Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities

Committee on Advances in Assessing Human Exposure to Airborne Pollutants, National Research Council

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Committee on Advances in Assessing Human Exposure to Airborne Pollutants
Board on Environmental Studies and Toxicology
Commission on Geosciences, Environment, and Resources
National Research Council

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Preface

Exposure assessment has been integrated into attempts by governmental agencies and other organizations to examine the contact of an individual or population with contaminants released in environmental media. As part of its attempts to understand better human exposures to hazardous substances, the Agency for Toxic Substances and Disease Registry (ATSDR) sponsored this study of advances in assessing exposure to airborne contaminants.

Numerous techniques have evolved concurrently to qualitatively and quantitatively establish exposure profiles. In industrial hygiene practice, assessments of worker exposure during a work shift have been conducted for many years in attempts to comply with guidelines or standards. The techniques industrial hygienists have used are now being refined and introduced with other new advanced techniques to study the community environment, where contaminant concentrations are usually much lower than those observed in the workplace.

The Environmental Protection Agency (EPA) has provided a starting point from which exposure assessors can consider the priorities among environmental media or contaminants as it develops guidelines for conducting exposure assessment for use in risk assessment. An important point made by EPA is the need to develop exposure assessment strategies—a need identified by scientists who are developing programs on human exposure.

As evidenced by the EPA guidelines and by engineers and scientists in the field, awareness is increasing of basic principles that place exposure assessment prominently within a continuum, starting with an emission from a contaminant source to the occurrence of subcellular changes and an expression of a biological effect within an exposed individual. The awareness provides an opportunity to link exposure assessment with the practical application of risk reduction and exposure-mitigation strategies.

In the context of the present report, the committee focussed on human exposure to contaminants that can be inhaled and potentially cause an adverse health or nuisance effect. The committee did not cover air contaminants

transferred to other media or other routes of entry into the body. The report emphasizes that inhalation must be placed in the context of total exposure assessment, which requires consideration of all pertinent environmental media and all routes of entry into the body.

The committee addressed the specific points in the charge from ATSDR and placed exposure assessment in the context of an evolving scientific discipline within the scope of environmental health. The committee used its judgment in choosing the amount of attention given in the report to specific exposure assessment methods. It considered numerous techniques, which are in different states of development and have different extents of application.

The committee also critically analyzed specific case studies of exposure assessment. The studies are in different stages of completion or design, but each point to areas of achievement or need for continued research. The committee was not charged with providing, nor does it provide, a "how to" manual on exposure assessment, or an encyclopedic accounting of all the important contaminants and the best technique for assessing exposures to those specific contaminants.

The committee's efforts were facilitated by an information-gathering workshop hosted by the John B. Pierce Laboratory, Yale University, October 19–20, 1988. Individuals who also assisted our efforts were Fredrica Perera (Columbia University), Paul Schulte (National Institute for Occupational Safety and Health), and Bruce Stuart (Brookhaven National Laboratory) who contributed to Chapter 4; Devra Davis (National Research Council) who contributed to the lead case study; Demetrios Moschandreas (Illinois Institute of Technology) and Lance Wallace (EPA), who contributed information for the VOC case study; and Timothy Larson (Washington University), who contributed to the acidic particulate matter case study; and Barry Ryan (Harvard University), who provided details on NO_2 exposure. We are indebted to Karen Hulebak (Environ Corp.), who was the original program director of this project, for many insights and comments during the development of the report.

We wish to give special thanks to Raymond Wassel, project director, who guided the report through the review process, provided valuable comments, and diligently ensured that the document was complete. Others of the BEST staff who contributed to the effort are James Reisa, director; Robert Smythe, program director; Lee Paulson and Norman Grossblatt, editors; and Felita Buckner and Sharon Smith, project secretaries.

Paul J. Lioy
Chairman
6 November 1990

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INTRODUCTION

The Bush Administration and Congress are considering new approaches intended to enhance the public health protection benefits of environmental programs within available resources. One general approach being explored would entail revising some federal strategies and priorities to place greater emphasis upon reducing health risks instead of simply responding to statutory requirements or reacting to public perceptions. Such an approach would need to rely heavily upon the application of scientific knowledge in risk assessments. The success of such an approach would therefore depend upon assessments of human exposures to toxic substances, because the exposure component of a risk assessment often entails greater uncertainty than the hazard component, and because reducing human exposure is directly relevant to reducing health risk for a given toxic substance.

Human exposure to air contaminants is one area in which a risk-reduction-based approach could be beneficial. Traditionally, public concerns about air-pollution have focused on highly visible emission sources such as industrial smokestacks and automobiles. Likewise, regulatory strategies mandated by the Clean Air Act have emphasized controlling outdoor sources of air pollution. Since 1970, these strategies have substantially reduced outdoor concentrations for five of the six pollutants for which National Ambient Air Quality Standards have been designated. It is important for these strategies to continue, because exposure to outdoor air pollutants continues to present significant public health risks. For example, outdoor exposures to the sixth pollutant, ozone, still threaten human health in many locations within the United States.

At the same time, air pollutants with major indoor sources are known to cause adverse health effects and personal discomfort, as described in the 1981 National Research Council (NRC) report, *Indoor Pollutants*. In part because the Clean Air Act has been interpreted as applying only to outdoor air, little

progress has been made during the past 20 years in reducing potentially harmful human exposures to air pollutants in many indoor locations. But most people in the United States spend far more time indoors than outdoors; thus risk reduction strategies that address only outdoor air quality are only partially effective. Such strategies need to be modified to better address the importance of indoor exposures.

Benzene (a human carcinogen) provides an example in which the proper application of exposure assessment methodology should be applied to identify areas where more effective strategies are needed to achieve greater reduction of risk. In response to its mandate in the Clean Air Act to control hazardous air pollutants, the U.S. Environmental Protection Agency promulgated regulations in August 1989 for industrial emissions of benzene to outdoor air. However, other large sources of exposure to benzene are not covered by that rulemaking. Exposures from smoking, consumer products in the home, and personal activities such as driving or painting have been estimated to account for more than 80% of nationwide exposure to benzene. Therefore, actual human exposures to benzene at the most significant concentrations and durations are likely to occur inside the home or while traveling within a motor vehicle (i.e., from sources not currently subject to Clean Air Act regulations). The issue of benzene exposure assessment is addressed in Chapter 7, under Volatile Organic Compounds.

The following report describes a conceptual framework and methods for assessing and analyzing the totality of exposures of an individual to air contaminants in the course of all activities over specified increments of time. Accurate and realistic assessment of human exposures from all environmental media can help to ensure that appropriate priorities are set to achieve optimal reduction of human exposures to significant contaminants. Exposure assessment research should be supported by government programs according to such priorities, commensurate with the importance of human exposures to environmental contaminants, whether outdoors or indoors.

THE CHARGE TO THE COMMITTEE

The Committee on Advances in Assessing Human Exposure to Airborne Pollutants was established in 1987 by the NRC's Board on Environmental Studies and Toxicology to review important new developments in exposure assessment methods and instrumentation that have been produced in pollution-related research, occupational medicine, and other disciplines during the past 10-15 years, especially as those developments apply to individual human exposures to airborne toxicants. The committee included members with expertise

in chemistry, mathematical modeling, engineering, physics, air-pollution, exposure assessment, medicine, biology, social science, statistics, and environmental policy. The committee's work was sponsored by the Agency for Toxic Substances and Disease Registry of the U.S. Public Health Service, whose mission is to prevent or mitigate adverse human health effects and diminution in quality of life resulting from exposure to hazardous substances in the environment.

The committee was charged to review new developments and developing technologies in exposure assessment, identify technological gaps, and recommend research and development priorities to fill those gaps. The committee was also charged to consider the value of various methods for estimating chemical exposures in risk assessment, risk management, pollution control, and regulatory programs. As part of the information-gathering process, the committee sponsored a 2-day symposium in October 1988, to obtain current information on the uses of exposure analyses, measurement instrumentation, analytical and survey techniques, biological markers, and study design.

THE COMMITTEE'S APPROACH TO ITS CHARGE

In response to its charge, the committee focused on human exposure to airborne contaminants that can be inhaled or absorbed through the skin and potentially can cause adverse health effects or discomfort for an individual. The committee did not consider in detail exposure to airborne contaminants that come in contact with humans only after the contaminants have transferred to another environmental medium (e.g., deposition of airborne contaminants into food or ingestion of contaminated soil or water). The committee acknowledges that exposure to airborne contaminants is only part of total exposure, which includes all exposures a person has to a specific contaminant; this includes all environmental media (air, water, food, and soil) and all routes of entry (inhalation, ingestion, and dermal absorption). Assessment of total exposure for specified contaminants requires the application of quantitative techniques to all pertinent environmental media and all routes. A single-medium exposure analysis, such as for air only, is appropriate only when supported by convincing evidence that a single-medium exposure predominates for the contaminants of concern.

The committee defines an exposure to a contaminant as an event consisting of contact at a boundary between a human and the environment at a specific environmental contaminant concentration for a specified interval of time; the

units to express exposure are concentration multiplied by time.[1] Exposure assessment involves numerous techniques to identify the contaminant, contaminant sources, environmental media of exposure, transport through each medium, chemical and physical transformations, routes of entry to the body, intensity and frequency of contact, and spatial and temporal concentration patterns of the contaminant. An array of techniques can be employed, ranging from basic techniques for estimating the number of people exposed, to sophisticated methodology employing contaminant monitoring, modeling, and biological markers.

An organizing construct was developed by the committee to facilitate its evaluation of exposure assessment techniques. The construct specified that techniques be evaluated for their usefulness in reducing the uncertainty about exposures and in reducing the invasiveness of the measurement techniques, while improving the efficiency of ways to obtain data on the concentration and duration of contaminant contact with the individual or population. Exposure of the individual was considered key, because the committee determined that knowledge of such exposures is essential to make inferences about the general population.

The committee recognized that good exposure assessment techniques do not guarantee meaningful exposure data; techniques must be applied properly. Therefore, exposure assessment techniques also were considered for their appropriateness in obtaining data within a scientifically sound conceptual framework for exposure assessment. The conceptual framework for exposure assessment defined by the committee is illustrated in Chapter 7 with a series of critical analyses of the ways in which exposure assessments could be and have been applied to specific public health concerns. It was not within the committee's charge to address in detail the proper application and further development of techniques to assess exposure to specific contaminants.

RATIONALE FOR PERFORMING EXPOSURE ASSESSMENTS

Exposure assessment is an integral component of environmental epidemiology, risk assessment, risk management, and disease diagnosis and treatment. It is a multidisciplinary endeavor that frequently requires the combined expertise

[1] Confusion often occurs with the use of the terms "exposure" and "dose." Dose is the amount of contaminant that is absorbed or deposited in the body of an exposed individual over a specified time. Therefore, dose is different from and occurs as a result of an exposure.

of engineers, environmental and industrial hygienists, toxicologists, epidemiologists, chemists, physicians, mathematicians, and social scientists. Exposure assessment methodology employs direct and indirect techniques, including measurement of environmental variables (e.g., indoor-air exchange rates); personal monitoring of contaminants in the breathing zone; and use of biological markers, questionnaires, and computational modeling. Exposure assessment is an equal partner with toxicology in defining human health risk and identifying exposure-response relationships.

As relationships between particular agents and health effects have become better understood, risk assessment methodology has evolved to estimate the likelihood that exposure to a given pollutant will produce a given health effect. As defined in the 1983 NRC report, *Risk Assessment in the Federal Government: Managing the Process,* risk assessment has four components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Figure 1 illustrates the integral role that exposure assessment plays in the risk assessment and risk management processes. Accurate exposure data on contaminant concentrations at the point of contact between a human and the environment are crucial to valid risk assessment.

Many advances in knowledge of exposure assessment have not been well integrated into standard risk assessment practice. A common approach to regulation of contaminants has been to focus attention on a specific single environmental medium (e.g., air) and to deal with the problems of contamination and human contact as a one-dimensional (single-medium) problem. Although multimedia approaches to environmental problems have received increasing attention in recent years (e.g., EPA's 1986 "Guidelines for Estimating Exposures," which specify identification of the principal environmental pathways of exposure), risk management practices generally remain dominated by single-medium and single-contaminant approaches.

FRAMEWORK FOR ASSESSING EXPOSURES TO AIR CONTAMINANTS

Exposure assessments for airborne constituents must be considered within a framework that recognizes the potential contributions from other environmental media. Furthermore, to achieve effective risk assessment, risk management, environmental epidemiology, and diagnosis and intervention in environmental medicine, all media and routes of exposure should be assessed for the relative magnitude of their contributions before an intensive assessment of one medium is conducted. To maximize opportunities for risk management, exposure assessments should include information on the specific sources

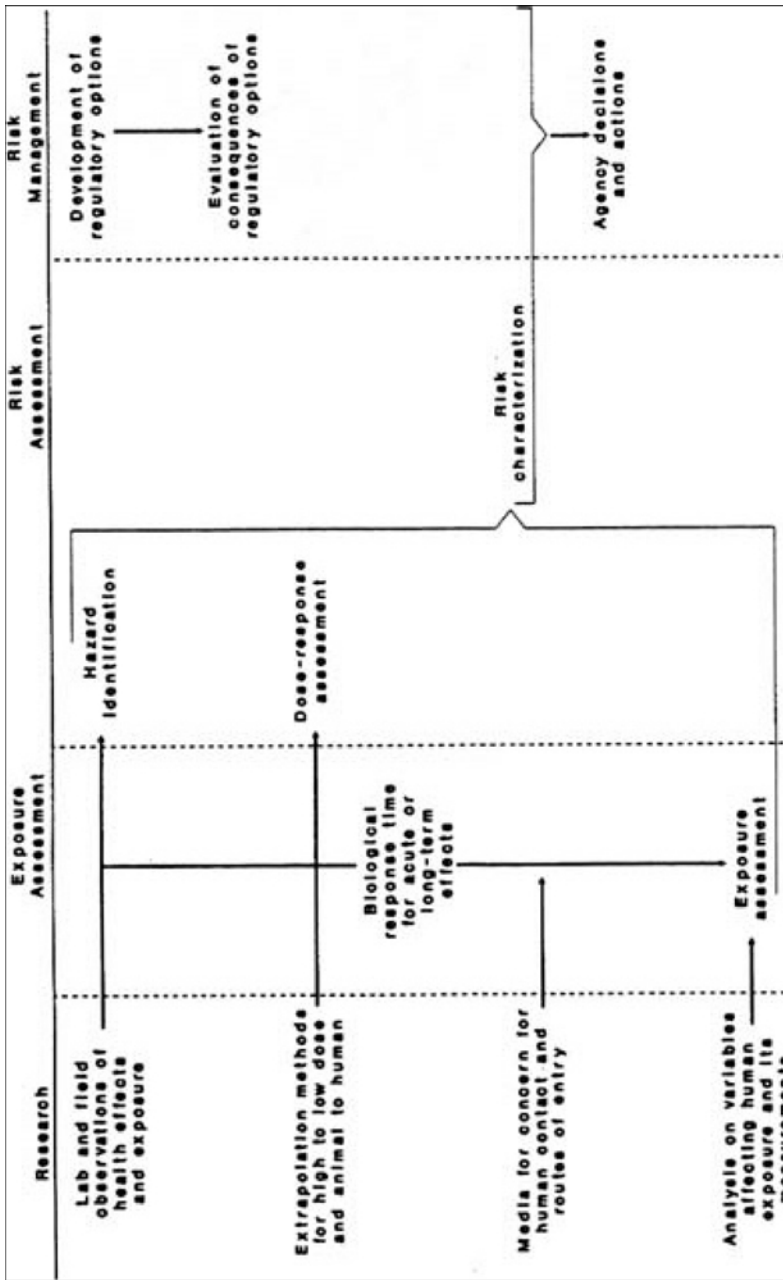

FIGURE 1 Elements of human exposure and their relationship to the process of risk assessment and risk management. (Source: Adapted from NRC, 1983a.)

of contaminants, locations of human contact with the contaminant, and environmental factors affecting the exposures to ensure that effective and appropriate mitigation measures can be formulated. Exposure data should be collected over intervals consistent with the expected biological response time to compounds; this requires knowledge of contaminant toxicity. Data on individual exposures can be integrated by summing over time (time-integrated exposure), over persons (population-integrated exposure), and over contaminants (contaminant-integrated exposure).

Studies to assess exposures to environmental contaminants, whether they are intended to improve environmental epidemiology, disease diagnosis and intervention, risk assessment, or risk management, need to consider the three principal methods of exposure assessment: personal monitoring, biological marker measurements, and indirect methods (e.g., microenvironmental concentration measurements coupled through models to time-activity data obtained from questionnaires). These methods then can be incorporated into the study design to the extent practical and necessary to meet the specific objectives of the assessment. It is not always necessary to monitor contaminant concentration in the breathing zone of each individual in a potentially exposed population. For example, if important contaminant sources and exposure locations were known from previous studies, only fixed-site monitoring data and knowledge of the frequency and duration of exposure of individuals at the contact location would be needed.

Exposure assessment has been practiced in several different disciplines, and numerous definitions and methods of estimating exposure have been developed, including those in the 1988 EPA publication, *Proposed Guidelines for Exposure-Related Measurements*.[2] These guidelines define exposure by units of mass. EPA's definition multiplies exposure (units of contaminant concentration and time) by a contact rate (e.g., breathing in units of volume per time). Time and volume units cancel in the equation, leaving mass. This is more appropriate as a definition of "dose" than of exposure, within the context described by the NRC Committee on Biologic Markers.

Because standard definitions are critical to developing coherence in the field of exposure assessment, the committee recommends that the scientific and regulatory communities, including those responsible for reviewing articles for scientific journals, use consistently the definitions of exposure and exposure assessment recommended in this report to ensure standardization across disciplines.

[2] The EPA guidelines are being modified to incorporate new and improved approaches to understanding exposure.

SAMPLING AND PHYSICAL-CHEMICAL MEASUREMENTS

Quality Control and Quality Assurance

Using advanced measurement techniques in exposure studies does not in itself ensure better data. Quality assurance (QA) programs are critical components of exposure studies; they must be established as part of initial study designs, at which point it should be decided what precision and accuracy are needed to test the study hypothesis. (Accuracy refers to the degree of agreement of a measurement with an accepted reference or true value; precision is a measure of the agreement among repeated individual measurements.)

QA activities, such as interlaboratory comparisons and measurement system audits, are carried out to ensure that the collected data achieve predetermined levels of precision and accuracy. The committee considers QA to include quality control, which comprises operational activities carried out before and during the measurement process to ensure that the accuracy and precision of data are sufficient to meet the needs of a study. An effective QA program is costly (approximately 15–25% of total study expenses) and should be considered when establishing a project's budget.

A major deficiency in the field of exposure assessment is the general lack of validation studies for most new samplers and analytical instruments. In this regard, attention should be given to the availability of reliable chemical standards (sample compounds of known composition and concentration) to use as validation references for measurement techniques. This is especially true for highly reactive compounds. These compounds often are of concern from a health perspective, and stable, known quantities can be difficult to prepare.

Sampling Techniques and Strategy

Most advances in exposure assessment science have occurred in the development of samplers and measurement techniques for fixed-site and personal air monitor studies; the latter have focused on activities and sources that contribute to individual and population exposures. However, new personal air sampling techniques have been underused—especially to provide data to support regulatory decision making.

The choice of a sampling strategy and a measurement method hinges on a study's specific aims and hypotheses. Physical, chemical, and biological characteristics of a pollutant dictate the method chosen to sample and measure its airborne concentration. Because a contaminant can have very different health effects in the vapor-phase versus the condensed phase, care must be

exercised that the selected sampling procedure does not present a false picture of a contaminant's physical state.

Airborne contaminants can be sampled actively or passively. Active sampling uses a pump to pull airborne contaminants through a collection device. Passive sampling relies on molecular diffusion to deliver airborne contaminants to the collection medium. Passive monitors are well suited to collect long-term integrated gas and vapor samples obtained over days or weeks, and they can be extremely useful for personal or microenvironmental studies. However, long-term sampling with passive monitors often places great constraints on the sorbent, which must retain the analyte of interest without promoting unintended reactions with other adsorbed analytes. Sorbent improvements are needed to allow long-term sampling for a wide variety of analytes.

Personal air-monitoring is the most direct approach for assessing human exposure to airborne pollutants. However, portability usually is attained at the expense of sensitivity (compared with fixed-site microenvironmental monitoring instruments). Personal monitors (active or passive) need to be developed for many potentially harmful airborne contaminants, including certain metals, polycyclic aromatic hydrocarbons and other semivolatile organic compounds, polar volatile organic compounds (e.g., vinyl chloride), and radon progeny. In some cases, personal monitors already exist but need to be refined, reduced in weight and size, or validated (e.g., airborne particles and certain pesticides).

Certain pollutants produce effects only at concentrations greater than a threshold value. Therefore, personal samplers of such pollutants are needed that will continuously monitor only exposures to concentrations greater than a designated threshold for community and occupational exposures.

Quiet and unobtrusive microenvironmental samplers are needed if fixed-site sampling is to be used widely; such samplers should be developed for the full spectrum of air contaminants.

New sorbents for polar volatile organic, highly volatile, and very reactive compounds are needed. Collection with sorbent sampling systems often is associated with a compromise in analytic sensitivity; this results from the large volumes used in liquid desorption techniques. Procedures such as supercritical fluid extraction that permit desorption with a minimum of dilution need to be developed.

Instrumental Techniques

Many advances have been made in instrument design, operation, and experimental deployment during the past 15 years. Liquid chromatography (LC)

techniques are being used to analyze for compounds not amenable to gas chromatography (GC). In particular, ion chromatography is being used increasingly to analyze highly polar air contaminants. LC combined with mass spectrometry also is being developed into a technique to complement GC combined with mass spectrometry. The development of new types of detector configurations (e.g., ion trap mass spectrometer) has made mass spectrometry a valuable air analysis device. Simple advances have been made for other GC and LC detectors.

Field applications of exposure assessment methods are restricted by instrument limitations. Portable, reliable, and rugged instruments such as gas chromatographs, gas chromatograph/mass spectrometers, ion trap mass spectrometers, and electrochemical sensors are needed. Sampling methods, instruments, and software to function with these instruments also are needed to permit unattended sample collection and analyses in field settings for extended periods. A sensitive, highly specific detector applicable to numerous compounds is needed for LC. Continued improvements in LC combined with mass spectrometry are beginning to fill this gap.

USE OF BIOLOGICAL MARKERS IN ASSESSING HUMAN EXPOSURE TO AIRBORNE CONTAMINANTS

Biological markers in an exposed individual can provide information about an original contaminant, a metabolite of a contaminant, or the product of an interaction between a contaminant agent and some target molecule or cell. As one progresses from markers of exposure to markers of health effect, variability associated with the individual becomes an increasingly significant problem.

Biological markers have been studied as a part of research on exposure to air pollutants for a limited number of compounds. Critical issues are associated with marker specificity and sensitivity to an exposure contaminant. In some cases, biological markers cannot be used without adjustments for exposures to background concentrations of contaminants from the same or other media and adjustment for seasonal or regional variation.

The use of biological markers in exposure assessment should normally be done in conjunction with personal or microenvironmental exposure-measurement techniques. Biological markers integrate all routes and sources of exposure and can provide measures of the actual dose of a contaminant an individual has received when appropriate metabolic data are available and when the relationships between times of exposure and sample collection are adequately

defined. However, the actual routes and sources of exposure cannot be detected without information on environmental contaminant concentrations.

Analytical techniques with improved chemical specificity and sensitivity for biologically significant markers are needed for exposure assessments; especially needed are flexible assays that can analyze several markers simultaneously or be readily adapted to analyze numerous markers sequentially. For such techniques, validation studies are needed to link biological markers conclusively to causative agents.

Pharmacokinetics is the quantitative description of the rates of absorption, distribution, metabolism, and elimination of a contaminant taken into a biological system. Better pharmacokinetic data are needed for an increasing number of chemicals. These data are needed to further the development and validation of sophisticated biological marker models and to further understanding of how to model multiple metabolic pathways as a function of exposure level.

SURVEY RESEARCH METHODS AND EXPOSURE ASSESSMENT

Although there have been major advances in personal monitoring equipment and in conducting sociological studies of time use, exposure-related data on human activity patterns are in short supply. The techniques normally employed are questionnaires and recall diaries to obtain information on location and duration of human activities. Elementary principles of statistical survey design, sample selection, and question format often are ignored in questionnaires and surveys used by exposure analysts. Collaboration of social scientists having expertise in survey statistics with exposure analysts can help to develop more appropriate questionnaires, to limit the effects of biased questions, and to validate survey instruments before their use in the field.

Far more attention needs to be given to the design of survey research in exposure studies. Exposure analysts need to employ the expertise of specialists in survey statistics and the measurement of human time-activity patterns through the use of questionnaires. Improvements are needed in the reliability (precision) and validity of survey results, especially with regard to estimates of frequency or duration of exposure. The estimation of long-term exposures presents challenges yet to be addressed by survey researchers.

In addition to resource intensive surveys of large populations, far more use should be made of well-designed, but less-expensive, sequential or one-time studies done at the community level. Such surveys could be especially important for personal exposure monitoring studies. In addition, a series of small

benchmark surveys of "normal" situations or environments are needed to help establish baselines for other studies (e.g., studies of time-activity in "healthy" buildings for comparison with similar studies in "sick" buildings).

MODELS USED IN ASSESSING HUMAN EXPOSURE TO AIRBORNE CONTAMINANTS

Mathematical models use systems of equations to quantify and explain the relationships between air-pollutant exposure and important variables, such as emission rates from contaminant sources, as well as for estimating exposures in situations where direct measurements are unavailable. These models are derived from assumptions and approximations that permit complex physical-chemical-behavioral problems to be represented by mathematical formulations.

Models considered by the committee were classified into two broad categories: those that predict exposure (in units of concentration multiplied by time) and those that predict concentration (in units of mass per volume). Exposure models obviate extensive environmental-or personal-measurement programs by providing estimates of population exposures that are based on small numbers of representative measurements. Although concentration models are not truly exposure models, the output of concentration models can be used to estimate exposures when combined with information on human time-activity patterns.

To improve the development and validation of models, measurements are needed of the concentrations of airborne pollutants in workplaces, homes, and other microenvironments. Simultaneous measurements of critical independent variables, such as source emission rates and indoor-ventilation rates, are also needed for models. Concentration gradients within defined microenvironments also need to be accurately measured.

Validation studies are needed for many existing models. In particular, immediate efforts are needed to validate the models used for decision making by EPA, ATSDR, and others about public and occupational health and to tailor the models to relate to the actual situations that can result in large population exposures. Valid emission rate models are needed to provide better estimates for multicomponent mixtures. Validated outdoor-dispersion models are needed to predict concentrations in complex terrain and to provide accurate exposure estimates for down- and up-gradient terrain conditions.

The same data set used to develop a model cannot be used to refine and validate it; new, independent data are required. In addition, all assumptions used in developing a model should be documented explicitly. Care should be

taken by investigators in any field-monitoring program to integrate measurements with modelers' information needs so that the requisite model input data are obtained or the measurement results can be used to test, refine, or validate appropriate models.

Little work has been done to model very short-term exposures (peak exposures) and gradients for dispersion, deposition, and ventilation in indoor environments. Measuring and modeling the temporal patterns of source strength as a function of readily identifiable or measurable source characteristics is a critical step in that process. In addition, more work is needed to model the relationship of indoor-air quality to the composition of the outdoor air.

Concentration Models

New developments in outdoor-dispersion models have improved prediction of the average and time-varying concentrations to which individuals are exposed. Receptor models can be compared with dispersion models as a means of checking the predictions of both models. They also can be used to identify sources of exposure. In many cases, however, data describing the source characteristics are not available on the time scale for which the model predictions are needed. Such mismatches of the time scale of the measurements with the time scale of the models impede model development, validation, and application to new exposure scenarios.

Source emission models are available to predict mass-emission rates for a variety of dynamic and steady-state emission problems. The available emission models allow the estimation of downwind exposure for continuous and catastrophic releases of pure compounds or binary mixtures. However, these models have not been validated. Dense cloud dispersion models are available to estimate downwind exposure for heavier-than-air vapor or aerosol releases; they also have not been validated.

Exposure Models

Models for predicting exposures to populations have been developed but have not been adequately validated. Limited validation studies of the EPA's "Simulation of Human Air-Pollution Exposure Model," for example, show that the average exposure values are well predicted but also show substantial discrepancies in the tails of the distribution. Further development and validation of these models are warranted. Exposure models used for regulatory decision

making should be developed and validated for microenvironments where significant exposures occur.

FUTURE DIRECTIONS FOR EXPOSURE ASSESSMENT

Air-exposure reduction strategies for a given contaminant should first consider exposures due to all media. If other media are found to contribute significantly to the total exposure even after air exposures are reduced, agencies responsible for or experienced with the other media should be apprised of the issue and be actively involved in the development of integrated exposure-reduction strategies.

Unless the health effect of a contaminant is unique or the source of the contaminant exposure is well characterized, it is difficult to relate an exposure to a health effect for one of a group of contaminants present in specific microenvironments. When a contaminant does not have a unique health effect, it is necessary to identify those situations where populations can have substantial exposures. Once the exposure is assessed, that information should be used to perform studies to establish the magnitude of the health outcome from exposure in those situations.

Attempts to assess human exposure to air contaminants have achieved varying degrees of success. It is easy to find flaws with any exposure study when we are only beginning to understand the ways in which human activity affects exposures of individuals and populations. It is clear, however, that the field of air contaminant exposure assessment has advanced significantly as a result of indoor-air-pollution studies. Further progress will be achieved as exposure study designs more completely address and rank potential contributions from all environmental media to all relevant microenvironments.

Assessing Human Exposure to Airborne Contaminants

1

Principles of Exposure Assessment

INTRODUCTION

Since the early 1970s, when federal regulatory agencies first focused their attention on the association of cancer and other chronic diseases associated with human exposure to toxic agents, rapid advances in bioassay techniques and other test methods have made it possible to discern relations between particular agents and cancer and other health effects. Risk assessment is a method for estimating the likelihood that a given pollutant will have a given health effect. Risk assessment has four components: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC, 1983a). Advances in hazard identification and dose-response assessment have been successfully incorporated into risk assessment practice. Advances in analytic instrumentation permit the detection of chemicals at lower and lower concentrations and these make it possible to detect the presence of chemicals that would have been missed earlier. Also, advances and improvements in mathematical and statistical manipulation of data have been major contributors to improvement in the practice of risk assessments. However, accurate data on exposure, i.e., contaminant concentrations at the boundary between a human and the environment and the duration of contact, are also crucial to valid risk assessment, but advances in exposure assessment have not been fully integrated into standard risk assessment practice.

Exposure assessment has seen important conceptual and practical advances. Perhaps the most fundamental has been the recognition that exposures to various contaminants can occur through contact of any tissue with any environmental medium at any time, and in all sorts of venues. That might seem obvious, but in major environmental regulations, exposures to contaminants have been—and to a large degree still are—thought of in the terms of 8-hour workplace exposures and 24-hour outdoor exposures of a "standard" 70-kg man. Such definitions assume the presence of a contaminant in a particular medium

(or microenvironment) just as they assume the presence of the person and the contact with that medium in that microenvironment. In fact, indoor concentrations of some pollutants can be higher than outdoor concentrations, most people spend far more time indoors than outdoors, and different population groups (e.g., young children and older persons) have different patterns of sensitivity and activity, which affect their likelihood of and responses to exposure.

The national environmental-policy implications of those findings could be enormous. For example, if indoor sources of airborne benzene were acknowledged, and it were determined that the average person's major exposure occurred indoors, rather than outdoors, the allocation of hundreds of millions of dollars for control of industrial emissions of benzene might appear less than optimal. The same could well be true of a number of other major elements (such as NO_2 from stoves) of concern to national environmental policy associated with substantial exposures.

The Committee on Advances in Assessing Human Exposure to Airborne Pollutants was established by the National Research Council's Board on Environmental Studies and Toxicology to review important new developments in exposure assessment instrumentation and methods that have arisen in pollution-related research, occupational medicine, and other disciplines over the last 10–15 years, especially as they apply to individual human exposures to airborne toxic substances. The committee's work was sponsored by the Agency for Toxic Substances and Disease Registry (ATSDR), whose mandate is to prevent or mitigate adverse human health effects and diminution in quality of life resulting from exposure to hazardous substances in the environment. In response to its charge and to national needs for improved understanding about exposures to environmental hazards, the committee has reviewed the new developments and developing technologies in exposure assessment, identified knowledge and technological gaps, and recommended research and development to fill those gaps. In this report, the committee also presents a conceptual framework for the science of exposure assessment and illustrates, with a series of case studies, how exposure assessments can be (and have been) properly and improperly applied and conducted. However, it was not within the committee's charge to perform an exhaustive study on the proper application and further development of techniques to assess exposure to any specific contaminant.

This chapter introduces the basic principles and definitions of exposure assessment. Chapter 2 presents the framework for conducting exposure assessments, the quantitative relationship among source and receptor characteristics, and the basic components of exposure assessment and how it may be employed. Sampling and physical and chemical measurements are discussed

in Chapter 3, biological markers in Chapter 4, questionnaires and survey issues in Chapter 5, and modeling techniques and instruments in Chapter 6. Chapter 7 contains a number of airborne-contaminant case studies that illustrate the application and misapplication of exposure assessment. The summaries of Chapters 1 and 2 contain general conclusions and recommendations. The summaries of Chapters 3 through 6 contain conclusions and recommendations relevant to the exposure assessment methods discussed in each chapter. Such methods can be incorporated into a study design to the extent practical and necessary to meet the specific objectives of the assessment. Conclusions presented at the end of each case study in Chapter 7 focus on broad implications for the discipline of exposure assessment, notable advances, and remaining needs.

BACKGROUND

Environmental contaminants found in the community or occupational settings long have been thought to be related to a wide range of adverse health and nuisance effects in humans. In the course of daily activities, humans are exposed to a variety of environmental contaminants through the air they breathe, water and beverages they drink, food they eat, and materials that contact their skin. These events occur in many settings—indoors (e.g., residential, industrial, occupational, and transportation) and outdoors. An exposure to a contaminant is defined as an event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time. Thus, an exposure has units of concentration and time. This definition is consistent with definitions of exposure presented in other NRC reports and is discussed in greater detail in Chapter 2.

Total human exposure accounts for all exposures a person has to a specific contaminant, regardless of environmental medium (air, water, food, and soil) or route of entry (inhalation, ingestion, and dermal absorption) (Lioy, 1990). For media other than air, the time increment could be infinitesimal, such as that incurred during the act of drinking a glass of water. It is a necessary concept to carrying out risk assessments or health studies for a pollutant. Sometimes total exposure is used incorrectly to refer to exposure to all pollutants in an environment. Total exposure to more than one pollutant should be stated explicitly as such.

Assessing the total exposure of an individual or population involves numerous techniques to identify the contaminant, contaminant sources, environmental media of exposure, transport through each medium, chemical and physical

transformations, routes of entry to the body, intensity and frequency of contact, and spatial and temporal concentration patterns of the contaminant. An array of techniques can be employed, ranging from estimates of the number of people exposed and contaminant concentrations to sophisticated methodology employing contaminant monitoring, modeling, and measurements of human biological markers. The type of exposure assessment methodology used largely determines the applicability of collected data to quantifying the relationship between exposure and biological response. Whatever application or technique is employed, the fundamental concern is human health and comfort. In response to its charge, the committee focused on human exposure to airborne contaminants that can be inhaled or absorbed through the skin and potentially cause adverse health or nuisance effects for an individual. The committee did not, nor was charged to, focus on exposure via other routes following deposition of airborne contaminants into other media (e.g., deposition of airborne contaminants into food or ingestion of contaminated soil or water).

Dose is the amount of a contaminant that is absorbed or deposited in the body of an exposed organism for an increment of time. Dose is not considered in detail in this report, except in discussions of biological markers.

The National Research Council's Committee on Biologic Markers has portioned dose into two components: internal dose and biologically effective dose (NRC, 1989). Internal dose is the amount of a contaminant that is absorbed into the body over a given time. Biologically effective dose is the amount of contaminant or its metabolites that has interacted with a target site over a given period so as to alter a physiological function.

Exposure assessment is central in environmental epidemiology, disease diagnosis and intervention, risk assessment, and risk management. In environmental epidemiology studies, exposure assessment historically has involved qualitative characterizations of whether contact was made with a contaminant rather than determination of actual concentrations, duration of human contact, and identification of all sources of the contaminant. Although a qualitative approach can provide order-of-magnitude estimates, it is unsatisfactory because it can result in misspecification[1] of exposure and can fail to account adequately for confounding factors (e.g., temperature affecting contaminant concentration). A qualitative approach can mask or overemphasize an actual exposure-response relationship. In some cases, if the pollutant and outcome are well defined, general indicator data can be used to describe important

[1] Misspecification or misclassification of exposure occurs when a contaminant or the place of contact with a contaminant is incorrectly identified.

response-exposure relationships. Good examples of the use of this kind of data are the studies by Bates and Sitzo (1987), Bates et al. (1990), and Ostro and Rothschild (1989) of ozone and particulate irritants and acute respiratory response.

Application of quantitative techniques to all pertinent media and to all routes is desirable to account for the influence of confounding factors. Quantitative methods also are important in defining subpopulations with the greatest potential for contracting a disease or exhibiting an adverse health effect.

Exposure assessment can be important in disease diagnosis and treatment. With careful evaluation of the factors that might have contributed to a specific disease, exposure assessment could be employed to define the intervention necessary to reduce and control contact with a contaminant and provide a basis for further analysis of a larger population.

Risk assessment methods are widely used by federal, state, and local agencies, as well as industry, to determine whether various chemical substances in the environment might induce adverse health effects in humans. Exposure assessment provides fundamental information for describing the distribution (including the high and low extremes) of contaminant exposures within a population, for estimating the doses received from different media, and for determining routes of entry into the body. Use of appropriate exposure assessment methodology in risk assessment reduces the error or uncertainty in the calculated risk.

After risk assessment shows that a contaminant poses an adverse health risk, regulatory agencies develop risk management plans. Such a plan involves formulating cost-effective mitigation efforts to reduce the risk associated with exposure to a contaminant and to monitor progress toward risk reduction. Exposure assessment is an essential part of risk management effort because it helps to determine the following:

- Concentration distributions in time and space for different environmental media.
- Populations or subgroups at high and low risk.
- Efficient, effective, and representative environmental monitoring programs.
- Chemical and physical contributions of various sources to concentrations.
- Factors that control contaminant release into environmental media, routes of environmental transport, and routes of entry into humans.
- Effective mitigation measures.
- Compliance through mitigation measures to achieve health standards.

Exposure assessment efforts traditionally have focused on one route of entry through one environmental medium and microenvironment (EPA, 1988a). A microenvironment is a three-dimensional space with a volume in which contaminant concentration is spatially uniform during some specific interval (Sexton and Ryan, 1988). A variety of microenvironments are encountered in spaces in offices, homes, vehicles, stores, schools, athletic fields, parks, backyards, and city streets. Efforts directed at studying only one micro-environment often have used unsophisticated techniques, such as questionnaires with little or no information on spatial and temporal distributions of contaminant concentrations and the human contact with those contaminants. These efforts have resulted in difficulties identifying significant exposures and in developing effective mitigation measures for airborne compounds that have multiple sources in one or more microenvironments (EPA, 1988a). More effective methods were not used for many reasons, including technological limitations in environmental monitoring methods, lack of adequate concentration-predictor models, unavailability of adequate human biological markers of exposure, limitations in available resources, inadequate understanding of media and routes of entry, and narrow public health mandates of individual regulatory agencies. As a result, agencies responsible for regulating chemicals for indoor and outdoor environments (emissions, use, etc.) have often not adequately integrated exposure assessment techniques and data into their regulatory actions.

The Environmental Protection Agency (EPA) has developed exposure assessment guidelines focusing on modeling (EPA, 1986a) and measurement (EPA, 1988b) to provide more accurate exposure assessments to use with risk assessments. The guidelines specify that an exposure assessment should include an identification of the principal environmental pathway of exposure, including indoor settings. These guidelines, however, do not adequately address the need for indoor-air data on important sources of exposures for individual contaminants. Advances in indoor-air exposure studies have demonstrated the significant health effects from indoor emissions and exposures to contaminants that had been regulated only as outdoor pollutants (e.g., NO_2) (Spengler and Sexton, 1983; Akland et al., 1985; Spengler et al., 1985; Leaderer et al, 1986; Wallace, 1986). These demonstrations of high indoor-contaminant levels showed the importance of accounting for incremental exposures[2] from microenvironments when making risk assessments for specific

[2] Incremental exposures are separate events of contact between an individual and a contaminant; they can be summed, and their units are $\mu g\text{-}hr/m^3$.

contaminants. For many outdoor contaminants, significant emission reductions have been achieved during the past few decades (e.g., sulfur dioxide).

EPA's Science Advisory Board recognized the need to consider exposure-reduction strategies in media and situations that yield cost-effective benefits (e.g., indoor air) and recommended that EPA develop a 5-year program on exposure assessment as one of its major new initiatives (EPA, 1988a).

Exposure Assessment in Environmental Epidemiology

During the past several decades, exposure assessment research has progressed most evidently in environmental epidemiology. This progress can be illustrated by tracing some of the major developmental steps in outdoor-air-pollution epidemiology and the accompanying air-monitoring efforts (Figure 1.1).

Early epidemiological methods for measuring the effects of outdoor-air-pollution concentrated on the definition, measurement, and verification of disease outcomes and physiological changes that were indicative of disease development. Considerable efforts were made to improve the interpretation and standardization of death certificates, to standardize reporting of pulmonary symptoms and definitions of chronic lung disease (e.g., chronic bronchitis and emphysema), and to standardize the measurement, interpretation, and reporting of lung-function measurements. Concurrent efforts were made to develop and apply statistical methods to outdoor-air epidemiologic data bases.

Early data on potential exposure to contaminated air were derived primarily from questionnaires that identified an individual's residence and indicated whether that individual had been exposed to a high level of air-pollution. Categories of exposure to outdoor pollutants were assigned with little information on confounders, such as smoking status or occupation, which led to misclassified exposure categories. In addition, when data were available on the spatial and temporal variations of the actual outdoor concentrations, they were for a very limited number of air contaminants. The factors affecting the accumulation of the measured outdoor concentrations (e.g., sources, meteorology, and chemical transformations) were poorly characterized or understood by the epidemiological investigators (Lippmann and Lioy, 1985). It commonly was assumed that the one or two routinely monitored contaminants or indicators (e.g., total suspended particles or sulfur dioxide) at fixed sites either were related to the health outcomes under study or were proxies for contaminants that posed a potential health threat. In time, ambient monitoring was expanded to cover a wider range of chemicals to better define the spatial and temporal variability, as well as to gather better information on the factors influencing

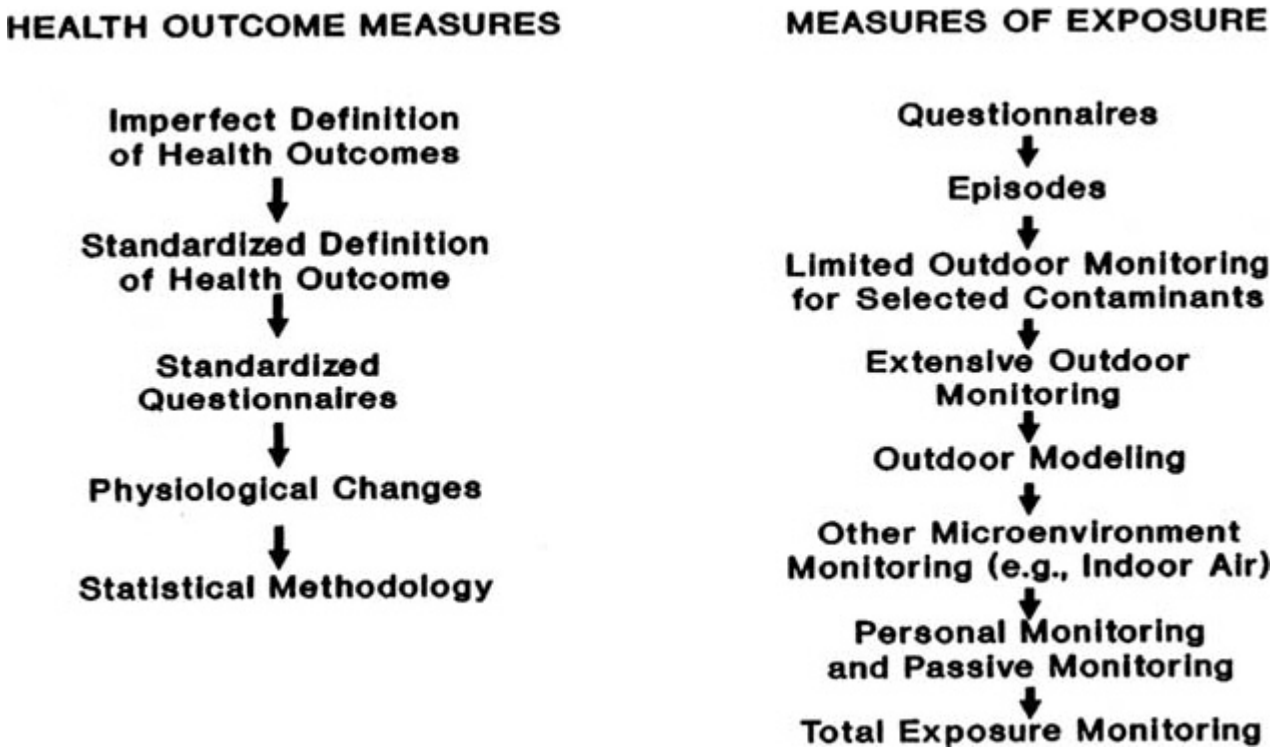

FIGURE 1.1 Time line of health outcomes and measures of exposure for outdoor-air-pollution epidemiology.

ambient levels. In addition, models that examined community source-receptor relationships were developed and improved to better identify sources and evaluate mitigation strategies.

These efforts, however, still were directed toward determining outdoor concentrations and ignored the presence of many air contaminants in homes and other indoor locations (NRC, 1985). Further problems with identification of contaminant exposures remain since exposures continue to be considered as occurring from one media with one route of entry. Within the past 10 years, air contaminant exposures have been recognized as taking place through many media and with different routes of entry. These multiple exposures need to be assessed by personal monitoring, biological monitoring, indirect measurement modeling, or combinations of monitoring methods. Recent advances in personal and passive monitoring instrumentation are examples of steps taken in this direction (Palmes et al., 1976; Geisling et al., 1982; Lewis et al., 1985; Mulik and Williams, 1986; Hammond and Leaderer, 1987). Methods for air sampling and analysis have developed in parallel to air-pollution epidemiological methodology (ACGIH, 1988a; Lioy and Lioy, 1983). When measures of internal dose or biological markers are available, attempts are being made to incorporate them into exposure assessment research designs (NRC, 1988).

Increasingly, air-pollution exposure monitoring has been included as an integral part of environmental epidemiology. These data have indicated the potential importance of indoor sources of contaminants. For example, exposure and emissions studies published during the past 10 years successfully have tested the hypothesis that there are major indoor sources of NO_2 (e.g., gas home appliances) and that concentrations and exposures in homes with these sources frequently yield higher NO_2 concentrations than outdoor levels (Leaderer et al., 1986; Southern California Gas Co., 1986). These studies have also shown that indoor NO_2 concentrations in homes without these sources are about half the outdoor concentrations, personal exposures to NO_2 are strongly associated with indoor levels (because people spend more time indoors than outdoors), and personal exposure is only weakly associated directly with outdoor concentrations even for residences with no sources (Ott, 1988). The advances in understanding exposure to NO_2 are due in part to the development of inexpensive passive personal or microenvironmental monitors. As a result, measurement of personal exposures to NO_2 with particular emphasis on indoor air is now used in the evaluation of health effects associated with NO_2 and in developing and specifying effective mitigation measures.

Exposure Assessment in Occupational Epidemiology and Risk Management

Exposure assessment techniques have also evolved in the fields of occupational epidemiology[3] and occupational risk management. In early occupational epidemiology studies, exposure was determined principally by questionnaires and implied contact with the contaminants of interest. This produced exposure data that were based on job category, which made it difficult to compare studies of identical occupational contaminants. In addition, general categorization of exposure by job title tended to yield erroneous assignments of exposure categories, because each person's time-activity profile would be different. Daily movements of workers and variability in exposures could not be adequately identified, which made any exposure-response relationship difficult to define. Occupational epidemiology studies now use strategies that obtain more quantitative information on exposure. An industrial hygienist can determine what to measure, how to measure, where to measure, whose exposure to measure, frequency of measurement, existence of possible confounding contaminants, and factors affecting contaminant exposures. As a result of more sophisticated exposure measurements, misclassification of subjects by exposure category is reduced, exposure-response relationships are more likely to be detected, and effective mitigation measures can be instituted. Occupational epidemiology studies and occupational risk management efforts are also beginning to incorporate measures of dose and biological markers (Lauwerys, 1983; ACGIH, 1988b).

Conceptual Framework for Human Exposure Assessment

Efforts to assess and reduce total human exposure to environmental contaminants and relate exposure to acute and chronic health effects or nuisance effects[4] must be guided by a theoretical framework or methodology. A general framework is shown in Figure 1.2 and is described in greater detail in

[3] For the terms "occupational epidemiology" and "environmental epidemiology" as used in this report, the committee considers "environmental" to include occupational settings with regard to exposure assessment.

[4] Nuisance effect is a subjectively unpleasant effect (e.g., headache) that occurs as a consequence of exposure to a contaminant; it may be associated with some physiological response, but it is not permanent.

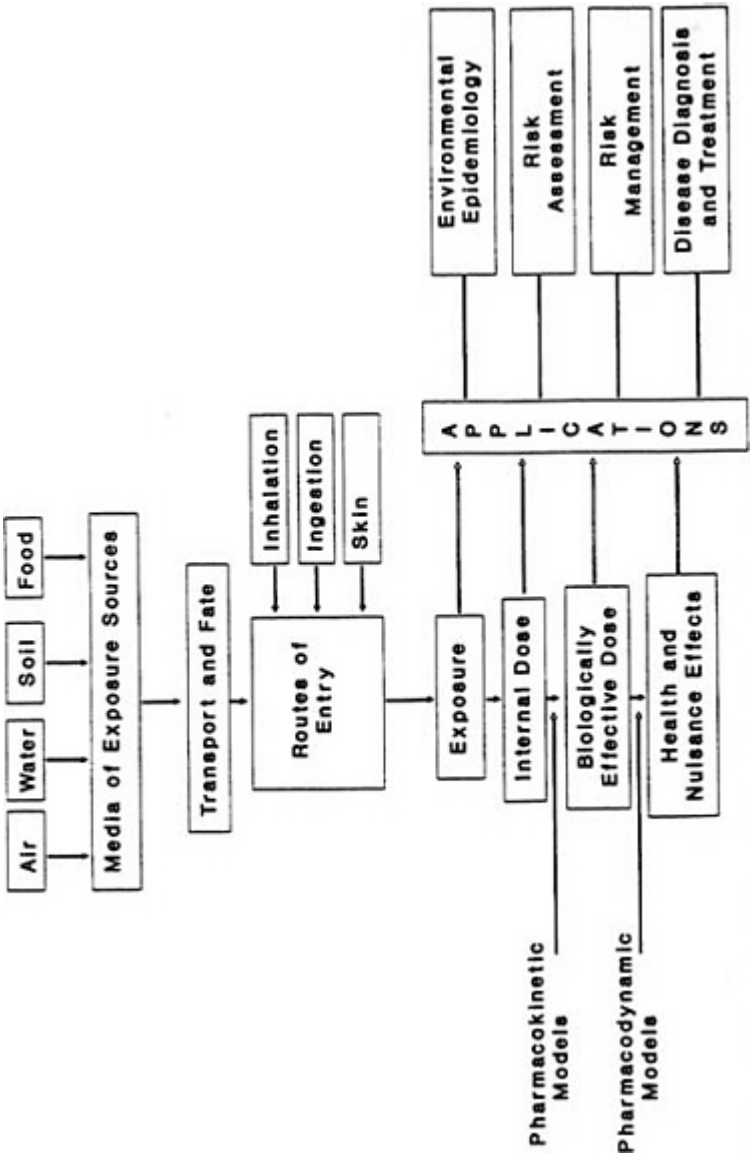

FIGURE 1.2 Contaminant sources and effects continuum.

Lioy (1990). Information on the doses that can cause effects associated with contaminant exposure is vital to the design of an exposure assessment protocol (Calabrese, 1987). It is difficult to identify a single effect associated with a single contaminant; it is even more difficult to determine a dose-response relationship. A health outcome often results from a complex situation that can include many factors such as health status, age, race, diet, personal habits, and occupation, as well as a variety of environmental contaminants emitted from several different sources. Generally, associations are explored among exposures to specific contaminants, general categories of contaminants or sources, and adverse biological responses, or health or nuisance effects. Confounding variables must be controlled or accounted for simultaneously. Although this report emphasizes the direct inhalation route, it must be recognized that the approaches described are developed within the framework of total exposure, which accounts for all exposures a person has to a specific contaminant, regardless of environmental medium (air, water, food, and soil). This report focuses on exposure to airborne contaminants; however, exposure is a necessary event for there to be any health or nuisance effects from contact with contaminants in the other environmental media (see Figure 1.2).

Exposure assessments for airborne constituents must be considered in the framework of potential contributions from other media and adding the incremental exposures from other media when necessary. Furthermore, to achieve effective risk assessment, risk management, environmental epidemiology, and diagnosis and intervention, all media and routes of exposure must be assessed for the relative magnitude of their contributions before an assessment of one medium is conducted.

Specification of a person's or a population's exposure to an environmental contaminant or categories of contaminants should take into account a time scale related to the biological response studied unless the exposure assessment is intended to provide data on the range of biological responses. Specification of biological response requires on contaminant toxicity and quantitative assessment of the exposures associated with the effects. Understanding of the etiology of an effect is central to the application of exposure assessment methodology.

The impact caused by exposure to environmental contaminants ideally should be evaluated in terms of the dose of the contaminant or its metabolites, which the committee defines as follows: Dose is the amount of a contaminant that is absorbed or deposited in the body of an exposed organism for an increment of time—usually from a single medium. Total dose is the sum of doses received by a person from a contaminant in a given interval resulting from interaction with all media that contain the contaminant. Units of dose and total dose (mass) are often converted to units of mass per volume of

physiological fluid or mass per mass of tissue, e.g., blood-lead levels in µg/DL.

Potential dose is the exposure multiplied by a contact rate (e.g., rates of inhalation, ingestion, or absorption through the skin) and assumes total absorption of the contaminant. Internal dose refers to the amount of the environmental contaminant absorbed in body tissue (Davis and Gusman, 1982) or interaction with an organ's membrane surface (e.g., asbestos deposited on the lung surface). Biological markers are being used increasingly as indicators of the internal effective dose of contaminants or metabolites (e.g., blood-lead levels, cotinine in urine or blood, and DNA adducts). The biologically effective dose is the amount of the deposited or absorbed contaminant that reaches the cells or target site where an adverse effect occurs (Davis and Gusman, 1982) or where that contaminant interacts with a membrane surface. Few indicators of biologically effective dose of environmental contaminants are well characterized. These definitions of internal dose and biologically effective dose are consistent with those given in recent NRC reports: *Biologic Markers in Pulmonary Toxicology* and *Biologic Markers in Reproductive Toxicology*.

Physico-pharmacokinetic models are used to describe or calculate a relationship between exposure and target-tissue concentrations of environmental contaminants. Such models can be simple with one compartment (Rappaport, 1985), or complex, with multiple compartments (Kjellstrom and Nordberg, 1978). Pharmacodynamic models describe the dynamic processes that relate the target tissue concentrations and tissue effects to the ultimate health effects. These models typically present a mathematical relationship between biologically effective dose and a health outcome. For risk assessment, the models are based upon toxicological data; contaminant exposures from different media; and the biologically effective dose, internal dose, or a health outcome.

