinman and Hackney, 1978; Avol et al., 1979
H_2SO_4 (0, 100, 300, or 1,000 μg/m^3 MMAD 0.5 μm (σg = 1.9)	60	10	Nasal	No pulmonary function effects Broncial mucociliary clearance ↑ following 100 μg/m^3 but ↓ following 1000 μg/m^3 mucociliary clearance distal to trachea more affected	Lippmann et al., 1980
H_2SO_4 100 μg/m^3 MMD 0.14 μm σg = 2.9	240*	28 normals	Chamber (exercise)	No pulmonary function effects	Kerr et al., 1981

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function were obtained 2 hours into the exposure, immediately following exposure and 2 and 24 hours post-exposure. These measurements were compared with control values obtained at comparable hours on the previous day when the subject breathed only filtered clean air in the chamber. No significant differences in pulmonary function were observed either during the exposure, immediately after exposure or 2 and 24 hours post-exposure.

13.6 SUMMARY

Human experimental studies of the health effects of exposure to pollutants in the ambient environment require strict controls so that their findings can be generalized to the entire population. Although no studies meet all the requirements for strict control, some basic information can be garnered from many published studies.

SO_2 has been found to have effects on several physiologic functions. Through subjective reports, the reliability of which has been questioned, a level of 5 ppm has been established for detecting SO_2, with considerable variation below that level. Several sensory processes are affected by generally agreed-upon levels of concentration of SO_2. The odor threshold averages 0.8 to 1 ppm, with 0.47 ppm set in one study performed under ideal conditions. The sensitivity of the eye to light increases at 0.34 to 0.63 ppm, is maximal at 1.3 to 1.7 ppm, and decreases to normal by 19.2 mg/m^3 during dark adaptation. During light adaptation, the figures increase and decrease similarly but at slightly higher levels of exposure. The alpha-wave has been found to be attenuated by 0.9 to 3 mg/m^3 SO_2 during 20 seconds of exposure.

Studies of the effects of SO_2 on the respiratory system of the body have arrived at conflicting conclusions. Although one study found respiratory effects after exposure to as little as 1 ppm SO_2, others could find no effect below 5 ppm. At the latter level, pulmonary flow resistance increased 39 percent in one study. Respiratory effects have been found to be proportional to the concentration of SO_2 to which study subjects are exposed. Although the bronchoconstrictive effects of exposure to SO_2 have been found to be fairly consistent, subjects vary considerably in response to exposures, and there are some especially sensitive subjects, which may represent as much as 10 percent of the population. Recent studies have shown that SR_{aw} significantly increased in asthmatics at 0.5 and 0.25 ppm SO_2 and even at 0.1 ppm in some asthmatic subjects.

Because SO_2 is readily water soluble, and nasal passages are high in humidity, the route of exposure will affect the response of individuals. Subjects report less throat and chest irritation when breathing through the nose, and pulmonary flow resistance increases less in subjects who are nose breathing. Regardless of the route of exposure, 5 ppm SO_2 had limited effects on specific airway conductance (airway bronchoconstriction), although higher levels had a dose-dependent effect; that is, higher concentrations decreased SG_{aw} more than lesser concentrations. The average decrease was greater after oral exposure than after nasal administration.

The level of activity of the subjects tested affects the results because the actual dose delivered to lungs and airways is greater when subjects breathe through their mouth, as during exercise. Just having subjects breathe deeply through the mouth significantly affected

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specific airway resistance during exposure to 1 ppm SO_2 in one study, although another study found no such effect. Respiratory effects of exposure either by nose or by mouth are greatest after 5 to 10 minutes of exposure. Recovery takes about 5 minutes in normal subjects, but much longer (10 to 60 minutes) in sensitive subjects and those who are asthmatic. Studies of nasal mucus flow rates and airway resistance following about 6 hours of exposure to 1 and 5 ppm SO_2 per day for 3 days found some effects maximal after 1 to 6 hours.

An early study found mucus clearance reduced increasingly as length and concentration of exposure to SO_2 increased. Long exposures to 5 ppm SO_2 increased mucociliary clearance in one study; a decrease had been found in nasal clearance rates in another study. Available studies have not found a significant interaction of smoking with SO_2.

The interaction of SO_2 and particulate matter is an important factor in respiratory effects studies. Airway resistance increased more after combined exposure to SO_2 and sodium chloride than after exposure to SO_2 or sodium chloride alone in several studies although others have failed to reach the same conclusion. This may have been due to formation of sulfuric acid mist during the study. $MEF_{50\%}$ was found to be significantly reduced after exposure to a combination of saline aerosol to 5 ppm SO_2. After exposure to combined hydrogen peroxide and 0.5 to 5 ppm sulfur dioxide, airway resistance was found to be significantly increased. The combination of SO_2 and ozone may have synergistic effects on lung function. At low concentrations (0.37 ppm) SO_2 had no effect on lung function, ozone impaired lung function, and the combination impaired lung function even more. A similar study did not find the same results. Other studies have found reductions in pulmonary function after exposure to low levels of SO_2 or ozone alone and in combination, with no synergistic effect observed with the combined exposure. Japanese studies involving exposure to O_3 alone and a combination of SO_2 (0.15 ppm) and O_3 (0.15 ppm) have observed a significant enhanced decrease in specific airway conductance (SGaw) after exposure to the combination pollutants compared to the decrease in SGaw in these subjects in O_3 exposure. They suggest that the effect is synergestic and not just additive.

Sulfuric acid and sulfates have been found to affect both sensory and pulmonary function in study subjects. The odor threshold for sulfuric acid aerosol has been set at 0.75 mg/m^3 in one study and 3 mg/m^3 in another. Light sensitivity has been found to be consistently increased by 25 percent at 0.7 to 0.96 mg/m^3 concentration of sulfuric acid mist (0.3 mg/m^3). Optical chronaxie has also been found to be increased after exposure of subjects to 750 $\mu m/m^3$ sulfuric acid mist.

Respiratory effects from exposure to sulfuric acid mist (0.35 to 5.0 mg/m^3) include increased respiratory rate and decreased maximal inspiratory and expiratory flow rates and tidal volume. Several studies of pulmonary function in normal subjects indicated that pulmonary function was not affected when subjects were exposed to 100-1000 $\mu g/m^3$ sulfuric acid for 10 to 60 minutes, although in one study the bronchoconstrictor action of carbachol was potentiated by the sulfuric acid and sulfate aerosols more or less in relation to their acidity. In studies with asthmatic subjects generally no changes in airway function have been

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demonstrated after exposure to sulfuric acid and sulfate salts at concentrations less than 0.1 mg/m^3. However, at higher concentrations (1.0 mg/m^3) reduction in specific airway conductance and FEV_1 have been observed after H_2SO_4 and NH_4HSO_4 exposures. Mucociliary clearance was affected by exposure to sulfuric acid, being significantly increased after exposure to 100 $\mu m/m^3$ and significantly decreased after exposure to 1000 $\mu g/m^3$. Another study found no pulmonary effect of exposure to sulfuric acid, ammonium bisulfate, and ammonium sulfate by normal and asthmatic subjects.

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ADDENDUM

Recent Abstract

Schlenker, E., and M. Jaeger. Airway response of young and elderly subjects to 0.5 ppm SO_2 and 0.5 ppm O_3. Physiologist 23:77, 1980a.

Ten elderly (73 ± 7.7 years of age) and ten young (25.5 ± 4 years of age) were first studied (presumably at rest) in a clean air environment and on the succeeding day were exposed to the combined pollutants for 1 hr. A follow-up period of 3 hr was made on each day. No pulmonary function changes were observed on either day in the old subjects. However, the young subjects had a decrease in MMFR (5.23 to 4.65 L/sec) during the pollutant exposure. Recovery to control levels was not complete in these young subjects in the following 3 hours in clean air.

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14. EPIDEMIOLOGICAL STUDIES ON THE EFFECTS OF SULFUR OXIDES AND PARTICULATE MATTER ON HUMAN HEALTH

14.1 INTRODUCTION

This chapter evaluates epidemiological literature concerning health effects associated with ambient air exposures to sulfur oxides and particulate matter. The main focus of the chapter is on: (1) the qualitative characterization of human health effects associated with exposure to atmospheric sulfur dioxide (SO_2), related sulfur compounds, and other particulate matter (PM); (2) quantitative delineation of exposure/effect and exposure/response relationships for the induction of such health effects; and (3) the identification of population groups at special risk for experiencing the health effects at ambient exposure levels.

The epidemiological data discussed here both complement and extend information presented as part of health effects analyses contained in preceding chapters (11,12,13) of this document. Those chapters focus on information derived from animal toxicology and controlled human exposure studies which offer the advantage of characterizing, under well-controlled laboratory conditions, differential patterns of respiratory tract deposition and clearance of: SO_2; sulfates (SO_4) and sulfuric acid (H_2SO_4); and other particulate matter of varying size and chemical composition. In addition, the animal toxicological studies provide evidence for notable health effects occurring in mammalian species as the result of such respiratory tract deposition of sulfur oxides and particulate matter, including: transient alterations in pulmonary functions; altered mucociliary clearance and other respiratory tract defense mechanisms; and increased susceptibility to infection and morphological damage seen especially after high level or prolonged exposures. However, while such results from animal studies are highly suggestive of analogous effects possibly being induced in human beings, caution must be exercised in directly extrapolating the findings or associated dose-effect relationships to human health. More direct delineation of quantitative dose-effect or dose-response relationships is possible through controlled human exposure studies, but such studies also have important limitations. For example, whereas controlled human exposure studies have demonstrated SO_2 or PM induction of transient pulmonary function decrements, altered mucociliary clearance patterns, and symptomatic effects consistent with animal toxicology study findings, observation of such effects has generally been confined to conditions involving single or a few repeated short-term (<3 hrs) exposures but not prolonged chronic exposure conditions. Also left unanswered by controlled human exposure studies are questions concerning whether or not more severe effects, e.g., increased vulnerability to respiratory diseases or marked morphological damage, are associated with either short-term or prolonged ambient exposure conditions.

Epidemiological studies, in contrast, offer several advantages beyond those of animal toxicology or controlled human exposure studies. Health effects of both short- and long-term pollutant exposures (including complex mixtures of pollutants) can be studied and sensitive members of populations at special risk for particular effects at ambient air concentrations

identified. Also, epidemiological evaluations allow for investigation of both acute and chronic disease effects and associated human mortality. Epidemiological studies, then, together with the results of controlled animal and human exposure studies, can significantly contribute to more complete understanding of health effects of sulfur oxides and particulate matter, especially in helping to characterize human health effects associated with those pollutants under ambient conditions. Despite such advantages, however, important limitations do exist in regard to the conduct, analyses, interpretation, and use of many of the available epidemiological studies on the health impact of SO_2 and PM, as discussed next.

14.1.1 Methodological Considerations

As noted by Lowrence (1976), epidemiological and other types of studies employed in generating information relevant to human risk assessment typically divide into four lines of investigation. These involve making measurements aimed at: (1) defining exposure conditions; (2) identifying adverse effects; (3) relating exposures to effects; and (4) estimating overall risk.

In relation to accomplishing these goals, one important limitation of most of the epidemiological studies reviewed here has been less-than-optimum characterization of community air quality parameters used to estimate exposures of population groups to varying atmospheric concentrations of sulfur oxides and particulate matter. Such characterization of air quality has generally involved relatively crude estimates of levels of pollutants present, allowing for only limited qualitative statements to be made regarding exposure conditions--e.g. whether a given site or time period had comparatively higher or lower atmospheric levels of SO_2 or PM than some other site or time period. Only very rarely have the epidemiological studies relied on measurement methods or practical field applications of those methods that permitted reasonably precise determinations of variations in airborne levels of the pollutants of concern so as to provide quantitative information on SO_2 or PM levels associated with observed health effects. Even when reasonable quantification of community air quality parameters was achieved, however, the use of such data in estimating actual population exposures has typically been further constrained by factors such as siting of air sampling devices in relation to the study population, frequency and duration of sampling periods, activity patterns of study population members, and contributions of indoor air pollution to overall exposures of study groups. These, and other limitations noted, arise in part from the fact that most of the presently-reviewed epidemiological studies utilized air quality monitoring data obtained from sampling networks originally established for purposes other than health-related research and, therefore, not optimally designed to provide the specific types or quality of aerometric data ideally needed for epidemiological assessment of health effects related to SO_2 and PM. Thus, the aerometric data utilized thus far should generally be viewed as yielding, at best, only approximate estimates of actual study population exposures.

Adequate characterization of health effects associated with various SO_2 and PM exposure conditions has represented a second major type of problem for many of the epidemiological studies evaluated in the present chapter. A variety of health endpoint measurements

(mortality, morbidity, and indirect measures of morbidity) have been employed in such studies and each have their own advantages and disadvantages, as has been discussed in detail in other reviews (Hill, 1968; Speizer, 1969; Holland, 1970; Goldsmith and Friberg, 1977; Higgins, 1974; Shy et al., 1978; NRC/NAS, 1978a; NRC/NAS, 1978b; Ferris, 1978; ATS, 1978; Macklen and Permutt, 1979; Fox et al., 1979). Some health outcome measurements have involved more or less direct observations of signs and symptoms of disease states or objective indicators typically closely associated with the occurrence of illnesses, e.g., patient visits to hospitals or clinics or absenteeism from school or work. Direct quantification of health effects has also included measurement of biochemical or physiological changes in study populations, as in the recording of pulmonary function changes by spirometry methods. Indirect measures or indices of health effects have also been used, e.g., in gathering information on frequency and duration of respiratory illnesses by means of telephone interviews, written questionnaires, or self-reported entries in diaries. The validity of such indirect measurements of health effects, however, is heavily dependent on the ability and motivation of respondents to recall accurately and report past or present health-related events; and this can be markedly influenced by numerous extraneous factors such as age, cultural and educational background, instructions from experimenters, sequencing of questions, and problems with interviewer variability and/or bias. Confidence in the results obtained by either direct or indirect measurement methods is greatly enhanced if possible interfering or biasing factors have been appropriately controlled for and, especially for indirect health endpoint measurements, if results have been validated against corroborating evidence such as physician or hospital records verifying reported health effect occurrences.

Adequately relating observed health effects to specific parameters of ambient exposure conditions is another objective that has been very difficult to achieve by epidemiological studies reviewed below, such that relatively few allow for confident qualitative or quantitative characterization of SO_2 or PM exposure/health effect relationships. For example, competing risks, such as cigarette smoking and occupational exposures, may contribute to observed health effects results and, therefore usually must be controlled for or taken into account in order for much confidence to be placed in reported health effects/air pollution relationships; however, numerous studies on SO_2 or PM effects have failed to control adequately for such factors. Similarly, the possible effects of other covarying or confounding factors such as socioeconomic status, race, and meteorological parameters have not always been adequately controlled for or evaluated in relation to study results. Also, further complicating the evaluation of the epidemiological data is the fact that exposure parameters are not subject to experimenter control, with ambient levels of a given pollutant often widely varying over the course of a study. This has made it extremely difficult to determine whether mean concentrations, peak concentrations, rapid fluctuations in levels, or other air quality factors are most important as determinants of the reported health effects. In addition, significant covariation between concentrations of SO_2, PM, and other pollutants has often made it very

difficult to distinguish among their relative contributions to the health effects demonstrated.

Estimation of overall risk by means of epidemiology studies requires still further steps beyond the delineation of exposure/effect relationships that define exposure conditions (levels, durations, etc.) associated with the induction of specific health effects. That is, estimation of risk also requires: (1) the identification of particular population groups likely to manifest the health effects under exposure conditions of concern; and (2) ideally, the determination of numbers or percentages of such individuals (responders) likely to be affected at various exposure or dose levels. Delineation of the first variable, i.e., identification of population groups at special risk for being affected at lower exposure levels of SO_2 and PM than other groups, has to some extent been accomplished through various epidemiological studies reviewed here. However, epidemiological definition of precise quantitative dose/response (or, more correctly, exposure/response) relationships, which define percentages of population groups likely to manifest a given health effect at various levels or durations of exposure to SO_2 and PM, has been extremely difficult to achieve and is largely lacking at this time.

Another limitation of the epidemiological information reviewed here concerns its usefulness in demonstrating cause/effect relationships versus merely establishing associations between various health effects and SO_2 or PM (which may be non-causal in nature). The interpretation of epidemiological data as an aid in inferring causal relationships between presumed causal agents and associated effects has been the subject of discussion by several expert committees or deliberative bodies faced with evaluation of controversial biomedical issues during the past several decades (U.S. Surgeon General's Advisory Committee on Smoking and Health, 1964; U.S. Senate Committee on Public Works, Subcommittee on Air and Water Pollution, 1968). Among the criteria selected by each group for determination of causality were many of those advocated by A. B. Hill (1965), which included the following: (1) the strength of the association; (2) the consistency of the association, as evidenced by its repeated observation by different persons, in different places, circumstances and time; (3) specificity of the association; (4) the temporal relationship of the association; (5) the coherence of the association in being consistent with other known facts; (6) the existence of a biological gradient, or dose-reponse curve, as revealed by the association; and (7) the biological plausibility of the association. Hill further noted that strong support for likely causality suggested by an association may be derived from experimental or semi-experimental evidence, where manipulation of the presumed causative agent (its presense or absence, variability in intensity, etc.) also affects the frequency or intensity of the associated effects.

It is important to note that Hill (1965) and the deliberative bodies or expert committees alluded to above were careful to emphasize, regardless of the specific set of criteria selected by each, that no one criterion was definitive by itself nor was it necessary that all be fulfilled in order to support a determination of causality. Also, Hill and several of the groups noted that statistical methods cannot establish proof of a causal relationship in an associ-

ation nor does lack of "statistical significance" of an association according to arbitrarily selected probability criteria necessarily negate the possibility of a causal relationship. That is, as stated by the U.S. Surgeon General Advisory Committee on Smoking and Health (1964): "The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." Statistical findings, nevertheless, as well as other types of observational and experimental information, are useful inputs in helping to determine likely causal relationships.

14.1.2 Guidelines for Assessment of Epidemiological Studies

Taking into account the above methodological limitations, it appears to be possible to delineate a reasonable set of guidelines by which to judge the relative scientific quality of epidemiological studies and their findings reviewed in the present chapter. Such assessment guidelines include consideration of the following questions:

1. Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures?

2. Were the study populations well-defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

3. Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

4. Were the statistical analyses employed appropriate and properly performed and interpreted, including accurate data handling and transfer at various steps of analyses?

5. Were potentially confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

6. Are the reported findings internally consistent, biologically plausible, and coherent in terms of being consistent with other known facts?

It is recognized that few, if any, epidemiological studies deal with each of the above points in a completely ideal fashion; nevertheless, these guidelines provide benchmarks by which to judge the relative quality of various studies and by which to select the best for detailed discussion here.

Detailed critical analysis of the vast number of epidemiological studies on the health effects of SO_2 and PM, especially in relation to each of the above questions, would represent an undertaking beyond the scope or purpose of the present document. Of most importance for present purposes are those studies which provide useful quantitative information on exposure/effect or exposure/response relationships for health effects associated with ambient air levels of SO_2 and PM likely to be encountered in the United States over the next 5-year period. Accordingly, the following criteria were employed in selecting studies for detailed discussion in the ensuing text:

1. Concentrations of both SO_2 and PM were reported, allowing for potential evaluation of their separate or combined effects.

2. Study results provide information on quantitative relationships between health effects and ambient air SO_2 and PM levels of approximately 1000 $\mu g/m^3$ or less.

3. Important methodological considerations were adequately addressed, especially (a) in controlling for likely potentially confounding factors and (b) in carrying out data collection, analysis, and interpretation so as to minimize errors or potential biases which could be reasonably expected to affect the results.

4. The study results have been reported in the open literature or are in press, typically after having undergone peer review.

In addition, some studies not meeting all of the above criteria are either briefly mentioned or discussed in the main chapter text below as appropriate in helping to elucidate particular points concerning the health effects of SO_2 and/or PM. Additional studies, including those mainly providing only qualitative information on SO_2 and PM health effects are concisely discussed in Appendices A and B.

As a starting point in the present assessment, important information discussed in Chapters 2 and 3 is summarized with regard to physical and chemical properties of SO_2 and particulate matter indexed by air quality measurements employed in community health epidemiology studies evaluated in this chapter. The ensuing discussion of community health studies is then subdivided into two main subsections: Section 14.3 deals with studies of acute mortality and morbidity effects most germane to development of health criteria for possible short-term (e.g., 24 hr) ambient air standards; and Section 14.4 discusses studies of mortality and morbidity effects associated with chronic exposures most pertinent for development of health criteria for long-term (annual-average) ambient air standards. The last major chapter section (14.5) attempts to provide an integrative summarization and interpretation of the overall pattern of results evaluated in the preceding sections.

The extensive presently available epidemiological literature on the effects of occupational exposures to SO_2 and PM is not reviewed here for several reasons:

1. Such literature generally deals with the effects of exposures to SO_2 or PM chemical species at levels many-fold higher than those encountered in the ambient air by the general population.

2. Populations exposed occupationally mainly include healthy adults, self-selected to some extent in terms of being better able to tolerate exposures to SO_2 or PM substances than more susceptible workers seeking alternative employment or other groups often at special risk among the general public (e.g., the old, the chronically ill, young children, and asthmatics).

3. Extrapolation of observed occupational exposure/health effects relationships (or lack thereof) to the general public (especially population groups at special risk) could, therefore, be potentially misleading in terms of demonstrating health effects among healthy workers at higher exposure levels than would affect susceptible groups in the general population.

The occupational literature does, however, demonstrate well links between acute high level or chronic lower level exposures to SO_2 or many different PM chemical species and a variety of health effects, including: pulmonary function changes; respiratory tract diseases,

morphological damage to the respiratory system; and, especially in the case of silica-related compounds, certain heavy metals and organic PM species, induction of respiratory tract cancers or many other types of carcinogenic and noncarcinogenic effects. The reader is referred to National Institute of Occupational Safety and Health (NIOSH) criteria documents and other pertinent reviews and assessments listed in Appendix C for information on health effects associated with occupational airborne exposures to SO_2 and various PM species and recommended or implemented occupational hygiene guidelines or standards aimed at protecting workers from such effects.

14.2 AIR QUALITY MEASUREMENTS

Of key importance for the evaluation of epidemiological studies reviewed here is a clear understanding of the physical and chemical properties of SO_2 and PM indexed by measurement methods employed historically in collecting ambient air aerometric data utilized in those studies. Such information on relevant air quality measurement methods and their limitations is concisely summarized below as background for the critical evaluation of epidemiological studies that follow. See Chapters 2 and 3 for more detailed discussion of measurement methods and related information on physical and chemical properties of SO_2.

14.2.1 Sulfur Oxides Measurements

Three main measurement methods or variations thereof have been employed in generating data cited for sulfur dioxide (SO_2) levels in epidemiological studies discussed below: (1) sulfation rate (lead dioxide) methods; (2) hydrogen peroxide measurements and (3) the West-Gaeke (pararosanaline) method.

Sulfation rate methods involve reaction of airborne sulfur compounds with lead dioxide in a paste spread over an atmospherically-exposed plate or cylinder. Rates of reaction of sulfur compounds with surface paste compounds are expressed in $SO_3/cm^2/day$. However, the reactions are not specific for SO_2, and atmospheric concentrations of SO_2 or other sulfur compounds cannot be accurately extrapolated from the results, which are markedly affected by factors such as temperature and humidity. Lead dioxide gauges were widely used in the United Kingdom prior to 1960 and provided aerometric data reported for SO_2 in some pre-1960s British epidemiological studies; sulfation rate methods were also used in certain American studies.

