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INTRODUCTION AND BACKGROUND

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This book identifies and critically reviews current knowledge on human exposure to selected chemical agents and physical factors in the ambient environment and the effects of such exposures on human health. It provides a state-of-the-art knowledge base essential for risk assessment for exposed individuals and populations to guide public health authorities, primary care physicians, and industrial managers having to deal with the consequences of environmental exposure.

Aside from professionals in public health, medicine, and industry who may use this book to guide their management functions, the volume can also be used in graduate and post-doctoral training programs in universities and by toxicologists, clinicians, and epidemiologists in research as a resource for the preparation of research proposals and scientific papers.

The subject is environmental toxicants, that is, chemical or physical agents released into the general environment that can produce adverse health effects among large numbers of people. Such effects are usually subclinical, except when cumulative changes lead to chronic effects after long exposure. Short-term responses following acute exposures are often manifest as transient alterations in physiological function that may, in some sensitive members of the population, be of sufficient magnitude to be considered adverse. Each of the specific topic chapters has a thorough discussion of the extent of human exposure as well as of toxic responses. The four chapters on the uses of the data for risk assessment, risk management, clinical applications, and industrial operations provide guidance for those performing individual and/or collective population hazard evaluations. The first provides individuals and public agency personnel with a basis for decisions on risk avoidance and relative risk assessment. The second outlines the operational philosophies and techniques used by environmental engineers in scoping and managing environmental risks. The third enables the primary care physician to recognize diseases and symptoms associated with exposures to environmental toxicants and to provide counsel to patients. The fourth assists decision makers in industry in evaluating the potential impacts of their plant operations and products on public health.

Environmental Toxicants, *Third Edition* Edited by Morton Lippmann

Although many books provide brief reviews of hundreds of chemicals encountered in the work environment at levels that can cause demonstrable health effects, both acute and chronic, they contain relatively little information on the effects of low-level exposures on large populations of primary interest in environmental health and risk assessment. This book has been designed to provide in-depth, critical reviews of the environmental toxicants of contemporary public health concern.

1.1 CHARACTERIZATION OF CHEMICAL CONTAMINANTS

1.1.1 Concentration Units

In environmental science, confusion often arises from the use of the same or similar sounding terms having different meanings in different contexts. This is especially true in describing the concentrations of air and water contaminants. Solutes are frequently expressed in parts per million (ppm) or parts per billion (ppb). However, when used for air contaminants, the units are molar or volume fractions, whereas when used for water contaminants, they are weight fractions. This problem can be avoided by expressing all fluid contaminant concentrations as the weight of contaminant per unit volume (e.g., m^3 or L) of fluid. In air, the units generally used are mg/m^3 or $\mu g/m^3$, whereas in water they are most often mg/L or μg/L.

1.1.2 Air Contaminants

Chemical contaminants can be dispersed in air at normal ambient temperatures and pressures in gaseous, liquid, and solid forms. The latter two represent suspensions of particles in air and were given the generic term "aerosols" by Gibbs (1924) on the basis of analogy to the term "hydrosol," used to describe disperse systems in water. On the contrary, gases and vapors, which are present as discrete molecules, form true solutions in air. Particles consisting of moderate- to high-vapor-pressure materials tend to evaporate rapidly, since those small enough to remain suspended in air for more than a few minutes (i.e., those smaller than about 10 μm) have large surface-to-volume ratios. Some materials with relatively low vapor pressures can have appreciable fractions in both the vapor and aerosol forms simultaneously.

1.1.2.1 Gases and Vapors Once dispersed in air, contaminant gases and vapors generally form mixtures so dilute that their physical properties, such as density, viscosity, enthalpy, and so on are indistinguishable from those of clean air. Such mixtures may be considered to follow ideal gas law relationships. There is no practical difference between a gas and a vapor except that the latter is generally considered to be the gaseous phase of a substance that is normally a solid or liquid at room temperature. While dispersed in the air, all molecules of a given compound are essentially equivalent in their size and probabilities of contact with ambient surfaces, respiratory tract surfaces, and contaminant collectors or samplers.

1.1.2.2 Aerosols Aerosols, being dispersions of solid or liquid particles in air, have the very significant additional variable of particle size. Size affects particle motion and, hence, the probabilities for physical phenomena such as coagulation, dispersion, sedimentation, impaction onto surfaces, interfacial phenomena, and light-scattering properties. It is not possible to fully characterize a given particle by a single size parameter. For example, a

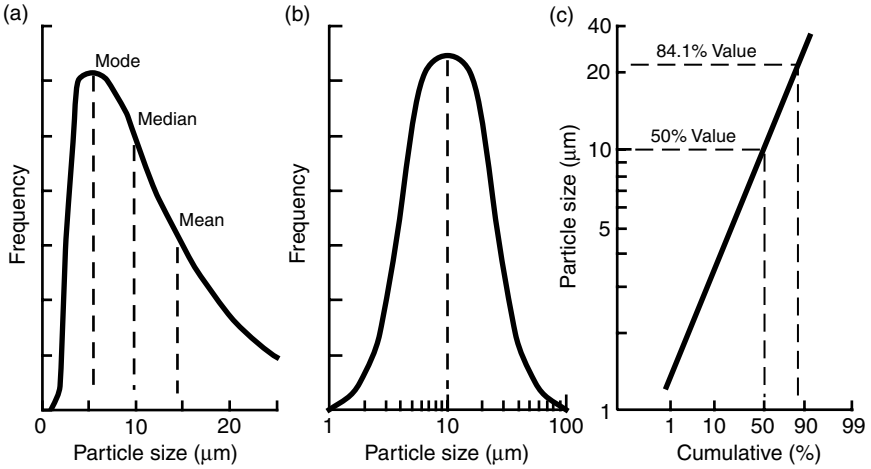

FIGURE 1.1 Particle size distribution data. (a) Plotted on linear coordinates. (b) Plotted on a logarithmic size scale. (c) In practice, logarithmic probability coordinates are used to display the percentage of particles less than a specific size versus that size. The geometric standard deviation (s_g) of the distribution is equal to the 84.1% size/50% size.

particle's aerodynamic properties depend on density and shape as well as linear dimensions, and the effective size for light scattering is dependent on refractive index and shape.

In some special cases, all of the particles are essentially the same in size. Such aerosols are considered to be monodisperse. Examples are natural pollens and some laboratory-generated aerosols. More typically, aerosols are composed of particles of many different sizes and hence are called heterodisperse or polydisperse. Different aerosols have different degrees of size dispersion. It is, therefore, necessary to specify at least two parameters in characterizing aerosol size: a measure of central tendency, such as a mean or median, and a measure of dispersion, such as an arithmetic or geometric standard deviation.

Particles generated by a single source or process generally have diameters following a lognormal distribution; that is, the logarithms of their individual diameters have a Gaussian distribution. In this case, the measure of dispersion is the geometric standard deviation, which is the ratio of the 84.16 percentile size to the 50th percentile size (Fig. 1.1). When more than one source of particles is significant, the resulting mixed aerosol will usually not follow a single lognormal distribution, and it may be necessary to describe it by the sum of several distributions.

1.1.3 Particle Characteristics

There are many properties of particles, other than their linear size, that can greatly influence their airborne behavior and their effects on the environment and health. These include

Surface: For spherical particles, the surface varies as the square of the diameter. However, for an aerosol of given mass concentration, the total aerosol surface increases with decreasing particle size. Airborne particles have much greater ratios of external surface to volume than do bulk materials and, therefore, the particles can dissolve or participate in surface reactions to a much greater extent than would massive samples of the same materials. Furthermore, for nonspherical solid particles

or aggregate particles, the ratio of surface to volume is increased, and for particles with internal cracks or pores, the internal surface area can be much greater than the external area.

Volume: Particle volume varies as the cube of diameter; therefore, the few largest particles in an aerosol tend to dominate its volume concentration.

Shape: A particle's shape affects its aerodynamic drag as well as its surface area and therefore its motion and deposition probabilities.

Density: A particle's velocity in response to gravitational or inertial forces increases as the square root of its density.

Aerodynamic diameter: The diameter of a unit-density sphere having the same terminal settling velocity as the particle under consideration is equal to its aerodynamic diameter. Terminal settling velocity is the equilibrium velocity of a particle that is falling under the influence of gravity and fluid resistance. Aerodynamic diameter is determined by the actual particle size, the particle density, and an aerodynamic shape factor.

1.1.3.1 Types of Aerosols Aerosols are generally classified in terms of their processes of formation. Although the following classification is neither precise nor comprehensive, it is commonly used and accepted in the industrial hygiene and air pollution fields:

Dust: An aerosol formed by mechanical subdivision of bulk material into airborne fines having the same chemical composition. A general term for the process of mechanical subdivision is *comminution*, and it occurs in operations such as abrasion, crushing, grinding, drilling, and blasting. Dust particles are generally solid and irregular in shape and have diameters greater than 1 μm.

Fume: An aerosol of solid particles formed by condensation of vapors formed at elevated temperatures by combustion or sublimation. The primary particles are generally very small (less than 0.1 μm) and have spherical or characteristic crystalline shapes. They may be chemically identical to the parent material, or they may be composed of an oxidation product such as a metal oxide. Since they may be formed in high number concentration, they often rapidly coagulate, forming aggregate clusters of low overall density.

Smoke: An aerosol formed by condensation of combustion products, generally of organic materials. The particles are generally liquid droplets with diameters of less than 0.5 μm.

Mist: A droplet aerosol formed by mechanical shearing of a bulk liquid, for example, by atomization, nebulization, bubbling, or spraying. The initial droplet size can cover a very large range, usually from about 2 μm to greater than 50 μm.

Fog: An aqueous aerosol formed by condensation of water vapor on atmospheric nuclei at high relative humidities. The droplet sizes are generally greater than 1 μm.

Smog: A popular term for a pollution aerosol derived from a combination of smoke and fog. It is now commonly used for any atmospheric pollution mixture.

Haze: A submicrometer-sized aerosol of hygroscopic particles that take up water vapor at relatively low relative humidities.

Aitken or condensation nuclei (CN): Very small atmospheric particles (mostly smaller than 0.1 μm) formed by combustion processes and by chemical conversion from gaseous precursors.

Accumulation mode: A term given to the particles in the ambient atmosphere ranging from 0.1 to about 1.0 μm, and extending up to 2.5 μm for hygroscopic particles in humid atmospheres. These particles generally are spherical, have liquid surfaces, and form by coagulation and condensation of smaller particles that derive from gaseous precursors. Being too few for rapid coagulation, and too small for effective sedimentation, they tend to accumulate in the ambient air.

Coarse particle mode: Ambient air particles larger than about 2.5 μm and generally formed by mechanical processes and surface dust resuspension.

1.1.3.2 Aerosol Characteristics Aerosols have integral properties that depend upon the concentration and size distribution of the particles. In mathematical terms, these properties can be expressed in terms of certain constants or "moments" of the size distribution (Friedlander, 1977). Some integral properties such as light-scattering ability or electrical charge depend on other particle parameters as well. Some of the important integral properties are:

Number concentration: The total number of airborne particles per unit volume of air, without distinction as to their sizes, is the zeroth moment of the size distribution. In current practice, instruments are available that count the numbers of particles of all sizes from about 0.005 to 50 μm. In many specific applications, such as fiber counting for airborne asbestos, a more restricted size range is specified.

Surface concentration: The total external surface area of all the particles in the aerosol, which is the second moment of the size distribution, may be of interest when surface catalysis or gas adsorption processes are of concern. Aerosol surface is one factor affecting light-scatter and atmospheric-visibility reductions.

Volume concentration: The total volume of all the particles, which is the third moment of the size distribution, is of little intrinsic interest in itself. However, it is closely related to the mass concentration, which for many environmental effects is the primary parameter of interest.

Mass concentration: The total mass of all the particles in the aerosol is frequently of interest. The mass of a particle is the product of its volume and density. If all of the particles have the same density, the total mass concentration is simply the volume concentration times the density. In some cases, such as "respirable," "thoracic," and "inhalable" dust sampling (Vincent, 1999), the parameter of interest is the mass concentration over a restricted range of particle size. In these applications, particles outside the size range of interest are excluded from the integral.

Dustfall: The mass of particles depositing from an aerosol onto a unit surface per unit time is proportional to the fifth moment of the size distribution. Dustfall has long been of interest in air pollution control because it provides an indication of the soiling properties of the aerosol.

Light scatter: The ability of airborne particles to scatter light and cause a visibility reduction is well known. Total light scatter can be determined by integrating the aerosol surface distribution with the appropriate scattering coefficients.