Data on biologically effective dose are useful for exposure assessment when a contaminant has only one significant route, and the metabolic pathway is well understood. For example, carboxyhemoglobin levels are a good measure of the dose received from CO exposures and are directly related to exposure, because inhalation of CO in air is the most significant cause of elevated levels of carboxyhemoglobins. However, the levels can be influenced by methylene chloride, whose metabolism will release CO that can bind to the hemoglobin.

Biologically effective dose is not practical in assessing the overall effect of exposure to an environmental contaminant because of limitations of knowledge; for example, uptake, distribution, metabolism, and site and modes of action of contaminants in humans are neither well understood nor easily measured. Moreover, information on biologically effective dose cannot be used directly to assess sources, environmental conditions, or location of human

receptors, which affect the accumulation of contaminants in the environment; the uptake of contaminants, including physical characteristics of the contaminants; and the physiological characteristics and activity levels of exposed persons.

The exposure assessment methodology employed must consider a wide range of aspects, including:

- Contaminant and potential biological response.
- Specification and selection of the target population.
- Available technology for personal environmental and biological marker sample collection and analysis.
- Spatial and temporal variability of concentration distribution patterns.
- Selection of the sampling period in appropriate relationship to the time scale of biological effect.
- Frequency and intensity of exposure.
- Precision and
- Costs and available resources.

Types of Studies

The development of exposure assessment methodologies has involved numerous professions and organizations. Such groups have employed different approaches although the general goals might have been similar, for example, to understand individual or population exposures to various contaminants within specific environments. Data from previous assessments on the magnitude of physical, chemical, and biological impacts and the routes of transport and entry into the body have aided in the identification of mitigation methods. Unfortunately, some data did not accurately address public health priorities, because the environments studied did not include those in which the most significant exposures would occur (EPA, 1988a). For example, exposure investigations conducted for various volatile organic compounds have shown that emissions in outdoor-air environments might not accurately reflect the major sources of exposure, because significant exposures occur in indoor environments, especially for certain contaminants, such as benzene and tetrachloroethylene (Wallace, 1987).

An accurate assessment of exposure used to test initial hypotheses can be employed with health data to establish relationships between exposure and health response. The type of exposure assessment and the acceptable level of uncertainty in the data vary according to whether the assessment is designed to generate or test hypotheses about exposure, test instruments, make risk

assessment decisions, or make regulatory enforcement decisions. At some point, however, exposure assessments must focus on the interrelationship of human activity patterns within segments of the general population and single or multiple contaminants suspected of contributing to acute or chronic effects.

Exposure assessments vary significantly, depending on the interests and training of the individuals or organizations conducting the studies. Some of the more common applications of exposure assessment include the following studies; the order of these studies does not imply rank.

Community Studies

Community studies involve segments of the general population and quantification of single-medium or total exposure to individual contaminants or complex mixtures. If the significant microenvironments or personal activities are identified, the significant biological effects can be determined or estimated through risk assessment (Johnson and Paul, 1981, 1983; Wallace, 1986; Lioy et al., 1988; Wallace et al., 1988). These studies can also include the results of clinical case studies to focus on the biological effects of specific contaminants (Pfaffenberger, 1987).

Epidemiological Studies

Direct or indirect population exposure data are used in conjunction with measures of adverse health outcomes to try to establish cause-and-effect relationships. These studies quantify human health impacts based on the assumption that the nature and extent of exposure can be adjusted for confounding factors and quantified for individual compounds or compound mixtures (MacMahon and Pugh, 1970; NRC, 1985). Epidemiological studies are conducted by industry, National Institute for Occupational Safety and Health (NIOSH), EPA, Occupational Safety and Health Administration (OSHA), ATSDR, state agencies, National Institutes of Health, and universities to identify causative agents when occupational or environmental health effects are suspected. The hypotheses tested in these studies are that contaminants are responsible for the health effects, and monitoring of the workplace or community can identify contaminants and sources or define exposure-effect relationships.

Industrial Hygiene Studies

Microenvironmental-, biological-, and personal monitoring studies are made in the workplace to quantify occupational exposure. The results are compared with health criteria developed by government agencies (e.g., OSHA) and organizations (e.g., American Conference of Governmental Industrial Hygienists), based on the assumption that knowing the actual exposures will allow prediction or quantification of biological effects, and subsequent reduction of exposure by personal protection or process control will lower such effects (Patty, 1978). Industrial hygiene studies are conducted by industrial firms to check for compliance with EPA and OSHA regulations and to define mitigation methods for actual or potential exposures. Those studies that employ personal sampling assume that the exposures can be traced to the sources and that those sources can be controlled.

Clinical Case Studies

Medical personnel identify health outcomes that are potentially related to environmental or occupational contaminants. Exposure assessments assist in quantifying the exposure-response relationship or focusing on diagnosis, treatment, or intervention. Clinical case studies are conducted by state agencies, industry, NIOSH, and OSHA to identify causative agents when occupational or environmental health effects are identified or suspected.

Engineering Studies

Models that estimate the intensity of exposure from chemicals emitted by various sources at outdoor downwind receptors may be used in conjunction with fixed-site monitors. Their use is based upon the assumptions that the exposure estimates of a plume impact represent actual exposures, and the results can be used to predict biological impacts using health criteria developed by other studies (Schroy, 1981; Fenstermacher and Ottinetti, 1987; Lipton and Lynch, 1987). EPA conducts engineering studies under the Clean Air Act, the Federal Insecticide, Fungicide and Rodenticide Act, and the Toxic Substances Control Act (TSCA). OSHA, NIOSH, the Nuclear Regulatory Commission, state agencies, and industry groups also conduct engineering studies. EPA (under TSCA) uses such studies to define exposure levels in the workplace and ambient environment for the premanufacture notice process before permitting introduction of a new chemical into commerce. It is assumed

that potential exposures can be defined by using exposure models for populations that will work with or use the chemical.

OSHA uses engineering studies for evaluating workplace-exposure criteria and effectiveness of engineering controls. The studies of workplace-emissions controls evaluate the emission rates defined for classes of equipment and apply results to all equipment in that class.

The Nuclear Regulatory Commission uses engineering studies to define the most appropriate design alternatives for new or modified nuclear power plants. The assumption for these studies is that providing the rigorous controls to prevent atmospheric emissions will protect the population around the plant.

An example of state agencies' use of engineering studies is for state implementation plans for permitting emission sources.

Industries use engineering studies to determine the most appropriate design alternatives for production and transportation facilities. The general assumption for these studies is that reduction in emissions results in reduction in exposure.

Industries also use engineering studies to help identify causative agents when occupational or environmental health effects are identified, as well as to check for compliance with EPA and OSHA regulations and to define mitigation methods for actual or potential exposures.

Animal Studies

Animals exposed to contaminants in actual environments can be used as exposure sentinels. The animals are assumed to represent acceptable models for humans. Also, experimentally defined exposure-response relationships are assumed to identify biological effects similar to those that will occur in humans (Calabrese, 1987).

Pharmacokinetic and Pharmacodynamic Studies

These studies link actual human-exposure measurements (personal or microenvironmental) to measurements of biological markers of internal or effective dose and biological response. The modeling could include whole-animal responses, based on the physiology of the species, and the toxicological data from molecular biological studies. For predicting human response to a contaminant the assumption is made that molecular biological processes studied on a cellular level can be translated to human responses by using models

that have been validated on a variety of other animals (Andersen et al., 1987; Smith, 1987; Saltzman, 1988a).

Behavioral Studies

The quantification of changes in human behavior is an indirect approach to measure the effects of physically, chemically, and biologically active contaminants. This is based on the assumption that biological stress results in behavioral change (e.g., as from inhalation of mercury vapor) that can be compared with the intensity of directly or indirectly determined exposure.

One or more of the above types of studies require measurements or estimation of exposure, because humans are constantly exposed to a broad range of synthetic and naturally occurring contaminants. Unfortunately, it is usually difficult to distinguish the effect of one or more contaminants from the ambient environmental mixture of contaminants. In addition, for long-term, low-level exposure, the evidence usually is inconsistent or inconclusive as to which contaminants shorten or end human life. Naturally occurring toxic contaminants often provide defense against predators of the animal or plant that produce them. Such agents are almost always biologically active in humans (Ames et al., 1987). Therefore, when designing exposure assessments, the intensity of exposure from contact with natural and anthropogenic contaminants must be defined qualitatively or quantitatively to help identify the important epidemiological and clinical applications.

The nature of exposure might vary with a specific health effect and might require special exposure-measurement methods for each assessment. For instance, when a health effect is sudden death or obvious illness, gross or short-term exposure measurements that highlight recent or instantaneous changes in exposures might be adequate to identify the cause-and-effect relationships. More subtle long-term measurements of exposures are required when the outcome is a subtle change in the human biological or behavioral system. Development of disease and death due to low-level, long-term exposure is very difficult to relate to specific contaminants using morbidity and mortality studies because of multiple intervening exposures. Identification of the specific contaminant causing the exposure-response relationship of concern is essential.

Inferences might be made more clearly in prospective studies because complicating factors can be measured or held constant. An example of a prospective study is an engineering study designed to forecast workplace exposures for proposed production units. Obtaining accurate previous exposure

and health histories or testing any hypothesis is difficult for retrospective studies.

SUMMARY

Exposure assessment is an integral and essential component of environmental epidemiology, risk assessment, risk management, and diagnostic and intervention efforts. It is a multidisciplinary endeavor that usually requires the combined expertise of engineers, environmental and industrial hygienists, toxicologists, epidemiologists, chemists, physicians, mathematicians, and social scientists. Exposure assessment methodology employs various direct and indirect techniques, including environmental measurements, personal monitoring, biological markers, questionnaires, and modeling.

Exposure assessments for airborne constituents must be considered in the framework of potential contributions from other media and adding the incremental exposures from other media when necessary. Furthermore, to achieve effective risk assessment, risk management, environmental epidemiology, and diagnosis and intervention, all media and routes of exposure must be assessed for the relative magnitude of their contributions before an assessment of one medium is conducted.

To maximize opportunities for risk management, exposure assessments should obtain information on the sources and environmental factors affecting the exposures to ensure that effective and appropriate mitigation measures can be formulated.

The plan developed to gather data for an exposure assessment should take into account the time scale related to the biological response being studied.

Exposure assessment is an equal partner with toxicology in defining human health risk and identifying exposure-response relationships and should be funded by government programs according to priorities commensurate with the importance of exposures to environmental contaminants.

Because the features of exposure assessments range from the straightforward to the complex, it is necessary to provide and maintain avenues for professional-society interaction, training, continuing education, publication, and education. Only in this way can the current state of research and applications discussed above continue to grow and address societal and technical concerns.

2

Framework for Assessing Exposures to Air Contaminants

INTRODUCTION

This chapter presents the mathematical relationships of the components of human exposure to airborne contaminants. It also presents an overview of the methods and their applications for assessing exposure. Each of the methods presented in this overview is discussed in detail in the following chapters in the context of the techniques currently available and the critical needs to advance exposure assessment.

Human exposure to air contaminants is associated with a wide variety of health and nuisance effects. Acute biological effects encompass outcomes, such as aggravation of existing disease (e.g., increase in frequency and severity of asthmatic attacks), acute respiratory infections (e.g., increase in the respiratory illness rates in children), transient deficits in lung function, and allergenic reactions. Chronic health outcomes include long-term decrements in lung growth, chronic obstructive lung disease (e.g., bronchitis), cancer, neuro-behavioral alterations, and heart disease. The most common effects encountered by large segments of the population, however, are nuisance effects. These often are acute and include noxious odors; eye, nose, and throat irritation; and coughing, which is a symptomatic respiratory response.

Air contaminants found in various industrial, occupational, residential, outdoor, and public access and transportation environments consist of a broad and complex spectrum of chemicals in gaseous and particle-associated forms, as well as particles of biological origin. Ideally, the air contaminants implicated in producing an adverse health or nuisance effect would be identified and an exposure assessment protocol would be designed. Frequently, the identification of the causes of an effect is confounded by air quality factors other than traditional air contaminants, including temperature, humidity, noise, and lighting. In practice, however, exposures to a class of contaminants,

source category, or a proxy contaminant often must be addressed when a specific contaminant cannot be identified or easily measured.

The air contaminant concentrations present in any environment are usually the result of several interrelated factors. In the indoor nonindustrial environment, these factors include the following:

- Number and location of sources, type of sources, and generation rate of the contaminants.
- Source use characteristics.
- Building or vehicle characteristics.
- Infiltration and ventilation rates.
- Air mixing.
- Removal rates by surfaces, chemical transformation, or radioactive decay.
- Existence and effectiveness of air contaminant removal systems.
- Penetration of outdoor contaminants.
- Meteorological conditions.
- Activities of humans and their pets.

In the outdoor environment, these factors include variables such as those below:

- Meteorological conditions.
- Atmospheric transport of contaminants.
- Atmospheric chemical reactions and physical removal processes.
- Source types.
- Source emission rates and emission density.
- Location and activities of the individual.

Air concentrations in the industrial environment are controlled by the same factors with the addition of material handling, local process exhaust systems,worker habits, and the use and effectiveness of personal protective equipment.

Development of accurate models to predict air contaminant levels requires information on the above factors. Questionnaires or environmental measurements used in assessing exposures should gather information on these factors as well. Such information also will aid in establishing effective risk management mitigation measures to eliminate or reduce air contaminant exposures.

MATHEMATICAL RELATIONSHIPS

The mathematical relationship for air contaminant exposure for a person can be represented by the following equation:

$$\Delta E = C \cdot \Delta t, \qquad \text{(Eq. 2.1)}$$

where ΔE is the exposure of a person to the air contaminant concentration (C) during a specific time period (Δt). The units of exposure are concentration multiplied by time (e.g., $(\mu g/m^3) \cdot hr$).

This can be defined in the integral form as

$$E = \int_{t_1}^{t_2} C(t)dt, \qquad \text{(Eq. 2.2)}$$

where $C(t)$ represents the functional relationship of concentration with time for an interval t_1 through t_2. This time interval can be instantaneous as well as representing longer contact periods.

An operational form of the above equation that delineates the exposures of an individual for different microenvironments in which that individual spends time is given by

$$\Delta E_{j,k} = C_{j,k}(\Delta t) \cdot \Delta t_{j,k}, \qquad \text{(Eq. 2.3)}$$

where $\Delta E_{j,k}$ = the exposure of person k to a given pollutant during time interval Δt as a result of that person's activities in microenvironment j; $C_{j,k}(\Delta t)$ = the average concentration to which person k is exposed during the time interval Δt while in microenvironment j; and $\Delta t_{j,k}$ = the time spent by person k in microenvironment j.

For acute health effects, t must have a short enough interval to ensure the average reflects the peak concentration that can cause an effect.

This equation can be written to include exposures of multiple contaminants to various persons in diverse microenvironments:

$$E_{i,j,k} = \sum_{i=1}^{I} C_{i,j} \Delta t_{j,k}, \qquad \text{(Eq. 2.4)}$$

where the k^{th} person is exposed to a concentration C_{ij} of the i^{th} chemical contaminant in the j^{th} microenvironment. The concentration, C_{ij}, is considered to be constant for that location during the interval $\Delta t_{j,k}$. The *integrated exposure*, E^T, then can be calculated for many different situations. For the exposure of the k^{th} person to the i^{th} contaminant, the time-integrated exposure for the k^{th} person is the sum of the individual exposures to the i^{th} contaminant over all of the possible microenvironments:

$$E_{i,k}^{T} = \sum_{j=1}^{J} C_{i,j} \Delta t_{j,k}. \qquad \text{(Eq. 2.5)}$$

Alternatively, population exposure can be calculated for a group of persons in contact with the i^{th} contaminant in a single microenvironment, such as for a person at a workstation:

$$E_{i,j}^{T} = \sum_{k=1}^{K} C_{i,j} \Delta t_{j,k}. \qquad \text{(Eq. 2.6)}$$

A time-integrated population exposure to a single contaminant, as shown below, also could be defined for a population of persons for a series of microenvironments:

$$E_{i}^{T} = \sum_{j=1}^{J} \sum_{k=1}^{K} C_{i,j} \Delta t_{j,k}. \qquad \text{(Eq. 2.7)}$$

Total airborne exposure to all contaminants can be defined by summing this

equation for all contaminants, $i = 1$ to I. Thus, a quantitative exposure assessment requires accounting of the time spent by each person in the presence of each different concentration of every different contaminant of biological significance.

Because a human must be in an air environment at all times, some researchers use the concept of "time-weighted average exposure." The equation below is the same as that for integrated exposure, except that $(\Delta t)_{i,j,k}$ refers to the proportion of T (time-weighted average associated with exposure) that a person k spends in microenvironment j, with the i^{th} contaminant:

$$T_k = \sum_{j=1}^{J} (\Delta t)_{i,j,k} \qquad \text{(Eq. 2.8)}$$

In the summation over exposures, Δt was not explicitly written, because the person k "brings" the time to the microenvironment. The microenvironment and the time interval are defined by the person being studied; an exposure occurs in a microenvironment only if person k is in that microenvironment at a specific time.

Exposure to a contaminant is defined as contact at a boundary between a human and the environment at a specific contaminant concentration for a specific interval of time; it is measured in units of concentration(s) multiplied by time (or time interval). Exposure has, however, often been defined and used differently. For example, exposure is defined in the 1988 EPA *Proposed Guidelines for Exposure Measurements* (EPA, 1988b) as concentration multiplied by contact rate multiplied by time.[1] In this mathematical relationship, volume and time cancel out leaving only the mass term, which is more appropriately considered potential dose, assuming 100% bioavailability and absorption, as defined in Chapter 1. Defining exposure as mass will lead to misinterpretations of exposure by those who conduct exposure assessments, because understanding of concentrations and actual time periods of exposure is critical for analysis and mitigation of adverse exposures. The field of exposure assessment should use standard definitions and practices. The scientific and regulatory communities, including those responsible for reviewing articles for scientific

[1] The 1988 EPA *Proposed Guidelines for Exposure Measurement* are being modified to incorporate new and improved approaches to understanding exposure.

journals, should use consistently the definitions recommended in this document.

MEASUREMENT AND ESTIMATION TECHNIQUES EMPLOYED IN EXPOSURE ASSESSMENT

Exposure to individual air contaminants, categories of air contaminants, or sources of air contaminants can be assessed by using personal monitoring of the concentration in the breathing zone of individuals (that can be directly inhaled) and in some cases by biological markers of exposure or by coupling models with measurement of air contaminant concentrations in microenvironments. Biological markers and personal monitoring are called direct measures of exposure while microenvironment monitoring is known as an indirect measure. A schematic of approaches for determining exposure is shown in Fig. 2.1.

Direct Measures of Exposure

Personal Monitoring

Personal monitoring provides direct measurements of the concentrations of air contaminants in the breathing zone of an individual. Samplers worn by subjects directly record the concentration or collect time-integrated samples of specific contaminants with which individuals come into contact for specific intervals. For specific compounds, samplers can be used for several hours to several days, thus including all time-concentration patterns during a specific period.

Samplers can be active or passive. Active samplers use small pumps either to draw air through a collection medium (e.g., filter or vapor trap) and collect the air contaminants or to draw air through a direct-reading detector. Passive gas samplers use diffusion or permeation to concentrate gases on a collection medium. They usually must be carried for several days to obtain contaminant masses greater than the detectable limit of the analysis method employed. The samples then are returned to a laboratory for analysis.

Personal monitoring can be a useful measure of an individual's exposure to an air contaminant or class of contaminants and has been used extensively by industrial hygienists in occupational settings. When combined with biological markers, personal exposure data can link air concentrations with internal dose. For example, air CO concentrations can be linked with blood carboxyhemoglobin levels, and air nicotine concentrations can be linked with blood, urinary, or salivary levels of continine.

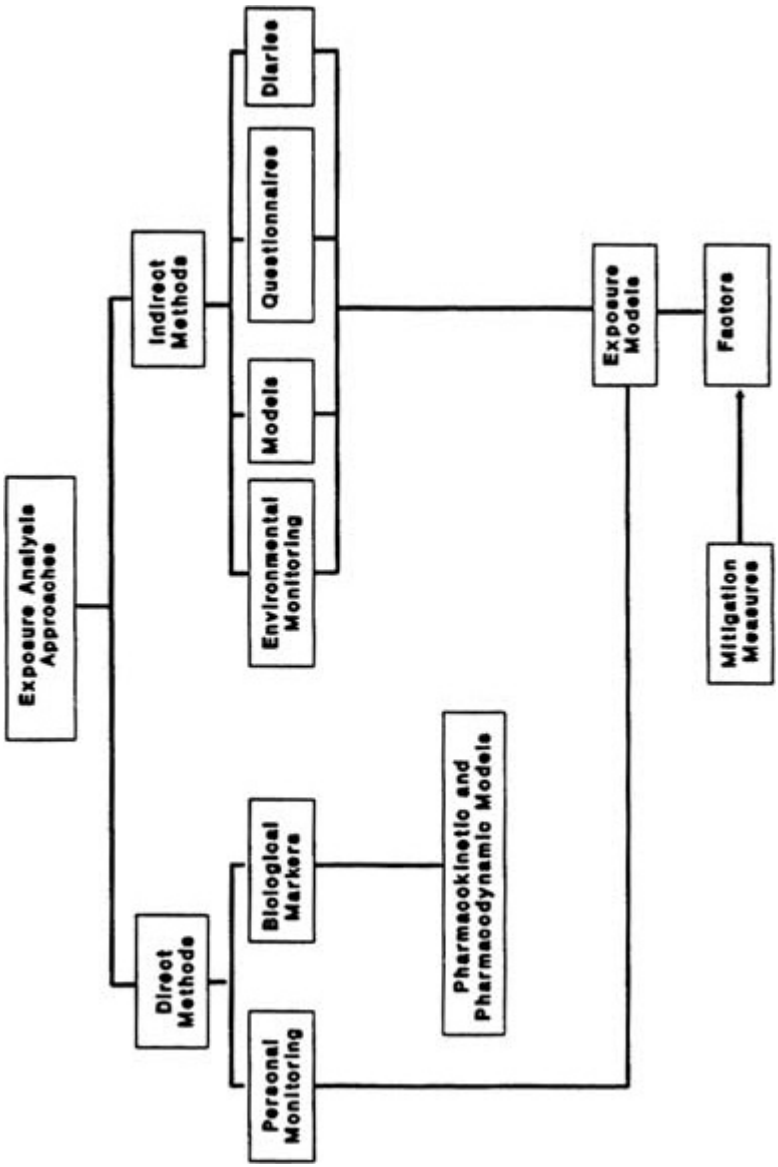

FIGURE 2.1 Possible approaches for analysis of air contaminant exposures.

Personal monitoring also provides a measure of the exposure across the various microenvironments where individuals spend their time. It usually does not supply information on the physical environment in which exposures occur or on the factors (e.g., emission rates) controlling concentrations in those environments. Hence, if effective mitigation measures are to be developed and instituted, measures of personal exposure need to be supplemented with measurements of the factors in the physical environment (e.g., temperature, humidity, and ventilation) that control the exposure, and information on human activity from questionnaires. In large field studies, it is difficult to obtain sufficient numbers of subjects willing to carry the samplers; furthermore, distribution and retrieval of samplers is manpower intensive, time consuming, and expensive. Therefore, personal sampling has practical limitations in its usefulness for assessing duration, intensity of exposures, and variability of periodic exposures. One important application is the development of protocols for long-term sampling of individuals, which ultimately would assist in demonstrating environmental improvements and reductions in exposures by regulatory agencies.

Several recent technological developments have made personal monitoring more widely useful. Passive samplers (e.g., badges) for air contaminants such as volatile organics (Lewis et al., 1985), formaldehyde (Geisling et al., 1982), nicotine (Hammond and Leaderer, 1987), nitrogen dioxide (Palmes et al., 1976), and other gases have been developed. These monitors provide the sensitivity and specificity necessary to conduct personal air-monitoring exposure assessments at reasonable cost. Recent advances also have been made in active personal monitors; for example, miniature denuder monitors for assessing personal exposures to acid particles and gases have recently become available (Koutrakis et al., 1989). Advances in the use of electrochemical sensors for active personal monitoring have recently been reported for NO_2 (Penrose et al., in press), CO (Penrose et al., 1990a) and ozone (Penrose et al., 1990b).

Biological Markers

Biological markers refer to cellular, biochemical, or molecular measures that are obtained from biological media such as human tissues, cells, or fluids and are indicative of exposure to environmental chemicals. A biological marker of exposure is an exogenous substance or its metabolite or the product of an interaction between an environmental contaminant [xenobiotic agent] and some target molecule or cell that is measured in a compartment within and organism (NRC, 1989). They are measures of dose when appropriate metabolic

data are available and the relationships between times of exposure and sample collection are adequately defined. This information can be used as a surrogate for exposure by using pharmacokinetic or pharmacodynamic models. Biological markers include: (a) unchanged exogenous agents (e.g., heavy metals, organic vapors, nicotine, asbestos fibers, and PCBs); (b) metabolized exogenous agents (e.g., phenol and cotinine); (c) endogenously produced molecules (e.g., alpha-1-antitrypsin and porphyrin ratio); (d) molecular changes (e.g., DNA adducts and hydroxyproline); (e) cellular or tissue changes (e.g., cell histology and sperm mobility); and (f) measurements of pulmonary response to an agent. Biological markers can be used as indicators of exposure (e.g., PCBs, cotinine, DNA adducts, and carboxyhemoglobin), disease susceptibility (e.g., alpha-1-antitrypsin), or disease state (e.g., cell histology and red blood cell counts). Some biological markers can indicate the integrated intake into the body of an air contaminant across all microenvironments and sources. They also can aid in elucidating relationships among exposure, dose, and health or nuisance effects. However, biological markers by themselves do not provide information on the microenvironment in which the exposures take place and hence on the factors that control exposure such as contaminant emission rates and fate. Without information on the microenvironment or the person's activities, effective mitigation measures cannot be developed and instituted. Use of biological markers alone as a measure of exposure is usually insufficient for air-pollution epidemiology, intervention, risk assessment, or risk management.

Biological markers of exposure have been used to study some environmental contaminants, such as urinary cotinine for tobacco smoke (Wald et al., 1984); carboxyhemoglobin levels in blood for exposure to CO (Radford and Drizd, 1982); and lead levels in blood, teeth, and hair for inhalation and ingestion of lead (Harlan et al, 1985); and benzo*a*pyrene-DNA adducts (Perera et al., 1988). Biological markers can be used to measure a specific contaminant, or they may be proxies for a number of contaminants.

The usefulness of a biological marker in a specific study depends on many factors: potential applications, type of testing (e.g., animal testing and human clinical testing), properties of the marker (e.g., specificity, sensitivity, metabolic characteristics, and invasiveness of sample collection), laboratory protocols (e.g., collection, handling, and cost), and experimental design issues (e.g., sample size and confounding variables).

Use of biological markers as measures of exposure is often limited for the following reasons:

- Difficulty in obtaining physiological samples from subjects.
- Poorly understood relationships among biological marker concentrations

and air concentration of a contaminant, specific sources of contaminants, duration of contact, and the adverse effect under study (e.g., relation between urinary cotinine concentrations and exposure to respirable suspended particulate matter or vapor-phase organics from environmental tobacco smoke (ETS)).

- Cost and available resources.
- Person-to-person variability.

Indirect Measures of Exposure

Indirect methods of assessing an individual's or population's exposure to air contaminants combine microenvironmental monitoring or modeling with questionnaires or with other information on human activities. Indirect methods supply information on contaminant concentrations in microenvironments and the physical and chemical processes that control those concentrations. Models that predict spatial and temporal concentration distributions of air contaminants in various microenvironments are an important component of an overall human exposure model. These models take three general forms: physical/chemical, empirical/statistical, and hybrid. Indirect methods generally provide exposure information at a lower cost than direct approaches. However, indirect approaches do not link air concentrations with internal contaminant dose or metabolites. In addition, the models generally used in exposure assessment have large uncertainties associated with their estimates, and few have been validated. Questionnaires in exposure assessment have been used extensively in the past and will continue to be relied upon heavily in the future.

Microenvironmental Measurements

Microenvironmental measurements involve monitoring air contaminant concentrations in the locations where exposures take place. Often, the physical and chemical factors that control air contaminant concentrations in those microenvironments are measured, although this is not always necessary to determine exposure. Monitoring studies can use long-term sampling at one location or spot or grab samples in several locations. A wide range of active and passive samplers with excellent specificity and sensitivity is available to assess the spatial distribution of the contaminants and the frequency distribution of peak and average concentrations. Monitoring physical and chemical processes (e.g., meteorological conditions, concentrations of precursor contaminants

in outdoor air, ventilation and deposition rates in indoor air, and hood ventilation rates in industrial settings) that control the spatial and temporal contaminant concentration distribution is critical to develop exposure models for contaminants.

As with any type of continuous or integrated environmental monitoring for individual contaminants, a sampling protocol must be carefully designed within the framework of the use of the data gathered and resources available. Care must be taken to specify what samples should be taken, where they should be taken, how many should be taken, and with what frequency.

Questionnaires

Different types or classes of questionnaires are used as indirect measures of exposure:

- Those that provide information on the physical properties of an environment.
- Those that provide a simple categorization of potential exposure.
- Those that obtain information on the activity patterns of individuals.

The first category provides information on the existence of sources, source use, and other characteristics of each microenvironment in a community or occupational setting. When combined with the results of fixed-site air monitoring of the environment, this information permits a model to be developed to estimate air contaminant levels in similar environments. This type of questionnaires used extensively in characterizing sources, source use, and building factors in studies of residential air quality and of buildings with occupancy complaints (sometimes referred to as "sick building syndrome"). Efforts are under way to standardize a questionnaire for residential indoor air quality studies (Lebowitz et al., 1989a). Recently a similar effort has been made for investigations of buildings with occupancy complaints. The development of such questionnaires and their use in field studies might make possible intercomparison of data acquired from different studies.

Categorization of exposure has been used extensively in epidemiological studies of environmental air contaminants for many years. For example, several epidemiological studies of environmental tobacco smoke and cancer determined exposure only by asking the subjects or household members whether they ever were exposed to environmental tobacco smoke. In occupational epidemiology, exposure categories often are determined by a worker's job classification. Categorical estimates of exposure are crude; however, if

carefully designed, questionnaires can be an inexpensive way to obtain general information on exposure categories for large populations.

The third category of questionnaire—activity patterns—is designed to take into account that an individual spends varying amounts of time conducting specific activities at various locations in the course of a day. To accurately model or estimate total exposures, microenvironments and time spent in them must be identified as a function of air contaminant concentrations. A recent review of adult time-activity pattern studies (Ott, 1988) found that people spend 65-70% of their time inside homes and more than 90% of their time indoors (home, transit, and work combined). Demographic and personal (e.g., smoking history) variables can affect time-activity patterns. These studies clearly highlight the need to consider concentrations in the indoor environment when assessing exposures. Of course, for some air contaminants, such as ozone, knowledge of time spent outdoors is essential to assessing exposure. Recognition of the importance of assessing the indoor environment has resulted in studies that focus on the spatial and temporal aspects of people's activities and the concentrations of contaminants present in specific environments. These efforts are essential in the modeling of total exposure to air contaminants, but present significant challenges in study design.

Models

In many situations, it is either impossible or impractical to measure directly the exposures of individuals or populations (e.g., predicting exposure for prospective industrial processes or sources or retrospectively estimating exposures in an epidemiological study). In such cases, models are used to estimate exposures. Models present a conceptual framework or a mathematical formulation of individual or population exposures based upon scientific principles. Exposure models generally include synthesized microenvironmental concentrations (measured or modeled) and estimates of the time spent in various microenvironments. However, the term "model" also can be used to refer to the conceptual framework that provides the basis for formulating a mathematical model or for planning exposure measurements.

When sufficient measurements cannot be made, microenvironmental concentrations are estimated using concentration models. These models are based upon the physics and chemistry of the environment. Concentration models have been developed for emissions from sources, atmospheric dispersion, ventilation, infiltration, transport, deposition, and atmospheric chemistry. Stochastic models describe the transport of contaminants by examining the

motion of large numbers of small parcels of air moving due to advection and diffusion (Sexton and Ryan, 1988).

Statistical/empirical models attempt to relate either the measured exposure or the concentration to variables associated with emissions, transformation, and accumulation in specific microenvironments. The results are used for hypothesis generation. Statistical/empirical models often use questionnaire responses as independent variables, e.g., source use or house volume to predict concentration or to identify the major factors controlling concentration or exposure.

The time spent in a microenvironment with a concentration is another important input to an exposure model. Time spent by individuals in various environments is typically obtained through observation, diaries, or activity logs. Time-activity patterns measured for a statistical sample of a population can be used to generate distributions of time-activity patterns for larger populations. These distributions are then combined in an exposure model with concentrations to yield population-exposure estimates. Population-exposure models are a recent advance in exposure modeling and there has been very limited work on their validation.

The principal advantage of models is their ability to estimate concentrations in different microenvironments or exposures of individuals or populations with little direct information, which may be difficult to obtain. The processes of formulating, testing, and refining models contribute to the fundamental understanding of exposure; such understanding is critical for designing exposure assessment studies. Models provide a conceptual and scientific framework for considering factors that control exposure and afford a means for designing and testing cost-effective mitigation measures. Model outputs are, however, only as good as the degree to which factors are identified and specified and depend on the quality of the input data. The assumptions employed in any model need to be clearly specified, and their applicability to a given exposure assessment needs to be considered. Furthermore, it is essential to test and validate models before they are used in exposure and risk assessments to better characterize the uncertainty in the model output.

Mitigation Measures

The choice of mitigation measures to be applied and the success of those measures in reducing or eliminating exposures to reduce health or nuisance effects are dependent on the sensitivity and accuracy of the model employed. As many of the relevant factors are accurately incorporated into an exposure model, the risk management effort should become more efficient and cost

effective. The choice of measures to be employed can range from source removal (the most effective) to source substitution, source emission reductions, altered ventilation, air filtration, and human-behavior modification. Air quality standards directed at controlling concentrations of a contaminant in different air environments, e.g., ambient air standards, also are employed, but are of no value unless followed by effective control strategies. Formulation and institution of a successful mitigation strategy depend strongly on the accuracy of the exposure model employed.

INTEGRATION OF EXPOSURE-ASSESSMENT TECHNIQUES

Studies to assess exposures to environmental contaminants, whether to complement environmental epidemiology, disease diagnosis and intervention, risk assessment, or risk management, must consider the three principal methods of exposure assessment: personal monitoring, biological markers, and indirect estimates. These studies should incorporate into their study design several methods (as many as practical) to accurately define exposure and estimate dose. Such studies need to determine the physical and chemical factors in the environment responsible for environmental concentrations, the multimedia routes of exposure and the number of microenvironments in which exposures take place so that cost-effective mitigation measures to reduce exposure can be identified and evaluated. Toward the development of consistent exposure assessment practices, the use of personal monitoring as well as microenvironmental monitoring should be considered in long-term studies that examine or determine changes in population exposures to airborne contaminants.

Exposure assessment studies need to explore the use of nested designs (Leaderer et al., 1986, 1990a). A nested exposure assessment strategy refers to obtaining an easily measured indicator of exposure (e.g., questionnaire) for all or a large segment of the study population, while simultaneously obtaining ever-increasing detail on the exposure measures for ever-decreasing numbers by using personal monitoring, monitoring of microenvironments, biological markers, etc. The former will provide data with a higher degree of uncertainty, while progressive application of the latter should incrementally reduce the uncertainty in the analysis of exposure. These different types of studies can be conducted simultaneously or in separate investigations for specific contaminants or classes of contaminants. The detailed measures of exposure can then be used to model the exposure of the entire population. Easily obtained measures of exposure can be incorporated or developed to validate the models. Such exposure assessment designs typically use all three methods

to a varying degree, based upon the applicability and practicality of available exposure assessment techniques. These efforts will require a fundamental change in simple approaches that have been used to assess exposure to airborne contaminants and will improve the quality of assessments by providing information on the extent and major sources of uncertainty in exposure assessments as part of the portrayal of exposure assessment results.

SUMMARY

Exposure to a contaminant occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time; the units of exposure are concentration multiplied by time. The occurrence of the concentration of a pollutant, a person s exposure, and a dose to target organs and tissues are different points in a continuum between emission of a contaminant and any resultant health effects.

Integrated air exposure is calculated from individual exposures by summing over time (time-integrated exposure), over persons (population-integrated exposure), or over airborne contaminants (contaminant-integrated exposure).

The field of exposure assessment should use standard definitions and practices. The scientific and regulatory communities, including those responsible for reviewing articles for scientific journals, should use consistently the definitions recommended in this document.

Toward the development of consistent exposure assessment practices, the use of personal monitoring as well as microenvironmental monitoring should be considered in long-term studies that examine or determine changes in population exposures to airborne contaminants.

3

Sampling and Physical-Chemical Measurements

INTRODUCTION

This chapter considers sampling and physical-chemical measurement methods available for assessing human exposures to airborne pollutants and emphasizes recent advances. These advances could be used to improve exposure assessment methods.

In assessing human exposures to airborne pollutants, numerous factors besides the contaminant must be measured especially if the assessment is based on fixed-site sampling or modeling. Accurate estimates in these instances depend not just on concentration measurements from fixed-site monitors in various locations, but also on knowledge of numerous factors that influence the environments where the exposures occur (see Chapter 2). Outdoors, these factors include temperature, humidity, precipitation, barometric pressure, wind speed and direction, turbulence, and mixing height. Insolation, as well as light scattering and absorbance, might also be important. Some of these factors also must be measured to model indoor environments. However, other factors are unique to indoor environments such as: ventilation rates, pressure differentials across building shells and between building compartments, removal efficiencies of building filters, and contaminant deposition rates on indoor surfaces. Furthermore, modeling frequently requires measurements of source strengths. Outdoors, source-strength measurements include emission rates from a major point source (e.g., power plants). Indoors, source emission rates could include volatile organic compound (VOC) emission rates derived from chamber studies of building materials, consumer products, and home furnishings (Tichenor, 1987). These areas are too broad to be discussed comprehensively in this chapter, whose focus is the measurement of airborne contaminants. Nonetheless, measurement methods that produce information about environmental factors or emission rates should be accounted for in the

development of useful indirect methods to identify and control the factors most significant to human exposure.

As outlined in Chapter 1, the choice of sampling and physical and chemical measurement methods to be used in an exposure assessment is driven by a study's specific aims. The analytical procedures should be chosen with attention to the specific needs of the study. The "why," "what," "when," and "where" all influence the selection of the "how" discussed in this chapter. It is important for the analyst to ask, "What are we ultimately trying to accomplish?"

Sampling frequency and duration are important elements of a sampling strategy. Certain analytical procedures provide real-time or instantaneous measurements of contaminant concentrations (e.g., long-path-length Fourier transform infrared spectrophotometers), while others provide an average value for the interval during which sampling occurs (e.g., collection of VOCs on the sorbent Tenax). Real-time measurements can be made consecutively to yield a continuous record of a contaminant concentration, or they can be made intermittently to yield a series of concentration "snapshots." Integrated measurements can be made consecutively or intermittently, or they can be overlapped, if more than one set of sampling apparatus is available.

If monitoring is done for compliance purposes, the sampling frequency and duration likely are specified by regulation. However, rigid specification usually is not necessary for most types of exposure assessment monitoring. If peak concentrations are important in assessing a potential health effect, then a sampling procedure should be integrated over a time scale no longer than that at which contaminant concentrations fluctuate. Furthermore, the sampling should be frequent enough to measure major fluctuations. Real-time continuous monitoring for a contaminant that causes a chronic health effect would be unnecessary, because the total contact is of concern. The time scale of the relevant biological effect for a contaminant must be considered in choosing the time scale of the sampling and measurement process (Lioy and Daisey, 1987).

Emissions of various airborne contaminants can be time-dependent. For example, at a manufacturing site, time of day and day of week can influence emission rates and, consequently, the airborne concentrations of various species. Diurnal, weekly, and seasonal variations in emission rates can affect outdoor airborne concentrations. Such factors must also be considered when planning sampling frequency and duration.

Spatial considerations are important in fixed-site monitoring. As stated in the National Research Council (NRC) report, *Complex Mixtures* (NRC, 1988), "The primary consideration should be the relevance of the sample site to potential human exposure." Selection of a sampling site can be purposive or probabilistic. Purposive sampling normally is conducted to answer questions

about a specific location (e.g., sampling near known emission sources, such as a power plant or a waste dump). Probability sampling seeks to provide an overall picture of an area. The choice of sampling sites should be influenced strongly by the nature of the potential human exposure. Table 3.1 is a summary of designs that can be applied to the selection of sampling sites. It also includes a brief evaluation of when the different strategies are most useful. (For a further discussion of sampling sites, see NRC, 1988).

QUALITY ASSURANCE

Using advanced techniques in exposure studies does not ensure the acquisition of better qualitative data, but allows the potential of obtaining better data. Whether that potential is realized depends on the quality assurance (QA) program that is designed into the study.

The terms precision and accuracy often are used in quantitative studies. Precision is a measure of the agreement among individual measurements made of the same property of the sample. Accuracy refers to the degree of agreement of a measurement (or an average of measurements of the same property) with an accepted reference or true value. QA and its complementary concept, quality control (QC), have many definitions. QA often is used to also include QC, and this report uses this convention. For environmental measurements, QC comprises operational activities that are carried out before and during the measurement process that are intended to ensure that data are of sufficient quality—data whose precision and accuracy are known and are sufficient to meet the needs of a study. Examples of QC are calibration procedures, maintenance of constant line voltage and temperature, use of blank and spiked samples, and use of traceable standard reference materials. QA also includes activities carried out to ensure that the collected data achieve the precision and accuracy required, such as interlaboratory comparisons, measurement system audits, and statistical procedures to highlight bad data or extreme values. These activities should be carried out by persons not involved in routine data-gathering operations. EPA has developed a comprehensive QA handbook that gives principles and recommended procedures for achieving quality data in air-pollution measurement systems (EPA, 1976a,b).

ERRORS

In designing a QA program to meet the needs of a specific exposure study, it is useful to consider the four activities involved in any environmental measurement that can cause errors in the data obtained:

TABLE 3.1 Spatial Considerations: Summary of Sampling Designs and When They Are Most Useful

Sampling Design	Condition for Most Useful Application
Haphazard sampling	Only valid when target population is homogeneous in space and time; hence, not generally recommended
Purposive sampling	Target population well defined and homogeneous, so sample-selection bias is not a problem; or specific environmental samples selected for unique value and interest, rather than for making inferences to wider population
Probability sampling	
Simple random sampling	Homogeneous population
Stratified random sampling	Homogeneous population within strata (subregions); might consider strata as domains of study
Systematic sampling	Frequently most useful; trends over time and space must be quantified
Multistage sampling	Target population large and homogeneous; simple random sampling used to select contiguous groups of population units
Cluster sampling	Economical when population units cluster (e.g., schools of fish); ideally, cluster means are similar in value, but concentrations within clusters should vary widely
Double sampling	Must be strong linear relation between variable of interest and less-expensive or more-easily measured variable

Source: NRC, 1988

- Selection of representative sampling sites.
- Collection of the environmental sample.
- Sample analyses.
- Data-handling.

Site-Selection Errors

The representativeness of the sampling site refers to selection for appropriate spatial and temporal definition. For example, a study to determine compliance with an ambient air quality standard for a given pollutant would require air samplers to be placed at community sites that represent typical outdoor air and to have the same measurement time as the standard. On the other hand, a study to determine total air exposure of a population to the same pollutant could require a sampling strategy that involves personal samplers or microenvironmental measurements combined with activity diaries. In many studies, site-to-site variability is the largest component of the total measurement error. EPA (1988b) guidelines for exposure studies provide general information on proper sitting of outdoor-air-monitoring stations.

Collection Errors

The study of most air contaminants requires that the air sample be moved from the microenvironment into a collection device or analytical instrument. Errors can result from physical and chemical changes in the sample during and after sample collection. Air-collection procedures usually concentrate molecules that normally are diffuse and isolated, thus enhancing the possibility of concentrated molecules interacting with each other or with the collection medium or sampler components. These interactions can render some collected molecules immeasurable by the chosen analytical procedure. Errors can also occur during handling, shipping, and storage of the samples.

Pumps can be significant sources of artifacts in collected samples. For example, particle artifacts may arise because of mechanical wear or oil-droplet emissions. Gas phase artifacts may arise as a result of emissions from hot pump oil or other pump lubricants. Also, the magnitude of the pump flow rate is an important consideration in microenvironmental sampling. The flow rate can be set so high that the sampling system decreases the contaminant concentration in the microenvironment being measured, and, near the end of the sampling period, the contaminant concentration in the microenvironment could be lowered artificially.

Another common source of error when sampling with a pump is a poorly defined flow rate. It is extremely important to calibrate and periodically check flow rates in any device that uses flow rate to quantify the volume of air sampled.

Sample collection artifacts can arise from components other than the pump. These include tubing, improper sealants, and incompatible plastics. Collection artifacts can also be a problem: (a) during sample collection set up (potential sources include idling motor vehicles, smoking, and the use of insect repellents); (b) when using a sorbent, if the collection efficiency is poor (sorbent breakthrough); and (c) during vapor- and particle-phase sampling when the collection procedure itself may alter the distribution between the phases.

Errors also can occur with samplers when study subjects do not wear or carry a personal sampler when they are expected to. Sometimes subjects are embarrassed by the noise or size of the samplers; subjects might change their activity patterns when wearing samplers to avoid embarrassing situations. A subject might wear the sampling device, but forget to turn it on. Other unintentional errors include accidentally sitting on the sampling line for a pump, effectively stopping the flow to the sampler. Although passive samplers might seem to alleviate many of these problems, an outer garment over the device seriously reduces sampling capability. Therefore, the design of personal samplers should include provisions to minimize their misuse and to ensure that they have been used properly.

Analytical Errors

Analytical errors are associated with the identification and quantitation of the chemical of interest in the sample collected. Qualitative errors can be minimized by increasing the selectivity of the analytical method that is used and by confirming compound identity by a second technique. This selectivity should minimize potential interferences, that is, the ability of chemicals other than the one of interest to interfere with the measurement process so as to give results either higher or lower than the true value.

The metrics used to describe analytical quantitation errors are precision and accuracy. Methods that have good precision and accuracy can be used. However, methods that have poor accuracy but good precision often can be useful in studies that require understanding only of the relative differences among properties of environmental samples (Watson et al., 1983). Critical operational procedures that can lead to analytical quantitative errors are poorly conducted calibration procedures and use of inadequate reference materials when carrying out calibrations. Even if these procedures are carried out carefully,

some errors are inherent in the analytical method—every method has a limit for precision and accuracy. Another factor that can lead to quantitative errors is the "ruggedness" of the method: its sensitivity to variations in the factors that affect the measurement (such as temperature, relative humidity, and line voltage). Furthermore, many measurement methods cited in the literature give reasonable precision and accuracy when used by highly trained research staff, but lose their precision and accuracy when used by less well-trained personnel who might not maintain stable operating procedures. The routine use of field blanks and field spikes can reduce the occurrence and magnitude of analytical errors.

Data-Handling Errors

Data-handling errors are among the errors that can occur during data manipulation. These errors include mistakes in reading instrumentation, in transposing data from one system to another (e.g., data-entry errors), and in calculating results in appropriate units. The EPA QA handbook (EPA, 1976a,b) gives guidelines for minimizing these errors. Many of these errors have been reduced through the extensive use of microprocessors that often collect and, in some cases, even analyze the data (Barnett, 1988; de Monchy et al., 1988), thus reducing human error in transcribing data and bias in data evaluation. Periodic human inspection of all steps of data collection, reduction, and reporting is essential as one further QC measure (Taylor, 1987). Inspection ensures that the automation of the data-analysis process does not obscure significant information not considered when the initial microprocessor programs were established. This is particularly true when programs are set to accept or reject data automatically.

One common error in data reporting is the error of omission—an omission of precision and accuracy information when reporting data. The literature is replete with misinterpretation and over interpretation of data thought to be more certain than they really were. *Experimental data always should be accompanied by precision and accuracy information. Precision and accuracy are integral parts of the measurement*.

Designing a measurement strategy for a field study seems straightforward, but designing one that minimizes the errors almost always is difficult. Further, designing a good QA program for environmental field measurements might be more difficult than one designed for laboratory experiments. More people of varying skills usually are involved in environmental field studies than in laboratory studies: different members of a staff will design the study, collect the samples, analyze the samples, report the data, statistically analyze the

data, and interpret the data. Without an organized QA program, such sharing of responsibility for data quality can result in information of poor quality, or perhaps worse, data of unknown quality. Furthermore, environmental field measurements cannot be replicated, i.e., a measurement made today cannot be repeated tomorrow.

Obviously, QA is a critical part of exposure studies, and a QA program must be established as part of the initial study design. The plan should fit the specific aims of the study. The QA program also must be considered when establishing the budget, because an effective QA program costs about 15–25% of the measurement budget. From a practical point of view, this translates into significantly less data—but data of a higher quality—than if QA were neglected. Those designing the study must take this reality into account when determining the statistical power of the study. Painful though it is to reduce the amount of exposure data, obtaining less data that are all good is much better than obtaining more data that are bad or unverifiable.

AIRBORNE ANALYTES

The nature of a given airborne pollutant—its physical, chemical, and in some cases, biological characteristics—determines the procedures appropriate to its sampling and measurement.

A contaminant can exist in a vapor-phase or particle-associated condensed phase, or it can be partitioned between these phases. The partitioning can result from the adsorption of a vapor-phase compound onto the surfaces of airborne particles, in which case the contaminant distribution is a function of the compound's liquid-phase (or subcooled liquid-phase if the compound is a solid at ambient temperature) vapor pressure and also the surface area of airborne particles per unit volume of air (Pankow, 1987; Bidleman, 1988; Junge, 1977; Ligocki and Pankow, 1989). *p,p'*-Dichlorodiphenyltrichloroethane is an example of an ambient contaminant commonly partitioned in this manner. Partitioning also can be due to dissolution of a vapor-phase compound in a liquid associated with airborne particles. An example is the dissolution of sulfur dioxide (SO_2) in water associated with hygroscopic particles. Organic vapors also can dissolve in liquids associated with airborne particles. Still another partitioning process involves attached and unattached radon daughters. Because a pollutant's dose to the lung can be very different in the vapor-phase from that of the condensed phase, care must be taken that a sampling procedure does not alter the distribution between phases and present a false picture of the pollutant's physical state (Van Vaeck et al., 1984; Bidleman, 1988; Coutant et al., 1988; Ligocki and Pankow, 1989).

If a pollutant is present in the condensed state, its distribution as a function of particle size is important information for assessing human exposure. Airborne particles range in size from a few nanometers to hundreds of micrometers (Finlayson-Pitts and Pitts, 1986). Particles frequently are classified as "fine" (<2.5 μm diam.) and "coarse" (>2.5 μm diam.). Fine particles are sometimes subclassified as nuclei mode (0.005-1 μm diam.) and accumulation mode (0.1-2.5 μm diam.). Fine and coarse particles tend to have different sources and, consequently, different chemical compositions. They also have different transport characteristics, such as settling velocities and diffusion coefficients, which lead to different atmospheric lifetimes. For these reasons, collection of size-fractionated particles (at least a fine and a coarse fraction) is useful when sampling with the intention of future chemical analyses. The American Conference of Governmental Industrial Hygienists has established cut sizes appropriate for fractionation in relation to inhalation hazard (Phalen et al., 1986).

In addition to size, other physical properties of airborne particles, such as morphology and water content, can strongly influence their effects on living organisms and should be considered in any sampling methodology. Particle shape and surface texture are important morphological features and are characteristic of the nature of the particle; research is in progress to represent this information as a few characteristic numbers (Hopke et al., 1988). Such research is concerned with the use of optical and electron microscopes as the major tools for determining these features with a primary focus on electron microscopes.

Chemical species are not always distributed uniformly throughout a particle. For some species, the surface concentration is significantly larger than the bulk concentration. Examples include semivolatile organic compounds that have been adsorbed on particle surfaces and trace metals with low boiling points, such as lead, zinc, and cadmium, that are surface enriched by high-temperature processes. In such cases, bulk analyses would yield much lower concentrations than those actually in contact with environmental surfaces. Hence, surface analyses using techniques that provide elemental or chemical information such as SAM (scanning auger microprobe), SIMS (secondary ion mass spectrometry), XPS (x-ray photoelectron spectroscopy), total reflectance IR (infrared), LAMMA (laser microprobe mass analysis), and FTIR (Fourier transform IR) are integral to a thorough evaluation of the health effects of certain pollutants.

The water content of airborne particles can affect partitioning of an inorganic gas between the vapor and condensed phases. The water content depends on the relative humidity (RH) of the air that contains the suspended particles, water-soluble salts associated with the particles, and different RHs

at which various salts deliquesce. When measuring the water content of particles, it is important to remember that this value can depend strongly on RH. It is also important to ensure that the measurement procedure does not alter the water content. However, in some situations, protocols might require that the measurement be made at a specified RH.

In considering the chemical nature of the analyte, some type of general classification scheme is useful in choosing sampling and analysis procedures. Such schemes can be as detailed as the outlines for inorganic and organic textbooks, or they can be fairly general. At the very least, the contaminant should be classified as organic or inorganic. If the contaminant is organic, subclassification into polar and nonpolar and as volatile, semivolatile, or nonvolatile is useful. If it is inorganic, subclassification by periodic group, solubility, acidity, hardness, and radioactivity might be helpful.

For biological analytes, an obvious distinction is that between viable and nonviable contaminants. The former include bacteria, viruses, spores, molds, and fungi. The latter include allergenic materials, such as arthropod fragments and insect excrement. Sampling for viable biological pollutants is complex, costly, and time consuming. A protocol for such sampling recently was developed by Morey and coworkers (1987).

CRITERIA FOR METHOD SELECTION

This section evaluates the requirements under which a method must operate, including sampling and analysis. The conditions for an ideal analysis are summarized in Table 3.2. However, optimal conditions for an analysis might require compromises.

Sensitivity

A method with adequate sensitivity is one in which an analyte can be detected at or below the level at which an adverse human-health problem is anticipated or observed. Ideally, a detection limit of at least an order of magnitude below the health-effect level is desirable. It also is desirable to have a broad linear range of 0.1X-10X the level of interest (i.e., a linear range of two orders of magnitude from the detection limit). Reproducibility of ±2% for replicate analyses and stability of ±5% during an 8-hour period also are desirable.

Achieving high sensitivity during a continuous analysis is a very difficult task. Therefore, one of the first compromises made in achieving high sensitivity

TABLE 3.2 Analytical Method Selection

Factor	Ideal Condition
Sensitivity	Detects analytes at levels below those causing adverse health effects; sensitivity 0.1X level of interest; range 0.1X-10X level of interest; precision and accuracy ± 5%; easy and accurate calibration
Selectivity	No response to similar compounds that might be present simultaneously with the analyte of interest
Rapidity	Short sampling and analysis times compared with biological response time or with significant changes in contaminant concentration; response time 90% in less than 30 sec; RS232 or equivalent output
Comprehensiveness	Sensitive to all contaminants that could result in adverse health effects
Portability	Sampling and analysis device is rugged and can be worn without modifying the normal behavior of individual; low-power consumption; battery operated; stabilization time less than 15 min; temperature range -20° to 40°C; humidity range 0-100%
Cost	Cost of sampling and analysis is not prohibitive; inexpensive, readily available components; few consumables; low maintenance

is to obtain a sample integrated over time, which reduces the temporal resolution in following the course of an exposure. This can have serious implications when short-term, high level exposures have adverse health effects and could go unnoticed in an integrated exposure. Another area of compromise is to sacrifice selectivity to obtain sensitivity. An example of this occurs in the analysis of polychlorinated biphenyls (PCBs). Great selectivity can be achieved in analyzing the 209 different congeners using high-resolution gas chromatographic (GC) techniques; the individual concentrations of the congeners can be summed to obtain a total PCB content. However, a technique with better sensitivity would be to chlorinate all PCBs to decachlorobiphenyl and analyze for the single compound. This improved sensitivity occurs at the expense of a detailed knowledge of which PCB congeners were present. Congener-specific information may be very important in an exposure assessment perspective (McFarland and Clarke, 1989).

Sensitivity also can be improved by using a type of fixed-base monitoring sampler compared with a portable device that could be worn on the body. Fixed-base samplers often use more sophisticated detection methods (and are usually more expensive and bulky) than portable samplers and thereby improve the overall sensitivity of the analyses.