Use of the hydrogen peroxide method was gradually expanded in the United Kingdom during the 1950s, often being coupled in tandem with apparatus for particulate matter (smoke) monitoring. The hydrogen peroxide method was adopted in the early 1960s as the standard SO_2 method used in the National Survey of Air Pollution throughout the United Kingdom and, as an OECD-recommended method, elsewhere in Europe. The method can yield reasonably accurate estimates of atmospheric SO_2 concentrations expressed in $\mu g/m^3$; but results obtained with routine ambient air monitoring can be affected by factors such as temperature, presence of atmospheric ammonia and titration errors. Very little quality assurance information exists on sources and magnitudes of errors encountered in use of the method in obtaining SO_2 data reported in specific British or other European epidemiological studies, making it difficult to assess the accuracy and precision of reported SO_2 values. Only in the case of the British

National Survey has extensive quality assurance information been reported (Warren Spring Laboratory, 1961; 1962; 1966; 1967; 1975; 1977; OECD, 1964; Ellison, 1968) for SO_2 measurements made in the United Kingdom and used in various British epidemiological studies.

The West-Gaeke (pararosanaline) method has been more widely employed in the United States for measurement of SO_2. The method involves absorption of SO_2 in potassium tetrachloromercurate (TCM) solution, producing a chemical complex reacted with pararosanaline to form a red-purple color measured colorimetrically. The method, suitable for sampling up to 24 hrs, is specific for SO_2 if properly implemented to minimize interference by nitrogen or metal oxides, but results can be affected by factors such as temperature variations and mishandling of reagents. Only limited quality assurance information (Congressional Investigative Report, 1976) has been reported for some American SO_2 measurements by the West-Gaeke methods.

Measurement approaches for suspended sulfates and sulfuric acid, used mainly in the United States, include turbidimetric and methylthymol blue methods. The former usually involves collection of samples on sulfate-free glass fiber filters by means of high-volume PM samplers. Sulfate is extracted and precipitated with barium chloride, and turbidity of the suspension is determined spectrofluorometrically. However, the method does not differentiate between sulfates and sulfuric acid, and secondary formation of such products from SO_2 in air drawn through the filter can affect estimation of atmospheric sulfate levels. Similar collection procedures and limitations apply for the methylthymol blue method, which involves reaction of extracted sulfate with barium chloride and complexing of the latter with methylthymol blue. Inability to differentiate between sulfates and sulfuric acid limit these two methods as specific measures of suspended sulfates, but their results can serve as rough indicators of atmospheric levels of sulfur-oxide related PM.

14.2.2 Particulate Matter Measurements

To be of maximum value, epidemiological studies on PM effects must utilize air quality measurement methods that provide meaningful data, not only regarding the mass or amount of atmospheric PM, but also quantitative information related to size and chemical composition of particles present. In actual practice, however, most epidemiological studies on PM effects have relied on air quality data from air monitoring instruments of questionable sampling accuracy and not specifically designed for health-related research. The resulting data thus typically only provide limited information regarding mass, size or chemical properties of the PM sampled.

Three main measurement approaches or variations thereof were used to obtain PM data reported in epidemiological studies reviewed below: (1) the British Smokeshade light reflectance method or variations used in the United Kingdom and elsewhere in Europe; (2) the American Society for Testing and Materials (ASTM) filter soiling method based on light transmittance and used in the United States; and (3) the high-volume sampling method most widely employed in the United States.

As discussed in Chapter 3, the British Smoke (BS) method and close variations of it in routine use have typically employed standardized monitoring equipment with a D_{50} cut-point of

≅ 4.5 μm at KPH (McFarland, 1979). Thus, regardless of whether or not larger coarse-mode particles were present in the atmosphere during the sampling period, the BS method collected predominantly small particles. The D_{50} of the instrument may, however, shift at higher wind speeds. The BS method neither directly measures the mass nor determines chemical composition of collected particles. Rather, it primarily measures reflectance of light from a stain formed by particles collected on filter paper, which is somewhat inefficient for collecting very fine particles (Lui, 1978). The reflectance of light from the stain depends both on density of the stain or amount of PM collected in a standard period of time and optical properties of the collected materials. Smoke particles composed of elemental carbon of the type found in incomplete fossil fuel combustion products typically make the greatest contribution to the darkness of the stain, especially in urban areas. Thus, the amount of elemental carbon, but not organic carbon, present in the stain tends to be most highly correlated with BS reflectance readings. Other non-black, non-carbon particles also have optical properties such that they can affect the reflectance readings (Pedace and Sansone, 1972).

Since highly variable relative proportions of atmospheric carbon and non-carbon PM can exist from site to site or from one time to another at the same site, then the same absolute BS reflectance reading can be associated with markedly different amounts (or mass) of particles collected or, even, carbon present. Site-specific calibrations of reflectance readings against actual mass measurements obtained by collocated gravimetric monitoring devices are therefore necessary in order to obtain approximate estimates of atmospheric concentrations of PM based on the BS method. A single calibration curve relating mass or atmospheric concentration (in $\mu g/m^3$) of particulate matter to BS reflectance readings obtained at a given site may serve as a basis for crude estimates of PM (mainly small particle) levels at that site over time, so long as the chemical composition and relative porportions of elemental carbon and non-carbon PM do not markedly change.

As part of British National Survey and OECD work in the early 1960s, site-specific BS mass calibration curves were determined for numerous urban areas in the United Kingdom and Europe and efforts were made to interrelate such curves (or normalize them) against certain standard curves. Two standard calibration curves were adopted: (1) a British standard smoke curve that defines relationships between PM mass and BS refectance readings for London's atmosphere in 1963, which was used to yield BS concentration estimates (in $\mu g/m^3$) reported in many published British epidemiological health studies; and (2) an international standard OECD smoke curve, against which smoke reflectance measurements made elsewhere in Europe were compared to yield smoke concentration estimates (in $\mu g/m^3$) reported in various European epidemiological studies on PM effects. Of crucial importance for evaluation of such studies is the fact that the actual mass or smoke concentration present at a particular site may differ markedly from the corresponding mass or concentration (in $\mu g/m^3$) associated with a given reflectance reading on either of the two standard curves; and, great care must be applied in interpreting exactly what any reported BS value in $\mu g/m^3$ means at all. Further complicating interpretation of smoke data used in most epidemiological studies is the lack of reporting of

specific quality assurance information for the cited aerometric measurements. Such information has only been reported in general terms for United Kingdom National Survey data utilized in numerous British studies (Warren Spring Laboratory 1961, 1962, 1966, 1967, 1972, 1975; OECD 1964; Moulds, 1962; Ellison, 1968).

The ASTM or AISI light transmittance method is similar in approach to the British smoke technique. The instrument has a D_{50} cut-point of ≅5 μm and utilizes an air flow intake apparatus similar to that used for the BS method, depositing collected material on a filter paper tape periodically advanced to allow accumulation of another stain over a standard time period. Opacity of the stain is determined by transmittance of light through the deposited material and filter paper, with results expressed in terms of optical density or coefficient of haze (CoHs) units per 1000 linear feet of air sampled (rather than mass units). Thus, CoHs readings roughly index the soiling capacity of PM in the air and, like BS readings, are most strongly affected by fine-mode elemental carbon particles. CoHs readings, however, are somewhat more markedly affected by non-carbon particles than BS measurements. The ASTM method does not directly measure mass or determine chemical composition of the PM collected. Attempts to ever relate CoHs to $\mu g/m^3$ would require site-specific calibration of CoHs readings against mass measurements determined by a collocated gravimetric device, but the accuracy of such mass estimates could be subject to question. Reasonably successful calibration of CoHs readings against corresponding particle mass levels has been reported for only one city (New York). That was accomplished by Ingram via a complicated intercomparison during the late 1960s between CoHs readings, BS reflectance readings, and gravimetric mass measurements obtained from collocated AISI tape samplers, BS instruments, and a modified high-volume sampling device with air intake equipment closely matching that used for the other two methods (Ingram, 1969; Ingram and Golden, 1973). The calibration results, however, are clearly applicable in only a highly limited fashion to New York aerometric data.

The high-volume (hi-vol) sampler method more widely used in the United States to measure total suspended particulates (TSP), collects particles on a glass-fiber filter by drawing air through the filter at a flow rate of approximately 1.5 m^3/min, thus sampling a higher volume of air per unit of time than the above PM sampling methods. This permits collection of sufficient PM in a 24-hr period to allow for direct weighing and chemical analysis of sampled material. The high flow rate, the geometric shape of the shelter housing the sampler, and other features of standard types of apparatus used result in sampling efficiency varying with windspeed. The D_{50} cut-point for the hi-vol sampler is typically around 25 to 30 μm and collection of larger particles tends to drop off rapidly above such cut-points (Wedding, 1977; McFarland, 1979). Nevertheless, it is important to recognize that the hi-vol sampler, as typically employed, collects coarse-mode particles that may include windblown crustal material of natural origin (especially in dry rural areas). Only rarely have cyclone samplers or other variations of the hi-vol sampler with smaller size cut-points thus far been utilized in epidemiological studies in an attempt to limit collected particles to an inhalable range, but even then the cutpoints achieved have not been very sharp or independent of wind speed.

Numerous factors other than wind speed, as discussed in Chapter 3, can affect PM measurements by hi-volume sampling techniques; however, quality assurance information for TSP measurements reported in most American epidemiological studies is largely lacking, except for extensive information on U.S. Environmental Protection Agency CHESS Program data (Congressional Investigative Report, 1976).

One consequence of the broader size range of particles sampled by the hi-vol method versus the BS or ASTM methods are severe limitations on intercomparisons or conversions of PM measurements by those methods to equivalent TSP units or vice versa. As shown by several studies, no consistent relationship typically exists, for example, between BS and TSP measurements taken at various sites or even during various seasons at the same site (Commins and Waller, 1967; Lee, 1972; Ball and Hume, 1977; Holland et al., 1979). The one exception appears to be that, during severe London air pollution episodes when low wind speed conditions resulted in settling out of larger coarse-mode particles and fine-mode particles markedly increased to constitute nearly 100 percent of the PM present, then TSP and BS levels (in excess of $\cong$ 500 $\mu g/m^3$) tended to converge as would be expected when both methods are essentially sampling only fine-mode particles (Holland et al., 1979).

Taking into account the foregoing information on SO_2 and PM measurement methods and factors affecting the quality of results obtained with routine field monitoring, aerometric data cited in various epidemiological studies must generally be viewed as providing at best only very approximate estimates of atmospheric levels of sulfur dioxide, other sulfur compounds, or other PM associated with reported health effects. Further, to the extent that the aerometric data cited are derived from use of techniques with limited specifity for the substance(s) purportedly measured or the relative contributions of sulfur oxides or PM to observed health effects cannot be distinguished from each other or from the effects of other covarying pollutants, then the aerometric data and associated health effects reported might be more appropriately viewed as relatively non-specific indicators of the effects of overall air pollutant mixtures containing sulfur oxides and PM.

14.3 ACUTE SO_x/PM EXPOSURE EFFECTS

14.3.1 Mortality

14.3.1.1 Acute Episode Studies--Detailed study of the human health effects associated with episodes of severe air pollution spans a period of less than 50 years. The earliest reliable documentation of such episodes describes an incident in the Meuse Valley of Belgium in 1930.

An intense fog covered the Meuse Valley from Liege to Huy (Firket, 1931) from December 1 to 5, 1930, and was accompanied by an anticyclonic high pressure area with low winds and large amounts of PM. Sixty deaths associated with the fog occurred among residents of the Valley on December 4 and 5. The people who died were sick for only a short time. Although there were no other immediate deaths, several persons affected by the fog died much later from complications associated with fog-induced injuries. The death rate in the area was 10.5 times normal. The illnesses abated rapidly when the fog dispersed.

A similar but smaller event later occurred in Donora, Pennsylvania (Shrenk et al., 1949). Donora was blanketed by a dense fog during October 1948, which adversely affected 43 per-

of the population of approximately 10,000 people. Twenty persons, mostly adults with preexisting cardiopulmonary diseases, died during or shortly after the fog due to cardiorespiratory causes; and 10 percent of the population was classified as being severely affected. No pollution measurements were made during the incident but SO_2, its oxidation products, and PM were undoubtedly significant contaminants. During subsequent inversion periods, presumably not as severe in terms of pollutant elevations as the one in October 1948, daily averages of SO_2 as high as 0.4 ppm (~1140 $\mu g/m^3$) were recorded (NAPCA). Cioco and Thompson (1961) found increased mortality rates and morbidity effects (e.g., heart disease, asthma, high blood pressure, chronic bronchitis) during an 8-year follow-up period for Donora residents who had reported acute illness during the 1948 episode in comparison to those reporting no acute illness.

As seen in Table 14-1, a series of episodes were documented in London between 1952-1975 (Ministry of Health, London, 1952; Martin and Bradley, 1960; Lawther, 1963; Clifton et al., 1960; Wilkins, 1954; Wilkins, 1954; Logan, 1953; Waller, 1978; Apling et al., 1977; Holland et al., 1979). Excess mortality reported during those episodes occurred mainly among the elderly and chronically ill adults. Various factors have been discussed which might help explain some of the excess mortality (Holland et al., 1979), including possible influences not only of increased air pollution, but also of high humidity (fog) and low temperatures. Regardless of the relative contributions of these different factors, one clear conclusion from these major London episodes is that increases in mortality were associated with air pollution episodes when concentrations of both SO_2 and BS exceeded 1000 $\mu g/m^3$ (Rall, 1974; NAPCA, 1969; Goldsmith and Friberg, 1977; Higgins, 1974; Shy et al., 1978; Holland et al., 1979; Higgins and Ferris, 1979; Speizer and Ferris, 1978; NRC/NAS, 1978a,b; WHO, 1979; Shy, 1979). The available data, however, do not allow for clear delineation of the effects of specific pollutants acting alone or in combination. Qualitative studies of milder episodes in the 1950's (Gore and Shaddick, 1958; Burgess and Shaddick, 1959) showed similar correlations of mortality with air pollution.

TABLE 14-1. EXCESS DEATHS AND POLLUTANT CONCENTRATIONS DURING SEVERE AIR POLLUTION EPISODES IN LONDON (1948-75)

Date	Duration, days	Deviation from $\bar{X}$ of total excess deaths	Maximum 24-hr pollutant concentration, $\mu g/m^3$	
			Smoke (BS)	SO_2 (H_2O_2 titration)
Nov. 1948	6	750	2780	2150
Dec. 1952	4	4000	4460*	3830
Jan. 1956	4	1000	2830	1430
Dec. 1957	4	750	2417	3335
Jan. 1959	6	250	1723	1850
Dec. 1962	5	700	3144	3834
Dec. 1975	2	100-200**	546	994

*Note that peak and 24-hr BS levels were likely much higher than 4460 $\mu g/m^3$ due to rapid saturation of filter paper by collected PM.

**Excess mortality during the 1975 London episode may be attributable in part to a concurrently occurring strike affecting medical care.

Episodes of acute air pollution have also occurred in the United States since the 1948 Donora episode, but no single event has reached the proportions of the major London episodes. Some studies suggest however, that slight increases in excess deaths and morbidity were associated with severe episodes in New York City (see Table 14-2). The estimates of excess mortality reported from the New York episodes were derived by comparing daily deaths during periods of high air pollution with daily deaths for the same period in the years immediately before or following the episode (Glasser and Greenburg, 1971) or by calculating daily deviations from a 15-day moving average of daily deaths (McCarroll and Bradley, 1966). Studies of the New York episodes listed in Table 14-2 controlled for meteorological variables and found an independent influence of the pollutants (McCarroll and Bradley, 1966; Glasser and Greenburg 1971). During at least one of the episodes (December, 1962), the increased death rates were predominantly in the 45 to 64 and 65 years and older age groups. During the episodes in January, 1963, some days did not have an excess mortality. The episode between January and February 1963 involved a peak death rate apparently superimposed upon an elevated death rate average due to the present of influenza virus in the community. There was one other period of excess mortality (April, 1963) which did not show sharp increases in air pollutants. The above studies appear to yield a pattern of results indicative of small increases in mortality among older adults occurring in New York City when SO_2 levels exceeded 1000 $\mu g/m^3$ in the presence of simultaneously elevated PM concentrations measured in the range of 5.0 to 7.0 CoH units. The numbers of excess deaths detected; however, were very low in comparison to the large total population of New York and the numbers of episode-related excess deaths observed in London (vida supra). Direct, precise comparisons of the pollution data from the London and New York episodes, as has been noted (Holland et al., 1979), cannot be made because of differences in methods used for measuring PM concentrations. However, even rough comparisons of the results obtained by the different (BS, CoHs) approaches suggest that the pollution must have typically been much greater in London.

When a marked increase in air pollution is associated with a sudden rise in the death rate or illness rate that lasts for a few days and both return to normal shortly thereafter (as documented in the above studies), a causal relationship is strongly suggested. Sudden changes in weather, however, which may have caused the air pollution incidents, must also be considered as another possible cause of the death rate increase. On the other hand, the consistency of the above associations between SO_2 and particulate matter elevations and increases in mortality render it extremely unlikely that weather changes alone provide an adequate explanation for all such observations. This view is further reinforced by (1) the fact that at least some episodes were not accompanied by sharp falls in temperature; and (2) other weather changes of similar magnitudes to those accompanying the above pollution episodes are not usually associated with such dramatic increases in mortality in the absence of greatly increased levels of SO_2, particulate matter, or other pollutants. In summary, the above London episode studies appear to provide clear evidence for substantial increases in excess mortality

TABLE 14-2. ACUTE AIR POLLUTION EPISODES IN NEW YORK CITY

Location	Date	Reference	Estimated excess deaths	24 Hour pollutant concentrations	
				SO_2, max $\mu g/m^3$	particulates, CoHs
New York City	Dec. 1962	McCarroll and Bradley, 1966	90	1890 (0.72 ppm)	5-6.5
New York City	Jan 1963	McCarroll and Bradley, 1966	*	1830 (0.7 ppm)	6.0
New York City	Jan-Feb 1963	Glasser and Greenburg, 1971	405-647**	1570 (0.6 ppm)	7.0
New York City	Feb.-Mar. 1964	Glasser and Greenburg, 1971	50	1570 (0.6 ppm)	5.0+

*Specific numbers of excess deaths not clearly reported in published paper.
**Influenza outbreak also present.

when SO_2 exceeded 1000 $\mu g/m^3$ in the presence of PM over 1000 $\mu g/m^3$ (BS). Certain of the New York studies yield some evidence for small increases in excess mortality at simultaneous elevations of 1000 $\mu g/m^3$ SO_2 and PM in the range of 5.0 - 7.0 CoHs.

14.3.1.2 Mortality Associated with Non-Episodic Variations in Pollution--A number of reports have investigated relationships between mortality and air pollution in England during periods with no unusual air pollution episodes (Weatherly and Waller, in press; Martin, 1964; Waller, 1969; Gore, 1958; Burgess, 1959; Scott, 1963; Martin, 1960; Riggan et al., 1975; Lawther, 1963; Clifton et al., 1960). For most of these studies, 15-day moving averages were constructed and the effects of pollution were assessed in terms of daily deviations from these baselines. Increases in daily deaths during the winter of 1958-59 were found (Lawther, 1963) to be associated with concentrations of BS >750 $\mu g/m^3$ and SO_2 >715 $\mu g/m^3$ (0.25 ppm) during a long (59-day) period of thick fog. Increases in daily deaths were not associated with pollutants at lower concentrations during 1958-59; nor did they occur at similar pollutant levels during the prior winter having only 8 days of fog. Similar studies in Sheffield (Clifton et al., 1960) did not yield confirmatory results; that is, while increases in deaths appeared to possibly be associated with very high concentrations of pollutants, random variations in the number of deaths were so large that firm conclusions could not be drawn.

Among the most important British studies bearing on acute health effects of sulfur oxides and particulate matter at levels below 1000 $\mu g/m^3$ are those of Martin and Bradley (1960) and Martin (1964). The first of these studies related daily mortality from all causes and from bronchitis and pneumonia to the level of SO_2 and smoke in London during the winter of 1958 to 1959. The authors found a considerable number of coincident peaks in pollution level and daily mortality. The correlation of mortality from all causes with pollutants measured on the log scale was 0.613 for smoke (BS) and 0.520 for SO_2. Martin and Bradley (1960) reported that neither temperature nor humidity was significantly correlated with London mortality studied during the winter of 1958-59, noting a very low correlation coefficient ($r = -0.030$) for temperature and deaths for the entire 1958-59 winter and the occurrence of several peaks in mortality during November and December, 1958, when temperatures were substantially over 38°F. They further noted that a range of 30-38°F is characteristic of most winter fogs and temperatures consistently below 30°F (when temperature effects on mortality can be expected) are the exception.

Though the authors emphasized the relationship between change in pollution level and number of deaths and lack of meteorological effects, an influenza epidemic during part of the study may have influenced some of the results. The authors, however, reported number of deaths, smoke levels, and SO_2 levels from November 1, 1958 to February 28, 1959. A further analysis of these data was performed by Ware et al. (1981) but excludes the month of February, in which an epidemic of Type A influenza also significantly influenced daily mortality. For the remaining 92 days, the deviations of daily mortality from the 15-day moving average (truncated at each end of the series) was computed and appeared to show a consistent and significant trend of increasing mortality with increasing BS and SO_2. Change in mean deviations

occurred between 500-600 $\mu g/m^3$ BS and 300-400 $\mu g/m^3$ SO_2 as levels above which small positive increases in mortality over the moving average were seen, although this is not intended to suggest a threshold for response. In fact, it is unclear at what level significant excess mortality first occurred, but the analysis suggests that notable increases occurred somewhere in the range of 500-1000 $\mu g/m^3$ BS and SO_2 and most likely when both pollutants exceeded 750 $\mu g/m^3$. Although temperature and humidity were not correlated with daily mortality, both pollution level and daily mortality increased throughout the period of study, and the possibility of other extraneous seasonal variables contributing to this association cannot be ignored.

An analysis similar to that used by Martin and Bradley (1960) was carried out by Martin (1964) for the winter of 1959-60. This winter had fewer incidents of high pollution. The significant positive correlation between mortality and pollution was, however, still present although the coefficients were somewhat lower than in the previous year. The Martin (1964) results were based on analyses combining high pollution days from 1958 to 1959 and 1959 to 1960, after excluding days on which pollution had fallen from a previously higher level. The mean deviation was positive for every BS level above 500-600 $\mu g/m^3$ and SO_2 level above 400-499 $\mu g/m^3$, but no clear threshold for significant increases in mortality could be clearly delineated although the most marked increases occurred for BS levels over 1200 $\mu g/m^3$ and SO_2 levels exceeding 900 $\mu g/m^3$. Considerable covariation in levels of the two pollutants, however, preclude attribution of the apparent mortality effects to either one alone. Bronchitis mortality was also significantly, though less strongly, correlated with pollution level, but pneumonia mortality was not correlated with pollution. Based on the above analyses, it appears that small increases in mortality may have occurred in London during 1958 to 1960 in association with covarying increases in BS and SO_2 levels in the range of 500-1000 $\mu g/m^3$, respectively. Holland et al. (1979), however, suggest that the increases in excess mortality most clearly occurred when particulate levels exceeded 750 $\mu g/m^3$ (BS) in the presence of SO_2 levels over 710 $\mu g/m^3$.

A number of investigators have also reported on relationships in the United States between mortality and daily variations in air pollution during non-episodic periods (Greenburg et al., 1967; Schimmel and Greenburg, 1972; Schimmel and Murawski, 1975; Schimmel and Murawski, 1976; Hodgson, 1970; Buechley et al., 1975; Buechley, 1977; Lebowitz, 1973a,b). These studies mainly provide, at most, qualitative evidence linking mortality effects to air pollution (see Appendix A). For example, Hodgson (1970) used multiple regression methods to examine the relationships between deaths and air pollution concentrations on a monthly basis in New York City. His correlations between excess deaths and SO_2 or particulate matter (CoHs) were significant. Buechley (1975, 1977) used similar models to relate daily deaths in the New York/New Jersey metropolitan area (1962 through 1972) to SO_2 measured at a single monitoring station; he showed significant correlation coefficiences as well, and showed a relation of residual mortality to levels of SO_2. Lebowitz (1973a,b) utilized a stimulus-response model to study daily air pollution exposures, meteorology, and daily mortality in New York (1962-1965),

Philadelphia (1963-1964), Los Angeles (1962-1965), and Tokyo (1966-1969). Adverse temperature and humidity changes were shown to be important, but cannot account for mortality increases which were closely associated with increases of air pollution. In each case no specific pollutant levels were clearly shown to be associated with significant increases in mortality.