1.1.4 Water Contaminants

Chemical contaminants can be found in water, in solution, or as hydrosols; the latter are immiscible solid or liquid particles in suspension. An aqueous suspension in liquid particles

is generally called an *emulsion*. Many materials with relatively low aqueous solubility will be found in both dissolved and suspended forms.

1.1.4.1 Dissolved Contaminants Water is known as the universal solvent. Although there are many compounds that are not completely soluble in water, there are a few that do not have some measurable solubility. In fact, the number of chemical contaminants in natural waters is primarily a function of the sensitivity of the analyses. For organic compounds in rivers and lakes, it has been observed that as the limits of detection decrease by an order of magnitude, the numbers of compounds detected increase by an order of magnitude, so that one might expect to find at least 10–12 g/L (approximately 1010 molecules/L) of each of the million organic compounds reported in the literature (NIEHS, 1977). Similar considerations undoubtedly apply to inorganic chemicals as well.

1.1.4.2 Dissolved Solids Water-quality criteria generally include a nonspecific parameter called "dissolved solids." However, it is customary to exclude natural mineral salts such as sodium chloride from this classification. Also, water criteria for specific toxic chemicals dissolved in water are frequently exceeded without there being an excessive total dissolved-solids content.

1.1.4.3 Dissolved Gases Compounds dissolved in water may also exist in the gaseous phase at normal temperatures and pressures. Some of these, such as hydrogen sulfide (HS_2), and ammonia (NH_3), which are generated by decay processes, are toxicants.

Oxygen (O_2) is the most critical of the dissolved gases with respect to water quality. It is essential to most higher aquatic life forms and is needed for the oxidation of most of the organic chemical contaminants to more innocuous forms. Thus, a critical parameter of water quality is the concentration of dissolved oxygen (DO). Another important parameter is the extent of the oxygen "demand" associated with contaminants in the water. The most commonly used index of oxygen demand is the 5-day biochemical oxygen demand (BOD after 5 days of incubation). Another is the chemical oxygen demand (COD).

1.1.4.4 Suspended Particles A nonspecific water-quality parameter that is widely used is "suspended solids." The stability of aqueous suspensions depends on particle size, density, and charge distributions. The fate of suspended particles depends on a number of factors, and particles can dissolve, grow, coagulate, or be ingested by various life forms in the water. They can become "floating solids" or part of an oil film, or they can fall to the bottom to become part of the sediments.

There are many kinds of suspended particles in natural waters, and not all of them are contaminants. Any moving water will have currents that cause bottom sediments to become resuspended. Also, natural runoff will carry soil and organic debris into lakes and streams. In any industrialized area, such sediment and surface debris will always contain some chemicals considered to be contaminants. However, a large proportion of the mass of such suspended solids would usually be "natural," and would not be considered as contaminants.

The suspended particles can have densities that are less than, equal to, or greater than that of the water, so that the particles can rise as well as fall. Furthermore, the effective density of particles can be reduced by the attachment of gas bubbles.

Gas bubbles form in water when the water becomes saturated and cannot hold any more of the gas in solution. The solubility of gases in water varies inversely with temperature. For example, oxygen saturation of fresh water is 14.2 ml/L at 0°C and 7.5 mg/L at 30°C, and in seawater the corresponding values are 11.2 and 6.1 mg/L.

1.1.5 Food Contaminants

Chemical contaminants of almost every conceivable kind can be found in most types of human food. Food can acquire these contaminants at any of several stages in its production, harvesting, processing, packaging, transportation, storage, cooking, and serving. In addition, there are many naturally occurring toxicants in foods as well as compounds that can become toxicants upon conversion by chemical reactions with other constituents or additives or by thermal or microbiological conversion reactions during processing, storage, or handling.

Each food product has its own natural history. Most foods are formed by selective metabolic processes of plants and animals. In forming tissue, these processes can act either to enrich or to discriminate against specific toxicants in the environment. For animal products, where the flesh of interest in foods was derived from the consumption of other life forms, there are likely to be several stages of biological discrimination and, therefore, large differences between contaminant concentrations in the ambient air and/or water and the concentrations within the animals.

1.2 HUMAN EXPOSURES AND DOSIMETRY

People can be exposed to chemicals in the environment in numerous ways. The chemicals can be inhaled, ingested, or taken up by and through the skin. Effects of concern can take place at the initial epithelial barrier, that is, the respiratory tract, the gastrointestinal (GI) tract, or the skin, or can occur in other organ systems after penetration and translocation by diffusion or transport by blood, lymph, and so on. As illustrated in Fig. 1.2, exposure and dose factors are intermediate steps in a larger continuum ranging from release of chemicals into an environmental medium to an ultimate health effect.

Exposure is a key step in this continuum and a complex one. The concept of total human exposure has developed in recent years as essential to the appreciation of the nature and extent of environmental health hazards associated with ubiquitous chemicals at low levels.

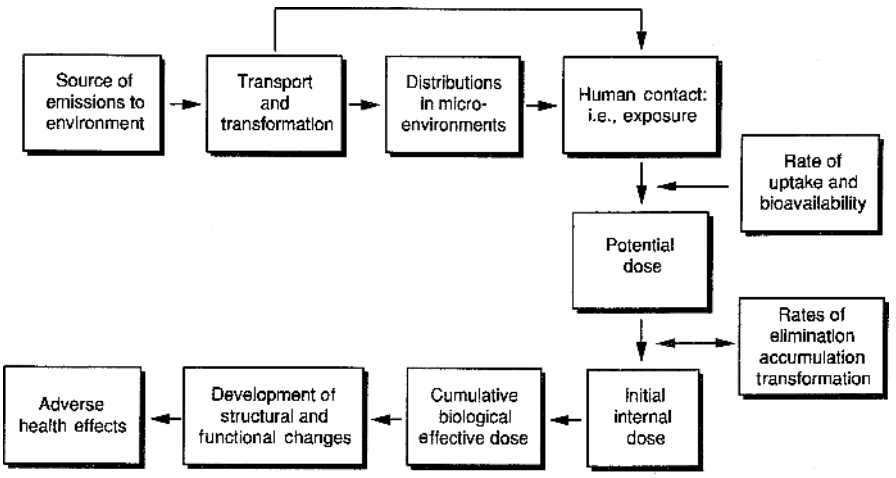

FIGURE 1.2 Environmental and biological modifiers of human exposure and health responses.

It provides a framework for considering and evaluating the contribution to the total insult from dermal uptake, ingestion of food and drinking water, and inhaled doses from potentially important microenvironments such as workplace, home, transportation, recreational sites, and so on. More thorough discussions of this key concept have been prepared by Sexton and Ryan (1988), Lioy (1990), and the National Research Council (NRC, 1991). Guidelines for Exposure Assessment have been formalized by the U.S. Environmental Protection Agency (U.S. EPA, 1992).

1.3 CHEMICAL EXPOSURES AND DOSE TO TARGET TISSUES

Toxic chemicals in the environment that reach sensitive tissues in the human body can cause discomfort, loss of function, and changes in structure leading to disease. This section addresses the pathways and transport rates of chemicals from environmental media to critical tissue sites as well as retention times at those sites. It is designed to provide a conceptual framework as well as brief discussions of: (1) the mechanisms for—and some quantitative data on—uptake from the environment; (2) translocation within the body, retention at target sites, and the influence of the physicochemical properties of the chemicals on these factors; (3) the patterns and pathways for exposure of humans to chemicals in environmental media; (4) the effects of chemicals at the cellular and organ levels; and (5) the influence of age, sex, size, habits, health status, and so on.

An agreed on terminology is critically important when discussing the relationships between toxic chemicals in the environment and human health. The terms used in this book are defined below:

Exposure: Contact with external environmental media containing the chemical of interest. For fluid media in contact with the skin or respiratory tract, both concentration and contact time are critical. For ingested material, concentration and amount consumed are important.

Deposition: Capture of the chemical at a body surface site on skin, respiratory tract, or GI tract.

Clearance: Translocation from a deposition site to a storage site or depot within the body, or elimination from the body.

Retention: Presence of residual material at a deposition site or along a clearance pathway.

Dose: Amount of chemical deposited on or translocated to a site on or within the body where toxic effects take place.

Target tissue: A site within the body where toxic effects lead to damage or disease. Depending on the toxic effects of concern, a target tissue can extend from whole organs down to specific cells to sub-cellular constituents.

Exposure surrogates or indices: Indirect measures of exposure, such as: (1) concentra tions in environmental media at times or places other than those directly encountered; (2) concentrations of the chemical of interest, a metabolite of the chemical, or an enzy me induced by the chemical in circulating or excreted body fluids; and (3) elevations in body burden as measured by external probes.

In summary, exposure represents contact between a concentration of an agent in air, water, food, or other material and the person or population of interest. The agent is the source

of an internal dose to a critical cell, organ, or tissue. The magnitude of the dose depends on a number of factors: (1) the volumes inhaled or ingested; (2) the fractions of the inhaled or ingested material transferred across epithelial membranes of the skin, the respiratory tract, and the GI tract; (3) the fractions transported via circulating fluids to target tissues; and (4) the fractional uptake by the target tissues. Each of these factors can have considerable intersubject variability. Sources of variability include activity level, age, sex, and health status as well as such inherent variabilities as race and size.

With chronic or repetitive exposures, other factors affect the dose of interest. When the retention at, or effects on, the target tissues are cumulative and clearance or recovery is slow, the dose of interest can be represented by cumulative uptake. However, when the agent is rapidly eliminated, or when its effects are rapidly and completely reversible on removal from exposure, rate of delivery may be the dose parameter of primary interest.

1.4 CONCENTRATION OF TOXIC CHEMICALS IN HUMAN MICROENVIRONMENTS

The technology for sampling air, water, and food is relatively well developed, as are the technologies for sample separation from copollutants, media, and interferences and for quantitative analyses of the components of interest. However, knowing when, where, how long, and at which rate and frequency to sample to collect data relevant to the exposures of interest is difficult, and requires knowledge of temporal and spatial variability of exposure concentrations. Unfortunately, we seldom have enough information of these kinds to guide our sample collections. Many of these factors are discussed in detail in the chapters that follow as they apply to the specific environmental toxicants being discussed.

1.4.1 Water and Foods

Concentrations of environmental chemicals in food and drinking water are extremely variable, and there are further variations in the amounts consumed because of the extreme variability in dietary preferences and food sources. The number of foods for which up-to-date concentration data for specific chemicals are available is extremely limited. Relevant human dietary exposure data are sometimes available in terms of market basket survey analyses. In this approach, foods for a mixed diet are purchased, cleaned, processed, and prepared as for consumption, and one set of specific chemical analyses is done for the composite mixture that is consumed.

The concentrations of chemicals in potable piped water supplies depend greatly on the source of the water and its treatment history. Surface waters from protected watersheds generally have low concentrations of both dissolved minerals and environmental chemicals. Well waters usually have low concentrations of bacteria and environmental chemicals, but often have high mineral concentrations. Poor waste disposal practices may contribute to ground water contamination, especially in areas of high population density. Treated surface waters from lakes and rivers in densely populated and/or industrialized areas usually contain a wide variety of dissolved organics and trace metals, the concentrations of which vary greatly with season (because of variable surface runoff), with proximity to pollutant sources, with upstream usage, and with treatment efficacy.

Uptake of environmental chemicals in bathing waters across intact skin is usually minimal in comparison to uptake via inhalation or ingestion. It depends on both the

concentration in the fluid surrounding the skin surface and the polarity of the chemical, with more polar chemicals having less ability to penetrate the intact skin. Uptake via skin can be significant for occupational exposures to concentrated liquids or solids.

1.4.2 Air

Although chemical uptake through ingestion and the skin surface is generally intermittent, inhalation provides a continuous means of exposure. The important variables affecting the uptake of inhaled chemicals are the depth and frequency of inhalation and the concentration and physicochemical properties of the chemicals in the air.

Exposures to airborne chemicals vary widely among inhalation microenvironments, the categories of which include workplace, residence, outdoor ambient air, transportation, recreation, and public spaces. There are also wide variations in exposure within each category, depending on the number and strength of the sources of the airborne chemicals, the volume and mixing characteristics of the air within the defined microenvironment, the rate of air exchange with the outdoor air, and the rate of loss to surfaces within the microenvironment.

1.4.3 Workplace

Exposures to airborne chemicals at work are extremely variable in terms of composition and concentration, depending on the materials being handled, the process design and operation, the kinds and degree of engineering controls applied to minimize release to the air, work practices followed, and personal protection provided. Workplace air monitoring often involves breathing zone sampling, generally with passive samplers for gases and vapors or with personal battery-powered extraction samplers for both gases and particles; these operate over periods of 1–8 h. Analyses of the samples collected can provide accurate measures of individual exposures to specific air contaminants.