Selectivity

A method that is selective (or specific) is one in which the response observed for a desired analyte is due only to that analyte and is not from an interfering analyte or artifact produced during sampling or analysis. When making an analytical determination, the quantitative results obtained must be for the correct analyte and only that analyte. If other compounds interfere in the analysis, then it is important to understand their contribution to the results so that the data can be properly interpreted or so that other, more selective methods can be sought.

High selectivity can be achieved using various high-resolution GC techniques coupled with appropriate selective detectors. However, chromatographic separations can be time consuming and require each analysis to be discrete. For example, in a continuous analysis for total aromatic compounds, the compounds can be fed directly into a photoionization detector (PID) without any chromatographic separation. Although the analysis is rapid, little information is gained about the chemical nature of the detected compounds. Separating the aromatic compounds on a high-resolution capillary column before PID detection reduces the rapid nature of the analysis, but greatly enhances the selectivity. Another means to increase selectivity of the analysis

is to use more sophisticated instrumentation, especially in the final detection of analytes. As an example, analyses can be carried out using GC in combination with mass spectrometry (MS) as the detection device. However, MS is significantly more expensive than PID and, due to its size, reduces the portability of the analytical system.

Rapidity

A method is considered rapid if either the sampling or the analysis can be carried out on a time frame that is short compared with any adverse health response observed in an exposed individual. In this definition of rapid, real-time analyses are not necessarily carried out; the concentration of the analyte to which the individual is exposed could be determined in a short time frame. For example, several discrete samples could be taken on adsorbent media and subsequently analyzed. Understanding of the pharmacokinetics of the analyte in question is important in determining the sampling time. It is unnecessary to sample frequently if an analyte's half-life in the body is long. However, if an analyte is excreted or metabolized rapidly, it might be necessary to analyze within a very short time (Rappaport, 1988).

Sensitivity often is abandoned to achieve rapid analysis. If sufficient sensitivity is available (i.e., 10% of the level of interest), then shorter sampling times can be used to achieve the necessary temporal resolution. This approach must be tempered with the knowledge that subsequent analyses are expensive, and the cost of the total analyses might be prohibitive. Selectivity also might be foregone to achieve rapid analyses. As with the earlier PCB example, if little discrimination is required in the analysis of aromatic compounds using PID, then the selectivity provided by the chromatography column could be eliminated and the analyses carried out rapidly to give the total concentration of aromatic compounds.

Comprehensiveness

A comprehensive method often is desired for analyzing all analytes that might be responsible for an adverse health effect, particularly when a synergistic effect between analytes might exist. Comprehensive analysis can be particularly important when trying to determine the ultimate source of a toxicant. It often is useful to track which compounds change concentrations in unison and use this information to identify their primary sources.

One way of attaining comprehensiveness is to have multiple methods running

simultaneously. The difficulty with this approach is that it can become very expensive and time consuming. In many cases, a method can handle several analytes if they are similar in chemical nature; thus, the necessary comprehensiveness can be achieved with a single method.

Portability

Personal sampling or analysis devices must be sufficiently small, light, and quiet to be worn by individuals without causing them to modify their normal behavior. In many cases, samples are collected and then analyzed later. In situations that require real-time continuous (rapid) analysis, the analysis device might need to be worn by the individual. The power consumption of the device must be low to minimize the weight of the batteries and their need for recharging. The unit should also be rugged, because it might need to endure extreme conditions of heat, humidity, and shock.

In addition to personal sampling, there is a continuing need for portable methods for air analysis that could be deployed in a variety of field settings (e.g., portable gas chromatographs and mass spectrometers). Portability might be difficult when determining many analytes, especially when multiple methods are required. In these instances, a fixed-based monitor would be needed to accomplish the desired analyses.

Using a passive sampler rather than an active one sometimes precludes continuous monitoring; however, the simplicity and low cost of passive monitors make them ideal for portability. Table 3.3 presents the status of personal monitor development for selected contaminants.

Cost

The cost of sampling and analyzing an analyte in a statistically sound manner should not be prohibitive. An excellent analytical technique might be available, but if the cost per analysis is too high, it could result in too few samples being taken to give a proper measure of exposure.

Automation can reduce the costs; sharing capital equipment eliminates the need for costly equipment duplication. Many times the increased demand for a particular type of analysis encourages laboratories to devise simpler, cheaper ways of carrying out the analyses.

One way to control sampling and analysis costs is to conduct a few preliminary comprehensive analyses to survey actual conditions and then analyze a subset of compounds. Another method is to take fewer samples, which means

TABLE 3.3 Status of Personal Monitor Development

Pollutants	Monitor needed		Monitor under development		Prototype under development		Tested and evaluated		Used in pilot studies		Used in large field studies		Ready for routine use	
	D	I	D	I	D	I	D	I	D	I	D	I	D	I
CO	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	
NO_2	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓
Inhalable particles (<10 μm diam.)	✓	✓	✓	✓	✓	✓		✓		✓		✓		✓
Formaldehyde	✓	✓		✓		✓		✓		✓		✓		✓
VOCs Polar VOCs	✓ ✓	✓ ✓		✓		✓		✓		✓		✓		
Pesticides	n/a	✓		✓		✓		✓		✓		✓		
Radon	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PAH	n/a	✓		✓		✓								
Biological aerosols	n/a	✓		✓		✓		✓		✓		✓		✓
House dust	n/a	✓		✓		✓		✓		✓		✓		✓
O_3	✓	✓		✓		✓		✓						

D = direct readout; I = integrating collection of samples; n/a = not applicable. Source: EPA, 1988a.

that fewer analyses must be performed. Conducting fewer analyses is a compromise when continuous analyses are prohibitively expensive; such a compromise requires that the sampling resolution be established at the outset of the exposure study. If portability is a factor, it can be expensive, and a less costly alternative is to use a fixed-based system.

METHODOLOGY

The Measurement Process

The measurement of an airborne contaminant can be visualized as a three-step process. First, the pollutant is sampled; then it is separated from other species also collected in the sample; finally, it is detected. In actual practice, these steps frequently overlap (Figure 3.1). In this figure the individual rings for sampling, separation, and detection show areas of overlap, as well as areas where no overlap occurs. Different measurement processes have different combinations of overlap, ranging from none to complete. An example of a measurement procedure with no overlap is the following approach to the determination of the airborne concentration of benzo*a*pyrene (BaP). First, respirable particles that might contain BaP are collected on a filter. Second, BaP is extracted from the particles and then separated from other compounds in the extract by thin-layer chromatography. Finally, BaP is detected using fluorometric techniques. Such measurement procedures (i.e., no overlap among the three steps in Figure 3.1) are usually labor-intensive. In many analytical procedures, two of the rings overlap; the overlap most frequently encountered is between separation and detection. For example, in GC with flame-ionization detection, one instrument combines the separation step (GC) with the detection step (flame-ionization detection). Less commonly, an analytical procedure involves overlap between sampling and separation. An example of such an overlap is a diffusion denuder, in which, as the vapor-phase pollutant is sampled it is also separated from the condensed-phase pollutant. Overlap between sampling and detection also occurs, as in a photometric ozone meter. Finally, in some analytical methods all three rings overlap (e.g., MS-MS).

The following sections discuss sampling, separation, and detection as isolated steps. However, there are necessarily areas of overlap in each section, just as there are areas of overlap in Figure 3.1.

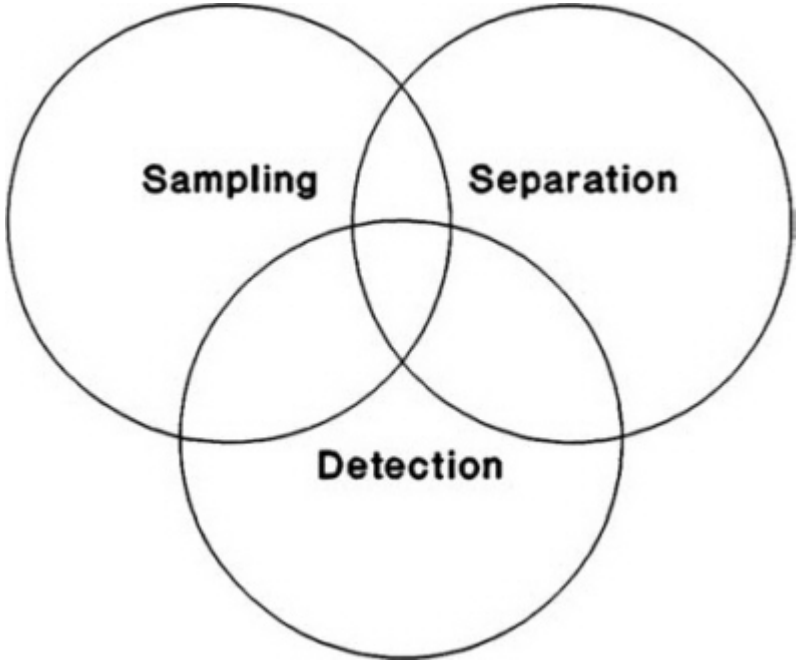

FIGURE 3.1 Steps in the measurement process. Different processes have overlap ranging from none to complete.

Sampling

Airborne contaminants are sampled actively or passively. Active sampling uses a pump to pull airborne contaminants through a collection device. Passive sampling—sometimes referred to as diffusive sampling—relies on diffusion to deliver airborne contaminants to the collection medium.

Passive Sampling

The major advantage of passive sampling is that it does not require elaborate equipment. No pumps need to be maintained or calibrated; the sampling site does not need to be close to a power source; and pump noise, a frequent complaint of active samplers, is not a factor. Because pumps and accessories are not required, passive sampling is less costly and easier to implement than active samplers. Extensive passive sampling programs have been conducted by mail (Sexton et al., 1986)—sample collection devices can be sent and returned in this fashion. Passive samplers are favored for personal monitoring; they are lighter, smaller, and less likely to interfere in daily activities than are active samplers. Consequently, participants are more likely to cooperate in passive sampling programs. Furthermore, since the sampling device can be worn in the breathing zone, pollutants whose spatial and temporal concentrations vary extensively can be integrated appropriately.

The major disadvantage associated with passive sampling is the long period required to collect sufficient material for analysis. Indeed, these long integration times mean that passive sampling is not suitable for pollutants whose health effects depend on peak exposures or pollutants that have immediate, acute health effects (e.g., hydrogen cyanide). Passive sampling also tends to be less accurate than active sampling. In addition, artifacts might arise from chemical transformations on the surface of the sorbent, a concern that increases as the length of the sampling period increases.

The first widely used passive sampler was an NO_2 monitor developed by Palmes (Palmes et al., 1976). Passive samplers have since been used for formaldehyde (Geisling et al., 1982), water vapor (Girman et al., 1986), nicotine (Hammond and Leaderer, 1987), and nonpolar volatile organic compounds (VOCs) (3M, 1982; Seifert and Abraham, 1983; Shields and Weschler, 1987). A fixed-site passive sampler for ozone has recently been described (Monn and Hangartner, 1990) and an ozone passive sampler suitable for personal monitoring has also been reported (Koutrakis et al., 1990). A passive monitor for CO is under development at the Lawrence Berkeley Laboratory. However, few passive sampling devices are available for polar VOCs (e.g., acrylonitrile and selected amines), highly volatile compounds, and extremely reactive compounds.

The nature of the sorbent varies with the nature of the analyte. Ideally, a linear concentration gradient exists from the open end of the sampler (ambient concentration) to the sorbent surface (zero). An effective passive sampler requires an efficient sorbent that will keep the sampled pollutant concentration near zero at the sorbent's surface. It must also be possible to desorb the pollutant or a derivative quantitatively for subsequent analyses.

The potential exists to develop passive samplers specific to numerous gaseous airborne pollutants. Many sorbents have not been tried or fully evaluated in passive devices; some materials recently introduced for GC and liquid chromatography might have application in passive sampling. Furthermore, promising new sorbents are being synthesized and developed. Some of these have been engineered at the molecular level and have binding sites or cavities specific to a given compound or class of compounds. To sample for extremely reactive compounds, the sorbent can be deliberately designed to react quickly and efficiently with an analyte to yield a stable, nonvolatile product that can be extracted and quantified.

An interesting approach for selected analytes is to interface passive samplers with active devices. Passive sampling can be combined with sensors to make portable instruments and obtain a real-time readout of concentration. Such devices are available for CO, combustible gases, and other pollutants (Stetter and Rutt, 1980; Stetter et al., 1984; Penrose et al., in press).

Active Sampling

Although passive sampling is well suited to vapor-phase pollutants, active sampling can be used for this as well as condensed-phase contaminants. For vapor-phase pollutants, a known volume of air commonly is pumped through an efficient absorbent (Pagnotto, 1983). Absorbents frequently used for organic compounds include Tenax, XAD-2, activated charcoal, Ambersorb XE-340, polyurethane foam, or a combination of these absorbents in series. When using solid absorbents in active sampling, it is important to know the collection efficiencies of the sorbent for the analytes in question (Senum, 1981; Pagnotto, 1983; Bidleman, 1985). A large body of literature exists on the retention and efficiency of numerous sorbents (e.g., Gallant et al., 1978; Figge et al., 1987; Maier and Fieber, 1988; Pankow, 1988). When a sorbent has not been previously characterized, "backup" sections should be utilized as a measure of analyte breakthrough.

An approach sometimes used with gas phase acids or bases is to pump air through a filter impregnated with an appropriate base or acid that will scavenge the airborne acid or base. Impingers with various absorbing solutions are commonly used for volatile pollutants. More recently, canister samplers have been designed in which an air sample is drawn into an initially evacuated stainless-steel canister. The internal walls have an inert chrome-nickel oxide surface to decrease wall reactions. Commercial versions of these samplers can collect as much as 8 L of air for subsequent analyses.

In each of these active approaches, some method is required to remove

airborne particles from the air stream before the volatile compounds are collected. The most common method is to place a filter upstream of the absorbent, treated filter, impinger, or evacuated canister. However, potential artifacts are associated with this approach. Semivolatile compounds adsorbed on collected particles can evaporate from the surface of the filter and these compounds are sampled downstream by the collection device. An error in the opposite direction results when vapor-phase compounds adsorb or react with particles on the filter or the filter matrix itself (Van Vaeck et al., 1984; Coutant et al., 1988; Ligocki and Pankow, 1989). In either case, the resulting measurements do not reflect accurately the partitioning of certain semivolatile compounds between vapor and condensed phases (see previous section on airborne analytes). This is potentially important information, because the phase of a pollutant can affect its chemistry, deposition site in the respiratory system, and toxicology.

Use of a diffusion denuder eliminates this problem (Ali et al., 1989). Air is pulled through a cylindrical tube whose walls are coated with an absorbent specific for the pollutant of interest. The interval dimensions of the tube and air velocity are such that only the vapor-phase pollutant diffuses to the walls; particles pass through to the other end (where they can be collected on a filter, if desired). Diffusion denuders can be configured using different absorbents and geometries and are potentially applicable to a wide variety of compounds. They could be very useful to evaluate the partitioning of a compound between vapor and condensed phases (Coutant et al., 1988; Lane et al., 1988). Many improvements have been made in diffusion denuders; annular denuders collect reactive atmospheric gases 15–20 times more efficiently than tubular denuders (Possanzini et al., 1983; Ali et al., 1989). However, these devices are too bulky for personal sampling. The annular denuder/filter-pack system to collect acidic gases and aerosols described by Koutrakis et al. (1988) is a promising monitoring device, but is more than 2 feet long.

Even with diffusion denuders, the analyst must be wary of artifacts. Species absorbed on the treated walls of the denuder can be oxidized or reduced (less common) by other reactive gas phase pollutants. For example, in laboratory studies, ozone has been demonstrated to oxidize nitrite ions on an alkaline denuder surface to nitrate ions (Febo et al., 1986). In some active sampling methods, the airborne pollutant is not collected, but passes through a flow cell, where some physical property of the pollutant is monitored. From this measurement, a concentration is derived. Different examples of this approach include ozone meters and optical particle counters. The former compares the absorption (at 254 nm) of ambient air and ambient air from which ozone has been removed selectively. The latter uses light scattering to monitor the number concentration versus diameter of airborne particles. In either case, ambient

air is pumped through a flow cell where the measurement is made. Most real-time continuous analyzers sample in this way.

Optical particle counters measure particle-size distributions based on light-scattering diameters. Measurements based instead on aerodynamic particle size can be made with a laser velocimetry technique. A commercial instrument is available that uses a split laser beam to monitor the velocity of particles leaving an accelerating nozzle. The device can monitor particles 0.5–15 μm in diameter for numerous size ranges. It provides not only data on number concentration versus aerodynamic diameter, but also on mass concentration and surface area concentration versus aerodynamic diameter. The sampling rate is 5.0 L/min. For health studies, aerodynamic sizing is preferable to sizing based on light scattering, since respiratory deposition relates more directly to the former.

Another instrument that provides data on the mass concentration of airborne particles is the piezobalance. The particles are sampled by electrostatic precipitation onto the surface of a piezoelectric device. The change in resonant frequency of the piezoelectric quartz crystal is used to monitor the mass gain. Electrostatic sampling is efficient for particles 0.01–10 μm in diameter. Commercial units sample at 1.0 L/min and can measure mass concentrations 10–10,000 $\mu g/m^3$ in real-time.

A similar instrument is the tapered element oscillating microbalance (TEOM). A variety of collection stages can be fitted to the narrow end of the oscillating tapered element. As mass is added to a particular collection stage, the frequency of oscillation decreases in relation to the amount of deposited mass. This instrument provides a particle sample that can be analyzed by other techniques. The TEOM can be used for personal monitoring and is more versatile than the piezobalance (Patashnick and Rupprecht, 1986), but it also is more expensive.

Particles can be counted in flow cells, but a collection procedure is required if subsequent chemical analysis is intended. The simplest approach is to pump air through a filter. High-volume (hi-vol) samplers do this at very high flow rates—typically 1.5 m^3/min. However, the size of airborne particles is an important factor in estimating potential human exposures, which argues for including size-fractionation as part of any procedure that samples airborne particles. Furthermore, chemical composition and biological activities are related to particle size (Phalen et al., 1986); these size ranges are based on the inhalation of particles by humans. The "inspirable mass fraction" comprises all particles that enter via the nose or mouth. The "thoracic mass fraction" is all particles that penetrate past the larynx. The "respirable mass fraction" is all particles that penetrate past the terminal bronchioles. Standard curves (the

percent penetrating to collector versus aerodynamic diameter) have been defined for each of these size fractions (Phalen et al., 1986).

To sample particles smaller than a certain diameter, size-selective inlets of various design can be placed upstream of the collecting filter. Size fractionation can also be achieved with dichotomous samplers. Such samplers size-fractionate airborne particles into fine and coarse modes. The fractionation is based on the particles' aerodynamic sizes; particles are separated by virtual impaction and are collected on filters downstream from the separation device. Dichotomous samplers normally are fitted with a 10 or 15 μm diameter size-selective inlet, which places an upper limit on the size of the particles sampled in the coarse mode. Dichotomous units sample at a relatively low rate (typically, 16.7 L/min) and, consequently, long sampling periods (1 day to 1 week) are required to collect sufficient material for chemical analyses.

Sampling of airborne particles in more than two size ranges usually is conducted with a cascade impactor. This device is simply a set of impactors, operating in series, arranged in order of decreasing cutoff size. An impactor plate collects the particles in each size range and the final impactor is followed by a filter. The separation is again based on aerodynamic particle size. Commercial devices are available with as many as eight stages. If there are too many stages, the collection curves between successive stages overlap; such overlap already occurs with an eight-stage impactor. Furthermore, more stages mean more sampling time required to collect sufficient material in each size range for gravimetric and chemical analysis and more samples to analyze. An additional problem encountered with cascade impactors is that of "particle bounce"—particles fail to stick to their appropriate impactor plate and become re-entrained with smaller particles. Particle bounce can be reduced by greasing impactor plates, but this is only reasonable when examining inorganic constituents of a sample. A virtual impactor (such as the dichotomous unit) avoids this problem, because it has no impactor plates.

There is a potential for sampling bias when collecting particles with a mass median aerodynamic diameter larger than 3 μm. The combination of a small sampling inlet running at a high flow rate will result in undersampling large particles because of the inertia of these particles at the inlet (Breslin and Stein, 1975; Selden, 1975; Agarawal and Liu, 1980).

Sampling programs designed to assess human exposure to airborne pollutants frequently include indoor sampling. When active sampling is conducted indoors, care must be taken that the pumping rate is not so great (relative to the space being sampled) as to alter the indoor environment. In small rooms, this limitation precludes the use of hi-vol samplers or certain cascade impactors. To collect useful amounts of airborne particles with devices that sample at lower rates, lengthy sampling intervals are required. Because the volume

of air cannot be increased without perturbing the sampled environment, the only way the sampling interval can be decreased in such studies is to improve the sensitivity of the subsequent particulate analyses. Recently, the indoor-air sampling impactor (IASI) was developed by Marple et al. (1987), which can operate at 10 or 4 L/min and has a sharp cut size at d_{50}[1] = 10 μm and d_{50} = 2.5 μm, respectively. Personal monitors that have a 2.5-μm d_{50} cut size have been used in industrial hygiene (ACGIH, 1988a). Recently, personal impactors with a 10-μm d_{50} have been used in community-based field studies (Lioy, 1988).

Separation

Chromatography

Chromatography is a separation process often used to isolate airborne contaminants from other compounds that might interfere in detection of specified contaminants. Chromatography involves the simple partitioning of analytes between mobile and stationary phases. Using this approach, tens to hundreds of compounds are readily separated. Stationary phases can vary widely, including silicones, silica, alumina, florisil, various polymers, silica in which various materials have been bonded to the surface, and most recently, commercially available liquid crystals. An important feature of the stationary phase is that it must not be miscible with the mobile phase, and must not dissolve or volatilize in the mobile phase.

Mobile phases also vary widely, ranging from gases to liquids, and include gases, which, when held above their critical pressure and temperature, behave as supercritical fluids. In most cases, chromatographic techniques derive their names from the nature of the mobile phase, e.g., gas chromatography (GC), liquid chromatography (LC), and supercritical fluid chromatography. However, thin-layer chromatography (TLC) derives its name from the manner in which the stationary phase is configured.

In TLC, the actual chromatographic process most often involves placing a sample on the head of a column packed with the stationary phase. The mobile phase then transports the components of the sample through the column, with the components separated based on the amount of time they spend in (adsorbed to or partitioned into) the stationary phase.

[1] d_{50} = diameter at which 50% of the particles penetrate to the collection medium.

Chromatographic techniques are often highly selective. However, this separation process takes time, which gives chromatographic techniques the disadvantage of being noncontinuous. The following discussion describes various chromatographic techniques and their application to analyzing airborne contaminants. It includes a discussion of each technique's advantages and disadvantages, recent developments in the field, and new applications of the technique.

Gas Chromatography

GC involves the separation of compounds based on their volatility and interaction with the stationary phase (Jennings, 1987). The mobile phase is a gas, and the stationary phase can be quite variable, ranging from molecular sieves to synthetic organic polymers and liquid crystals. Because the separation process involves compounds in the gas phase, GC is ideal for the analysis of many airborne contaminants. The National Institute for Occupational Safety and Health (NIOSH) describes more than 500 methods to analyze gases and vapors. Of these methods, 51% are by GC (Saltzman, 1988b).

Advantages. The most significant advantage of GC in the analysis of airborne contaminants is that it combines the inherently high resolving power (high selectivity—the ability to separate individual components) of the chromatographic column with easy interfacing to a variety of detection devices. The application of capillary columns, with internal diameters of 0.25–1 mm, has become increasingly popular during the past decade. Preparing these columns from fused silica has given them the inertness of glass columns with the flexibility of metal columns, making them particularly easy to use. Advances in capillary-coating techniques have permitted thick film columns to be developed, which are ideal to separate highly volatile air contaminants (Jennings, 1987). This provides a tremendous amount of selectivity in isolating an analyte of interest, even in complex matrices. However, the chromatographic column only separates compounds; it does not provide for their detection. Fortunately, GC is readily interfaced to a variety of detectors that provide either nonspecific (universal) detection of compounds eluting from the column or their highly specific and often highly sensitive detection.

GC instruments can be made transportable and, in many respects, even portable. They are rugged enough to be transported in vehicles and taken to a site for field analysis. Many GC-detector system combinations are inexpensive and readily obtained. GC-detector combinations are also very flexible—they can be configured to analyze for a very wide range of compounds. If sufficient sample is available and does not need to be analyzed immediately,

then a GC-detector system can be set up to analyze low-molecular-weight compounds and then reconfigured with a column suited for higher-molecular-weight compounds and, in this manner, achieve a more comprehensive analysis. If a high degree of specificity is needed, then the analysis of a specific analyte can be carried out using one type of chromatographic column, followed by reanalysis on a second column of a different character than the first, and the results from the two columns can be compared. This type of confirmation is carried out to reduce the possibility that multiple compounds might coelute on a specific column, resulting in misleading results (Overton et al., 1988).

GC is readily automated, which allows for unattended operation. This distinct advantage greatly facilitates the analysis of large numbers of samples and helps keep the cost per analysis low. Liquid auto injectors for GC are available and are extremely useful in analyzing solutions such as those derived from the solvent desorption of air-sampling devices (e.g., carbon disulfide desorption of charcoal tubes). Automated thermal desorption devices are also available for the analysis of air sampling tubes (e.g., Tenax sorbent trapping devices) (Kester and Zaffiro, 1987). In addition, the recent popularity of "passivated" air sampling canisters (e.g., SUMMA-treated canisters) has led to techniques to sample automatically from several gas containers (Blacha et al., 1988). Furthermore, the combination of GC with mass spectrometry has made this a very popular tool for both the qualitative and quantitative analysis of a wide range of airborne contaminants.

Disadvantages. The separation process that gives GC high specificity requires time. During this time, no other analyses can be conducted, which eliminates the continuous nature of any analysis. Many attempts have been made to work around this problem. These attempts include high-speed analyses in which thin-film capillary columns can separate 30–40 compounds in approximately 1 min (Hewlett-Packard, 1987). Another approach is to proceed with the analysis until the analyte of interest elutes; the column is then backflushed to eliminate any late-eluting compounds from interfering in subsequent analyses. If confirmational analyses involve a second column or different detector, then sufficient sample must be available, and it must be stable until the second analysis can be carried out, taking even more time. Some of these problems can be minimized by having two columns installed in the same chromatograph and splitting the sample between the two columns. In a similar fashion, multiple detectors can be used simultaneously by splitting the eluant from the column between multiple detectors (Earp and Cox, 1984). In all these instances, the selectivity can be increased, but the time needed to do the analyses prevents the technique from being continuous.

New developments in GC also might help to resolve some of the limitations.

Multiplexing the analysis of samples has been used to decrease analysis time without greatly modifying the method (Phillips, 1980). In this method,a second sample is injected onto the chromatograph before all the compounds have eluted from the first injection. Computer software tracks which peaks belong to which injection. Multiplexing can be an excellent technique for decreasing the analysis time without extensively modifying the method or purchasing additional hardware.

Another disadvantage of GC is that it is not necessarily comprehensive. Certain highly reactive compounds are difficult or impossible to put through a chromatography column. These compounds either decompose at the temperatures required to be chromotographed or react with the stationary phase or the column material. In other instances, a compound decomposes on the column to form another, giving misleading results. An example of such a process is the on-column decomposition of *N*-nitrosodiphenyl amine to form diphenyl amine. In many instances, the chromatograph is operated in a temperature-programmed mode to increase the range of compounds that can be analyzed. This serves as an alternative to first analyzing for low-molecular-weight compounds and then reconfiguring for higher-molecular-weight compounds. This programming requires time for the analysis and for the chromatograph to recover to the initial starting point before beginning any subsequent analyses. Temperature programming also requires elaborate electronics to control the column temperature reproducibly. This increases instrument cost and, in some cases, increases its size and weight, making it less portable, although portable gas chromatographs now are available that are capable of limited temperature programming.

As chromatographs become smaller and smaller, a "gas chromatograph on a microchip" could be fashioned (Angell et al., 1980; Overton et al., 1988). Such a device might be so inexpensive that analysis time could be cut in half by doubling the number of chromatographs: the sample would be sent to one GC and, while the compounds are eluting from it, the next sample would be sent to the second chromatograph. In this manner, any reasonable time resolution desired could be obtained. Such small chromatographs also would be more readily temperature programmed due to their small mass. They could thus be used to analyze a broad range of compounds while maintaining relatively short analysis times.

Another technique that is gaining widespread use is multicolumn GC (Ligon and May, 1984). In this technique, the compounds first are separated on a primary column, and then fractions are cut from that column onto secondary columns. A nice application of this technique in air analysis involves the use of the primary column to separate water (the major component) from low-molecular-weight oxygenated hydrocarbons (Lin et al., 1988). These hydrocarbons

then can be routed to a second analytical column without the deleterious effects of water, and the detector can be run at a high sensitivity, because the major constituent has been eliminated. Multicolumn GC has also been used recently to separate all of the PCB congeners in commercial mixtures(Schmalz et al., 1989). The multicolumn chromatography can further be used to increase the comprehensiveness of analysis without seriously increasing the analysis time. The primary column routes highly volatile compounds to a secondary column ideally suited to separate these types of compounds and then routes the low-volatility compounds to a second column designed for their analysis. The analysis for these two classes of compounds goes on simultaneously, which shortens the analysis time. The hardware for multicolumn chromatography is expensive and method development can be difficult, but the versatility of the technique should see its wider application in future air analysis programs.

Liquid Chromatography

LC involves the separation of compounds when the mobile phase is a liquid (Snyder and Kirkland, 1979). In many applications of LC the back pressure developed by the column requires the use of sophisticated pumping systems and has been named either high pressure or high-performance liquid chromatography (HPLC). The mobile phases used with LC columns can vary quite widely depending on the nature of the analytes and the stationary phase. Typical mobile phases include hexane, methylene chloride, mixtures of water with acetonitrile or methanol, and various buffer solutions. The stationary phases are also quite diverse; they include silica, alumina, and florisil bonded phases in which an organic molecule has been attached to a silica surface, and a wide variety of ion-exchange resins. Use of ion-exchange columns has resulted in an LC class known as ion chromatography (IC), which uses a special type of ion-IC suppressor column to permit sensitive detection of the separated ionic species using electrolytic conductance techniques (Small et al., 1975). IC is used routinely to identify and quantify the major anions and cations associated with airborne particles, including sulfate, nitrate, chloride, ammonium, sodium, potassium, magnesium, and calcium.

For all types of LC, the analytes of interest are dissolved in the mobile phase and then pass through a column packed with the stationary phase. The compounds elute from the column in the order determined by the extent of their interaction with the stationary and mobile phases. Again, as with GC, LC, only separates compounds, it does not detect them. However, several

detectors can be interfaced to LC to provide for the sensitive and selective detection of eluted compounds.

LC is not used as widely as GC to separate and analyze airborne contaminants. LC is used to analyze such contaminants when the compounds are so thermally labile, highly reactive, highly polar, or nonvolatile that GC analysis is difficult or impossible. Inorganic acid gases (e.g., HF, HCl, H_3PO_4, HNO_3, HBr, and H_2SO_4) are examples of these types of compounds. These gases can be collected from ambient air using water impingers or silica tubes, subsequently eluted with water, and the ionic species (e.g., F- and Cl-) are then analyzed by IC (Eller, 1984a). A similar approach can be used to analyze organic acids (Rosenberg et al., 1988). LC also can be applied to the analysis of airborne contaminants that are difficult to trap or concentrate because of their reactive nature. An example of this class of compounds is the various aldehydes that can be collected in a solution of 2,4-dinitrophenylhydrazine (DNPH). DNPH reacts with the aldehydes, forming a hydrazone derivative that can be extracted and separated from interferences using LC. A particularly useful feature of the DNPH derivatization is that it forms a compound with a strong chromophore, which makes it amenable to sensitive ultraviolet (UV) adsorption detection (Riggin, 1984).

Thin layer chromatogrophy (TLC) has direct ties to LC and often is used as a prescreening tool for in situ scanning of the TLC plate to determine the best mobile and stationary phases to use for a particular LC separation. TLC's main application to the analysis of airborne contaminants is for the analysis of semivolatile compounds present on airborne particles that are small enough to be taken into the lung. A typical application would be for the separation of polycyclic aromatic hydrocarbons (PAHs) extracted from particulate matter, with the PAHs detected spectrofluorimetrically (Lioy et al., 1988).

Advantages. A major advantage of LC techniques is that the separation processes are done at lower temperatures than GC, allowing analysis of compounds that might be destroyed during GC analysis. For example, *N*-nitrosodiphenylamine can be separated from interfering compounds on an LC column whereas, as stated before, this compound breaks down to diphenylamine during GC analysis. LC also is useful to separate organic compounds that are too polar or not sufficiently volatile for routine GC procedures. This applies to certain organic species associated with airborne particles. Thus, LC can be combined with GC techniques to give comprehensive analyses. Furthermore, since the columns and mobile phases used with LC can be tailored to particular analytes, the comprehensiveness of LC techniques is enhanced. LC techniques are readily automated, which allows for unattended operation if many samples must be analyzed. The use of high-resolution columns also gives LC a high degree of selectivity. Recently, portable LC instruments have

been demonstrated (Berg and Buckley, 1987; Otagawa et al., 1986), which may lead to applications in field-monitoring.

A variety of LC detection techniques can be used to provide sensitive detection of eluants, including spectrophotometric, fluorometric, electrochemical, and refractivity detectors. In most instances, the original air contaminant is detected directly after separation. An example is the fluorescence detection of PAHs extracted from particulate matter (Wise et al., 1986). In other cases, air contaminants such as aldehydes can be reacted with a reagent, such as dinitrophenyhydrazine (DNPH) before LC analysis to enhance their detection by UV.

Another advantage of LC is that the column eluants are in a liquid medium; they can be manipulated chemically (oxidized, reduced, or derivatized) to enhance their detection. For example, nitrated PAHs from airborne, inhalable particles are reduced to amino-PAHs using a post-column, and the amino-PAHs are then detected using fluorescense techniques (Greenberg et al., 1986; Tejada et al., 1986). This process is done continuously; no analysis time is lost, and the procedure can be automated. A slightly different twist to post-column derivatization and detection has been used to analyze aldehydes (Takeuchi et al., 1988). In this technique, nicotinamide adenine dinucleotide (NAD) was included as part of the mobile phase. When an aldehyde eluted from the column, a post-column reactor of immobilized 3-alpha-hydroxysteriod dehydrogenase reacted with the NAD in the presence of the aldehyde to form NADH, the reduced form of NAD. The NADH was then detected by fluorometry. This technique further illustrates the versatility of detecting eluants from an LC column.

Disadvantages. LC equipment tends to be more costly than GC and typically less portable. LC shares the GC disadvantage of the time required for high selectivity, which prevents the analysis from being continuous. Mass-transfer limitations prevent LC from attaining the high-speed analyses achievable with GC. Other techniques, such as multiplexing (multiple separations and detections occurring simultaneously), might be tried with LC to attempt to decrease the time between analyses.

LC is used only if an analysis cannot be done by GC. Although several detectors are available for LC, the wide array of detectors available for GC make it the choice for analysis. Many GC detectors are difficult or impossible to use with LC. LC needs a universal detector comparable to the GC flameionization detector. Techniques are available to interface LC to mass spectrometry, and their development and application will complement, but not replace, GC as the primary chromatographic tool for the analysis of airborne contaminants.

Supercritical Fluid Chromatography

Future developments in the chromatographic analysis of airborne contaminants will occur in the area of supercritical fluid chromatography (SFC). SFC uses supercritical fluids—best thought of as very dense gases with unique solvating properties—as the chromatographic mobile phase. The chromatographic principles of SFC are very similar to those for GC and LC, and SFC can be considered as a bridge between GC and LC (Chester and Innis, 1985; Chester, 1986; White and Houck, 1986).

The primary factor that affects the solvating or elution power is the density of the gas used as the mobile phase, which can be readily adjusted by varying the pressure and, to a lesser extent, the temperature. Density is analogous to temperature in GC or mobile phase composition in LC, affecting the chromatographic separation of a matrix. Various gases and liquids, such as CO_2, Ar, freons, NH_3, N_2O, hydrocarbons, and even water, can be used as mobile phases to provide a wide range of polarities to affect separations. Modifying agents can also be added to the mobile phase to alter elution characteristics.

SFC uses the unique solvating and elution power of supercritical solvents. Unlike GC, SFC allows for chromatography of relatively high-molecular-weight nonvolatile compounds. The technique is similar to LC in that many thermally labile components are chromatographable due to the low temperature solvating power of the mobile phase. (Components with relatively high mobile phase densities that provide analyte elution can be reached at low operating temperatures.

The use of capillary columns, as opposed to packed columns, combined with an instrument capable of simultaneous density and temperature programing has greatly extended the usefulness of SFC. Packed columns suffered from limited resolution, and the high mobile phase flow rates made detector interfacing difficult.

SFC has been successfully interfaced to numerous detectors, including GC-like detectors, such as flame ionization, flame photometric, thermionic, microwave plasma, and electron capture detectors, as well as mass spectrometers, and Fourier transform IR spectrometers. SFC also has been interfaced to LC-like detectors such as UV-absorbance and fluorometric detectors. The ability to interface SFC with so many detectors greatly enhances the versatility of the technique in comparison with LC methods.

The one major problem confronting capillary SFC is the column's limited sample capacity, which in turn limits the ultimate sensitivity of the method. New injection techniques are being devised in which more analyte is introduced onto the column while limiting the amount of solvent (Andersen, 1988; Anderson et al., 1989). These techniques should be useful in overcoming the

limitations of capillary SFC. When used with capillary columns, SFC obtains near capillary GC-like resolution. This resolution is invaluable since it permits additional compounds to be added to the sample matrix such as internal standards that are resolvable from the compounds already present in the sample. Although GC is capable of higher resolution than SFC in a shorter time, capillary column SFC offers potentially greater resolution than LC in less time (Schoenmakers and Verhoeven, 1987). If an analysis can be done by GC, that is the method of choice. However, if it cannot be done by GC or can be done only if extensive derivatization procedures are necessary, then use of SFC may be a useful alternative. Although SFC cannot replace GC or LC, it plays an intermediary role between these techniques and needs to be evaluated further.

Permselective Membranes (Microfiltration)

Semipermeable membranes have been used to separate species collected in the environment in selected applications. Nafion is a fluoropolymer with a cation-exchange capability. It can be used to adsorb ions from solution or to scrub water from an air stream during sampling. The fluorocarbon, Teflon-like matrix gives Nafion the inert quality to remove humidity or add humidity to a sampling stream without altering the chemical nature of the sample.

Porous Teflon membranes (e.g., Zitex and Gortex) can be purchased in a variety of pore sizes to separate particles from gases and vapors. These materials often are used in particulate sampling devices, as protectors or limiters for passive sampling devices, and in electrochemical sensors to keep the electrolyte in but allow exposure to a gaseous analyte. Nonporous Teflon membranes are used in oxygen sensors to separate oxygen from a variety of potential interferents. Also, nonporous silicone membranes are used to separate relatively nonpolar organic compounds from water vapor and other polar species.

A new development, called solid-supported liquid membranes, has been used to remove and concentrate radioactive waste selectively from water streams. This same approach has been suggested as a method for cleaning breathing air in gas-mask applications. The basic principle consists of a bundle of porous and hollow fibers. The pores of the fibers are filled with a nonvolatile (or nonsoluble) liquid such as a high-molecular-weight alcohol. This liquid acts as a conduit to pass an analyte from an outside sample to a small volume inside a sampler, thus acting as a concentrating device.

Sequential Solvent Extraction

Sequential solvent extraction, also referred to as liquid-liquid partitioning, is used to separate complex mixtures of chemicals into smaller, more tractable groups. The approach is applied most commonly to mixtures of organic chemicals, such as the organic constituents of airborne particles or fly ash (Pellizzari et al., 1978; Chrisp and Fisher, 1980; Daisey et al., 1980). A set of solvents is chosen with different solvent properties (e.g., polarity or acidity), and the mixture is extracted, in turn, with each of the solvents. An additional analytical procedure (e.g., GC, high-pressure liquid chromatography (HPLC), or TLC) usually is brought to bear on the resulting extracts.

This approach is especially useful in the hands of an imaginative and knowledgeable analyst. Many solvents and solvent properties can be used in innumerable combinations to separate compounds with different chemical and physical properties. The purified extracts reduce the selectivity and specificity restraints on further analytic techniques. Consequently, solvent separations can greatly simplify subsequent analyses; in some cases, they are required. Furthermore, knowledge of the chemical classes present in each of the solvent extract fractions can be inferred from the chemical and physical properties of the solvent responsible for that fraction.

This approach has several drawbacks. It often requires a large amount of time and is difficult to automate. For each solvent used in the process, there is a separate extraction step. Each of these steps can be quite lengthly, especially if Soxhlet extraction apparatus are used. Typically, large solvent volumes (>50 mL) are required for each extraction, requiring time consuming solvent reduction steps prior to analysis. Solvent artifacts can also be a serious problem, and both the acquisition of high purity solvent and their subsequent disposal can be costly. During transfers and solvent reduction steps, material can be lost through volatilization or adsorption on the walls of glassware. Sequential solvent extraction does not yield clean cut separations of pollutants; spillover frequently occurs among the fractions. Finally, there is the potential for reaction between the extracting solvent and the pollutants of interest. Despite these disadvantages, sequential solvent extraction with new solvent combinations is a promising tool for separation and purification of complex mixtures.

Supercritical Fluid Extraction

Supercritical fluids can be used to desorb trapped airborne contaminants from various adsorbents. VOCs and semivolatile organic compounds

(SVOCs) are often concentrated before analysis by trapping onto some type of adsorbent, typically charcoal or Tenax. These compounds then are stripped from the adsorbent using either solvent or heat. However, solvent desorption tends to dilute trapped analytes, and thermal desorption can decompose thermally labile compounds. Supercritical fluids can be used effectively to desorb analytes from these adsorbents (Raymer et al., 1987; Wright et al., 1987; Hawthorne et al., 1989a,b). When CO_2 is used as the desorbing solvent, the compressed CO_2 can be depressurized on the head of a capillary GC column, where it deposits any analytes extracted from the adsorbent (Hawthorne and Miller, 1987). During depressurization, cooling also occurs, which further serves to retain even many volatile compounds on the head of the capillary column. Thus, the extraction and concentration of analytes can occur in a single step. This technique could be very useful in the analysis of passive samplers. If these devices are to be used for long-term exposure monitoring (>24 hours), then highly retentive adsorbents must be used (Mulik and Williams, 1986) to minimize any reversible losses from the sampler (Hourani and Underhill, 1988). Some common fluids have low critical temperatures (e.g., CO_2, 31.3°C, and supercritical fluid extraction (SFE) at mild temperature could be used as an alternative to thermal desorption for directly desorbing analytes from passive samplers into a GC column. This SFE-GC method avoids high thermal desorption temperatures that can cause thermal degradation of heat-sensitive compounds and generate sorbent-derived artifacts. SFE-GC can be configured to deposit all or a large portion of the analytes contained on the sorbent into the GC column (Hawthorne et al., 1989a,b). This method can dramatically increase method sensitivity. SFE also allows for the desorption of higher molecular weight (low volatility) compounds not amenable to thermal desorption. Since some fluids are also gases at ambient temperatures, off-line SFE allows for rapid concentration of the analytes by simple venting of the gaseous extraction solvent.

Another distinct feature of extractions using supercritical fluids is that the solvent strength is controlled by adjusting the pressure (density) of the fluid. Therefore, if the adsorbent is first desorbed with low-pressure CO_2, only the relatively nonpolar or lower molecular weight compounds are obtained. More polar and higher molecular weight compounds are then desorbed by increasing the pressure, adding a modifier to the fluid, or by changing to a different fluid (Hawthorne and Miller, 1987; King, 1989). Thus, the desorption process can also become a selective extraction process.

The use of supercritical fluids for extraction and chromatography deserves greater research attention in the assessment of airborne contaminants.

Liquid Chromatography for Sample Preparation

LC can be used strictly as a separation device for the fractionation of collected pollutants into some type of class groups before actual analysis. An example of this approach is the work of Lamparski and Nestrick (1989) during which stack gas effluents were analyzed for the presence of trace levels of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs). Samples were collected using a modification of EPA's Reference Method 5 sample collection train. The entire sample in the train was extracted with benzene, and the crude extract was subjected to classical liquid column chromatography (LC on silica gel and silica gel treated with various reagents and alumina). These simple LC steps remove many interfering classes of compounds including pesticides and PCBs. The extracts were then subjected to two HPLC separations, which further segregate the PCDDs and PCDFs into chlorine classes. The extracts were then fractionated on a silica HPLC column. The fractions were collected and further separated on a reverse-phase HPLC column and then analyzed for PCDDs and PCDFs by combined GC mass spectrometry (GC-MS), a highly selective and sensitive technique discussed in a subsequent section. This method of sample preparation is extremely thorough and shows the degree of sample preparation steps that may be necessary to analyze airborne contaminants. It also illustrates how simple LC and the more elaborate HPLC can be used for the preparation of samples for subsequent analysis.

Detection

In detection, an analyte typically is converted into some measurable signal that is indicative of the chemical identity or the amount of analyte that is present. Some detection devices might include some selectivity (not so much separation as discrimination), so overlap of detection and separation occurs. Most detectors can be used in a stand-alone mode, where an air sample is fed directly into a detector, and an analog signal is measured and related to a given concentration of analyte. This offers the advantage of being continuous but often at the expense of selectivity, particularly for nonspecific detectors, which respond to a broad range of compounds. Increases in selectivity can be achieved using more specific detectors, which discriminate against many compounds and only respond to a narrow range of compound classes or functional groups.

These same detectors can be used in combination with some type of chromatographic separation. The continuous nature of the analysis is lost, but the

specificity of the analysis increases. Selected detection devices are discussed in the following sections.

Chromatography Detection Devices

Nonspecific Detectors

Foremost among the nonspecific (or universal) detectors is the flame-ionization detector (FID) (Sevcik, 1976). This detector responds to any compound containing carbon-carbon or carbon-hydrogen bonds. It is sensitive to inorganic species, such as N, O, CO_2 or water, which makes it ideal to analyze trace-level organics in ambient air. It has excellent sensitivity and a dynamic range of 5–6 orders of magnitude. However, the near-universal detection capability of the FID can lead to interference problems, especially for complex matrices.

The photoionization detector (PID) is another very popular detector (Driscoll, 1977). PID ionizes molecules via the absorption of a photon. The energy of this photon must be greater than the ionization potential of the analyte. Various lamps can be used that generate photons with different energies, thus allowing some selectivity to be achieved, if desired. PID differs from FID in that FID combusts all of the eluant in the ionization process, while the PID leaves most of the molecules intact. PID is considered nondestructive and can be connected in series with other detectors. Although PID is not as universal as FID in its response to organic compounds (which depends on the particular lamp), its simple design makes it advantageous for field analyses. PID in combination with GC is particularly portable because it does not require special gases for its operation, as do many other detectors including the FID; PID can also use air as the mobile phase, greatly simplifying its operation.

Selective Ionization Detectors

Highly selective detectors include electron-capture detection (ECD) (Sevcik, 1976), which frequently is used for selective analysis of halogenated compounds. However, a wide variety of nonhalogenated compounds also give an ECD response; in particular, oxygen interferes with ECD operation and thus limits its usefulness for direct analysis of air samples (Simmonds et al., 1976).

The thermionic ionization detector (TID) is an adaptation of FID. TID has high selectivity for nitrogen or phosphorous containing compounds, but has little response to other organics (Farwell et al., 1981). An example of the

usefulness of this detector is for the selective detection of HCN or acrylonitrile in an air sample containing high quantities of other organics. Another TID application involves the derivatization of a nonnitrogen-containing analyte with a nitrogen-containing agent. The nitrogen will respond to TID, but any interfering compounds that are not derivatized will not respond to TID unless they originally contained nitrogen. This provides enhanced sensitivity and selectivity for the desired analyte. For example, acrolein can be collected using a tube containing a sorbent coated with 2-(hydroxymethyl)piperidine. The acrolein reacts to form oxazolidine, which is desorbed from the tube and analyzed by GC-TID (Eller, 1984b).

Flame photometric detectors (FPDs) operate by combusting a sample and then monitoring for a specific wavelength of light that is emitted (Sevcik, 1976). FPD can be operated in a mode in which it is sensitive for phosphorous-containing compounds, but is most widely used in air- monitoring studies to detect sulfur-containing compounds. Various other detectors based on chemiluminescence techniques have been used with GC for selective detection of nitrosamines and other nitrogen(Britten, 1989) and sulfur-containing (Benner and Stedman, 1989) compounds.

Thermal Conduction Devices

The thermal conductivity detector (TCD) is another universal detector (Sevcik, 1976). This detector responds to all compounds with thermal conductivity in the gas phase different from the gas (usually the mobile phase in GC) used to bring samples into the detector. It is extremely useful to analyze ambient gases that do not give a response to FID. However, because TCD responds to everything, background contamination is a problem that limits TCD's usefulness in trace analyses.

Organoleptic Methods

An organoleptic or odor-appraisal method involves some type of separation of volatile compounds (typically by GC) followed by odor appraisal of the eluting compounds by humans (McGorrin et al., 1987). This type of analysis can be very important: in that odor problems are a typical complaint in air contaminant exposures. The previously mentioned detectors determine the nature and amount of a wide variety of compounds, but they cannot point out which compounds contribute to odors. This is particularly true if certain compounds have a low odor threshold and can be masked by the presence of other compounds.

Mass Spectrometry

MS is one of the most widely used detection methods for organic compounds. The mass spectrometer is a tunable detector that can be set to monitor species characteristics of any analyte that can pass through a gas chromatograph. (MS can also be used to detect compounds that cannot pass through a gas chromatograph.) The species that are monitored are molecular ions or molecular ion fragments that can be produced by a variety of techniques, including electron impact ionization, positive and negative chemical ionization, and atmospheric pressure ionization (Watson, 1985). Each technique has particular advantages and disadvantages that depend on the analyte in question. The particular ion being monitored is selected by a mass-selection process. This selection can be carried out in a nondiscriminating manner (low resolution), in which ions with unit mass difference are just resolved (e.g., ions with mass 28 are just resolved from ions with mass 29) or with high discrimination (high-resolution) in which ions differing by just millimass units can be resolved (i.e., an ion with mass 28.0000 is resolved from an ion with mass 28.0028). The higher the resolving power, the higher the cost and sophistication of the instrumentation.

The high degree of sensitivity of this technique comes from two sources. First, because ions are formed and mass selected, ion-detection techniques can be used that are inherently very sensitive. Second, the high discriminating power of MS (i.e., rejecting everything but the mass of interest) removes a great deal of the interfering background signals and thus has good signal-to-noise ratio and sensitivity. Thus, the mass spectrometer can be used as a stand alone detection device for air-monitoring. In this regard it has the distinct advantage of giving instantaneous results. However, in many cases multiple compounds will give similar responses which limit the spectrometer's stand alone capability. Combining the power of MS with the separation capability of a chromatograph, especially GC, helps to eliminate many of these interferences but with the loss of instantaneous results.

GC-MS is particularly well suited to the analyses of airborne contaminants, but is limited by requiring that the analytes be thermally stable and volatile under GC conditions. This restricts the usefulness of GC-MS when analyzing metals, metal salts, high molecular-weight compounds and compounds susceptible to thermal decomposition. Since most airborne pollutants are thermally stable and volatile under GC conditions, GC-MS is a useful analytical technique. Organic compounds sorbed onto particles can be analyzed, provided they can be desorbed (using either heat or solvent) and passed through a gas chromatograph intact (Weschler and Fong, 1986). In some instances, a reactive molecule can be stabilized by derivatizing it and making it susceptible to

GC-MS analysis. GC-MS can also be useful in analyzing biological marker compounds and metabolites to determine human exposure to airborne contaminants (see Chapter 4). Again, the criterion that the compounds be thermally stable in the gas phase must be met, and for many compounds (particularly metabolites of the desired analyte), derivatization may be necessary.

A particularly useful feature of GC-MS is the ability to use stable isotope-labeled isomers as surrogates in the analyses. Such surrogates are identical to the analyte except that they contain one or more isotopically labeled atoms. For example, hexadeuterobenzene (fully deuterated benzene) can be used as a surrogate for benzene. The mass spectrometer is capable of distinguishing these surrogates from the original analyte, because the surrogates differ in mass. The surrogates are particularly useful for accurate quantitation (Lewin et al., 1987). If an analyte is being trapped on a sorbent such as Tenax, then the surrogate can be placed on the adsorbent before actively pulling air through the adsorbent (i.e., a field spike). Any losses that occur in the analyte breaking through the adsorbent or losses that occur in incomplete desorption of the analytes from the adsorbent will be matched by the surrogate. In this fashion, an excellent degree of quality control can be achieved with virtually every sample that is taken. The usefulness of surrogates in the analysis of volatile compounds has been recognized by EPA in the use of surrogates in Method 1624, which is used in the analysis of water samples for purgeable volatiles.

MS also offers another unique feature in environmental analyses through its ability to discriminate various isotopes of an element. In many cases, particular isotopic ratios vary slightly, depending on the original source of the element or the environmental processes it has undergone. An example of this approach is the study of lead in California children, where the variability in the lead isotopic ratios from various products were used as a discriminator of the children's original lead source (Yaffe et al., 1983). A similar discrimination can be made in the various sources of sulfur oxide based on the oxygen isotope ratios (van Everdingen and Krouse, 1988). Thus, MS can be invaluable not only in determining the existence of exposure to an airborne contaminant but also in providing information as to its source.

GC-MS has several disadvantages. First, most units are not very portable, and, in most cases, samples must be brought to the instrument rather than taking it to the sampling location. Newer, more compact units are being made and can readily be transported in specially built vans, but portability into indoor facilities often is limited. A GC-MS system was sent on the space craft to Mars. Designs are under way to have a mass spectrometer (and possibly a GC-MS system) compact enough that a soldier could carry it in a backpack to serve as a monitoring device for chemical warfare agents. Such a device

could be ideal for personal monitoring studies, providing the unit was lightweight and simple to use.

Another disadvantage of MS in general and GC-MS in particular is that the systems are expensive. Samples from multiple sites usually are brought to an instrument rather than having units at multiple locations. Most GC-MS units are readily automated, which makes them capable of analyzing around the clock, which in turn allows many samples to be analyzed from numerous sites. Such automation includes the analysis of solvent desorbed traps, thermally desorbed traps, and most recently, the automated analysis of Summa syringes to determine highly volatile compounds that do not lend themselves to trapping. Summa syringes are samplers made of highly passivated stainless steel, which renders them inert to many pollutants (Krasnec, 1986). A sampling system with those syringes can be programmed through a microprocessor to collect samples at designated times and to dispel the collected samples into a GC-MS unit for analysis. Automated data reduction programs are also available, thus maximizing the output of the instrumentation and minimizing the cost per sample.

The future for GC-MS lies in the simplification of the mass spectrometer so that it is easy to operate and is possibly controlled by a microprocessor-based "expert system." Future units should be compact, inexpensive, and easy to use. Many of these features are incorporated into a new type of mass spectrometer, the ion trap mass spectrometer. This new and innovative device might resolve many of the disadvantages of present MS units. The ion trap detector is discussed in the next section.) It is also worth noting that simple "benchtop" GC-MS systems are available for less than $55,000.

Mass Spectrometry-Mass Spectrometry

The technique of MS-MS shares many disadvantages of GC-MS. It is very expensive and not very portable. It also shares many of the advantages of GC-MS, such as good selectivity and sensitivity and the ability to use surrogates. Good selectivity comes from the actual MS-MS process. A compound enters the mass spectrometer without passing through a gas chromatograph. The sample is then ionized, and particular masses selected that are characteristic of the analytes of interest. The selected ions undergo a decomposition process in which they are fragmented, and smaller ions are formed from the original ions. These decomposition ions are then analyzed by a second mass spectrometer, and fragment ions characteristic of the parent analyte are monitored. A two-step separation process is achieved, much like GC-MS, in which the first separation occurs on the gas chromatograph while the second occurs

with the mass spectrometer. In MS-MS, the process occurs in two successive mass spectrometers. The advantage of the MS-MS process is that the separation processes occur at very high speeds (milliseconds or less). Thus, continuous monitoring is possible while retaining a high degree of specificity and sensitivity. This is not possible with a GC-MS system, because the continuous nature of the analyses are limited by the time required by GC for the separation. However, it must be emphasized that MS-MS often is incapable of discriminating between simple compounds such as *o*-xylene and ethylbenzene, while such a separation by GC is straightforward (Sushan et al., 1987).