In another study, possibly yielding useful quantitative information, Glasser and Greenberg (1971) carried out an analysis of daily mortality in New York City during the 5 year period 1960 to 1964, using only data from the months October through March. Deaths were analyzed both as deviations from a 15-day moving average and as deviations from the 5-year average for each day. Results from the two analyses were said to be qualitatively similar. Twenty-four hour average pollution data were based on hourly SO_2 and bihourly smoke shade (CoH) readings. The results are adequately summarized by the unadjusted analysis, which suggests a trend in mortality over the full range of SO_2 and smoke shade (CoH) levels, with marked positive mean deviations above 5.0-5.9 CoHs and SO_2 levels above 786-1048 $\mu g/m^3$. Variations in the two pollutants, however, are markedly confounded due to their colinearity, not allowing one to discern the relative contributions of each to reported excess mortality effects. In cross-tabulation of daily mortality by SO_2 and smoke shade level, however, SO_2 was reported to be more strongly related to mortality and was used as an index of pollution in some analyses; and, in a multiple regression analysis with temperature and rainfall, SO_2 was reported to be more strongly associated with mortality than either weather variable. This association persisted in analyses of bimonthly periods. Although the observations are dependent, Glasser and Greenberg computed standard errors for the mean deviations by assuming independence. As in the case of other New York non-episode mortality studies listed above (e.g., Greenburg et al., 1967; Schimmel and Greenberg, 1972, etc.), the results of this study are open to question on the basis of data from only a single monitoring station in central New York having been used to generate exposure estimates for the entire metropolitan area, but arguments can be made for those data possibly being reasonably representative for the entire city under markedly elevated pollutant conditions (see Appendix A).

14.3.1.3 Morbidity--Morbidity studies of acute or short-term air pollution exposures are much less common in the epidemiologic literature than morbidity studies of chronic or long-term air pollution exposures. This reflects the dual complications of the difficulty of having adequate estimates of pollution exposure as well as the statistical analytical problems of the health data being collected. The main focus here is on studies providing information on quantitative relationships or associations between ambient air concentrations of SO_2 or particulate matter and acute exposure morbidity health effects.

Several British studies have been published on health effects associated with acute or short-term exposures of adults to sulfur oxides and particulate matter which appear to provide useful information on quantitative dose-effect relationships.

Illness data were obtained in many of the early severe pollution episodes discussed above; this information did little more than support the mortality results reported in those

studies. There was evidence, however, that increases in illness occurred along with increases in deaths, although the effects were less sudden. Waller and Lawther (1955), for example, reported that when smoke (BS) concentrations in London increased tenfold during the course of 2 hours, there was a deterioration in the clinical condition of some patients with bronchitis or asthma. On this day, peak smoke (BS) concentration may have reached 6500 $\mu g/m^3$. SO_2 also increased to a maximum of about 2860 $\mu g/m^3$ (1.0 ppm) but H_2SO_4 did not, on the basis of washings from impactor slides. Most of the mass of particulate matter was determined by microscopic studies to consist of particles less than 1 μm in diameter.

Lawther (1958) studied associations between daily variations in smoke and SO_2 pollution and the self-indicated health status in 29 British patients with chronic bronchitis. Patients maintained diaries on which their daily condition was indicated in relation to their usual condition. The alternatives were "better," "same," "worse," and "much worse." Figure 14-1 shows graphically the effects of high pollution levels observed in the 29 bronchitic patients studied in January 1954. During the month of January 1954, an episode of relatively high pollution resulted in a sharp increase in the number of patients whose condition worsened as 24-hour smoke (BS) increased from about 400 to 2000 $\mu g/m^3$ and 24-hour SO_2 increased from about 450 $\mu g/m^3$ (0.15 ppm) to ~1300 $\mu g/m^3$ (0.20 ppm).

In the winter of 1955, the study was extended to include 180 patients in the London area. The prevalence of exacerbation of preexisting illness was related more closely to pollution than to temperature or humidity during the winter months, and the relationship disappeared when the levels of pollution decreased in the spring. Actual numerical data are not given in the report, but inspection of the figures indicate that exacerbation of illness increased as smoke (BS) increased to about 300-350 $\mu g/m^3$ and SO_2 to about 500-600 $\mu g/m^3$. The data suggest that during the winter months, SO_2 was associated more closely with variations in health status; however, in the spring of the year, when pollution concentrations were no longer associated with health status, SO_2 continued to occur in intermittent peak concentrations as high as those associated with increased illness during the winter. However, the association between pollution and illness decreased when smoke (BS) concentrations fell to a fairly consistent 24-hour concentration of less than 250 $\mu g/m^3$. The few short higher peaks in smoke (BS) after this time had little effect on illness status. These investigators noted that worsening of subjects' conditions were more likely associated with markedly higher short-term peaks in pollution rather than the 24-hr average levels noted above and that the results are not necessarily indicative of causal relationships, but rather that the measurements of smoke (BS) and SO_2 may only be indicators of whatever is the cause.

A later report by Lawther et al. (1970) gave the results of further extension of these studies into the winters of 1959-60 and 1964-65. The techniques used were similar except that the patients now reported on health status in relation to the previous day rather than in relation to usual conditions. These studies supported the results in previous years in that the worsening of health status was associated clearly with increases in air pollution. The authors stated that, although exact relationships between the responses of patients and the

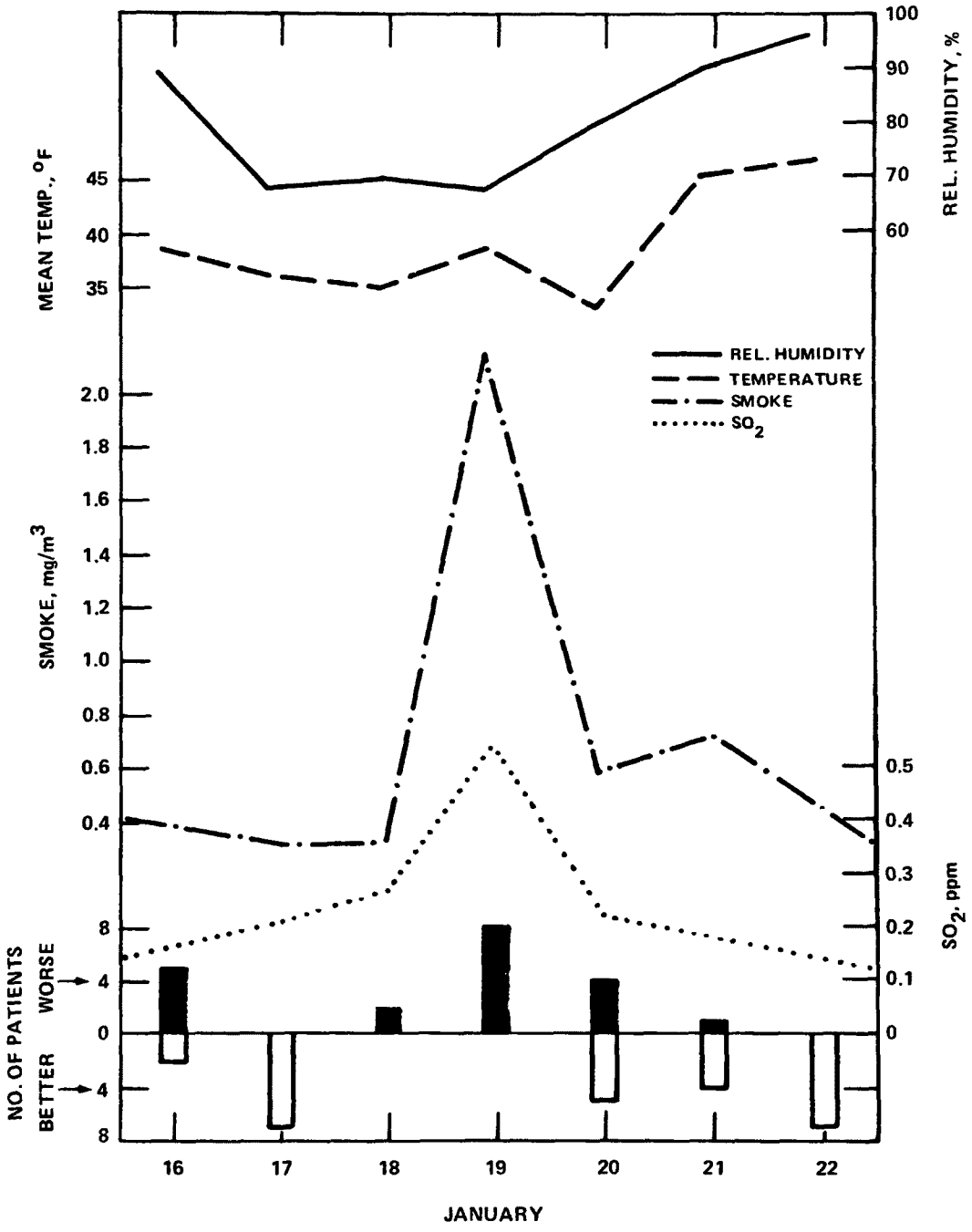

Figure 14-1. Graph showing effect on 29 bronchitic patients (St. Bartholomew's Hospital) of high pollution without fog.

concentrations of smoke and SO_2 could not be determined, the minimum pollution leading to any significant response was about 500 $\mu g/m^3$ (0.17 ppm) SO_2, together with about 250 $\mu g/m^3$ smoke (BS). Lawther et al. (1970) also emphasized that these responses may reflect the effects of brief exposures to maximum concentrations several times greater than the 24-hour average (i.e., presumably in excess of 1000 $\mu g/m^3$ for both BS and SO_2 levels). As in the earlier studies, the results appear to relate more closely during the first part of the winter and, in some instances, there was little reponse to higher concentrations of pollutants near the end of the winter. Although the concentrations of smoke and SO_2 closely correlate, examination of the data again suggests that often higher concentrations of SO_2 near the end of the winter, occurring with generally lower concentrations of smoke, produced less response in the study subjects than did the same concentrations of SO_2 earlier in the winter, when smoke was higher. There was some evidence for a loss of interest by participants. When the association between exacerbations and SO_2 concentrations were compared in the two winters, the impression was of a slightly reduced and less consistent, but definite effect during the second winter. The declines in concentrations were from 342 $\mu g/m^3$ to 129 $\mu g/m^3$ BS and from 299 $\mu g/m^3$ to 264 $\mu g/m^3$ SO_2 (Lawther et al., 1970). These studies among chronic bronchitis patients in London continued into the 1970s as the frequency of periods of high pollution declined. There were no sharp increases reported in illness scores in the winter of 1969-70 (Lawther, 1970) nor in the winter of 1974-75 (Waller, 1971).

Martin (1964) examined applications for hospital admissions for the winter of 1958-59 and found for men ages 45-79 (after adjustment for day of the week and correction for 15-day moving average) significant correlations for both cardiovascular and respiratory conditions with smoke ($r = 0.46$) and sulfur dioxide ($r = 0.40$). Analogous significant correlations were found for the same male age group for such conditions in relation to both smoke ($r = 0.41$) and SO_2 ($r = 0.43$) for the winter of 1959-60. The average deviations associated with increasing SO_2 and smoke levels during both winters are summarized in Tables 14-3 and 14-4. As seen in those tables, whereas no clear threshold for the onset of mean positive deviations across the exposure ranges can be distinguished, very marked increments in the positive mean deviations can be discerned starting at 800-899 $\mu g/m^3$ for SO_2 and 1100-1510 $\mu g/m^3$ for PM (BS). Presentation by the authors of their results separately in relation to SO_2 and BS (and the present summarization in Tables 14-3 and 14-4) is not meant to imply that the relative individual contributions of SO_2 and BS alone to the observed effects can be ascribed to the concentrations listed, in view of considerable covariation in SO_2 and BS levels during the two winters studied.

In addition to the above British and European studies, several American studies may provide useful information on the effects of acute (24 hr) exposures to sulfur dioxide and particulate matter.

For example, McCarroll and colleagues (Mountain et al., 1968; Thompson et al. 1970; Cassell et al., 1969, 1972; Lebowitz et al., 1972; Lebowitz, 1977) demonstrated significant

TABLE 14-3. AVERAGE DEVIATION OF RESPIRATORY AND CARDIAC MORBIDITY FROM 15-DAY MOVING AVERAGE, BY SO_2 LEVEL (LONDON, 1958-1960)

SO_2 level ($\mu g/m^3$)	Number of days	Mean deviation
400-499	9	2.2
500-599	6	5.1
600-799	9	6.9
800-899	6	12.8
900-1280	5	12.8

TABLE 14-4. AVERAGE DEVIATION OF RESPIRATORY AND CARDIAC MORBIDITY FROM 15-DAY MOVING AVERAGE, BY SMOKE LEVEL (BS) (LONDON, 1958-1960)

Smoke level ($\mu g/m^3$, BS)	Number of days	Mean deviation
500-599	9	3.2
600-699	6	-0.7
700-799	9	2.4
800-1099	8	4.9
1100-1510	7	12.9

multiple correlations between acute respiratory symptoms and air pollution, controlling for season, weather, and social class, when seasonal SO_2 means in the range of 0.10-0.24 ppm (~280-700 $\mu g/m^3$) seasonal smoke shade means in the range of 1.56-3.15 CoHs. Initially, multiple regression analyzes showed conflicting findings in that the pollutants were occasionally absent from or negative in their regressions. This led to a separation of the combined meteorological and air polluant conditions into categories of: (1) stormy weather (low temperatures, occasional precipitation, high wind speed) when the pollutants were low; (2) stagnation periods (low wind speed, moderate temperatures) when SO_2 and TSP were high; (3) periods of change in pollutant levels during the fall through spring periods; and (4) high photoxidant conditions in the summer. This analysis revealed significant correlations between the pollutants and acute symptoms for 1800 individuals studied weekly in New York (1962-65) during stagnation periods and significant correlations of the same acute respiratory symptoms (predominately common colds) with meteorological conditions during stormy periods. They also found a lag of one to three days in symptoms and corresponding increases in school absenteeism. Some individuals (mostly under the age of 10) were found to have reacted consistently and frequently to increases in the pollutants, and their respiratory symptoms were of greater duration and severity than "nonsensitive" individuals (Lebowitz et al., 1972). Those who were sensitive during the first part of the period under study were found to be sensitive later on in the study. The attack rates per person year were about double for the "sensitive", and occurred predominately in the winter period. Additional qualitative studies demonstrating effects of acute exposure to SO_2 and PM on the health of children and other sensitive groups, e.g., asthmatics, are summarized in Appendix B.

In summary, studies on acute exposure effects tend to suggest that the elderly, those with chronic cardiorespiratory diseases, children, and asthmatics may constitute populations at risk for manifesting morbidity effects in response to acute exposure to elevated atmospheric levels of sulfur dioxide and particulate matter. Lawther's studies in London, for example, appear to demonstrate worsening of health status among bronchitic patients to be associated with acute 24-hr exposures to BS of 250-500 $\mu g/m^3$ in the presence of SO_2 levels in the range of 500-600 $\mu g/m^3$ or peak 1-hr exposures to each of the pollutants at levels presumably in excess of 1000 $\mu g/m^3$. In contrast, no effects on bronchitics appeared to be detectable at 24-hr BS levels below 250 $\mu g/m^3$ in the presence of 24-hr SO_2 levels below 500 $\mu g/m^3$. Also, increased applications by adults aged 45-79 for admissions to London hospitals for cardiac and respiratory morbidity most clearly occurred, based on Martin's studies, when 24-hr BS and SO_2 levels approached or exceeded 900-1000 $\mu g/m^3$; and Martin's data suggest that such effects may have occurred at somewhat lower levels down to 500 $\mu g/m^3$ for both SO_2 and BS. Insufficient epidemiological information exists, however, by which to determine specific quantitative acute exposure levels at which the health of other sensitive groups, e.g., children and asthmatics, might be adversely affected.

14.3.2 Chronic SO_2/PM Exposure Effects

14.3.2.1 Mortality

Numerous studies have been performed comparing general or cause-specific mortality in areas of lowest-to-highest pollution concentrations. Most of these studies do not account for cigarette smoking, occupation, social status, and/or mobility differences between areas, thus making it difficult to define accurately any quantitative relationships between mortality and air pollution parameters. Many such qualitative studies are summarized in Appendix B. Essentially no epidemiological studies are presently well-accepted as providing valid quantitative data relating respiratory disease mortality of chronic (annual average) exposures to sulfur oxides or particulate matter.

Certain studies have more specifically attempted to relate lung cancer mortality to chronic exposures to sulfur oxides, particulate matter undifferentiated by chemical composition, or specific particulate matter chemical species. However, little or no clear epidemiological evidence has been advanced to date to substantiate hypothesized links between SO_2 or other sulfur oxides and cancer. Nor does there presently exist credible epidemiological evidence linking increased cancer rates to elevations in PM as a class, i.e., undifferentiated as to chemical content. Some epidemiological studies (e.g., of occupationally exposed workers) do provide evidence of increased cancer risk associated with exposure to some types of particulate matter, e.g., certain organic compounds or metals, often found in the fine- and coarse-mode particulate fractions of many urban aerosols (see Appendix C). However, no well-accepted basis currently exists by which to quantitatively define any consistent relationships concerning relative contributions or levels of such PM components to possible carcinogenic effects of PM pollution as a whole.

14.3.2.2 Morbidity

14.3.2.2.1 Respiratory effects in adults. Several extensive studies on associations between air pollution and chronic respiratory disease have been conducted on European populations, but few provide more than qualitative information on possible SO_2 or PM effects, as summarized in Appendices A and B.

In one of the few English studies possibly yielding useful quantitative data, Lambert and Reid (1970) surveyed nearly 10,000 British postal workers (age 35 to 59) for respiratory symptoms indicated by response to a self-administered MRC questionnaire. Concurrent air pollution data during 1965 were used to determine associations with symptoms where possible. However, the areas from which such data were available included only about 30 percent of the study group. Consequently, an index of pollution developed by Douglas and Waller in 1952, from domestic coal consumption, was used as well. The areas covered by the index included 88 percent of the study group. The results summarized in Table 14-5, adjusted for age and smoking habits but not as well for socioeconomic status, appeared to show relationships between health effects and air pollution indices for both males and females. That is, a greater prevalence of cough and phlegm was found to occur in more polluted areas, where annual

mean BS concentrations exceeded 100 $\mu g/m^3$ and SO_2 150 $\mu g/m^3$ than in areas where annual BS or SO_2 concentrations were less than 100 $\mu g/m^3$ (based on concentrations for the 30 percent of study areas actually monitored). These investigators also developed data showing that smoking was an important factor in acquiring chronic bronchitis and that the combined effect of smoking and pollution exceeded the sum of the individual effects. However, failure to consider socioeconomic status might have affected the results, (Holland et al., 1979), although this is not very likely since the entire population consisted of a single occupational group (Higgins, 1974; WHO, 1979).

TABLE 14-5 SYMPTOM-PREVALENCE RATIOS (PERSISTENT COUGH AND PHLEGM) STANDARDISED FOR AGE AND SMOKING BY AIR-POLLUTION INDICES

Concentration (µg./c.m.)	Smoke		Sulphur dioxide		Douglas-Waller index	Males	Females
	Males	Females	Males	Females			
<100	97 (82)	93 (35)	87 (11)	103 (7)	Very low	88 (201)	95 (93)
100–	112 (90)	120 (45)	96 (59)	110 (31)	Low	91 (217)	94 (97)
150–	116 (97)	116 (47)	120 (118)	115 (53)	Moderate	117 (188)	97 (75)
200+	134 (50)	129 (23)	118 (122)	120 (56)	High	118 (109)	115 (81)

Figures in italic type show observed numbers of symptom-positive respondents. Smoke and sulphur dioxide concentrations are based on values at residential sites in March, 1965 (National Air Pollution Survey).

From: Lambert and Reed, 1970.

Impairment of pulmonary function is likely to be one of the effects of exposure to air pollution since the pulmonary system includes the tissues that receive the initial impact when toxic materials are inhaled. Acute and chronic changes in function may be significant biological responses to air pollution exposure. A number of studies have been conducted in an effort to relate pulmonary function changes to the presence of air pollutants in various European, Japanese, and American communities. However, very few provide more than qualitative evidence relating pulmonary function changes to elevations in SO_2 or PM (see Appendices A and B).

A series of studies, reported on from the early 1960s to the mid-1970s were conducted by Ferris, Anderson, and others. The initial study involved comparison of three areas within a pulp-mill town in northern New Hampshire. In the original prevalence study (Ferris and Anderson, 1962; Anderson et al., 1964), no association was found between questionnaire-determined symptoms and lung function tests in the three areas with differing pollution levels after standardizing for cigarette smoking. The authors discuss why residence is a limited indicator for exposure (Anderson et al., 1964). The study was extended to compare Berlin, New Hampshire, with the cleaner city of Chilliwack, British Columbia in Canada (Anderson and Ferris, 1965). Sulfation rates (lead candle method) and dustfall rates were higher in Berlin than in Chilliwack. The prevalence of chronic respiratory disease was greater in Berlin, but the authors concluded that this difference was due to the interaction between age and smoking habits within the respective populations. Higher levels of respiratory function in some cigarette-smoking groups in the cleaner area were observed, but this difference could be due to socioeconomic and ethnic differences as well as air pollution. Ethnic differences could also have been a confounding factor (Higgins, 1974).

The Berlin, New Hampshire, population was followed up in 1967 and again in 1973 (Ferris et al., 1971, 1976). During the period between 1961 and 1976, all measured indicators of air pollution fell. In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg SO_3/100 cm^2/day) while TSP values fell from 131 to 80 $\mu g/m^3$. Only limited data on SO_2 was available (the mean of a series of 8-hr. samples for selected weeks) (WHO, 1979). During the 1961 to 1967 period, standardized respiratory symptom rates decreased and there was an indication that lung function also improved. Between the period 1967 to 1973, age-sex standardized respiratory symptom rates and age-sex-height standardized pulmonary function levels were unchanged. Given that the same set of investigators, using the same standardized procedures, conducted the symptom surveys and pulmonary function tests over the entire course of these studies, it is unlikely that the observed improvements in Berlin were due to variations in measurement procedures, but rather appear to be likely associated with decreases in TSP levels from 180 to 131 $\mu g/m^3$. The relatively small changes observed, however, argue for caution in placing much weight on these findings as quantitative indicators of observed effect/no effect levels for TSP-induced health changes.

Becklake et al. (1979) used pulmonary spirometric and closing volume function tests (and symptom reporting) in three areas of Montreal, Canada and did not find significant differences in children or adults (other than in closing capacity) that were associated with TSP levels. In the three areas studied, ambient SO_2 was reported to be 15, 123, and 59, and annual mean high-volume TSP values were 84, 95, and 131 $\mu g/m^3$, respectively, for the low-, intermediate-, and high-pollution areas, but there was a large overlap between areas. In a later report (Aubry et al., 1979) discriminant analysis was utilized to control for smoking, after which differences in health variables were not significant. This study, however, cannot be taken as showing lack of effects at the listed SO_2 and TSP levels because the power of the study was too low to expect an effect to be seen with the small number of subjects studied.