Workplace air monitoring is also frequently done with fixed-site samplers or direct reading instruments. However, air concentrations at fixed sites may differ substantially from those in the breathing zones of individual workers. The fixed-site data may be relatable to the breathing zone when appropriate intercomparisons can be made, but otherwise they represent crude surrogates of exposure. The characteristics of equipment used for air sampling in industry are described in detail in *Air Sampling Instruments* (ACGIH, 2001).

1.4.4 Residential

Airborne chemicals in residential microenvironments are attributable to their presence in the air infiltrating from out-of-doors and to their release from indoor sources. The latter include unvented cooking stoves and space heaters, cigarettes, consumer products, and volatile emissions from wallboard, textiles, carpets, and so on. Personal exposures to chloroform, largely from indoor residential sources, are illustrated in Fig. 1.3, and the influence of smoking in the home on indoor exposures to respirable particulate matter is illustrated in Fig. 1.4. Indoor sources can release enough nitrogen dioxide (NO_2), fine particle mass (FPM), and formaldehyde (HCHO) that indoor concentrations for these chemicals can be much higher than those in ambient outdoor air. Furthermore, their contributions to the total human exposure are usually even greater, since people usually spend much more time at home than in the outdoor ambient air.

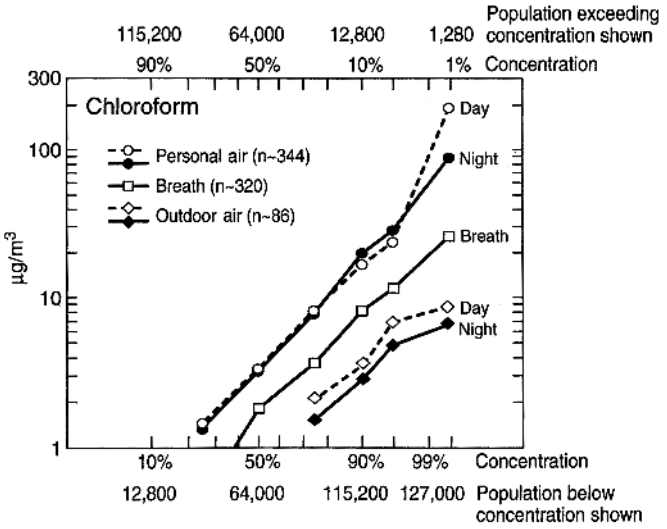

FIGURE 1.3 Estimated frequency distributions of personal air exposures to chloroform: outdoor air concentrations, and exhaled breath values in Elizabeth-Bayonne, NJ area. *Note*: Air values are 12-h integrated samples. Breath value was taken following the daytime air sample (6:00 a.m. to 6:00 p.m.). Outdoor air samples were taken near participants' homes. *Source*: Wallace et al. (1985).

1.4.5 Outdoor Ambient Air

For pollutants having national ambient air quality standards (NAAQS), there is an extensive network of fixed-site monitors, generally on rooftops. Although these devices generate large volumes of data, the concentrations at these sites may differ substantially from the concentrations that people breathe, especially for tailpipe pollutants such as carbon monoxide (CO), and reactive chemicals, such as ozone (O_3) and sulfur dioxide (SO_2). Data for other toxic pollutants in the outdoor ambient air are not generally collected on as routine a basis.

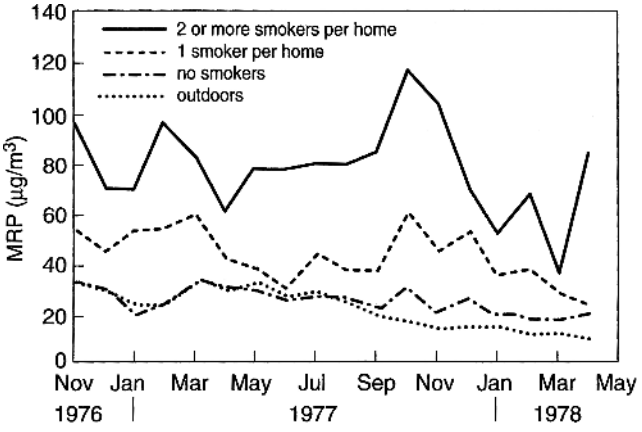

FIGURE 1.4 Respirable particle concentrations, six U.S. cities, November 1976 to April 1978. *Source*: National Academy of Science (1981).

1.4.6 Transportation

Many people spend from 1/2 to 3 h each day in autos or mass transport as they go to work, to school, or shopping. Inhalation exposures to CO in vehicles and garages can represent a significant fraction of total CO exposures.

1.4.7 Recreation and Public Spaces

Recreational exposure while exercising may be important to total daily exposure because the increased respiratory ventilation associated with exercise can produce much more than proportional increases in delivered dose and functional responses. Spectators and athletes in closed arenas can be exposed to high concentration of pollutants. For example, Spengler et al. (1978) documented high exposures to CO at ice rinks from exhaust discharges by the ice-scraping machinery.

1.5 INHALATION EXPOSURES AND RESPIRATORY TRACT EFFECTS

1.5.1 Deposition and Absorption

The surface and systemic uptake of chemicals from inhaled air depend on both their physical and chemical properties and on the anatomy and pattern of respiration within the respiratory airways. The basic structure of the respiratory tract is illustrated in Fig. 1.5. The following discussion outlines some of the primary factors affecting the deposition and retention of inhaled chemicals. More comprehensive discussions are available in recent reviews (ICRP, 1994; NCRP, 1997; U.S. EPA, 1996). Figure 1.6, from the 1994 ICRP Report, summarizes the morphometry, cytology, histology, function, and structure of the human respiratory tract, while Fig. 1.7 shows the compartmental model developed by ICRP (1994) to summarize particle transport from the deposition sites within the respiratory tract.

Gases and vapors rapidly contact airway surfaces by molecular diffusion. Surface uptake is limited for compounds that are relatively insoluble in water, such as O_3. For such chemicals, the greatest uptake can be in the lung periphery, where the residence time and surface areas are the greatest. For more water-soluble gases, dissolution and/or reaction with surface fluids on the airways facilitates removal from the airstream. Highly water-soluble vapors, such as SO_2, are almost completely removed in the airways of the head, and very little of them penetrates into lung airways.

For airborne particles, the most critical parameter affecting patterns and efficiencies of surface deposition is particle size. The mechanisms for particle deposition within respiratory airways are illustrated in Fig. 1.8. Almost all of the mass of airborne particulate matter is found in particles with diameters greater than 0.1 μm. Such particles have diffusional displacements many orders of magnitude smaller than those of gas molecules, and they are small in relation to the sizes of the airways in which they are suspended. Thus, the penetration of airborne particles into the lung airways is determined primarily by convective flow; that is, the motion of the air in which the particles are suspended.

Some deposition by diffusion does occur for particles <0.5 μm in small airways, where it is favored by the small size of the airways and the low flow velocities in such airways. For particles >0.5 μm, deposition by sedimentation occurs in small to midsized airways. For particles with aerodynamic diameters >2 μm, particle inertia is sufficient to cause particle motion to deviate from the flow streamlines, resulting in deposition by impaction on surfaces

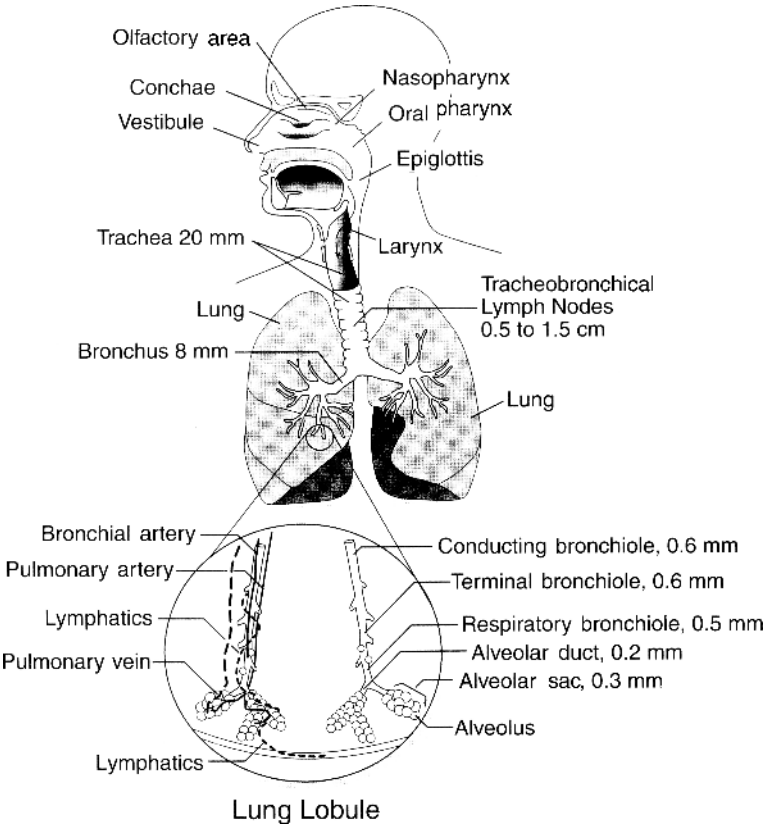

FIGURE 1.5 Structure of the respiratory tract. Reproduced from National Research Council (1979).

downstream of changes in flow direction, primarily in mid- to large-sized airways, which have the highest flow velocities. The concentration of deposition on limited surface areas within the large airways is of special interest with respect to dosimetry and the pathogenesis of chronic lung diseases such as bronchial cancer and bronchitis.

Although particle inertia accounts for much of the "hot-spot" deposition on the trachea below the laryngeal jet and at the bifurcations of large lung airways, some of the concentrated deposition is attributable to inertial airflow, which directs a disproportionately large fraction of the flow volume toward such surfaces and, at the same time, lessens the boundary layer thickness. Thus, there is some preferential deposition of submicrometer-sized particles and gas molecules at small airway bifurcations.

Quantitative aspects of particle deposition are summarized in Figs. 1.9–1.12. It can be seen that deposition efficiencies in the major structural–functional regions of the human respiratory tract are both strongly particle size dependent and highly variable among normal humans. Additional variability results from structural changes in the airways associated with disease processes. Generally, these involve airway narrowing or localized constrictions, which act to increase deposition and concentrate it on limited surface areas.

All of the preceding was based on the assumption that each particle has a specific size. For particles that are hygroscopic, there is considerable growth in size as they take up water vapor

Functions	Cylology (Epithelium)	Histology (Walls)	Generation Number	Anatomy	Regions used in Model: New	Regions used in Model: Old*	Zones (Air)	Location	Airway Surface	Number of Airways
Air conditioning; temperature and humidily, and cleaning; fast particle clearance; air conduction	Respiratory epithelium with goblet cells; Cell types: - Ciliated cells - Nonciliated cells: • Goblet cells • Mucous (secretory) cells • Serous cells • Brush cells • Endocrine cells • Basal cells • Intermediate cells	Mucous membrane, respiratory epithelium (pseudostratified, ciliated, mucous), glands Mucous membrane, respiratory or stratified epithelium, glands		Anterior nasal passages	ET_1	(N-P)	Conditioning	Extrathoracic	2×10^{-3} m^2	—
				Nose, Mouth, Pharynx posterior, Larynx, Esophagus	ET_2	(N-P)	Conditioning	Extrathoracic	4.5×10^{-2} m^2	—
		Mucous membrane, respiratory epithelium, cartilage rings, glands	0	Trachea	BB	(T-B)	Conditioning	Extrapulmonary	3×10^{-2} m^2	511
			1	Main bronchi	BB	(T-B)	Conditioning	Extrapulmonary	3×10^{-2} m^2	511
		Mucous membrane, respiratory epithelium, cartilage plates, smooth muscle layer, glands	2 – 8	Bronchi	BB	(T-B)	Conditioning	Extrapulmonary	3×10^{-2} m^2	511
	Respiratory epithelium with clara cells (No goblet cells) Cell types: - Ciliated cells - Nonciliated cells • Clara (secretory) cells	Mucous membrane, respiratory epithelium, no cartilage, no glands, smooth muscle layer	9 – 14	Bronchioles	bb	(T-B)	Conduction	Extrapulmonary	2.6×10^{-1} m^2	6.5×10^4
		Mucous membrane, single-layer respiratory epithelium, less ciliated, smooth muscle layer	15	Terminal bronchioles	bb	(T-B)	Conduction	Extrapulmonary	2.6×10^{-1} m^2	6.5×10^4
Air conduction; gas exchange; slow particle clearance	Respiratory epithelium consisting mainly of clara cells (secretory) and few ciliated cells	Mucous membrane, single-layer respiratory epithelium of cuboidal cells, smooth muscle layers	16 – 18	Respiratory bronchioles	AI	P	Gas-exchange transitory	Pulmonary	7.5 m^2	4.6×10^5
Gas exchange; very slow particle clearance	Squamous alveolar epithelium cells (Type i), covering 93% of alveolar surface areas Cuboidal alveolar epithelial cells (Type il. Surfactant-producing), covering 7% of alveolar surface area Alveolar macrophages	Wall consists of alveolar entrance rings, squamous epithelial layer, surfactant	**	Alveolar ducts	AI	P	Gas-exchange transitory	Pulmonary	140m^2	4.5×10^7
		Interalveolar septa covered by squamous epithelium, containing capillaries, surfactant	**	Alveolar sacs	AI	P	Gas-exchange transitory	Pulmonary	140m^2	4.5×10^7
				Lymphatics		L				

LN_{ET} (New) and LN_{TH} † (New) — Old*: (N-P) and (T-B)

Zones (Air): Conditioning; Conduction; Gas-exchange transitory; 0.175×10^{-3} m^3 (Anatomical Dead Space); 0.2×10^{-3} m^3; 4.5×10^{-3} m^3

Location: Extrathoracic; Thoracic; Extrapulmonary; Pulmonary

* Previous ICRP model.
** Unnumbered because of imprecise information.
† Lymph nodes are located only in BB region but drain the bronchial and alveolar interstitial regions as well as the bronchial region.