The GC process and the MS-MS analysis can also be coupled to give GC-MS-MS. This approach combines the advantages of both techniques, particularly where a high degree of resolving power is necessary to discriminate the desired analyte from other interfering compounds. Likewise, MS-MS analyses have also been combined with HPLC and SFC. A particularly useful feature of these combinations is their inherent flexibility. The separation processes can be juggled between the chromatograph and the MS-MS system to minimize both the analysis times and any interferents in the analyses. The greatest amount of experience with MS-MS for atmospheric analyses comes from the Sciex TAGA 6000E (Sushan et al., 1987). This unit is made transportable by placing it in a van that is usually brought near a sampling site (e.g., a home). The sample (e.g., air from the interior of the home) is brought to the instrument via a long transfer line. This unit requires experienced operators to ensure the quality of the data.

The ion trap detector (ITD) is a new type of MS system. The ITD is small and of simple construction and requires only a modest vacuum (Louris et al., 1987; Busch et al., 1988; SCIEX, 1989). It contains a trapping cell consisting of two hyperbolic end electrodes and a single hyperbolic central electrode. The ionization and mass selection occur in this cell. The ITD can selectively trap and hold a specific ion, while rejecting other nondesired ions. In other words, the ITD serves as a trapping device collecting a specific ion (compound), while selectively rejecting others. This trapping process is limited only by space-charging occurring in the cell. The ITD can be operated in the MS-MS mode (Stafford et al., 1984). In this mode, a single mass (m/z, mass/charge) ion is selected and all others rejected from the ITD. A collision gas is then introduced, which causes the fragmentation of the selected ion. This fragmentation spectrum can then be examined to discern the structure of the original ion as in other MS-MS procedures. If desired, this process can be repeated on one of the fragment ions to allow MS-MS-MS procedures to be carried out as many times as necessary. The ITD has also been interfaced to an atmospheric-pressure ion source in similar fashion to that used on the TAGA MS-MS system (Asano et al., 1988). The successful interfacing of this

particular source should make the ITD a valuable air sampling device deserving greater research attention in the future.

Ion Mobility Spectrometer

The ion mobility spectrometer (IMS) first was known as a plasma chromatograph (Karasek, 1974). It operates on the principle of atmospheric-pressure ionization (the same principle as used on the TAGA MS-MS system) of any air contaminants, and the ions that are formed are analyzed by their drift time through a drift gas at atmospheric pressure. The technique was plagued by problems of ion clusters that varied with atmospheric conditions. A heated membrane device has been included that passes to the ion source only organics that are permeable to the membrane (Carrico, 1986). This has helped to minimize the clustering problem and has eliminated interferences from water, ammonia, and nitrous oxides. The IMS has the advantage of operating at atmospheric pressure, which eases the operational problems associated with mass spectrometers, which normally operate at reduced pressures. The IMS has shown sensitivities of less than 1 ppb and good response times (0.1 to 10 seconds), which would make it ideal for continuous analysis. However, it also has the disadvantage that the range of compounds that it can monitor is limited by the necessity of the membrane inlet.

Electrochemical Detectors

Electrochemical detectors can be divided into three general types: potentiometric, amperometric, and conductimetric. Studies of human exposure to air pollutants have used electrochemical detectors as direct personal, microenvironmental, and area monitors. Examples include the amperometric detectors for NO_2 that were used in homes (Leslie et al., 1990) and the CO personal monitor carried by people (Akland et al., 1985). Potentiometric detectors such as pH and ion selective electrodes typically are used in the laboratory in supportive analytical procedures but also are available in portable kits for field use.

Potentiometry

Simple pH electrodes have been used widely in the laboratory since the introduction of the pH meter by Dr. Arnold Beckman in 1935. The typical

potentiometric detector for pH or selected ions operates by measuring a potential or voltage developed at the sample/solution interface. This interfacial potential is ideally measured under conditions of zero current flow (infinite impedance) so that the potential reflects the Nernstian or thermodynamic potential of a specific chemical interaction at a membrane/solution interface. In this manner, the potential of the device can be made to reflect the concentration of the species of interest. In addition to pH, potentiometric probes have been developed for many different ions of interest (such as Na^+, K^+, Ca^{++}). The attachment of enzymes and biological substrates to the sensing membrane has allowed potentiometry to be used to measure biological materials (Rechnitz, 1981; Arnold, 1983). Miniature, inexpensive, microfabricated ion-sensitive devices have also been introduced (Lauks and Zemel, 1979), and combination of the field effect transistor (FET) and a micropotentiometric-sensor has facilitated the detection of gases and vapors in different media (Janata and Bezegh, 1988).

The most common, oldest, and best-understood ion-selective electrode is the glass pH electrode. The glass membrane can exchange protons with the solution with which it is in contact. On one side of the membrane is a solution with fixed proton activity (constant $[H^+]$ acid solution), and on the other side is the measurement solution. Each solution exchanges H^+ with the glass to an extent determined by the chemical equilibrium. If the solutions are of different concentrations, a potential will be developed, because the extent of proton exchange is different on each side of the membrane. This potential is detected by having a reference electrode inside the membrane and a second electrode in the sample solution. The outside electrode must not be sensitive to changing $[H^+]$ so that only the membrane potential is observed. Selectivity is achieved because certain glasses will exchange only H^+ and not other ions. Different glasses and materials that exchange different ions are substituted for the glass membrane to generate ion-selective electrodes and electrodes sensitive to a variety of analytes (Myerhoff et al., 1989).

Although potentiometric probes most frequently are used to determine various ionic/reactive analytes in solutions, the Sevringshaus electrode for gaseous CO_2 is an example of the adaptation of the pH electrode for measurement of gases. The outside solution of the pH electrode is trapped by a gas-permeable membrane and held in place around the pH electrode. This external solution contains a buffer whose pH is altered by absorption of CO_2. Thus, the more CO_2, the greater the change in pH and the larger the signal from the pH electrode. The Sevringshaus electrode has been used for many years in the measurement of CO_2 levels in blood. Similar potentiometric gas sensors exist that can be made to respond to ammonia and other gases in the air with reversibility. Selectivity generally is not great in such detectors, because

anything that affects the pH of the solution that surrounds the pH sensor will generate a response.

Solid electrolytes have been used in high-temperature, potentiometric sensors for O_2, SO_2, and NO_x, and some other species. Such oxygen sensors are used in stack gas monitoring and automobiles. The sensor response depends upon a specific reaction equilibrium and, therefore, can be extremely sensitive and selective. Recent work has contributed to the understanding of these devices and their microfabrication (Nicoloso et al., 1988).

Conductimetry

Conductimetry is used to detect gross ionic pollution in water (e.g., the YSI conductivity meter) and as a detector in chromatography (e.g., the Hall electrolytic conductivity detector—HECD) (Hall, 1974). This detector operates on the principle of combusting the halogenated compound to form an HCI gas, which is then taken into a deionized, aqueous solution. The HCI is a strong acid and dramatically increases the conductivity of the solution, which is detected by the solution passing through a conductance cell. The HECD also can be operated in a configuration in which it is selective for nitrogen-containing compounds. It has the advantage of not being sensitive to oxygen, which makes it a useful detector for direct air analysis. Such devices could be used to detect and analyze for acidic and basic (or strongly ionic) materials in the field or laboratory. Their use in exposure assessment is not widespread.

Amperometry

Amperometric devices have been used in exposure assessment studies as personal monitors and area monitors (Hartwell et al., 1984; Leslie et al., 1990). The typical CO amperometric sensor operates by generating a current proportional to the amount of CO reacted (amperometrically) in the sensor. In such devices, the gas travels in a path that contacts a gas- porous membrane. On the inside of the porous membrane, the gas contacts an electrode and an electrolyte (the electrolyte cannot go through the membrane). The analyte dissolves in the electrolyte, migrates to the electrode surface, and reacts electrochemically, producing or using electrons. The electrons can be counted in an external electric circuit and the result displayed. The more analyte present, the more current produced by the amperometric sensor; the current is proportional to the concentration.

Such amperometric devices have been built in portable and fixed-site monitors

for O_2, CO, H_2S, NO, NO_2, hydrazines, HCN, NH_3, formaldehyde, H_2, EtOH, and many other compounds (Stetter et al., 1984; Janata and Bezegh, 1988). The sensors have even been modified to be sensitive to hydrocarbons (Stetter et al., 1984), and the approach could be applied for many electroinactive species. The galvanic (and electrolytic) sensors for oxygen measurement in the ambient air are well known in industrial hygiene and safety. The medical application began with the Clark electrode (Clark et al., 1953) for O_2, and modern microprobes have been built for measurement of the O_2 partial pressure in a single living human cell.

Many other amperometric techniques (e.g., anodic stripping voltammetry for metals and differential pulse polarography) are used in the laboratory for a variety of analytes but have not been applied in the field or used in exposure assessment to a significant degree.

Electrochemical devices have the advantages of being extremely low-power and small size and hence, portable and reasonably inexpensive. These characteristics make electrochemical approaches ideal for field use and direct measurement of human exposure to airborne pollutants. The challenge for electrochemical devices is the attainment of adequate analytical performance in a practical field situation; combined sensitivity, selectivity, stability, lifetime, and ruggedness are needed. This combination has been demonstrated for several applications, including pH and CO, and could be used for many more applications, such as NO_2 in indoor air (Stetter et al., 1979; Chang and Stetter, 1990). The selectivity of electrochemical detectors can be enhanced by using sensor arrays, selective filters, and GC techniques. The electrochemical gas sensor has been used successfully as a GC detector (Stetter et al., 1976; 1977; Blurton and Stetter, 1978) and can enhance portability, because no special carrier flame gases are required. Recent advances in microfabrication of structures and materials that can be used to construct amperometric (Buttner et al., 1990) and potentiometric detectors and the required circuitry (Turner et al., 1987) offer promise for lower cost, uniform, and exceptionally portable detectors. The combination of sensor arrays and chemometrics promises to increase the information content of existing systems (Zaromb and Stetter, 1984; Stetter et al., 1986). Advanced electroanalytical methods that are effective in the laboratory, such as differential techniques (Borman, 1982), could be applied to enhance the sensitivity, selectivity, and response time of electrochemical field monitors.

Spectroscopic Detectors

Spectrophotometric methods of chemical analysis are among the oldest

techniques that are used routinely to analyze airborne pollutants. A review of these procedures is presented in the third edition of the manual of methods adopted by the Intersociety Committee for a Manual on Methods of Air Sampling and Analysis (Lodge, 1989). What follows are some recent advances that could extend the capabilities of selected spectrophotometric methods.

Charge-coupled device (CCD) array detectors are an advance that promises to improve significantly the limits of detection in selected analytical areas (*Chemical & Engineering News*, 1989). CCDs are arrays of p-doped silicon that are extremely sensitive to light falling on their surfaces. They respond over a wide spectral range (a quantum efficiency of at least 10% between 200 nm and 1000 nm), have a large dynamic range (10^5 to 10^6), and are more rugged than conventional photomultiplier tubes. Furthermore, they are well suited to multichannel detection applications. In numerous analytical instruments (e.g., fluorometers, Raman spectrometers, emission spectrographs, and detectors for HPLC), CCDs are likely to replace photomultiplier tubes.

The rectangular shape of currently available CCDs is a drawback in certain applications, because many spectrographs have astigmatic distortion. However, optics can and have been configured to use the CCD shape. In certain applications, the two-dimensional nature of the CCD has been an advantage. An example is TLC, where the plates are essentially two-dimensional. Entire TLC plates can be imaged onto a CCD detector, and the required response integration times can be less than a minute.

CCDs are expensive (starting at approximately $30,000 for a functional system). However, as their applications expand and their production increases, the price is likely to drop significantly.

Diode-array detectors use a one- or two-dimensional array of photodiodes to detect ultraviolet or visible radiation. Scanning time is very brief (approximately 5 milliseconds) with such a device. Diode-array detectors have been used primarily to identify eluants of HPLC, although recently they have been applied to GC analyses (Kube et al., 1985).

A number of simple and inexpensive luminescence techniques have been developed recently and applied to the analyses of airborne pollutants. These include synchronous luminescence and room-temperature phosphorescence (RTP) to estimate the amount of polynuclear aromatic species in air particulate extracts (Vo-Dinh et al., 1984a). RTP is part of a detection scheme that has been used in the development of a passive sampler to monitor personnel exposure to vapors of polyaromatic pollutants (Vo-Dinh, 1985). The heavy-atom salts used as an adsorbent also serve as a direct sample medium (inducer) for RTP detection.

Surface-enhanced Raman spectrometry (SERS) is a technique with great sensitivity for compounds with a large Raman cross-section. The analyte also

must couple effectively with the substrate (typically silver, gold, or copper) used to achieve the effect. Within the past 5 years, SERS has been applied to the analyses of selected trace organic compounds (Vo-Dinh et al., 1984b) and chlorinated pesticides (Alak and Vo-Dinh, 1988). Unfortunately, results obtained with SERS are difficult to quantify. This is due primarily to two factors: variability in electrostatic field effects and variability in chemical site effects (Moskovits, 1985).

Infrared Detection

The use of infrared (IR) detection with GC always has been limited severely by low IR absorption coefficients, which results in poor sensitivity. Most IR techniques used to monitor for ambient levels of organics make up for this poor sensitivity by having long path length cells (typically 1 to 20 m). These types of cells are incompatible with GC detection, because the large volume of these cells produces such a large dead volume that all analyte resolution achieved during the chromatography is lost during detection. One IR technique that has gained popularity in volatile organic analysis involves matrix isolation. The sample eluting from the GC column is frozen in an argon matrix onto a cryogenically cooled disc which revolves while the various analytes are eluting. The eluted compounds are frozen in place so that they can be subsequently analyzed by a variety of techniques, including Fourier transform IR (Bourne et al., 1984). These frozen chromatograms can be stored for several weeks without loss in resolution. Since the sample molecules are frozen in place, extended signal averaging of the IR spectra is permitted, resulting in excellent sensitivity. Another advantage of the matrix isolation is that the spectra are very sharp, resulting from the elimination of band broadening due to molecular rotations and intermolecular interactions.

GC-matrix-isolation/FTIR is being used for the qualitative analysis of airborne contaminants (Childers et al., 1987). The technique complements qualitative GC-MS analyses by providing additional structural information about matrix-isolated compounds. The matrix-isolation interface is expensive, which limits its usefulness in ambient air analysis to specialized qualitative analyses. The actual collection of spectra can be very time consuming, and therefore, the technique should not be considered when massive numbers of samples are to be analyzed or when the real goal of the analysis is to quantify the various analytes.

Microsensors

For the purpose of this discussion, "microsensors" are defined as tiny detectors typically manufactured by microfabrication processes; included in this definition are small detectors created using wire electrodes and the like.

The major types of microsensors are summarized in Table 3.4. Most of these kinds of sensors have been fabricated using microelectronic process technology. The commercial potential of these devices depends upon their characteristics and their state of development.

A passive microsensor often will operate in a diffusion-limited mode, because the analyte of interest will be at a very low partial pressure (few ppb). Even at 10^{-6} torr (about 1 ppbv), a clean surface will be contaminated in about a second. Thus, the response time of a microsensor might be limited at very low concentrations. However, for human exposure monitoring, a response time of a few seconds almost always will be acceptable. The response magnitude will be limited by the size of the effect produced in the microsensor. The effect can be a chemical or physical change, and this change can be monitored by spectroscopic, thermal, electrochemical, dielectric, electronic, or other variable properties of the microsensor.

Chemiresistors are simple devices and have been studied and used for many years. The chemiresistor interacts with a pollutant and changes conductivity (or more correctly, impedance). The amount of change of resistance is a measure of the gas/vapor analyte concentration. These devices typically are not very selective but can be very inexpensive and are used around the world (e.g., Figaro detectors) for detection of hydrocarbons, combustible gases, CO, and alcohol. When used in an array with the application of chemometrics, selectivity can be increased. The hot wire/catalytic bead detector uses a platinum resistance thermometer to detect explosive levels of combustible gases. It can be a very portable device but, in its present form, is not sufficiently sensitive for ambient measurements of hydrocarbons.

The FET (field effect transistor) and other devices, such as capacitors and Shottky diodes, have been used as the basis for chemical detection (NRC, 1984). A very sensitive and selective H_2 sensor can be made from an FET with a Pd gate, and preparation with an ultra-thin film gate can lead to reactivity for other gaseous species. Capacitive sensors for humidity are also possible using a device called the charge flow transistor.

The SAW (surface acoustic wave elements) (Wohltjen, 1984), lambda wave, and the piezoelectric balance are all similar devices. The SAW is smaller and more sensitive than a simple piezoelectric balance, and the lambda wave device can be used at low frequencies. In a typical gas-sensitive device, the surface of the device is coated with a sorbent layer that reacts with the analyte

TABLE 3.4 Microsensors Potentially Applicable to Airborne Contaminants

Biosensors
Electrochemical sensors
Potentiometry
Amperometric devices
Contact potential sensitive elements
Thermal sensors
Thermistor and resistance thermometer elements
Thermoelectric/bolometric sensors
Semiconductor-based elements
Piezoelectric oscillator thermal sensitivity
Pyroelectric sensors
Black body measurements
Stress and pressure sensors
Photoacoustic effect
Mass sensitive elements
Bulk piezoelectric elements (thickness monitors)
Surface acoustic wave elements (SAW)
Plate mode oscillators
Interface impedance
Elastic constant sensitive fiber optic elements
Electromagnetic properties sensors: passive
Solid state conductivity measurements (chemiresistance)
Dielectrometry
Dielectric property measurements
Absorptivity
Index of refraction
Phase shift and interface impedance (e.g., ellipsometry)
Spectral "fingerprint"
Surface-enhanced Raman spectrometry
Electromagnetic properties sensors: active
Nonlinear behavior, including frequency doubling
Fluorescence

Source: Developed from a representation made by J. Zemel at the "Workshop on Advances in Assessing Human Exposure to Airborne Pollutants," Yale University, October 19–20, 1988.

gas of interest. Weight changes in the adsorbent layer are detected by the piezoelectric substrate. Sensitivity depends upon the weight of the film. Thicker films and strongly interacting compounds are most readily detected; however, thicker layers have slower response times. SAW devices and piezoelectric balance sensors for gas detection are commercially available for some analytes, and detection is typically in the ppm range, but ppb detection can be achieved for selected analytes.

Fiber optic sensors have some application in light-pipe devices for PNAs and for specific analytes, such as O_2 and ammonia in air.

In addition to chemical sensing, advances in microengineering include mechanical devices such as pumps, balances, gears, wheels, springs, valves, motors, and similar mechanical structures that are micron-dimension. The application to small field samplers and exposure assessment in the future seems appropriate, but these new technologies have not been applied toward use in exposure measurements. The possibility for microsampling and microanalytical devices exists, and their potential application to exposure assessment could yield some exciting results. Microdetectors, including MS, PID, FID, and TCD, could be commercially available.

Several microsensors have been reported (NRC, 1984). Some devices are available; others are in various stages of development and commercialization. The physical microsensors, e.g., for pressure, temperature, and flow, are better developed than the chemical sensors. Microsensors for detection of certain physical properties are readily available. However, chemical microsensors need further development to make a substantial impact on applied science. For example, the microthermal conductivity detector for GC applications has been developed, but no comparable micro-FID or micro-FPD exists. Also, microelectrochemical sensors have been reported but are just now being introduced commercially.

Electron Microscopy

Electron microscopy has been an important tool in the examination of submicron features since it became commercially available in the 1960s. However, in the analysis of ambient particle samples, it could only serve as a qualitative or, at best, semiquantitative tool because of the time necessary to find particles manually, focus the microscope, and obtain image and x-ray spectral data for a given particle. During the past decade, an alternative approach that has shown the ability to provide quantitative microscopic examination of particle samples for source identification and apportionment is computer-controlled scanning electron microscopy (CCSEM). The CCSEM system has

been described in detail by Casuccio et al. (1983) and Hopke (1985). The system automatically steps across a field of particles using the back scattered electron intensity to determine when it has struck a particle. When a particle is detected, the control system decreases the step size and determines the geometric center of the particle by constructing diagonals across the particle. The diagonals are then reconstructed to converge at the particle centroid. The electron beam is focused at the centroid, and the fluoresced x-ray spectrum is obtained with a windowless Si(Li) detector that permits detection of light element x-rays. With the high vacuum in an electron microscope and new ultrathin vacuum windowed detectors, it is possible to observe the x-rays from carbon to uranium. In this manner, CCSEM can perform elemental analysis from carbon through uranium on extremely small quantities of matter. However, the cross-sections for vacancy production are low for electrons, and the total excited volume is small. It is generally only possible to observe elements present at a few tenths of atom percent levels or higher. Trace elements generally are not observable. It must be noted also that the presence of a high vacuum in the microscope causes particles formed of moderate to high vapor pressure materials, including NH_4NO_3, to evaporate, and thus be unobservable (Leong et al., 1983).

From the pattern of observed x-rays, a density can be assigned. From the physical size and density, an aerodynamic diameter can be calculated. Thus, the CCSEM provides size, shape, and elemental composition data for each particle. Because of the low-fluorescence yields for the light elements, the x-ray spectra typically are accumulated for 15 seconds each. The use of CCSEM can greatly increase the information available on the physical and chemical characteristics of ambient or collected source-emitted particles.

A recent improvement in the computer control of the microscope focusing now permits individual particle images to be captured at 256 by 256 pixels per image in 256 gray levels to accompany the elemental composition data. This secondary electron image provides a three-dimensional image showing the particle morphology and surface texture. Thus, information on the size, shape, and composition are directly available from the microscopic examination.

These properties then can be used to group the particles into different classes (Kim and Hopke, 1988a). The mass fractions associated with each of these classes become the variables on which the source apportionment will be made. A particle-class balance assumes a linearly additive sum of class-mass fractions times a fractional contribution of aerosol mass by the particulate sources analogous to the chemical mass-balance used for bulk sample composition data. The ability to assign particles unequivocally to well-defined particle classes will provide a better set of variables for the apportionment

study, because these better-defined classes will have more specificity, and thus less noise in the mass-balance-fitting process (Kim and Hopke, 1988b).

The image data have not been fully exploited in receptor modeling because of the lack of quantitative methods to interpret them in an automated process. Hopke et al. (1988) suggested the use of fractal dimensions calculated from these single particle images as an approach to characterize the particle texture. Their preliminary results were encouraging, but clearly showed the need for further study.

Instrumental Neutron Activation Analysis (INAA)

The basic concept of instrumental neutron activation analysis (INAA) is that a small fraction of the stable nuclei present in a sample becomes radioactive when bombarded with neutrons in a reactor. Neutrons can penetrate into the nucleus because of the absence of any repulsive forces; capture probabilities are relatively large. Thus, for most elements, stable nuclei can be corrected to ones that are radioactive in a reproducible manner.

Following many of the subsequent beta-decay processes that occur in the induced radioactivity, one or more high-energy photons or gamma rays are emitted. A high-resolution semiconductor detector interacts with a gamma ray and yields an electronic pulse, the maximum voltage of the pulse being proportional to the gamma-ray energy. This pulse is amplified, shaped, and then sorted by a pulse-height analyzer so that gamma rays of different energies result in counts in different locations in a computer memory. The energy of a gamma ray is unique to a particular isotope of a specific element so that a qualitative analysis can be made by observing which peaks are found in the spectrum of gamma-ray energies emitted by the activated samples. A quantitative analysis can be made by relating the number of gamma rays emitted by the sample relative to a standard containing a known amount of that element. The standard is irradiated either simultaneously with the sample or with flux monitors (typically thin wires containing elements that are easily activated to gamma emitting radionuclides) that are used to measure the neutron flux to which the sample and the standard have been exposed. The gamma-ray spectra from a series of samples and standards are recorded. Appropriate computer codes can then reduce the gamma-ray counting data to elemental concentrations.

Samples can include biological materials (plants, proteins, enzymes, insect blood, human blood, and hair), geological materials (soils and ores), and environmental samples (water, airborne particles, street dust, and fly ash). The analysis does not require extensive sample preparation and chemical manipulations.

If the sample can be packaged in a container that permits irradiation in the reactor and subsequent gamma-ray counting, it can be analyzed by INAA. Although there is some low-level residual radioactivity associated with the samples, the technique is relatively nondestructive of the sample. Neutron activation analysis can provide information on as many as 40 elements with sensitivities ranging from picograms to micrograms of analyte element. There are elements, such as lead, that do not produce gamma-ray emitting products. These elements cannot be analyzed by INAA. Neutron activation is a well-established method that is now widely used to characterize environmental trace elements (De Soete et al., 1972).

X-ray fluorescence (XRF) is another common multielement method for aerosol samples. A good discussion of XRF applied to the analyses of airborne particles is presented in Malissa and Robinson (1978). The resolution of XRF is such that particles <100 μm diameter are effectively analyzed as if they were homogeneous.

Radon and Radon Progeny Measurements

Radon is a naturally occurring gaseous radioactive element that is found ubiquitously throughout the environment and is typically found in higher concentrations in indoor atmospheres than in outdoor air. It decays to a series of four short-lived decay products that can be deposited in the human respiratory tract either directly or after attaching to pre-existing ambient particles. EPA reported in a September 1988 press conference that the decay of these radioactive progeny can induce lung cancers and might be responsible for 20,000 lung cancer deaths per year in the United States. Measurements can be made of radon and decay products, and methods for each of these measurements are presented.

Radon

Radon can be measured directly at environmental levels using the ability of the emitted alpha particle to excite a ZnS(Ag) scintillator to produce measurable emitted light. Hemispherical (Lucas, 1957) and simple right-circular cylindrical (George et al., 1976) detector cells with optically clear, flat windows, and interior walls coated with ZnS(Ag) have been used. For simple grab measurements, the cell is evacuated. A valve into the chamber is opened, and the chamber is filled with ambient air. The cell is then placed on a photomultiplier tube, and the count rate of light pulses is measured.

With proper calibration, this count rate can be related to the ambient radon concentration. However, the concentration of radon in a building is highly variable. Thus, grab samples of radon rarely reflect the long-term, average indoor concentration.

An alternative approach is an active system to pull air through the scintillation chamber using inlet and outlet connectors. The counts in a given time (e.g., 15 minutes) can be converted to an approximate radon concentration. Because of the accumulation of decay products in the chamber, the actual radon concentration is related to the activity counted through complex calculational methods. As in all active systems, pump failure is possible and careful flow control is needed. Therefore, this system is not convenient for long-term monitoring.

Two methods are available to obtain an integrated measure of radon concentration. For short intervals (2–7 days), canisters containing activated carbon can be set in a room. The radon is adsorbed on the carbon and accumulates over time. After the sampling period is over, the canister is sealed, and the decay products build up in the container. Because equal activities of the shorter-lived decay products will develop after about 4 hours, a measurement of the emitted gamma radiations from the progeny can be used to determine the radon concentrations. However, the carbon canisters, dependent on diffusion for eventual contact between the radon and the sorbent, are useful only for a limited period and can have difficulties because of water-vapor adsorption reducing the amount of adsorbed radon.

A better, long-term, integrated measurement can be made using a track-etch detector. In these detectors, a small piece of a special type of plastic is placed in a small plastic cup and sealed with a moisture-proof plastic film. The radon can diffuse through the plastic film. Its decay and those of its decay products will cause the plastic detector to be bombarded with alpha particles. The alpha particles produce a track of radiation damage in the plastic that can be more easily dissolved than the bulk material. Thus, when the plastic detector is etched in a mild alkaline solution, microscopic holes can be seen where the number of holes per unit area can be related to the radon concentration. These detectors can be used for several weeks to as long as one year and thereby provide more accurate annual average values for the radon exposure.

A recent development is the use of an electret for passive radon measurements (Kotrappa et al., 1988). The concept is similar to the track-etch detector in that the detector is placed in a cup so that the radon can enter it. However, the measure of radon exposure is the decrease in surface electric charge on an electret made of Teflon FEP. Such a system has a simple read-out device that only has to measure the residual surface charge on the electret

and provides a useful alternative measurement method for periods of several weeks to several months.

Radon-Decay Products

The measurement of the radon-decay products is difficult, because the concentration and size distribution must be determined for the decay products. The decay product behavior is quite complex because of the ability to attach to airborne particles, as well as to indoor surfaces such as walls, ceilings, and furnishings. The particle size determines the ability of the radioactivity to be deposited in the room and in the respiratory system. The respiratory deposition provides the dose to the critical tissues; the sizes of most concern are those less than 10 nm. These highly diffusive particles can most easily deposit in the body, whereas only about 20% of the particles with diameters around 100 nm are retained in the respiratory tract (James, 1988).

Measurement of the total concentration of alpha-emitting particulate matter is relatively easily determined. Air is drawn though a membrane filter, and the collected alpha activity can be measured using either a ZnS(Ag) scintillator for total alpha counting or a solid-state detector that provides alpha-spectroscopic determination of the specific decay products. From multiple sequential counts and the known decay kinetics of the radon progeny, the concentrations of each of the decay products (^{218}Po, ^{214}Pb, ^{214}Bi) can be calculated. The proper choice of filter can provide quantitative collection of activity and an adequate radioactive source for accurate measurement of the collected activity.

Size measurement of the decay products is a difficult problem. George (1972) proposed a method for measuring the "unattached" fraction in which air is drawn through a filter that is covered with a 60-mesh screen. The highly diffusive activity attaches to the screen. The activity counted on the screen is the unattached activity, and that which passes through the screen to the filter is the attached activity. Activity-size distributions have been measured with diffusion batteries down to sizes of 10 to 15 nm (Knutson, 1988), because conventional diffusion batteries have relatively little resolving power for ultrafine particle sizes. Ramamurthi and Hopke (1988) reviewed several measurement systems for unattached fractions in the context of the improved understanding of penetration of particles through single screen.

It is now understood that the unattached activity is not a single species with one fixed diffusion coefficient, but rather an ultrafine mode in the particle size spectrum between 0.5 and 5 nm. Improvements in measurement methods (Reineking and Porstendörfer, 1986; Holub and Knutson, 1987) have made

it possible to determine the full range of sizes for grab samples. There remains a need to develop a system that will provide a series of size and concentration measurements.

Radon concentrations are determined as a measure of exposure rather than decay product concentrations, because integrated radon measurements are relatively simple, inexpensive, and accurate, and dosimetric models suggest that radon is a reasonable surrogate for the decay products. However, the development of new methods to measure decay product size and concentrations would permit direct long-term measurement of the species that are the proximate cause of the health effects.

Chemometrics

Chemometrics is a new field of chemistry that deals with the extraction of maximal information from chemical data that have been produced using the techniques described in the previous sections. Chemometric methods have been extensively described by Sharaf et al. (1986) and by Massart et al. (1988). It has applications to analytical chemistry in that often information content of a detector system is used only partially by simple data-reduction techniques. In addition, many of the newer analytical methods are truly multivariate techniques. To optimize the sensitivity and selectivity of such methods, it is necessary to use a proper multivariate design for calibration (Deming and Morgan, 1987). It is impossible to fully optimize many modern analytical instruments with a one-variable-at-a-time approach. Similarly, interferences also must be treated in a multivariate manner with a proper statistical design if the value of multiple-species-measurement instruments are to be used fully.

One immediate application is in the analysis of data from several sensors, where qualitative and quantitative analysis can be performed on the air sample (Stetter, 1986). These methods can be used to resolve and quantitate the components of mixtures that the separation methods do not separate fully. Often the patterns obtained from the chemometric analysis of the analytical data can reveal the origin of the contaminants or information on their reactivity in the air.

In addition, time-dependent response of a detector such as a drifting calibration can contain information that can be extracted easily using techniques such as Kalman filtering (Brown, 1986). Thijssen et al. (1984a) developed a model for random drift, and a criterion was developed for deciding when to recalibrate or to measure the next unknown. Such methods have been extended to include optimization of the calibration scheme (Thijssen et al., 1984b) and to incorporate a generalized standard additions approach to calibration

(Vandeginste et al., 1983). In many instances in the past, drifting calibration data would not have been recognized as such or would have been discarded because of the observed drift.

Considerable work has been completed on developing structure-activity relationships so that the behavior of some of the easily measured compounds might be useful in predicting the atmospheric or physiological behavior of other structurally related compounds. Although much of the prior work has been on compounds of possible pharmacological activity, structure-activity studies also could help predict other biological responses, such as toxicity, bioconcentration potential, and other aspects of ecosystem behavior.

Chemometric methods have been used to identify the sources of mutagenicity observed in collected airborne particulate matter (Daisey et al., 1986; Wallace, 1987; Lewis et al., 1988) and are likely to be more widely used in the future to help relate observed atmospheric composition to various toxicological responses. When applied to resolving sources of airborne particulate matter or applications to interpreting airborne mutagenicity, chemometric methods commonly are called receptor models and are discussed more fully in Chapter 6.

SUMMARY

In assessing human exposures to airborne pollutants, numerous factors besides the contaminant must be measured, especially if the assessment is based on fixed-site sampling or modeling. Accurate estimates in these instances depend not only on concentration measurements from fixed-site monitors in various locations, but also on knowledge of numerous factors that influence the environments where exposures occur. The measurement of an airborne contaminant can be visualized as a three-step process. First, the pollutant is sampled; then it is separated from other species also collected in the sample; finally, it is detected. The choice of the measurement methods to be used in an exposure assessment is driven by a study's specific aims and by the nature of a given airborne pollutant.

Quality Control/Quality Assurance

Quality assurance is a critical part of exposure studies and must be established as part of the initial study design, at which point it should be decided what precision and accuracy are needed to test the study hypothesis. An effective

quality assurance program is costly (approximately 15–25% of total expenses) and should be considered when establishing a project's budget.

The use of field and lab spikes and blanks should be a routine practice. Simple techniques for generating or supplying analytical standards in the field need to be developed. Particular attention should be given to standards for highly reactive compounds, which often are of the greatest concern from a human health perspective and for which stable standards often are difficult to prepare. Techniques could include the use of permeation devices; novel onsite generation of standards (e.g., reactors that quantitatively produce an analyte); and compressed-gas standards, where containers are made of highly deactivated materials. Highly passivated, stainless-steel canisters might be useful for this purpose.

Validation studies of samplers and analytical instruments used in exposure assessments are required. Validations should be performed in settings similar to those used in exposure studies.

Sampling Techniques and Strategy

The choice of a sampling strategy and a measurement method hinges on the study's specific aims and hypotheses. Physical, chemical, and biological characteristics of the pollutant dictate the method chosen to sample and measure airborne concentrations.

A contaminant can have very different health effects in the vapor-phase and in the condensed phase. Care must be exercised that a sampling procedure collects all of the appropriate phases and does not present a false picture of a contaminant's physical state.

Personal monitoring (active or passive) is the most direct approach for assessing human exposure to airborne pollutants. However, the portability requirement of this technique typically decreases method sensitivity compared with stationary microenvironmental monitoring. Personal monitors need to be developed for many contaminants, including certain metals, PAHs, other semivolatile organic compounds, polar VOCs, and radon decay products. In some cases, personal monitors already exist, but need to be refined, reduced in weight and size, and validated (e.g., airborne particles, certain pesticides). More general instrument needs include personal sampling pumps with improved reliability, stability, and wide ranges of accurate flow rates and low noise levels. Lighter batteries with longer lives will contribute to improved personal monitoring.

For pollutants whose effects might be related to peak exposures, personal samplers are needed that will monitor continuously for only short-term peak

exposures. Samplers based on electrochemical principles potentially could meet this need. In such an application, with the use of an electronic discriminator, the signal characteristic of the analyte could be recorded only when it exceeds a preset threshold value. For monitoring devices using other chemical or physical principles, the measurement of short-term peak exposures is a more difficult problem and requires additional research.

Quiet and unobtrusive microenvironmental samplers (active or passive) are needed if they are to be used more widely; such samplers should be available for the majority of atmospheric contaminants.

Passive samplers are well suited to the collection of long-term integrated samples collected over days or weeks and can be extremely useful in a personal or microenvironmental study. However, long-term sampling with a passive monitor places great constraints on the sorbent; it must retain the analytes without promoting unintended reactions among adsorbed analytes during the sampling period. Improved sorbents are needed that would permit long-term sampling for a wide variety of analytes. New sorbents are also required for polar organics, highly volatile compounds, and very reactive species. Ideally, passive samplers should be easily desorbed with the proper solvent or thermal techniques. New desorption processes need to be developed. Procedures that permit desorption with a minimum of dilution, such as supercritical fluid extraction, would be especially useful. Such improvements would avoid the compromise in analytic sensitivity that often results from the large volumes used in liquid desorption techniques.

Instrumental Techniques

Numerous advances have been made in instrument design, operation, and experimental deployment during the past 10–15 years. LC techniques are being used to analyze for compounds not amenable to GC. In particular, IC (ion chromatography) is being used increasingly to analyze for highly polar air contaminants. In addition, LC-MS is developing into a productive technique to complement GC-MS. The development of new MS instrumentation (e.g., ion trap mass spectrometers) has made MS a valuable air analysis device. Microsampling and microanalytical devices have been developed but are not yet widely applied. A summary of attributes of different measurement techniques is presented in Table 3.5. (Table 3.5 does not summarize all the techniques discussed in this chapter; it does include some established techniques that were not discussed in this chapter.)

Some contaminants are not distributed uniformly over the surfaces of airborne particles. To evaluate health effects properly, particulate analyses

TABLE 3.5 Summary of Attributes of Different Measurement Techniques

	Factor*					
Technique	Sensitivity	Selectivity	Continuous	Comprehensiveness	Portable	Cost
Ion chromatography	xx	x	no	x	no	$$
High-performance liquid chromatography/ultraviolet	x	xx	no	xx	no	$$
High-performance liquid chromatography/fluorometry	xx	xx	no	xx	no	$$
Gas chromatography—flame ionization detection	xxx	x	no	xx	no	$
Gas chromatography—photoionization detection	xxx	x	no	xx	yes	$
Gas chromatography—mass spectrometry	xxx	xxxx	no	xx	no	$$$
Mass spectrometry—mass spectrometry	xxx	xxxx	yes	xxx	no	$$$$
Gas chromatography—Fourier transform infrared	x	xxx	no	xx	no	$$$
Potentiometry	x	xx	yes	x	yes	$
Conductimetry	x	x	yes	x	yes	$
Amperometry	x	xx	yes	x	yes	$

	Factor*					
Technique	Sensitivity	Selectivity	Continuous	Comprehensiveness	Portable	Cost
Piezoelectric elements	xx	xx	yes	xx	yes	$
Surface acoustic wave elements	xxx	xx	yes	xx	yes	$$
Ultraviolet-visible spectroscopy	x	x	yes	xx	yes	$
Nuclear magnetic resonance spectroscopy	x	xxx	no	x	no	$$$
Atomic absorption spectrometry	xxx	xxxx	no	xx	no	$
Inductively coupled plasma spectroscopy	xxx	xxxx	no	xxx	no	$$$
Proton-induced x-ray emission (PIXE)	xxx	xxxx	no	xxx	no	$$$$**

*The ideal conditions for these factors are presented in Table 3.2. The number of x or $ symbols assigned to each cell is positively correlated with the degree to which a technique exhibits a factor.

**$ for analysis performed by an outside laboratory.

should include surface techniques that provide elemental or chemical information.

Field-Study Instruments

Research and development should focus on better instrumentation for field studies. These include more portable, reliable, and rugged gas chromatographs, gas chromatograph/mass spectrometers, and ion trap mass spectrometers. Sampling methods, instruments, and software that interfaces with such instruments are also needed to permit unattended sample collection and analyses in field settings.

A sensitive, highly specific detector applicable to numerous compounds is needed for the liquid chromatograph; continued improvements in LC-MS are beginning to fill this gap.

4

Use of Biological Markers in Assessing Human Exposure to Airborne Contaminants

INTRODUCTION

As used in this report, biological markers are indicators of changes or events in human biological systems. For example, a metabolite of some exogenous substance found in a person's blood or urine might be considered a marker of the person's exposure to that substance in the environment. If a tissue response to the person's exposure to the substance parallels a disease process, but does not itself constitute a disease process, the tissue response might be considered a marker of effect. The use of biological indicators of exposure to toxic substances is not a new concept—it has been used in occupational health monitoring for many decades. However, as the emphasis on conducting accurate exposure assessments increases, biological markers of exposure will be used more frequently. A dramatic indicator, particularly in occupational epidemiology studies, is death. Less drastic and more manipulable biological measures of health outcome do exist and continue to be developed.

Unfortunately, terminology is confusing, the array of technological subtleties is bewildering, and there is a potential for ethical dilemmas. By virtue of their collaborative and interdisciplinary nature, investigations involving biological markers are highly demanding in terms of personnel, cost, and effort to develop mutual understanding between researchers in different fields. Incorporation of biological markers into exposure assessment engenders new and significant methodological problems in the design of studies that use human subjects and in analysis of data. It also introduces important ethical questions into health effects research, particularly when information on biological markers of uncertain relation to adverse health effects is given to a possibly exposed person. Successful use of biological markers will require an understanding of the fate and effects of a contaminant within a person to permit the

relation of marker data to the exposure and the establishment of relationships among biological markers of effect and exposure.

This chapter discusses how biological markers might be used as surrogates for or in combination with other measures of exposure, including comments on their limitations.

FROM EXPOSURE TO HEALTH EFFECTS: KINDS OF MARKERS

As defined in Chapter 1, exposure to an airborne contaminant is the product of the concentration of the contaminant and the period during which exposure is at that concentration. "Dose" is defined as the actual amount of a given contaminant that is absorbed or deposited in the body of an exposed organism in a given period (usually with reference to a single medium or route of exposure). "Potential dose" assumes total absorption of a contaminant. The term dose can be subdivided into internal dose and biologically effective dose—both are discussed in this chapter with regard to biological markers. "Effect" is defined as an adverse health outcome or nuisance resulting from exposure. An exposure might or might not lead to a dose, and a dose to a health or nuisance effect. Each of these compartments may also be subdivided into stages representing a progression from exposure to adverse health effect, as shown in Figure 1.2 in Chapter 1. These stages are not discrete. The progression from exposure to effect is a result of the physiological changes that can occur within the organism. The progression can be affected at any point by internal biological factors or by external interventions.

The classes of biological markers are depicted in Figure 4.1, an elaboration of Figure 1.2 in Chapter 1. Biological markers can be used for each stage in the progression and can be used either to determine the exposure to the causative agent or to predict adverse health effects (Committee on Biological Markers of the National Research Council, 1987). Markers can be divided into three broad classes: markers of exposure, markers of health effects, and markers of susceptibility (NRC, 1989). The committee focuses in this chapter on the application of biological markers to assessment of exposure to contaminants rather than their use to predict health effects. However, the use of markers to predict health effects should not be disregarded.

As discussed in Chapter 1, biological markers of exposure integrate all routes of exposure to a particular contaminant. For example, lead concentrations as measured in a human tissue, such as blood, can reflect exposure via any or all of such routes, including inhalation of lead in ambient air, ingestion of vegetables contaminated by deposition of airborne lead and ingestion of

lead in drinking water or dust, especially by children with pica. This integrating process of biological markers of exposure can be important for risk assessment and risk management. In the case of lead, for example, the amount inhaled might be assessed with procedures described in Chapter 3. If only a very small portion of the observed dose of lead could be accounted for via inhalation, other exposure routes and sources might then be sought.

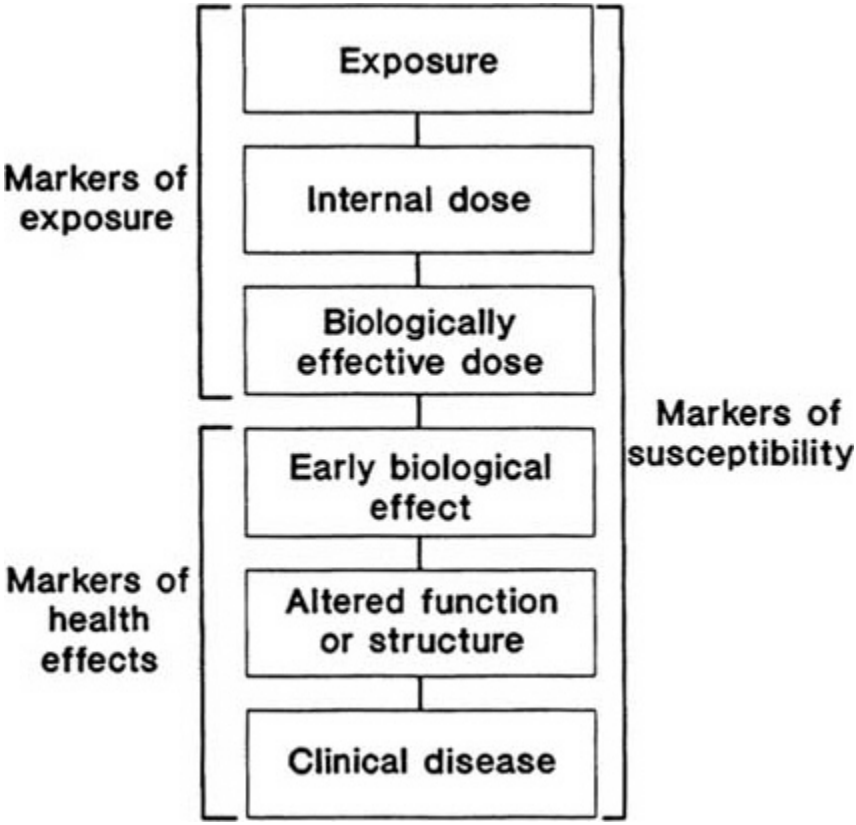

FIGURE 4.1 Kinds of biological markers.
Source: Adapted from Committee on Biological Markers, 1987.

Biological markers provide information on dose that can be related to exposure by using pharmacokinetic or pharmacodynamic models (e.g., blood lead or carboxyhemoglobin). Internal dose is the amount of contaminant that is absorbed into the body in a given period. Biological markers of internal

dose directly measure the exposure substance or its metabolites in cells, tissues, or body fluids. The biologically effective dose is the amount of contaminant or its metabolites that has interacted with a target site over a given period so as to alter a physiological function. Such an interaction can lead to disease or be subjected to repair.

Biological markers of health effects (referred to in this chapter as biological markers of effect) represent a further step away from exposure and a step closer to the clinical manifestation of disease. A marker of early biological effect provides information on an event resulting from a toxic interaction, either at a target or at an analogous site. An early effect is considered an irreversible step in pathogenesis or a qualitative or quantitative correlate of a disease process. Biological markers of effect also include preclinical alterations in organs, tissue structure, or function directly associated with disease. To be useful in disease prevention, these markers of effect should be measurable at preclinical stages.

Biological markers of susceptibility span the entire range of markers shown in Figure 4.1. They indicate an organism's inherent or acquired limitations that affect its response to an exposure to a particular contaminant. These markers can be useful in understanding the relationships that exist between markers of exposure and effect.

Relating a biological marker directly to an exposure becomes more uncertain as one obtains information on the stages within the progression shown in Figure 4.1. Accordingly, the Committee on Biological Markers of the National Research Council (1987) has stated that "markers of health effects are often less readily related to environmental exposures than are the markers of exposure." Therefore, greater emphasis is given to markers of exposure. Biological markers of effect can be used for exposure analysis if and only if information concerning contaminant identity and route of exposure is incorporated into the exposure assessment.

An attempt to use biological markers as surrogates for measurements of exposure might raise ethical questions. When humans are directly involved in biological-marker studies, caution must be exercised in reporting results to study subjects, to avoid undue psychological stress when the significance of the marker for future adverse health effects is uncertain (Ashby, 1988).

Pharmacokinetics is the quantitative description of the rates of absorption, distribution, metabolism, and elimination of a contaminant taken into a biological system (Leung and Pastenbach, 1988). Pharmacodynamics is the description of the processes that relate biologically effective dose to health effects. Pharmacokinetic modeling techniques are used to aid in the extrapolation of test results from animals to humans; pharmacodynamic models are just being developed (Menzel, 1987). The pharmacokinetic models attempt to

compensate in part for the physiological and biochemical differences between humans and test animals, which can cause markedly different responses to the same substance. The models use mechanistic, biochemical, and physiological information to describe the disposition of a contaminant once taken in. Mechanistic studies provide information on the target tissues, metabolic pathways, and nature of a contaminant's chemically stable metabolites or reactive intermediates. Pertinent biochemical data include partition coefficients and permeation coefficients. Pertinent physiological factors include tissue volumes, blood flow rates, and ventilation rates. Much of this information can be obtained from published sources or through the use of in vitro techniques.

A physiologically based pharmacokinetic model is constructed as a set of biologically defined compartments—tissues and target organs are group into well-perfused, moderately perfused, or poorly perfused compartments for describing the process of metabolic transformation in the lungs, kidneys, or liver. Each compartment has a defined volume, blood flow, partition coefficient, and metabolic constants (Travis et al., 1990). The growing availability of sophisticated simulation packages that can solve large numbers of mass-balance differential equations makes the construction and testing of models increasingly easier.

An example of use of pharmacokinetic techniques to relate various biological markers to each other and to an exposure is the study of halothane concentrations in the breathing zone and blood of operating-room personnel (Fiserova-Bergerova, 1987). Anesthesiologists had the highest breathing-zone concentrations but lower blood concentrations than nurses, who had substantially lower breathing-zone concentrations. Pharmacokinetics accounted for the difference: the anesthesiologists had a primarily sedentary job, whereas the nurses were actively moving about the room and therefore had higher ventilation rates and cardiac output.

Pharmacokinetics and pharmacodynamics can also be used to indicate which tissues are to be sampled and when samples should be taken, as discussed in Chapter 2. For example, the pharmacokinetics of cadmium indicate that, if one is interested in recent cadmium exposure, one should analyze blood; if accumulation is of interest, one should analyze urine (ACGIH, 1986). Another study involved the effect of ethylene glycol ethers on sperm count. Pharmacodynamic studies did not show a relationship between sperm count and methoxyacetic acid, the primary metabolite of ethylene glycol ethers (Smith, 1988). However, because the sperm production cycle takes 80 days, there is a lag of approximately 80 days between toxic exposure and reduced sperm count. Therefore, exposure and effect measurements had to be offset by approximately 80 days.

An understanding of the pharmacokinetics of a contaminant is important

in relating biological markers to the original exposure. As pharmacodynamic modeling advances, relationships will then be established between biological markers of exposure and biological markers of effect (Menzel, 1987).

APPLICATIONS OF HUMAN BIOLOGICAL MARKERS

Markers of Exposure

Sensitive physicochemical methods can detect and measure very low concentrations of xenobiotic substances in the body (Sheldon et al., 1986). They are being used in industrial hygiene with biologic exposure indexes as reference values for workplace exposure monitoring (ACGIH, 1986, 1988b; Fiserova-Bergerova, 1987). Concentrations of a contaminant are usually measured in exhaled air, blood, or urine, but breast milk and semen have also been used. Each biological medium has a unique relevance to exposure and health outcome, and interpretation of the resulting data requires an understanding of the pharmacokinetics of the substance in question. For example, concentrations in exhaled air generally reflect only inhalation, whereas concentrations in blood, other tissues, and other fluids might reflect recent exposures from several sources and stored body burdens.

Measures of internal dose can be characterized according to chemical specificity and selectivity. Highly selective markers of exposure typically represent measures of unchanged contaminants in biological media and thus provide the most clear-cut evidence of a specific environmental exposure. Studies of volatile airborne contaminants usually involve the measurement of a specific substance in exhaled air. The unchanged compound or its metabolite in urine may also be analyzed where variations in urinary volume can be accounted for by normalizing the concentration of the analyte to the creatinine levels. If it is necessary to analyze for a metabolite, rather than its parent substance, a procedure can lose some specificity in relating the biological marker to exposure. For example, exposure to styrene and exposure to ethyl benzene each give rise to mandelic acid in urine, so a finding of mandelic acid in urine would have to be supplemented with another assay (e.g., of breath) to determine which compound the subject was exposed to.

Measures of biologically effective dose include DNA and hemoglobin adducts in peripheral blood and other cells and tissues—e.g., lung macrophages, sputum, bronchial washes or bronchoalveolar lavage fluid, buccal mucosa, bone marrow, placental tissue, and lung tissue. Such measures can be used as markers of exposure only when the analyzed cells or tissues are the target of the exposure contaminant or its metabolites. Many carcinogens and reproductive

toxicants are metabolically activated to electrophilic metabolites that covalently bind to DNA. Adducts on DNA, if they occur at critical sites and are not repaired, can cause gene mutation, which has been shown to be an initiating step in the multistage carcinogenic process. Several methods to detect DNA-chemical adducts in lymphocytes and target tissues are available, including radio- or enzyme-linked immunoassays that use polyclonal or monoclonal antibodies, ^{32}P-postlabeling, and synchronous fluorescence spectrophotometry (Watson, 1987; Santella, 1988).

The first use of antibodies to detect polycyclic aromatic hydrocarbon (PAH)-DNA adducts involved lung tissue and peripheral white blood cells from lung-cancer patients and controls (Perera et al., 1982). They have since been used to analyze white blood cells and other tissues from persons exposed to PAHs in cigarette smoke and in occupational settings (e.g., foundries and coke ovens) (Harris et al., 1985; Shamsuddin et al., 1985; Haugen et al., 1986; Perera et al., 1988). Antibodies are available to assess formation of DNA adducts in humans with several carcinogenic substances: aflatoxin B_1, benzo*a*pyrene (BaP) and other PAHs, cisplatinum, and methoxypsoralen. Immunoassays can detect frequencies as low as one adduct per 10^8 nucleotides. Assays that use monoclonal antibodies are highly specific for a given substance, but those with polyclonal antibodies, such as PAH-DNA antibodies, can react with multiple structurally related compounds and thus lose specificity. The value of immunoassays depends on the development of appropriate antibodies, and the highly specific monoclonal assays can be time consuming and technically difficult.

In contrast with the monoclonal assays, ^{32}P-postlabeling can be used to recognize various adducts without characterizing their chemical compositions. It can be more sensitive than monoclonal assays; it can detect one adduct per 10^{10} nucleotides. The method produces an image that constitutes an idiosyncratic "fingerprint" of the exposure. However, researchers developing this assay have faced difficulties in identifying the adducts formed. If the adducts can be isolated and identified, further analyses can be carried out with immunoassay techniques, once the appropriate antibody has been developed. The postlabeling method generally is limited to the measurement of bulky adducts that might limit the usefulness of the technique to smaller airborne contaminants, and the results of the method are only semiquantifiable. Effective use of the postlabeling method requires the synthesis of an internal standard since the efficiency of labeling can vary according to the substance.

The technique of ^{32}P-postlabeling has been applied to the identification of various alkylating and methylating agents (Reddy and Randerath, 1987). It is possible to characterize methylating agents using HPLC (high-performance liquid chromatography); however, this is not a routine technique. Application

to populations exposed to airborne pollutants has been limited to assessment of BaP and other PAH exposure of foundry workers and roofers (Hemminki et al., 1988; Phillips et al., 1988). Some investigators have related placenta and lung adduct measurements to cigarette smoking with postlabeling techniques (Everson et al., 1986); others have not seen smoker-nonsmoker differences in bone marrow, white blood cells, or buccal mucosa (Dunn and Stich, 1986; Phillips et al., 1986; Jahnke et al., 1990).

A third approach uses synchronous fluorescence spectrophotometry, which has recently been applied to coke-oven workers with a reported sensitivity of one BaP adduct per 10^7 nucleotides (Vahakangas et al., 1985). The method has been used to confirm the presence of BaP-DNA adducts in placental tissue from smokers (Weston et al., 1988). HPLC and fluorescence spectroscopy have been used to detect excised carcinogen-DNA adducts in urine (Autrup et al., 1983). The technique is limited in that it is useful only for detecting compounds that fluoresce, such as PAHs.