14.3.2.3 Respiratory Effects in Children--Several British studies have reported quantitative relationships between respiratory disease incidence in children and elevations in sulfur dioxide and particulate matter (BS). In one of the best known and frequently cited investigations, Douglas and Waller (1966) studied a cohort of a national sample of children born in the United Kingdom during the first week in March 1946. They prospectively examined the occurrence of respiratory illness in the children in relation to the estimated intensity of air pollution in the area of their residence. The areas in which the children lived were assigned to one of four pollution groups on the basis of estimates derived from domestic coal consumption in 1951-52. An effort to validate the index later, on the basis of measured smoke (BS) and SO_2 measurements in 1962 and 1963, indicated that the categorization of study groups by estimated pollution level was reasonably good. At the time of the 1962-63 measurements, SO_2 varied from about 90 $\mu g/m^3$ (0.03 ppm) in representative low-pollution areas sampled to about 250 $\mu g/m^3$ (0.09 ppm) in representative high-pollution areas actually sampled, as shown in Table 14-6. Also, BS varied from about 67 $\mu g/m^3$ to 205 $\mu g/m^3$ in comparable areas. Information on respiratory illness and symptoms was obtained from the children

when they were 6, 7, and 11 and, if they had lived the first 11 years of their lives in the same area, similar information was gathered when they were 15, 20, and 25 years of age. No significant relationship was observed between upper respiratory tract infections and increasing air pollution levels, in contrast to a highly significant and clear dose/response relationship between increasing air pollution indices and lower respiratory tract infection prevalence rates seen in Table 14-6, as indexed by virtually all of the health measures used. It has been noted that: "Higher illness rates were noted in all higher pollution classes" (NRC/NAS, 1978); and "Socio-economic status was important in the study but a relationship... still existed within separate social classes" (WHO, 1979). These results appear to provide qualitative evidence linking the occurrence of lower respiratory tract infection in children under age 11 to long-term exposures to polluted air containing elevated levels of SO_2 and PM.

TABLE 14-6. FREQUENCY OF LOWER RESPIRATORY TRACT INFECTIONS OF CHILDREN IN BRITAIN BY POLLUTION LEVELS, %[a]

Lower respiratory tract infections		1962-1963 Mean annual pollution levels, $\mu g/m^3$			
		Very low	Low	Moderate	High
	Smoke:	67	132	190	205
	SO_2:	90	133	190	251
First attack in first 9 months		7.2	11.4	16.5	17.1
At least one attack in first two years		19.4	24.2	30.0	34.1
More than one attack in first two years:		4.3	7.9	11.2	12.9
Boys		5.7	8.1	10.9	16.2
Girls		2.9	7.7	12.1	9.7
Middle class		3.0	4.0	7.7	9.3
Manual working class		5.1	10.8	13.9	15.4
Admission to hospital in first five years:					
Lower respiratory infection		1.1	2.3	2.6	3.1
Bronchitis		0.0	0.9	1.0	1.4
Pneumonia		1.1	1.4	1.6	1.8

[a]From Douglas and Waller (1966).

It is impossible, however, (based on the above reported results) to estimate specific quantitative levels of SO_2 or PM that may be associated with the observed health effects in the study. Douglas and Waller (1966) suggested that these children probably were exposed to higher pollution concentrations in their early lives than suggested by the measurements made in 1962-63 because of the improvement that followed the 1956 United Kingdom Clean Air Act. Furthermore, attempting to retrospectively estimate past pollutant exposure levels from limited (1-2 yrs) data following known or suspected marked changes in study area pollutant

concentrations usually tends to invalidate or substantially decrease confidence in study findings, at least concerning quantitative air pollution/health effects relationships. Thus, fundamental deficiencies preclude the use of the aerometric data quantitatively, e.g., the lack of data for all study areas and apparent failure to have used site-specific calibrations for BS readings in all areas.

Further study of the Douglas and Waller population at 20 years of age indicated that in the then now young adults, cigarette smoking had the greatest effect on respiratory symptom prevalence, followed by a history of lower respiratory tract illness under 2 years of age. At this time of their lives, social class and air pollution had little effect. The standardized prevalence rate (percent), however, was higher among the group who had lived in high-pollution areas (11.51) than in those who had lived in the low-pollution area (10.20) but the difference was not significant. This study would appear to indicate that the effects of exposure to air pollutants in high concentrations during the first 11 years of life had disappeared by age 20, unless there was a history of lower respiratory illness before age 2. However, no specific information is provided in the report to indicate the concentration of pollutants to which the children were exposed after 1957 when they were 11 years old.

A final survey, when the study population was 25 years old, confirmed the observation made 5 years earlier. At this time, Kiernan et al. (1976) reported that smoking continued to have the greatest effect on respiratory symptoms and lower respiratory illness. The association with air pollution was again a positive one and stronger than had been observed 5 years earlier, but was not statistically significant.

An association between air pollution and lower respiratory tract illness in children was also observed by Lunn et al. (1967). These investigators studied respiratory illness in 5- and 6-year-old schoolchildren living in four areas of Sheffield, England. Air pollution concentrations showed a gradient in 1964 across four study areas for mean 24-hour smoke (BS) concentrations from 97 $\mu g/m^3$ to 301 $\mu g/m^3$ and the same gradient for annual mean 24-hour SO_2 concentrations from 123 $\mu g/m^3$ to 275 $\mu g/m^3$. The following year, the annual concentrations of smoke were about 20 percent lower and SO_2 about 10 percent higher, but the gradient was preserved for each pollutant. In high-pollution areas, individual 24-hour mean smoke concentrations exceeded 500 $\mu g/m^3$ 30 to 45 times in 1964 and 0 to 15 times in 1965 for the lowest and highest pollution areas, respectively. SO_2 exceeded 500 $\mu g/m^3$ 11 to 32 times in 1964 and 0 to 23 times in 1965 for the lowest and highest pollution areas, respectively. Information on respiratory symptoms and illness was obtained by questionnaires completed by the parents, by physical examination, and by tests of pulmonary function ($FEV_{0.75}$ and FVC). Socioeconomic factors (SES) were considered in the analyses, but home heating systems were not. Although certain differences in SES between areas were noted, the gradients between areas would exist even when the groups were divided into social class, number of children in house, and so on (1977). Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56 percent more frequent

in the higher pollution areas than in the low-pollution area ($p < 0.005$). Also, decrements in lung function as measured by spirometry tests were closely associated with the occurrence of respiratory disease symptoms.

The authors of the study (Lunn et al., 1967) highlighted the following points in discussing their results:

> "The respiratory measurement findings showed no association with area, social class, children in the house, and sharing of bedrooms, although Attercliffe, the area of highest pollution, showed reduced $F.E.V._{0.75}$ and F.V.C. ratios. On the other hand, very clear evidence of reduced $F.E.V._{0.75}$ ratios emerged where there was a past history of pneumonia and bronchitis, persistent or frequent cough, or colds going to the chest. It must be stressed that these findings relate to first year infant schoolchildren and that measurements were made during the summer term when pollution levels were low and acute respiratory infections few and far between. In other words, a pattern of respiratory disability had appeared at an early age and was sufficiently established to persist although the factors of pollution and infection were temporarily absent or at a low level."

In a second report, Lunn et al. (1970) gave results for 11-year-old children studied in 1963-64 that were similar to those provided earlier for the younger group. Upper and lower respiratory illness occurred more frequently in children exposed to annual average 24-hour mean smoke (BS) concentrations of 230 to 301 $\mu g/m^3$ and 24-hour mean SO_2 concentrations of 181-275 $\mu g/m^3$ than in children exposed to smoke (BS) at 97 $\mu g/m^3$ and SO_2 at 123 $\mu g/m^3$. This report also provided additional information obtained in 1968 on 68 percent of the children who were 5 and 6 years in 1963-64. By 1968, the concentrations of smoke (BS) were only about one-half of those measured in 1964, and SO_2 concentrations were about 10 to 15 percent below those measured in 1964. By 1968 the pollution gradient no longer existed, so the combined three higher pollution areas were compared with the single original low-pollution area. Lower respiratory illness prevalence measured as "colds going to chest" was 27.9 percent in the low-pollution area and 33.3 percent in the combined high-pollution areas, but the difference was not statistically significant ($p > 0.05$). (Ventilatory function results were similar.) Also, the 9-year-old children had less respiratory illness than the 11-year-old group seen previously. Since 11-year-old children generally have less respiratory illness than do 9-year-olds, this represented an anomaly that the authors suggested may have been the result of improved air quality. It should be noted that these Lunn et al. (1967, 1970) findings have been widely accepted (Rall, 1974; Higgins, 1974; Holland and Bennett et al., 1979; National Research Council, 1978a; National Research Council, 1978b; WHO, 1979) as being valid, and, on the basis of the results reported it appears that increased frequency of lower respiratory symptoms and decreased lung function in children clearly occur with long-term exposures to annual BS levels in the range of 230-301 $\mu g/m^3$ and SO_2 levels of 181-275 $\mu g/m^3$. Also, based on the 1968 follow-up study results, it appears to be warranted to conclude that no observed effect levels were demonstrated by the study for BS levels in the range of 48-169 $\mu g/m^3$ and SO_2 levels in the range of 94-253 $\mu g/m^3$.

Rudnick (1978), as part of a well-designed and methodologically-sound study, collected information by a self-administered questionnaire on respiratory symptoms and disease in 3805 children, 8 to 10 years old, living in three communities in Poland with differing air pollution concentrations. The questionnaire sought information on respiratory symptoms and symptoms of asthma during the previous 12 months. Mean pollutant concentrations in the higher pollution area for the years 1974 and 1975 were 108 to 148 $\mu g/m^3$ for SO_2 (OECD) and 150 to 227 $\mu g/m^3$ for smoke (OECD). The low pollution areas had SO_2 concentrations of 42 to 67 $\mu g/m^3$ and smoke concentrations of 53 to 82 $\mu g/m^3$. Most symptoms of respiratory illness in both boys and girls occurred more frequently in the high pollution area but the differences were, in general, nonsignificant. There was a higher prevalence of breathlessness, sinusitis and asthma attacks in boys living in the high pollution area but only "runny nose in the last 12 months" occurred more frequently in girls in the same area. There were no significant differences between the frequencies of nonchronic cough, attacks of breathlessness, shortness of breath, or multiple cases of pneumonia associated with the different pollution levels. These results, however, cannot be taken as indicative of no-effect levels at above SO_2 and smoke concentrations due to ambiguities concerning the measurement methods used, e.g., whether site-specific calibrations were employed in generating the mass estimates for smoke rather than the OECD standard curve, and given that at least some weak indications were reported for increased symptomatology in the high pollution areas.

In the United States, a retrospective survey conducted by Hammer (1976, 1977) regarding the frequency of lower respiratory illness in children was undertaken in 1971 in two southeastern cities, using similar questionnaire sampling as employed in certain other EPA "CHESS" program studies (Hammer and Miller et al., 1976; French and Lowrimore, 1975). Data were obtained by questionnaire from parents of about 10,000 children aged 1 to 12 years. The two communities represent intermediate and high particulate exposures (annual averages of 74-112 $\mu g/m^3$ and 133-169 $\mu g/m^3$ TSP, respectively, for 1960 to 1971), with low annual average SO_2 exposures (<25 $\mu g/m^3$ in both communities). The analysis of data indicated that in the high exposure community (Birmingham) there was significantly increased respiratory disease over that for the lower exposure community (Charlotte), based on statistically significant results obtained on 10 of 17 measures of respiratory morbidity. This included more pneumonia and croup among blacks and more lower respiratory disease, bronchitis and croup among whites in Birmingham than in Charlotte. There was also a consistent trend for the association of more illness and hospitalization with higher pollution to become stronger in older children. This suggests that the effect increased with extended exposure. The investigators concluded that differences in parental recall, questionnaire reliability, family size, crowding, or parental smoking habits were not likely explanations for the excess morbidity in the high-pollution areas, since these factors were not statistically significantly different between communities. The results, therefore, were taken to be indicative of associations between increased lower respiratory disease rates in children and exposure to moderately elevated particulate matter

levels in the presence of low SO_2 levels. Asthma rates clustered in families, were higher in male children and female parents, and were comparable to other studies. Significant increases of lower respiratory disease were also reported for asthmatic children in the high exposure community. The above aspects of the Hammer (1976, 1977) study appear to provide a basis for arguing that it demonstrates, at least qualtitatively, that significant respiratory effects in children are associated with elevated particulate matter air concentrations in the presence of very low levels of SO_2.

Certain other aspects of the study, however, argue for caution in fully accepting its reported findings and conclusions. The investigators assumed that cigarette-smoking for children under age 13 in the South was minimal, equally distributed, and did not affect their results. Also, although the response rates were excellent in both communities, they were significantly lower in Charlotte (88 percent) than in Birmingham (95 percent) and significantly lower for Blacks (84 percent) than for Whites (89 percent) within Charlotte. Such small differences in response rates in absolute terms may be unlikely to have affected the overall study results but the possibility cannot be completely discounted; nor can the possible confounding effects of smoking be ruled out completely. Nor were the questionnaire results checked for test-retest reliability to verify accuracy and consistency of parental recall of illnesses for their children or validated against doctor or hospital records. Furthermore, major reservations exist regarding the extent to which the reported air quality data are accurate and adequately representative of the respective study population exposures; most notably, exposures over much of the lifetimes of the older children (i.e., over 4 years of age) were estimated using monitoring data from a single site or at best a few sites that were not located directly in the residential areas being studied.*

In another American study, possible pulmonary function decrements were studied in Cincinnati schoolchildren in 1967-1968 by Shy et al. (1973). Children from schools in an industrial valley of Cincinnati were compared with children from schools in a non-industrial river valley on the east side of the metropolitan area. Two each upper-middle white, lower-middle white, and lower-middle black schools were selected from each valley. Air monitoring stations within three blocks of the schools showed that 7-month average TSP values were from 18 to 32 $\mu g/m^3$ higher in the industrial valley than in the non-industrial valley, but little or no differences existed in corresponding levels for SO_2. Arithmetic averages over the 7 months of the study ranged for TSP from 96 to 114 $\mu g/m^3$ in the more polluted industrial area and from 77 to 82 $\mu g/m^3$ in the cleaner areas. The 7-month average for SO_2 ranged from 39 to 51 $\mu g/m^3$ in the polluted areas and from 40 to 45 $\mu g/m^3$ in the clean areas. Ventilatory function was measured as the forced expiratory volume at .75 second ($FEV_{.75}$) on a Stead-Wells

*Note that the health effects results described here for the Hammer (1976; 1977) dissertation study were based on analysis of unvalidated computerized data tapes. Recent realysis of the data based on validated data tapes, however, has produced results very close to those reported in the Hammer dissertation and the results are in the process of being prepared for peer review and publication.

water-filled spirometer once weekly on each child during each of the study months. The better of two satisfactory forced expiratory maneuvers obtained on each test day was used for all computations. Height, sex, and race were used to make adjusted $FEV_{.75}$ comparisons. The study was confined to 394 second graders who participated in weekly measurements during November 1967, February 1968, and May 1968. These students represented 93 percent of second graders in the classrooms selected. Mothers were interviewed to obtain socioeconomic data. The educational attainment of fathers was similar for corresponding schools in the industrial and non-industrial valleys.

The Shy et al. (1975) data showed that average height adjusted $FEV_{.75}$ in "clean" schools exceeded that in "polluted" schools in all 3 months for lower-middle class whites and in 2 of 3 months for upper-middle whites. Blacks consistently had lower $FEV_{.75}$ values, and a pollution effect was seen among blacks during only one of three study periods. The absolute differences in average $FEV_{.75}$ were roughly 40-120 ml (<10 percent) in most cases. A multivariate analysis of variance was applied which allowed for testing of community effects adjusted for a possible month effect and for the covariates height, sex, race, and social class. The dependent variable for each child was his vector of three monthly average $FEV_{.75}$ values. However, the authors reported that no association existed between acute exposures to 24-hr TSP levels and pulmonary function test results obtained on the same or following days, making it difficult to ascribe the relatively weak observed differences in pulmonary function between the study areas to the very small differences in annual average TSP levels in the respective study areas.

In summary, one set of the above studies, by Lunn et al. (1967, 1970) in Sheffield, England, provides clear evidence for significant pulmonary function decrements and increased respiratory disease illnesses in children being associated with chronic exposure to SO_2 and PM in the ambient air. Two American studies (Hammer, 1976, 1977; Shy et al., 1975) also provide suggestive but controversial (mainly qualitative) evidence indicative of possible increases in lower respiratory tract diseases and pulmonary function decrements in children being associated with elevations in ambient air PM in the absence of marked elevations in SO_2 levels.

14.5 CHAPTER SUMMARY AND CONCLUSIONS

Some of the epidemiological studies reviewed above appear to provide meaningful quantitative information on health effects associated with ambient air exposures to PM and SO_2. Others, however, do not meet as fully the various objectives discussed earlier under Section 14.1.2 or ambiguity exists regarding clear interpretation of their reported results. Only some of the study results can, therefore, be accepted with a relatively high degree of certainty or confidence, whereas others may be seen as providing, at best, only suggestive evidence for the reported associations between air pollutant parameters and health effects. The main focus of the present section will be on summarizing results and conclusions derived from selected key studies having a relatively high degree of certainty associated with their findings.

In general, the epidemiological studies reviewed above provide strong evidence for severe health effects, such as mortality and respiratory diesease, being induced in certain populations at special risk by marked elevations at atmospheric levels of sulfur dioxide and particulate matter. Those populations at special risk for such effects appear to include, mainly, the elderly and adults with chronic pre-existing cardiac or respiratory diseases (e.g., bronchitics). Increased lower respiratory tract illnesses and more transient (likely indicator) effects, e.g., decrements in pulmonary function, also appear to be associated for children with lower chronic exposures to sulfur dioxide and PM. Also, some qualitative epidemiological evidence suggests that asthmatics may be a susceptible population at special risk for experiencing pulmonary function decrements in response to elevations in SO_2 and PM.

14.5.1 Health Effects Associated with Acute Exposures to Sulfur Oxides and Particulate Matter

As noted earlier in the present chapter, it is widely accepted that increases in mortality occur when either SO_2 or particulate matter levels increase beyond 24-hr levels of 1000 $\mu g/m^3$. Such increased mortality, mainly in the elderly or chronically ill, may logically also be most directly attributed to very high short-term peak levels in the pollutants, which at times increased to several thousand $\mu g/m^3$ during certain major pollution episodes.

Much more difficult to establish are to what extent significant increases in mortality and morbidity are associated with exposures to SO_2 and/or particulate matter levels below 1000 $\mu g/m^3$. Concisely summarized in Table 14-7 are several key studies that appear to demonstrate with a reasonably high degree of certainty, mortality and morbidity effects associated with acute exposures (24 hrs) to these pollutants. The first two studies cited, by Martin and Bradley (1960) and Martin (1964), deal with a relatively small body of data from London in the late 1950s. No clear "threshhold" levels were revealed by their analyses regarding SO_2 or BS levels at which significantly increased mortality began to occur. Based on their findings, there appears to be little question that mortality in the elderly and chronically ill was elevated in association with exposure to ambient air containing simultaneous SO_2 and BS levels somewhere in the range of 500-1000 $\mu g/m^3$. Greatest certainty applies for levels in excess of 700-750 $\mu g/m^3$. Much less certainty is attached to lower estimates possibly derived from a reanalysis of the same data set by Ware et al. (1981), which applies to mortality data from very brief periods during the two London winters. It seems more likely that levels well in excess of 500 $\mu g/m^3$ BS and SO_2 are typically necessary in order to induce mortality among highly susceptible elderly or chronically ill individuals.

Only very limited data exist by which to attempt to delineate any specific physical and chemical properties of PM associated with the observed increases in mortality. Based on information noted earlier (Section 14.2), it would seem that marked increases in small particles to levels above 500-1000 $\mu g/m^3$ appear to be most clearly associated with increased mortality, based on the BS aerometric measurements reported, although contributions from larger coarse-mode particles cannot be completely ruled out. Nor is it possible to state with certainty specific PM chemical species associated with the increases in mortality. We do know

TABLE 14-7. SUMMARY OF QUANTITATIVE CONCLUSIONS FROM EPIDEMIOLOGICAL STUDIES RELATING HEALTH EFFECTS OF ACUTE EXPOSURE TO SO_2 AND PARTICULATE MATTER TO AMBIENT AIR LEVELS

Type of study	Effects studied	24-hr average pollutant level ($\mu g/m^3$) particulate matter CoH	particulate matter BS	particulate matter TSP	SO_2	Reference
Mortality	Likely increases in daily total mortality above a 15-day moving average during winter 1958-59 among persons with existing respiratory or cardiac disease in London.	-	≥1000	-	≥1000	Martin and Bradley (1960)
	Slight indication of likely increases in daily total mortality above a 15-day moving average during winters of 1958-59 and 1959-60 among persons with existing respiratory or cardiac disease in London.	-	750-1000	-	710-1000	Martin (1964)
Morbidity	Likely worsening of health status among a group of chronic bronchitis patients	-	250-500	-	500-600	Lawther et al. (1958, 1970)
	No apparent response or worsening of health status among a group of chronic bronchitis patients	-	<250	-	<500	Lawther et al. (1970, 1975)

that large amounts of pollutants (e.g., elemental carbon, tarry organic matter, etc.) from incomplete combustion of coal were present in the air, but no single component or combinations of particulate pollutants can clearly be implicated. Nor can the relative contributions of SO_2 or particulate matter be clearly separated based on these study results or possible interactive effects with increases in humidity (fog) completely ruled out; but temperature changes do not appear to be important in explaining the mortality effects observed in Martin's studies.

A study by Glasser and Greenberg (1971), not listed in the table, similarly appears to suggest, with less confidence, that slight mortality increases were associated with increases in SO_2 above 786-1048 $\mu g/m^3$ and in CoHs levels of 5.0-7.0. These latter levels likely correspond to concentrations in excess of 570-720 $\mu g/m^3$ BS equivalent units based on calibration studies by Ingram alluded to above. Again specific particulate chemical species cannot be clearly implicated nor the relative contributions of SO_2 and particulate matter separated. It should be noted that, whatever, the causal agents, only very small increases in mortality may have been detected at the above pollutant levels in New York City.

Similar analysis of Lawther morbidity studies listed in Table 14-7 suggests that acute exposure to elevated 24 hr PM levels in the range of 250-500 $\mu g/m^3$ (BS) in association with 24-hr SO_2 levels of 500-600 $\mu g/m^3$ were likely associated with the induction of respiratory disease symptoms in chronically ill London bronchitis patients. Again, little can be said, however, in terms of specifying physical or chemical properties of PM associated with the observed effects beyond the comments noted above in relation to Martin's studies on mortality.

In regard to chronic exposure effects of SO_2 and particulate matter, the best pertinent epidemiological health studies are summarized in Table 14-8. The Lambert and Reid (1970) study suggests that respiratory disease symptoms (cough and phlegm) are associated with long-term (annual-average) exposures of adults to PM levels in the range of 100-200 $\mu g/m^3$ (BS) or above in association with SO_2 levels in the range of 150-200 $\mu g/m^3$ or above. The studies by Ferris et al. (1973, 1976) suggest that lung function decrements may occur in adults at TSP levels in excess of 180 $\mu g/m^3$ in the presence of relatively low estimated SO_2 level, whereas no effects were observed by the same investigators at TSP levels below 130 g/m^3 or by other investigators (Holland and Stone, 1965; Deane et al., 1965; Comstock et al., 1973) at TSP levels in the range of 70-163 $\mu g/m^3$, based on surveys of chest illness and symptoms prevalence. Other studies listed in Table 14-8 suggest that significant respiratory effects occur in children in association with long-term (annual average) PM levels in the range of 230-301 $\mu g/m^3$ (BS) in association with SO_2 levels of 181-275 $\mu g/m^3$. No effects were seen for children, however, at PM levels in the range of 48-169 $\mu g/m^3$ (BS) or at SO_2 levels of 94-253 $\mu g/m^3$. One study, by Hammer suggested possible respiratory effects in children at an annual average TSP level of 135-169 $\mu g/m^3$in the presence of very low SO_2 levels, but controversy and questions regarding the conduct of the study, data analysis, and aerometric measurements cloud its interpretation.