FIGURE 1.6 Morphometry, cytology, histology, function, and structure of the respiratory tract and regions used in the 1994 ICRP dosimetry model.

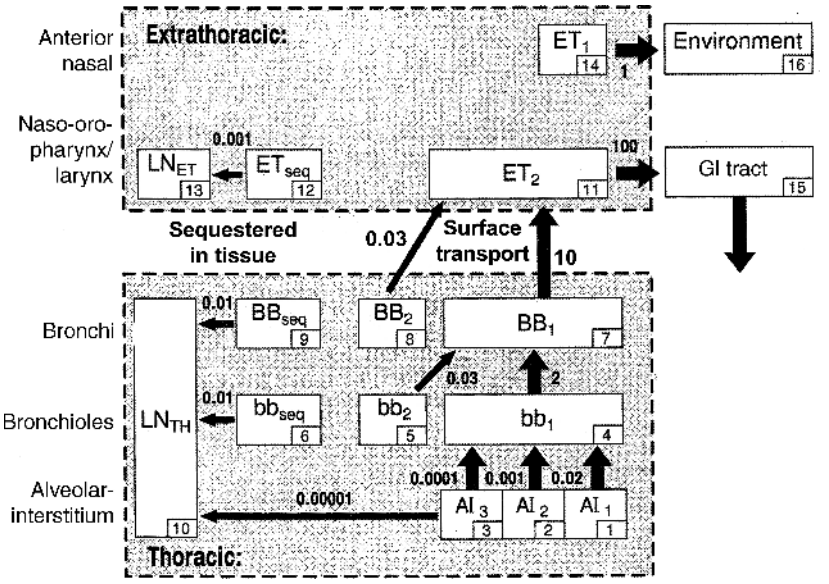

FIGURE 1.7 Compartment model to represent time-dependent particle transport from each region in 1994 ICRP model. Particle transport rate constants shown beside the arrows are reference values in d^{-1}. Compartment numbers (shown in the lower right-hand corner of each compartment box) are used to define clearance pathways. Thus, the particle transport rate from bb_1 to BB_1 is denoted $m_{4,7}$ and has the value $2\,d^{-1}$.

in the airways. Some hygroscopic growth curves for acidic and ambient aerosols are illustrated in Fig. 1.13.

Materials that dissolve into the mucus of the conductive airways or the surfactant layer of the alveolar region can rapidly diffuse into the underlying epithelia and the circulating blood, thereby gaining access to tissues throughout the body. Chemical reactions and metabolic processes may occur within the lung fluids and cells, limiting access of the inhaled material to the bloodstream and creating reaction products with either greater or lesser solubility and biological activity. Few generalizations about absorption rates are possible.

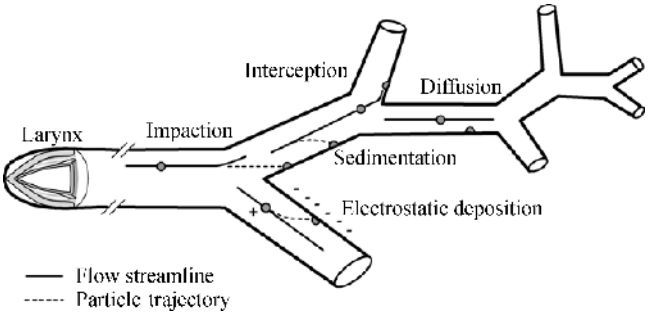

FIGURE 1.8 Schematic of mechanism for particle deposition in respiratory airways. *Source*: Lippmann and Schlesinger (1984).

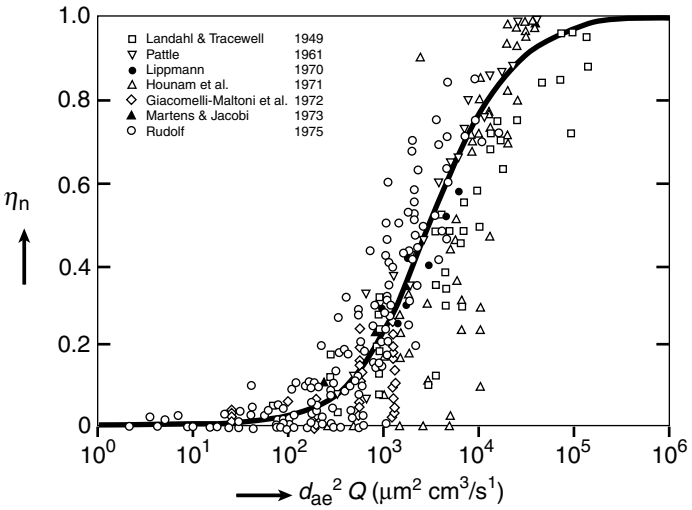

FIGURE 1.9 Inspiratory deposition of the human nose as a function of particle aerodynamic diameter and flow rate ($d_{ae}^2 Q$). From: EPA (1997).

1.5.2 Translocation and Retention

Particles that do not dissolve at deposition sites can be translocated to remote retention sites by passive and active clearance processes. Passive transport depends on movement on or in surface fluids lining the airways. There is a continual proximal flow of lung surfactant from alveolar epithelial cells to and onto the mucociliary escalator, which begins at the terminal bronchioles, where it mixes with secretions from Clara and goblet cells in the airway epithelium. Within midsized and larger airways there are additional secretions from goblet cells and mucus glands, producing a thicker mucous layer having a serous subphase and an

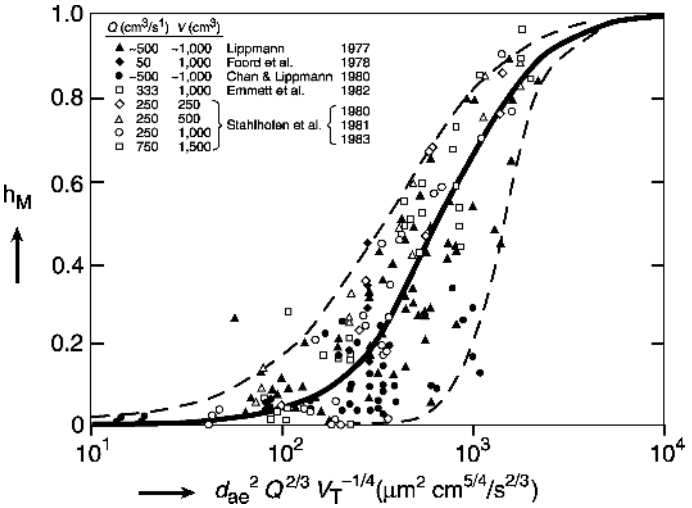

FIGURE 1.10 Inspiratory extrathoracic deposition data in humans during mouth breathing as a function of particle aerodynamic diameter, flow rate, and tidal volume ($d_{ae}^2 Q^{2/3} V_T^{-1/4}$). From: EPA (1997).

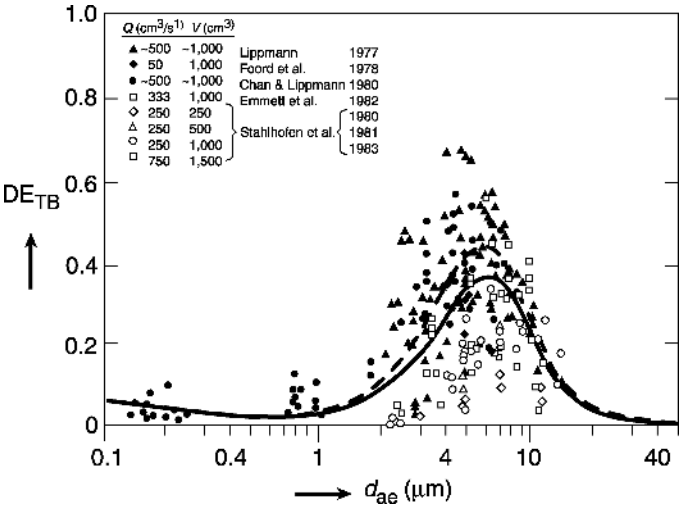

FIGURE 1.11 Tracheobronchial deposition data in humans at mouth breathing as a function of particle aerodynamic diameter (d_{ae}). The solid curve represents the approximate mean of all the experimental data; the broken curve represents the mean excluding the data of Stahlhofen et al. From: EPA (1997).

overlying more viscous gel layer. The gel layer, lying above the tips of the synchronously beating cilia, is found in discrete plaques in smaller airways and becomes more of a continuous layer in the larger airways. The mucus reaching the larynx and the particles carried by it are swallowed and enter the GI tract.

The total transit time for particles depositing on terminal bronchioles varies from ~2 to 24 h in healthy humans, accounting for the relatively rapid bronchial clearance phase. Macrophage-mediated particle clearance via the bronchial tree takes place over a period of

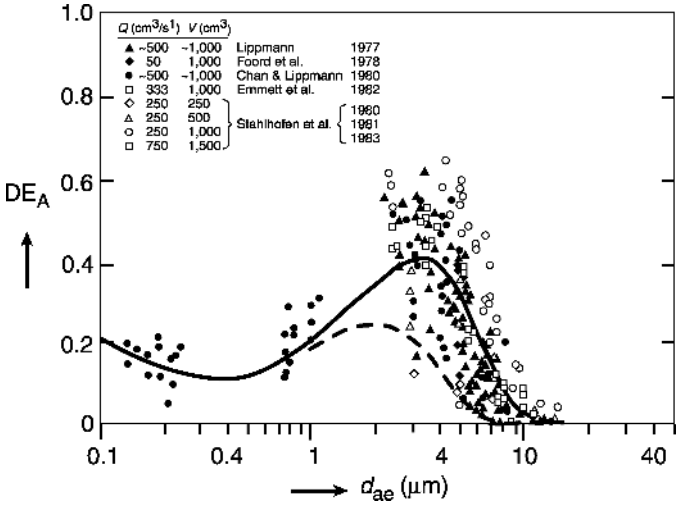

FIGURE 1.12 Alveolar deposition data in humans as a function of particle aerodynamic diameter (d_{ae}). The solid curve represents the mean of all the data; the broken curve is an estimate of deposition for nose breathing by Lippmann (1977). From: EPA (1997).