Assays that measure protein adducts, including adducts of direct binding agents and metabolites with hemoglobin, can in some cases be a good surrogate for DNA-adduct measurements. That use is supported by correlations in animal studies between protein and DNA binding by BaP, vinyl chloride, ethylene oxide, methyl methanesulfonate, and trans-4- dimethylaminostilbene (IARC, 1984; Neumann, 1984; Bartsch, 1988). Methods available for measuring those adducts include immunoassays, amino acid analysis by ion-exchange LC, and the combination of gas chromatography and mass spectrometry (GC-MS) with both conventional ionization and negative chemical ionization techniques. GC-MS has been successfully applied to the quantitation of 4-aminobiphenyl (4-ABP) hemoglobin adducts in smokers (Bryant et al., 1987; Perera et al., 1987). Sensitive GC-MS methods can measure protein adducts in persons exposed to ethylene oxide from cigarette smoke and workplace sources (Osterman-Golkar et al., 1984; Farmer et al., 1986; Törnqvist et al., 1986). Because of the 3-month life span of hemoglobin, those assays reflect relatively recent exposures; DNA adducts in lymphocyte subpopulations reflect exposure integrated over a longer period. Protein adducts are more abundant than their DNA counterparts and therefore provide a more sensitive measure of exposure.

Markers of Effect

Markers of biological effect can be useful for exposure assessment, provided that they can be related to the exposure responsible for an effect. A number of markers might signal a preclinical or presymptomatic stage in disease

development, some of which are specific to a chemical; others might signal adaptive changes that are not themselves pathological. For example, the presence of carboxyhemoglobin in the blood signals that damage related to carbon monoxide exposure is occurring, but the source could be the inhalation of carbon monoxide or the metabolism of methylene chloride. Red blood cell delta-aminolevulinic acid dehydratase (delta-ALAD) has been used as an indicator of early toxic effects of lead exposure (Friberg, 1985), but the American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended its use as a biological exposure index, because of "interpretative difficulties" (ACGIH, 1986). Reduction in plasma acetylcholinesterase activity has been specifically linked to organophosphate insecticides, but thiocarbamates can induce the same effect (Fiserova-Bergerova, 1987). Nonspecific markers of reproductive impairment include plasma ollicle-stimulating hormone, plasma luteinizing hormone, salivary progesterone, and urinary hydroxyproline or hydroxylysine (which could reflect tissue remodeling (collagen turnover) after inhalation exposure to environmental pollutants) (NRC, 1988).

Cytogenetic techniques provide another direct, although nonspecific, method of identifying changes that occur on the chromosomal level after exposure to environmental contaminants. Cytogenetic changes include alterations in chromosome number, such structural chromosomal changes as breakage and rearrangement, and exchanges between reciprocal portions of a single chromosome referred to as sister-chromatid exchanges (SCE). The mechanism responsible for inducing SCEs is not well understood. Many classes of carcinogens and mutagens are known to increase SCE frequency, and that could limit the usefulness of SCE frequency for exposure assessment. For example, increased SCE frequency has been found in workers exposed to ethylene oxide, styrene, benzene, arsenic, chloromethyl ether, chloroprene, organophosphates, or ionizing radiation (Evans, 1982).

Chromosomal aberrations have been used successfully as a biological dosimeter to measure absorbed radiation in humans (IAEA, 1986); however, ionizing radiation acts through mechanisms that are different from those of most other atmospheric contaminants. Micronuclei, fragments of nuclear material left in the cytoplasm after replication, are considered an indication of the prior existence of chromosomal aberrations. Cytogenetic markers can be identified in lymphocytes and sometimes in other tissue with stimulated cell culture and staining techniques in conjunction with light microscopy (Livingston et al., 1983; Carrano and Natarajan, 1988). Many types of human cancers are associated with specific alterations (e.g., adult leukemia) or nonspecific aberrations, and there is increasing evidence that chromosomal aberrations might be linked to the carcinogenic process related to exposure to some chemicals (Yunis, 1983).

New techniques have been based on the fact that a specific mutagen (such as a chemical agent) induces a specific pattern of gene mutation (Benzer and Freese, 1958). Techniques have been developed to screen for patterns in genes from human peripheral blood lymphocytes that contain mutations in the non-essential enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) (Cariello and Thilly, 1986). One technique involves the use of denaturing gradient gel electrophoresis, which can separate short DNA molecules according to their melting (uncoiling) properties. The melting behavior of the DNA fragments is extremely sequence-dependent; a single base-pair substitution can change migration on the gel. That type of tool provides a convenient means of examining HGPRT for genetic alterations (according to the generation of mutation-related spectra on the gel) and then relating the alterations to specific causative agents (Cariello et al., 1988). The technique depends on the use of a high-fidelity polymerase chain reaction to provide in vitro amplification of a given region of the genome and thus improve sensitivity and provide enough material for sequencing. The application of the technique to exposure assessment holds the potential for being specific for a substance causing mutation and so would be useful in epidemiological studies, risk assessment, and risk management. In addition, it leads to a measure of a biological effect and thus could be more directly related to potential adverse health outcomes than biological markers of exposure. Extensive validation of the technique is necessary.

Another new approach to assessing genetic effects involves measurement of single-strand breaks in lymphocyte DNA. A linear dose-response relationship was found in mice exposed to styrene (Walles and Orsen, 1983), and increased frequencies of breaks were found in workers exposed to styrene (Walles et al., 1988). The assay was also used to demonstrate differential styrene metabolism and clearance by various organ systems (Walles and Orsen, 1983). Alkylating agents, such as *N*-nitroso-*N*-methylnitroguanidine and ethyl methylsulfonate, which are negative in standard cell transformation assays, have also been shown to be strong inducers of single-strand breaks (Lubet et al., 1983).

DNA hyperploidy measured in exfoliated bladder and lung cells has been shown to be a biological marker of response to exposure to carcinogens. It has been detected with flow cytometry of stained cells (Melamed et al., 1977), but this approach requires large samples and cannot be used to evaluate individual cells. The more recently developed technique of quantitative fluorescence image analysis involves the scanning of the fluorescence of individual stained cells in a microscopic field (Hemstreet et al., 1986). This technique has shown DNA hyperploidy to be highly correlated with magnitude of exposure in workers exposed to aromatic amines (Hemstreet et al., 1988). Further

validation is needed to determine the specificity of DNA hyperploidy markers for causative agents and for actual magnitudes of exposure in the environment.

Activated oncogenes and their protein products can be used as markers of effect. During oncogenesis, a normal segment of DNA (a proto-oncogene) is activated to a form that causes cells to become malignant. Activation can occur through several mechanisms, including gene mutation and chromosomal breaks and rearrangements. Of particular interest in assessment of ambient environmental exposures is the *ras* oncogene, first identified in rat sarcoma, later in human bladder, colon, and lung cancers (Slamon et al., 1984; Spandidos and Kerr, 1984). Activated *ras* oncogenes containing a point mutation have been produced in vitro by a number of ambient pollutants, including BaP, dimethylbenzanthracene, and *N*-nitroso compounds (Sukumar et al., 1984). Activation of the *ras* oncogene can be measured with complex immunoblotting techniques. A more convenient and relatively simple method involves measurement of the gene's abnormal protein product, designated P21. P21 can be measured in tissue or sputum with monoclonal antibodies, as well as in blood and urine with immunoprecipitation techniques. The assay is still in the early validation stage (Brandt-Rauf, 1988). It is likely that more than one oncogene needs to be activated to convert a normal cell to a cancerous one (Stowers et al., 1987). More studies will be needed to reveal the sequential requirements for oncogene activation.

Assays that detect changes in the function of target or analogous tissue, such as decreased sperm counts after dibromochloropropane exposure, provide markers that are closely linked to disease end points. An increased concentration of erythrocyte zinc protoporphyrin (EPP) indicates a later stage in lead toxicity than does delta-ALAD deficiency (Friberg, 1985) and is a better indicator of past chronic exposure to lead then is blood lead concentration (Blumberg et al., 1977; Franco et al., 1984). ACGIH recommends the use of EPP as a measure of lead exposure (ACGIH, 1986), although it points out that iron deficiency can also increase EPP (Lamola and Yamane, 1974).

Some markers can indicate the presence of disease at preclinical or early clinical stages. For example, serum alpha-fetoprotein, although not specific to liver cancer, has been successfully used in China to indicate preneoplasia of the liver (Committee on Biological Markers of the National Research Council, 1987). However, the lack of specificity of tumor markers (such as alpha-fetoprotein) severely restricts their usefulness (Hulka and Wilcosky, 1988).

UTILITY OF BIOLOGICAL MARKERS

Advantages

Improved Exposure Assessments

Central to establishing the relationship between exposure to a contaminant and the presence of biological markers is the characterization of exposure-dose-effect relationships. Dose used to be determined on the basis of exposure, and the principal limiting factors were the quality and quantity of exposure data for a particular contaminant from all possible sources. Exposure data were obtained primarily from historical records of ambient or workplace monitoring, mathematical modeling, and questionnaires, and not from measurements. The underlying assumption that all persons with comparable exposure receive a similar internal or biologically effective dose is incorrect, as has been shown, for example, in studies of halothane uptake by operating-room personnel. Uptake, absorption, and distribution of a substance can vary with sex, age, health status, diet, hormonal status, and presence of other environmental exposures (Committee on Biological Markers of the National Research Council, 1987). Biological markers help to compensate for many of those variables by integrating all routes of exposure and not only permit individual exposure assessments, but also support estimation of individual biologically effective doses. Thus, when combined with inhalation exposure assessments, biological markers can be used to indicate whether, for instance, inhalation is a major or minor source of a contaminant.

Properly measured, biological markers can reduce misclassification error as to degree of exposure and can increase the power of epidemiological studies to identify associations between exposure and disease. Persons who are highly susceptible to effects from exposure contaminants could be identified in terms of biologically effective dose or early biological effect.

Biological markers also have the potential to differentiate the effects of varied exposure patterns. For example, experimental studies have suggested that induction of heritable mutations by ethylene oxide exposure can vary with dose rate (Generoso et al., 1986).

Validation of Pharmacokinetic Models

Biological markers can, in theory, be useful in developing and validating pharmacokinetic models aimed at relating external exposure to dose (NRC, 1989). As discussed previously in this chapter, pharmacokinetic models have

been developed in experimental animals and then adjusted for physiological characteristics of humans to permit extrapolation across species and from different doses to dose in humans. They are often based on limited experimental data for which parallel information in humans is lacking. Therefore, direct measurements of dose in experimental animals and humans would allow more valid comparisons between animal models and humans for purposes of risk assessment. For example, the combination of measurement of alveolar styrene, personal workplace monitoring data, blood styrene content, and urinary mandelic acid content can provide an accurate description of styrene uptake, metabolism, and elimination under different conditions of exertion (Droz and Guillemin, 1983).

Detailed modeling approaches are now being used to determine biologically effective dose. Young and Kadlubar (1987) used a three-compartment model to predict the release of the N-OH arylamines in the bladder lumen and the formation of arylamine-DNA adducts in blood as markers of biologically effective dose. This model is being validated in dogs given radio labeled amino biphenyl.

The ability of doses in surrogate tissues to model the dose received by a target tissue has been assessed in studies involving ethylene oxide. At issue was whether adducts of hemoglobin reflected the dose to DNA in the target cell. Comparison of the alkylation of *N*-(2-hydroxyethyl) histidine in hemoglobin with the alkylation of guanine at the N7 position in DNA from rat livers and testes showed that hemoglobin alkylation gives a reasonable approximation of DNA dose (Osterman-Golkar et al., 1984). Given the degree of alkylation of hemoglobin, it was possible to estimate ethylene oxide exposure during the preceding few months (Calleman, 1984).

Improvement of Risk Extrapolation

Biological markers have the potential to improve risk extrapolation between species and between populations, and to allow better predictions of human risk. Parallel studies of markers, such as biologically effective dose or early response, in experimental animals and human populations can be used to evaluate whether mechanisms or modes of action are similar across species. Given the same substance, the studies can allow calibration of measurements (e.g., chromosomal effects, DNA adducts, or somatic cell mutations) in human populations whose relative risks of cancer are unknown with measurements in experimental animals for which tumor incidences are established.

Comparative monitoring data on several human populations could allow extrapolation from a population whose relative risks of cancer are established

historically (e.g., cigarette smokers and coke-oven workers) to a population facing similar exposure whose relative risks are unknown.

Finally, validation of molecular markers through parallel in vivo animal and human studies might ultimately provide support for applying marker methods to human cells in culture as a substitute for long-term bioassays as a basis for risk assessment (Perera et al., 1987).

Timely Identification of Persons or Groups at Increased Risk of Disease

Biological markers of exposure and effect can provide an early warning of hazard or potential risk of disease. In general, they can signal the need for greater surveillance or even action to reduce exposure. However, before such action can be taken, a marker must give some indication as to causative agent. For example, if increased blood EPP (indicative of chronic exposure to lead) is observed, greater surveillance could include blood lead measurements to discern recent exposure and to ensure that the EPP concentration is not due to an artifact. Environmental concentrations would also be necessary for assessing whether the exposure route was inhalation, skin absorption, or ingestion, so that appropriate corrective action could be taken.

Biological markers can aid in distinguishing exposure groups and be used to identify eligible participants in "exposure registries," which can be used to assess potential exposures to hazardous substances, e.g., around a toxic-waste dump, explosion, or other untoward event (Schulte and Kaye, 1988). Biological markers of effect indicating altered structure and function should trigger immediate remedial or preventive action, provided that the causative agent and routes can be determined. By providing this information in a timely fashion, in some cases decades before clinical disease would appear, biological markers can be valuable in disease prevention.

Improved Epidemiological Study Design and Inference

Accurate exposure assessments can reduce misclassification error and enhance the power of an epidemiological study. Early biological events are generally more common than disease end points, so markers of effect also expand a study's statistical power (Gann et al., 1985).

Markers permit more cost-effective studies. Appropriately processed tissue samples can be stored in specimen banks, sometimes for long periods, and retrieved for assay when needed later. Specimen banks could be used to

determine retrospectively whether a particular contaminant was elevated in the general population at an earlier time. This is especially relevant when new analytical techniques are developed with vastly improved sensitivity or specificity.

Other advantages include reduction in time needed for follow up, better characterization of confounders and cofactors, and improved evidence of causal associations.

Disadvantages and Limitations

Lack of Validation

A major limitation of using biological markers for exposure assessments stems from the fact that most are in a developmental stage and not fully validated or field-tested. Methodological problems are similar to those faced in the development of any new technology and include limited availability of standardized protocols and reporting criteria; interlaboratory differences, including variability in quantitation methods and in sensitivity; and the costliness and labor intensiveness of most procedures.

Markers have not yet been developed to study many important environmental exposure-response relationships. For example, nearly all existing markers for carcinogens reflect interaction with somatic genetic material and provide information about the initiation or progression stages in the carcinogenic process. Markers relevant to later events important in the promotion and progression of carcinogenesis are not yet available for human studies.

Ambiguity of Many Markers

A key question regarding biological markers of exposure is, "Given a measured amount of a marker in a specific tissue, what compounds and exposures could have produced the marker?" If multiple compounds can result in the same marker, additional studies might be necessary to reduce the ambiguity. For example, if urinary phenol is indicative of benzene exposure, one must be concerned with other possible sources of phenol in the body that can be related to the use of phenol-containing disinfectants or medications (Fishbeck et al., 1975) or eating meat. Therefore, some other measure of benzene, such as that in end-exhaled air, might be warranted to confirm the exposure. However, on the basis of pharmacokinetics, urinary phenol indicates past exposure, and end-exhaled air only the most recent exposure. The reverse

situation can also result in ambiguity. If one is using urinary phenol as a specific measure of phenol exposure (in this case, the unchanged analyte, phenol, is the same compound as metabolized benzene), it would require some type of monitoring for benzene (possibly in end-exhaled air) to eliminate that as a possible source of the urinary phenol.

In other instances, multiple compounds might produce the same metabolite, and that could hinder the proper interpretation of the biological marker. Examples of compounds sharing metabolites are styrene and ethyl benzene yielding mandelic acid and tetrachloroethylene and 1,1,1-trichloroethane yielding trichloroacetic acid. If those metabolites where found in urine, additional tests, such as breath measurements, would have to be made to try to determine which compound was involved in the exposure.

Variability of Markers

The goal in assessment of exposure to airborne contaminants is to relate concentration models to exposure models and then to dose models. It is important to know whether similar exposures—i.e., similar products of concentration (c) and time (t)—will result in similar occurrences of biological effect. Yager (1987) exposed rabbits to ethylene oxide at 200 ppm for 6 hr/day, 5 days/week or at 1,500 ppm twice a day for 15 minutes until all groups reached at a specific concentration-time interval (ct) of 7.8×10^4 ppm-hr. If there were a similar relationship between exposure and biological response, various markers would occur with the same frequency, despite the difference in exposure rate. The study showed similar frequencies of *N*-3-(2-hydroxyethyl) histidine in hemoglobin and of sister chromatid exchanges and thus demonstrated Haber's rule of equitoxicity (Haber, 1924): if $c_1t_2 = c_2t_2$, two exposures will produce the same response. The study also showed that the finding is not universal for all biological responses; analysis of rabbit bone marrow smears after a ct of 4.8×10^4 ppm-hr showed mild but consistent degenerative and focal necrotic changes in the group exposed at 1,500 ppm, but not in the other group. Generoso et al. (1986) observed a dose-rate effect for dominant lethal mutations in mice after ethylene oxide exposure. Yager (1987) considers that contradictory findings should be expected, in that they reflect differences in target tissue related to proliferative state, repair capacity, and the likelihood that different genotoxic end points reflect different kinds of damage. The results illustrate the need to evaluate a marker in an appropriate experimental setting before use in the field and to clarify the different effects that occur at different dose rates.

Biological markers can present problems in establishing quantitative relationships

between exposure and response at low exposures. Examples come from recent research on carcinogen-DNA and carcinogen-protein adducts. Extensive data on DNA, RNA, and protein binding in experimental systems indicate that these macromolecular effects at the lowest administered doses generally follow first-order kinetics; i.e., the degree of initial binding in target organs in vivo is usually directly proportional to presented dose. In some cases, that relationship also holds at very low doses similar to doses that might be encountered by humans as a result of environmental contamination (Neumann, 1984; Wogan and Gorelick, 1985).

Human data on adducts, however, do not demonstrate a proportional relationship between exposure and adduct frequency (response). For example, frequencies of 4-aminobiphenyl (4-ABP) hemoglobin adducts were significantly higher in smokers than in nonsmokers, but there was no significant correlation with amount smoked (Bryant et al., 1987; Perera et al., 1987). That is undoubtedly because of the wide interindividual variation in response to xenobiotic exposure, including nutritional factors (some people ingest anticarcinogens) (Wattenberg, 1983). Variability might also be due to the inability to determine individual exposures precisely when one is dealing with chronic, low, and variable exposures to single or multiple media. However, for ethylene oxide and propylene oxide—unlike PAH and 4-ABP, which must be metabolically activated and for which greater interindividual variability would be anticipated—the frequency of carcinogen-hemoglobin adducts in humans is expected to be reasonably proportional to the estimated dose received. That was indeed the case in the initial study of ethylene oxide-hemoglobin adducts (Calleman et al., 1978), but a later study did not show a correlation between exposure and hemoglobin-adduct frequency (van Sittert et al., 1985), possibly because airborne concentrations of ethylene oxide were very low (less than 0.05 ppm), as would be very likely in a nonoccupational exposure. For workers exposed to propylene oxide, good agreement was seen between the degree of hemoglobin alkylation and estimated propylene oxide exposure (Osterman-Golkar et al., 1984).

Better defined exposure-response relationships were shown by the significant correlation between PAH-DNA adducts measured by immunoassay in peripheral white blood cells from Finnish foundry workers and their occupational exposure to PAH (Perera et al., 1988). Workers were classified as having high (more than 0.2 $\mu g/m^3$), medium (0.05-0.2 $\mu g/m^3$), or low (less than 0.05 $\mu g/m^3$) exposure to BaP (as an indicator PAH). The mean adduct concentrations (in femtomoles of adduct per microgram of DNA) were 1.5 (high-exposure group), 0.62 (medium), 0.24 (low), and 0.066 (controls—unexposed, healthy workers seen at same clinic). These results were corroborated with the postlabeling method carried out on white-cell DNA

from the same worker population (Hemminki et al., 1988; Phillips et al., 1988). However, despite the correlation between DNA adducts and exposure at the group level, there was significant variation among individuals within the exposed groups. Adducts measured with immunoassay ranged from nondetectable to 2.8 fmol/μg. On the basis of the work of Lioy et al. (1988), it is possible that workers were receiving exposures by other routes, mainly food.

Harris et al. (1985) did not find BaP-DNA adducts in 10 of 41 coke-oven workers evaluated. They suggested that that was probably due to variation in exposure, in individual metabolic balance between activation and deactivation, and in DNA repair capacity. Because DNA repair is both inducible and saturable, differences related to dose are likely (Swenberg et al., 1987; Danheiser et al., 1989).

The manner and timing of sample collection can produce ambiguous or meaningless results. For example, in a study to determine exposure to environmental tobacco smoke with nicotine or its metabolites as markers, different results were obtained when different sampling protocols were used. Physiological pharmacokinetic modeling has demonstrated that the single-time point sampling protocol is of little use, unless a marker has a long half-life, which is rare for most exposures (Schwartz and Balter, 1988). Therefore, a good understanding of the pharmacokinetics is essential for proper timing of sample collection.

Difficulty of Establishing Links Between Exposure and Markers of Effect

Biological markers of effect are usually not exposure-specific. For example, pathophysiological changes, such as alterations in sperm structure or function and hormonal changes indicative of early reproductive disease, are not specific to chemicals and routes of entry. The same is true of most markers of preclinical and clinical immunological, cardiovascular, neurological, and renal dysfunction (EPA, 1988a). With respect to tumorigenesis, most preclinical effect markers—such as fetal proteins, oncogene protein products, structural changes in oncogenes, and chromosomal deletions—do not reveal the identity of the environmental exposure responsible. Increased specificity can be achieved if future studies, such as those suggested by Cariello and Thilly (1986), show that mutagens are specific with regard to the kind and position of mutation, and this specificity can be considered as a chemical fingerprint left on the DNA. The fingerprint would be a powerful tool in establishing the cause-effect relationship. However, Sukumar et al. (1984) observed the same

ras oncogene is activated in neoplastic cells derived from exposure to several different chemicals, so this lesion cannot act as a fingerprint.

The search for effect markers for pulmonary toxicants is also frustrated by the lack of specificity of pulmonary responses to etiologic agents (NRC, 1988). Those responses include altered breathing patterns and airway constriction, cell injury leading to inflammation, persistent alteration of lung structure (e.g., fibrosis, chronic obstructive pulmonary disease, and granulomatous disease), and neoplasia.

There is a need for research to identify biochemical correlates of structural changes, as well as to distinguish effects caused by a chemical from effects that are responses to cell injury (Smith et al., 1986). It is therefore desirable to incorporate chemical-specific markers of exposure and early biological effect into a study design to complement the nonspecific biological markers. As discussed later, however, relating even a chemical-specific marker to a defined exposure period is not clear-cut.

Confounding Influences on Biological Markers

Biological markers of exposure reflect diverse behavioral, biological, and methodological processes. Hence, they can be more subject to confounding influences than are measurements of ambient airborne contaminants. Droz (1985) evaluated effects of confounding factors on dose with simulation models. He identified six confounding factors that could influence the dose of organic solvents: intraday and interday fluctuation of exposure, repetition of exposure, physical workload, body build, and metabolism. The factors were applied to four solvents (benzene, styrene, methyl chloroform, and tetrachloroethylene) that differ in blood solubility and metabolism. Droz suggested that such models provide a means for assessing the role of confounding factors in internal dose.

Complexity and Resource Intensiveness

By virtue of their collaborative and interdisciplinary nature, biological marker investigations are highly demanding in terms of personnel, cost, and effort to develop understanding among researchers in different fields. Most also require clinical interaction with subjects. Incorporation of biological markers engenders new and important methodological problems in study design and in analysis of data (Schulte, 1987, 1989). It also introduces important ethical questions into health-effects research, particularly if information

is given to a person concerning a biological marker of effect when the relationship to an adverse health effect is unclear.

Use of Exposure Markers in Conjunction with Traditional Measures

The most effective method of characterizing exposure is to combine methods for assessing ambient exposure with various biological markers (Friberg, 1985). Used together, they enhance the precision and accuracy of exposure information, as exemplified in a study of hospital sterilizer operators occupationally exposed to ethylene oxide (Yager et al., 1983). Ambient and breathing-zone ethylene oxide concentrations were measured, as well as SCEs. Workers were classified into two groups according to estimates of amounts potentially absorbed: low, a mean of 13 mg of ethylene oxide over 6 months; and high, a mean of 500 mg over 6 months. A nonexposed control group was also evaluated. The high-exposure group had a mean of 10.7 SCEs/cell, which was significantly different ($p = 0.002$) from both that in the low-exposure group (7.8 SCEs/cell) and that in the control group (7.6 SCEs/cell). Without the use of ambient measurements to distinguish the two exposure groups, the difference in mean SCE frequency between exposed and control groups would have been only marginally significant ($p < 0.05$).

CRITERIA GOVERNING THE VALIDATION AND USE OF BIOLOGICAL MARKERS

Biological markers can be used to identify discrete components in the exposure-health-effects relationship (Figure 4.1). For a given exposure and disease, it is possible to identify most of the components of the relationship. Whether the relationship is linear or follows some other form, such as a branched network, is uncertain, but the linear concept of a relationship should suffice for research planning. Use of this model, however, should not obscure the need for efforts to explore the relationship between markers that might be represented by more accurate, nonlinear models (see Schulte, 1989, for review).

The current use of biological markers for exposure assessment is not without its pitfalls, and in some cases it cannot occur without adjustments and a stipulation of an independent determination of confounding variables. For example, there will be requirements to account for exposure to background concentrations of contaminants from the same and other media and to adjust

for seasonal or regional variation in some markers. These adjustments notwithstanding, the conventional techniques for assessing exposure-disease associations, screening for exposure of individuals in populations and handling multiple variables can be practiced for any two components in the relationship (e.g., exposure and internal dose). The major assumption that permits this approach is the causal or positive association between components of the relationship. For investigations involving markers of components from the central regions of the relationship (e.g., biologically effective dose), there is an increased need to test assumptions and hypotheses, evaluate misclassification, and identify and control confounding factors. That is because it is difficult to define the central markers in terms of either exposure or health effect when so many confounding factors (e.g., kinetics, medical history, and rates of transition) can affect the pathognomonic relationships.

Validation and Selection of Biological Markers

The validity of a biological marker for environmental studies should be determined on the basis of the fundamental criteria reviewed by Perera (1987) and discussed below.

Exposure Assessment

There must be a clear hypothesis or model of exposure-response relationships defining the role of the specific marker in relation to the possible exposure scenario. The relevance of markers of exposure is generally easier to establish than that of effect markers when assessing exposure. Relating markers of early biological effect to an original causative agent and routes of exposure is much more difficult, requiring extensive validation studies with careful linkage of an exposure to a marker of effect.

Understanding of Pharmacokinetics and Temporal Relevance

The proper selection and use of biological markers depend on an understanding of the underlying pharmacokinetics and pharmacodynamics of suspected contaminants (WHO, 1986; Andersen, 1987; Smith, 1987; Yager, 1988). Knowledge of pharmacokinetics is important in determining the frequency and timing of sampling and the tissues or fluids most appropriate for study. It also

guides the interpretation of dose and effect data obtained in a target tissue or a surrogate.

The temporal relationship of markers to external exposure or to disease end points must be clear. Whether an exposure marker reflects recent or cumulative exposures, or peaks or averages, depends on the pharmacokinetics of the contaminant, the persistence of the marker in the biological sample being assayed (which is in large part a function of the turnover rate or half-life of the sample), and repair rates.

Understanding of temporal relevance is essential for developing monitoring strategies and interpreting results. Most measures of internal dose, for example, reflect recent exposures. An exception would be a substance that is fat-soluble and is stored in adipose tissue. Hemoglobin is a good integrating dosimeter over the 4-month half-life of erythrocytes, which, unlike white blood cells, lack repair systems. Human serum albumin has a half-life of 20-25 days. Albumin is synthesized in the liver, where many carcinogens are metabolically activated, so it might reveal adducts not detected in hemoglobin.

The period reflected by white blood cells or lymphocytes is considerably more complex (Perera, 1987; Carrano and Natarajan, 1988). For example, adducts on DNA from white cells can reflect both past and current exposures, because a subset (T cells) is very long-lived. A review of white-cell subpopulations shows that measurements of DNA adducts in these cells will be influenced by the longer-lived T cells and will therefore reflect exposures that occurred both recently and several decades in the past. T cells make up approximately 60-90% of lymphocytes, which in turn constitute about 22-28% of peripheral white cells in circulating blood. Thus, T cells constitute a maximum of 25% of white cells. The estimated half-life of T cells is 3 years. In contrast, B cells and monocytes constitute roughly 1-2% and 1-7%, respectively, of circulating white cells and have lifetimes ranging from days to weeks. Granulocytes make up the remaining 66-85% of white cells and are short-lived (hours to days). Thus, one should consider DNA adducts only in cells damaged while in circulation and not white-cell adducts in circulating white cells, which might result from damage to stem or precursor cells in the bone marrow. When all DNA from a sample of peripheral blood is assayed for DNA adducts, one sees that the long-lived T cells are the major contributor in cases of past discontinued exposure, largely because of their lifetime, which is 100-1,000 times longer. In addition, lymphocytes have lower repair activity than do cycling cells, so DNA lesions are likely to be more persistent in lymphocytes. In cases of current, recent, or long-term uninterrupted exposure to carcinogens, T cells will contribute less importantly to total adducts. The preponderance of adducts will be measured in the shorter-lived granulocytes, B cells, and monocytes.

In retrospective case-control studies, for example, one would want a permanent marker left decades earlier by an initiating carcinogen. In the case of discontinued exposures, even the longes-lived markers will be diluted by cell turnover, thereby leading to underestimation of past or cumulative dose. Only if exposure had been continuous and had not changed substantially over the decades (and only if the disease had not altered metabolism) would current measurements of the marker be directly representative of critical prior exposure. At the very least, however, such markers as adducts reflect a person's responsiveness to carcinogenic exposures, provided that metabolism was unchanged by disease. Many other exposure patterns are relevant to case-control and cohort studies (current but interrupted, continuous but of varying magnitude, etc.). Each pattern would lead to a different distribution of adducts among white-cell populations and hence to a varied pattern of persistence.

Understanding of "Background" Variability and Confounding Variables

It is essential to know the range of values of a given biological marker in a "normal" population. Care must be taken not to be deceived by the extensive variation in biochemical individuality; what is considered "healthy" in some might indicate a health risk in others (Schulte, 1987). The range of "normal" can be large. For example, it is well known that cholinesterase activity in people not exposed to organophosphorus insecticides covers a wide range (WHO, 1975).

Interindividual variation and intraindividual variation are important contributors to "noise" or background in monitoring or epidemiological studies and should be characterized before large-scale application of a particular biological marker. Such data, however, can be generated only by large-scale surveys with repeated sampling and efforts to control for confounding variables. Thus, a background study is an important exposure assessment exercise in itself. With respect to carcinogen-DNA and carcinogen-protein adducts, substantial interindividual variation and intraindividual variation have been observed with PAHs, 4-ABP, and nitrosamines (Harris et al., 1985; Umbenhauer et al., 1985; Bryant et al., 1987; Perera, 1987). SCEs also vary widely within and between subjects (Carrano and Natarajan, 1988).

As discussed earlier, biological markers are subject to greater variability than conventional exposure assessment techniques, because the body actively participates in the collection, distribution, and elimination of absorbed contaminants. Confounding variables that must be accounted for in studies that

use biological markers include age, sex, race, cigarette smoking, alcohol consumption, diet, drugs or other environmental exposures, genetic factors, and pre-existing health impairment. In fact, it is known that alcohol intake is the most common cause of reduced metabolism of industrial chemicals (Fiserova-Bergerova, 1987). Thus, in a study of those chemicals in which the chemical or a metabolite is used as a biological marker of dose, one would have to account for alcohol consumption if one were to understand and interpret the data properly.

Most reports of cytogenetic studies have given no information on the impact of smoking and other exposures to carcinogens or mutagens on their results. Life-style factors (e.g., smoking and diet) and other chemical exposures (e.g., environmental, recreational, and therapeutic) are also potential confounding factors with respect to SCEs and most other markers. Additional potential confounders are host factors (e.g., health and immune status) and exposures that influence the marker of interest. In a study of PAH-DNA adducts in workers, for example, it is necessary to account for all other background exposures to PAHs and, ideally, for factors that could induce or inhibit metabolism and binding. Those inducers include cigarette smoke, char-broiled meat, alcohol, sedatives, and PCBs; the inhibitors include methylxanthines in foods, steroids, solvents, and spray paints. Thus, even pilot studies attempting to evaluate biological markers can become complex epidemiological exercises that involve careful interviewing.

Reproducibility, Sensitivity, and Specificity

Chemical specificity is a prime criterion for marker selection. Markers should be chemical-specific or at least highly correlated with the contaminant exposure of concern. That is important if effective mitigating steps are to be taken to prevent later exposures.

In addition to being specific, markers should also be "sensitive" to the agents involved in the exposures, detecting a high percentage of persons in the exposed group. Given interindividual variation, not all exposed persons would be expected to be positive; but it is important that the method for assaying a marker be sensitive enough to determine background, so that a true comparison of the exposed and unexposed can be made. Another criterion for sensitivity might be biological relevance. Some postlabeling techniques are able to detect progressively lower numbers of adducts, so a point might well be reached where adducts are of no phenotypic significance. That point could be determined in animal carcinogenicity studies (Ashby, 1988).

Assays should be reproducible, with limited variability ascribable to laboratory

personnel or the assay method itself (Gann et al., 1985). Reproducibility includes interlaboratory and intralaboratory reproducibility. When it is possible, different methods for assaying a given marker are useful for detecting artifacts in a method. An example of such a process is the cross-validation of various DNA-adduct marker techniques with immunoassays, ^{32}P-postlabeling and GC-MS, such as that carried out on PAH adducts of Finnish foundry workers.

Feasibility

The biological sample to be assayed must be readily available in humans so that procedures cause minimal discomfort to the participant. Often, understanding of the pharmacokinetics can assist in determining which tissue is most appropriate for sampling.

Assays must be cost-effective. Most assays are still in the experimental stage and cost about $300-500/sample. If multiple assays are performed in tandem on the same biological samples, costs of a study are greatly reduced. That is also the case if stored samples from a prospective study or biological specimen banks are available.

Storage of samples must not allow degradation of the relevant marker. Preparation and assay of samples are generally time consuming, because repeat assays are needed to ensure reproducibility, but an assay should not require unusually complicated processing or storage efforts.

Study Design

Adequate Sample Size

Sample size is determined by the expected differences in marker frequency or concentration between comparison groups, by the anticipated background in the exposed group, and by variability in measurement data. Considerable groundwork is required to establish those characteristics.

Appropriate Control Populations

Ideally, depending on the type of study (e.g., cohort vs. case-control), controls must be selected from persons expected to be nonexposed. However, in most studies of environmental exposures, there are numerous and often important

background sources. For example, when one is evaluating inhalation exposure of PAH, ethylene oxide, or styrene from industrial sources, background exposures could include cigarette smoke, diet, and indoor-air-pollution. It is necessary to control and analyze for potentially confounding sources of exposure. The definition of the nonexposed group will be the results of analysis of the chemical and biological markers. In many instances, assays have detected a substantial background of industrial compounds in nonindustrial persons, owing to the domestic use or misuse of the compounds. Hence, it may not always be necessary to be marker-free at the beginning of a longitudinal cohort study; however, they should have similar frequencies in each group.

Control of Potential Confounding Variables

This issue has been discussed above. Adequate control necessitates eliciting detailed environmental histories from study subjects. Where it is possible, an array of biological markers should be used to quantify their relationship to the exposure of interest, confirm the validity of the markers, and attempt to detect artifacts. Biological markers of susceptibility are useful to document the presence of confounding conditions.

Use of Batteries of Biological Markers

As noted previously, combination of markers is necessary to account for confounding factors. Multiple markers should also be used to distinguish between recent and earlier exposures. A battery of markers designed to assess the role of occupational exposure to aromatic amines in bladder cancer, for example, might include breathing-zone monitoring for the amines, immunoassays of specific aromatic amine-DNA adducts in white cells (lifetimes of days to years), and cytogenetic effects in T cells (half-life, 3 years). Cotinine in plasma could be used to learn about cigarette-smoke exposure, a potential confounding variable for bladder cancer.

Analysis

For a detailed discussion of the analytical considerations in biological-marker studies, the reader is referred to Thompson (1983), Sheldon et al. (1986), Schulte (1987, 1989), and Margolin (1988).

ETHICAL ISSUES

The availability of highly sensitive assays that can identify dose and effects resulting from the interplay between low-level exposures and genetic or acquired susceptibility raises several thorny ethical and moral questions. The reader is referred to Ashford (1986), Committee on Biological Markers of the National Research Council (1987), Schulte (1987), and Weiss (1989) for discussion of those issues. Primary among them is the use that is to be made of biological-marker information. Take, for example, the theoretical case of a biological marker known to reflect susceptibility. Should a worker who tests positive or has an increased measurement be removed from the workplace? If so, should he or she be offered an equivalent job in the same industry? Or should the workplace be cleaned up to protect the most sensitive worker?

In reality, few, if any, biological markers are established as predictors of individual risk associated with inborn traits, exposure, or a combination of the two. Therefore, it is important to inform research-study participants in advance that the results are interpretable only on the group level. Participants in such studies should be provided test results that are presented and discussed in context with available information (or lack thereof) on the variability within and between people in the normal (nonexposed) population, as well as that observed in the research-study group.

SUMMARY

Biological markers can be divided into three broad classes: markers of exposure, markers of effects, and markers of susceptibility. The committee focused on the application of biological markers to assessment of exposure to contaminants rather than their use to predict health effects. Markers provide information on dose that can be related to exposure using pharmacokinetic or pharmacodynamic models. However, these markers integrate all routes of exposure, and the actual routes cannot be detected without personal or micro-environmental exposure information. Biological markers, therefore, are best used in conjunction with conventional measures of exposure.

Biological markers range from measures of the intact original contaminant to measures of adverse health effects caused by that contaminant. Relating a marker directly to an exposure becomes more uncertain as measurements are obtained within the progression toward an effect, because the variability associated with the human "receptor" increases along that progression.

Properly measured, biological markers can reduce misclassification errors of degree of exposure and can increase the power of epidemiological studies

to identify associations between exposure and disease. Markers can, in theory, be useful in developing and validating pharmacokinetic models aimed at relating exposure to dose. They have the potential to improve risk extrapolation between species and between populations and to allow better predictions of human risk. Markers can provide an early warning of hazard or potential risk of disease. Markers measured in stored specimen banks can allow retrospective determination of whether a particular contaminant was elevated in the general population at an earlier time.

Use of biological markers for assessing exposure has several disadvantages and limitations. A major limitation is that most markers are in the development stage and have not been fully validated or field tested. A key question regarding markers of exposure is what compounds and exposures could have produced a marker of a measured amount in a specific tissue. The variability of markers can present problems in establishing quantitative relationships between exposure and response at low-exposure concentrations. Markers reflect diverse behavioral, biological, and methodological processes. Hence, they can be subject to more confounding influences than are measurements of ambient airborne contaminants. By virtue of their collaborative and interdisciplinary nature, investigations of biological markers are demanding in terms of personnel, cost, and effort to develop understanding among researchers.

Analytical techniques with improved chemical specificity and sensitivity for biologically significant markers are needed to apply to exposure assessments, especially flexible assays that can analyze a number of markers simultaneously or be readily adapted to analyze numerous markers sequentially. For such techniques, validation studies are needed to link conclusively biological markers to putative causative agents.

Better pharmacokinetic data are needed for an increasing range of chemicals. These data are needed to further the development and validation of more sophisticated biological-marker models and to further understanding of how to model multiple metabolism pathways as a function of exposure level.

5

Survey Research Methods and Exposure Assessment

INTRODUCTION

Survey research has become an integral and routine approach to organizational decision making and scientific estimation. Hardly any product can be marketed or political candidate nominated without survey data on public acceptability. However, the quantity of survey research might have outstripped the scientific quality of survey practice. In many surveys, interviewers with little scientific training do little more than hold conversations with other survey respondents. Such surveys are not likely to maintain the methodological standards that are required for scientific validity. Moreover, when surveys appear expensive and sponsors who must pay for them look for ways to reduce costs, methodological standards are usually among the first factors to be sacrificed. That situation probably characterizes most of the survey research associated with exposure assessment studies. The committee examined many prominent studies in the field and found notable departures from sound survey practice; even the most sophisticated and laudable efforts toward improving survey quality, such as the standardized Environmental Inventory Questionnaire, contain some problematic survey practices.

Properly designed and conducted survey research can provide the precise population estimates needed for exposure assessment relatively inexpensively. The relevant types of information that can be obtained from surveys for exposure assessment include:

- Percentage of the U.S. population or a specific group or community that uses gas stoves, pesticides, or lives in homes with attached garages.
- Numbers of persons who smoke cigarettes, pump gasoline, or apply pesticides on a particular day.
- Amounts of time per day that people spend outdoors, in automobiles, or in the presence of people who smoke.

Such types of data on time use or time-activity patterns have become important in exposure-assessment research and are central to this chapter.

The methodological steps in collecting time-activity data and all other data collected by surveys include:

- Choosing samples of persons with random-probability methods from complete and carefully constructed sample frames.
- Selecting the most appropriate mode(s) of data collection—usually face-to-face or telephone interaction or the subjects' own completion of a survey form.
- Reaching a sample of adequate size for statistical analyses.
- Achieving a high response rate from the selected sample.
- Deciding on the most appropriate measurement approach—in exposure assessment, these include personal exposure monitors combined with time-activity diaries (direct), time-activity diaries alone (indirect), and single questions or self-reports (questionnaire).
- Designing survey protocols that are understandable by respondents, usable by interviewers, and appropriate for sample projection.
- Framing specific survey questions in language that is simple, direct, and unambiguous.
- Coding and storing collected information in computer-readable form.
- Analyzing the data with appropriate statistical techniques.
- Deriving statistically valid conclusions from the data.

Specific considerations of coding, analysis, and dissemination of survey data are treated only minimally in this chapter, because those aspects of survey research are familiar and present relatively few problems. What is less familiar and recognized is how much the results of survey studies depend on the quality of collected data, particularly when too little attention has been given the first seven steps listed above. This chapter concentrates on those steps.

The seven methodological steps apply to *all* data involving human populations and not just to activities labeled as surveys. For example, data collected in a laboratory or field study that used an inappropriate or inadequate sample might be given undue weight.

Table 5.1 provides a general outline for the three topics to be addressed in this chapter: sample selection, measurement approach, and questionnaire framing and wording. This chapter focuses on advanced survey methods for exposure assessment and is not a how-to guide to survey research. Several useful textbooks on survey research methods can be recommended for the latter purpose: Warwick and Lininger (1975), Fowler (1984), Converse and Presser (1986), and the more elementary introduction of Bradburn and Sudman

(1988). EPA (1984a,b) has also produced a comprehensive and useful guide for conducting surveys. It would be a mistake, however, to assume that any text can make one a survey-research specialist. The elements of survey research and questionnaire construction are subtle arts, currently aided by little scientific guidance and, even more, by professional experience and wisdom. Even in well-established areas of research, each study and study instrument must be shaped by experienced practitioners to meet the study's unique objectives.

TABLE 5.1 Methodological Factors in Exposure-Assessment Surveys

Sample selection	Probability versus nonprobability method
	Sample frame (target population)
	Equal sampling versus oversampling of groups
	Response rate
	Sample size and related sampling error (precision)
	Other (e.g., sequential sampling and Bayesian estimation)
Measurement approach	Survey mode (face-to-face, telephone, etc.)
	Direct approach (personal monitor and time-activity diary)
	Indirect approach (time-activity diary alone)
	Questionnaire approach
Questionnaire framing and wording	Open versus closed questions
	Single versus multiple items
	Long versus short questions
	Explicit versus implicit questions
	Aspects of time

Exposure assessment survey research presents challenging problems because it is heavily involved with obtaining information about time. Personal exposure to pollutants is cumulative and complicated regarding time, and exposure assessors want to document when an important exposure to a contaminant has occurred. They also want to know the frequency of exposure, its sources, its location, and its contaminant concentrations in air and the

factors that effect them (e.g., ventilation), the breathing rates and other physiological states of the exposed person, and the general health status of the exposed person. The question "How long and how often was the exposure?" raises some difficult estimation problems. At one extreme, one can look at a very short period, such as an hour or a day; such studies require a high degree of control or precision. At the other extreme, one can look at far longer periods, such as a decade or a lifetime; these entail much less precision or control. Survey researchers can ask how often an individual respondent might have been in a situation that was likely to involve significant exposure, but the respondent's memory of such occasions is extremely problematic. Research on respondent memory has revealed a host of biasing factors and ambiguities (Tulving, 1983; Bradburn, 1987; Pierson et al., in press). Thus, there has been increased interest in the more precise measurement of activity during very short periods, such as the day or the hour, for which the time-activity diary is very promising as a measurement option. Most exposure assessment studies begin with only a general statement of the issues. To paraphrase a summary from another field:

> Some exposures to some contaminants of some sources for some periods at some frequency and concentration in some environments with some ventilation during some activities at some breathing rates have some health effects on some people.

Such a statement might seem at first glance vague or capricious. But it does show that many variables must be taken into account in estimating exposures and effects. It also shows that a few simple guidelines and checklists will not suffice in exposure assessment. Obtaining necessary information on the temporal and spatial distributions of contaminants of interest and on the population possibly exposed to them requires a highly coordinated multidisciplinary approach. Thus, it is not reasonable to expect a single breakthrough in technique, such as automated diaries or less obtrusive monitors, to address more than part of the overall estimation problems.

Once the variables mentioned earlier are considered in the study design and study participants are identified, the central problem is to ensure that the survey instrument used in the study is completed in an appropriate and understandable manner that will result in useful information.

SAMPLE SELECTION

The matter of selecting study participants is more straightforward than survey design, but strict guidelines need to be followed. Statistically proper sample selection is crucial for valid and accurate extrapolation from sample characteristics to general-population characteristics. Sample selection procedures for survey research on human behavior have a solid scientific and quantitative basis. The mathematical principles involved are rather simple and straightforward, but often neglected in conducting surveys. Selection of samples should have the following characteristics:

- The selection of individuals within a target population or within a specified period must have a random probability basis. Otherwise, the resulting data will have at best limited generalizability.
- The design of a sample frame involves identifying potential participants and implies series of rules to be followed in selecting individuals in the target population. Each individual must be identified in the frame and have a known chance of selection.
- The selection process should ensure that all individuals in the frame have an equal chance of selection or specify that some individuals of particular interest (e.g., older people, asthmatics, or people in rural areas) have a greater (but known) chance than others of being selected and oversampled.
- The sample frame should make it possible to calculate a response rate, the proportion of sampled individuals who participate in the study (i.e., provide the required data). That is a crucial gauge of the quality of the sample. If a sample frame specifies that 1,000 persons be selected into the sample, but only 200 or 300 actually participate (respond), the response rate is only 20% or 30%. Such a low response rate will raise important questions about the generalizability of the data, particularly if those who do respond can be said to have self-selected themselves into the sample and thus have biased the sample-selection process. Only careful follow-up methodological studies can determine how serious such response-rate problems can be for exposure assessment.
- Assuming that a probability sample has been drawn, that nonresponse bias is negligible, and that measurement error also is negligible, statistical formulas should be used to calculate the sampling error of an estimate based on the sample. Calculated estimates of precision are not appropriate if the response rate is low or if there are substantial measurement errors or problems.

Target Population

In studying human exposures, it is first necessary to determine whose exposures are to be assessed—i.e., one needs to determine the target population or sampling frame. Depending on the goal of a study, one could select from a variety of target populations, e.g., the U.S. national population, persons who reside in a particular community of interest, or persons who satisfy particular eligibility criteria. For epidemiological studies, one might be interested in a susceptible population, such as asthmatics or school-age children. For compliance studies, one might be interested in the general population of a geographic region.

If the target population is small, it might be possible to take a census and measure every individual in the population. Otherwise, one needs to select a sample from the target population and measure the individuals in the sample. Even when the population is small enough for a census, it might be preferable to use a sample and obtain more detailed information from those measured.

It is crucial in selecting the sample to use an appropriate probability sampling method, so that each individual has a known and nonzero chance of being selected. Depending on the goal of the study and the availability of prior information, one could set the sampling probabilities to be equal or unequal. If a specific subpopulation is of interest, one might oversample from that subpopulation, i.e., use higher sampling probabilities for individuals in it. If it is known or believed that the outcome of interest might be more variable in a subpopulation, one might also oversample from that subpopulation. When the goal of the study is to estimate characteristics of an entire population by combining information obtained from subpopulations, the Neyman allocation technique (Cochran, 1963) can be used to designate sample sizes for subpopulations. It is always important that each individual have a nonzero sampling probability, if the sample is to be generalizable to the target population.

Samples not based on probability sampling methods are often used in preliminary stages of exposure assessment. For example, investigators might conduct a pilot study of a new instrument on their colleagues or on volunteers. The results of such measurements might be useful for evaluating the instrument or testing overall field procedures, but the data collected usually cannot be generalized to any wider population. The same is true for studies performed with small or unrepresentative samples.

Response Rate

If one is to generalize from a sample to a target population, one must obtain a high proportion of responses from those sampled. Low response rate is probably the source of most of the quality problems associated with survey research. The U.S. Census Bureau and other government agencies can often obtain responses from more than 90% of those eligible. Academic research organizations usually have 65–75% response rates. Most commercial firms seem satisfied with 40–50% response rates. In many surveys that receive wide attention (e.g., in the mass media), effective response rates are less than 20%.

Low response rates warrant careful scrutiny, because they raise the possibility of substantial nonresponse bias. If respondents and nonrespondents are different, the data collected on the respondents are of questionable generalizability to the entire target population. Therefore, each survey should include an evaluation of the nature of nonresponse and the presence of nonresponse bias, particularly if the response rate is much less than 70%.

Nonresponse can have a variety of causes, such as failure to locate potential respondents, refusal to participate, inability to provide required information (e.g., due to illiteracy or language problems). Perhaps most importantly, potential respondent's might lack interest in the study or topic. In carefully designed surveys, exact percentages of different types of nonresponse are calculated. Some types are unlikely to be associated with the outcome of interest and therefore do not lead to nonresponse bias. Analysis of the causes of nonresponse is useful for identifying the potential for nonresponse bias and for reducing nonresponse.

A low response rate by itself does not necessarily lead to nonresponse bias, but it suggests a potential for it, especially in studies that make great demands on survey participants. To evaluate the presence of nonresponse bias, one needs to compare respondents and nonrespondents. Several survey devices are available, such as collection of a minimal set of data from a sample of nonrespondents with a short and less burdensome questionnaire, offering of monetary incentives to a sample of nonrespondents to persuade them to participate, and comparisons of groups of respondents, e.g., stragglers versus early respondents.

If nonresponse analysis indicates little or no difference between respondents and nonrespondents, one might assume that nonresponse is random and does not cause nonresponse bias; one can then analyze the observed data directly. However, if respondents and nonrespondents do differ (e.g., if urban residents are more likely to respond than rural residents), it will be necessary to adjust for the difference. Given an adequate amount of background information on respondents' residence locations, demographic characteristics, etc.,

it might be possible to generalize from the observed sample to the target population with statistical techniques, such as the reweighting or imputation steps presented by Kalton and Kasprzyk (1986). The techniques generally assume that, if nonrespondents have the same background characteristics as respondents, their exposures (and exposure distributions) are the same. The respondents' exposures are thus used to impute the nonrespondents' exposures.

Sampling Error

Statistical formulas can be used to estimate sampling error. Three factors are involved: the variance in the sampling, the sample size, and the sampling rate (the fraction of the entire population that is sampled). The sampling rate usually can be disregarded if the sample comprises less than 10% of the population from which it is drawn. For a simple random sample taken to estimate a specified population proportion (e.g., smokers or persons exposed to a specified contaminant on a particular day), sampling error is calculated according to the following equation:

$$\textit{sampling error} = [(p)(1 - p)/n]^{1/2}$$

(Eq. 5.1)

where p is the estimated proportion of the population having the characteristic (e.g., smokers) in the sample and n is the sample size. Multiplying the sampling error value by 1.96 and adding and subtracting the result from p gives a rough 95% confidence interval for the sample estimate; multiplying the sampling error value by 2.54 and adding and subtracting the result from p gives a rough 99% confidence interval. If the sample size represents more than 10% of the total population of interest, then the error can be reduced by a factor: $(1 - \text{proportion of population sampled})^{1/2}$. For example, if, in a sample of 600 people, 40% are found to have a characteristic, equation 5.1 leads to an estimated sampling error of 2%. With 99% confidence, the true proportion lies between 35% and 45% (i.e., 40% ± (2% × 2.54)). Use of the equation assumes a random sample, no important response-rate anomalies, no clustering of respondents, and no generalization beyond the original population. The above calculation of the confidence interval assumes a normal distribution for the sample estimate. In practice, the assumptions for equation 5.1 are not often met. In such cases, a correction factor is used. For example, for in-home personal interviewing with high clustering of respondents,

equation 5.1 produces error estimates that are too small and need an appropriate inflation factor.

The size of the sample is important in reducing sampling error, but sample size alone does not ensure sample quality. Determination of a proper sample size depends on the type of inference to be drawn, the sample variance, the degree of precision desired, and the adequacy of the response rate. It is important to note that sampling error varies inversely with the square root of the sample size.

Other Features

Three further features of sample design can increase a survey's effectiveness. Rather than a single large survey, a series of small samples can be drawn sequentially until stability in estimates and inferences is achieved. That can be especially important in personal monitor studies, which are extremely expensive.

Efficiencies in sampling design also can be achieved by using data from existing time-activity pattern studies (described later). Fairly consistent estimates of time spent outdoors or time spent in travel, for instance, have been published, and the background factors that are associated with larger or smaller portions of time spent in such activities also are fairly predictable (Robinson, 1977; Juster, 1985). For example, day of the week, employment status, and educational level have more to do with time spent away from home than do age, region of the country, or season. That means that well-executed samples of single local areas taken at single times of the year can provide considerable insight into exposure conditions in other locations. In other words, activity patterns in Denver, Cincinnati, and Jackson (Michigan) do not appear that different from each other and closely resemble national patterns of time use.

A third sample-relevant consideration is the use of panel studies that involve multiple periods of observation of the selected respondents. Especially in exposure studies, one needs exposure readings for individuals on more than a day or a week. Following the same individuals across time provides an essential perspective for future exposure assessment studies.

MEASUREMENT APPROACHES

The process of exposure takes place across time, and exposure assessment needs to be sensitive to the time element in all data collections. Three measurement

approaches can be distinguished in population-based exposure assessment: direct, indirect, and questionnaire. In the direct approach, respondents report in time-use diaries and carry personal exposure monitors that record their exposures for short periods. In the indirect approach, exposure is imputed from the activities that respondents report in time-activity diaries. In the more traditional questionnaire approach, exposure is imputed from responses to self-reported factual questions (e.g., occupation, age of dwelling unit, and fuels used for heating and cooking) or to general questions regarding activities (e.g., frequency of using pesticides). Personal exposure monitors are not used in the indirect approach or the traditional questionnaire approach.

Direct Approach

With the direct approach, human subjects carry personal monitors while they engage in their daily activities. Exposures are thus measured directly and objectively and without the reporting problems associated with questionnaires. However, without some respondent self-report or outside information, there is no way to understand the contaminant pollution sources that led to exposures or the reasons why notable exposures were recorded by a monitor. Therefore, one usually needs detailed activity reports, such as those available from a time-activity diary.

The other major problems that arise in personal monitor studies result from the cumbersome nature of most personal monitors. The use of cumbersome devices can result in high noncompliance rates. Also, presence of the monitors can reduce the utility of the data that are obtained by affecting the behavior of the respondents. Respondents might be more likely to restrict their activities when they carry equipment. When interacting with other people, subjects might try to conceal the equipment or otherwise wear it improperly. (Such phenomena can also affect the quality of data that respondents provide in related questionnaires.)