TABLE 14-8. SUMMARY OF QUANTITATIVE CONCLUSIONS FROM EPIDEMIOLOGICAL STUDIES RELATING HEALTH EFFECTS OF CHRONIC EXPOSURE TO SO_2 AND PARTICULATE MATTER TO AMBIENT AIR LEVELS

Type of study	Effects studied	Annual average pollutant levels ($\mu g/m^3$) particulate matter CoH	particulate matter BS	particulate matter TSP	SO_2	Reference
Cross-sectional (4 areas)	Greater prevalence of cough and phlegm in areas of elevated BS and SO_2 pollution, observed in survey of 10,000 British postal workers.	-	100-200+	-	150-200+	Lambert and Reid (1970)
Cross-sectional (4 areas)	Likely increased frequency of lower respiratory symptoms and decreased lung function in children	-	230-301	-	181-275	Lunn et al. (1967)
Cross-sectional (4 areas)	No observed effect on respiratory symptoms and lung function in children	-	48-169	-	94-253	Lunn et al. (1970)
Longitudinal and cross-sectional	Apparent improvement in lung function of adults in association with decreased PM pollution in Berlin, N.H.	-	-	180	-	Ferris et al. (1973, 1976)
Longitudinal and cross-sectional	Apparent lack of effects and symptoms, and no apparent decrease in lung function in adults	-	-	80-131	-	Ferris et al. (1973, 1976)
Cross-sectional (5 cities)	No apparent evidence of increased symptom prevalence or chest illness among telephone plant workers	-	-	70-163	-	Holland and Stone (1965) Deane et al. (1965) Comstock et al. (1973)

Again, no specific particulate matter chemical species can clearly be implicated as causal agents associated with the effects observed in those studies listed in Table 14-8. Nor can potential contributions of relatively large inhalable coarse mode particles be ruled out based on these study results; and, it should be remembered, that various occupational studies listed in Appendix C at least qualitatively suggest that such sized particles of many different types of chemical composition can be associated with significant pulmonary decrements, respiratory tract pathology, and morphological damage.

It should also be noted that certain studies not listed in Tables 14-7 and 14-8 but discussed in Sections 14.3 and 14.4, or Appendices A and B, suggest that respiratory effects (usually pulmonary function decreases) may occur in association with lower annual average exposure levels that those seen in Tables 14-7 and 14-8. Particular features of most of those studies or ambiguities about their results, however, preclude acceptance of their findings with much confidence at this time.

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Winkelstein, W., Jr., and S. Kantor. Respiratory symptoms and air pollution in an urban population of northeastern United States. Arch. Environ. Health 18:760, 1969.

Winkelstein, W., S. Kantor, E. Davis, C. Maneri, and W. Mosher. The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in men. I. Suspended particulates. Arch. Environ. Health 14:162-170, 1967.

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Yashizo, T. Air pollution and chronic bronchitis. Osaka Univ. Med. J. 20:10, 1968.

Yoshida, R., K. Motomiya, H. Saito, and S. Funabashi. Clinical and epidemiological studies on childhood asthma in air polluted areas in Japan. In: Clinical Implications of Air Pollution Research. Acton, Massachusetts, Publishing Sciences Group, Inc., 1976.

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Zeidberg, L. D., R. A. Prindle, and E. Landau. The Nashville air pollution study. I. Sulfur dioxide and bronchial asthma. A preliminary report. Am. Rev. Res. Dis. 84:489, 1961.

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APPENDIX A

ANNOTATED COMMENTS ON COMMUNITY HEALTH EPIDEMIOLOGICAL STUDIES NOT DISCUSSED IN DETAIL IN MAIN TEXT OF CHAPTER 14.

APPENDIX A

Numerous community health epidemiological studies have been cited during the past 10 to 20 years as providing quantitative evidence for particular atmospheric levels of sulfur oxides and/or particulate matter being associated with mortality or morbidity effects. In the course of the present assessment, close examination of such studies and published evaluations or reinterpretations of their findings have led to the conclusion that methodological considerations or published results reported for many of them substantially limit or preclude their usefulness in helping to define quantitative air pollution/health effects relationships especially at levels below 1000 $\mu g/m^3$. Based on this, many were excluded from detailed discussion or consideration in the main text of Chapter 14 or mentioned only briefly in support of certain points made in the chapter. Provided below are annotated comments addressing limitations of various studies for helping to quantify the health effects of sulfur oxides and particulate matter and exposure levels at which such effects occur. Many of the studies listed, however, do provide qualitative evidence helpful in characterizing sulfur oxides and particulate matter health effects and are therefore cited as such either in the main text of Chapter 14 or in tables summarizing qualitative studies in Appendix B.

A. STUDIES OF MORTALITY EFFECTS OF ACUTE EXPOSURES

1. British, European, and Japanese Studies

The following studies all concern early (1950s-60s) severe air pollution episodes in England, when atmospheric concentrations of particulate matter (BS) and sulfur dioxide markedly exceeded 1000 $\mu g/m^3$:

Burgess, S. E., and C. W. Shaddick. Bronchitis and air pollution. R. Soc. Health J. 79:10-24, 1959.

Clifton, M., D. Kerridge, J. Pemberton, W. Moulds, and J. K. Donoghue. Morbidity and mortality from bronchitis in Sheffield in four periods of severe pollution. In: Proc. 1959 Int. Clean Air Conf. London, National Society for Clean Air. 1960. p. 189.

Gore, A. T., and C. W. Shaddick. Atmospheric pollution and mortality in the County of London. Br. J. Prev. Soc. Med. 12:104-113, 1958.

Logan, W. Mortality in the London fog incident. Lancet 1:336-338, 1953.

Scott, J. A. Fog and deaths in London, December 1952. Pub. Health Rep. 68:474-479, 1953.

Scott, J. A. The London fog of December, 1962. Med. Off. 109: 250-252, 1963.

Ministry of Health. Mortality and Morbidity During the London Fog of December 1952. London, Her Majesty's Stationery Office. 1954.

Wilkins, E. Air pollution and the London Fog of December, 1952. J. Roy. Sanit. Inst. 64:1-21, 1954a.

Wilkins, E. Air pollution aspects of the London Fog of December, 1952. Roy. Meterol. Soc. J. 80:267-271, 1954b.

These studies are mainly useful in being indicative of mortality effects occurring at BS/SO_2 levels well in excess of 1000 $\mu g/m^3$ and are widely accepted as such, regardless of particular methodological flaws or limitations associated with each.

Biersteker (1966) also reported the following study of a high pollution episode in Rotterdam in December 1962:

Biersteker, K. Polluted Air Causes, Epidemiological Significance, and Prevention of Atmospheric Pollution. Assen, Netherlands, Van Gorcum and Co., pp. 21-23 (in Dutch), 1966.

During the episode, 24-hr mean concentrations were recorded for particulate matter and sulfur dioxide at about 500 $\mu g/m^3$ and 1000 $\mu g/m^3$, respectively (OECD smoke /sulfur dioxide methods), together with increased hospital admissions for the elderly (over 50 years old) with cardiovascular diseases and weak indications of increased mortality. However, these results were observed only once in Rotterdam and could have been due to other causes and do not provide evidence of a strongly convincing statistical relationship between observed mortality and hospital admissions and the air pollution levels reported. Nor is it possible to determine precisely what the reported smoke levels (in $\mu g/m^3$) mean in terms of actual particulate matter mass present in Rotterdam at the time.

A Japanese study, on relationships between mortality and air pollution in Osaka was reported by Watanabe:

Watanabe, H. Health effects of air pollution in Osaka City. J. Osaka Life Hyg. Assoc. 10:147-157(in Japanese), 1966.

Increases in mortality (about 20%) appeared to occur when daily concentrations of particulate matter (as measured by a light scattering method) exceeded 1000 $\mu g/m^3$ (4-day average) in association with SO_2 (probably sulfation method) levels of 250 $\mu g/m^3$. Low temperatures present may have contributed to the effects and it is not possible to assess with confidence the statistical relationship between observed mortality and the reported pollutant levels which were apparently based on data from a single monitoring station. Nor is it possible to interpret the exact meaning of the reported suspended particulate matter measurement results as to how they might relate to fine-particulate mode, inhalable coarse-mode, or total suspended particulates levels.

2. American Studies

The following series of studies, employing mainly regression analysis techniques attempted to define relationships between daily mortality and

variations in particulate matter and SO_2 in New York City during the periods of the 1950s, 1960s, and 1970s:

Greenburg, L., M. B. Jacobs, B. M. Droletti, F. Field, and M. M. Braverman. Report of an air pollution incident in New York City, November, 1953. Public Health Rep. 77:7-16, 1962.

Glasser, M., L. Greenburg, and F. Field. Mortality and Morbidity During a Period of High Levels of Air Pollution, New York, November 23-25, 1966. Arch. Environ. Health 15:684-694, 1967.

Glasser, M., and L. Greenburg. Air pollution and mortality and weather, New York city, 1960-64, Arch. Environ. Health 22:334-343, 1971.

Schimmel, N., and L. Greenburg. A study of the relationship of pollution to mortality, New York City, 1963-1968. J. Air Pollut. Control Assoc. 22:607-616, 1972.

Schimmel, H., and T. J. Murawski. The relation of air pollution to mortality. J. Occup. Med. 18:316-333, 1976.

Among the disadvantages of these studies is the fact that only data from a single air pollution station in Manhattan was used in attempting to correlate changes in air pollution with mortality in the entire city, raising questions regarding how representative those aerometric measurements are of exposures for the entire study population. Goldstein and Landowitz (1977a,b) found that most correlations between pollutant levels recorded at any two New York City monitoring stations were ≤ 0.40 and concluded that use of aerometric data from any single station generally did not adequately represent pollutant levels for the entire city. A possible exception to this may occur during severe air pollutant episodes when markedly increased pollutant levels at all stations may tend to approach a common ceiling elevation. Lastly, many criticisms have been advanced regarding specifics of the statistical approach employed (e.g., some correlations likely to be significant by chance alone from among a very large number run) and some of the same and other investigators have since reinterpreted these studies as generally not providing evidence of any association between mortality and SO_2 levels and only very weak associations with particulate matter levels. Generally speaking, then, little evidence can be derived from

these studies for excess mortality having been associated with either elevated SO_2 or particulate matter levels in New York City, with the possible exception of during severe pollution episodes.

Several other American studies of New York or other United States cities utilized primarily multiple regression analysis techniques that mainly allow only for qualitative statements to be made regarding possible associations between daily mortality and SO_2 or particulate matter levels. These studies include:

Buechley, R. W., W. B. Riggan, W. Hasselblad, and J. B. Van Bruggen. SO_2 levels and perturbations in mortality. A study in New York-New Jersey metropolis. Arch. Environ. Health 27:134-137, 1973.

Buechley, R. W. SO_2 Levels, 1967-1972 and Perturbations in Mortality. Contract No. ES-5-2101. Report available from National Institute of Environmental Health Sciences, Research Triangle Park, N.C., 1977.

Hodgson, A., Jr. Short-term effects of air pollution on mortality in New York City. Environ. Sci. Technol. 4:589-597, 1970.

Lebowitz, M., P. Bendheim, G. Cristea, D. Markovitz, J. Misiaszek, M. Staniec, and D. Van Wyck. The effect of air pollution and weather on lung function in exercising children and adolescents. Am. Rev. Respir. Dis. 109:262-273, 1974.

One other American study reported on possible mortality effects associated with a 1975 episode in Pittsburgh, Pennsylvania:

Riggan, W. B., J. B. Van Bruggen, L. E. Truppi, and M. B. Hertz. Mortality models: A policy tool. EPA-600/9-76-016, 196-198, 1976.

This report concerned an analysis of excess mortality associated with the same air pollution episode studied by Stebbings et al. (1976). Only 20 excess deaths were noted and these were associated with extremely high peak 1-hour air pollution concentrations over 1000 $\mu g/m^3$. Also, this report has not undergone peer review.

B. MORBIDITY EFFECTS AND ACUTE EXPOSURES

1. British, European, and Japanese Studies

Comments on certain individual acute exposure morbidity studies are as follows for each.

FOR Carne, S. Air pollution study. Proc. R. Soc. Med. 57:30-34, 1964.

This study of general practicioners records of illness during the winter of 1962-63 in London provides evidence of morbidity effects among elderly patients during the December, 1962, pollution episode when levels of smoke and SO_2 markedly exceed 1000 g/m^3. However, the health effects results cannot be reliably linked quantitatively to specific pollutant levels.

FOR: Angel, J. H., C. M. Fletcher, I. D. Hill, and C. M. Finker. Respiratory illness in factory and office workers. Br. J. Dis. Chest 59:66-80, 1965.

This study of acute respiratory illness attack and prevalence rates in a working population of London correlated such rates with weekly peaks of pollution measured at several nearby sites. No clear conclusions were stated by the authors regarding pollutant levels associated with notable illness increases. Based on the reported data only some apparent increase seems to occur, generally, when smoke and SO_2 levels exceed 1000 $\mu g/m^3$.

FOR: Gervois, M., G. Dubois, S. Gervois, J. M. Queta, A. Muller, and C. Vorsin. Atmospheric pollution and acute respiratory disease. Denoin and Quavrechoin epidemiological study. Rev. Epidemiol. Sante Publique 25:195-207, 1977.

This article, in French, gives little methodology information and especially about the quality of aerometry or health measurements. A positive association was reported between pollution concentration and acute respiratory disease within one town (Quavrechoin) but not another (Denoin), although there were no clear differences in pollutant levels between the towns. Use of this study is limited because of uncertainty about its validity and also because insufficient information was given to allow conclusions to be drawn about quantitative relationships.

FOR: Van der Lende, R. Epidemiology of Chronic Non-Specific Lung Disease (Chronic Bronchitis). Assen, Royal Van Gorcum, and Springfield, Ill., Charles C. Thomas. 1969.

Van der Lende, R., J. P. M. de Kroon, G. J. Tammeling, B. F. Visser, K. de Vries, J. Wever-Hess, and N. G. M. Orie. Prevalence of chronic non-specific lung disease in a non-polluted and an air polluted area of the Netherlands. In: Ecology of Chronic Non-Specific Respiratory Diseases. Z. Brzezinski, J. Kopczynski, and F. Sawicki, ed., Warsaw, Panstwowy Zaklad Wydownictw Lekarskick. 1972. p. 27-33.

Van der Lende, R., G. J. Temmeling, B. F. Visser, K. de Vries, J. Wever-Hess, and N. G. M. Orie. Epidemiological investigations in the Netherlands into the influence of smoking and atmospheric pollution on respiratory symptoms and lung function disturbances. Pneumonologie 149:119-126, 1973.

Van der Lende, R., C. Huygen, E. J. Jansen-Koster, S. Knijpstra, R. Peset, B. F. Visser, E. H. E. Wolfs, and N. G. M. Orie. A temporary decrease in ventilatory function of an urban population during an acute increase in air pollution. Bull. Physiopathol. Respir. 11:31-43, 1975.

Studies in the Netherlands reported by van der Lende and colleagues (van der Lende et al., 1969, 1972, 1973, 1975) compared lung function in a large population group in 1969 and again in 1972. In a more polluted area, age-, health-, and smoking-adjusted $FEV_{1.0}$ values in men increased from the first to the second survey rather than decreasing with age as expected. This was associated with a concurrent decrease in air pollution concentrations. The investigators considered other possible causes of the improved pulmonary function but concluded that the most plausible was the effect of reduced air pollution, but little hard evidence was advanced to support this hypothesis. In fact, the changes over time in PFT test results may be likely due to different experimenters performing the tests from the earlier to later years.

2. American and Canadian Studies

Comments on several American (United States) and one Canadian acute exposure morbidity studies are as follows for each.

FOR: Cassell, E. J., M. D. Lebowitz, I. M. Mountain, H. T. Lee, D. J. Thompson, D. W. Wolter, and J. R. McCarroll. Air Pollution, Weather, and Illness in a New York Population. Arch. Environ. Health 18:523-530, 1969.

McCarroll, J. R., E. J. Cassell, W. T. Ingram, and D. Wolter. I. Health and the Urban Environment. Am. J. Public Health 56:266-275, 1966.

Mountain, I. M., E. J. Cassell, D. W. Wolter, and J. D. Mountain. Health and the Urban Environment. VII. Air Pollution and Disease Symptoms in a Normal Population. Arch. Environ. Health 17:343-352, 1968.

Thompson, D. J., M. D. Lebowitz, E. J. Cassell, D. Wolter, and J. McCarroll. Health and the Urban Environment. VIII. Air Pollution, Weather, and the Common Cold. Am. J. Public Health 60(4):731-739, 1970.

These reports from the Cornell study gave results for correlations of CoHs and SO_2 levels with numerous health endpoint measurements. Many of the effects measured, such as tearing, are of modest health significance. Also, numerous analyses are reported, predominantly multiple regression analysis; and coefficients frequently change sign and magnitude as variables are added and deleted, making it difficult or impossible to quantify health effects/air pollution relationships from these qualitative studies.

FOR: Greenburg, L., F. F. Field, J. I. Reed, and C. L. Erhardt. Air pollution and morbidity in New York City. J. Am. Med. Assoc. 182:161-±64, 1962.

Greenburg, L., C. Erhardt, F. Field, J. I. Reid, and N. S. Seriff. Intermittent air pollution episode in New York City, 1962. Public Health Rep. 78:1061-1064, 1963.

Greenburg, L., F. Field, J. I. Reed, and C. L. Erhardt. Asthma and temperature change. An epidemiological study of emergency clinic visits for asthma in three large New York Hospitals. Arch. Environ. Health 8:642, 1964.

Peak pollution levels during these studies were often much higher than 1000 $\mu g/m^3$, especially when 1-hour values are considered. Also, methods of analyses preclude clear quantitative statements on pollutant/health effect relationships.

FOR: Carnow, B. W., M. H. Lepper, R. B. Shekelle, and J. Stamler. Chicago air pollution study. Arch. Environ. Health 18:768-776, 1969.

No particulate matter concentrations were given, and individual exposures to SO_2 were estimated from air pollution monitoring network data in combination

with assumptions about individual activity patterns. Positive associations between SO_2 levels and health effects were restricted to seriously ill elderly patients over age 55 with grades 3 and 4 bronchitis. Subject attrition was high during the course of the study.

FOR: Levy, D., M. Gent, and M. T. Newhouse. Relationship between acute respiratory illness and air pollution levels in an industrial city. Am. Rev. Respir. Dis. 116:167-175, 1977.

This Canadian study related hospital admissions records for acute respiratory conditions to changes in average weekly levels of an air pollution index (combining CoH and SO_2 measurements) and found significant correlations even after effects of temperature were taken into account. However, no clear quantitative associations between specific CoH or SO_2 levels and increased acute respiratory conditions could be deduced from the reported results.

FOR: Stebbings, J. H., D. C. Fogleman, K. E. McClain, and M. C. Townsend. Effect of the Pittsburgh air pollution episode upon pulmonary function in schoolchildren. J. Air Pollut. Control Assoc. 26:547-553, 1976.

Stebbings, J. H., Jr., and D. G. Fogleman. Identifying a Susceptible Subgroup: Effects of the Pittsburgh Air Pollution Episode Upon Schoolchildren. Am. J. Epidemiol. 110:27-40, 1979.

Measurements of air pollution levels during the episode investigated in these studies were made after highest levels of pollution had already past, as were the health endpoints measured (mainly pulmonary function, e.g. FEV, tests). Method of subject selection and lack of clear association of health results to specific particulate matter (TSP) or SO_2 levels precludes quantitative conclusions regarding health effects/air pollution relationships.

NOTE: Several published reports on EPA CHESS Program studies contain information potentially bearing on acute exposure morbidity effects of sulfur oxides and particulate matter. Most CHESS studies, however, provide information mainly on chronic exposure morbidity effects and are discussed below under Section D.

C. MORTALITY AND CHRONIC EXPOSURES

1. British, European, and Japanese Studies

Comments on several British studies earlier interpreted as ueilding quantitative information on mortality relationships to particulate matter (BS) and SO_2 exposures are as follows for each.

FOR: Buck, S. F., and A. D. Brown. Mortality from Lung Cancer and Bronchitis in Relation to Smoke and Sulfur Dioxide Concentration, Population Density, and Social Index. Research Paper No. 7. London, Tobacco Research Council. 1964.

This study attempted to relate standardized mortality ratios from 214 areas in the United Kingdom (1955-59) to daily smoke (BS) and SO_2 levels for March, 1962. Several factors make it difficult to interpret or accept this study's results, including: (1) pollution levels for 1962 do not provide an adequate basis for quantitatively estimating what were probably much higher BS and SO_2 levels possibly contributing to mortality occurring in 1955-59; (2) it is not clear what the reported 1962 BS data in $\mu g/m^3$ mean in terms of actual mass indexed from the various U.K. areas, likely including many for which no site-specific calibrations were carriod out; (3) the 1962 BS levels calculated were likely affected to an unknown extent by the computer error reported by Warren Spring Laboratory for British National Survey BS data during 1961-64; and (4) potential effects of differences in occupational exposure were not taken into account.

FOR: Stocks, P. Air Pollution and Cancer Mortality in Liverpool Hospital Region and North Walls. Inter. J. Air Pollut. 1:1-13, 1958.

Stocks, P. Cancer and bronchitis mortality in relation to atmospheric deposit and smoke. Br. Med. J. 1:74, 1959.

Stocks, P. On the relations between atmospheric pollution in urban and rural localities and mortality from cancer, bronchitis and pneumonia with particular reference to 3:4-benzopyrene, beryllium, molybdenum, vanadium, and arsenic. Br. J. Cancer 14:397-418, 1960.

These studies on associations in the 1950s between standardized mortality ratios for bronchitis, lung cancer, and other cancers and particulate matter (BS) levels in 101 urban and rural areas of Wales and England provide no way to clearly determine quantitative relationships between BS and mortality effects. Interpretation of the BS aerometry data alone is clouded by ambiguities regarding the actual mass of BS (in $\mu g/m^3$) indexed by measurements reported for various areas of England and Wales (i.e. were site-specific calibrations used to make the $\mu g/m^3$ estimates?). Also, differences in smoking history were not assessed as possibly accounting for reported urban-rural differences.

FOR: Wicken, A. J., and S. F. Buck. Report on a study of environmental factors associated with lung cancer and bronchitis deaths in areas of northeast England. Research Paper No. 8. London, Tobacco Research Council. 1964.

In this study of cancer and bronchitis in 12 areas of England, no actual measurements of particulate matter (BS) or SO_2 were available except for 2 areas (North and South Eston) during 1963-1964 and an effort was made to relate these levels to mortality during 1952-1962. Similar objections to retrospective linking of later aerometry data to earlier mortality information apply here as were stated above for the Buck and Brown (1964) study. Also mortality differences for the two Easton areas may have been due as easily to differences in study population age levels and smoking patterns as to any air pollution gradient.

FOR: Lave, L. B., and B. P. Seskin. Air pollution and human health. The quantitative effect, with an estimate of the dollar benefit of pollution abatement is considered. Science 169:723-733, 1970.

Lave and Seskin (1970) attempted to demonstrate, by mathematical analyses mainly involving regression analyses, relationships between BS measurements in the United Kingdom and bronchitis mortality data once the effects of other factors such as smoking and socioeconomic status (SES) are removed. This Lave and Seskin (1970) study has been extensively critiqued in detail by others

(Holland et al., 1979; Ware et al., 1980), who have noted, for example, difficulties in justifying inclusion of smoking, SES, and air pollution levels in the Lave and Seskin analyses as if they were completely independent variables and the failure to make some direct allowance for smoking habits in the actual analyses. Nor is there any basis to determine specific quantitative levels of pollutants associated with mortality from the reported results.

2. American and Canadian Studies

Among published American reports on mortality associations with chronic particulate matter and sulfur oxides exposures are the following regarding results from the Nashville air pollution study:

> Hagstrom, R. M., H. A. Sprague, and E. Landau. The Nashville air pollution study. VII. Mortality from cancer in relation to air pollution. Arch. Environ. Health 15:237-248, 1967.
>
> Zeidberg, L. D., R. A. Prindle, and E. Landau. The Nashville air pollution study. I. Sulfur dioxide and bronchial asthma. A preliminary report. Am. Rev. Res. Dis. 84:489, 1961.
>
> Zeidberg, L. D., R. J. M. Horton, E. Landau, and V. Raymond. The Nashville air pollution study. Mortality and diseases of the respiratory system in relation to air pollution. Arch. Environ. Health 15:214-224, 1967.