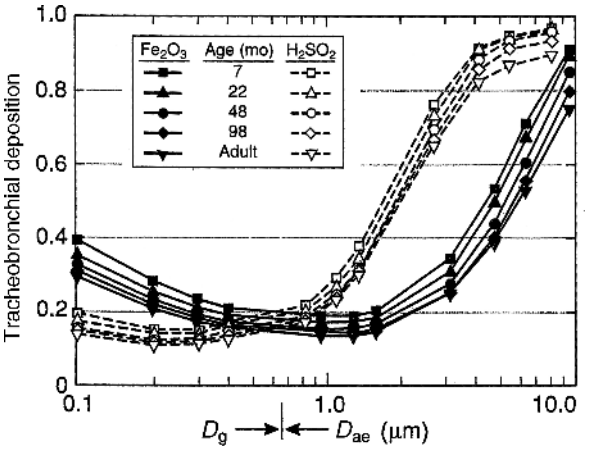

FIGURE 1.13 Tracheobronchial particle deposition as a function of particle size at various ages for both stable iron oxide particles and hygroscopic sulfuric acid droplets that grow in size in the warm moist respiratory airways. *Source*: Martonen (1990).

several weeks. The particles depositing in alveolar zone airways are ingested by alveolar macrophages within about 6 h, but the movement of the particle-laden macrophages depends on the several weeks that it takes for the normal turnover of the resident macrophage population. At the end of several weeks, the particles not cleared to the bronchial tree via macrophages have been incorporated into epithelial and interstitial cells, from which they are slowly cleared by dissolution and/or as particles via lymphatic drainage pathways, passing through pleural and eventually hilar and tracheal lymph nodes. Clearance times for these later phases depend strongly on the chemical nature of the particles and their sizes, with half-times ranging from about 30 to 1000 days, or more.

All of the characteristic clearance times cited refer to inert, nontoxic particles in healthy lungs. Toxicants can drastically alter clearance times. Inhaled materials affecting mucociliary clearance rates include cigarette smoke (Albert et al., 1974, 1975), sulfuric acid (H_2SO_4) (Lippmann et al., 1982; Schlesinger et al., 1983), O_3 (Phalen et al., 1980; Schlesinger and Driscoll, 1987), SO_2 (Wolff et al., 1977), and formaldehyde (Morgan et al., 1984). Macrophage-mediated alveolar clearance is affected by SO_2 (Ferin and Leach, 1973), NO_2 and H_2SO_4 (Schlesinger et al., 1988), O_3 (Phalen et al., 1980; Schlesinger et al., 1988), and silica dust (Jammet et al., 1970). Cigarette smoke is known to affect the later phases of alveolar zone clearance in a dose-dependent manner (Bohning et al., 1982). Clearance pathways as well as rates can be altered by these toxicants, affecting the distribution of retained particles and their dosimetry.

1.6 INGESTION EXPOSURES AND GASTROINTESTINAL TRACT EFFECTS

Chemical contaminants in drinking water or food reach human tissues via the GI tract. Ingestion may also contribute to uptake of chemicals that were initially inhaled, since material deposited on or dissolved in the bronchial mucous blanket is eventually swallowed.

The GI tract may be considered a tube running through the body, the contents of which are actually external to the body. Unless the ingested material affects the tract itself, any systemic response depends on absorption through the mucosal cells lining the lumen. Although

absorption may occur anywhere along the length of the GI tract, the main region for effective translocation is the small intestine. The enormous absorptive capacity of this organ results from the presence in the intestinal mucosa of projections, termed *villi*, each of which contains a network of capillaries; the *villi* result in a large effective total surface area for absorption.

Although passive diffusion is the main absorptive process, active transport systems also allow essential lipid-insoluble nutrients and inorganic ions to cross the intestinal epithelium and are responsible for uptake of some contaminants. For example, lead may be absorbed via the system that normally transports calcium ions (Sobel et al., 1938). Small quantities of particulate material and certain large macromolecules, such as intact proteins, may be absorbed directly by the intestinal epithelium.

Materials absorbed from the GI tract enter either the lymphatic system or the portal blood circulation; the latter carries material to the liver, from which it may be actively excreted into the bile or diffuse into the bile from the blood. The bile is subsequently secreted into the intestines. Thus, a cycle of translocation of a chemical from the intestine to the liver to bile and back to the intestines, known as the *enterohepatic circulation*, may be established. Enterohepatic circulation usually involves contaminants that undergo metabolic degradation in the liver. For example, DDT undergoes enterohepatc circulation; a product of its metabolism in the liver is excreted into the bile, at least in experimental animals (Hayes, 1965).

Various factors serve to modify absorption from the GI tract, enhancing or depressing its barrier function. A decrease in gastrointestinal mobility generally favors increased absorption. Specific stomach contents and secretions may react with the contaminant, possibly changing it to a form with different physicochemical properties (e.g., solubility), or they may absorb it, altering the available chemical and changing translocation rates. The size of ingested particulates also affects absorption. Since the rate of dissolution is inversely proportional to particle size, large particles are absorbed to a lesser degree, especially if they are of a fairly insoluble material in the first place. For example, arsenic trioxide is more hazardous when ingested as a finely divided powder than as a coarse powder (Schwartz, 1923). Certain chemicals, for example, chelating agents such as EDTA, also cause a nonspecific increase in absorption of many materials.

As a defense, spastic contractions in the stomach and intestine may serve to eliminate noxious agents via vomiting or by acceleration of the transit of feces through the GI tract.

1.7 SKIN EXPOSURE AND DERMAL EFFECTS

The skin is generally an effective barrier against the entry of environmental chemicals. In order to be absorbed via this route (*percutaneous absorption*), an agent must traverse a number of cellular layers before gaining access to the general circulation (Fig. 1.14). The skin consists of two structural regions, the epidermis and the dermis, which rest on connective tissue. The epidermis consists of a number of layers of cells and has varying thickness depending on the region of the body; the outermost layer is composed of keratinized cells. The dermis contains blood vessels, hair follicles, sebaceous and sweat glands, and nerve endings. The epidermis represents the primary barrier to percutaneous absorption, the dermis being freely permeable to many materials. Passage through the epidermis occurs by passive diffusion.

The main factors that affect percutaneous absorption are degree of lipid solubility of the chemicals, site on the body, local blood flow, and skin temperature. Some environmental chemicals that are readily absorbed through the skin are phenol, carbon tetrachloride,

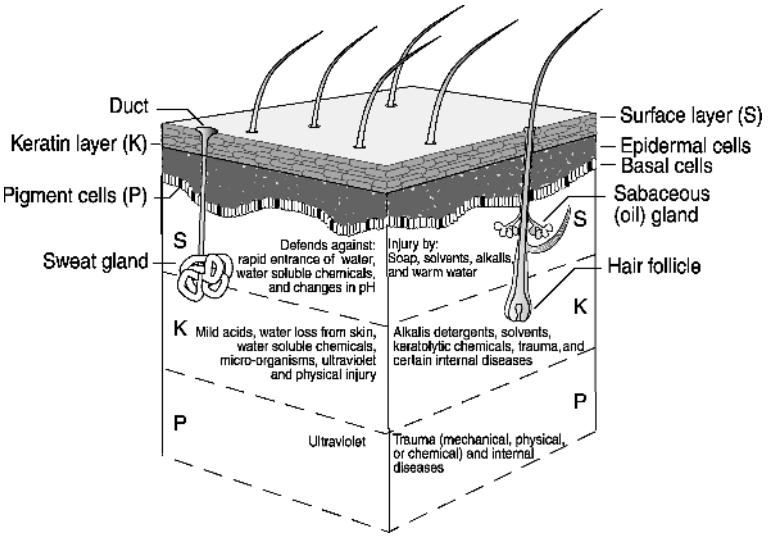

FIGURE 1.14 Idealized section of skin. *Source*: Birmingham (1973).

tetraethyl lead, and organophosphate pesticides. Certain chemicals, for example, dimethyl sulfoxide (DMSO) and formic acid, alter the integrity of skin and facilitate penetration of other materials by increasing the permeability of the stratum corneum. Moderate changes in permeability may also result following topical applications of acetone, methyl alcohol, and ethyl alcohol. In addition, cutaneous injury may enhance percutaneous absorption.

Interspecies differences in percutaneous absorption are responsible for the selective toxicity of many insecticides. For example, chlorinated hydrocarbons (HC are about equally hazardous to insects and mammals if ingested but are much less hazardous to mammals when applied to the skin. This is because of their poor absorption through mammalian skin compared to their ready passage through the insect exoskeleton. Although the main route of percutaneous absorption is through the epidermal cells, some chemicals may follow an *appendageal* route, that is, entering through hair follicles, sweat glands, or sebaceous glands. Cuts and abrasions of the skin can provide additional pathways for penetration.

1.8 ABSORPTION THROUGH MEMBRANES AND SYSTEMIC CIRCULATION

Depending upon its specific nature, a chemical contaminant may exert its toxic action at various sites in the body. At a portal of entry—the respiratory tract, GI tract, or skin—the chemical may have a topical effect. However, for actions at sites other than the portal, the agent must be absorbed through one or more body membranes and enter the general circulation, from which it may become available to affect cells and internal tissues (including the blood itself). The ultimate distribution of any chemical contaminant in the body is, therefore, highly dependent on its ability to traverse biological membranes. There are two main types of processes by which this occurs: passive transport and active transport.

Passive transport is absorption according to purely physical processes, such as osmosis; the cell has no active role in transfer across the membrane. Since biological membranes contain lipids, they are highly permeable to lipid-soluble, nonpolar or

nonionized agents and less so to lipid-insoluble, polar, or ionized materials. Many chemicals may exist in both lipid-soluble and -insoluble forms; the former is the prime determinant of the passive permeability properties for the specific agent.

Active transport involves specialized mechanisms, with cells actively participating in transfer across membranes. These mechanisms include carrier systems within the membrane and active processes of cellular ingestion; that is, phagocytosis and pinocytosis. Phagocytosis is the ingestion of solid particles, whereas pinocytosis refers to the ingestion of fluid containing no visible solid material. Lipid-insoluble materials are often taken up by active-transport processes. Although some of these mechanisms are highly specific, if the chemical structure of a contaminant is similar to that of an endogeneous substrate, the former may be transported as well.

In addition to its lipid-solubility characteristics, the distribution of a chemical contaminant is also dependent on its affinity for specific tissues or tissue components. Internal distribution may vary with time after exposure. For example, immediately following absorption into the blood, inorganic lead is found to localize in the liver, the kidney, and in red blood cells. Two hours later, about 50% is in the liver. A month later, approximately 90% of the remaining lead is localized in bone (Hammond, 1969).

Once in the general circulation, a contaminent may be translocated throughout the body. In this process it may(1) become bound to macromolecules, (2) undergo metabolic transformation (biotransformation), (3) be deposited for storage in depots that may or may not be the sites of its toxic action, or (4) be excreted. Toxic effects may occur at any of several sites.

The biological action of a contaminant may be terminated by storage, metabolic transformation, or excretion, the latter being the most permanent form of removal.

1.9 ACCUMULATION IN TARGET TISSUES AND DOSIMETRIC MODELS

Some chemicals tend to concentrate in specific tissues because of physicochemial properties such as selective solubility or selective absorption on or combination with macromolecules such as proteins. Storage of a chemical often occurs when the rate of exposure is greater than the rate of metabolism and/or excretion. Storage or binding sites may not be the sites of toxic action. For example, CO produces its effects by binding with hemoglobin in red blood cells; on the contrary, inorganic Pb is stored primarily in bone but exerts it toxic effects mainly on the soft tissues of the body.

If the storage site is not the site of toxic action, selective sequestration may be a protective mechanism, since only the freely circulating form of the contaminant produces harmful effects. Until the storage sites are saturated, a buildup of free chemical may be prevented. On the contrary, selective storage limits the amount of contaminant that is excreted. Since bound or stored toxicants are in equilibrium with their free form, as the contaminant is excreted or metabolized, it is released from the storage site. Contaminants that are stored (e.g., DDT) may remain in the body for years without effect. On the contrary, accumulation may produce illnesses that develop slowly, as occurs in chronic Cd poisoning.

A number of descriptive and mathematical models have been developed to permit estimation from knowledge of exposure and one or more of the following factors: translocation, metabolism, and effects at the site of toxic action.

The use of these models for airborne particulate matter generally requires knowledge of the concentration within specific particle size intervals or of the particle size distribution of the compounds of interest. Simple deposition models break the respiratory tract into regions (summarized by Vincent, 1999):

Head airways, nasopharynx, extrathoracic: nose, mouth, nasopharynx, oropharynx, laryngopharynx.

Tracheobronchial: larynx, trachea, bronchi, bronchioles (to terminal bronchioles).

Gas exchange, pulmonary, alveolar: respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli.

Size-selective aerosol sampling can mimic the head airways and tracheobronchial airway regions so that airborne particle collection can be limited to the size fraction directly related to the potential for disease.

More complex models requiring data on translocation and metabolism have been developed for inhaled and ingested radionuclides by the International Commission on Radiological Protection (ICRP, 1966, 1979, 1981, 1994).