Exposure researchers must take particular care not to overburden the subjects when collecting survey data from them in exposure studies. When time-activity data were collected in early exposure studies, such as the TEAM study conducted in the early 1980s in Denver and Washington (e.g., Hartwell et al., 1984; Johnson, 1984), completion of the diary was one of many requirements for the respondents. Sometimes, neither respondents nor interviewers were adequately prepared for the demands and rigors of completing the time-activity diary. As a result, some diaries contained more than 24 hours' worth of activities, others less than 24 hours' worth. Large periods were not accounted for; e.g., some respondents reported no meals or sleep during 24 hours.

In some diaries, the periods of instruction by interviewers or technicians were recorded as normal daily activity. Activities like child care or shopping were seriously underreported or not reported at all. Nonetheless, the researchers were able to use the diaries to identify certain locations (e.g., parking garages) or activities that involved maximal exposure. The estimates of time that respondents spent in those locations might have been flawed, but the personal exposure data could be merged with more carefully designed and conducted time-activity studies.

Indirect Approach

The indirect approach does not involve the problems and expenses associated with using personal monitors. Instead, one separately measures the activity patterns of a sample of human subjects and merges the data with data on contaminant concentrations found in independent samples of microenvironments (e.g., from fixed-site monitoring) to assess exposure. The main advantage of the indirect approach is that it places less burden on respondents than personal monitoring and is thus able to achieve higher response rates.

Time-activity data can be obtained with several procedures, such as estimation by respondents in the study sample, by direct observation, or from time-activity diaries. In the estimation approach, people are asked to estimate the amount of time they spent in various activities during a given period, such as the previous year or the previous week. This is usually the least burdensome technique, although its reliability and validity are unknown and highly subject to the frailties of human memory and understanding.

In the observational approach, respondents' activities are monitored by outside observers. That adds a valuable degree of realism and completeness to the data collection, but the presence of an observer is likely to influence a respondent's activities. It is also likely to entail high rates of refusal to participate in a study.

Time-activity diaries have the greatest potential utility of the three indirect approaches. Respondents are asked to described sequentially all the activities in which they engage during a given period, usually a day or a week. The diary can be filled out concurrently with participation in the activities as in the Total Human Environmental Exposure Study (THEES) (Lioy et al., 1988), in which respondents were instructed to record all their activities for a 24-hour period. It can also be done by recall, as in the California Air Resources Board (CARB) Activity Study, in which respondents were asked to recall sequentially all their activities of the previous day. More burdensome for respondents than simple estimation, diaries provide a far more informative

and comprehensive account of daily activities. The reliability and validity of data from diaries have been encouraging when tested against independent measurements (Robinson, 1977, 1985; Juster, 1985).

Most diary studies have been for sociological purposes, not for pollution estimation or environmental research. For exposure assessment purposes, that means that crucial activities, such as smoking and working with engines or solvents, are not distinguished in the coded data. An important exception is the current statewide study being conducted by CARB. The CARB study was designed specifically for exposure assessment, and it measures periods of exposure to environmental tobacco smoke, time spent in specific rooms in the home, and occurrences of exposure to solvents and other pollutants (Robinson et al., 1989). The estimates generated from the study represent important advances in obtaining more refined and detailed estimates of specific exposures.

Methodological research has indicated that time-activity diary data are generally reliable and valid, although more definitive validity work should be undertaken. The use of time-activity diaries has several advantages over other ways of measuring time spent in activities:

- It is complete, in that respondents are asked to report on all their activities over a full 24-hour period.
- It is natural, in the sense that it resembles the way most people seem to organize, store, and retrieve information on their daily activities.
- It relies less on respondents' recall ability by concentrating attention on a single day or week, rather than asking respondents to provide hypothetical estimates of their usual activities or of their cumulative hours or minutes over longer periods (which vary by day of the week or season and thus can be very difficult to estimate).
- It can indicate unanticipated changes in the trends of activity patterns because it uses the 24-hour "zero sum" property of time: all activities must sum to 24 hours. Thus, if time is spent on some new activity, it occurs at the expense of other activity. It is therefore possible to identify tradeoffs in activities across time; e.g., what changes occur in people's activities if they spend more time playing sports or less time cooking.
- The use of open-end activity descriptions (i.e., in the respondent's own words) in the diary makes it possible to recombine or recode activities to fit different objectives of an investigation. This has become streamlined with the development of computer-assisted telephone interview (CATI) programs to record time-activity information, as in the CARB study (Robinson et al., 1989).

The diary makes it possible to extend traditional census demographic techniques and population counts to portray human activity with a time dimension and that makes it possible to approximate a census of behavior or activity in society on a person-day basis. In such an activity census, the person-day framework allows extrapolation to the population at large. One can estimate with some precision how much time a target population spends working on automobiles, going to the dry cleaners, cooking meals, and, at least theoretically, any other activity that takes place. Of more concern is the possibility of estimating time spent in microenvironments, such as outdoors in transit or at home, etc. The work of Chapin (1974) showed how this research can be extended to include spatial coordinates of activity and thus give a fully spatial-temporal set of activity accounts.

Results of several national time-diary studies conducted with the general approach (e.g., Szalai, 1972; Robinson, 1977; Juster, 1985) provide a basis for national estimates of time spent in specific environments and activities and of the times of day for specific activities and locations. They also indicate that some important changes in activity are taking place, such as the time that women are now spending away from home, or the increased proportion of at-home time they spent watching television (Gershuny and Robinson, 1988).

Some aspects of time use important for environmental research are missing from national time-diary collections. Some of the missing elements are these:

- Differentiation of key microenvironments, which are coded crudely. For example, time at home is not differentiated by room in the home.
- Specification of potential high-pollution microenvironments (like parking garages, dry cleaners, and auto repair shops). Time spent in those locations cannot be separated from time spent in low-pollution environments.
- Breathing rates during activities. Because few people can describe their exact breathing rates, they must be estimated from type of activity.
- Other ambient conditions during activities (e.g., presence of smokers or open windows).
- Distance from important potential pollution sources (e.g., gas ovens and pesticides).
- Information on the general structure of the home or workplace (number of rooms, presence of an attached garage, open spaces, etc.).
- Health status of respondent (e.g., asthma and handicaps).
- Information about children (under the age of 18).

The most recent national data, collected in 1985 (Gershuny and Robinson,1988), are available for only a single day, so long periods of exposure cannot be estimated for most of the population. That is especially important for

segments of the population who might be at risk from cumulative multiple exposures.

Thus, although some available national data are useful for general activity-estimation purposes, important gaps in detail greatly limit their value for modeling population exposures. The time-activity data usually need to be integrated with specific independent data on airborne chemicals or biological markers or their surrogates. That was a main reason behind the CARB decision to adopt the basic time-activity diary method for environmental-exposure estimation (Robinson et al., 1989). In particular, the CARB studies of 1987–1989 included the following measurement features:

- A detailed location code that differentiated rooms in the home.
- Fine-grained activity codes stored in original verbatim format from respondents and coded into more than 100 categories.
- Information on exposure to several possible pollution sources (e.g., gasoline engines and pesticides).
- Information on exposures in the workplace.
- Information on passive exposure to tobacco smoke for each activity throughout the day.
- Information on the daily activities of children, especially those under 12.

As detailed and focused as the CARB survey was for exposure research, it did not include information on the general health status of the respondents, their exact distances from possible pollutants, their breathing rates during activities, or open spaces in their workplaces or home. Moreover, the activity analyses were confined to a single day for each respondent. Utility for predicting or estimating exposures over longer periods, such as a week or a month, is unknown.

The 1975 University of Michigan time-diary study (Juster, 1985) did collect information on 4 days (2 weekdays and 2 weekend days to provide estimates of a "synthetic" week's activities), but the days were scattered across the year. Even though only a minority of respondents in this study described their single diary day as "typical," there was considerable predictability of activities from one day to the next, especially across weekdays (Kalton, 1985). Estimation of longer-term cumulative activities of individuals from single-day diaries is problematic, and a useful goal of future research would be to identify the level of predictability by collecting diary data across a full week. That has been done in England, although the response rates were less than 50% (Gershuny et al., 1986).

Even a week might be too short a period for detecting cumulative exposures to many pollutants. Until some kind of prospective panel study can be

arranged in which respondents agree to keep accounts of their activities and likely exposure for a month or a year, the only option is to obtain data with questionnaires, which incur the many problems associated with respondent memory. Obtaining long-term, multiple-day diary information from a representative sample of respondents remains a major subject of needed research —particularly with respect to cumulative risks for various pollutants.

The measurement of activity patterns can be seen to involve the five elements who, what, where, when, and why:

- Who is in the target population and the sampling frame?
- What are people doing at various times of the day?
- Where do the activities take place (such as outdoors and in automobiles)?
- When and for how long, during the day or year, do activities take place?
- Why do activities take place?

The detail of activity-pattern measurement depends on the goals of a study and the contaminants being studied. For general-purpose studies such as the TEAM study that deal with a wide variety of contaminants, coarse descriptions of activities (such as indoor vs. outdoor or smokers present or absent) might be sufficient. For studies, such as THEES, that are focused on a specific pollutant, more information is needed on the sources of contaminants and the types of situations in which large exposures can occur, especially activities (like cooking and bathing) that could generate particular pollutants. The time of contact with contaminants also needs to be estimated accurately. Daytime outdoor exposures might be considered different from evening outdoor exposures for pollutants, such as ozone, that have diurnal cycles.

For some microenvironments—such as homes, shops, and offices—standard probability sampling methods (e.g., use of area probability samples) can be readily applied. For other microenvironments, such as automobile trips, appropriate sampling techniques are less obvious and need to be developed.

Integrating Personal-Monitor and Diary Information

Time-activity diary information should provide a better understanding of exposure and predictions of exposures based on personal monitoring studies. Ideally, of course, one would like to have continuous activity and air contaminant monitoring, so that one could identify activities or locations in which peak exposures occur. With passive air contaminant monitors, however, that

task becomes much more difficult, because the time of episodes of peak or unusual exposure cannot be identified. Personal monitor studies raise sampling problems in addition to time-specification issues. If monitors are not worn at a respondent's breathing height, for example, measured concentrations of contaminants might be higher or lower than those to which the respondent is actually exposed. A respondent with a small passive monitor might cover it with an overcoat or sweater to conceal it or to keep warm.

Time-activity data from representative diary studies can be used to calibrate or adjust personal monitor data that are unrepresentative with respect to the samples of people who cooperate or activity patterns that were affected by the very presence of monitors. Data from time-activity diary studies can be used as benchmarks to reveal whether special high-risk groups deviate from the rest of the population in activity patterns (e.g., by spending more time in bars, dry-cleaning establishments, or gasoline stations). Diary data can be used to identify population groups whose activity patterns can lead to large exposures and to identify their special demographic features (e.g., younger people or urban residents). As noted in Chapters 2 and 6, time-activity data can be used in modeling general activity or exposure within various microenvironments. Diary data might be less useful for modeling pollutant effects that are difficult to detect over short periods, such as a day or a week. The data can be used to identify high-risk and low-risk populations, without further specification of such factors as sources of pollution, distance from sources, or ventilation and dispersion factors. To be optimally used for such purposes, more detailed diary data, along the lines described earlier, are needed.

A well-designed set of traditional questionnaire items might help to identify high-risk populations and to predict exposure. They could include estimated frequency of exposure to tobacco smoke, gas ovens in enclosed areas, and distance from those exposure sources. In general, time-diary studies do not indicate large variations in activity or location patterns by such basic variables as marital status, presence of children, region of the country, or season by themselves. But season, age, and day of the week can make a difference in the likelihood of going to work. Going to work outside the home usually implies a change in activity patterns and location. Sex, level of education, and health status (and less critically, income) are important factors and should be included and controlled for in future monitor studies. The responses to such questions should be validated and calibrated with time-activity diary information.

As mentioned previously, time-activity patterns at a single location (e.g., Jackson, Michigan) appear to resemble national patterns closely. The general consistency of time-activity data across geographic areas in practical terms means that one can gain generalizable insight from personal monitor and diary

studies conducted at single times of the year in single communities, provided that samples are drawn randomly, so that all segments of the community are represented equally or in proportion to their risk of exposure.

Questionnaire Approach

Almost all studies depend on some kind of traditional questionnaire to identify the background of respondents through factual information, such as their ages, occupations, general life styles, and access to household technology. The framing and wording of any questionnaire have a great effect on the responses to it and the inferences that are drawn from them. In general, the more standardized the question, the better it is for supporting inferences across studies.

The development of the Environmental Inventory Questionnaire (EIQ) (Lebowitz et al., 1989b) constitutes an excellent beginning in improving the quality of questionnaires for exposure- assessment research. It contains seven items on geographic location, eight on housing, nine dealing with occupation and family members, two on smoking in the home, six on home appliances, six related to radon, and six related to organic pollutants.

EIQ's strengths might lie more in the variables that it defines than in its specific question framing wording. Perhaps that is best illustrated by the questions related to estimated exposure episodes. In the case of tobacco smoke, for example, questions are asked about the amount of smoking in the home on the "most recent weekday" and "most recent weekend day." If interviews and smoking are distributed evenly across the week, that means that Sundays have six times as many chances to be selected as Saturdays, and Fridays three times as many chances as each of the other weekdays. If the family was away one day, estimated exposure will be underrepresented.

In the case of heating sources, the EIQ asks about the use of gas ranges, space heaters, etc., "during cold weather" and "during the winter." Those obviously are subjective terms with no clear referent period. The questions should specify months or temperatures. The response alternatives for some questions include "3+ days a week", "1–2 days a week", and "only in the morning to take the chill off (less than 1 hour)." Those scale inequities (days vs. hours) make it difficult for respondents to answer precisely. Similarly, questions about use of pesticides and herbicides outdoors refer only to episodes longer than 1 hour over the previous 6 months, whereas shorter duration or frequency of use need to be considered as well.

Finally, the EIQ asks a number of factual questions about number of rooms and construction materials. Those seem straightforward at first, but

might be difficult for less-handy respondents or renters—who probably make up a majority of the population—to answer. Even the number of rooms in a house might not be clear. Year of construction and number of stories could entail difficulty for recent occupants (if roughly 20% of Americans move every year). Such terms as "attached carport" and "closed completely" are susceptible to misunderstanding. Questions that ask only about the fuel used most often miss important details.

Even though the EIQ is a laudable advance in data-collection methods, its questions need to be adapted to and modified for particular study purposes—this could be done most effectively by persons trained in survey techniques.

Factual Questions

When contaminant-concentration measurements are not possible, factual questions can be asked to indicate the presence of exposure-related events or situations. For example, one might ask respondents whether they have been exposed to specific potential pollution sources, such as smokers, gasoline engines, and paints.

Although it does not provide much quantitative information, the factual approach can be a useful screening device for revealing the presence of excess exposure. Answers to factual questions can identify smokers or people whose occupations put them at high risk. The exposure models discussed in Chapter 6 usually require data on factual features of a person's life that can also be considered surrogate measurements, such as occupation, year of construction of residence, types of fuel used for heating and cooking, and presence of attached garages. Those types of questions were developed for the EIQ.

QUESTIONNAIRE FRAMING AND WORDING

Questionnaire results are subject to measurement error in the same way as physical and chemical measurements based on personal monitors. Both questionnaires and monitors can produce readings that differ from the actual value of the characteristic being measured. But a main advantage of exposure data obtained from monitors is the avoidance of many problems inherent in asking respondents questions.

The sources of problems that arise in asking questions are endless, and there are few solid scientific guidelines for framing and wording questions. However, a substantial body of research literature and experience has developed in the field of survey research, and recent studies have addressed the

issues with the method known as the split ballot (e.g., Schuman and Presser, 1981; Bishop et al., 1982). In this method, one randomly chosen half of a sample group is asked a question in one form and the other half in another form. Unfortunately for exposure assessment, most of the experimental studies have involved questions of opinion, rather than behavior, and there is minimal translation of different ways of asking opinion questions to ways of asking factual and behavior questions. How one resolves inconsistencies when two forms of a factual question produce different results remains a problem. Some form of validation will eventually be needed, through either direct observation, dual measurements, triangulation, or other techniques.

To illustrate the reporting problems encountered with straightforward factual questions, we can consider respondents' reports of whether their homes had basements. Between two periods in one panel study, roughly a 10% inconsistency rate was reported; that is, there was only 90% agreement from one time to another regarding the presence of a basement in the home (Beveridge, 1983). Because any change implies that people either filled in their existing basements or dug out new basements between the study periods, a 10% difference must be a reporting error—on a factual matter that should be readily observable and reportable. This example provides a sobering perspective on the ability of survey respondents to report accurately on their own behavior or circumstances. However, responses to time-estimate questions will more likely reflect potential exposure if an activity is more regular or repetitive (e.g., commuting to work versus taking clothes to the dry cleaners).

Because a simple decision to word a question one way or another can result in discrepant estimates, it is necessary to conduct split-ballot experiments to identify the magnitude of discrepancies or measurement error. To illustrate more options that are available, we discuss five below:

- Open-end versus closed-end questions.
- Single versus multiple questions.
- Long versus short questions.
- Explicit versus implicit questions.
- Long versus short reporting periods.

In contrast with closed-end questions, open-end questions yield responses that are in respondents' own words, provide insights into respondents' frame of reference regarding the questions, are more detailed, and minimize the frames of reference imposed by the researcher. Closed-end questions have the advantages of ease of administration, ease of coding, unambiguity of response, and lower costs. Cost factors invariably favor closed-end questions, which offer respondents no opportunity to describe situations in their own

words. Time-activity diary studies, in which respondents describe activities in their own words, provide a much richer and more widely useful data base than studies in which interviewers enter activity information into a limited number of precoded categories. The open-end approach has been a feature of national time-diary studies and the TEAM study; the closed-end approach has been used by Spengler et al. (1985), Lioy (1988), and Leaderer (1990a).

In general, it is assumed that a series of questions provides more complete data than a single question, because a series reminds respondents of instances that they might not otherwise have considered. In exposure research, rather than asking respondents whether they generally use detergents, one could read them a list of the names of the most popular detergents as part of a question series.

Much the same issues arise with regard to question length. In general, the conventional belief has been that shorter questions are better, because they are easier to follow, are less ambiguous, and involve less time (cost) to ask than longer questions. That view is now being reconsidered in light of research showing some benefits of longer questions. Like series of questions, longer questions tend to remind respondents of instances they might not otherwise have considered. Although longer questions can change the level of response, responses might show the same pattern of correlations with age, occupational status, emission source, etc., as shorter questions.

It is usually preferable to ask respondents explicit questions, rather than expect them to retrieve information from memory in response to implicit questions. For example, it is considered easier for respondents to answer the question "Were you in the company of anyone who smoked yesterday?" than the question "Are you in the company of smokers often, sometimes, or never?" Implicit terms like "often" mean different things to different respondents and require more inference, whereas "yesterday" should have the same meaning to all respondents. Similarly, in the case of long versus short reporting periods, one should expect more accurate reporting about short and recent periods (e.g., yesterday or last week) than about long or more distant periods. Nevertheless, experimental data are needed to substantiate the expectation or to calibrate for corrections.

Throughout the process of question development and evaluation, one needs to ensure that questions are tailored as closely as possible to respondents' abilities and willingness to answer. Multiple pilot tests with respondent debriefings or analyses of taped interviews are to be encouraged. Results of split-ballot experiments provide the most persuasive case for asking a question one way rather than another.

Because there is no best way to ask a question, a realistic approach is to consider all questions as having their imperfections and problems that require

researchers' attention. Moreover, what might improve a question on one criterion might not on another.

No questionnaire can eliminate measurement error entirely. Although it is important to estimate the magnitude of measurement error for a questionnaire, such estimation does not appear to be a common feature of survey questionnaires. In some situations, it might be possible to validate respondents' answers directly. For example, after a telephone interview, interviewers might visit a selected sample of respondents' homes to verify the presence of a basement or a type of insulation. When direct validation is not possible, repeated measurements can be used to estimate the reliability of responses. But reliability does not address the problem of systematic errors or bias: respondents might well report the same mistake, no matter how the question is framed.

IMPROVING SURVEY QUESTIONS

There is a major need to develop reliable and valid questions for exposure assessment research. Failure to appreciate many elementary principles of question format and design is evident in questionnaires done to date, even the praise worthy EIQ. Building on the results of metholological studies and more refined time-activity diary studies, one should be able to develop a concise inventory of exposure-related questions for a variety of contaminants to identify populations at risk. That should be done in conjunction with personal monitoring studies, in which both short-term (diary) and long-term (estimate) questions could be asked of the same respondents. How well can one predict cumulative exposure (as measured by a monitor) from the time-activity diary and the estimate questions? Both diary and estimate questions would need to be tailored to capture aspects of exposure not examined extensively to date (e.g., breathing rates, distance to source, and ventilation). The advantages of a panel-study design, involving multiple periods of observation of selected respondents, are especially evident, in that long-term behaviors and effects can be assessed or modeled.

The committee proposes the following guidelines on question wording:

- Questions with precise time frames (e.g., "2 days per week" or "10 times per year") are clearer to respondents and give more consistent results than questions with imprecise time frames (e.g., "often" or "most of the time").
- The narrower the time frame (e.g., "2 hours per week," rather than "3 days per week"), the clearer the question is to respondents and probably the more consistent the results.

- Estimate tasks should be broken into manageable subtasks (e.g., if "hours per week" is desired, ask for daily estimates for each day of the week).
- Where possible, respondents' time estimates should be forced to sum to a specified total (e.g., 168 hours a week or 52 weeks a year) to increase accuracy survey and comparability across respondents.
- Multiple-scale responses clarify a respondent's task (e.g., "about 3 hours per day *or* about 21 hours a week").
- Memory aids can be useful for specific activities, microenvironments, or contaminant sources (e.g., it is sometimes useful to ask respondents to recall the most recent occurrence of the phenomenon of interest).

Throughout, one needs to recognize that survey respondents' concern over and attention to issues are far lower than those of professional researchers. Therefore the researcher must help the respondent to understand the reasons for the questions and the type of information being sought.

Although researchers should be wary of the lack of precision in respondents' estimates, such estimates can be very useful for relative measurement purposes. For instance, people who estimate that they use pesticides 10–19 days per year might report more related health effects than those who estimate pesticide use at less than 10 days per year—and both groups might show less effect than those who estimate 20–29 days per year. Similarly, those who have worked in high-exposure occupations for 5–9 years might report more related effects than those who have worked in such occupations for less than 5 years. Of course, there is no guarantee that such monotonic relations will be found, and the extent of such statistical correlations needs to be empirically documented.

INCORPORATING SURVEY-RESEARCH METHODS INTO EXPOSURE ASSESSMENT

Exposure assessment should enlist the expertise of multidisciplinary teams of specialists including survey statisticians and field specialists. Many assessments are being conducted independently by investigators whose interests are restricted to single subjects, such as modeling, monitoring, or time-activity estimation. As a result, current exposure studies are unnecessarily restricted to laboratory studies, epidemiological analyses, personal monitor studies, or national surveys. Specialists need to increase their communication with one another if more-integrated exposure assessments are to be designed and conducted.

Exposure research would benefit from the involvement of survey statisticians

and field specialists, who could help to reduce survey-related errors and the wide variations in survey responses observed in present studies. There seems to be little recognition of the need for probability samples or high response rates, which are as important in small studies as in large ones. A series of small benchmark surveys of normal activity patterns or microenvironments would help to establish a basis for comparison in future exposure assessments by, for instance, defining healthy buildings for studies of the sick building syndrome.

Application of survey-research methods can also contribute to improving the effectiveness of exposure-study design. It can help to identify the contaminants and microenvironments likely to result in the most important health or nuisance effects. It can also help exposure assessments to target study efforts on chronic or peak exposures on a basis consistent with the biological response time of the contaminant of concern.

SUMMARY

Exposure assessment presents challenging problems for survey research applications because of its intimate involvement with obtaining information about time. Personal exposure to pollutants is cumulative and complicated regarding time, and exposure assessors want to document when an important exposure to a contaminant has occurred. They also want to know the frequency of exposure, its sources, its locations, and its contaminant concentrations in air and the factors that affect them, the breathing rates and other physiological states of the exposed person, and the general health status of the exposed person.

Survey researchers can ask how often an individual respondent might have been in a situation that was likely to involve significant exposure, but the respondent's memory of such occasions is problematic. Thus, interest has increased in more precise measurement of activity during very short periods, such as the day or the hour, for which the time-activity diary is promising as a measurement option. Sample selection, measurement approach, and questionnaire framing and wording are the general aspects considered in this chapter for collecting time-activity data and all other data collected by surveys.

Statistically proper sample selection is crucial for valid and accurate extrapolation from sample characteristics to general-population characteristics. The mathematical principles involved are rather sample and straightforward, but often are neglected in conducting surveys. Individuals within a target population or within a specified period must be selected on a random probability basis. Each individual must be identified in the sample frame (target population)

and have a known chance of selection. All individuals in the frame should have an equal chance of selection or some greater, but known, chance than others of being selected and oversampled. The sample frame should make it possible to calculate the proportion of sampled individuals who participate in the study (i.e., provide the required data). Statistical formulas should be used to calculate the sampling error of an estimate based on the sample.

Three measurement approaches can be distinguished in population-based exposure assessments: direct, indirect, and questionnaire. In the direct approach, respondents report in time-use diaries and carry personal exposure monitors that record their exposures for short periods. In the indirect approach, exposure is imputed from the activities that respondents report in time-activity diaries. In the more traditional questionnaire approach, exposure is imputed from responses to self-reported factual questions or to general questions regarding activities. Time-activity data from representative diary studies can be used to calibrate or adjust personal monitor data that are unrepresentative for the samples of people who cooperated in the study or for activity patterns that were affected by the presence of monitors. Diary data can be used to identify population groups whose activity patterns can lead to large exposures and to identify their special demographic features. A well-designed set of traditional questionnaire items might also help to identify high-risk populations and to predict exposure.

Almost all studies depend on some kind of traditional questionnaire to identify the background of respondents. The framing and wording of any questionnaire have a great effect on the responses to it and the inferences that are drawn from them. In general, the more standardized the question, the better it is for supporting inferences across studies. Recognizing the general need to develop reliable and valid questions for exposure assessment, the committee proposed guidelines to improve question wording. The modification or adaptation of questions for particular study purposes could be done most effectively by persons trained in survey techniques.

The committee offers the following recommendations to foster the development of survey-research methods as effective tools for exposure assessment:

- Individual researchers should examine each survey question for its appropriateness for the purpose at hand. A trained survey methodologist can offer sound advice.
- More use can be made of less-expensive surveys conducted in communities or in sequential fashion (particularly given the high cost of personal monitor studies).
- Basic research is needed on the reliability (precision) and validity (accuracy) of respondents' answers, especially for estimating frequency or dura

tion of exposure to various pollutants. Well-designed studies in a single community is an inexpensive way to develop more valid estimates.

- When the situations of high-exposure readings on personal monitors need to be identified more clearly, researchers should assess the feasibility and usefulness of having trained personnel observing respondents and collecting exposure data as unobtrusively as possible. Such a technique would require respondents' consent and selection of observation periods.

6

Models

INTRODUCTION

Mathematical models use systems of equations, based on a conceptual framework, to describe interactions among components of physical, chemical, or biological systems. The conceptual component of a model consists of the assumptions and approximations that reduce a complex problem to a simplified, more manageable one. Models are used because they are an efficient way to examine the cause-effect relationships among components (or variables) in a system.

The bases of mathematical models are the fundamental physical and chemical laws, such as the laws of conservation of mass, energy, and momentum. Modelers must choose the level of detail in which components of a system are described. Clearly, an extremely rigorous model that includes every phenomenon in microscopic detail would be so complex that it would take a long time to develop and might be impossible to use. A compromise is always required between a rigorous description and getting an answer that is meaningful for a specific application with limited resources. This compromise involves making many simplifying assumptions, which should be carefully considered and listed. They impose limitations on the model that should always be kept in mind when evaluating the model's results.

Models are useful tools for quantifying the relationship between air-pollutant exposure and important variables, as well as for estimating exposures in situations where measurements are unavailable. Exposure models may obviate extensive environmental or personal measurement programs by providing estimates of population exposures that are based on small numbers of representative measurements. The challenge is to develop appropriate models that allow for extrapolation from relatively few exposure measurements to a much larger population (Sexton and Ryan, 1988).

A practical approach to assessing exposure through modeling requires

decisions as to how precise and accurate the assessments need to be. The ultimate focus is on the biological effects of exposure, so decisions on accuracy and precision require some quantitative knowledge of the biological effects. Limitations on resources require the exposure analyst to choose the most economical methods to answer the question, "How accurately must the exposure or exposure potential estimate be to provide the needed information for risk estimation, risk management, or epidemiology?" For risk-related problems, the analyst seeks a magnitude of exposure that defines the threshold of "significant risk." In some cases, the threshold has already been set with the establishment of an exposure limit (e.g., by ACGIH, OSHA, or EPA). In other cases, the threshold needs to be ascribed on the basis of available information on possible health effects of the contaminant of interest or a structural analogue. The judgement of those assigning limits should be driven by the quality of the data.

For risk assessment and management, health-effects data bases with a high degree of uncertainty should result in concomitantly high levels of attributed risk/(unit exposure)—that is, a low exposure limit—as a prudent safeguard against underestimating the health-effects potential of the agent. Thus, extremely meager information on contaminants and biological effects will result in low exposure limits until the data base can be improved to justify a higher limit.

For epidemiological studies, the modeler must understand the study design sufficiently to recognize the trade-offs between levels of uncertainty in exposure estimates and the ultimate risk evaluation that also depends on the level of uncertainty in the health-effects data.

Given an exposure limit, the analyst needs to determine whether any particular exposure scenario constitutes a significant fraction of that limit. However, the analyst needs only to use models with "enough" sophistication to do the job with the least cost. Simple models can be used first to explore an exposure scenario, because they require relatively few data and are thus less expensive to implement than the more sophisticated techniques. Simple models generally yield biased estimates of exposure. It is recommended that only models known to be conservative be used in screening calculations so that any bias that exists is protective of the individual exposed. Consider a contaminant with a vapor pressure of 0.1 torr, a molecular weight of 100, and a daily exposure limit of 8,000 $(mg/m^3) \cdot hr$ (an 8-hour time-weighted average of 1,000 mg/m^3). A simple model that assumes complete saturation of the air with this compound will render an estimated exposure of 4,300 $(mg/m^3) \cdot hr$, or about 50% of the exposure limit. Assuming further that this compound is not present in particulate form (which would increase the amount of contaminant inhaled) allows one to estimate a lack of significant risk vis-a-vis the

exposure limit. The true exposure will most likely be below this very conservative estimate, but greater quality of assessment is not needed, because this is a worst-case scenario.

Exposure models can be used to identify major exposure parameters (e.g., sources, emission rates, etc.) and to assist epidemiological studies and risk assessments. Although the input required for exposure models depends upon the nature of the model, all exposure models require information on who is exposed, to what contaminant, for how long, and under what circumstances (Davis and Gusman, 1982). Many models also require information on the sources, transport, transformation and fate of the contaminant(s) of interest.

Models generally rely on assumptions and approximations to quantitatively describe cause and effect relationships that are otherwise difficult to determine. In this way models are used to estimate exposures when it is impractical or impossible to measure exposures of an individual or population to a contaminant. Despite the simplifications inherent in models, they provide insights and information about the relationships between exposure and independent variables that determine exposure.

Models discussed in this chapter are classified into two broad categories: those which predict exposure (in units of concentration multiplied by time) and those which predict concentration (in units of mass per volume). Although concentration models are not truly exposure models, their output can be used to estimate exposures when combined with information on human time-activity patterns (see Figure 6.1). Since exposure occurs when humans are in contact with contaminant(s), exposure models generally combine information on the concentrations in microenvironments with information on activity patterns. The output of such models is a prediction or description of exposure for individuals or populations.

Exposure models can be used to estimate individual exposures or the distribution of individual exposures in a population. Activity patterns and microenvironmental contaminant concentrations—inputs to exposure prediction models—can be measured or modeled. The microenvironmental concentrations and the activity pattern can vary from individual to individual, and from time period to time period. Three types of models have been developed to estimate population exposures: (a) simulation models such as SHAPE (Ott, 1981, 1984) and NEM (Johnson, 1984; Johnson and Paul, 1984), (b) the convolution model by Duan (1981, 1982, 1985, 1989), and (c) the variance components model by Duan (1989).

As shown in Figure 6-1, concentration models are separated into several types: models based on the principles of physics and chemistry, and models that statistically relate measurements of concentrations to independent variables thought to be direct determinants of concentration (e.g., gas emission

rate from a cooking range) or indirect indicators (e.g., the presence of a gas range). There are also many hybrids of these two basic approaches to model contaminant concentrations.

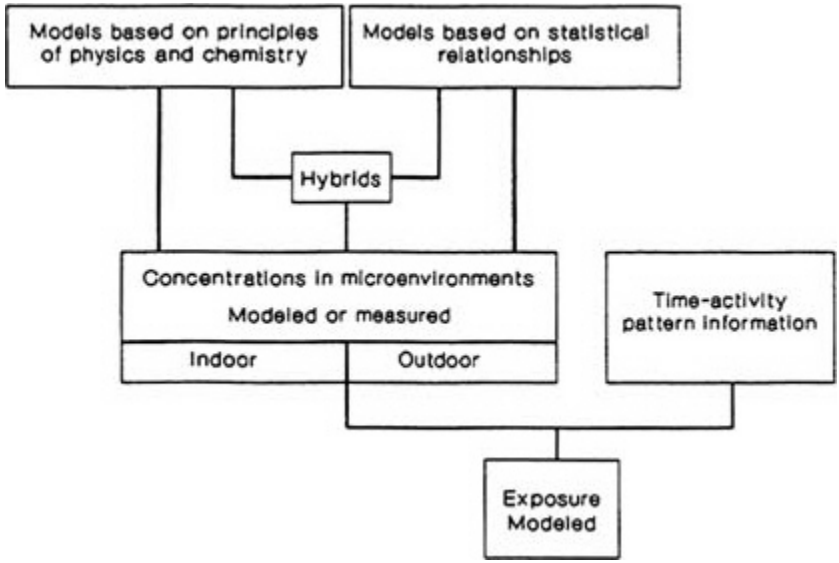

FIGURE 6.1 Schematic diagram of models used in exposure assessment

Concentration models based on physical principles quantitatively estimate emission source dispersion, deposition in the environment (indoor or outdoor), and transport to the receptor for a given contaminant. The transfer of a contaminant from one medium to another can also be modeled in this way. If a contaminant undergoes chemical reaction in the environment, then models based on chemical reaction kinetics principles are used to predict the outdoor concentrations of the secondary contaminants (products of reaction). Ozone and sulfuric acid aerosols are examples of secondary contaminants formed by chemical reactions of primary contaminants as they are dispersed and transported in the outdoor atmosphere. Models to describe and predict their concentrations and, ultimately, human exposures must, therefore, incorporate the rates and products of the chemical reactions.

The development of faster, larger, and less costly computers has greatly enhanced our ability to model complex phenomena like the turbulent flow of air in the outdoor and indoor environments. An approach to modeling the dispersion of contaminants from sources is to approximate the random motion of individual air parcels. However, random motion requires total independence

of one time interval from another and this requirement is not met for diffusion in the atmospheric boundary layers. Instead, a correlation will exist between o modeled approximately and the motion of a large number of individual parcels can be calculated.

IMPORTANT MODEL CHARACTERISTICS

Limited information is available regarding the accuracy of most contaminant concentration models and less is known about exposure models because most models have not been adequately validated. Model users should understand that model outputs have uncertainties, not just those arising from the uncertainties in the input data, and that actual exposure lies somewhere in the range of that uncertainty. The results of models should be presented with their estimated uncertainties. To the extent possible, the description of the model results should distinguish between input and model uncertainty. A major objective for improving models should be to reduce uncertainty due to the model itself so that the estimated exposure is closer to the real exposure and the uncertainties are primarily associated with the uncertainties in the input data.

Concentration and exposure models do not always include sufficient documentation (fundamental equations, assumptions, whether parameters were lumped, etc.) that enable new users to identify and adjust critical model parameters to fit new applications and or to compare their problems with previous applications. The inclusion in a model of particular complex terrain, of specific contaminant source locations, unique source types, or other unusual features of a particular air-shed may result in a model of high specificity; portions of such specific models may be applied to other air-sheds only if the models are well documented. For example, a model developed for the Los Angeles urban atmosphere could not be used to estimate contaminant concentrations in Denver's atmosphere unless the model takes account of the change in air density from sea level to Denver's 5,000 foot elevation along with other geographical differences. Although of limited use, sophisticated models are valuable research tools and provide valuable information on concentrations or exposures. With greater computational power becoming increasingly available, these models could be more widely applied in the future. It is important that users fully understand the models they apply, because improper use of a complicated model increases the likelihood of obtaining misleading results.

Computer models need to be transferable from one computer system to another so that the validity of the model can be checked by others and the

model can be applied to other problems. Source codes for models (e.g., computer language code) in general should be provided in a form complete enough that programmers need not resort to any functions or subroutines other than those commonly available in the compiler for the model's language. In addition, as expert systems are developed to assist the application of models, attention must be paid to ensuring that these systems can be operated by new users.

CONCENTRATION MODELS

Models are used extensively to estimate outdoor contaminant concentrations at specific sites. These models use physical, chemical, and statistical methods to address the contaminant source release, dispersion, reaction, and deposition. Models are also used to estimate indoor contaminant concentrations; most of these applications have occurred in occupational/ industrial settings. They generally focus on measuring the contaminant concentration in a worker's breathing zone. The following discussion reviews outdoor concentration models (e.g., emission, dispersion, atmospheric chemistry) and indoor concentration models (industrial and nonindustrial), including a review of deposition and mixing within and between rooms. Variability is discussed for both types. The section concludes with a discussion of recent advances in outdoor and indoor concentration models.

Outdoor Models—Contaminant Source Emissions

Emission models based on the properties of the chemicals, design parameters of the emission sources, the physics of mixtures, and the ambient weather conditions can provide an alternative to source monitoring (Owens et al., 1964; MacKay and Matsugu, 1973; Reinhardt, 1977; Tung et al., 1985). The type and structure of a model depend on the source and type of contaminant releases; some sources are continuously replenished and can be considered to be at steady-state, while other releases change in temperature or concentration. Hanna and Drivas (1987) describe in detail various models available for dynamic and steady-state sources.

Accurate estimation of emissions from point, area, and volume sources is necessary for accurate quantification of downwind ambient concentrations. Quantification of point sources such as stack discharges from manufacturing units can be accomplished by a number of methods, including monitoring of the sources directly and standard chemical engineering design procedures

based on material and heat balances. For example, boiler emissions can be defined by knowledge of the composition of the fuel burned and the ash produced by the fuel combustion. Estimating releases from other processing equipment may require knowledge of the reaction kinetics, vapor-liquid behavior of the reaction mixtures, and the operating temperatures and pressures.

Emissions from nonpoint sources are more difficult to monitor. A number of attempts have been made over the past decade to develop monitoring techniques for vapor and particulate emissions from pits, ponds, and lagoons (Harrison and Hughes, 1976, 1981; GCA, 1982; Thibodeaux et al., 1982) and fugitive emissions from chemical process equipment (EPA, 1988c). The Chemical Manufacturers' Association (CMA, 1987, 1989) and the EPA (1988c) have published extensive data and models for the quantification of fugitive emissions from chemical process equipment. EPA and the American Petroleum Institute have published models for quantifying the emissions from large storage tanks (EPA, 1985a). Emissions are estimated for working losses (filling and draining the vessels) and breathing losses (losses caused by the diurnal temperature change). The EPA estimation procedure is frequently updated for use by federal and state regulators and the manufacturing organizations in permit negotiations and development of state implementation plans for compliance with federal regulations.

The development of empirical models for emission rate estimations has focused mainly on issues related to fugitive emissions. The rate of fugitive emissions at any process point (valve, pump, etc.) is assumed to characterize all similar process points or similar equipment items. Although this assumption is known to be incorrect, data are insufficient to provide better emission predictions. High emission rate predictions are obtained with these models and thus the subsequent exposure predictions may be overly conservative.

Models for sudden releases of hazardous materials are generally based on fundamental principles of physics. The mass and heat balances (Bird et al., 1960) used by the modelers have used either a dynamic solution or a steady-state solution of the system of equations which describe these episodes. For spills on land, a model was developed for quantification of liquefied natural gas releases (Shaw and Briscoe, 1978). For spills on land or water, a model was developed for characterizing the emissions of chemicals in the workplace (Wu and Schroy, 1979). These and related models are discussed by Hanna and Drivas (1987).

Models are used to calculate emissions of carbon monoxide, NO_x, and organics from motor vehicles. Seitz (1989) contrasts the methods used by the state of California with those used by the federal government for transportation and emission analysis.

Validation

To ensure that their concentration estimates are appropriate, it is necessary to validate emission models with data from operating systems. The type of validation depends on the type of model and the ability of monitoring protocols to quantify actual emissions accurately. For fugitive emissions, the rate of losses to the environment can be measured directly by enclosing individual sources to quantify the emission rate. The accuracy of the emission rate measurement depends on the size and type of equipment, operating conditions, and the chemical and physical properties of the chemicals being handled. For example, the petroleum refining industry commonly involves high-temperature processing of chemicals in large equipment, but the chemical industry commonly uses ambient temperatures and small equipment and has substantially lower emission rates.

Losses from large open ponds and pits are more difficult to quantify and have caused difficulty in validation of emission models. The evaporation of water from large lakes, monitored for many years by the U.S. Weather Service, provides the best validation data base. Spill tests with chemicals such as ammonia and liquefied natural gas offer another data base for validation and calibration of emission models. Validation of models for aerated basins, tanks, and lagoons can use standard data from the chemical engineering transport literature when no reactions or other removal mechanisms are involved. When a biological oxidation-reduction process is providing a competitive removal mechanism, the validation of emission models is much more difficult. Kinetic information is needed for biological degradation as an event separate from losses due to volatilization. Much of the literature of biological reaction kinetics combines volatilization and degradation losses and attributes the total loss to kinetic reactions. This procedure makes the resulting data bases difficult to apply to specific sources.

Contaminant Dispersion

Models using annual average emission rates that were either measured or estimated have been available since the early 1930s (Sutton, 1932) for simulating the dispersion of emissions from point sources. However, it was only in the late 1960s and the early 1970s that there was substantial development of computer programs for air dispersion of contaminants. For example, EPA has supported the continuing development of a variety of Gaussian plume models in its Users Network for Applied Modeling in Air-Pollution (UNAMAP) series of programs.

The basic concept of Gaussian plume models is that the turbulent dispersion of contaminants in the air has a random character of large-scale eddy motion that is analogous to the Brownian motion of molecules. From this analogy, a differential equation based on Fick's law is obtained and the solutions are Gaussian functions. For atmospheric dispersion, motion in the direction of the wind (advection) is modeled as the average wind speed. Horizontal and vertical dispersion perpendicular to the prevailing wind direction are modeled as Gaussian functions with the standard deviations functions of atmospheric stability and distance from the source (Hanna et al., 1982). To incorporate some of the source characteristics that affect dispersion, buoyant plume rise was included in the dispersion models (Briggs, 1969, 1971).

In 1978, EPA designated certain dispersion model computer codes as "approved models" for developing state implementation plans to achieve compliance with National Ambient Air Quality Standards (NAAQS) (EPA, 1978). With EPA's endorsement of these models, they have become the principal tools in plans for controlling contaminant sources. In developing control strategies for contaminants regulated by the NAAQS, EPA developed models that combined source emission rates with atmospheric dispersion to predict the concentrations of the contaminants at a receptor site and to test the effectiveness of control strategies. Prediction of the concentration of ozone, a contaminant regulated by the NAAQS, requires modeling of the photochemical transformation of its precursors, i.e., volatile organic compounds and NO_x, as well as their transport.

Dispersion modeling also can be done statistically. The air can be considered as a number of parcels or particles, which move in a random fashion (Taylor, 1921). The path of a single parcel can be described by a statistical function. If the parcel is assumed to have independent motion at any step during transport, it can be modeled as a "random walk," in analogy to Brownian motion of molecules. That concept was extensively developed in the 1950s, but the methods became so complicated by the need for empirical factors that they were replaced with the simpler Gaussian plume methods (Hanna et al., 1982).

In recent years, stochastic modeling of atmospheric dispersion has increased in popularity, because it is relatively simple, it can be applied to complicated problems, and it has been made more practical by improvements in computer capability and costs. Probabilistic models can easily incorporate physical phenomena, such as buoyancy, droplet evaporation, polydispersity of released particles, and dry deposition.

Stochastic modeling is typically implemented as a numerical Monte Carlo model. Boughton et al. (1987) describe a Monte Carlo simulation of atmospheric dispersion in which parcel displacement or velocity is treated as a

continuous-time Markov process. They restrict the model to crosswind-integrated point sources and assume that dispersion in the mean wind direction is negligible. That reduces the analysis to one dimension. Liljegren (1989) has extended the model to incorporate horizontal and vertical dispersion perpendicular to the mean wind direction. The results of the latter model agree well with published concentration data (William E. Dunn, University of Illinois, Urbana, personal communication, 1988). It appears that three-dimensional stochastic models will offer considerable predictive improvement (including predictions of concentration change with time) over conventional Gaussian plume models.

Most of the studies to calibrate and validate plume dispersion models have involved the release of inert tracer gases from near the ground in nonbuoyant plumes—conditions very different from real stack plumes. In general, the studies have not covered a sufficient distance downwind to test the models beyond a few kilometers, so the results might not be reliable. Tracer programs and in-plume aircraft flights do not provide sufficient data to permit evaluation of the models' ability to predict short-term peak concentrations. Long-term average values have been estimated with data from sparse networks of continuous monitors, but their spatial resolution might be too low for estimation of impacts of peak concentrations. Thus, validation is still inadequate.

With support of the Electric Power Research Institute, a major study to validate plume models was mounted in the early 1980s. The first study was of a large coal-fired power plant situated in relatively simple terrain, to minimize topographical uncertainties. The study compared three Gaussian plume models and three stochastic models with ground-level concentrations obtained with both routine and intensive measurements programs (Bowne and Londergan, 1983). The results indicated serious deficiencies in the particular dispersion models tested; they do not address complicating effects—such as complex terrain, surface roughness, atmospheric chemistry, and large sources of heat that cause localized climatic change—and therefore are of uncertain validity.

Little is known about how a plume is affected by the objects it passes over. For instance, a large manufacturing plant may emit much heat that creates localized climate changes that directly affect the plume. In what is called the heat-island effect, large masses of hot air rise and change the local climate. This can change weather patterns over large cities.

The behavior of buoyancy, neutral buoyancy, and dense clouds in regions of complex terrain constitutes a problem for the dispersion modeler. The buoyancy and neutral-buoyancy plume models developed to date provide little encouragement that the problems can be solved to permit reasonable predictions

of exposure. Little research has been done on the behavior of dense clouds.

The dense and neutral-buoyancy models use mixing factors to represent the surface under a plume. For example, the factors used for rural terrain are equivalent to flat, low-friction surfaces, which cause a minimum of plume turbulence. For urban terrain, the impacts of homes, businesses, and factories have been quantified by calibration experiments. Rural factors are usually used to ensure that results do not underestimate contaminant concentrations. However, surface roughness and the interaction of a plume with a building can have substantial effects. If the plume is spread sideways by such an interaction, the results might well be catastrophic for a plant poorly designed for the community setting.

Atmospheric Chemistry

It is now possible to describe in detail many of the individual reactions occurring in photochemical smog (Niki et al., 1972; Demerjian et al., 1974; Seinfeld, 1988). Use of explicit and detailed mechanisms in air-shed or long-range transport models, however, is not always practical, and detailed information on the rate constants of the precursors, intermediates, and products is not complete. The limitations on the understanding and quantitations of the complex chemical reactions can severely limit the accuracy of the output prediction. In addition, the computer time required for the integration of the rate equations associated with the hundreds of individual compounds involved is prohibitive using current computer systems.

For urban air-shed models, condensed or (lumped) chemical mechanisms are generally used (Finlayson-Pitts and Pitts, 1986; Seinfeld, 1988); i.e., reactions or chemical species are grouped and an overall rate constant is used for each group (Falls and Seinfeld, 1978; Whitten et al., 1980; McRae et al., 1982). This approach can affect the spatial and temporal accuracy and precision of a model. In addition, the lumping process limits the fundamental understanding of the specific pathways and interesting chemistry may be hidden by the lumping process. To estimate ozone concentrations with a model, for example, it is necessary to estimate the concentrations of reactive intermediates. The resulting concentrations of these other substances reflect many of the simplifying assumptions and may lead to erroneous results, even if the specific concentration sought—i.e., ozone—is accurately predicted.

Ozone models have been critically reviewed by Seinfeld (1988). Improved ozone models incorporate wind fields, chemical reaction mechanisms, turbulent dispersion, and removal processes. The newer, more sophisticated models

are gridded: the area of interest is divided into two- or three-dimensional zones in which photochemical reactions take place and wind and turbulence transport chemical constituents from one grid zone to another. The chemistry of the inorganic compounds involving NO_x, O_3, and HO_x is included. However, because of the large number of possible constituents and the enormous number of possible chemical reactions among them, reduced or lumped mechanisms are used, as mentioned above. The compounds may be combined into chemically similar classes, such as alkanes, alkenes, carbonyls, and aromatics, or carbon atom groups may be lumped according to bond type (single bond, double bond, aromatic bond, etc.), structure, and reactivity of subgroups. In either case, the chemistry is simplified to provide results with reasonable amounts of computational resources. The simplification is analogous to that necessary to model the dispersion of the chemically reacting mixture.

Models describing the reactions of SO_2 to form sulfuric acid aerosol involve many fewer chemical reactions than do photochemical smog models. The models must incorporate all important phases—gas, aqueous, and those on solid surfaces—and the reactions proceed in several phases (Rodhe et al., 1981; Seigneur et al., 1984). Although the rates and mechanisms of gas phase reactions of SO_2 are fairly well understood, there are large uncertainties in aqueous and solid-surface reaction rates (Scire and Venkatram, 1985). Furthermore, wet and dry deposition processes must be incorporated into the models, because such processes are significant for long-range transport (Lee and Shannon, 1985).

Production and transport of the components of acid deposition are predicted by the Regional Acid Deposition Model (RADM) developed at the National Center for Atmospheric Research for EPA (Chang et al., 1987). The model combines many of the chemical mechanisms of the ozone models with liquid-phase reactions (Stockwell et al., 1986). It includes long-range transport, deposition formation and related cloud processes, and chemistry. Initial validation studies have suggested good agreement between the model and actual deposition chemistry. However, only limited studies have been made and substantial additional testing and validation studies are planned before the RADM becomes the principal tool for acid-deposition-control planning in the United States.

The modeling of acidic particle (e.g., sulfate) formation and transport is in its rudimentary stages. Previously, most particulate sulfate models dealt with the transformation of SO_2 to the SO_4 = ion, but did not follow the transformations to the ammonium salts, partly because of lack of information on the location, emission rates, and transport of ammonia and partly because of lack of information on the concentrations of particulate NH_4NO_3 and gaseous and particulate HNO_3. Those deficiencies lead to large uncertainties in predicting

when acidic particles will persist or will be neutralized. The issues of neutralization and nitrate concentration need to be resolved to facilitate the prediction of the conditions conducive to acidic particle exposures and the types of locations where human exposures occur. Graedel and coworkers have considered dynamic processes by using a model of the aerosol consisting of a solid core surrounded by an aqueous solution and an organic file (Graedel and Weschler, 1981; Graedel et al., 1983). This model predicts substantial inhibition of mass-transfer at the gas-liquid interface and a potential for retarding liquid-phase oxidation in the atmosphere. Such a model may also be useful in explaining the dynamics of neutralization of acidic aerosols.

Certain organic compounds, termed semivolatile, are distributed between the vapor and particle phases in the atmosphere (Cautreels and Van Cauwenberghe, 1978; Yamasaki et al., 1982; Bidleman, 1988; Coutant et al., 1988; Ligocki and Pankow, 1989). Since the deposition properties of vapors and particles differ, this partitioning of semivolatile organic compounds between the two phases can have substantial effects both on dose of these compounds to the lungs and on their atmospheric lifetimes. Efforts to develop models for this partitioning have increased over the last decade. Junge (1977) was the first to develop an equation, based on the BET isotherm, to estimate vapor-particle partitioning as a function of aerosol surface area and the saturation vapor pressure of the semivolatile compound. Yamasaki et al. (1982) used a linear Langmuir isotherm to explain the vapor-partitioning of polycyclic aromatic hydrocarbons in outdoor air as a function of temperature and aerosol mass. The equivalence of these two approaches has been shown by both Bidleman and Foreman (1987) and Pankow (1987). Pankow (1987) has extended these modeling efforts to incorporate some of the fundamental properties of the semivolatiles including molecular weight and a characteristic molecular vibration time. Although the models based on linear adsorption isotherms have been successful in explaining the vapor-particle partitioning of many semivolatile organics, the models do not yet address the problem of the presence of multiple semivolatile compounds or the dynamic aspects of vapor-particle partitioning. In addition, more refined experimental data are needed to test these models fully, particularly those that address dynamic processes.

Receptor Models

Receptor models use data on contaminants at a specific site to identify the sources of contaminants. They are not predictive but can be used to validate predictive dispersion models, as in the Portland Aerosol Characterization

Study (Cooper and Watson, 1979, 1980; Core et al., 1982). Receptor models use several methods, which have been described in detail by Hopke (1985).

In general, receptor modeling uses measured constituents of ambient samples as tracers to infer the contributions of different sources to the ambient air on the basis of a mass-balance and expected differences in the properties of particles emitted from different sources (Miller et al., 1972). For example, assume that the airborne lead measured at a site is the sum of lead from several sources of different types, such as automobiles (auto), incinerators (incin), and non-ferrous metal smelters (smelt):

$$Pb_T = Pb_{auto} + Pb_{incin} + Pb_{smelt} + \ldots, \quad \text{(Eq. 6.1)}$$

where Pb_T is the total airborne lead concentration (ng/m^3), Pb_{auto} is the amount of lead contributed by automobiles, etc. However, the automobile particles contain other elements besides lead, so that

$$Pb_{auto} = a_{Pb,auto}\, f_{auto}, \quad \text{(Eq. 6.2)}$$

where $a_{Pb,auto}$ is the concentration of lead in automobile particles (ng/mg), and f_{auto} is the concentration of automobile particles in the air (mg/m^3). If this analysis is expanded to a series of elements, then the airborne concentration of particulate element, x_i, is given by

$$x_i = \sum_{k=1}^{P} a_{ik} f_k \quad \text{(Eq. 6.3)}$$

where a_{ik} is the concentration of the i^{th} element in particles emitted by the k^{th} source and f_k is the contribution to the airborne particulate mass concentration from the k^{th} source. The summation is over all p sources in the air-shed. Thus, if a suite of elements has been measured, a series of simultaneous equations is available to solve to estimate the contributions of the various source types to the airborne particulate concentrations.

There are two main approaches to receptor modeling: one applies the principle of mass-balance and the other applies multivariate statistics. The mass-balance approach to obtaining a data set for receptor modeling is to determine and measure a number of chemical constituents, such as trace elements, in a number of samples collected from source emission streams and the ambient environment. The mass-balance approach can be used to account for all independent sources of the measured constituents in each sample. The methods require that samples be obtained at locations of interest (receptor sites) and be analyzed for properties that are characteristic of various sources (Hopke, 1985; Daisey and Kneip, 1980).

If no a priori knowledge of the number and nature of the sources is available, multivariate methods involving eigenvector analysis can be used. The mass-balance equation must be extended to a series of samples that have been analyzed and in which the various sources contribute different amounts to the airborne particle mass loadings. Methods such as target transformation factor analysis (Hopke et al., 1988) or absolute principal components analysis (Thurston and Spengler, 1985) can be used to obtain the elemental composition profiles associated with each source and their associated mass contribution.