One purpose of the Nashville study was to study relationships between air pollution levels and mortality (total and respiratory disease specific) in areas of the Nashville, TN, SMSA. Particulate matter and sulfur oxides measurement obtained during 1958-1959 were related to dealths occurring during 1949-1960, opening this study to criticisms regarding retrospective use of later aerometry data in looking for links with earlier mortality. Also, data regarding smoking habits and occupational exposures were not taken into account.

Two further publications by Lave and Seskin (1972, 1977) attempted to extend their original U.K. analyses approach (Lave and Seskin, 1970) to metropolitan statistical areas in the United States:

> Lave, L. B., and B. P. Seskin. Air pollution, climate, and home heating: Their effects on U.S. mortality rate? Am. J. Public Health 62:909-916, 1972.

Lave, L. B., and B. P. Seskin. Air Pollution and Human Health. Baltimore, The Johns Hopkins University Press. 1977.

Similar comments as indicated above for the earlier Lave and Seskin (1970) publication apply here. No clear information on quantitative relationships between particulate matter or sulfur oxides levels and mortality can be derived from these published analyses.

Another set of widely cited American mortality studies was conducted in Buffalo, NY, by Winkelstein and associates:

Winkelstein, W., S. Kantor, E. Davis, C. Maneri, and W. Mosher. The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in men. I. Suspended particulates. Arch. Environ. Health 14:162-170, 1967.

Winkelstein, W., S. Kantor, E. Davis, C. Maneri, and W. Mosher. The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in man. II. Oxides of Sulfur. Arch. Environ. Health. 15:401-405, 1968.

Winkelstein, W., and S. Kantor. Stomach cancer. Arch. Environ. Health 14:544-547, 1967.

Winkelstein, W., and M. Gay. Suspended particulate air pollution. Relationship to mortality from cirrhosis of the liver. Arch. Environ. Health 22:174-177, 1971.

Numerous criticisms of these studies bave been discussed in detail by Holland et al. (1979) and Ware et al. (1980). Among the more salient problems noted were: (1) the use of 1961-1963 particulate matter and sulfur oxides measurement data in trying to relate air pollution to mortality among the elderly during 1959-1961; (2) inadequate controls for possible age differences between study groups that may have covaried with the air pollution gradient used; (3) lack of information on lifetime, including occupational, exposures; and (4) failure to correct for smoking habits. In a later presentation, Winkelstein (1972) comments on several of these points and later attempts to correct for some of them:

Winkelstein, W. Utility or futility of ordinary mortality statistics in the study of air pollution effects. In: Proceedings of the Sixth Berkeley Symposium on Mathematical Statistics and Probability. L. LeCam, J. Newyman, and E. Scott, eds., University of California Press, Berkeley, CA, 1972. pp. 539-554.

Still, this 1972 discussion does not lay to rest many of the different major concerns regarding the Winkelstein Buffalo mortality findings.

D. MORBIDITY AND CHRONIC EXPOSURES

1. British, European and Japanese Studies

Comments on several British studies often cited as demonstrating morbidity effects to be associated with chronic exposures of particulate matter (BS) and sulfur oxides are as follows for each.

FOR: Burn, J. L., and J. Pemberton. Air pollution bronchitis and lung cancer in Salford. Int. J. Air Water Pollut. 7:5-16, 1963.

This study demonstrates increases in sickness absences for bronchitis in association with increases in BS levels, but failed to test for effects of temperature decreases which covaried with the occurrence of pollution increases.

FOR: Ministry of Pensions and National Insurance. Report on an Enquiry into the Incidence of Incapacity for Work. II. Incidence of Incapacity for Work in Different Areas and Occupations. London, Her Majesty's Stationery Office, 1965.

In this study, rates of illness, absences for diseases such as bronchitis were related to smoke (BS) and SO_2 measurements from six areas of England, Scotland and Wales in 1961-1962, yielding apparent correlations between bronchitis and pollutant levels in some areas but not others. However, socioeconomic and several other possible confounding factors were not taken into account. Also, BS aerometry measurements were likely impacted by the computer error affecting 1961-1964 British National Survey BS data and one cannot determine what the reported BS levels actually mean in terms of $\mu g/m^3$ mass estimates in the absence of information on site-specific mass calibrations.

FOR: Fletcher, C. M., R. Peto, C. M. Tinker, and F. E. Speizer. The Natural History of Chronic Bronchitis and Emphysema (an eight year study of early chronic obstructive lung disease in working men in London). Oxford University Press, 1976.

This latter study above did concern relationships between smoke (BS) levels and morbidity effects. However, although certain apparent relationships were detected, the authors (FLetcher et al, 1976) noted several factors which complicate interpretation of their findings in such terms, and it is difficult to link observed effects to quantitative levels of BS.

FOR: Holland, W. W., T. Halil, A. E. Bennett, and A. Elliot. Factors influencing the onset of chronic respiratory disease. Br. Med. J. 2:205-208, 1969.

Holland, W. W., T. Halil, A. E. Bennett, and A. Elliot. Indications for measures to be taken in childhood to prevent chronic respiratory disease. Milbank Mem. Fund Q. 47:215-227, 1969.

Bennett, A. E., W. W. Holland, T. Halil, and A. Elliot. Lung function and air pollution. Chronic inflammation of the bronchi. Prog. Respir. Res. 6:78-89, 1971.

These reports concern a study of pulmonary function in children living in four areas of Kent, England. Differences in Black Smoke concentrations were small and SO_2 concentrations were not given. Inconsistencies existed for pulmonary function test results in relation to estimated air pollution gradients across the different areas.

FOR: Holland, W. W., H. S. Kasap, J. R. T. Colley, and W. Cormack. Respiratory symptoms and ventilatory function: A family study. Br. J. Prev. Soc. Med. 23:77-84, 1969.

This study examined respiratory disease and pulmonary function in families of Harrow, England (a suburb of London) during 1962-1965. During this period, mean winter smoke levels declined in $\mu g/m^3$ from 108 (1962-1963) to 72 (1964-1965) in two "clean" areas and from 175 (1962-1963) to 73 (1964-1965) in two "dirty" areas, but SO_2 levels for the same areas, respectively, were higher in 1963-1964 and 1964-1965 for the "dirty" areas than the "clean" ones. The observed differences in respiratory symptoms may have been related to earlier higher pollutant levels.

FOR: Irwig, L., D. G. Altman, R. J. W. Gibson, and C. Du V. Florey. Air Pollution: Methods to study its Relationship to Respiratory Disease in British Schoolchildren. Proceedings of the Intermath Symp on Recent Advances with Asses. of the Health Effects of Environ. Pol., Luxembourg: Commission of the European Communities, Vol 1, 1975 pp. 289-300.

Melia, R. J. W., C. Florey and A. V. Swan. The effect of atmospheric smoke and sulfur dioxide on respiratory illness among British schoolchildren: A preliminary report. Paper presented at VIII Int. Scil. Meeting Int. Epidemiol. Assoc., Purerto Rico, 1977.

These are preliminary reports from a study not yet completed of children in many areas of the United Kingdom. The results reported are not based on final analyses of data and have not been subjected to peer review. Also, aerometry data for BS measurements employed appear to be based on mass estimates derived from calibration of reflectance readings for the British National Survey standard curve (for London air in 1963) not necessarily accurately reflecting actual BS mass levels in $\mu g/m^3$ existing in non-London study areas.

FOR: Sawicki, F. Chronic non-specific respiratory disease in the city of Cracow. X. Statistical analysis of air pollution by suspended particulate matter and sulfur dioxide. Epidemiol. Rev. 23:221, 1969.

Sawicki, F. Chronic non-specific respiratory disease in the city of Cracow. XI. The cross-section study. Epidemiol. Rev. 23:242, 1969.

Sawicki, F. Air pollution and prevalence of non-specific chronic respiratory disease. In: Ecology of Chronic Non-Specific Respiratory Diseases. Z. Brzezinski, J. Kopczynski, and F. Sawicki. ed., Warsaw, Panstwowy Zaklad Wydawnictw Lekarskich. 1972. p. 3-13.

Sawicki, F., and P. S. Lawrence, eds. Chronic Non-specific Respiratory Disease in the City of Cracow--Report of a 5 year Follow-up Study Among Adult Inhabitants of the City of Cracow. National Institute of Hygiene, Warsaw, Poland, 1977.

A series of studies from Poland by Sawicki (1969, 1972, 1977) reported higher prevalence rates of chronic bronchitis in males (all smoking categories) and females (smokers and nonsmokers but not ex-smokers) in a high-pollution community. However, many of the reported differences by air pollution gradient disappeared when rates were adjusted for age, sex, and smoking habits. Also, no consistent relationship was found between the chronic bronchitis prevalence rate and length of residence in the high-pollution community. Several reviewers (e.g., Holland et al., 1979) have taken this as being evidence indicating that Sawicki's findings do not show a relationship between air pollution and bronchitis.

In a repetition of this study in 1973, Sawicki and Lawrence (1977) found some evidence suggesting a further relationship between the prevalence of chronic bronchitis and air pollution levels. By 1973, annual smoke concentrations in the high pollution area averaged 190 $\mu g/m^3$ (OECD) compared with 86 $\mu g/m^3$ (OECD) for the low-pollution area. Ambiguities exist regarding whether site-specific calibrations were employed in generating the OECD smoke estimates. SO_2 average annual concentrations were 114 and 46 $\mu g/m^3$, respectively, for the high and low pollution areas. Both chronic bronchitis and asthma were more prevalent in the high pollution area in males and females aged 31 to 50 and in smokers. Chronic bronchitis was also more prevalent in female non-smokers in the high pollution area in both 1968 and 1973. The investigators demonstrated an interaction between air pollution and smoking. However, the authors concluded that air pollution, in comparison to other factors, such as smoking, exerted a relatively minor effect on the health of their study populations.

FOR: Petrilli, F. L., G. Agnese, and S. Kanitz. Epidemiologic studies of air pollution effects in Genoa, Italy. Arch. Environ. Health 12:733-740, 1966.

Petrilli et al. (1966) studied chronic respiratory illness, rhinitis, influenza, and bronchopneumonia in several areas of Genoa, Italy, in relation to air pollution concentrations, between 1954 and 1964. Respiratory illness rates in non-smoking women over age 64 with a long residential history and no industrial exposure history was strongly correlated with SO_2 concentrations (Higgins and Ferris, 1978). These investigators found that all illness rates were higher in industrial districts with higher annual mean pollution concentrations. However, differences in socioeconomic status between study areas were not adequately controlled for and ambiguities exist regarding methodology and interpretation of reported aerometric measurements.

2. American and Canadian Studies

Numerous American and Canadian studies are often cited as showing associations between morbidity and chronic exposures to particulate matter or sulfur oxides. Comments on two Canadian studies as examples are as follows.

FOR: Aubrey, F., G. W. Gibbs, and M. R. Becklake. Air Pollution and Health in three urban communities. Arch. Environ. Health 34:360-368, Sept/Oct 1979.

This study of three communities in the Montreal area was marked by relatively small air pollution differences between cities. Cough and phlegm were weakly associated with air pollution concentration, but lung function was not. Little meaningful quantitative information can be extracted from the report.

FOR: Neri, L. C., J. S. Mandel, D. Hewitt, and D. Jurkowski. Chronic obstructive pulmonary disease in two cities of contrasting air quality. Can. Med. Assoc. J. 113:1043-1046, 1975.

This study compared the prevalence of symptomatic disease and the level of pulmonary function in Sudbury, a mining community, and in Ottawa. Although chronic bronchitis was more prevalent in Sudbury men, 58 percent of Sudbury men had an occupational history suggesting high pollution exposure. Lung function levels were lower for both men and women in Sudbury. Very high periodic peak SO_2 exposure levels (exceeding 1000 $\mu g/m^3$) more likely account for any pollutant effects than long-term chronic exposures to relatively low annual average levels of SO_2 or annual mean particulate levels (which didn't vary by much between Sudbury and Ottowa).

Two examples of recently published American studies possibly relevant for present purposes are those by Bouhuys et al. (1978) and Manfreda et al. (1978). Comments on each are as follows.

FOR: Bouhuys, A., G. J. Beck, and J. B. Schoenberg. Do present levels of air pollution outdoors affect respiratory health? Nature 276:466-471, 1978.

Although the authors report that the two communities studied had very different air pollution histories, concentrations during the study period were actually very similar. Only a few associations were found with air pollution concentration among several illness measures and lung function measurements studied, perhaps not unexpectedly in view of the limitations of this study regarding and pollution concentrations.

FOR: Manfreda, J., N. Nelson, and R. M. Cherniack. Prevalence of respiratory abnormalities in a rural and an urban community. Am. Rev. Respir. Dis. 117:215-226, 1978.

This was a qualitative study of urban-rural differences in two communities with similar air pollution concentrations and provides no clean quantitative information on the health effects of SO_2 or particulate matter.

Not included in the discussion in the main text of Chapter 14 concerning quantitative studies of morbidity associated with acute or chronic exposures to airborne sulfur oxides and particulate matter is a series of studies conducted by the U. S. Environmental Protection Agency under the Community Health and Environmental Surveillance System (CHESS) program, an integrated set of epidemiological studies performed between 1969 and 1975. In those studies, the health status of volunteer participants was either ascertained during single contacts or followed for time periods of up to nine months. Attempts were made to coordinate these health measures with air pollution observations from the residential neighborhoods of the study participants in an effort to derive information on quantatitive relationships between morbidity effects and both acute and chronic exposures to sulfur oxides, particulate matter and other air pollutants.

The results of approximately ten CHESS studies were published in summary or review form in the early 1970's and were later presented in more detail in a 1974 EPA monograph entitled "Health Consequences of Sulfur Oxides: A Report from CHESS 1970-1971," U.S. EPA document No EPA-650/1-74-004 (May, 1974). The manner in which the CHESS results were reported and interpreted in the 1974

monograph raised questions regarding inconsistencies in data collection and analyses, as well as possible mis- or overinterpretation of results, for CHESS data sets discussed in the early published reports or the 1974 monograph.* Of particular concern with regard to many of the studies was the adequacy of aerometric data or other estimates of air quality parameters, as well as the collection and analysis of health endpoint measurement data, upon which numerous key conclusions were based regarding possible air pollution-health effects relationships. Many questions regarding the validity of most CHESS study findings published in the early 1970s still remain to be fully resolved. In view of this, their potential usefulness in yielding information on quantitative relationships between health effects and well-defined air concentrations of sulfur oxides and particulate matter is extremely limited at this time; such CHESS Program study results are, therefore, not included in the discussion in the main chapter text concerning morbidity effects.

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*The matter of misinterpretation or overinterpretation of data or results of analyses of data collected as part of the CHESS Program contributed to considerable controversy regarding the validity and accuracy of results of early CHESS studies, as interpreted and reported in a 1974 EPA monograph entitled "Health Consequences of Sulfur Oxides: A Report from CHESS" 1970-71, U.S. EPA Document No. EPA-6550/1-74-004 (May 1974). The controversy eventually led to the 1974 "CHESS Monograph" becoming the subject of U.S. Congressional oversight hearings in 1976. Subcommi of the U.S. House of Representatives Committee on Science and Technology produced a report on the Monograph, other aspects of the CHESS Program, and EPA's air pollution research programs generally--a report entitled "The Environmental Protection Agency's Research Program with Primary Emphasis on the Community Health and Surveillance System (CHESS): An Investigative Report." Of primary importance for the present discussion, that report, widely referred to either as the "Brown Committee Report" or the "Investigative Report" (IR), contained various comments regarding sources of error in CHESS Program air quality and health effects data and quality control problems associated with such data collection and analysis. The I.R. also contained various recommendations to be implemented by the Administrator of EPA pursuant to Section 10 of the Environmental Research, Development, and Demonstration Authorization Act of 1978 ("ERDDAA," P.L. 95-155, 91 Stat. 1275, November 8, 1977). ERDDAA also requires that EPA and the Agency's Science Advisory Board report to Congress on the implementation of the IR recommendations.

One recommendation of the IR was that an addendum to the 1974 sulfur oxides monograph be published, to be used in part to qualify the usefulness of the CHESS studies, and to apprise the public of the controversy surrounding CHESS. An addendum has been published, and is available from EPA, as announced in the Federal Register of April 2, 1980, 45 F.R. 21702. The addendum is incorporated by reference in this document in partial qualification of the CHESS studies cited herein, and is part of the public file (or docket) established for revision of this criteria document. The addendum contains the full text of the IR, reports to Congress by EPA, on its implementation of the IR recommendations, and a report to Congress by EPA's Science Advisory Board on the same subject.

Perhaps most controversial were studies discussed in a 1974 Monograph reporting on certain of the CHESS studies, entitled: "Health Consequences of Sulfur Oxides: A Report from CHESS, 1970-1971." Subcommittees of the House Committee on Science and Technology of the U.S. Congress later produced a report on the Monograph, the CHESS Program, and EPA's air pollution programs in general--a report entitled: "The Environmental Protection Agency's Research Program with Primary Emphasis on the Community Healhth and Environmental Surveillance System (CHESS): An Investigative Report." This report, cited in the present criteria document as the Investigative Report or "IR (1976)," is a comprehensive reference for qualifying the use of the CHESS Monograph, and the CHESS studies generally. The full text of the IR (1976) is contained in an Addendum to the CHESS Monograph, EPA-600/1-80-021, which is available from EPA as noticed in the Federal Register on April 2, 1980, 45 FR 21702.

A proper evaluation of any CHESS study cited in this document should include careful reference to the entire IR (1976). To put the evaluation of problems associated with CHESS studies into perspective, the passage on General Problems of Epidemiologic Investigations of Pollution Effects in Section VI of the IR (1976) should be read. Based on considerations outlined in that passage, critiques of specific CHESS studies in the 1974 monograph were presented by the IR (1976). Those critiques which specifically address studies cited in the present Chapter 14 or its appendices are reprinted verbatim on the following pages.

No.1, "Prevalence of chronic respiratory disease symptoms in adults: 1970 survey of Salt Lake Basin Communities." Reported by Chapman et al.[212]

APPENDIX A

A Recapitulation of the Aerometric and Meteorological Findings of the Investigation as They Relate to Specific Sections of the CHESS Monograph and the Health Findings

A. INTRODUCTION

This section contains citations of errors and omissions found in a careful review of the CHESS Monograph which show that the use of aerometric and meteorological data in correlation with health effects end point measurements can easily mislead the reader of the CHESS document into inferences which are not wholly or even partially supported by the data in the report. Page, paragraph, and figure references are to the 1974 CHESS Monograph.

Since an important application of the aerometric data is to determine correlations with health effects, any errors or overusage of aerometric data based upon estimates or improper measurements will obviously reduce or negate the value of any health effects correlations which are attempted. This misusage or overusage of aerometric data will be particularly damaging as the extension of the conclusions is made in an attempt to discover possible threshold effects.

B. CRITIQUE

1. Prevalence of Chronic Respiratory Disease Symptoms in Adults: 1970 Survey of Salt Lake Basin Communities

Observed concentrations for only one year have been used to crudely estimate concentrations of sulfur dioxide and suspended sulfates relating to a 4–7 year exposure. The 1971 observed annual average concentration of sulfur dioxide was used with the 1971 emission rate from the smelter to obtain a ratio that was then multiplied by emission rates for other years to estimate concentrations for the other years. The estimated sulfur dioxide concentrations were then used in a regression equation based on a 1971 relationship to estimate suspended sulfate concentrations. Possible changes in meteorological conditions and mode of smelter operations were neglected. Acknowledgment is not given in the discussion and summary that the critical concentrations relating to health effects are nothing more than estimated concentrations.

It is questionable whether or not long-term exposures should have been attempted for Magna, based on only one year's record of observations that are abnormal because of the smelter strike. It would certainly have been appropriate to have mentioned that only estimated long-term data were available and indicated their degree of uncertainty in the discussion and summary.

Further, we find many errors on Page 2–37, Table 2.1.A.14. It seems that this table should have never been included in the report. Aside from the misuse of the diffusion model (discussed in Chapter IV) this table lists suspended sulfate values for Magna for the years 1940–1970, that are not the same as listed in Table 2.1.A.16, on page 2–39. The values are estimated by a simple ratio from the smelter emission rates, but this is not explained. On page 2–39 a regression equation is used for the same purpose. All of the sulfate concentrations under the heading CHESS are estimated observations except those for the year 1971. This has not been properly indicated, e.g. by the use of parentheses.

On pages 2–37 emission rates are not sulfur dioxide rates as indicated but emission rates in tons of sulfur per day. This means that the sulfur dioxide emissions were twice the values listed. It also means that the dispersion model estimates are incorrect. However, the listed estimated concentrations in Magna and Kearns, which are based on a simple ratio between observed concentrations in 1971 and some emission rate for 1971, whatever it might be, are not changed.

Note that the regression equation for suspended sulfates, Salt Lake City, (pages 2–39) which is:

$$SS=0.101(TSP)-3.65$$

is quite different than that which can be obtained from Table 2.1.4, i.e.:

$$SS=0.065(TSP)+1.93$$

SO_2 exposures were derived by multiplying the yearly smelter emission of SO_2 by the ratio of the 1971 measured annual average SO_2 concentration to the 1971 SO_2 emission rate (193 tons/day).

Estimates of suspended sulfates were derived from the estimates of SO_2, using the following regression equation for 1971:

$$SS=0.09(SO_2)+6.66$$

The annual TSP exposures were derived by multiplying the yearly smelter production of copper by the ratio of the 1971 measured annual arithmetic mean TSP concentration to the 1971 copper production rate (260,000 tons/year).

Smelter emissions of sulfur dioxide in the early 1940's were roughly three times greater than they were after 1956 although copper production has remained more or less constant. The method for estimating suspended sulfate, which is based on sulfur dioxide estimates leads to very high values in the 1940's whereas the total suspended particulate are estimated lower in 1940 than in 1971. The procedure used produced very high ratios between SS and TSP for the earlier years. For example, the 1940 ratio (34.6/63) is 0.55. This ratio is so large that it is obviously questionable.

The audacity of the estimates can be seen in Figure 2.1.17. The lowest value, which occured in 1971, is extrapolated all the way back to 1940, reaching unusually high annual average concentrations of more than one part per million. Considering the effects of wind direction, which would result in low concentrations much of the time because the smelter stack plume would not be blowing toward the town, such an annual average would result in short-period concentrations many times

the annual average. It is questionable that such high concentrations ever occurred. If they did, they would be well-remembered, and living conditions in Magna would be different than in 1971. Such unreasonably high estimates should have been further investigated before being presented.

The grossness of the estimates made overrides other shortcomings in this study pertaining to exposure that might be mentioned. However, more carefully made estimates would have required considerably more work, including obtaining meteorological records and details of smelter operations affecting plume behavior over the period of years studied. Such a large effort may not have been worthwhile considering the inexactness of some of the other aspects of the study. Nevertheless, a study of this nature seems to call for actual observations, more accurate estimates, or considerably less exactitude in its conclusions.

2. Frequency of Acute Lower Respiratory Disease in Children: Retrospective Survey of Salt Lake Basin Communities, 1967–1970

The same comments apply to this study as for the preceding study on the prevalence of disease symptoms in adults. Inadequate recognition is given to the fact that only estimated concentration data are being used in the discussion and summary.

3. Aggravation of Asthma by Air Pollutants: 1971 Salt Lake Basin Studies

In this study, daily entries in a dairy were used to determine weekly asthma attack rates. A statistical relationship was then determined between the attack rates (weekly) and observed air pollution concentrations (averaged weekly). Participants lived within a 2-mile radius of air monitoring stations.

Daily exposure of asthmatics in a community such as Magna, which is close to the smelter, are poorly characterized by a single monitoring station. On a given day, one side of the community could be much more affected by the smelter stack plume than the other, and high concentrations from looping or fumigation might affect one neighborhood but not others. The study inadequately assesses the effects of peak exposures and episodes.