1.10 INDIRECT MEASURES OF PAST EXPOSURES

Documented effects of environmental chemicals on humans seldom contain quantitative exposure data and only occasionally include more than crude exposure rankings based on known contact with or proximity to the materials believed to have caused the effects. Reasonable interpretation of the available human experience requires some appreciation of the uses and limitations of the data used to estimate the exposure side of the exposure–response relationship. The discussion that follows is an attempt to provide background for interpreting data, and for specifying the kinds of data needed for various analyses.

Both direct and indirect exposure data can be used to rank exposed individuals by exposure intensity. External exposure can be measured directly by collection and analysis of environmental media. Internal exposure can be estimated from analyses of biological fluids and *in vivo* retention. Indirect measures generally rely on work or residential histories with some knowledge of exposure intensity at each exposure site and/or some enumeration of the frequency of process upsets and/or effluent discharges that result in high-intensity short-term exposures.

1.10.1 Concentrations in Air, Water, and Food

Historic data may occasionally be available on the concentrations of materials of interest in environmental media. However, they may or may not relate to the exposures of interest. Among the more important questions to be addressed in attempts to use much data are:

(1) How accurate and reliable were the sampling and analytical techniques used in the collection of the data? Were they subjected to any quality assurance protocols? Were standardized and/or reliable techniques used?

(2) When and where were the samples collected, and how did they relate to exposures at other sites? Air concentrations measured at fixed (area) sites in industry may be

much lower than those occurring in the breathing zone of workers close to the contaminant sources. Air concentrations at fixed (generally elevated) community air-sampling sites can be either much higher or much lower than those at street level and indoors as a result of strong gradients in source and sink strengths in indoor and outdoor air.

(3) What is known or assumed about the ingestion of food and/or water containing the measured concentrations of the contaminants of interest? Time at home and dietary patterns are highly variable among populations at risk.

1.10.2 Biological Sampling Data

Many of the same questions that apply to the interpretation of environmental media concentration data also apply to biological samples, especially quality assurance. The time of sampling is especially critical in relation to the times of the exposures and to the metabolic rates and pathways. In most cases, it is quite difficult to separate the contributions to the concentrations in circulating fluids of levels from recent exposures and those from long-term reservoirs.

1.10.3 Exposure Histories

Exposure histories *per se* are generally unavailable, except in the sense that work histories or residential histories can be interpreted in terms of exposure histories. Job histories, as discussed below, are often available in company and/or union records and can be converted into relative rankings of exposure groups with the aid of long-term employees and managers familiar with the work processes, history of process changes, material handled, tasks performed, and the engineering controls of exposure.

Routine, steady-state exposures may be the most important and dominant exposures of interest in many cases. On the contrary, for some health effects, the occasional or intermittent peak exposures may be of primary importance. In assessing or accumulating exposure histories or estimates, it is important to collect evidence for the frequency and magnitude of the occasional or intermittent releases associated with process upsets.

1.11 CHARACTERIZATION OF HEALTH

1.11.1 Definitions of Health

There is no universally accepted definition of health. Perhaps the most widely accepted one today is that of the World Health Organization, which describes health as a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity. Unfortunately, by a strict interpretation of this rather idealistic definition, very few people could be considered healthy.

The discussion to follow is limited largely to physical well-being. The health effects discussed are those that can be recognized by clinical signs, symptoms, or decrements in functional performance. Thus, for all practical purposes, in this volume we consider health to be the absence of measurable disease, disability, or dysfunction.

1.11.2 Health Effects

Recognizable health effects in populations are generally divided into two categories: mortality and morbidity. The former refers to the number of deaths per unit of population

per unit time, and to the ages at death. Morbidity refers to nonfatal cases of reportable disease.

Accidents, infectious diseases, and massive overexposures to toxic chemicals can cause excess deaths to occur within a short time after the exposure to the hazard. They can also result in residual disease and/or dysfunction. In many cases, the causal relationships are well defined, and it may be possible to develop quantitative relationships between dose and subsequent response.

The number of people exposed to chemical contaminants at low levels is, of course, much greater than the number exposed at levels high enough to produce overt responses. Furthermore, low-level exposures are often continuous or repetitive over periods of many years. The responses, if any, are likely to be nonspecific, for example, an increase in the frequency of chronic diseases that are also present in nonexposed populations. For example, any small increase in the incidence of heart disease or lung cancer attributable to a specific chemical exposure would be difficult to detect, since these diseases are present at high levels in nonexposed populations. In smokers they are likely to be influenced more by cigarette exposure than by the chemical in question.

Increases in the incidence of diseases from low-level long-term exposure to environmental chemicals invariably occur among a very small percentage of the population and can only be determined by large-scale epidemiological studies (epidemiology is the study of the distribution and frequency of diseases in a specific population) involving thousands of person-years of exposure. The only exceptions are chemicals that produce very rare disease conditions, where the clustering of a relatively few cases may be sufficient to identify the causative agent. Notable examples of such special conditions are the industrial cases of chronic berylliosis caused by the inhalation of beryllium-containing dusts, a rare type of liver cancer that resulted from the inhalation of vinyl chloride vapors, and pleural cancers that resulted from the inhalation of asbestos fibers. If these exposures had produced more commonly seen diseases, the specific materials might never have been implicated as causative agents.

Low-level chemical exposures may play contributory, rather than primary, roles in the causation of an increased disease incidence, or they may not express their effects without the co-action of other factors. For example, the excess incidence of lung cancer is very high in uranium miners and asbestos workers who smoke cigarettes but is only marginally elevated among nonsmoking workers with similar occupational exposures. For epidemiological studies to provide useful data, they must take appropriate account of smoking histories, age, and sex distributions, socioeconomic levels, and other factors that affect mortality rates and disease incidence.

1.11.2.1 Mortality In industrialized societies, there is generally good reporting of mortality and age at death but, with few exceptions, quite poor reporting of cause of death. In studies that are designed to determine associations between exposures and mortality rates, it is usually necessary to devote a major part of the effort to follow-up investigations of cause-of-death. The productivity of these follow-ups is often marginal, limiting the reliability of the overall study.

1.11.2.2 Morbidity Difficult as it may be to conduct good mortality studies, it is far more difficult, in most cases, to conduct studies involving other health effects. Although there is generally little significant variability in the definition of death, there is a great deal of variation in the diagnosis and reporting of many chronic diseases. There are variations

between and within countries and states, and these are exacerbated by the differences in background and outlooks of the physicians making the individual diagnoses. Furthermore, there are some important chronic diseases that cannot be definitively diagnosed *in vivo*.

Many epidemiological studies rely on standardized health status questionnaires, and the success of these studies depends heavily on the design of the questionnaires. Of equal importance in many studies are the training and motivation of the persons administering the questionnaires. Similar considerations apply to the measurement of functional impairment. The selection of the measurements to be used is very important; those functions measured should be capable of providing an index of the severity of the disease. Equally important here are the skills of the technicians administering these tests and their maintenance and periodic recalibration of the equipment.

Some studies try to avoid bias from the administrators of the questionnaires and functional tests by having the selected population enter the desired information themselves. They may be asked to make appropriate notations in notebook diaries or to call a central station whenever they develop the symptoms of interest. Other investigations use non-subjective indices such as hospital admissions, clinic visits, and industrial absenteeism as their indicators of the health effects to be associated with the environmental variables.

1.12 EXPOSURE–RESPONSE RELATIONSHIPS

Exposure–response relationships can be developed from human experience, but there are many chemicals that are known to be toxic in animals for which the extent of human toxicity, if any, is unknown. In order to use animal bioassay data for the prediction of human responses to environmental exposures, it is necessary to make two major kinds of extrapolation. One is determine or estimate the relative responsiveness of humans and the animal species used in the bioassays. The second is to extrapolate from the observed effects resulting from relatively high administered doses to the much lower levels of effects still of concern at much lower levels of environmental exposure.

To deal with interspecies extrapolation, estimates are made on the basis of whatever is known about differences in uptake from environmental media, metabolic rates and pathways, retention times in target tissues, and so on, and tissue sensitivities. As uncertain as these extrapolations are, they are more straightforward than the low-dose extrapolation.

The goal of the dose–response assessment is to predict what response, if any, might occur, 10- to 1000-fold below the lowest dose tested in rodents (this is more representative of the range of doses to which humans are usually exposed). Because it would require the testing of thousands of animals to observe a response at low doses, mathematical models are used (Munro and Krewski, 1981). To appreciate the level of uncertainty in the dose extrapolation process and the typical regulatory use of low-dose models, it is useful to discuss the dose–response curve. However, reliance on the results of only one mathematical model is a potential pitfall in the dose–response assessment.

There are at least six different modeling approaches that may need to be considered when estimating the risks at low doses. These models include the probit, multihit, multistage, Weibull, one-hit, and the Moolgavkar–Knudson–Venzon (MKV) biologically based approaches (Moolgavkar et al., 1988). Nearly all of them can yield results that are plausible. No single statistical model can be expected to predict accurately the low-dose response with greater certainty than another. As discussed by Paustenbach (1990),

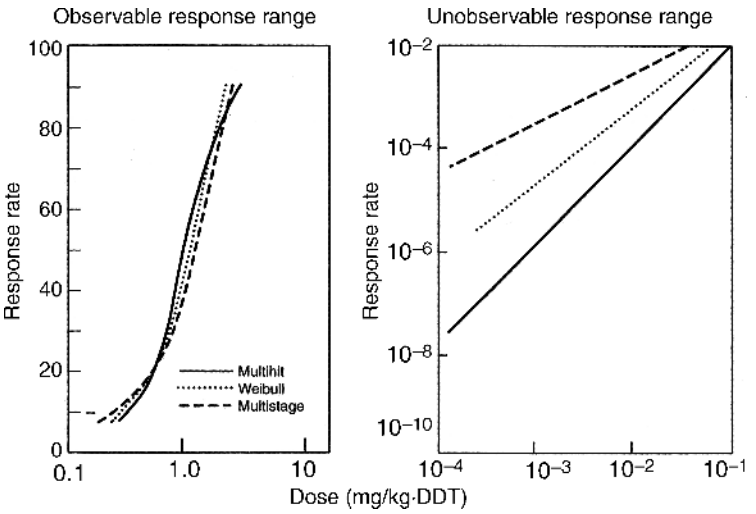

FIGURE 1.15 The fit of most dose–response models to data in the range tested in animal studies is generally similar. However, because of the differences in the assumptions on which the equations are based, the risk estimates at low doses can vary dramatically between different models. *Source*: Paustenbach (1990).

one possible way to resolve this problem is to present the best estimate of the risk from the two or three models that are considered equally reasonable along with the upper- and lower-bound estimates. An alternate approach is to identify a single value based on the "weight of evidence," as the EPA did for dioxin (U.S. EPA, 1988)

Low-dose models usually fit the rodent data in the dose region used in the animal tests. However, they often predict quite different results in the unobserved low-dose region (Fig. 1.15). The results of the most commonly used low-dose models usually vary in a predictable manner because the models are based on different mathematical equations for describing the chemical's likely behavior in the low-dose region.

In general, the scientific underpinnings of the dose–response models are based on the present understanding of the cancer process caused by exposure to ionizing radiation and genotoxic chemicals (NRC, 1980). Both types of agents may well have a linear, or a nearly linear, response in the low-dose region. However, promoters and cytotoxicants (e.g., nongenotoxicants) would be expected to be very nonlinear at low doses and may have a genuine or practical threshold (a dose below which no response would be present) (Squire, 1987; Butterworth and Slaga, 1987). Thus, the linearized multistage model may be inappropriate for dioxin, thyroid-type carcinogens, nitrolotriacetic acid, and, presumably, similar nongenotoxic chemicals (Paynter et al., 1988; Andersen and Alden, 1989). For these types of chemicals, the MKV model, or one of the other biologically based models, should be more appropriate (Moolgavkar, 1978; Ellwein and Cohen, 1988).