The U.S. NAAQS for total suspended particles (TSP) created the need to identify particle sources so that control strategies could be designed and implemented. The initial efforts used dispersion models; the resulting strategies to control point sources substantially reduced TSP levels. However, as the amount of needed additional control became smaller, it became more difficult to identify the sources with continuing problems. That difficulty was due in part to the general failure to address fugitive and other nonducted emissions in dispersion models. Receptor models have been useful in identifying such sources and estimating their contributions and in deciding what strategies to use to meet new standards for particulate matter (e.g., the PM-10 standard). In the guidance documents regarding the new PM-10 standard (EPA, 1987), receptor models are explicitly approved for use in the planning process with the traditional dispersion models.

Sexton and Hayward (1987) recently suggested that receptor models could be useful for apportioning the contributions of indoor sources to contaminant concentrations, although identification of characteristics that distinguish among the sources of indoor contaminants would be required. Daisey and Gundel (1989) have reported that carbon and nitrogen thermograms might provide a rapid and inexpensive method for distinguishing sources of indoor particulate matter with receptor models. Generally, indoor source emissions have not been sufficiently well characterized for this application of receptor models.

INDOOR CONTAMINANT CONCENTRATIONS

Industrial Environments

The first work on quantifying indoor-air contamination was done by industrial hygienists in the early 1900s and focused primarily on measuring hazardous substances by direct sampling and measurement (Gerhardsson, 1988) at different locations and sources in the workplace. Exposure was then modeled by time-weighting the concentrations measured at various locations. This approach was, in essence, microenvironmental modeling. Recent attempts have been made to use this approach in a more sophisticated way, referred to as job exposure profiling (Corn and Esmen, 1979), to describe workers' exposure by identifying their presence and residence in known or estimated concentration fields. Recent work with this concept is discussed later in this chapter.

The time-weighted average model has been widely used in industrial settings. This is a statistical modeling approach that generally uses measurements of concentrations in each microenvironment or a source-oriented mass-balance model to predict concentrations for each microenvironment. The average concentration for a given period (typically 24 hours) is calculated as the time-weighted average of the concentrations in each microenvironment.

In the industrial workplace, routine and accidental exposures to hazardous materials are of special concern. For routine releases, standards are specified as a maximum concentration of an air contaminant that should not be exceeded over a specified period, frequently the 8-hour workday. A time-weighted average concentration has long been used as both a conceptual and a mathematical model for routine exposures. Direct measurement of individual worker exposures has become more common in recent years.

The historical emphasis of industrial hygiene evaluation of workroom air quality by direct measurement of concentration has led to relatively little attention to the study and measurement of the mechanisms of contaminant generation and loss. Current interest in this area is high and important work is under way. Attempts have been made to estimate airborne contaminants in workroom air by using the physicochemical properties of the substance combined with information on site variables, such as ambient air temperature, temperature of the substance, production rates, surface area, and ventilation. One of the most notable past developments was the application of the box model to predict the dilution ventilation required to control worker exposure to open solvent baths. The concentration of a contaminant in a defined "box" of workroom air is determined on the basis of an assumption of perfect or at least good mixing of contaminant in air and first-order kinetics in the buildup

and loss of pollutant in the box. This approach is the basis of a number of estimation techniques (Mutchler, 1973; Wadden and Scheff, 1983).

The box model, which has been applied to industrial and nonindustrial environments (indoors and outdoors), involves equation 6.4 for the contaminant concentration based on a mass-balance.

$$VdC = Gdt + C_i Q_i dt - CQ_r Edt - CKdt \qquad \text{(Eq. 6.4)}$$

where V is the volume of the box, t is the time, C is the concentration in the box at any given time, C_i is the concentration of contaminant in the inlet air from outside the box, Q_i is the volume flow rate of intake air into the box, G is the rate of generation of pollutant within the box, Q_r is the volume flow rate of recirculated air, and E is the contaminant removal rate for any recirculated air, e.g., the efficiency of the air cleaning device in the recirculating air stream, and K is the removal rate by mechanisms other than ventilation and filtration such as deposition to surfaces and chemical reactions. The equation can be modified to incorporate partial mixing through the use of a mixing factor, m. The mixing factor is the fraction of ventilation air that is completely mixed with the box air and is multiplied by the second, third, and fourth terms on the right side of equation 6.4 (Ishizu, 1980). When this equation is applied to indoor industrial environments, the outdoor air is assumed to be contaminant-free. In many cases the mixing factor is assumed to be unity. Measurements in indoor environments have shown that this second supposition is not always valid even in relatively small rooms (Drivas et al., 1972; Ishizu, 1980), and the empirical mixing factor should be retained in the model. In most industrial settings, air cleaning is not used and Q_r is zero. For outdoor-air models, the recirculation air flow is also set to zero and the mixing factor is set to 1.

Jayjock (1988) has proposed a model that combines physical and statistical modeling techniques. Its purpose is to predict concentrations around localized sources in large industrial rooms. This model uses a stochastic relationship for the displacement of diffusing elements to determine the size of the box of uniform concentration air within the workspace. It then uses this input in a first-principle mixed-box model to estimate the airborne concentration. This model attempts to describe the practical size of the box (i.e., the volume V) around the source to render meaningful predictions of concentration for this assumption. This determination is done by sizing the box to contain most of the molecules that leave the source in a time frame consistent with their removal via ventilation purging. Lavenda (1985) described the manner in

which diffusing elements containing contaminants will travel outward from a point source. One can calculate a time-dependent concentration gradient for the instantaneous batch release of a finite amount of contaminant. Finding a distance from the source that will contain a majority of the releases in an interval when ventilation purging of these releases is well under way (e.g., the time for one air change) allows the sizing of the affected volume. This volume is then used in the box model to predict the concentration in the affected volume.

A fundamentally different approach is presented in a ventilation-driven dispersion model in which airborne concentration decreases monotonically from any point source (Roach, 1981). The approach describes a concentration gradient from a contaminant source to a receptor (potential human contact). Although diffusion models have been widely used in describing the ambient concentrations from source emissions, this approach was not used in the indoor environment until Roach presented a simple indoor diffusion model. To illustrate its importance in describing the variability of concentrations within a room, consider an industrial room 30 meters square and 4 meters high with a point source of gas at its center. If the room is ventilated at 3 mixing changes per hour, the air flow for a 3,600-m^3 room is calculated to be 10,800 m^3/hr. Alternatively, consider an imaginary box (a 2-meter cube) within this room and surrounding the source. If the ventilation is consistent throughout the room, then this box is also ventilated at 3 mixing changes per hour resulting in a flow of 24 m^3/hr. Thus the purging air flow proximate to the source is only 0.02% of the total in the room. Since dilution ventilation purging is proportional to cube of the volume, its effect near point sources in typical industrial rooms can be considered small. Because molecular and turbulent diffusion combine to yield a diffusion coefficient that is independent of volume, the diffusion model describes the concentration gradient near the source.

For distances from the source at which convection is significant, Roach derived an equation that combines ventilation and diffusion. All these models presuppose that diffusion is constant in space and time and assume nondirectional or random air flow in the room.

Steady-state source models, based on equation 6.4, assume that the input (generation) rates and the output (control) rates are constant and that enough time has passed to yield a steady-state ($dC/dt = 0$). That holds for continuous processes, but may not be valid for intermittent or "batch" jobs that start with $C = 0$ at $t = 0$ and end well before steady-state can be achieved. For example, any volume with 1 mixing air change per hour will reach 90% of equilibrium in 2.3 hours. At 10 mixing air changes per hour, this time is 0.23 hour. Since concentration is increasing during this entire period, the time-average

concentration will be significantly lower than the concentration at equilibrium. Exposure resulting from indoor operations that begin and end in a period of minutes to a few hours should explicitly consider determination of the time-weighted average exposure potential during concentration buildup and falloff. Jayjock (1988) has discussed this specific topic.

Application of the box model described above frequently assumes complete mixing and no gradient of exposure. Less than ideal ventilation air mixing is handled by the use of the mixing factor (m). Those assumptions appear to be justified if the diffusion and dispersion of airborne contaminants from sources in the room are indeed large relative to the size of the room. The modeler uses the room volume (V) and ventilation rate (Q_i) in equation 6.4 to estimate contaminant concentrations in the workroom air. The assumptions are not valid in small rooms with stagnant air, very high flow rate of air, or in large industrial rooms with moderate air flow rates, in which the majority of airborne contaminant is contained within a relatively small space, compared with the room volume.

Knowledge of dispersion from diffusion is important to our understanding of mixing and concentration gradients. Molecular diffusion of gases in air is a poor dispersion mechanism. For instance, consider that the molecular diffusion coefficient for ethanol vapor in air is about 8×10^{-5} m^2/min. By comparison, Franke and Wadden (1985) measured eddy diffusion coefficients between 1 and 12 m^2/min in a large (120 x 160 x 16 ft) room with air exchanged 0.3 times per hour. Air movement in rooms from temperature gradients, ventilation, or the movement of objects in the room causes eddy diffusion that is about 1,000 to 10,000 times greater than molecular diffusion. Small rooms with high levels of eddy diffusion meet the assumption of the mixing model. Using a mixing model in a large room or a small room with a low diffusion rate may dramatically underestimate contaminant concentrations and exposures near sources in the room.

The above models assume omnidirectional diffusion of contaminant outward from the source. That presupposition has not been tested in real workrooms or residences, and might be true only for long averaging times but not for short periods.

Most predictions of contaminant movement assume that the contaminants are gaseous. Particles and gases behave quite differently, however. Particles do not lend themselves to physicochemical predictions of their generation rate into air, and, once airborne, they act in a manner consistent with their aerodynamic diameter and not necessarily like the rest of the air column. Attempts have been made to model particulate matter in workroom air (Cooper and Horowitz, 1986), but more theoretical and experimental work is needed before a generally useful model is available.

Finally, some contaminants, termed semivolatile contaminants, can occur in both gaseous and particulate phases. Changes in temperature and particulate surface area can shift the phase distribution of such substances and influence the characteristics of exposure to them (Yamasaki et al., 1982; Pankow, 1987; Bidleman, 1988; Coutant et al., 1988).

Nonindustrial Environments

Over the last decade, research in air quality in nonindustrial indoor environments has dramatically changed the understanding of human exposures to many airborne contaminants. The Harvard Six Cities Studies showed that exposures to respirable particulate matter and to NO_2 were, on average, higher in homes than outdoors (Dockery and Spengler, 1981a,b; Dockery et al., 1981). Similarly, measurements of volatile organic compounds (Molhave and Moller, 1979; Hollowell and Miksch, 1981; Wallace et al., 1982) and of radon (Sachs et al., 1982; Nero et al., 1983) showed that concentrations were generally higher indoors than outdoors. These findings and the growing recognition that humans typically spend 80–90% of their time indoors (Szalai, 1972; Chapin, 1974; Sexton et al., 1984) have increased the attention to indoor-air exposures.

Residential exposure differs from industrial in a number of critical factors. For example, the indoor exposed population includes members who are very young, very old, or infirm. The potential indoor exposure duration in residences is 168 hours per week for a lifetime, compared with a typical industrial exposure of 40 hours per week for a working career. The concentrations of contaminants and ventilation rates are often much lower in residences than in industrial environments.

Some contaminants enter residences with outside air, which then becomes the source of indoor-air contaminants. But some contaminants are commonly much more highly concentrated indoors than outdoors because of indoor sources. The fundamental approach to modeling indoor-air concentrations is a mass-balance or box model analysis for each room or area to be modeled. In many buildings—such as stores and houses, in which interior doors are left open—the air is fairly well mixed, and the single-compartment mass-balance equation can be usefully applied to the total volume of the building.

The single-compartment mass-balance model (Eq. 6.4)—which describes the average concentration in an enclosed space as a function of source emission rates, infiltration of outdoor air, and losses by processes other than exfiltration—has been the most commonly used source-oriented model for indoor-air modeling (Turk, 1963; Drivas et al., 1972; Shair and Heitner, 1974). Turk

(1963) proposed the use of an empirical mixing factor, defined by Brief (1960) as the ratio of effective air changes to theoretical air changes. Drivas et al. (1972) determined that the value of the mixing factor ranged from 0.3 to 0.7 for small rooms without fans. This model is now used extensively for indoor-air modeling (Ishizu, 1980; Wadden and Scheff, 1983). In many instances, the mixing factor is assumed to be unity, although it should be otherwise (Esmen, 1978; Ishizu, 1980).

Models more complex than the single-compartment model are needed for multistory buildings or buildings with basements if the basement is a major entry path for a contaminant (e.g., radon). The simplest multicompartment models developed for indoor air consist of a combination of single-compartment models in which some or all of the air exhausted from one room or zone becomes the inlet air to another (Rodgers, 1980; Sandberg, 1981; Ozkaynak et al., 1982; Wadden and Scheff, 1983; Ryan et al., 1988). These simple multicompartment models constitute mass-balance approaches, but the total quantities of contaminants for the combined rooms or zones must be accounted for. Equations have been written for more complex multicompartment models in which there is air flow between multiple compartment or zones. Such models, however, require more input data and much more computation time, which is approximately proportional to the cube of the number of zones modeled.

Infiltration and exfiltration of air are key components in modeling contaminant concentrations in indoor air. Infiltration of outdoor air can dilute indoor contaminants, as well as carry outdoor pollutants into indoor spaces. Infiltration is driven largely by pressure differences between inside and outside air. These pressure differences are caused by wind, temperature differences, and mechanical ventilation. Many buildings do not have specific provisions for mechanical ventilation, i.e., they have no air ducts for the transport of air into or out of the building. Ventilation of such buildings occurs through infiltration and exfiltration of air through cracks, windows, doors, and other openings.

The first infiltration model, an empirical model, was developed some 40 years ago by Dick and Thomas (1951). Little work was done on infiltration models until the energy crisis of the 1970s gave impetus to the development of such models to support energy conservation efforts. The models developed in the early 1970s were generally empirical models in which infiltration was expressed as a function of temperature difference and wind speed; multivariate statistical methods were used to fit coefficients and exponents from experimental data (Ross and Grimsrud, 1978). Sherman (1980) derived the first model of infiltration based on first principles of physics. Sherman and Grimsrud (1980a,b) then obtained outdoor values of parameters for the model, e.g.,

leakage area and height of the structure, inside-outside temperature difference, wind speed, terrain class of the structure, and local shielding. In a validation study, the Lawrence Berkeley Laboratory single-compartment model (Sherman and Grimsrud, 1980a,b) and the National Research Council multicell model of Canada (Liddament and Allen, 1983) performed best among the models tested.

For many models of indoor-air contaminants, it is important to include the decay rates of the contaminants in the indoor space. The one-compartment model was applied in analyzing indoor ozone decay (Sabersky et al., 1973; Shair and Heitner 1974), particulate matter in tobacco smoke (Hoegg, 1972), and CO_2 from respiration (Kusuda, 1976). Sabersky et al. (1973) determined heterogeneous decay rates for O_3 on various indoor materials (decay occurs through interaction with surfaces). Using a single-compartment mass-balance model, they calculated the indoor concentration of O_3 over time as a function of the decay losses and concluded that indoor O_3 decreases rapidly once infiltration of outdoor air is decreased, i.e., when windows and doors are closed. Unfortunately, decay rates have been determined for very few contaminants. Moreover, even if the decay rate of a specific material is known, it cannot be used effectively in modeling unless the surface area of the material and the fluid dynamics of the chamber are also known.

Jacobi (1972) provided the basic form of the model that incorporates the formation of the decay products of radon (^{222}Rn), the radioactive decay of one progeny to the next, attachment to existing airborne particles, and deposition (plateout) of the particle-attached and unattached activity on macroscopic surfaces in a room. Improvements have been made in assigning values to parameters (Porstendörfer et al., 1978; Knutson et al., 1983; Vanmarcke et al., 1985), but there are still difficulties related to the degree to which aerosol dynamics have been simplified and to the failure to incorporate fluid dynamics into models.

Empirical models have been used to try to identify the major contributors to indoor-contaminant concentrations or exposures to contaminants. Spengler et al. (1981) used stepwise regression of personal exposure measurements of respirable particles against outdoor and indoor concentrations and such indicator variables as smoke exposure, employment status, and time spent at home and work. They found that indoor concentrations in homes explained almost half the variance in personal exposures and that outdoor concentrations had little predictive value.

Dockery and Spengler (1981b) developed empirical models for respirable particles and sulfates in indoor air; they combined a basic physical model (the simple mass-balance or box model) with variables that are indicators of suspected sources. Their model regressed indoor concentrations against time-paired

outdoor concentrations for each house to fit a slope and intercept. The slope, identified from the physical model, is the penetration factor for outdoor air. The intercept is the product of house volume and the ratio of the average particle (or sulfate) emission rate for all the sources in a given house to the average ventilation rate. The values of the slopes and intercepts for all houses are regressed against indicator variables appropriate to each. For example, the slopes can be regressed against a binary variable, *A*, related to whether a house is fully air conditioned. The intercept is interpreted to be the average penetration factor for respirable particles, and the coefficient of *A* is interpreted as the effect of full air conditioning in reducing penetration.

Leaderer et al. (1987) developed an empirical model for indoor NO_2 as a function of types of NO_2 sources (such as unvented kerosene heaters, gas appliances, and smoking), source use, and physical attributes of the residences (e.g., house volume, air-tightness, and fan use). More than 60% of the variation in indoor NO_2 could be accounted for by source type and use. Variations in infiltration and removal rates, which were not well characterized, were suggested as the major sources of unexplained variation in NO_2 concentrations.

Ryan et al. (1986) have developed a class of indoor-outdoor models for respirable particles and NO_2 and other contaminants. The models sum the exposures in the occupied microenvironments to predict indoor concentrations. Efforts are under way to change indoor-outdoor models to simulation models and to model distributions of population exposures to NO_2 (Ryan et al., 1988).

Variability in Emission Rates

Variability in contaminant emission rates is important, although often ignored, in modeling of both indoor and outdoor air. Most concentration models use measured, rather than modeled, emission rates. The measurements are generally limited to a few examples of a given source type and a narrow range of operating or environmental conditions. Emission rates can vary substantially from one source to another, however, because of design, manufacturing, or construction differences. Hubble et al. (1982), for example, summarized published emission factors for CO and particulate matter for wood-burning stoves. Emission rates varied by a factor of more than 30, because of variations in type of wood, size of pieces, burning rate, and draft conditions. Traynor et al. (1988) compiled published data on the emission rates of CO, NO_2, and respirable particles from indoor unvented combustion appliances. Emission rates, in some instances, vary by a factor of 100. To model concentrations effectively, it is essential to have knowledge of the variability

of emission rates and to incorporate those into the model. Traynor et al. (1988) used distributions of measured emission rates, rather than a single emission rate, to model indoor air.

For retrospective exposure modeling for epidemiological studies or prospective modeling for risk assessment over a lifetime, it is generally assumed that emission sources and processes do not change over long periods. That is not generally true, but it is difficult to model exposure without that assumption.

Mixing Within and Between Rooms

Mixing of air within and between rooms varies spatially and temporally. Therefore, the mass-balance model might not characterize the concentration of an airborne contaminant accurately or adequately unless mixing is taken fully into account, so single-compartment and multicompartment mass-balance models generally incorporate a mixing factor. The mixing factor is either determined empirically or assumed to be unity. Empirical values measured using a sulfur hexafluoride tracer gas range from 0.3 to 0.6 in small rooms without fans (Drivas et al., 1972). Ishizu (1980) found that particle concentrations from side stream tobacco smoke in rooms with high ventilation rates (9–45 air changes per hour) were underestimated by about 50% if the mixing factor was assumed to be unity, i.e., actual mixing factors ranged from about 0.3 to 0.6.

Measurements made in the absence of occupants are misleading. Movement and body heat (whether of humans or animals) tend to increase mixing. In fact, the very presence of a person would increase air mixing in an environmental chamber. The effects of human occupation on air mixing have not been systematically investigated, but measurements made in the absence of occupants might lead to underestimates of mixing and overestimates of concentrations in exposure modeling.

Very low and very high ventilation rates can cause large deviations of the mixing factor from unity. However at moderate ventilation rates, the mixing factor is closer to unity. Girman and Hodgson (1986), for example, measured exposures to methylene chloride from paint strippers in an environmental chamber with moderate ventilation (0.5 and 3 air changes per hour). Average concentrations measured in the breathing zone were only about 20% higher than those measured in the chamber at large.

Short of fluid dynamical modeling or experimental measurement (Fisk et al., 1985, 1988), there is no simple means to predict the mixing factor or ventilation efficiency for a given room or zone. The experimental data suggest that the variation in indoor concentrations due to variations in air mixing is

a factor of about 2 or 3. Although that is substantially less than the variations in source emissions, some research is clearly needed to identify situations in which a more accurate determination of the mixing factor is needed.

Deposition

Deposition onto surfaces can account for losses of gaseous and particulate contaminants. On striking a surface, a molecule can bounce off, be adsorbed, or be absorbed. An adsorbed or absorbed molecule can subsequently desorb or react on the surface to form another species, which, in turn, can either remain on the surface or desorb into the air. The net effect and importance of deposition processes on subsequent indoor airborne concentrations depend on the relative magnitude of the deposition sink compared with other indoor sink and source terms. Reactive gas phase species and airborne particles, especially larger particles, are the contaminants most likely to be influenced by deposition processes.

In equation 6.4, the term CQ_rEdt represents the loss rate of a contaminant from the "box" by means other than ventilation. With enough time and reactivity, chemical transformations can account for substantial loss. However, many indoor pollutants do not have long residence times in the air and are not highly reactive.

Little experimental work has been done on this subject in modeling of exposure to indoor air. Deposition of radon decay products has been modeled by Jacobi (1972) and by Porstendörfer et al. (1978). Deposition velocities of the major water-soluble salts associated with fine and coarse particles have been measured in some buildings (Sinclair et al., 1985, 1988) and incorporated in a mass-balance model that can calculate steady-state concentrations in similar buildings (Sinclair et al., 1985; Weschler and Shields, 1988). Nazaroff and Cass (1986, 1989) have described the deposition of reactive nitrogenous species and modeled the loss rate of particles and highly reactive gases to indoor surfaces for homogeneous turbulence, laminar forced convection, and laminar natural convection. Deposition velocities were found to vary by a factor of 10,000 over the range of pollutant diffusivities and particulate sizes encountered.

Indoor environments have larger surface-to-volume ratios than outdoor environments, so surface deposition and reactions are likely to be more important in indoor environments. Much less is known about chemical reactions in indoor air than in outdoor air; therefore, although the widely used mass-balance model for indoor air explicitly incorporates a term for removal processes other than exfiltration into outdoor air, removal rates have generally not been

measured and so cannot be included in the model. For chemically unreactive contaminants, such as CO, the removal rate is commonly assumed to be zero.

Spicer et al. (1986, 1987) and Nishimura et al. (1986) reported that some materials found in indoor environments chemically reduce NO_2 to NO. Pitts and coworkers (1985a) experimentally demonstrated the production of nitrous acid (HONO) from NO_2 in an indoor environment. Nazaroff and Cass (1986) have presented a general model for predicting the concentrations of chemically reactive compounds in indoor air that accounts for the effects of ventilation, filtration, heterogeneous removal, direct emission, and photolytic and thermal chemical reactions. The discrepancy between the calculated formation of HONO from homogeneous reactions in their model and that measured by Pitts et al. (1985a) suggested to them that heterogeneous reactions are important in HONO formation in indoor air. That hypothesis was supported by results of Gundel and Daisey (1988): high rates of conversion of NO_2 to HONO were observed for heterogeneous reactions on polyurethane foam and wool carpet. Chemical transformations should be incorporated into models where appropriate.

It is still difficult to evaluate the importance of indoor chemistry. Rates of contaminant removal and generation by indoor surface reactions will be important only if they are at least as large as rates of infiltration and ventilation.

Air Cleaning

Air cleaning devices are used to remove particles from the intake air of buildings. Although a term for the efficiency of particle removal can be easily incorporated into the mass-balance model (Eq. 6.4), its actual value is generally not known or easily determined for a given building. Filters used in commercial building air ducts are sometimes installed (improperly) in such a way as to leave a gap between a filter and a duct. Moreover, the efficiency of a filter can vary widely with time and with particle size. Efficiency of particle removal often increases with filter loading.

Some air cleaners incorporate activated carbon and other catalysts or reactants to remove gases and volatile organic compounds. Only limited information is available on the efficiencies of these devices (Wadden and Scheff, 1983). A problem with these devices is that adsorbent beds become saturated and lose their collection efficiency with usage, sometimes quite rapidly (Daisey and Hodgson, 1989). More work is needed to incorporate air cleaning systems into indoor-air exposure models.

Recent Advances

Most advances in indoor-air modeling have come from increasing the sophistication and complexity of the models. One effort to improve the data base on airborne contaminant concentrations and on emission and ventilation variables is the cooperative EPA-Southwest research project (EPA, 1986b) on workplace exposure estimation. That project plans to examine exposures of groups of operators in the chemical industry. It will characterize the concentrations of airborne contaminants, contaminant generation rates from principal sources, local exhaust systems, and rates of dilution ventilation. Several models treat air flows in multicompartment buildings, but rely on mainframe computers and are not generally user-friendly. Feustel and Sherman (1989) recently developed a simplified multizone infiltration model that can be run on a calculator for determining air flow distribution in a complex building. Information on buildings, categorized on the basis of their leakage ratios and lumped physical parameters (e.g., volume, resistance to flow, etc., combined and expressed as a constant), is used to calculate overall infiltration-exfiltration rates. There was good agreement between the results from the simplified multizone infiltration model and a standard model for an eight-story building. A more detailed multizone infiltration model has been developed as part of COMIS (Conjunction of Multizone Infiltration Specialists), a year-long international workshop held at the Lawrence Berkeley Laboratory (Feustel et al., 1989). The objective of COMIS was to develop a user-friendly program for multizone infiltration, taking into account crack flow, air-conditioning systems, single-sided ventilation, and transport through large openings. The model is modular and can be expanded to incorporate new knowledge. It will be validated with several sets of multitracer gas measurements.

Tracer gases are commonly used to measure building ventilation. The measurements have generally used single tracer gases, but there have now been efforts to use multiple tracer gases to measure air flows in multiple zones in buildings (Sherman, 1989). The flows determined from the tracer measurements and the relevant continuity or mass-balance equations are associated with large uncertainties. Sherman (1989) reported a method for using exogenous physical information on physical constraints to reduce the uncertainties in ventilation measurements based on tracer gases.

The entry of radon from soil into houses has been shown to be dominated by pressure-driven flow of soil gases (Nero and Nazaroff, 1984; Nazaroff and Doyle 1985; Nazaroff et al., 1987). This pressure difference between soil and house interior is due to indoor-outdoor temperature differences, wind, unbalanced mechanical ventilation, and operation of combustion devices that draw indoor air for combustion and vent products outdoors. The structure of the

house and the characteristics of the soil, such as permeability, are important factors influencing pressure-driven flows of soil gases. Efforts to model radon entry from soil and the consequent indoor radon concentrations are only beginning. Mowris and Fisk (1988) have developed an analytical (closed-form) model of soil-gas flow based on its analogy to heat transfer. The model was used to evaluate the impact of exhaust ventilation on indoor radon concentrations in two houses. It underpredicted radon concentrations by 23% and 13% for two different periods in one house and overpredicted by 22% in a second house, but the authors noted that comparison with measured concentrations was encouraging. Loureiro (1987) has developed a theoretical model to predict indoor radon concentrations. It simulates rates of generation and decay of radon in soil, its transport through the soil due to diffusion and convection induced by a pressure disturbance at a crack in the basement, and its entrance into the house through the crack. Two computer programs were developed to calculate the pressure distribution in the soil and the resulting velocity distribution of the soil gas and to solve the radon mass-transport equation, calculate radon entry rates, and calculate the indoor radon concentration. Indoor radon concentrations were found to be directly, although not linearly, related to the indoor-outdoor pressure difference.

Domestic water contaminated with gases, such as radon and volatile organic compounds (VOCs), is a source of exposure that has only recently been recognized as important. Dissolved gases in contaminated water are released indoors during such residential uses as showering and dish-washing (Andelman, 1985; Gesell and Prichard, 1975; McKone, 1987; Jo et al., in press[a]). McKone has developed a mass-transfer model to estimate human exposures to VOCs due to their transfer from tap water to indoor air. It estimates the release of VOCs from water and uses a three-compartment model to simulate the 24-hour concentration profile in the shower, the bathroom, and the rest of the house. A preliminary data base on household characteristics and time-activity patterns has been used to calculate a range of concentrations and human exposures to seven VOCs. Nazaroff et al. (1987) used a single-compartment mass-balance model with a long averaging time to calculate the distribution of indoor-air radon in U.S. homes from tap water.

In another recent advance in modeling indoor concentrations of contaminants in homes, Traynor et al. (1988) developed a single-compartment mass-balance model for combustion emissions, specifically CO, NO_2, and respirable particles. Input data for the model include distributions of housing stock characteristics (e.g., volumes and air-exchange rates), use of combustion appliances and sources (e.g., cigarettes), distribution of source emission rates, and source use. The model uses deterministic and Monte Carlo simulation techniques to generate distributions of average weekly concentrations of CO, NO_2,

and respirable particles for four regions of the country. The modeled distributions have generally compared well with available field measurements. The model can also be used to rank indoor pollutant sources, identify high-risk populations, identify key factors for attempts at control and mitigation, and estimate exposures for epidemiological studies.

Nazaroff and Cass (1986) recently developed the first model for chemically reactive pollutants in indoor air. It combines the multibox ventilation model of Shair and Heitner (1974) with a modified version of the Falls and Seinfeld photochemical kinetic model (Falls and Seinfeld, 1978; Russell et al., 1985). The model accounts for the effects of ventilation, filtration, heterogeneous removal of gaseous pollutants, direct emissions, and homogeneous gas phase reactions and predicts concentrations of such chemically reactive contaminants as HNO_2, HNO_3, and N_2O_5. Nazaroff and Cass (1986) tested the model in a museum gallery; predicted and measured concentrations of several pollutants were in reasonably good agreement. They also compared their modeled steady-state ratio of HNO_2 to NO_2 due to homogeneous gas phase reactions with that measured by Pitts et al. (1985a) in an indoor environment; the experimental ratio was about 35 times the modeled ratio. Heterogeneous reactions appear to play an important role in indoor production of HNO_2, and models for indoor atmospheric chemistry probably will eventually have to incorporate heterogeneous chemical reactions. However, very little is known about such reactions today.

EXPOSURE-ASSESSMENT MODELS

Current exposure models are based on relatively general assumptions about the distribution of contaminant concentrations in microenvironments, the activity patterns that determine how much time people spend in each microenvironment, and the representativeness of a sample to the population that might be exposed to a contaminant.

Individual Exposures

In a model of individual exposure, contaminant concentrations in each microenvironment are measured or modeled and time-activity patterns are used to estimate the time spent in each microenvironment. (Exposure is the product of time and contaminant concentration.) An individual's overall exposure can be separated into the sum of products of concentration and time in

each microenvironment; this is termed a microenvironment decomposition (Duan, 1981).

Microenvironment decomposition can be extended to other summary exposure measures, such as peak concentrations. If we are interested in total exposure, microenvironmental decomposition is assumed to include all possible locales and activities. Duan (1981, 1985) developed a criterion for stratifying microenvironments to improve the precision of estimated average exposures and applied it to identify the important microenvironments for CO exposures.

Some models for predicting exposures make assumptions regarding the independence between contaminant concentrations and time spent and activity in a microenvironment. Such assumptions should be validated for specific applications. Duan (1985) has suggested that there is no correlation between CO concentrations and time on the basis of data from the Washington, D.C., CO study (Akland et al., 1985). However, there will be problems in the existing models if correlations between occupancy periods and concentrations exist for other contaminants, because the independent variables, time and concentration, would not be truly independent. If the correlation is very high, the predictions based on models might not be valid because of an inappropriate assumption of independence. The committee is unaware of any empirical data quantifying the extent of problems caused by the correlations. It is likely that for contaminants such as particles, the presence of a person might change the particle concentration of a previously unoccupied microenvironment. Further study of the problems such correlation would produce is needed.

Stock et al. (1985) used personal activity profiles and household characteristics to partition the locations into seven broad microenvironments: three indoor, two outdoor, and two transportation modes. From measured concentrations of the criteria pollutant gases (ozone, NO_2, SO_2, CO), aeroallergens, aldehydes, TSP, and inhalable particles and the time in each partition, exposure estimates were calculated. The results will ultimately be combined with epidemiological data to determine the health effects of exposure to specific pollutants in a community environment.

More or less sophisticated versions of partitioning are used in the workplace, where they are referred to as job exposure profiling (JEP). JEP sometimes consists of grouping and compiling work tasks with durations of exposure at breathing-zone concentrations (Austin and Phillips, 1983). The product of such analysis is a prediction of exposure of any employee involved in the tasks covered by the JEP. Hansen and Whitehead (1988) recently monitored the activities and breathing-zone concentrations of printing-press operators and modeled time-weighted average exposures as a function of location and the number of times a "hazardous task" was performed.

Population Exposures

Modeling exposure of populations requires the combining of microenvironment concentrations with individual activity patterns and extrapolation of the results to a population. Data on human activity patterns have been combined with measured outdoor concentrations in the NAAQS exposure model (NEM) to estimate exposures to CO (Biller et al., 1981; Johnson and Paul, 1983). The NEM was modified to include indoor exposures by incorporation of the indoor-air quality model (IAQM) (Hayes and Lundberg, 1985). The IAQM, based on the interactive solution of a one-compartment mass-balance model, incorporates three basic indoor microenvironments: home, office or school, and transportation vehicle. It has been used to estimate distributions of ozone exposures (Hayes and Lundberg, 1985) and to evaluate strategies for mitigating indoor exposures to selected pollutants in five situations, e.g., CO exposure from a gas boiler in a school (Eisinger and Austin, 1987).

As mentioned in the introduction to this chapter, three types of models have been developed to estimate population exposures: (a) simulation models such as SHAPE, (b) the convolution model, and (c) the variance-component model. The simulation of human air-pollution exposure model (SHAPE) (Ott, 1981) is a computer model that generates synthetic exposure profiles for a hypothetical sample of human subjects; the profiles can be summed into compartments or integrated exposures to estimate the distribution of a contaminant of interest. The bulk of the model estimates the exposure profile of contaminants attributable to local sources; the contribution of remote sources is assumed to be the same as the background. The total exposure is therefore estimated as the sum of exposure due to local sources and the ambient background.

For each individual in the hypothetical sample, the model generates a profile of activities and contaminant concentrations attributable to local sources over a given period, say, 24 hours. Activity profiles are generated or accepted as input. At the beginning of the profile, the model generates an initial microenvironment and duration of exposure according to a probability distribution. At the end of that duration, the model uses transition probabilities to simulate later periods and other microenvironments. The procedure is repeated until the end of a selected long period. For each time unit, say, 1 minute, in a given microenvironment, the model generates a contaminant concentration according to a microenvironment-specific probability distribution: each microenvironment has a specific probability distribution for each contaminant concentration. Such models obviously require validation with measured exposure data for a subset of microenvironments and patterns.

Duan (1981, 1985, 1989) developed the convolution model for integrated

exposures. It calculates distributions of exposure from distributions of concentrations observed in defined microenvironments and the distribution of time spent in those microenvironments.

The variance-component model (Duan, 1989) assumes that short-term contaminant concentrations can be decomposed into components that vary in time and those that do not. SHAPE deals mainly with the time-varying component; the convolution model deals mainly with the time-invariant exposure.

The two components can be summed or multiplied to yield an estimated concentration value. It is necessary to determine the distributions of the two concentration components. If continuous personal monitoring data are available, it is possible to estimate the distributions of the two components directly. If integrated personal-monitoring data are available, the methods described by Duan (1989) can be applied. Once the concentration distributions are available, exposure distributions can be estimated with a computer simulation similar to SHAPE. Instead of generating a contaminant concentration for each time unit independently, as in SHAPE, a time-invariant concentration and a time-varying concentration are generated for each unit and combined to determine 1-minute concentrations. The remainder of the simulation is identical to that in SHAPE.

All three types of models (SHAPE, convolution, and variance-component) need to make assumptions about independence. The critical difference among the three types is in those assumptions. SHAPE assumes that the short-term pollutant concentrations (e.g., 1-minute averages) within the same microenvironment are stochastically independent and independent of activity patterns. It follows that the microenvironmental concentration is not correlated with activity time in that microenvironment. Furthermore, the variance of concentration decreases in inverse proportion to activity time. For longer activities in the same microenvironment, the concentration is averaged over more time units. Similar assumptions were made in an earlier version of NEM; a more recent version of NEM incorporates serial correlation in the 1-minute averages (Johnson et al., 1990).

The convolution model assumes that microenvironmental concentrations are statistically independent of activity pattern. That implies that they are not correlated with activity time and that the variance of the concentration also stays constant, irrespective of time. That needs to be validated. Switzer (Stanford University) noted in a private communication with Duan in 1982 that the forms of the variance functions used in both models might be unrealistic and that some compromise between the two might be desirable.

With either the additive or multiplicative form of the variance component model, the time-invariant components are assumed to be stochastically independent of the time-varying components. It is further assumed that for different

time units, the time-varying components are independent from one interval to the next. Alternatively, it can be assumed that the time-varying components have an auto correlation structure.

Duan (1985) examined data from EPA's Washington, D.C., CO study and found that concentrations and intervals were unrelated. Ott et al. (1988) used data from EPA's CO study in Denver to examine the validity of SHAPE, comparing exposure distributions of CO estimated with SHAPE and with the direct approach (personal monitoring). They found the estimated average exposures to be similar and the estimated exposure distributions to be different at the extremes of the distributions. That result might be due to failure to account for auto correlation and the time-invariant component. Duan (1989) examined several statistical parameters for microenvironments in data from the Washington, D.C., CO study and found the time-invariant component to be dominant.

Temporal Aspects

One cause of inaccuracy in exposure modeling is failure to obtain measurement data on an appropriate time scale. Outdoor air is often sampled in the summer, and concentrations for an entire year are then estimated on the basis of a single season. But sampling and analysis programs must cover enough time for concentrations to be reasonably estimated for a full year, if they are to serve as reliable inputs to exposure models. Very few sampling studies have extended over a long enough period to reveal seasonal and year-to-year variations.

An example of good sampling design was that of the Portland Aerosol Characterization Study (Cooper and Watson, 1979). The researchers attempted to learn the representative composition of airborne particulate matter and its sources without having to sample every day and analyze every sample. They stratified the year into eight defined meteorological regimes and took samples when conditions and time of year were appropriate. Although many samples were taken, only enough were analyzed to yield useful average values for each regime. The regime averages were then combined in proportion to their probability of occurrence during the year. Representative annual concentration averages were obtained at a reasonable level of effort for both sampling and analysis. However, because of the variability of occupancy times, it may be that different averaging times are appropriate in estimating average exposures as compared with average concentration.

Many estimates of annual average concentrations of indoor radon are based on measurements taken over periods of a few days under conditions that are

quite unrepresentative of those existing in a house over a whole year. The estimates so derived can easily differ from true annual averages by a factor of 2 or more, because, for example, the conditions that give rise to indoor radon change from season to season (Nero et al., 1986).

Modeling of very long exposures, as is required in assessing risk associated with exposure to carcinogens, presents several major difficulties. The typical practice is to measure or model the concentration of a contaminant at one time and determine lifetime exposure by multiplying that concentration by a long period, e.g., the lifetime of a person. However, both exposures and activity patterns change substantially over a lifetime. Industrial processes also change over time. Sources (such as wood-burning stoves) are introduced, and sources (such as catalytic converters in motor vehicles) are eliminated or modified. Large facilities typically have a design life of 30 years, so considerable uncertainty can be anticipated in a typical calculation of 70-year lifetime exposure.

Time-activity patterns and locations of people also vary substantially over long periods. In the United States, people change their place of residence frequently and rarely live in the same place over a lifetime. For agents such as radon, such mobility can have a substantial impact on exposure and thus on the use of exposure estimates in an epidemiological study.

A person's activity patterns shift from childhood through early adulthood and middle age to old age. There have been some efforts to address differences in exposure associated with aging, but this aspect of variability in exposure over long periods has generally not been addressed in exposure modeling.

The modeling of short-duration peak exposures is also attended by temporal problems. Typical steady-state airborne-concentration models are not able to provide estimates for periods shorter than 1 hour and have difficulty in modeling time-varying concentrations, which can lead to high short-term exposures. If an exposure model is to estimate the effects of peak exposures on sensitive populations, the concentration model must provide reliable estimates on biologically relevant time scales. Some important developments in stochastic models that might be able to provide such estimates have not yet been incorporated into exposure-estimation procedures.

SUMMARY

Models are useful tools for quantifying the relationship between air-pollutant exposure and important variables, as well as for estimating exposures in situations where measurements are unavailable. Models may obviate extensive environmental or personal measurement programs by providing estimates of

population exposures that are based on small numbers of representative measurements. They can be used to identify major exposure parameters and to assist epidemiological studies and risk assessments. Models generally rely on assumptions and approximations to describe quantitatively cause-and-effect relationships that are otherwise difficult to determine. Despite the simplifications inherent in models, they provide insights and information about the relationships between exposure and independent variables that determine exposure.

Models discussed in this chapter are classified into two broad categories: those that predict exposure (in units of concentration multiplied by time) and those that predict concentration (in units of mass per volume). Although concentration models are not truly exposure models, their output can be used to estimate exposures when combined with information on human activity patterns. Exposure models can be used to estimate individual exposures or the distribution of individual exposures in a population. Activity patterns and microenvironmental contaminant concentrations—inputs to exposure-prediction models—can be measured or modeled.

Concentration models are separated into several types within two categories: models based on the principles of physics and chemistry and models that statistically relate measurements of concentrations to independent variables thought to be direct determinants of concentration. Many hybrids of these two basic approaches to model contaminant concentrations also exist.

Concentration Models

These models are used extensively to estimate outdoor contaminant concentrations at specific sites. These models use physical, chemical, and statistical methods to address the contaminant source release, dispersion, reaction, and deposition. Models are also used to estimate indoor contaminant concentrations; most of these applications have occurred in occupational or industrial settings. They generally focus on measuring the contaminant concentration in a worker's breathing zone.

Over the past decade, research in air quality in nonindustrial indoor environments has dramatically changed the understanding of human exposures to many airborne contaminants. Many critical factors involved in residential exposures differ from those in industrial exposures. For example, the indoor exposed population includes members who are very young, very old, or infirm. The potential indoor exposure duration in residences is much longer compared with a typical working career. The concentrations of contaminants and ventilation rates are often much lower in residences than in industrial environments.

Most advances in indoor-air modeling have come from increasing the sophistication and complexity of the models.

Outdoor

New developments in stochastic dispersion models offer improvements in the prediction of the average and time-varying concentrations to which individuals are exposed. Receptor models can be used to cross-validate dispersion models. They also can be used to identify sources of exposure.

In many cases, the data describing the source characteristics are not available on the time scale at which the model predictions are needed. Such mismatches in the time scale of the measurements with the time scale of the models preclude adequate model development, validation, and application to new biologically relevant exposure situations. Because of the changing nature of sources and source emissions with changes in production and control technology and in the economic conditions, it is necessary to measure periodically the amounts and chemical characteristics of sources of airborne contaminants.

Improvements in photochemical models now permit far more accurate predictions of the spatial and temporal variability of ozone and some other atmospheric constituents than were previously possible. However, it is still not possible to incorporate the complete, explicit mechanisms into air-shed or long-range transport models.

Indoor

Current models used to predict worker exposures to airborne toxicants are relatively simple, undeveloped, and unvalidated. This deficiency has caused practitioners to use models—instead of estimation techniques—as though they were conservative screening techniques.

Little work has been done to model very short-term exposures (peak exposures) and gradients relative to dispersion, deposition, and ventilation in indoor environments. The sources of indoor-air-pollution need to be characterized. Measuring and modeling the temporal patterns of source strength as a function of readily identifiable or measurable source characteristics are critical steps in that process. In addition, more work is needed to model the relationship of indoor-air quality to the composition of the ambient atmosphere. Furthermore, the chemistry of the indoor atmosphere remains to be investigated.

The variability of concentrations in indoor industrial air over short time

frames needs to be measured for emergency situations. The validation of the models to predict concentrations is linked to appropriate sampling time frames and methods with adequate sensitivity to specific chemical species.

Indoor-Air Chemistry

Indoor-air chemistry needs substantial research, including surface reactions on various materials, sorption, deposition, and rates for these processes relative to ventilation or other loss mechanisms.

Exposure Models

Current exposure models are based on relatively general assumptions about distribution of contaminant concentrations in microenvironments, the activity patterns that determine how much time people spend in each microenvironment, and the representativeness of a sample to the population that might be exposed to a contaminant. In a model of individual exposure, contaminant concentrations in each microenvironment are measured or modeled, and time-activity patterns are used to estimate the time spent in each microenvironment. Modeling exposure of populations requires the combining of microenvironmental concentrations with individual activity patterns and extrapolation of the results to a population.

Models for predicting exposures to populations have been developed recently. They have not, however, been adequately validated. Limited validation studies of the SHAPE exposure model, for example, have shown that the average values are well predicted but show substantial discrepancies in the tails of the distribution. Further development and validation of the models are warranted. One cause of inaccuracy in exposure modeling is failure to obtain measurement data on an appropriate time scale. Sampling and analysis must cover sufficient time for concentrations to be reasonably estimated for a full year, if they are to serve as reliable inputs to exposure models.

Source Models

Source emission models are available to predict mass emission rates for a variety of dynamic and steady-state emission problems. The available emission models allow the estimation of downwind exposure for continuous or catastrophic releases of pure compounds or binary mixtures. These models

have not been validated. Dense-cloud dispersion models are available to estimate downwind exposure for heavier-than-air vapor releases; they also have not been validated.

Emission-rate estimation protocols are available for defining losses from chemical-processing equipment. Emission modeling coupled with dispersion modeling and time-activity estimates allow estimation of exposures for work-place-population exposure concerns before construction of new production facilities.

Validation

Further validation studies are needed for virtually all existing models, including concentration prediction and exposure models. In particular, immediate efforts are needed to validate the NEM model and modify the model to more accurately reflect the actual situations that can result in high population exposures. Valid emission-rate models are needed to provide precise estimates for multicomponent mixtures. Validated dispersion models are needed to predict downwind concentration for complex terrain to provide accurate exposure estimates for down- and up-gradient terrain conditions. The same data set cannot be used to refine and validate a model; new, independent data are required to validate any refined model. All assumptions used in developing a model should be documented explicitly. Care should be taken by investigators in any field-monitoring program to integrate their measurements with the modeling community needs so that the requisite model input data are obtained, and the measurement results can be used to test, refine, or validate appropriate models.

Measurements are needed of the concentrations of airborne pollutants in workplaces and homes along with the critical independent variables, such as source emission rate distributions and the indoor general ventilation fields. Concentration gradients within physically defined microenvironments also need to be measured accurately. When planning measurement campaigns, consideration should be given to the sampling strategies that would permit the extrapolation of the results to biological time frames other than those of the measurement program.

7

Current and Anticipated Applications

INTRODUCTION

The previous chapters in this report dealt with the basic principles and methodological elements of exposure assessment. To illustrate the state of the science and its application to the mitigation of deleterious effects on health or nuisance effects, this chapter analyzes some current and emerging problems of exposure to environmental contaminants in the form of case studies: volatile organic compounds, environmental tobacco smoke, polycyclic aromatic hydrocarbons, lead, acidic particulate matter, substances in buildings that cause occupancy complaints (sick building syndrome), chemicals released from manufacturing facilities, and radon. These do not represent all the important issues but illustrate the state of the science in particular areas, such as biological markers, multiroute exposure, and personal monitoring. Each section addresses the completeness and results of the approaches in question, the sophistication of the methods used, the requirement for improvement or redirection, the misapplication (if any) of results, and the use of scientific results in making regulatory decisions.

Discussions of several of the case studies in the context of exposure through environmental media other than air, such as water, food, or soil, relate to the general framework for exposure assessment discussed in Chapter 1. Accordingly, approaches to assess exposure through inhalation should be considered within the framework of total exposure, which accounts for all exposures a person has to a specific compound regardless of environmental medium. Therefore, strategies to reduce air exposures to a given contaminant should consider exposures due to other media. If other media are found to contribute significantly to the total exposure even after air exposures are reduced, agencies responsible for or groups experienced with the other medium should be apprised of the issue and play an active role in the development of integrated exposure reduction strategies.

Unless the hazard of a contaminant is unique or the source of the contaminant exposure is well characterized, it is difficult to conduct an assessment on one contaminant out of a group present in specific microenvironments. When the contaminant does not have a unique health effect, it is necessary to identify those situations where populations have important exposures. Once the exposure is assessed, that information should be used to perform studies to establish the magnitude of the health outcome from exposure in those situations.

These case studies focus on the development of a new paradigm for exposure assessment in risk assessment, risk management, epidemiology, and the application of clinical intervention. The conclusions focus on broad implications for the discipline of exposure assessment, notable advances, and remaining needs. The committee hopes that these case studies will stimulate continued or accelerated development of basic principles of exposure assessment and suggest ways to improve the investigations required for specific air contaminants and general problems.

VOLATILE ORGANIC COMPOUNDS

Introduction

Some volatile organic compounds (VOCs)—such as benzene, formaldehyde, and vinyl chloride—are classified as hazardous because of their role in human carcinogenicity. This discussion deals mainly with VOC exposure of the U.S. population in general; occupational exposure is not specifically considered. The discussion examines EPA's current approach to assessing exposure as part of regulatory investigations of selected VOCs as air contaminants and the advances made by EPA's Total Exposure Assessment Methodology (TEAM) study in evaluating human exposure to VOCs. Benzene is used to examine an exposure assessment dichotomy found between the TEAM study and EPA's regulatory investigations.

Current Approaches to Exposure Assessment Under the Clean Air Act

EPA is required, under Section 112 of the Clean Air Act, to establish National Emission Standards for Hazardous Air Pollutants (NESHAP) that provide an ample margin of safety to protect the public from harmful exposure to VOC contaminants. NESHAPs are set by considering major source

categories of emissions, determining exposures, calculating health risks associated with each contaminant, and focusing regulation on categories with the greatest risk potential.

EPA's selection of source categories is often based on the assumption that sources emitting the greatest amounts cause the greatest exposures. Outdoor stationary sources (e.g., chemical plants and petroleum refineries) are usually identified as the greatest contributors to exposure. The EPA approach to exposure assessment relies heavily on modeling and uses little, if any, actual monitoring data. The human-exposure model combines source emission rates with atmospheric-dispersion equations to predict concentrations of VOC contaminants at various receptor sites in the general population and test the effectiveness of various emission-control strategies.

Modeling extremely long-term exposures, as is required for a NESHAP risk assessment for exposure to carcinogens, presents several major difficulties. The typical practice is to measure or model the concentration of a contaminant at one time and determine lifetime exposure by multiplying that concentration by a fixed number of years, e.g., the average human lifetime. Model input data are source locations and estimated emission characteristics, population census data, and meteorological data. It is assumed that population density remains unchanged for 70 years and that ambient concentrations are constant for 24 hours/day throughout the assumed lifetime.

However, the nature of sources of exposure can change substantially over a lifetime. Large facilities commonly have a design life of 30 years, so considerable change can be anticipated in the sources over the 70-year human lifetime. In addition, individual time-activity patterns can vary substantially over very long periods. In the United States, people change their place of residence often, and few live in the same place over a lifetime.

Recent studies of exposures to some VOCs cast considerable doubt on the NESHAP modeling approach and showed clearly that most people's exposures depend far more on their activities than on whether they live near an industrial source of benzene emissions. The TEAM study has shown that in many circumstances focusing on industrial sources is ineffective in determining human exposure to select VOCs (Wallace, 1987).

Total Exposure-Assessment Methodology Study

Overview

An assessment of human exposure to airborne VOCs has been carried out through the TEAM study. The program originally intended to develop techniques

to measure total human exposure to a broad range of toxic chemicals, including selected volatile and semivolatile organic compounds and metals, but analysis of those chemicals in air, water, and food presented serious methodological problems except for a group of VOCs (Wallace, 1987).

An implicit hypothesis was that the observed personal exposures to selected VOCs could be related to point sources (e.g. from industry) and that the farther one moved from these sources the smaller the observed exposures would be. Stated another way, this implicit hypothesis was that there is no difference between VOC exposure estimates made from stationary monitoring networks and from direct personal exposure measurements as made in the TEAM program. For the small group of VOCs measured, the hypothesis has been rejected.

The TEAM study measured exposure to selected VOCs directly with personal monitors that were worn by subjects. The monitors were designed to be small, and the permit unobtrusive but accurate and precise sampling.

Monitoring of VOCs is complex, because VOCs are typically found at trace levels. Contamination and artifact problems can affect the reliability of the data, and the applied analytical methods generally require laboratory-based instruments (Moschandreas and Gordon, in press). An extensive quality control and quality assurance program was carried out to ensure the proper interpretation of data. Sufficient sample size and probability sampling were used to support inferences regarding the target population and to permit the extrapolation of results to the general population. (Probability sampling is an experimental design that provides unbiased estimates of statistics, including precision, by weighting probability of selection, stratification, and clustering.)

The TEAM study measured 24-hour personal exposures to 20–35 target VOCs in air and drinking water, including halogenated alkanes, alkenes, and aromatic compounds. Subjects were monitored in urban (heavy and light industry) and rural environments. In addition to personal samples, concurrent outdoor samples were collected from the backyards of a subset of the subjects. A comparison of matched indoor and outdoor samples showed that the concentrations of most of the chemicals were higher indoors. That conclusion has been confirmed by other studies that analyzed for a comparable set of VOCs (Molhave and Moller, 1979; Jarke et al., 1981; Seifert and Abraham, 1982; De Bortoli et al., 1984; Gammage et al., 1984; Lebret et al., 1984; Monteith et al., 1984). In particular it should be noted that Molhave and Moller (1979) found higher concentrations of benzene indoors than outdoors.

Measurement Methods

The sampling system used a single-tube containing Tenax sorbent through which a known volume of air was drawn with a personal sampling pump. The adsorbent and pump were combined in a vest that was worn by the test subject. Two consecutive 12-hour samples were collected (6 a.m. to 6 p.m. and 6 p.m. to 6 a.m.). While the subject slept and bathed, the vest was placed carefully in a convenient location. Because most subjects remained at home overnight, the overnight samples were considered indoor samples. Outdoor samples were taken simultaneously near the house. The indoor-outdoor relationships were then established. The disadvantages of Tenax are that it will not retain very volatile compounds (vinyl chloride and methylene chloride) well and it cannot be used to trap reactive compounds (such as formaldehyde). Samples were thermally desorbed from the Tenax onto a gas chromatograph, where the analytes were separated, and then detected using mass spectrometry, which is highly specific and sensitive. Recently, the TEAM study employed canisters for the indoor measurements.

Biological Markers

At the outset of the TEAM study, blood samples were taken at the end of the sampling period and analyzed for the selected VOCs. However, the invasive nature of the sampling and poor detection limits associated with the analysis of blood led to the discontinuation of the technique. Fortunately, breath samples were also taken at the end of the sampling period. Breath sampling involved the use of a special spirometer in which the person exhaled approximately 20 L of air into a Tedlar bag, the contents of which were passed through the same type of Tenax traps as used in the air sampling. The same analytical techniques were used for the breath samples as for the air samples. The breath studies showed significant correlations with the personal monitoring analyses for all 11 prevalent chemicals and showed no correlation with outdoor-air analyses (Wallace, 1987).

To understand the relation of the breath analyses to the air measurements, it is necessary to know the rates of absorption, distribution, metabolism, and elimination of the analytes in the body (physical pharmacokinetics). In fundamental studies, subjects remained in an exposure chamber for a specified period breathing selected VOCs at specified concentrations. The subjects then left the chamber and their respired breath was analyzed repeatedly after specific periods to establish the half-life of the VOCs in the blood. Half-lives ranging from a few hours (benzene) to 21 hours (tetrachloroethylene) were

observed (Gordon et al., 1985). Similar results have been seen by Jo et al. (in press[b]) for chloroform. The half-lives can be used to determine the most appropriate sampling time for the use of breath measurement as an indicator of exposure.