This report does not make clear that the minimum temperatures used were from the Salt Lake City airport. The assumption seems to have been made that temperature was uniform over the entire study area. This is not true because of the differences in elevation and the effects of the mountains, and the lake. Perhaps the differences were not important, but they should have been considered. It is not clear why days were stratified by minimum rather than mean temperature.

Minimum temperatures occur during the early morning when people are generally indoors and perhaps in bed. When temperatures are low, windows are generally closed. Also, lower minimum temperatures are correlated with other meteorological phenomena that could also affect asthma attack rates, e.g., lower humidity and lower wind speed. Further there may be a correlation with wind direction. A lower than average minimum temperature probably is also associated with a strong temperature inversion which would be conducive to lofting the smelter stack plume. Because of the many questions raised, the findings pertaining to temperature merely suggest further study and have no general application.

Near the middle of the left hand column, page 2-89, the following sentence appears. "The shut-down of operations by the strike was accompanied by a pronounced improvement in air quality and a reduction in asthma attack rates that occurred sooner and were larger than seasonal reductions observed in the more distant study communities some 2 weeks later." Here there is a lack of appreciation of the natural climatic differences that exit in the Salt Lake Basin. Some effects of summer weather could easily be delayed two weeks before reaching Ogden. The average date for the last killing frost in Ogden is about May 6, whereas the average date of the last killing frost at Saltair (the climatic station nearest to Magna with a long record) is about April 12.

On Page 2-76 (near middle of page, right hand column) the smelter is not "5 miles north of Magna."

On page 2-81 the first graph in Figure 2.4.1 is incorrectly drafted. After the 17th week the broken line should be solid and the solid line broken. The temperature curve should appear as in the graph for the high exposure community.

Figure 2.4.2, page 2-81, shows a weakness in the argument that the sulfur dioxide concentrations are responsible for the asthma attack rate. In the High Exposure Community the attack rate starts up at the 18th week as the sulfur dioxide concentrations approach zero, or near zero, and remain very low for about six weeks. It is noted that this same graph shows the highest SO_2 peak occurring at the 9th week, which seems to begin about May 9. The graph on page 2-16 seems to show the peak in April.

In Figure 2.4.4, page 2-82, with respect to the High Exposure Community, it may be noted that the sulfate concentrations are not particularly well-correlated with the sulfur dioxide concentrations plotted in Figure 2.4.2, on the preceding page. The highest sulfate reading occurs in the 3rd week, whereas the sulfur dioxide levels build up to a peak in the 9th week.

On page 2-87, left hand column, it is stated that a threshold concentration of 1.4 $\mu g/m^3$ was calculated for suspended sulfates for the higher temperature range. In Figure 2.4.4 all of the plotted concentrations are greater than this value. Considering the background of suspended sulfates generally observed, this low threshold value seems to have no practical significance.

The third paragraph that appears in the right hand column, page 2-89, probably applies to Magna, however, this is not made clear. There is a possibility that the paragraph could be given broader interpretation than actually intended since the last three sentences seem to refer to conditions in urban areas generally. The paragraph probably should have been divided into two separate paragraphs. However, the main fault with the paragraph is that important conclusions are drawn that are not supported by information presented elsewhere in the report. It says "excess asthma attributable to sulfur dioxide might be expected 5 to 10 percent of summer days", "total suspended particulates could occur on up to 5 percent of summer days and 30 percent of fall and winter days", and "excesses due to suspended sulfates are likely to occur on 10 percent of fall and winter days and 90 percent of summer days." Assuming that the stated relationships

between concentrations and temperature are true, the report does not explain how the percentages of days were obtained. The study covered only 26 weeks, but these conclusions apply to an entire year. The percentages given seem to be rough estimates since they appear to be given only to the nearest 5 or 10 percent. The percentages might have been obtained from daily values for the minimum temperature, pollutant concentrations and asthma attack rate; but it is not clear how they were obtained.

Presumably daily average concentration levels of specific pollutants were used in the construction of the "hockey stick" curves shown on pages 2–86 and 2–88. The discussion implies that "24-hour levels" were used, but the precise nature of the air quality data used in the threshold analyses is not made clear.

There could be various reasons not explored by the study why the thresholds for asthma attacks were lower on warmer days. One of these is that there may be more plume looping on warmer days. This might result in localized, short-period, high concentrations, but relatively low average concentrations.

The validity of scientific work can be tested by the repeatability of results. In this and the other CHESS studies there were factors affecting asthma attack rates that were not considered and whose effects are unknown. Such factors are: time spent outdoors, percentage of time windows are open, temperature change, relative humidity, etc. The incompleteness of the study and the lack of understanding of the causes of the asthma attacks suggest that it might be repeated with significantly different results.

Short-term exposures to concentrations much higher than average annual or weekly concentrations could have occurred in the communities studied that were near large sources of air pollution such as smelters. There exists the possibility that asthma attacks could be triggered by brief-duration high concentrations. Such exposures could have been determined only inadequately by the procedures used in the study. The report does not make clear why more attention was not devoted to peak concentrations.

4. Human Exposure to Air Pollutants in Five Rocky Mountain Communities, 1940–1970

On pages 3–7 through 3–12 beginning with the second column, paragraph near middle of page, which begins "By comparing . . .". There is not a simple relationship between average daily pollutant emissions and average annual pollutant concentrations because the receptor area is often now downwind. Also, some consideration should have been given to determining if the years for which data are available were representative meteorologically.

(Page 3–11) Second paragraph, left hand side of page. Information obtained during this investigation indicates that the ratio 1.63 ± 0.21 should be 1.42 ± 0.21. (The value 1.63 is the upper limit of this ratio.)

(Page 3–12) Emission ratios of particulate and sulfur dioxide for 1971 are omitted from this report. Therefore, it is not possible to verify the ratios given here.

(Page 3–12) According to information obtained during this investigation, the two values for TSP listed as 99.5 for the years 1971–70, should be 98.1 for both years.

No. 7, "Prevalence of chronic respiratory disease symptoms in military recruits: Chicago induction center." Report by Chapman et al.[212]

ties where certain health effects were observed, the source of the suspended sulfate is inadequately determined. The study findings are much too incomplete to call for the stringent control of suspended sulfates as has been done on page 3-51.

7. Prevalence of Chronic Respiratory Disease Symptoms in Military Recruits: Chicago Induction Center (Paragraph 4.2)

Exposure estimates in this study are extremely crude. In the summary the following statement is made, "Available evidence indicates that exposures lasting 12 years or more to ambient air pollution characterized by elevated annual average levels of sulfur dioxide (96 to 217 $\mu g/m^3$), suspended particulates (103 to 155 $\mu g/m^3$) and suspended sulfates (14 $\mu g/m^3$) were accompanied by significant increases in the frequency of chronic respiratory disease symptoms."

The 96 $\mu g/m^3$ value is the average urban core value for 1969–70, which ranges from 54 to 138 $\mu g/m^3$, whereas the 217 $\mu g/m^3$ is an average value for five suburban communities for the year 1969. Going back 12 years concentrations were much higher. During the period 1960 through 1965, the lowest value was 222, and there was a high of 344 in 1964. For the five suburban communities there was data only for one other year. It averaged 183 $\mu g/m^3$. The 14 $\mu g/m^3$ concentration for sulfates is for a period of 7 years, not 12 as stated. It basically represents data for the Chicago core area, with some scattered observations from East Chicago and Hammond, Ind. The average concentrations for the city should be somewhat less than in the core area. Use of the core area value would generally result in an overestimate.

It is difficult to characterize exposures lasting 12 years for the entire Chicago area. Either this should have been done in very general terms, nonquantitatively, or a greater effort should have been made to present more representative estimates.

The assumption is being made that sulfate observations made at a central urban location in Chicago, averaged with a few observations from East Chicago and Hammond, Ind. are generally representative of the entire Chicago area.

(Page 4-8) Referring to the Chicago area the following statement is made: "Each sampler location, identified by a station name in Figure 4.1.2, represents the central business-commercial district of that particular area." This statement is not true. Practically all, if not all the samplers are located on the roofs of school buildings in an effort to obtain representative community values: They were not located deliberately in business commercial districts and do not slightly overestimate area-wide concentrations as suggested.

(Page 4-23) In reading this paper about the prevalence of chronic respiratory disease symptoms in military recruits, questions arise about the actual locations from which the men came and the local pollution levels to which they might have been exposed. Some rural occupations result in high exposures to dusts, plant allergens, etc.

(Page 4-35) (Summary) The 12-year value for suspended sulfates should be 16 micrograms per cubic meter, not 14, as stated. Also, it appears that the concentrations of sulfur dioxide and suspended particulate are for only the period 1969–1970 and not for 12 years as is stated. (See Table 4.1.A.6)

No. 8, "Prospective Surveys of Acute Respiratory Disease in Volunteer Families: Chicago Nursery School Study, 1969-1970." Report by Finklea et al.[117]

8. Prospective Surveys of Acute Respiratory Disease in Volunteer Families: Chicago Nursery School Study, 1969–1970

On page 4–41, in Table 4.3.1, it is not clear where the sulfur dioxide data for the years 1959–63 come from. The Chicago network, which would have provided community data, was not operating effectively until 1964.

On the same page the suspended sulfate data are probably representative for the core area but are high to be used as an average for the city as a whole.

A serious weakness in this study is that the communities are ranked Intermediate, High, and Highest according to a ranking that was determined by suspended particulate values, whereas the most important finding pertains to sulfur dioxide. Referring back to Table 4.1.A.1, it can be seen that a considerably different ranking would have resulted if the communities had been ranked according to sulfur dioxide concentrations. In Table 4.3.1, it may be noted that during the study that the "High" community had the lowest concentration of sulfur dioxide.

Also note in Table 4.1.A.1 that the Highest communities include GSA, which happens to be on the south edge of the Chicago Loop area. This station probably contributed considerably to the high concentration of sulfur dioxide attributed to the Highest community during 1969–1970, yet it is very nonrepresentative of a nursery school. Also, note that the Highest stations include Carver, which for some reason ranks highest because of suspended particulate concentrations whereas the sulfur dioxide concentrations are relatively low.

Sulfates are not considered in the summary of this study, which seems to focus on sulfur dioxide without quantitative considerations of suspended sulfate levels.

(Page 4–54) In the first paragraph of the Summary, the following statement appears: "It is also possible that more recent lower air pollution levels contributed to increased respiratory illness." On page 4–51 the following statement is found. "Acute respiratory morbidity was significantly lower among families living in neighborhoods where sulfur dioxide levels had been substantially decreased." These two statements are contradictory and require clarification. The first statement is remarkable. It can be interpreted to mean that some air pollution is good for you. Did the authors intend to say this? Such an important finding is inadequately supported by the contents of the report.

9. Human Exposure to Air Pollution in Selected New York Metropolitan Communities, 1944–1971

An overusage of estimated data can be found on page 5–19. The following two statements appear: (Left hand column, middle paragraph) "Measured values for suspended sulfates for 1956–1970 were available from the Manhattan 121st Street Station, and these values were used for citywide values." (Last paragraph on page) "The observed annual ratios of suspended sulfate to dustfall for New York City were used to estimate the suspended sulfate levels in Queens and Bronx."

No. 10, "Prevalence of Chronic Respiratory Disease Symptoms in Adults: 1970 Survey of New York Communities." Report by Chapman et al.[212]

10. Prevalence of Chronic Respiratory Disease Symptoms in Adults: 1970 Survey of New York Communities

Three communities were compared: Riverhead, Long Island, a low exposure community, Queens, an intermediate exposure community, and the Bronx, a high exposure community. Parents of all children attending certain elementary schools located within 1.5 miles of an air monitoring station in each community were asked to participate in the study. Each child was given a questionnaire to be filled out by his parents and returned.

Regarding exposure, were the concentrations measured at the monitoring stations generally representative? Assuming a person remains reasonably near the station, in this case within 1½ miles, and breathes the outside air, the station measurements would be generally representative for long-term average exposure. Maps of annual concentrations which are for sulfur dioxide and suspended particulate matter, show reasonably uniform concentrations across the study areas. However, as has been mentioned in the report (5.1) Human Exposure to Air Pollution Selected New York Metropolitan Communities, 1944–1971, by Thomas D. English, et al., the Queens Community lies about 1 mile west of the John F. Kennedy International Airport. The effect of this airport and the various other possible sources of air pollution that could have affected particular local areas were not determined.

The fact that the CHESS monitoring sites were the same as used in the city air pollution control programs suggests that the sites were picked and are being used because they seem to be generally representative.

More important than the representativeness of the monitoring site locations in this study is the proper interpretation of the effects of the greatly reduced pollution levels during the period 1969–1971. It is not meaningful to draw conclusions from sulfur dioxide exposures ranging from 144 to 404 $\mu g/m^3$ and sulfate exposures ranging from 9–24 $\mu g/m^3$, as was done in this study. The implication is that health effects can be caused by the lowest concentrations mentioned, and this is not shown in the study. Also, it is stated that annual sulfur dioxide levels of 50 to 60 $\mu g/m^3$ (accompanied by annual average suspended sulfate levels of about 14 $\mu g/m^3$ and annual arithmetic mean total suspended particulate levels of about 60 to 105 $\mu g/m^3$) could be associated with such effects. These are levels that were measured in 1971, whereas in the study there seems to have been no way to have differentiated between the effects of pollution in 1971, or that might have occurred during some earlier time. It is not reasonable to infer that lower pollution levels are responsible for the observed health effects.

No. 11, "Prospective Surveys of Acute Respiratory Desease in Volunteer Families: 1970-1971 New York Studies." Reports by French et al,[306] Hammer et al,[214] and Chapman et al.[212]

11. Prospective Surveys of Acute Respiratory Disease in Volunteer Families: 1970–1971 New York Studies

In this study families were telephoned once every two weeks and questioned about possible health effects. The families resided within 1 to 1.5 miles of the air monitoring stations.

In the discussion it is stated that acute lower respiratory disease morbidity can be attributed to exposures to 2 to 3 years involving annual average sulfur dioxide levels of 256 to 321 $\mu g/m^3$ (accompanied by elevated annual average levels of total suspended particulate of 97 to 123 $\mu g/m^3$ and annual average suspended sulfate levels of 10 to 15 $\mu g/m^3$). These values are average values for the period 1966–1970, a five year period, and not period of 2 to 3 years as indicated. Also, they are the averages for the Bronx and Queens, respectively, and therefore do not represent a range of concentrations that would have occurred in any particular community, as implied. For example, the sulfur dioxide concentrations in the Bronx ranged from 184 to 472 $\mu g/m^3$ and in the Queens from 131 to 420 $\mu g/m^3$, during the five year period. Three year averages are 174 to 247 $\mu g/m^3$, and two year averages, lower still.

On page 5–16 the dustfall concentrations shown in Figure 5.1.21 seem to be greater than would be obtained from the data presented in Figure 5.1.16.

On page 5–36 (Table 5.2.1) the values in this table seem to come from Table 5.1.A.8. The values in the column headed 1949–58 are, except for dustfall, for shorter time periods. For example, the values for Queens come from data for the years 1956–58.

On page 5–45 (Summary) we find that since the concentration data base comes from Table 5.1.A.8, the long term exposure values represent a period of less than 20 years.

Further, it is stated that there is a distinct possibility that increased susceptibility to acute lower respiratory illness is maintained or induced by exposures involving annual average sulfur dioxide levels of 51 to 63 $\mu g/m^3$ (accompanied by annual average total suspended particulate levels of 63 to 104 $\mu g/m^3$ and annual average suspended sulfate levels of 13 to 14 $\mu g/m^3$). The 51 to 63 $\mu g/m^3$, is a range resulting from two different analyses of samples (see page 5–53). It represents uncertainty in measurement techniques rather than a range of exposure as would be interpreted. These concentrations and the suspended sulfate concentrations of 13 to 14 $\mu g/m^3$ happen to have occurred in the Intermediate I and the Intermediate II communities during 1971. This particular study as conducted could not have differentiated between the effects of these levels of pollution and the effects of higher levels that occurred earlier.

Only average annual concentrations were considered and not peak or episode concentrations.

No. 12, "Aggravation of Asthma by Air Pollutants: 1970-1971 New York Studies." Reports by Finklea et al.[122-123]

12. Aggravation of Asthma by Air Pollutants: 1970–1971 New York Studies

Panelists who lived within a 1.5 mile radius of three monitoring stations in communities identified as Low, Intermediate I, and Intermediate II, because of their average air pollution concentrations, recorded asthma attacks each day in a diary for a period lasting 32 weeks, October 1970–May 1971. From a statistical association between asthma attack rates, 24-hour average concentrations from the monitoring stations, and daily minimum temperatures from airports near the study communities, it was concluded that 24-hour suspended sulfate levels of 12 $\mu g/m^3$ on cooler days (T_{min} equal to 30 to 50°) and 7.3 $\mu g/m^3$ on warmer days (T_{min} greater than 50°F) were thresholds for the induction of excessive asthma attacks. No firm evidence could be found to associate elevations in sulfur dioxide (100 to 180 $\mu g/m^3$ on 10 percent of days) with excessive asthma attack rates on either cold or warmer days.

Regarding exposure levels, there is much less assurance that daily average levels throughout a community would be more or less uniform than would be the case with annual average levels. More monitoring stations might have been operated, or mobile stations used, to determine how pollution exposure varied from location to location. The determination of such differences in air pollution concentrations might have been important, but probably more important is that the other factors (in addition to the observed air pollutants) that could have caused or contributed to the asthma attacks were not examined. It would not be worthwhile to refine the information on the distribution of the air pollutants studied, unless a greater effort were made to study all of the various possible causes of the asthma attacks more thoroughly.

The study focused on the effects of minimum temperature. The possible effects of other meteorological variables could also have been explored. Of particular interest would be the effects of sudden, large temperature changes.

It is not made clear why minimum instead of average, or even maximum, temperatures were picked for correlation. Generally there would be less actual exposure to minimum temperature, which usually occurs about sunrise, than to warmer temperatures. Asthmatics would generally be expected to protect themselves from colder temperatures, staying indoors and keeping windows closed, whereas on warmer days they might be more subject to exposure to outdoor air with its assortment of possible allergens. There are diverse reasons why temperature might be an important factor determining asthma attack rates. No attempt was made in the study to provide an explanation.

It is expected that there would be noticeable temperature differences between Riverhead (the Low community) and Queens (the Intermediate I, community). Although it is stated that the temperatures come from nearby airports, the temperature curves plotted in Figure 5.4.1 seem to be identical for both communities. It may be noted that a different curve is plotted for the low community Figure 5.5.2.

(Figure 5.4.4) Although at a glance it appears that for the Intermediate community that the "Attack Rate" and the "Suspended Sulfate" curves are similar, close inspection shows that more often than not, they are out of phase. Between the 2nd and 3rd week the attack rate (AR) curve continues down as the suspended sulfate (SS) curve starts up, between the 10th and 11th week the AR-curve continues down after the SS-curve starts up, between the 14th and 16th week the AR-curve goes up while the SS-curve continues down, between the 19th and 20th week the AR-curve starts up while the SS-curve continues down, and again on the 27th week the AR-curve rises a week before an increase in the suspended sulfate concentrations. In all, three of the five increases in attack rate precede, rather than follow, increases in suspended sulfate concentrations.

13. Frequency and Severity of Cardiopulmonary Symptoms in Adult Panels. 1970–1971 New York Studies (Paragraph 5.5).

Symptom diaries were maintained daily for the 32-week period October 8, 1970 through May 22, 1971, by four panels, depending on state of health. The panelists were distributed in three communities and lived within 1.5 miles of air pollution monitoring stations. It was concluded that elderly panelists in the low exposure community reported higher symptom rates on days when sulfate levels exceeded 10 $\mu g\ m^3$. There seemed to be good evidence of a threshold effect between 6 and 10 $\mu g/m^3$, with a greater morbidity excess on warmer days.

Since suspended sulfates seem to be more uniformly distributed than a pollutant such as sulfur dioxide, the concentrations determined by monitoring should be generally representative of outdoor exposure and in most cases indoor and outdoor average exposures would be expected to be similar. The question not answered by this study is whether or not the panelists are also being exposed to some other causative agent, or stress factor, that might happen to correlate with the sulfate concentrations. It, and not the suspended sulfate concentrations, might be the cause of the observed health effects.

(Page 5–91) (Figure 5.5.3) The low value of sulfur dioxide that began at the 19th week and continued until the 24th week are suspected of not being true values. Near the end of the last paragraph on the preceding page it is suggested that meteorological conditions may have been responsible. A careful study of the meteorological conditions and fuel usage would be necessary to determine if these might have caused the persistent low concentrations. However, a scanning of the daily local climatological data shows no obvious reason for the reported low values.

Furthermore, the minimum temperature curve for the Low community in Figure 5.5.2 is not the same as given in Figure 5.4.1.

The New York Department of Air Resources also reported a large drop in concentrations following the mid-winter peak at the Queens (Intermediate I) monitoring station, but reported values were never as low, and a period of low values was not followed by a rise as shown in the Figure. Further, the low values shown, which are about 25 $\mu g/m^3$, or .01 ppm or less, are quite low for the New York metropolitan area. Average weekly low values two or three times this value would generally be expected for a comparable period.

No. 14, "Ventilatory Function in School Children: 1970-1971 New York Studies." Report by May et al.[215]

14. Ventilatory Function in School Children: 1970–1971 New York Studies (Paragraph 5.6).

Pulmonary tests were made in three elementary schools in communities with different air pollution levels, and there were four rounds of testing, November-December 1970, January 1971, February-March 1971, and April 1971. The children lived within 1.5 miles of a particular air monitoring station. The Queens monitoring station is on top of a school where the testing was done. However, the Bronx station is on top of a "court house in the center of a busy commercial area" (page 5–6) and may not be close to the school. For the Riverhead community it is not made clear whether or not the school and the monitoring station are at the same location or near each other. It is assumed that the schools in Riverhead and the Bronx were within 1½ miles of the monitoring stations, but this is not actually stated.

It was concluded that 9 or more years exposure to annual sulfur dioxide levels of an estimated concentration of 131 to 435 $\mu g/m^3$ (accompanied by suspended particulate levels of about 75 to 200 $\mu g/m^3$) and suspended sulfate levels of about 5 to 25 $\mu g/m^3$ can be associated with a small but significant impairment in ventilatory function. These values are from Table 5.6.2, and are the extreme high and low values listed. There is an implication here that the low concentrations, 131 $\mu g/m^3$ for sulfur dioxide and 5 $\mu g/m^3$ for suspended sulfates represent threshold values. Actually they are only annual average concentrations for the years 1969 and 1970. The observed health effects may have been the result of exposure to much higher concentrations in other years, or to some other cause.

15. Ventilatory Function in School Children: 1967–68 Testing in Cincinnati Neighborhoods (Paragraph 6.1).

This study included a pair of public elementary schools in each of six neighborhoods differing in socioeconomic level, race, or pollution exposure. All children in one or two classrooms of the second grade of the elementary schools were asked to participate in the study to achieve sample sizes of 60 to 75 children in each of the six study sectors. Ventilatory performance as measured by a spirometer was obtained 12 times from each child: once weekly in the months of November 1967 and February and May 1968. The tests were administered on Tuesday and Wednesday mornings.

Air monitoring stations were placed in locations within three blocks of each school to provide samples representative of the air quality in the neighborhood served by the school. No information is reported on the distances of the homes of the children from the school. Apparently it was assumed that the home environment and the school environment were the same. Indoor soiling index and sulfur dioxide observations were taken in the schools, but results are not reported. It is reported that it was determined that indoor and outdoor sulfur dioxide, soiling index, and suspended particulate levels measured over the 24-hour or 4-hour period directly preceding pulmonary function tests did not consistently correlate with the test values.

Details of this lack of correlation are not given, but it was concluded that "ventilatory performance of children thus did not appear to be acutely affected by variations in pollutant levels on the day of the test." Possible exposures over intermediate periods, say three days or one week, prior to testing were not considered. Conclusions seem to be based on possible long-period exposures, probably over a lifetime.

Concentrations of sulfur dioxide were low (less than 52 $\mu g/m^3$) in all areas, so health effects were attributed to particulate pollutants independent of atmospheric levels of gaseous sulfur dioxide.