1.12.1 Summary of Exposure- and Dose-Related Responses

Studies of the specific responses of biological systems to varying levels of exposure can provide a great deal of information on the nature of the responses, their underlying

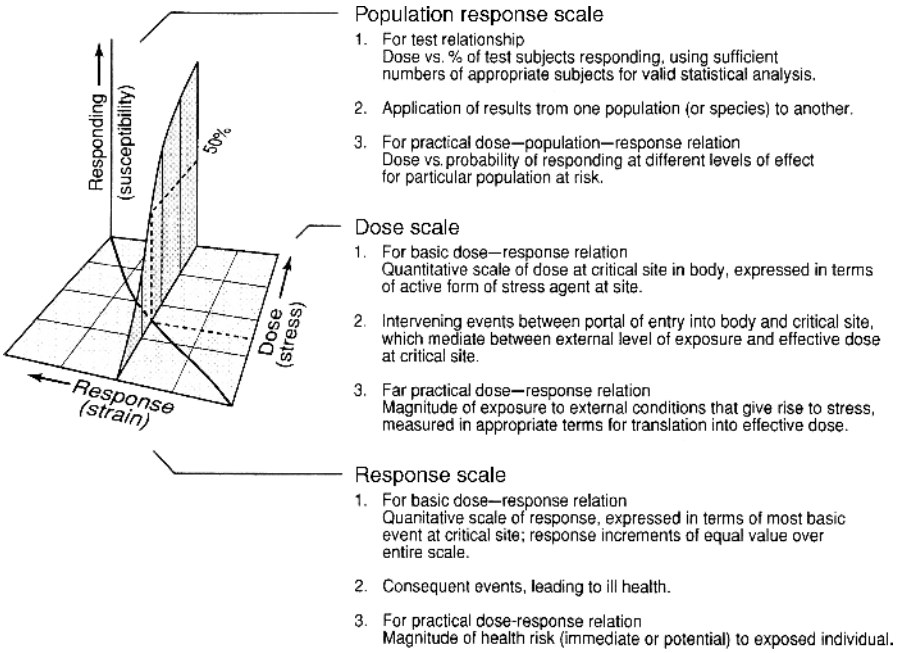

FIGURE 1.16 Dose (population) response relationship with suggested distinction between basic (toxicological) and practical (health) scales on the three axes. The illustrative curve on the horizontal plane portrays the dose–response relationship for the middle (50%) of the exposed population; the curve on the vertical plane shows the percentages of population response of the indicated degree over the whole range of doses. The vertical line from the dose scale indicates the magnitude of dose needed to produce the indicated degree of response at the 50% population level. *Source*: Hatch (1968).

causes, and the possible consequences of various levels of exposure. However, it must be remembered that the data are most reliable only for the conditions of the test and for the levels of exposure that produced clear-cut responses.

Generally, in applying experimental data to low-level environmental exposure conditions, it is necessary to extrapolate to delivered doses that are orders of magnitude smaller than those that produced the effects in the test system. Since the slope of the curve becomes increasingly uncertain the further one extends it beyond the range of experimental data, the extrapolated effects estimate may be in error by a very large factor.

The basic dimensions of the dose–response relationship for populations were described by Hatch (1968), as illustrated in Fig. 1.16. Many factors affect each of the basic dimensions.

1.12.1.1 Factors Affecting Dose The effective dose is the amount of toxicant reaching a critical site in the body. It is proportional to the concentrations available in the environment: in the air breathed, the water and food ingested, and so on. However, the uptake also depends on the route of entry into the body and the physical and chemical forms of the contaminant. For airborne contaminants, for example, the dose to the respiratory tract depends on whether they are present in a gaseous form or as an aerosol. For contaminants that are ingested, uptake depends on transport through the membranes lining the gastrointestinal tract and, in turn, is dependent on both aqueous and lipid solubilities.

For contaminants that penetrate membranes, reach the blood, and are transported systemically, subsequent retention in the body depends on their metabolism and toxicity in the various tissues in which they are deposited.

In all of these factors, there are great variations within and between species, and therefore great variations in effective dose for a given environmental level of contamination.

1.12.1.2 Factors Affecting Response The response of an organism to a given environmental exposure can also be quite variable. It can be influenced by age, sex, the level of activity at the time of exposure, metabolism, and the competence of the various defense mechanisms of the body. The competence of the body's defenses may, in turn, be influenced by the prior history of exposures to chemicals having similar effects, since those exposures may have reduced the reserve capacity of some important functions. The response may also depend on other environmental factors, such as heat stress and nutritional deficiencies. These must all be kept in mind in interpreting the outcomes of controlled exposures and epidemiological data and in extrapolating results to different species and across various age ranges, states of health, and so on.

1.12.1.3 Factors Affecting Individual Susceptibility The complete evaluation of the pathogenesis of human disease requires identification and assessment of the genetic, lifestyle, and environmental risk factors. Environmental factors are clearly critical to disease prevention because, at the societal level, they are determined by the most controllable processes. Thus, the overall purpose of environmental medicine is to improve our knowledge of the more commonly encountered environmental agents that present the greatest concern to human health.

In the past, diseases were categorized by the main etiological factor into either (a) genetic, (b) lifestyle-induced, or (c) environmental-induced disorders. Illustrative examples for each category include (a) alpha-1 antitrypsin [serine (or cysteine) proteinase inhibitor, clade A, member1] deficiency-induced chronic obstructive pulmonary disease; (b) cigarette-induced lung cancer; and (c) asbestos-induced mesothelioma, respectively. Environmental medicine almost exclusively focused on the latter category, and has had its best impacts when armed with knowledge of quantifiable exposure (e.g., occupational diseases). Fortunately, additional cases of occupational diseases (e.g., mining-related coal workers pneumoconiosis or asbestosis) are becoming increasingly rare among the general population due to improved work practices.

However, while categorizations based on etiological factors have allowed the development of therapeutic strategies to treat disease, they also may have limited past attempts to prevent disease. Disease prevention has a greater ability than most common treatment modalities to reduce incidence and to extend life expectancy. In the illustrative examples above, preventative approaches would include: (a) genetic counseling and possibly gene-replacement therapy; (b) public health education and smoking cessation pharmaceuticals; and (c) reduction or elimination (banning widespread usage) of asbestos exposure. Each of theses approaches have had tremendous value in focusing efforts on disease causalities and thus has had dramatic impacts on disease prevention.

Although the application of these simple approaches to disease prevention has been partially successful, further success will require more sophisticated approaches based on a deeper understanding of disease pathogenesis. With the widespread use of genetic screening, it soon became apparent that homozygotic recessive carriers (individuals inheriting both copies of the disease susceptibility alleles) often did not developed major signs and

symptoms of the "genetic" disease. For example, homozygotic twins do not have 100% concordance in disease outcomes. Similarly, disease discordance is noted in lifestyle-induced diseases. For example, among individuals with exposures exceeding 50 pack-years, only four out five cigarette smokers develop a tobacco-related disease and these diseases vary in the population (i.e., multisite cancer, cardiovascular, and respiratory disease). Likewise, although diseases such as asbestosis, lung cancer, and mesthelioma are enriched in populations with excessive asbestos exposure, the incidence of affected workers given equivalent exposures in not 100%.

What can explain a lack of penetrance (affected individuals/genotype positive individuals) in equally susceptible, equally risky, equally exposed populations? It is the interactions of additional factors within and among each etiological category. Common pathological conditions are complex and involve multiple rather than a single gene(s). Single gene diseases with strongly expressivity typically appear early in life, but due to a lack of complete penetrance affect only a few members of the population. Alternatively, most diseases involve multiple gene–gene interactions and are present in a large percentage of the population. Genetic polymorphisms that are strongly fixed in the genome probably did not arise from modern lifestyle or environmental factors (e.g., coal mining), but from ancient lifestyle factors or infectious agents.

Another reason why most common diseases are complex is because the selective advantage to a population that stabilizes a genetic polymorphism is likely to be dependent on multiple alterations in multiple genes. Many polymorphisms also may have been acquired from phylogenetic ancestry (which are likely to be greater than those that uniquely arise within a given species). Thus, the mechanisms by which bacteria combat virus, or how drosophila resist bacteria (toll-receptors), or how mice resist influenza, may be conserved throughout species. This situation is further complicated by the fact that genes that impart sensitivity may also impart resistance to another disease. For example, the protection from tuberculosis may be advantageous to the population, but may impart increased susceptibility to chronic inflammatory diseases, like arthritis, to a portion of the population.

From a solely genetic stand point, it would be advantageous if multiple genes contribute to a survival phenotype from a severe disease entity [i.e., the fully developed phenotype being dependent on gene–gene interactions (epistasis)]. Phenotypes with complex gene interaction require only a few members of an outbred population (humans) to carry the exact set of all the resistant alleles. Phenotypes dependent upon multiple genes thereby reduce the negative consequences of the combinatorial effects of multiple alleles to only a few individuals. Several other members of a population could inherit in partial combinations that would have little observable phenotypic expression. Thus, while only a few members of the population might survive an infectious epidemic, many members of population share the risky alleles.

With the initial assembling of the entire human genome by the Human Genome Project, substantial research has been invested in the identification of all disease causing genetic polymorphisms. However, individual susceptibility to common diseases is not solely controlled by multiple gene–gene interactions. Rather disease penetrance is also influenced by multiple gene–lifestyle, gene–environment, lifestyle–environmental, and gene–lifestyle–environmental factors. Using our illustrative disease example, clear synergistic interactions occur among individuals who have: (a) alpha-1 antitrypsin deficiency and smoke cigarettes (gene–lifestyle interaction); (b) glutathione *S*-transferase pi 1 deficiency and are exposed to environmental tobacco smoke or to excessive air pollution (ozone and particulate matter) (gene-environment interaction); or (c) smoke and work with asbestos or radon (lifestyle–environment interactions).

1.12.2 Genomic Approaches to Understanding Gene-Lifestyle-Environmental Factors in Complex Disease Pathogenesis

Environmental health sciences have developed a wonderful cadre of tools to obtain global (nearly complete) evaluations of the genetic variants, transcriptional profile, protein usage and activation state, and the metabolic capability of individuals and populations following environmental stress. Using high-throughput microarray or fluidic luminesence systems, genomics seeks to evaluate the entire genetic makeup of an individual and thereby identify candidate gene suspected to have a role in determining susceptibility. Genomics is based on known biological functional, cellular location, or pathophysiological roles of a gene, and seeks to identify the allelic variants that associate with increased risk. Moreover, the mapping of over 150,000 single nucleotide polymorphisms (SNPs) throughout the genome allows nearly complete coverage of all human variability and through linkage disequilibrium identification of small chromosomal region (areas of a few tens of thousands base pairs). Particularly attention is focused on nonsynonymous SNPs that result in alteration of RNA recognition codons and lead to amino acid changes in the predicted protein. Because regions of chromosomes are often inherited together, the number of independently inherited SNPs is reduced. Thus, the reduction to informative differences (tag-SNPs) make these analyses even more powerful and essentially entire genome coverage is possible. Supportive of genome wide linkage analysis is transcriptomics, proteomics, and metabonomics.

Transcriptomics studies large sets of messenger ribonucleic acid (mRNA) molecules, or transcripts produced by cells in culture (revealing cell-type specificity), isolated tissue, or a whole organism. The transcriptome, unlike the genome, which is fixed (excluding acquired mutations), can be altered by the environment and reflects the cell's attempt to acclimate to adverse conditions. The supportive high-throughput technology includes DNA microarrays that typically monitor steady-state transcript levels of 30,000 genes. This includes essentially all known genes and genes yet to be fully understood and annotated (e.g., predicted gene products and expressed sequence tags). Confirmational approaches to key genes identified by microarray include quantitative reverse transcription polymerase chain reaction, ribonuclease protection assay, and Northern blot that are conducted on single or small sets of transcripts.

Like the transcriptome, the proteomics is a global approach to evaluate altered protein usage and activation state induced by environmental signaling. Indeed, it includes many signaling peptides (e.g., kinases) that generate amplifying cascades that alter cell functions including motility, transcription, cell–cell communication, proliferation, immunity, and apoptosis. The proteome includes nascent propeptides, mature inactive peptides, activated peptides, and peptide marked secretion or degradation. While the number of genes and possible transcripts are estimated to be less than 35,000 in humans, the proteome may have over 1 million members. Moreover, proteomics focuses on protein–protein, and protein–macromolecular interactions, and is thus closer to functional significance than genomics or transcriptomics. High-throughput technologies supporting proteomics include, gas (gas chromatography), fluidic (high-pressure liquid chromatography) or gel (electrophoresis) separation and large scale, mass spectrometric protein identification. Confirmational approaches include immuno (Western) blot, antibody arrays, and enzyme-linked immunosorbent assays (ELISA), and radioimmunoassay.

Also under rapid development, metabonomics (or metabolomics) is the global approach to the assessment of the metabolic response of living systems to environmental stimuli. Typically the variety of small molecule metabolites generated by a living system is relatively

small (<5000 compounds) when compared to the genome, transcriptome, or proteome. Metabonomic profiles reflect the nutritional status of the organism, and thus this approach is useful in determining lifestyle-environmental interactions. In addition, the metabolic consequences of genetic manipulation can be assessed using this approach (bypassing assessment of the transcriptome or proteome). The focus is typically on body fluids (serum or urine) and minimally-invasive sampling (salvia or breath analysis). Another major advantage of metabonomics is safety. Although metabolic profiles may be shifted due to altered pathologies, metabolic capacities often can be predicted a very low doses of known toxicants (below the levels inducing any adverse response) or by surrogate that is handled much like a toxicant (e.g., caffeine). Supportive technologies include mass spectrometry and nuclear magnetic resonance (NMR). The latter is commonly preferred because does not require separation, does not destroy the sample, and can be performed with small volumes (0.01–0.1 mL).