Average sulfate levels during the period of the study were observed to be between 8.9 and 10.1 $\mu g/m^3$, in the polluted lower middle white community, but previous average exposure was estimated to be 10.7 to 12.1 $\mu g/m^3$, based on the National Air Surveillance Network station. The average suspended sulfate level in the clean white sectors was 8.3 $\mu g/m^3$, a relative difference of 13 percent. (The largest differences in area exposure were in the concentrations of suspended particulates. Levels of total suspended particulates were 131 $\mu g/m^3$ in polluted sectors and 61 to 92 $\mu g/m^3$ in clean sectors.

In reading this paper one wonders about the psychological interaction between the children and the team members administering the tests, who could anticipate the outcome of the experiment. The curves for the black children in Figure 6.1.3, are particularly interesting.

APPENDIX B

Qualitative Community Health Epidemiology Studies of Particulate Matter and Sulfur Oxides (PM/SO_x) Morbidity Effects

Contents

Table B-1. Qualitative Studies of Morbidity Effects Associated with Acute PM/SO_x Exposures

Table B-2. Qualitative Studies of Air Pollution and Prevalence of Chronic Respiratory Symptoms and Pulmonary Function Declines

Table B-3. Qualitative Association of Geographic Differences in Mortality with Residence in Areas of Heavy Air Pollution

TABLE B-1. QUALITATIVE STUDIES OF MORBIDITY EFFECTS ASSOCIATED WITH ACUTE EXPOSURES TO PARTICULATE MATTER AND SULFUR OXIDES

Study	Characteristics	Findings
Levy et al. (1977)	Hospital admissions for respiratory disease in Hamilton, Ontario, correlated with sulfur oxide/particulate air pollution index.	Increased hospital admissions on heavy pollution days, except at one hospital far removed from major pollution sources.
Zeidberg et al. (1961)	Study during 1 year of 49 adults and 34 children with asthma in Nashville, Tenn.	Doubling of asthma attack rates in persons living in more SO_2 polluted neighborhoods. No adjustment for demographic or social factors.
Cowan et al. (1963)	History of asthma, and skin tests of University of Minnesota students, in relation to dust from nearby grain elevator.	Significant association between grain-dust particulate matter exposure and asthma attacks.
Greenberg et al. (1964)	New York City hospital emergency room visits for asthma in month of September.	Emergency room visits strongly associated with onset of cold weather but not with degrees of air pollution during the one month of study.
Weill et al. (1964) Carroll (1968)	Retrospective study of emergency room visits to New Orleans Charity Hospital.	Periodic "epidemics" of asthma in New Orleans could not be traced to any common pollutant exposure.
Phelps (1965) and Meyer (1976)	"Tokyo-Yokohama asthma" in American servicemen stationed in Japan after World War II.	Disease primarily in smokers attributed to allergic response to atmospheric substances that could not be characterized. Patients improved after leaving the area and were immediately affected on return. Some had long-term effects afterwards.
Glasser et al. (1967)	Emergency room visits in seven New York city hospitals during the November 1966 air pollution episode.	Increased emergency room visits for asthma in three of seven hospitals studied.
Chiaramonte et al. (1970)	Emergency room visits at a Brooklyn hospital during a November 1966 air pollution episode.	Statistically significant increase in emergency room visits for asthma and for all respiratory diseases, continuing to 3 days after the peak air pollution concentrations.

TABLE B-1 (continued).

Study	Characteristics	Findings
Derrick (1970)	Nighttime emergency room visits for asthma in Brisbane, Australia.	Negative correlation between asthma visits with degrees of smoke shade.
Rao (1973)	Pediatric emergency room visits for asthma at Kings County Hospital, Brooklyn, October 1970-March 1971.	Negative correlation of asthma visits with degrees of smoke shade. Lack of temperature adjustments. Considerable distance of hospital district from air monitoring stations.
Goldstein and Black (1974)	Emergency room visits for asthma at a hospital in Harlem and in Brooklyn, September-December 1970 and September-December 1971.	Temperature adjusted asthma rates positively correlated with SO_2 values in Brooklyn but not not in Harlem. In 1971 period, 50-90% increase in asthma visits on 12 days of heaviest pollution.
Sulz et al. (1970)	Hospitalizations for asthma (1956-61) and for eczema (1951-61) in Erie County NY. Attack rates of patients stratified into air pollution/social class categories.	Area gradients in asthma and eczema hospitalization rates, adjusted for social class differences, corresponded to the air pollution gradient. Meterological differences between areas not analyzed.
Dohan and Taylor (1960), Dohan (1961) and Ipsen et al. (1969)	Weekly industrial absenteeism rates in women RCA workers in several locals, 1957-63.	Correlations with sulfation explained by temperature and season.
McCarroll et al. (1967) Mountain et al. (1968) Thompson et al. (1970) Cassell et al. (1969, 1972) Lebowitz et al. (1972, 1977)	Frequency of cough and eye irritation in a New York population living close to an air monitoring station.	Maximal effect on cough frequency occurred 1 or 2 days after peak air pollution concentrations, and cold incidence and prevalence correlates with SO_2 and Cohs levels independent of weather.
Ministry of Pensions and National Insurance (1965)	Incidence survey of worker incapacity from bronchitis and other illness in representative samples throughout Britain, 1961/1962.	Incapacity due to bronchitis correlated with winter concentrations of smoke and SO_2 in each of four 10-year age groups. Socioeconomic and other characteristics of the areas may have contributed to the associations.

TABLE B-1 (continued).

Study	Characteristics	Findings
Lebowitz et al. (1974)	Acute pulmonary function changes in normal children in a copper smelter town.	Pulmonary function decreased with increasing air pollution especially after exercise. Temperature was controlled.
Emerson (1973)	Weekly spirometry on bronchitis patients in London, 1969-71.	No correlation with air pollution levels.
Carnow et al. (1969)	Daily symptoms in chronic bronchitis patients in Chicago, 1960s.	Patients over 55 with moderate-severe bronchitis had increased symptoms correlated with increased SO_2 levels.
Burrows et al. (1968)	Daily symptoms in chronic bronchitis patients in Chicago, 1960s.	No relation of symptoms with SO_2 when data were adjusted for temperature and season.
Kalpazanov et al. (1976)	Daily incidence of influenza in Sofia, Bulgaria, 1972, 1974/75.	Incidence was significantly correlated with SO_2 and dust.
Kevany et al. (1975)	Cardio-respiratory hospital admissions in Dublin, 1972-73.	Low but significant correlations between cardiovascular admissions and SO_2/BS in winters.
Sterling et al. (1966, 1967)	Hospital admissions by disease in Los Angeles with measures of various pollutants.	Significant decrease of respiratory admissions with decreasing SO_2, though SO_2 was low. Other pollutants and weather may have been more important.
Verma et al. (1969)	NYC insurance workers' absenteeism.	Respiratory disease absenteeism correlated with SO_2, controlled for temperature and season.
Burn and Pemberton (1963)	Absenteeism among workers due to bronchitis in Salford, England.	Significantly correlated with SO_2.
Heimann (1970)	Acute morbidity and mortality in Boston episodes, 1955-66.	Respiratory patient visits higher, but mortality wasn't during episodes.
Gregory (1970)	Sickness abseenteeism for Sheffield steelworkers in 1950s.	Correlation of weekly absences with SO_x/TSP.
Gervois et al. (1977)	Daily sickness absence of French workers in 2 areas of Northern France in winter period.	Association found in one town after adjusting for temperature. Monitoring method unknown.

TABLE B-1 (continued).

Study	Characteristics	Findings
Lawther et al. (1973, 1974a,b)	Day-to-day changes in ventilatory function of a small group of normal adult subjects and 2 bronchitics in London.	After multiple regression analysis to remove effects of time trend, SO_2 concentrations explained the largest proportion of variance in peak flow rates. Clearest associations were shown after exercise in periods of heavy pollution. In some subjects it was difficult to detect any consistent effects of pollution.
Ramsey (1976)	Pulmonary function in 7 male nonsmoking asthmatics (ages 19-21) daily over 3 months.	Multiple regressions showed significant correlation of some tests in 5 subjects but weather variables, but not with TSP or SO_2.
Stebbings et al. (1976, 1979)	Acute pulmonary function in children after a pollution episode in Pittsburgh.	Continued decline seen during very very short periods of study. "Sensitive" subgroup defined by improvement during period.

TABLE B-2. QUALITATIVE STUDIES OF AIR POLLUTION AND PREVALENCE OF CHRONIC RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION DECLINES

Study	Characteristics	Findings
Fairbairn and Reid (1958)	Comparison of respiratory illness among British postmen living in areas of heavy and light pollution.	Sick leave, premature retirement, and death due to bronchitis or pneumonia were closely related to pollution index based on visibility.
Mork (1962)	Questionnaire and ventilatory function tests of male transport workers 40-59 years of age in Bergen, Norway and London, England.	Greater frequency of symptoms and lower average peak flow rates in London. Differences were not explained by smoking habits or socioeconomic factors.
Deane et al. (1965) Holland and Reid (1965)	Questionnaire and ventilatory function survey of outdoor telephone workers 40-59 years of age on the west coast of U.S.	No differences in symptom prevalence between San Francisco and Los Angeles workers, although particulate concentrations were approximately twice as high in Los Angeles. Increased prevalence of respiratory symptoms, adjusted for smoking and age, a larger volume of morning sputum and a lower average ventilatory function in London workers, and in the English compared with American workers.
Cederlöf (1966) Hrubec et al. (1973)	Chronic respiratory symptom prevalence in large panels of twins in Sweden and in the U.S. Index of air pollution based on estimated residential and occupational exposures to SO_2, particulates, and CO.	Increased prevalence of respiratory symptoms in twins related to smoking, alcohol consumption, socioeconomic characteristics, and urban residence, but not to indices of air pollution.
Bates et al. (1962, 1966) Bates (1967)	Comparison of symptom prevalence, work absences, and ventilatory function in Canadian veterans residing in 4 Canadian cities.	Lower prevalence of symptoms and work absences and better ventilatory function in veterans living in the least polluted city.

TABLE B-2 (Continued).

Study	Characteristics	Findings
Bates (1973)	10-year follow-up study of Canadian veterans initially evaluated in 1960, and followed at yearly intervals with pulmonary function tests and clinical evaluations.	Least decline in pulmonary function with age in veterans from least polluted city.
Yashizo (1968)	Bronchitis survey of 7 areas of Osaka, Japan, 1966, among adults 40 years of age and over.	Bronchitis rates, standardized for sex, age, and smoking were greater among men and women in the more polluted areas. Bronchitis rates followed the air pollution gradient.
Winkelstein and Kantor (1969)	Survey of respiratory symptoms in a random sample of white women in Buffalo, New York.	In nonsmokers 45 years of age and over, and among smokers who did not change residence, respiratory symptoms were correlated with particulate concentrations obtained in the neighborhood of residence. No association of symptom prevalence with SO_2 concentrations.
Ishikawa et al. (1969)	Comparison of lungs obtained at autopsy from residents of St. Louis and Winnipeg.	Autopsy sets, matched for age, sex and race, showed more emphysema in the more polluted city. Autopsied groups may not reflect prevalence of disease in general population.
Fujita et al. (1969)	Prevalence survey (Medical Research Council questionnaire) of post office employees in Tokyo and adjacent areas, 1962 and re-surveyed in 1967.	Two-fold increase over time in prevalence of cough and sputum production in same persons, irrespective of smoking habits. Change was attributed to increasing degrees of air pollution.
Reichel, (1970) Ulmer et al. (1970)	Respiratory morbidity prevalence surveys of random samples of population in 3 areas of West Germany with different degrees of air pollution.	No differences in respiratory morbidity, standardized for age, sex, smoking habits, and social conditions, between populations living in the different areas.

TABLE B-2 (Continued).

Study	Characteristics	Findings
Nobuhiro et al. (1970)	Chronic respiratory symptom survey of high and low exposure areas of Osaka and Ako City, Japan.	Higher prevalence of chronic respiratory symptoms in more polluted areas.
Comstock et al. (1973)	Repeat survey in 1968/1969 of east coast telephone workers and of telephone workers in Tokyo.	After adjustment for age and smoking, no significant association of respiratory symptom prevalence with place of residence.
Speizer and Ferris (1973a,b)	Comparison of respiratory symptoms and ventilatory function in central city and suburban Boston traffic policemen.	Slight but insignificant increase in symptoms prevalence among non-smokers and smokers, but not ex-smokers, from the central city group. No group differences in ventilatory function.
Linn et al. (1976)	Respiratory symptoms and function in office working population in Los Angeles and San Francisco, 1973.	No significant difference in chronic respiratory symptom prevalence between cities; women in the more polluted community more often reported nonpersistent (<2 years) production of cough and sputum.
Prindle et al. (1963)	Comparison of respiratory disease and lung function in residents of Seward and New Florence, PA.	Increased airway resistance in inhabitants of more polluted community. Differences in occupation, smoking, and socioeconomic level could account for these differences.
Watanabe (1965)	Peak flow rates in Japanese school children residing in Osaka.	Lower peak flow rates in children from more polluted communities. Improved peak flow rates when air pollution levels decreased.
Anderson and Larsen (1966)	Peak flow rates and school absence rates in children 6-7 years of age from 3 towns in British Columbia.	Significant decrease in peak flow rates in 2 towns affected by Kraft pulp mill emissions. No effect on school absences. Ethnic differences were not studied.

TABLE B-2 (Continued).

Study	Characteristics	Findings
Collins et al. (1971)	Death rates in children 0-14 years of age, 1958-1964, in relation to social and air pollution indices in 83 county boroughs of England and Wales.	Partial correlation analysis suggested that indices of domestic and industrial pollution account for a greater part of the area differences in mortality from bronchopneumonia and all respiratory diseases among children 0-1 year of age.
Toyama et al. (1966)	Respiratory symptoms and spirometry in an agricultural area of Japan, 1965, 678 subjects ages 40-65, by smoking and sex.	Much lower prevalence rates and and higher lung function than elsewhere. SO_2<0.01 ppm, mean TSP of 90 $\mu g/m^3$.
Tsunetoshi et al. (1971)	Prevalence survey of chronic bronchitis in 9 areas of Osaka and Hyogo Pref., Japan, in residents ages 40 or more.	Multiple regression analysis indicated increasing prevalence, adjusted for age, sex and smoking, corresponding to the area gradient of air pollution.
Suzuki et al. (1978)	Prevalence survey of respiratory symptoms in housewives ages 30 or over in Japan.	Prevalence rates correlated with various pollutants, especially in older smokers.
Yoshida et al. (1976)	Prevalence of asthma in schoolchildren in areas of Japan.	Increased prevalence rates in areas with higher sulfation rates.
Kagawa and Toyama (1975) Kagawa et al. (1975)	Respiratory function of Tokyo schoolchildren.	Correlation seen with various pollutants after controlling for temperature.
Zaplatel et al. (1973)	Pulmonary function in schoolchildren in Czechoslovakia.	Some children living in areas of high air pollution had functional abnormalities.
Holland et al. (1969) Colley and Holland (1967)	Chronic bronchitis prevalence in 2365 families in 2 London suburbs, 1965.	More symptoms in previously polluted area in mothers and in children, controlling for smoking, social class, a area of residence, place of work, overcrowding, family size and genetic factors.

TABLE B-2 (Continued).

Study	Characteristics	Findings
Holland et al. (1969a,b) Bennet et al. (1973)	Prevalence of respiratory symptoms, degrees of ventilatory function, and past histories of respiratory illness in more than 10,000 school-children 5-16 years of age residing in 4 different areas of northwest London, 1964/1965. Greatest differences among areas were found in degrees of air pollution.	Childhood smoking habits and degree of air pollution were found to have the greatest influence on respiratory symptom prevalence and ventilatory function. Social class, family size, and past history of respiratory disease also contributed. All factors operated independently and exerted their effects additively.
Colley and Reid (1970)	Respiratory disease prevalence in more than 10,000 children 6-10 years old, England and Wales, 1966.	Definite gradient of past bronchitis and current cough from lowest rates in rural areas to highest rates in the most heavily polluted areas. Differences were more clear in children of semi-skilled and unskilled workers. No effect on upper respiratory illness rates.
Ramaciotti et al. (1977)	Bronchitis symptoms and peak flow in 1182 men in Geneva in relation to SO_2, smoke and NO_2 at residence, smoking, and age, 1972-76.	Regression analysis showed independent effect of SO_2, smoke and NO_2 after controlling for smoking and age.
Bouhuys et al. (1978)	Respiratory symptoms in an urban and a rural Connecticut community, adjusting for sex, race, age, smoking, occupation and previous residence.	Communities had low concentrations of TSP and SO_2, (<64 and 14 $\mu g/m^3$, resp.) No differences were found among smokers. More asthma in rural area.
Biersteker and van Leeuwen (1970a,b)	Peak flow rates in 935 school-children living in 2 districts of Rotterdam, one relatively affluent and having good air quality (40 μg of smoke per m^3 and 120 μg of SO_2 per m^3) and the other less affluent, and having 50% higher concentrations of smoke and SO_2.	No significant area differences in peak flow, adjusted for height and weight. Significantly more childhood bronchitis in more polluted district, but differences were judged to be due to poor living conditions, because low pollution area of of higher class residences.
Yoshii et al. (1969)	Chronic pharyngitis and histopathological changes in 6th grade children in 3 areas of Yokkaichi, Japan.	Correlation of both with sulfation rates seen.

TABLE B-2 (Continued).

Study	Characteristics	Findings
Waller et al. (1974)	Ventilatory function and respiratory symptom prevalence among 18-year-olds born in London just before and after the smog episode of 1952.	No differences were found between the 2 groups. Both were exposed to high degree of pollution during the 1950s. History of lower respiratory illness in childhood had major influence on current symptoms and ventilatory function.
Hammer et al. (1976)	Retrospective survey of lower respiratory illness in children 0-12 years of age living in 4 New York City area communities, 1969-1972.	Rates of total respiratory illness croup, bronchitis, and other chest infections were significantly higher among black and white children residing in communities with heavier air pollution. Differences in family size, crowding, parental smoking, and social class could not explain the findings.
Chapman et al. (1973)	Retrospective survey of chronic respiratory disease (CRD) rates in elementary and high school children living in four Utah communities, 1970.	CRD prevalence rates reflected community pollutant level differences, with statistically significant differences in CRD rates between high and low areas within sex and smoking status groups. Communities differed mainly in SO_2 levels, in the presence of similar TSP levels, suggesting qualitative relationship between CRD effects and elevated SO_2 levels. Errors in aerometry measurements around period of CRD rate measurement and limitations of retrospective estimation of earlier exposure levels preclude determination of quantitative health effects/air pollution relationships.

Qualitative Community Health Epidemiology Studies of Particulate Matter and Sulfur Oxides (PM/SO_x) Mortality Effects

Contents

Table B-3. Qualitative Association of Geographic Differences in Mortality with Residence in Areas of Heavy Air Pollution

TABLE B-3. QUALITATIVE ASSOCIATION OF GEOGRAPHIC DIFFERENCES IN MORTALITY WITH RESIDENCE IN AREAS OF HEAVY AIR POLLUTION

Study	Characteristics	Findings
Pemberton and Goldberg (1954)	1950-1952 bronchitis mortality rates in men 45 years of age and older in county boroughs of England and Wales.	Sulfur oxide concentrations (sulfation rates) were consistently correlated with bronchitis death rates in the 35 county boroughs analyzed.
Stocks (1958, 1959, 1960a,b)	Bronchitis mortality, 1950-1953, in urban and rural areas of Britian, with adjustments for population density and social index.	Significant correlation of mortality from bronchitis and pneumonia among men, and from bronchitis among females, with smoke density.
Gorham (1958, 1959)	1950-1954 deaths, 53 counties of England, Scotland, and Wales.	Bronchitis mortality was strongly correlated with acidity of winter precipitation.
Gore and Shaddick (1958) and Hewitt (1956)	Mortality in London, 1954-1958 and in 1950-1952, respectively.	Duration of residence in London significantly correlated with bronchitis mortality, after adjusting for social class.
Hagstrom et al. (1967) Zeidberg et al. (1967) Sprague and Hagstrom (1969)	1949-1960 deaths for each cause in Nashville, Tenn., categorized by census tract into 3 degrees of air pollution and 3 economic classes (levels not accurately determined).	Within the middle social class, total respiratory disease mortality, but not bronchitis and emphysema mortality, were significantly assoicated with sulfation rates and social index. White infant mortality rates were significantly related to sulfation rates.
Lepper et al. (1969)	1964/1965 mortality rates in Chicago census tracts stratified by socioeconomic class and SO_2 concentration.	Increased respiratory disease death rates in areas of intermediate and high SO_2 concentration, within a socioeconomic status, without a consistent mortality gradient between the areas of intermediate and high SO_2 concentration.
Jacobs and Landoc (1972)	1968/1970 mortality rates in Charleston, S.C., industrial vs. non-industrial areas.	Higher total and heart disease mortality rates in industrial area.
Morris et al. (1976)	1960-72 mortality rates compared to 1959-60 air pollution levels.	Mortality higher in smokers with lower air pollution exposures.

TABLE B-3 (Continued).

Study	Characteristics	Findings
Collins et al. (1971)	Death rates in children 0-14 years of age, 1958-1964, in relation to social and air pollution indices in 83 county boroughs of England and Wales.	Partial correlation analysis suggested that indices of domestic and industrial pollution account for a differences in mortality from bronchopneumonia and all respiratory diseases among children 0-1 year of age.
Toyama (1964)	Mortality in districts of Tokyo.	Bronchitis mortatliy associated with dustfall (but not cardio-vascular, pneumonia or cancer mortality).
Lindeberg (1968)	Deaths in Oslo winters.	Average deaths per week, 1958-65 winter, correlated with pollution.
US/Canada Internat. Joint Commission (1960)	Mortality, episodic and non-episodic in Detroit and Windsor (Canada in 3 areas, 1953.	Respiratory cancer and infant mortality correlated with episodic and non-episodic levels of TSP and SO_x (as did morbidity).
Buck and Brown (1964)	Bronchitis mortality in 214 areas of Britain, 1955-1959, evaluated with respect to SO_2, particulates, social index, and population density.	Social index and SO_2 accounted for 36 percent of the variation in bronchitis mortality within county and noncounty boroughs and in urban districts. Within London boroughs, social index was the most important factor.
Winkelstein et al. (1967), Winkelstein and Kantor (1967), Winkelstein and Gray (1971)	120 census tracts in Buffalo stratified into 4 degrees of particulate pollution and cross-stratified into 5 economic classes.	Within an economic class, death rates of white male 50-69 years of age, for all causes and for chronic respiratory disease corresponded to the gradient of particulate, but not SO_2 pollution.
Zeidberg et al. (1967)	1949-1960 deaths for each cause in Nashville, Tenn., categorized by census tract into 3 degrees of pollution and 3 economic classes.	Within the middle social class, total respiratory disease mortality, but not bronchitis and emphysema mortality, were significantly associated with sulfation rates and social index. White infant mortality rates were significantly related to sulfation rates.

TABLE B-3 (Continued).

Study	Characteristics	Findings
Burn and Pemberton (1963)	1950/59 deaths from all causes, bronchitis and lung cancer in 3 polluted areas of Salford, U.K.	The gradient of mortality from all causes and from bronchitis and lung cancer followed the pollution gradient.
Wicken and Buck (1964)	1952-62 deaths from bronchitis and lung cancer in areas of northeast England.	Differences in death rates between areas were correlated with their differences in air pollution.
Kevany et al. (1975)	1970-73 deaths from various causes in Dublin, Ireland.	Partial correlation analysis was significant for air pollutants and some specific causes of death.
Watanabe and Kaneko (1971)	1965-66 mortality by cause in 3 areas of Osaka, Japan.	A stepwise increase in circulatory mortality was related to air pollution independent of temperature.

APPENDIX C

OCCUPATIONAL HEALTH STUDIES ON PARTICULATE MATTER AND SULFUR OXIDES

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