1.13 STUDY OPTIONS FOR HEALTH EFFECTS STUDIES

In the discussion of the health effects in the chapters that follow, it is important to appreciate the strengths and limitations of the various kinds of studies that generated the data.

1.13.1 Controlled Human Exposures

For O_3, SO_2, concentrated $PM_{2.5}$, and CO, there are databases from studies in which selected human volunteers were exposed to the pollutant in purified lab air for specific time intervals ranging from minutes to eight hours. Most studies involve a series of such exposures in random order, in which there are exposures at one or more concentrations as well as a sham exposure to purified air. Many of them involved prescribed periods and intensities of exercise during the exposure interval. The most commonly measured pulmonary effects were changes in forced expiratory flow rates and volumes and/or changes in airway resistance and compliance.

A broad variety of other pulmonary function tests require the inhalation of special breathing mixtures and hence more elaborate controls and protocol reviews. These include the inhalation of (1) a single breath of pure oxygen for the nitrogen washout test of small airway function (Buist and Ross, 1973); (2) 0.3% CO to determine diffusing capacity at the alveolo-capillary membrane (Crapo, 1986); and (3) a low density inert gas, such as helium (He), or a high density gas, such as sulfur hexafluoride (SF_6), to measure inhomogeneities in flow distribution (Scott and Van Liew, 1983). Large-scale spatial inhomogeneities in ventilation can be detected using radioactive xenon (Xe) and external γ-emission imaging equipment such as the Anger camera (Robertson et al., 1969).

Functional tests made before and after administration of bronchoactive agents can also be of diagnostic value. These can include bronchodilators such as isoproterenol, epinephrine, and atropine to measure reversible bronchoconstriction. They also include bronchoconstrictors, such as histamine, carbachol, methacholine, cold air, and SO_2, to detect airway hyperresponsiveness.

Other tests of demonstrated utility and/or with potential for supplying important diagnostic information can also be applied. The permeability of the respiratory epithelium can be determined from the externally measured rate of clearance from the lung of γ-emitting [99mTc] tagged diethylenetriaminepentaacetate (DTPA), inhaled as a droplet aerosol (Oberdorster et al., 1986).

Inert, insoluble, nonhygroscopic, γ-tagged aerosols can be used to measure the regional deposition and clearance rates for inhaled particles. Thoracic retention of such aerosols after 1 day is considered to represent deposition in the nonciliated alveolar lung spaces, while the difference between the retention measured immediately after the particle inhalation and that at 1 day represents the aerosol that deposited on the conductive airways of the tracheobronchial tree (Lippmann, 1977). By appropriate control of particle size and respiratory parameters, the deposition efficiency data can be used to characterize airway obstruction (Chan and Lippmann, 1980). The rate and pattern of mucociliary particle clearance can be determined from serial measurements of thoracic retention during the first day, and the much slower rate of particle clearance from the gas-exchange region can be determined from serial retention measurements made after the first day (Albert et al., 1969).

More recently there have been studies in which cardiac function measurements, such as heart rate and heart rate variability, have been made for O_3 (Gong et al., 2003; Brook et al., 2002; Urch et al., 2004), SO_2 (Tunnicliffe et al., 2001), and concentrated $PM_{2.5}$ (Brook et al., 2002; Urch et al., 2004; Devlin et al., 2003).

The advantages of controlled human exposure studies are: (1) the opportunity to carefully select and carefully characterize the subjects, whether they be healthy normals, atopics, asthmatics, smokers, and so on; (2) the willingness and ability of most volunteer subjects to perform various levels and durations of exercise during the exposures; (3) the ability to deliver and monitor the preselected challenge atmospheres during the exposure; (4) the ability of the subjects to reproducibly perform respiratory maneuvers required for some functional assays affected by the exposures and to provide information on mild symptomatic responses; and (5) avoidance of the need to make interspecies extrapolations in evaluating human exposure–response relationships.

The limitations of controlled human exposures are: (1) that ethical constraints limit the challenges and effects assays that can be performed. In effect, we are limited to challenges that produce only transient functional changes. The most invasive assay that has been used involves analyses of the contents of lung lavage; (2) the numbers of repetitive challenges and assays are limited by subject tolerance and cooperation; and (3) the number of subjects that can be studied is limited by the generally large costs of performing the studies and/or by the availability of sufficient numbers of subjects with the desired characteristics.

In summary, controlled human exposure studies are most useful for studying the nature and extent of transient functional changes resulting from one or a few brief controlled exposures. They can provide information on chronic pollutant effects only to the extent that prior exposures affect the transient response to single exposure challenges. Furthermore, interpretation of the results of such tests is limited by our generally inadequate ability to characterize the nature and/or magnitude of the prior chronic exposures.

1.13.2 Natural Human Exposures

There is a substantial database emerging from studies of the responses of natural populations to acute exposures to air pollutants (Lippmann, 1989b; Spektor et al., 1991; Thurston et al., 1997). Studying natural populations for evidence of acute health effects associated with exposures to ambient air pollutant is a challenging task. Among the more difficult challenges are: (1) identifying an accessible population at risk whose relevant exposures can be defined and adequately characterized; (2) specifying measurable indices of responses that may be

expected to occur as a result of the exposures of interest; (3) collecting an adequate amount of suitable quality-assured data on exposure and responses at times when exposures of magnitudes sufficient to elicit measurable responses actually occur; and (4) collecting sufficient data on identifiable host characteristics and environmental exposures to other agents that may influence the response variables and confound any of the hypothesized pollutant exposure–response relationships that may be present. In addition, one must also account for the usual operational problems encountered in performing population studies, especially studies in the field, such as maintaining (1) the motivation and skills of the field personnel for collecting reliable data; (2) the cooperation of the subjects in producing reliable data; and (3) access to sufficient numbers of subjects with the preselected characteristics in each category as may be needed.

The basic design premise in field studies involving air pollutant exposures is to maximize the signal-to-noise ratio for the pollutant exposure versus response relationships. The noise on the response side of the relationships has been the focus of much work by others, and guidance on these aspects is available from the American Thoracic Society (1985). Focus is also needed on the reduction of the noise in the exposure variables. For example, the summer pollution haze is regional in scale and enriched in secondary air pollutants such as O_3 and H_2SO_4, both of which form gradually during daylight hours in air masses containing diluted primary pollutants transported over long distances from industrial, power plant, and motor vehicle sources, especially SO_2, NO_2, and HC).

For the NYU field studies (Lippmann et al., 1983; Lioy et al., 1985; Spektor et al., 1988a, 1991; Thurston et al., 1997), populations of children attending summer camp programs were selected for three main reasons: (1) cigarette smoking and occupational exposure to lung irritants would not be confounding factors; (2) the program of camp activities insured that they would be out of doors and physically active during the daytime periods when O_3 and H_2SO_4 exposures are highest; and (3) the cooperation of the camp staff provided effective access to the children on a daily basis for the administration of functional tests and symptom questionnaires. Exposures to O_3 and H_2SO_4 are almost always higher outdoors than indoors, and, as regional-scale secondary pollutants, their concentrations do not vary greatly from site to site within the camp's activity areas or from those measured at nearby samplers or monitors. In addition, there was little variation of activity level among the children in the camp program.

The 1985 summer study (Spektor et al., 1988b) on the effects of the summer haze pollutants on respiratory function in healthy nonsmoking adults engaged in a regular program of outdoor exercise had a similar absence of confounding exposure factors as well as similar exposures to the ambient secondary air pollutants. Each of the adult volunteers maintained a constant daily level and duration of exercise, but they differed widely from one to another in these important variables. This increased the variability of the response among the population but also provided a means of studying the influence of these variables on the responses.

In summary, natural human exposure studies are most useful for studying the magnitude and extent of the acute responses to naturally occurring pollutants among people engaged in normal outdoor recreational activities. They provide little information on the possible influence of prior chronic exposures on acute responses to the exposure of the day or immediately preceding days. Also, since the ambient mixture contains varying amounts of a variety of pollutants, it may sometimes be difficult to apportion the responses to one or more of the pollutants or to other, uncontrolled variables such as temperature, humidity, and each individual's precise level of exercise or ventilation.

1.13.3 Population-Based Studies of Chronic Health Effects of Air Pollution

Since neither controlled human exposure studies in the laboratory nor natural human exposure studies in the field can provide any direct information on chronic effects of prolonged human exposures to air pollutants, the only way to get such information is to use the conventional epidemiological approach of comparing data on: (1) reductions in lifespan and function; and (2) increases in symptom frequency, lost activity days, hospital admissions, clinic visits, medical diagnoses, and so on, in relation to estimates of chronic exposure intensity. There are many confounding factors affecting the effects indices of concern in such studies. The characteristics of the populations under study are highly variable in terms of age, sex, smoking history, cohabitation with smokers, health status, disease history, occupational exposures, hobby activities that generate air pollutants, use of unvented stoves and heaters at home, and so on. Also, their exposures to outdoor pollutants are difficult to quantitate, and are influenced by their proximity to the monitor that provides their exposure index, the time they spend outdoors, and whether this includes hours when the pollutant is high as well as the amount and duration of vigorous exercise during periods of high exposure.

Because of the large number of possible confounders and the difficulty of properly classifying exposures, very large populations must be studied in order to find significant associations between exposures and effects. Any statistically significant effects that are attributed to air pollution would tend to be underestimated because of the influence of the confounders. Alternatively, they could be spurious if the effects are really caused by variables that are colinear with the pollutant being studied.

In summary, epidemiological studies offer the prospect of establishing chronic health effects of long-term air pollution exposure in relevant populations and offer the possibility that the analyses can show the influence of other environmental factors on responses to exposure. On the contrary, the strengths of any of the associations may be difficult to establish because of the complications introduced by uncontrolled cofactors that may confound or obscure the underlying causal factors.

1.13.4 Controlled Exposures of Laboratory Animals

The most convenient and efficient way to study mechanisms and patterns of response to pollutants, and of the influence of other pollutants and stresses on these responses is by controlled exposures of laboratory animals. One can study the transient functional responses to acute exposures and establish the differences in response among different animal species and between them and humans similarly exposed. One can also look for responses that require highly invasive procedures or serial sacrifice and gain information that cannot be obtained from studies on human volunteers. One can expose the animals to a single pollutant, or to a complex mixture as found in the environment, or from a specific source. Finally, one can use long-term exposure protocols to study both short-term and cumulative responses, and the pathogenesis of chronic disease in animals. Other advantages of studies on animals are the ability to examine the presence of and basis for variations in response that are related to age, sex, species, strain, genetic variations, nutrition, the presence of other pollutants, and so on. As in controlled human exposure studies, the concentrations and duration of the exposure can be tightly controlled, as can the presence or absence of other pollutants and environmental variables. Another important advantage of controlled animal studies is that relatively large numbers of individuals can be simultaneously exposed, creating the possibility of detecting responses that only affect a limited fraction of the population.

Among the significant limitations to the use of exposure–response data from animal studies in human risk assessments is our quite limited ability to interpret the animal responses in relation to likely responses in humans who might be exposed to the same or lower levels. Controlled chronic exposure protocols can be very labor-intensive and expensive, which tends to limit the number of variables that can effectively be examined in any given study.

1.13.5 Controlled Exposures *In Vitro*

For studies focused on the biochemical mechanisms of epithelial cells' responses to O_3, cells can be harvested from humans or animals and exposed to O_3 *in vitro*. Techniques have been developed for reasonably realistic O_3 exposures to cells and cell cultures *in vitro* (Valentine, 1985) for characterizing the release of eicosanoids from such cells (Leikauf et al., 1988), and for examining cell function (Driscoll et al., 1987). The main advantage of *in vitro* studies is their efficiency and relatively low cost. Interspecies comparisons of cellular response can often be made, and relatively few animals can provide much study material. However, our ability to interpret the results of *in vitro* assays in relation to likely effects in humans cells. *In vivo* are of limited value, even when the studies are done with human cells. The cellular response *in vitro* may differ from that of the same cells *in vivo*, and the *in vivo* controls on cellular metabolism and function, which may play a significant role in the overall response, are absent.

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