Questionnaires

Two questionnaires were used. The first was a household questionnaire, which included age, sex, occupation, household characteristics and activity characteristics of the participant and other members of the household. The information was used to obtain a probability sample of subjects and to ensure the inclusion of highly exposed subjects in the studies. The second questionnaire involved a 24-hour recall and was administered immediately after the end of the 24-hour monitoring period. The participants were asked whether they had been exposed to potential sources of target chemicals. Monitoring data were then compared with data from the second questionnaire. Variables related to smoking, occupation, home characteristics, personal activities, and automobile travel were found to be the most important determinants of exposure. Benzene concentrations were 30–50% higher in homes of smokers than in homes of nonsmokers. Subjects were heavily exposed to benzene (over 1 mg/m^3) when filling automobile gas tanks; benzene exposure could often be related to automobile use, which also includes time spent inside of an automobile compartment (Wallace, 1989).

Models

No models were used specifically to assess exposure in the TEAM study. However, the use of pharmacokinetic models was considered essential for the proper use and interpretation of breath measurements as indicators of exposure. A simple two-compartment model accounted for the effect of the initial breath concentration and the residence time of VOC measured in the TEAM study within the body (Wallace et al., 1983). The model successfully predicted the time needed for clearance of tetrachloroethylene from the body when compared with the chamber studies mentioned earlier (Gordon, 1985).

Benzene

Results of the TEAM study indicate that personal benzene-exposure concentrations

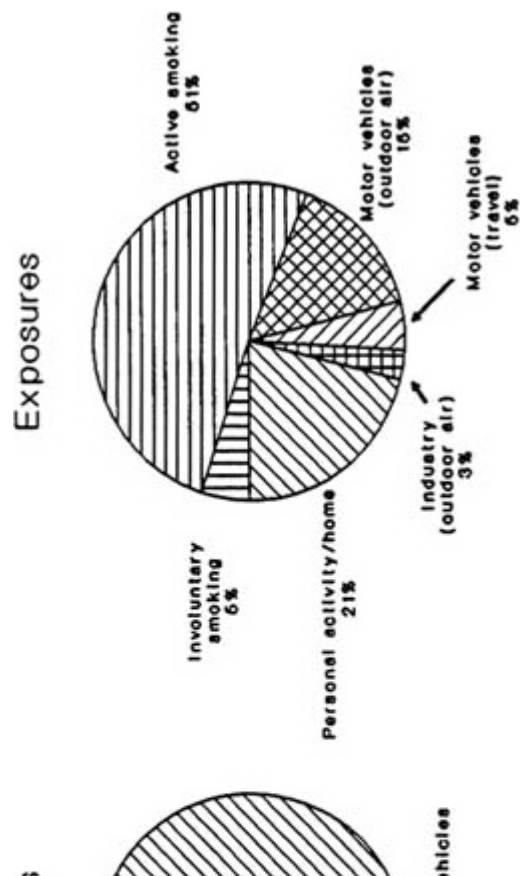

FIGURE 7.1 Benzene emissions versus exposures. Source: Wallace, 1989."Personal activity/home" refers to benzene from materials such as paints,adhesives, and marking pens. For individuals who do not actively smoke, the "active smoking" contribution to exposure is zero, and the other exposure categories increase proportionally.

exceed ambient outdoor concentrations (Wallace, 1989). Figure 7.1 shows industrial sources represent about 14% of total emissions of benzene, but their contribution to exposure is relatively small—only about 3% of the total. Thus programs and regulations to reduce emissions from major stationary point sources could affect, at most, 3% of total exposure nationwide. Nevertheless, a recent rule-making has established national emission standards for benzene from industrial source categories: maleic anhydride plants, ethylbenzene-styrene plants, benzene storage, equipment leaks, and coke by-product recovery plants. Other larger indoor and personal sources of exposure are not covered by this rule-making (EPA, 1988d). Exposures from active smoking, involuntary smoking, products in the home, and personal activities such as driving or painting have been estimated to account for more than 80% of nationwide exposure to benzene. The sources of exposure labeled "motor vehicles (outdoor air)" do not include personal use, such as driving or riding in an automobile; such uses are included in "motor vehicles (travel)." (Note that the TEAM subjects were drawn from areas with little use of woodstoves or kerosene heaters, which are potentially important sources of exposure to benzene (Wallace, 1989)). These important sources of exposure must be re-evaluated and considered for regulation and education. In addition, similar types of integrated analyses are necessary for other VOC contaminants, which may have both indoor and outdoor sources.

Recommendations

To incorporate all significant exposure findings into future rule-makings for other hazardous VOCs, exposure analysts and risk managers need to interact. Regulatory investigations should not be limited to some readily identifiable and measurable point sources that might have insignificant impacts on exposure. The findings of TEAM are at odds with conventional approaches used to control VOC exposure. Therefore a major rethinking of the approaches used to identify public health risk is warranted. Exposure analysts must continue to refine techniques that can identify important sources of contaminant exposures, whether those sources are indoors or outdoors.

The VOCs examined in the TEAM study were almost exclusively in a single exposure medium (air), were chemically stable, and had a volatility that permitted their effective collection and concentration with the sorbent Tenax. New analytical techniques should be developed to broaden the range of analytes that can be collected and measured, so that the "T" in TEAM will actually stand for "Total," and not for "Targeted compounds," as is now the case. In particular, greater attention should be given to analyzing for highly reactive

compounds. Passive dosimeters (Lewis et al., 1985) that match the time resolution of active monitors should continue to be developed, because they are less expensive and usually more convenient to wear.

Better microenvironment monitoring data and time-activity data, including quality assurance and quality control, are needed to improve the modeling of VOC exposures.

ENVIRONMENTAL TOBACCO SMOKE

Introduction

The health hazards associated with smoking have received extensive study and are well known. Thus, it is not surprising that there is now a growing concern that exposure to environmental tobacco smoke (ETS) might affect the health and comfort of nonsmokers. The health and nuisance effects of so-called involuntary smoking have been extensively reviewed in a National Research Council report (NRC, 1986) and in a report of the Office of Smoking and Health (1986). Both reports concluded that exposure of nonsmokers to ETS results in acute irritation of the eyes, nose, and throat; unacceptable odor; upper-airway problems in children, including increased prevalence of respiratory symptoms (cough, sputum production, and wheezing), decreased lung function, increased lower-respiratory-tract illnesses, and increased rate of chronic ear infections; and increase risk of lung cancer. The reports also noted that other outcomes related to the growth and health of children had positive associations in studies, including low birth weight and reduced growth and development. However, the results of some of these studies continue to be debated, and other related studies are ongoing. Thus, it is important to examine ways to improve techniques to assess more accurately exposure to ETS.

Until recently, epidemiological studies of the acute and chronic health effects of ETS have been handicapped by limitations in assessing exposures to ETS. Exposures occur at a wide range of concentrations for highly variable periods and in numerous indoor environments. Unlike active smoking, exposure to ETS cannot now be easily assessed with standardized methods. Previous epidemiological studies of the chronic effects of ETS, particularly lung cancer, have determined exposure solely by questionnaire, which have not been standardized or validated. The questionnaires have usually obtained information on smoking habits of occupants of residences to permit assessment of ETS exposures and have not adequately addressed the impact of occupational exposures. The use of such questionnaires might pose problems

in misclassification of subjects by exposure status and obscure possible exposure-effect relationships.

In the past few years, new techniques have been developed that permit a more accurate assessment of individual exposures to ETS (Leaderer, 1990). They are being applied to test hypotheses in epidemiological studies on the relationships between ETS and acute and chronic health and nuisance effects. The methods use advances in the applications of markers or proxies of ETS, air-monitoring, modeling, questionnaire survey, and biological markers.

Air-Contaminant Measurement

ETS is a complex mixture of more than 3,800 chemicals in the particle and vapor-phases. Given the broad range of chemicals that make up ETS, surrogates or marker compounds have to be identified and measured if one is to assess exposures. Results of recent chamber studies indicate that two such markers are vapor-phase nicotine and the very general category of respirable suspended particles (RSP).

In contrast with mainstream smoke, approximately 95% of the nicotine in ETS is in the vapor-phase (Eudy et al., 1985; Eatough et al., 1986; Hammond et al., 1987). It is not known how nicotine concentrations are related to concentrations of other contaminants in ETS (particle or gas phase) or to those contaminants that might be associated with health (e.g., benzene) or nuisance effects. Results of recent chamber studies (Rickert et al., 1984) and one residential field study indicate that vapor-phase nicotine might be a good marker of ETS-generated RSP (Leaderer and Hammond, 1990). Various active methods (Muramatsu et al., 1984; Hammond et al., 1987; Eatough et al., 1989) have been developed for sampling vapor-phase or phase-distributed nicotine in air, and can be used to measure nicotine in different microenvironments or personal monitoring situations for periods ranging from a few hours to approximately 24 hours. A passive monitor has been developed from an active method of sampling for nicotine (Hammond et al., 1987) and from the knowledge that ETS nicotine exists primarily in the vapor-phase. This passive monitor measures personal exposures to nicotine and nicotine concentrations in indoor environments in periods of 1 day to several weeks (Hammond and Leaderer, 1987). It might permit the assessment of ETS exposures in large segments of the population.

The combustion of tobacco results in the emission of large quantities of RSP into the indoor environments—amounts that result in easy measurement of increases over background (Spengler et al., 1981). A model that incorporates an application of a mass-balance equation has been used for estimating

ETS-generated RSP in various indoor microenvironments (Repace and Lowrey, 1980, 1982). It is also being used to estimate ETS exposures retrospectively and to assess risk (Repace and Lowrey, 1990). As input, the model uses known rates of RSP emission from tobacco combustion and data from several sources, including measured and estimated smoking densities, infiltration and ventilation rates, and deposition rates. The tapered element oscillating microbalance could be used to continuously monitor indoor concentrations of RSP (Patashnick and Rupprecht, 1986).

Biological Markers

Physiological fluids can be analyzed for specific biological marker compounds indicative of exposure to ETS. Thiocyanate, carboxyhemoglobin, nicotine and cotinine, hydroxyproline, *N*-nitrosoproline, aromatic amines, and protein or DNA adducts have all been considered as indicators of dose of tobacco smoke (NRC, 1986; Office of Smoking and Health, 1986). Those biological markers indicate that exposure has taken place, but might not be directly related to the source or to the specific adverse effect under study. Furthermore, a biological marker of exposure might not be specific for the contaminant related to the effect, does not provide an exact measurement of ETS exposure in a single environment, and does not provide information on the environmental factors that affect the concentration in the environments in which people spend time. Biological markers of ETS exposure can also vary widely from person to person, because of differences in uptake, distribution, and metabolism. Some markers are not specific for ETS exposure (e.g., carboxyhemoglobin); while others (e.g., thiocyanate) might be useful for active smoke exposure, but not sensitive enough for ETS exposure. Cotinine and nicotine measurements in the blood, urine, and saliva are specific for tobacco-smoke exposure, and have been widely used as indicators of ETS exposure (NRC, 1986); they are valuable in determining the total or integrated short-term (hours to days) dose of ETS across all locations in which a person spends time.

Questionnaires

Questionnaires have been used extensively in epidemiological studies for the classification of people into broad categories of ETS exposure on the basis of reported exposure. Questionnaires are also used to obtain information on the physical environments in which exposures take place, the factors affecting

the exposures in those environments (volume, number of cigarettes, etc.) and the amounts of time people spend in those environments. They afford an indirect measure of exposure and so cannot provide information on specific exposure magnitudes, although information obtained with them is essential for use in models aimed at predicting ETS concentrations in different environments and total exposure. An effort is under way to develop a standardized questionnaire for estimating indoor concentrations of ETS-related contaminants and personal exposures (Lebowitz et al., 1987).

Future Applications

Advances in assessing ETS exposures are now being incorporated into epidemiological studies of the health and nuisance effects associated with ETS exposure. The use of any particular method in an epidemiological study is determined by the overall objective of the study and the resources available. Some studies use only one of the techniques available; others use several. Many studies use nested exposure assessment designs, in which small samples of the study population are subjected to extensive direct and indirect measurement of exposure (questionnaires, personal monitoring, biological markers, etc.), and the whole study population is subjected to less intensive measurement methods (questionnaires). That approach can be cost-effective. One current study (Leaderer et al., 1989) tests the hypothesis that pregnant women passively exposed to ETS are at increased risk of delivering an infant with low birth weight, or before 37 weeks of gestation, with intrauterine growth retardation. The study uses all the techniques of assessing ETS exposure discussed above in a nested design. That permits efficient use of scarce resources to obtain as complete an estimate of ETS exposure as possible and comparison of results of different exposure assessment techniques. If successful, similar approaches should be considered for use by other exposure analysts in the design of studies of other pollutants or biological end points.

POLYCYCLIC AROMATIC HYDROCARBONS

Introduction

The polycyclic aromatic hydrocarbons (PAHs) are a class of hydrocarbons found in polycyclic organic matter, a very broad class of compounds that have two or more fused rings and are produced by incomplete combustion. Many individual PAHs, as well as various PAH mixtures from different combustion

sources, are carcinogenic in animals and in humans (Santodonato et al., 1981; NRC, 1983b). Exposure to PAHs in workplace environments has long been recognized as posing risks of skin and lung cancer (NRC, 1983b). Although that recognition led to concern about community exposures to PAHs and cancer risk, efforts to link outdoor concentrations of the compounds to lung-cancer rates over many years were largely unsuccessful, in part because it was difficult to detect a relatively small risk of cancer related to PAH-polluted air against a large background of lung cancer due to cigarette smoke using standard epidemiological methods. In addition, there was also a failure to accurately assess personal exposures to PAHs, and epidemiological studies were based on the assumption that measurements of PAHs in outdoor air yielded a reasonable estimate of total exposures. In the last decade, indoor air has been recognized as much more important in exposure to PAHs because most of the population spends 80–90% of the day indoors. There has also been growing awareness that other pathways of exposure, such as diet, can be as important as airborne exposures (Santodonato et al., 1981; Lioy et al., 1988).

Outdoor sources of PAHs include combustion of wood, coal, oil, and gas; motor vehicles; and some industrial sources, such as coke ovens (Daisey et al., 1986). Natural sources, such as forest fires, can also contribute to the atmospheric burden of PAHs. Many sources are present in indoor environments, including tobacco smoke (active and environmental), unvented space heaters, and food preparation (Howard and Fazio, 1980; Wilson et al., 1985; Traynor et al., 1987; Lioy et al., 1988). PAHs produced from combustion of tobacco smoke are directly inhaled during smoking. A one-pack/day smoker inhales approximately 0.4 μg of benzo*a*pyrene (BaP), which is only one of the many PAHs in the complex mixture of tobacco smoke. Nonsmokers can also be exposed to PAHs in environmental tobacco smoke.

The ubiquitous nature of PAHs in the community environment requires the measurement or estimation of total inhaled PAHs in multiple microenvironments. In addition, PAH contamination of water, food, and soil can contribute to personal exposures through other routes of entry into the body.

Airborne concentrations of PAHs depends on the nature, location, magnitude, and duration of multiple combustion sources and vary widely. Lioy and Greenberg (1990), for example, compared urban and suburban locales and found wide variations in outdoor concentrations. Their analyses indicated that the highest PAH concentrations occurred in communities that burned wood as a major source of space-heating. Personal exposures to PAHs from space-heating in communities depend on the kinds of space heaters used, time of year, time spent indoors and outdoors, direct emissions from heaters into indoor air, and penetration of PAHs in outdoor air into indoor environments. Daisey et al. (1989) showed that indoor concentrations of individual PAHs in

homes with woodstoves were 2–47 times greater during wood-burning than non-wood-burning periods. Both direct emissions into indoor air and penetration from outdoor air were inferred to contribute to indoor concentrations. Many particulate PAHs penetrate to the indoors, because they are normally associated with respirable fine particles. The 2- and 3-ring PAHs are largely in the vapor-phase and can also readily infiltrate into indoor environments. The penetration of particulate BaP has been demonstrated in nonsmoker homes as part of the Total Human Environmental Exposure Study (THEES) (Lioy et al., 1988). Indoor BaP was significantly correlated ($r > 0.80$, $p < 0.01$) with simultaneous outdoor values for these homes. In fact, BaP penetration accounted for most of the inhalation exposure of the residents of the non-smokers' homes studied.

It is difficult to determine the contribution of various sources of airborne PAHs to human exposure. Determining human dietary intake of PAHs is equally difficult. Exposure to PAHs in food depends not only on the source of food, but also on the style of cooking and personal eating habits (Howard and Fazio, 1980). BaP can be deposited from outdoor air onto surfaces of agricultural crops, e.g., spinach, lettuce, and cabbage. The edible portions of those crops have relatively large surface areas exposed to the air and tend to collect large amounts of BaP. Beverages made from coffee beans and tea leaves contain BaP. General information can continue to be obtained from market-basket surveys, but population-based measurements of diets are necessary to define the magnitude of exposures in food, compared with other media.

PAHs are typically found in the atmosphere and in other media as complex mixtures of several hundred compounds associated with organic compounds of many other classes. Low-molecular-weight PAHs, such as phenanthrene, are found in the vapor-phase whereas high-molecular-weight PAH, such as BaP, are almost wholly in the particulate phase (Cautreels and Van Cauwenberghe, 1978; Hunt and Pangaro, 1985; Pysalo et al., 1987). Particulate PAHs in air are preferentially concentrated on particles smaller than 2–3 μm in diameter, because they generally result from direct emission from combustion sources, which produce predominantly smaller size particles (Pierce and Katz, 1975; Miguel and Friedlander, 1978; Van Vaeck and Van Cauwenberghe, 1985). The distribution of semivolatile PAHs (between the vapor and particulate phases) depends on their sub-cooled liquid-phase vapor pressures (and thus on temperature) and on the surface area of the particles (Yamasaki et al., 1982; Bidleman et al., 1986; Bidleman, 1988; Ligocki and Pankow, 1989). Sampling is difficult if all the PAHs are to be collected in a way that truly reflects their true physical state in the air. Inhalation exposures to PAHs included compounds present in both the vapor-phase and the particulate phase

and the potential risk associated with them depends not only on the concentrations and duration of contact with these compounds but on their distribution between particulate and vapor-phases (Boulos, 1985). Differences in penetration of various PAHs to the indoors and in the indoor distribution of PAHs between vapor and particulate phases are not well established. Data on those differences would assist in establishing inhalation exposure relationships for total PAHs. For the quantitative analysis of total-PAH exposure, it is critical to develop sensitive techniques for sampling and analysis of particulate-phase and vapor-phase material collected on low-flow personal samplers (e.g. less than 10 L/min).

The relative amounts of the hundreds of different PAHs in a complex mixture from a combustion or industrial source can vary substantially (Daisey et al., 1986; Masclet et al., 1986). The overall chemical composition of combustion emissions also varies. For example, cigarette smoke has higher proportions of nitrogen-containing organic compounds than do emissions from wood-burning or diesel and automobile exhaust (Schmeltz and Hoffmann, 1977; Albert et al., 1983; Daisey and Gundel, 1989). Such differences result in differences in the biological potencies of complex mixtures. Mumford et al. (1987), for example, reported substantial differences in mutagenic activity in an Ames assay, in carcinogenic activity in mice, and in the chemical composition of particulate matter from Chinese homes that used different fuels—smoky coal, wood, and smokeless coal. They also reported higher lung cancer rates in communities that used smoky coal than in communities that used the other two fuels. Albert et al. (1983) reported substantial differences in chemical composition and biological potency of emissions from coke ovens, roofing tar, cigarette smoke, and various motor vehicles.

It is difficult and expensive to measure all the PAH compounds in a complex mixture as part of an exposure assessment. Therefore, BaP, an animal carcinogen that is found in all PAH mixtures as a more easily measured indicator compound, has been widely used as a surrogate indicator compound to characterize exposure to many PAHs and other complex mixtures (Santodonato et al., 1981; Osborne and Crosby, 1987). There is considerable evidence that BaP is at best a crude indicator of exposure to PAHs, to complex mixtures containing PAHs, and to carcinogens of other classes (Albert et al., 1983; NRC, 1988). The EPA report on toxic air-pollution (EPA, 1985b), which used BaP as a surrogate for total PAHs, estimated that half the risk associated with exposure to BaP was probably due to other products of incomplete combustion. That was probably an underestimate in that the report did not take into account differences in the potencies of various complex mixtures or, more important, indoor exposures to PAHs. It might be possible to measure multiple index compounds to characterize exposures to complex PAH

mixtures with different biological potencies. This, however, has not yet been done, and BaP continues to be used as the indicator compound for characterizing exposure to complex mixtures of PAHs.

Hypothesis and Study Design

Exposures to PAHs in community settings occur through multimedia pathways, including air, water, soil, and food. There is a need to determine the contributions of various pathways and sources of the biologically active PAHs as a basis for reducing the risk of cancer.

In the THEES (Total Human Environmental Exposure Study), exposure to BaP present in multiple media in an urban population is being investigated (Lioy et al., 1988). The study includes simultaneous measurements of BaP in air (indoor, outdoor, and breathing-zone air), water, soil, and food. The results will be used in mass-balance studies on BaP metabolites in the participants' urine and feces and on DNA adducts in their blood. This approach is being developed for generalization to assessments of exposure to other PAHs that require multimedia assessment.

The multimedia microenvironmental results from the first phase of the study were averaged for smoker homes, nonsmoker homes, and a coal-burning home (Lioy and Greenberg, 1990). Data compiled were for indoor and outdoor air samples on 14 consecutive days, weekly composites of food consumed by the participants, spot samples of tap water, and the soil around each home. THEES showed that inhalation and food ingestion provided the greatest exposures (Lioy et al., 1988). Inhaled BaP was derived primarily from indoor microenvironments (including BaP generated indoors and BaP that penetrated from outdoors). Tap water yielded minimal exposure. The homes where the highest calculated ingested doses occurred (more than 400 mg for one subject) also showed the highest inhalation doses, and that suggests a need for further research on the relationships of BaP inhalation and cooking. Inhalation resulted in the highest dose in 7 of the 12 exposure weeks in nonsmoker homes, but food ingestion yielded a higher mean dose during the high food-exposure week. These were doses 3–16 times greater than the inhaled dose. If one adds an estimate of direct BaP inhalation by smokers in the smoker homes as a separate category, their BaP doses will increase by a factor of more than 5. The second and third phases of THEES included personal and biological monitoring and provided information supporting the importance of food and inhalation routes of exposure and on the utility of current biological markers (Waldman et al., in press).

Measurement Methods

PAHs in air are usually collected using high-volume air samplers containing a filter to collect particles followed by an adsorbent trap to collect vapors. However, separating and collecting artifact-free samples of vapor- and particle-phase PAHs are difficult using these samplers. These artifacts include adsorption of vapors by the filter matrix itself; PAH blow-off losses from or adsorption gains to particles collected on the filter; and losses of PAHs from chemical reactivity with ozone and other reactive species drawn through the sampler (Van Vaeck et al., 1984; Finlayson-Pitts and Pitts, 1986; Coutant et al., 1988; Ligocki and Pankow, 1989).

Many scientists who sample air believe that an improved way to separate and collect both phases simultaneously would be to use a sampling train with a diffusion denuder followed by a filter and then by a sorbent. With this sample collection system, compounds in the vapor-phase are removed by the diffusion denuder and, therefore, are not available to adsorb onto the particles collected on the filter or onto the filter matrix itself during sampling. Particles pass through the denuder and are collected on the filter. The sorbent behind the filter collects vapor-phase compounds desorbed from the particles collected on the filter. The sum of the analyte concentration on the filter and on the sorbent behind the filter provides the analyte's particle-phase concentration.

Recent experiments by Coutant et al. (1988), using a denuder system similar to that described above, have shown that at a high-volume filter face velocity of about 33 cm/sec, low-molecular-weight PAHs—phenanthrene, anthracene, fluoranthene, pyrene, chrysene, and benz*a*anthracene—all displayed some tendency for volatilization losses from the filter. High-molecular-weight PAHs, such as BaP, did not appear to be affected. In principle, the sampler that they developed for experiments on sampling artifacts could be adapted and used to measure the vapor-phase and particulate PAHs in indoor air more accurately. But applications would require four rather than two analyses for each collected sample, because chemical interferences prohibit the analysis of vapor-phase PAH removed by the denuder. Thus, vapor-phase PAH must be determined by difference. Two samplers are used in this method, one with and one without a PAH denuder, to determine the concentrations of particulate-phase PAH and total PAH, respectively. The filters and backup sorbents for each sampler must be analyzed, requiring four analyses for each sample. Denuder systems that permit desorption of collected vapors (Lane et al., 1988) would be very useful for collection of airborne PAH.

Samples of particles or vapors on a sorbent are typically extracted with an organic solvent and concentrated, sometimes fractionated, and then commonly analyzed with gas chromatography-mass spectrometry (GC-MS) or high-pressure

liquid chromatography (HPLC) with fluorescence detection. Wilson et al. (1985) have reported that extracts of PAHs from particulate matter and the sorbent can be analyzed directly (without cleanup) with positive-chemicalionization GC-MS. They collected large air volumes (100 m^3 in 8 hours) in indoor environments. Indoor air-sampling rates should be less than 5–10% of indoor air-exchange rates for the room with the sampler, to minimize the perturbation caused by sampling. This method could be modified by reducing the total solvent extract volume (and thus concentrating the sample) or using longer sampling times at a lower flow rate.

In THEES (Lioy et al., 1988), samples of airborne particulate matter are being collected indoors and outdoors and analyzed for BaP. The samples are extracted, concentrated, and then separated and analyzed for BaP with thin-layer chromatography and in situ spectrofluorimetry.

Analysis of PAHs in food samples typically involves extraction and digestion in alcoholic potassium hydroxide followed by various cleanup and separation steps (Howard and Fazio, 1980; Lawrence and Das, 1986; Grimmer and Jacob, 1987; Vaessen et al., 1988). Considerable cleanup is generally required for food samples and losses of PAHs can be substantial. The PAH-enriched fraction is then analyzed with the same methods as for airborne PAHs.

It is important to include both positive (known standards or surrogate compounds) and negative (field and lab blanks) controls in the sampling and analysis of PAH for exposure measurements and to determine and report the accuracy and precision of all measurements.

Biological Markers

There has been considerable development of methods for the analysis of biological markers of PAH exposure in the last decade. Methods have been developed for PAHs and their metabolites in urine (Becher and Bjorseth, 1983) and for PAH-DNA adducts in blood and tissue (Perera et al., 1982; Burlingame et al., 1983). The method developed by Becher and Bjorseth for measurement of PAHs and their metabolites in urine involves reduction of the metabolites to the parent PAHs followed by HPLC with fluorescence detection of total PAHs. That method has been used for biological monitoring of PAHs in workers in an aluminum plant. Other analytical methods are being explored for use with urine samples. Mass-spectrometric methods have also been developed for biological markers of PAH exposure (Burlingame et al., 1983). Several investigators (Perera et al., 1987; Harris et al., 1985; Everson et al., 1986) have used an immunoassay for determination of PAH-DNA adducts in tissue samples and in blood samples from smokers, nonsmokers,

and workers in high-PAH-exposure industries. Application to the community exposure situation needs further research and development.

Questionnaires

Questionnaires should be used in any study of exposure to PAHs to provide information on the various sources that contribute to exposure. They should include questions on smoking; indoor sources, such as smokers in the home, kerosene heaters, woodstoves, fireplaces, and gas stoves; cooking practices, and diet; and local outdoor sources. In the THEES (Lioy et al., 1988), a person in each participating household fills out a daily activity questionnaire that includes questions about time spent in the home, personal activities, indoor combustion sources, smoking, and ventilation. Information about hobbies, home repairs, and personal-product use is included and is necessary for defining the important pathways and sources of exposure. Details on the contents of each meal eaten at home and at other locations are also obtained.

Models

Several types of models have potential application in community exposure assessments for PAHs. The mass-balance model can be used in various ways to estimate indoor and outdoor inhalation of PAHs. Receptor models might be used to estimate the contributions of various sources to PAH exposures, if appropriate tracers can be identified for the major source types. The macromodel —developed by Traynor et al. (1988) for particulate matter, CO, and NO_x in indoor air—could be developed to provide estimates of population exposures to PAHs and identify major sources and factors that contribute to large exposures.

Future Needs

PAHs emitted and accumulated in various environmental media require the development and application of sensitive personal monitoring methods for determining the individual compounds present and routes of exposure to them. Research conducted on airborne BaP and other selected PAHs clearly demonstrates that they can accumulate indoors as well as outdoors. The data indicate that many 3–4 ring PAHs are present in both particulate and vapor-phases. Therefore, new techniques for sampling PAHs simultaneously in both

phases are required for indoor-environment and personal monitoring studies; they will increase the accuracy of exposure and risk assessments for total PAHs.

The reactivity of PAHs requires further investigation, because it appears that a number of nitrogenated and oxygenated PAHs can be produced during sampling (Arey et al., 1988) or by atmospheric reactions (Pitts et al., 1985b; Greenberg and Darack, 1987). Some nitrogenated and oxygenated PAHs are directly emitted by combustion sources (Finlayson-Pitts and Pitts, 1986). Some of these components are highly mutagenic and will need to be factored into PAH exposure assessments. In addition, methods that will minimize or eliminate artifacts during sampling or analysis will have to be developed.

The THEES strategy has been developed for the measurement of BaP exposure through multiple pathways. Inhalation exposures could be derived from indoor combustion sources, penetration of outdoor air to the indoors, and personal activities, such as cooking and smoking. The strategy should be extended to other PAHs and important PAH derivatives to assist in studying related indoor and outdoor exposures and in identifying the primary routes of exposure for use in risk assessment and risk management. Those conducting the research and those involved with development and application must interact to ensure that the major pathways of exposure continue to be studied and effective strategies developed.

LEAD

Introduction

Mined and processed since antiquity, lead is a ubiquitous toxic substance that poses special challenges for exposure assessment. Like a number of persistent environmental pollutants, lead appears in all media (NRC, 1987b). Over the past 3 decades, the decrease in the body burden of lead that is deemed to be toxic and the detection of widespread lead poisoning in young American children have spurred recognition of the importance of controlling an array of sources. The American Academy of Pediatrics and the American Public Health Association recommend routine testing of infants and children to reduce the neurological deficits inflicted by exposure to lead—a previously silent epidemic that can permanently impair vital physiological functions and cognition in workers and children. Given the absence of adequate systematic environmental monitoring of lead and the lack of routine body-burden screening, lead-poisoned children all too often are the primary means of

identifying a lead-poisoned environment. Pinpointing precise sources remains difficult.

Over the past 2 decades, measurement of airborne lead concentrations has provided a clear method for tracking and enforcing overall reductions in airborne exposure. Despite real success in reducing airborne lead exposure in the United States and concomitant reduction in blood lead, the Agency for Toxic Substances and Disease Registry (ATSDR, 1988) estimates that about 17% of all children under five have enough lead in their blood to cause permanent deficits in intelligence and development. Approximately 40% of all children in poverty in 1984 are believed to be so affected. Children absorb lead from multiple sources including air, drinking water, food, house dust, play area soil and dust, interior and exterior paints, improperly glazed ceramics, and toys (EPA, 1986c).

Children are at special risk from lead exposure, because their higher rate of mineral turnover in bone allows them to absorb and retain more lead per unit of mass than adults and because the developing nervous system is especially vulnerable to lead. Some children are exposed to high doses of lead through deliberate swallowing (e.g., pica), mouthing of lead-containing non-food objects, or hand-to-mouth activity after exposure to lead-contaminated dust or soil.

The relative intensities and durations of exposure to lead also influence toxicity. The recommended maximal daily intake of lead for infants is 100 μg from all sources. In the late 1970s, one could slide a finger along a long table and accumulate more than 100 μg of lead in common, urban dust contributed by emissions from motor vehicles combusting gasoline containing lead. A single chip of 50% lead paint (500,000 parts per million) will produce acute poisoning if eaten by a young toddler. Daily ingestion of 1 or 2 liters of water with lead at or above 20 μg/L occurs from 20% of public drinking water supplies in the United States. This level of lead can result in developmental problems, as can playing on the ground or floor in an area with modest lead contamination over the same period.

We review here the recent history of the successful application of exposure assessment methods to the problem of airborne lead. This section discusses the development of evidence on the contribution of lead from gasoline, stationary sources (including municipal incinerators), and dusts and soil to airborne lead and notes the clear link between the recent decline in airborne lead and at least a portion of the decline in blood lead in the U.S. population.

Lead from Gasoline

In the 1970s, as more and more cases of lead poisoning occurred in children who did not live in dwellings with lead-based paint, researchers explored the link between leaded gasoline and outdoor-air lead concentrations. It was found that most of the lead in the atmosphere resulted from combustion of leaded gasoline. Two regulations were promulgated by EPA. One (EPA, 1973) required the availability of unleaded fuel for automobiles designed to meet federal standards for emission of VOCs with lead-sensitive emission-control devices (e.g., catalytic converters); the second (EPA, 1986c) required a reduction of the lead content in leaded gasoline. As shown in Figure 7.2, the control of lead in gasoline over the last several years has resulted in a decrease in peak outdoor-air lead concentrations. Based on data from a larger number of monitoring stations, the downward trend shown in Figure 7.2 has continued. The most recent data from EPA show that in 1988 the maximum quarterly average concentration of lead in outdoor air was less than 0.1 $\mu g/m^3$ and approximately 3×10^3 tons of lead was emitted due to gasoline combustions (EPA, 1990). Figure 7.3 shows findings of the National Health and Nutrition Evaluation Survey from 1976 to 1980, establishing a clear association between lead in children's blood and lead used in gasoline (NRC, 1980; Annest et al., 1983; Rabbinowitz, 1990). In a number of major U.S. cities, trends in childhood lead concentrations correlated closely with those of sales in leaded gasoline (NRC, 1980). At one time, exposure to airborne lead accounted for 40–50% of blood lead in children (ATSDR, 1988).

Use of leaded gasoline has been declining since the 1970s and it is projected that the gasoline-lead phase down now in progress will lower blood lead concentrations to less than 15 µg/dL in millions of children between now and 1992; pediatric lead toxicity is considered to begin when blood lead exceeds 10 µg/dL. But present and past airborne depositions (fallout) of lead onto soil and buildings will produce exposures for years to come, and continued monitoring of lead in air and other media remains important.

Lead in the ambient air is routinely monitored in accordance with the Lead National Ambient Air Quality Standards (*Fed. Reg.*, 1978, 1981). In urban areas, airborne lead is presumed to be correlated directly with the remaining lead in gasoline, although municipal incineration and other point sources can also be important.

Airborne Lead from Stationary Sources

Stationary sources are fixed operations that emit lead. The United States

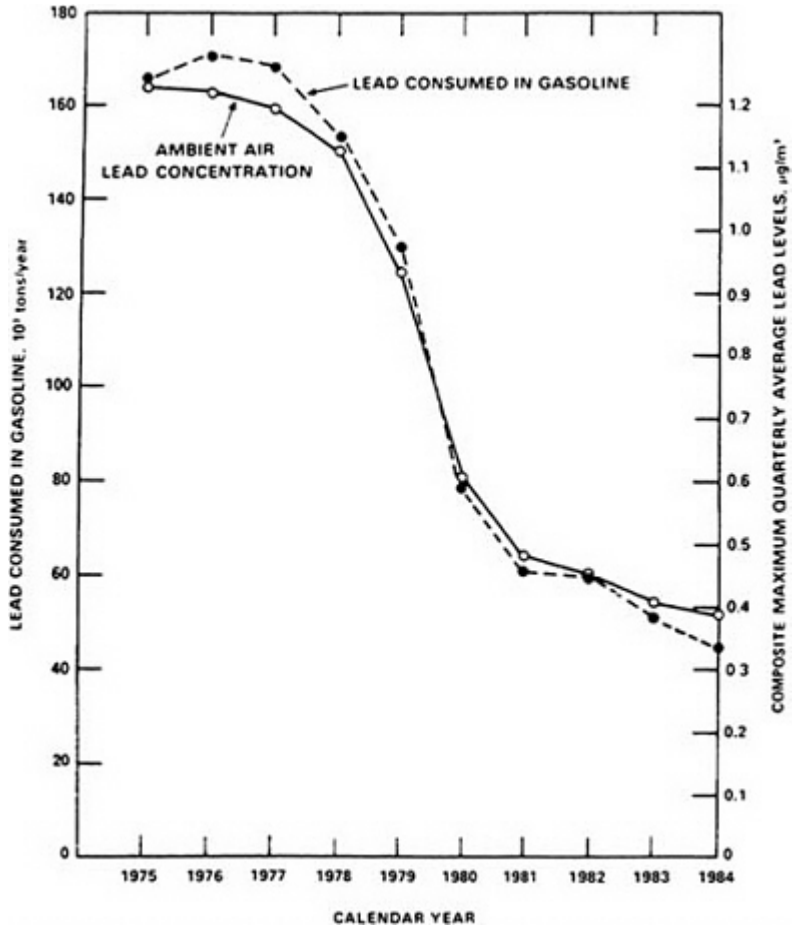

FIGURE 7.2 Gasoline lead emissions and outdoor lead concentrations 1975-1984.
Source: EPA (1986c).

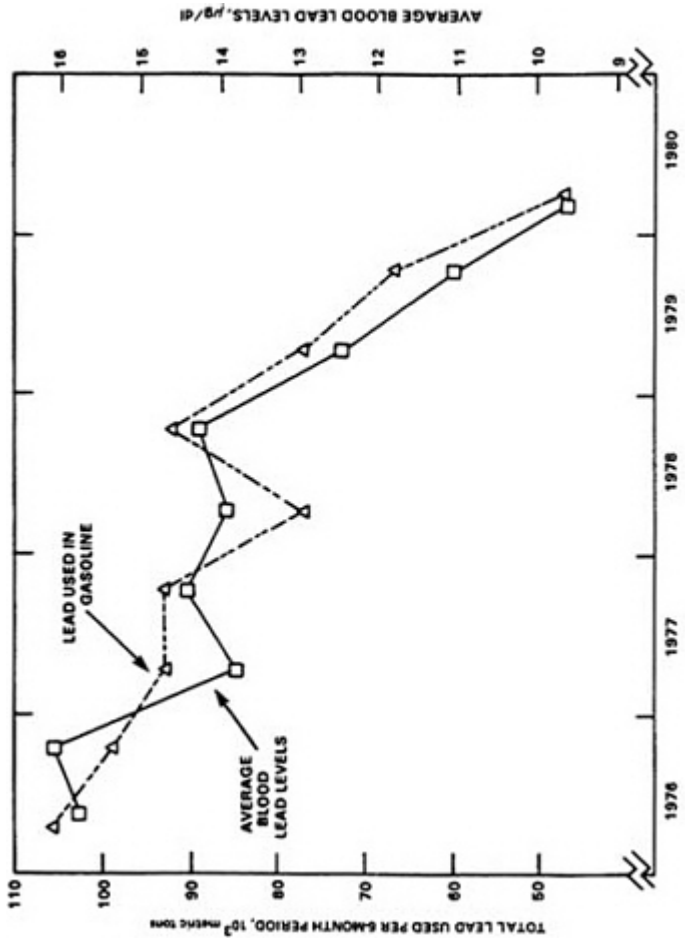

FIGURE 7.3 Parallel decreases in blood lead values observed in the NHANES II and amounts of lead used in gasoline during 1976-1980. Source: EPA (1986c).

today has 11 mines, five primary smelters and refineries, 60 secondary smelters, 132 plants where lead-acid batteries are manufactured, and thousands of other local sources, including municipal incinerators, demolished structures, and uses of contaminated sewage sludge. The latter are especially difficult to pinpoint. The most severe pediatric lead poisonings in the United States have been noted in the vicinity of primary lead smelters (Baker et al., 1977; CDC, 1985). Exposure from stationary sources might be concentrated, because of adverse climatic conditions, such as aridity, low wind speeds, and thermal inversions. Children are also being exposed to lead at some hazardous sites that are on the National Priorities List for Superfund remedial action (ATSDR, 1988). Small numbers of children are affected, but their exposures are often large.

Lead in Dusts and Soils

Soil dusts, street dusts, and household dusts can all contain substantial amounts of lead deposited from air, although some is linked with degrading paint and municipal ash transportation or incineration. Direct exposure by inhalation is only one way that lead in the air can affect children. In time, lead settles out from the air and can be ingested through soil consumption and consumption of contaminated foods. Deposition of atmospheric lead over many years accounts for the high concentrations of lead found in soil and dust (Groth, 1981; CDC, 1985). Studies in New Jersey (Caprio et al., 1974; CDC, 1985) and California (Johnson et al., 1975; CDC, 1985) have shown that children living within 100 feet of major roadways have higher blood lead concentrations than those living farther away.

Urban soil lead has numerous sources, such as the burning of trash rich in lead, the residue of demolished structures, the dumping and burning of lead batteries and their cases, the historical use of lead pesticides, emissions of refuse incinerators, and use of sewage sludge as fertilizer (Chaney and Mielke, 1986). Lead from flaking paint, particularly in and around houses, can be an important lead source for soils (Chaney et al., 1984). (Note: Yaffe et al. (1983) used stable isotopes of lead to trace paint lead to soil, from there to house dust, and from there to blood lead in children. Plant uptake of lead from soil and transport into edible plant tissues is another source of lead exposure (Chaney and Mielke, 1986).)

Outdoor-Air Measurements

At the beginning of 1988, EPA had 353 monitoring stations that directly measured lead in air in the United States. Roadside and neighborhood monitors dominate the network now, but greater monitoring around point sources is planned. EPA's monitoring for lead in air uses high-volume samples with fiberglass filters.

Biological Markers

The human body is an integrator of lead from different sources. Whether ingested or inhaled, lead accumulates in the blood, brain, and bone; the proportion retained is greatest after ingestion. In humans recent exposure to lead is commonly measured in terms of blood lead, which indicates exposure in the preceding 4 months. The heme biosynthetic pathway is exquisitely sensitive to lead. An increase in erythrocyte protoporphyrin or an increase in delta-aminolevulinic acid (ALA) in urine is often an early and reliable marker of functional impairment due to lead absorption (EPA, 1986c; ATSDR, 1988). Research is under way to measure cumulative lead exposures in the dentin of deciduous teeth or by x-ray fluorescence of major bones, such as the tibia. In any given population, a range of internally absorbed blood lead will reflect individual variation in metabolism of toxicants and other host factors, such as nutritional status and age (ATSDR, 1988).

Lead in inhaled air is eventually absorbed in a two-part process: some absorbed from the pulmonary tract, and some swallowed and absorbed from the gastrointestinal tract (ATSDR, 1988). Low concentrations in a number of media can add up to a large intake over time. Moreover, the developing fetus and the young remain at special risk, both because their metabolism is high and because their growing brains more readily absorb lead.

The biological basis of lead toxicity is closely linked to the ability of lead to bind to ligating groups in crucial biomolecular structures. Lead competes with calcium and other essential metals for binding sites and can inhibit enzyme activity. Anemia, a common manifestation of chronic lead intoxication, is associated with reduced hemoglobin production and shortened erythrocyte survival. An increase in erythrocyte protoporphyrin is often construed as a marker of recent lead absorption in young children. Many believe that ALA in urine and inhibition of the activity of the enzyme ALA-dehydrose (ALA-D) are the most sensitive markers; however, interpretive difficulties might arise, as mentioned in Chapter 4.

Piomelli and others have shown, however, that blood lead can underestimate

cumulative exposure. They used EDTA chelation tests to stimulate the release of lead from bone and showed that substantial stores of lead can be found in children with modest blood lead concentrations (Piomelli et al., 1984).

Questionnaires

The studies reported above did not use individual questionnaires. Rather, biological markers became the indicator or validator of sources of lead exposure. Thus, in investigations of a neighborhood near a smelter, blood lead concentrations in children were determined by hematofluorimeter evaluations of whole blood drawn by venipuncture, and these were correlated with distance.

Models

In preparing its justification for the regulation of lead, EPA relied on a series of crude models that correlated gross figures on production of leaded gasoline with estimates of airborne lead and blood lead. More sophisticated models now use radiographic tracers to simulate lead deposition, absorption, and pharmacokinetics in the pulmonary tract and its environmental cross-media cycling (EPA, 1989a). Studies have confirmed the direct causal link between amounts of lead in gasoline, air, and blood.

Conclusions

The best integrator of recent exposure to lead in the young child is the blood, which reflects exposures that occurred over the preceding 4 months. However, inferential methods for determining the relative sources of blood lead in the child, such as the isotope-ratio method developed by Yaffe et al. (1983), are expensive. Table 7.1 summarizes various strategies for estimating exposure from a number of important sources described here. In few of the strategies have studies of individual activity patterns been undertaken. Most rely on extrapolations from a few samples or on surrogate indicators from production or consumption patterns.

From the earliest Roman times, humans have been exposed to lead from numerous sources. Methods for estimating exposure to lead across media have changed, reflecting the field of exposure assessment itself and different

TABLE 7.1 Categories of Estimation Methods for Children Exposed to Lead by Source

Source Category	Level of Precision	Basis of Exposure Measurement
Lead in paint	Potential exposure	Determination of numbers of children in housing with highest likely lead-paint burdens
	Potential exposure with a better indication of actual exposure risk	Number of children estimated to be in lead-paint housing with deterioration: peeling paint, broken plaster, damage
	Likely actual exposure	Use of a specifically determined prevalence for an NHANES II stratum matching such children; other, regional survey data
Lead in gasoline	Potential exposure (blood lead changes) in a subset of U.S. urban child population	Total number of young children in 100 largest U.S. cities
	Actual exposures based on leaded gasoline combustion	Logistic regression analysis to estimate numbers of children falling below selected blood lead criterion values
Lead from stationary sources	Potential exposure	Total of young children in communities within certain proximity of lead operations

Lead from stationary sources	Actual exposure	Prevalence of indicated blood lead at or above some criterion level in actual field studies of stationary sources
Lead in dusts and soils	Potential exposure	Summing of potential exposure numbers from the above three categories
	Actual exposure	Summing of corresponding actual exposure numbers from first three actual exposure categories or use of multimedia regression equations (not possible with present data)
Lead in drinking water	Potential exposure	Number of young children either in homes with old lead plumbing or in new homes with lead solder
	Actual exposure measurable, but not highest risk of toxicity	Number of young children in homes with lead in drinking water > 20 μg/L
Lead in food	Potential exposure at or near toxic magnitude	Number of children in age group
	Actual exposure	Fraction of potentially exposed children whose food-lead intake might raise blood lead high enough to cause concern

Source: ATSDR, 1988.

hypotheses as to critical sources. Exposure to lead has often been estimated with crude surrogates of different source terms, such as production and consumption figures for specific applications. There is no systematic monitoring of environmental lead across media today, nor is there routine testing and screening of children for lead toxicity.

More focused exposure studies are needed that include observation of activities of the young child, individual monitoring, and detailed cross-media uptake monitoring (which can be affected directly or indirectly by air emission). Such studies would ensure that future control expenditures were appropriately based on exposure-response relationships.

ACIDIC PARTICULATE MATTER

Introduction

Airborne acidic particulate compound species, which include primarily sulfuric acid (H_2SO_4) and ammonium bisulfate (NH_4HSO_4), and surrogates have been measured by a number of researchers over the last 20–30 years, but their health effects have been appreciated only recently (Utell et al., 1983; Spektor et al., 1989; Koenig et al., 1989; Speizer, 1989; Spengler et al., 1990).

As discussed by Lippmann et al. (1987), there appear to be two different responses of humans to inhaled acidic aerosols: reflex bronchoconstriction and altered mucociliary clearance (which might lead to chronic bronchitis). Both are supported by numerous animal studies. Controlled human-exposure studies that have attempted to define a dose-response relationship have involved short-term exposures to acidic aerosol concentrations in excess of those typically found in outdoor air. However, the exposures were comparable with those estimated during specific pollution episodes (Lioy and Waldman, 1989). For bronchoconstriction, the lowest observed-effects concentration of sulfuric acid in asthmatics was reported in four studies to be 68 $\mu g/m^3$ for 30 minutes at rest and 10 minutes of exercise (Koenig et al., 1989), 450 $\mu g /m^3$ for 16 minutes (Utell et al., 1983), 1,000 $\mu g/m^3$ for 1 hour at rest (Spektor et al., 1989) and 75 $\mu g/m^3$ for 2 hours including rest and four 10-minute periods of exercise (Bauer et al., 1988)—a wide range. The lowest observed-effects concentration for altered mucociliary clearance was reported in two studies to be 100 $\mu g/m^3$ for 1 hour at rest (Leikauf et al., 1981, 1984; Spektor et al., 1989).

Recent epidemiological evidence supports the hypothesis that chronic, low-level exposure to acidic particles can be associated with respiratory disease. That is very important, because the exposure pattern is typical of the ambient

atmosphere (Lioy and Waldman, 1989). Speizer (1989) has reported that in four of the six cities in the Harvard study in which acidic particles were measured, there was a better correlation of the prevalence of chronic bronchitis (as diagnosed by a physician) with hydrogen ion concentration in the particles than with total respirable-particle concentration.

The Clean Air Science Advisory Committee (CASAC) of EPA recommended to the administrator that an analysis of the available and emerging scientific information on acidic particles be prepared and that exposure and health research be conducted to provide a scientific basis for a decision on the promulgation of a National Ambient Air Quality Standard (NAAQS). This is based on the conclusions and recommendations in Acid Aerosol Issues Paper (EPA, 1989b).

Hypothesis

Health effects associated with exposures to acidic particles have been observed in controlled human studies, and epidemiological studies have yielded suggestive evidence of exposure-response relationships at exposures detected in the ambient environment. Therefore it is necessary to examine the occurrence of exposures to and health effects of acidic particles in sensitive groups in the general population.

Measurements

The chemical variable relevant to health appears to be total particle acidity or sulfuric acid concentration, although the aqueous concentration of hydrogen ion in the airborne particles might be useful. There are several reasons for that. First, titratable acidity has been suggested as the appropriate indicator of irritant potency (Fine et al., 1987). Second, animal-toxicity studies of acidic sulfate aerosols have shown that it is the acidity (i.e., the hydrogen ion concentration), rather than the acid anion concentration, that is related to respiratory effects (Lippmann et al., 1987). Finally, although airborne acid aerosols are found as highly concentrated solution droplets whose acids might not be fully dissociated, the acids in the droplets become fully dissociated when the droplets are inhaled and later come to rest on the relatively alkaline surfaces of the respiratory tract. Therefore, particle acidity appears to be the relevant measure from a public health perspective.

Based on a total of about 10 reported studies, typical outdoor concentrations of particle acidity range from 1 to 40 microequivalence of hydrogen ion

per cubic meter of air over 1–12 hours of sampling. The highest reported concentrations were associated with the longer sampling times (Tanner and Marlow, 1977; Pierson et al., 1989). The associated exposure during a pollution episode can be estimated from the reported concentration and the episode duration and can be as high as approximately 1,000 $\mu Eq(H^+) \cdot hr/m^3$ (Lioy and Waldman, 1989).

An important exposure characteristic is particle size. Airborne acidic particles can range in diameter from 0.01 to more than 10 μm. The smallest particles are formed from condensation of acidic gases, such as sulfur trioxide. The largest are found in fogs. However, most airborne acidic particles have a mean diameter of 0.3–0.6 μm (on an aerodynamic mass basis). Depending on the size, the particles will be deposited in various regions of the respiratory tract. Particle size also determines the ratio of particle surface area to volume, which in turn determines the rate of chemical neutralization by atmospheric and respiratory ammonia (Larson, 1989). Very few measurements of acidic aerosol size distribution exist, so no estimate can be made of episode exposure as a function of particle size.

Clearly, there is a great need for more complete exposure assessments than have resulted from epidemiological studies. Lioy and Waldman (1989) have identified at least three ambient situations (urban wintertime fogs, summertime haze, direct source emissions) in which high acidic concentration can be anticipated, and Leaderer et al. (1990b) have identified sources that could lead to indoor exposure. It is imperative to focus on situations that embody the most important exposure-response relationships in the outdoor and indoor environments. However, the metric of acidity of concern should be measurable with methods developed for use in the field.

Methods

The most direct sampling method for strongly acidic particles involves drawing ambient air through a diffusion denuder tube and a collecting the particles on a Teflon filter. The denuder tube removes airborne bases, such as ammonia, that might otherwise neutralize some of the acidity collected on the filter. When the sample collection is complete, the filter is returned to the laboratory, and the acidity is extracted and titrated. That method has much appeal: it is relatively straightforward and involves an acid-base titration of aerosol acidity. Its drawbacks include relatively long collection times (it is not a continuous method), the need for laboratory analysis of the filters, and potential sampling artifacts. The potential sampling artifacts occur under two conditions: in sampling of acidic particles that coexist in the air with other,

more alkaline particles, such as sea salt and surface dust; and in sampling of particles that are coated with an acidic surface layer, such as those studied by Amdur and coworkers (Amdur et al., 1986). The first potential artifact results from the inability of the diffusion denuder to remove alkaline particles, which penetrate past the size selective inlet. Therefore these particles land on the same filter as (and potentially react with) the acidic particles of interest. The second potential artifact also results from the failure of the denuder to prevent chemical reactions between the particle and its acid coating. The second artifact is probably not too severe, because the acid-coated particles are not the major form of atmospheric acidity and are expected to be important only near some combustion sources.

The other approach to measuring acidic particles focuses on the continuous measurement of specific acidic compounds, notably the ammonium salts of sulfuric acid, using a flame photometric detector modified to discriminate the species by using volatilization as a function of temperature (Tanner et al., 1980; Slanina et al., 1985). Continuous methods avoid many of the problems associated with filter sampling. However, these methods cannot distinguish ammonium bisulfate from ammonium sulfate, because these compounds have similar thermal-decomposition characteristics; airborne total acidity might therefore be underestimated. In addition, the methods do not measure total particulate acidity, but focus on a few sulfur compounds that contribute to the total.

It is evident that ideal monitoring methods would measure titratable acidity in airborne particles or all acidic particle species. Ideal methods would not be subject to artifacts resulting from particle-particle reactions on filters and would be continuous and rapidly responding. No reported measurement method has all those attributes.

Conclusions

Once an acidic particulate contaminant of health concern is agreed upon, an intensive program should be developed to design or validate instrumental and analytical techniques for indoor and outdoor studies. Closely associated is the need to gather further information on acidic particle precursor sources and primary acidic particle sources, particle size distributions, the situations in which acid exposures can occur indoors and outdoors, and accurate predictive models of exposure. The techniques should then be used in epidemiological studies of chronic or acute effects. The results of exposure assessments related to atmospheric acidic species should provide a basis for comparisons of toxicity of acidic mixtures. Accurate measurement of exposure to acidic

particles in a variety of microenvironments is necessary if exposure analysts and other environmental health professionals are to define exposure-response relationships. Accurate exposure assessment is imperative for use by regulators and managers in establishing a basis for recommendations of mitigation steps necessary to minimize indoor and outdoor exposures and community health effects.

SICK-BUILDING SYNDROME

Introduction

Environmental measurements made during the last decade have revealed that indoor concentrations of some air pollutants are often higher than outdoor concentrations and sometimes even higher than outdoor health-based air quality standards (Spengler and Sexton, 1983; Spengler and Soczek, 1984; Wallace et al., 1986). Furthermore, other research demonstrates that, on the average, people spend 80–90% of their time indoors (Szalai, 1972; NRC, 1981). Thus, indoor exposures to some pollutants are greater than outdoor exposures because of higher indoor concentrations, longer exposure durations, or both. Because of the large amount of time spent indoors, some indoor exposures can be greater even when indoor concentrations are lower than those outdoors. Thus, it is important to identify and take into account all important microenvironments when determining total exposures to airborne contaminants (Girman et al., 1987). Many types of studies are being carried out to determine exposures in various indoor microenvironments and should consider using the state-of-the-art concepts as discussed throughout this report. One type of indoor study—the study of the sick building syndrome (SBS)—especially could profit from the use of new methods.

The incidence of SBS has increased with the development of energy-efficient buildings, the attendant reduction in ventilation, and the increased use of synthetic building materials and furnishings. Outbreaks of SBS are a cause for great concern, because of their impact on public health and the economic impact of direct expenses (for environmental exposure monitoring, medical care, and litigation) and indirect expenses (productivity losses and reduced marketability of office space).

There are two types of building-related problems. One, called building-related illness (BRI), can be generally thought of as an outbreak in a set of occupants of subchronic disease or symptoms caused by one or a few environmental constituents near or above a health-effect threshold, such as legionellosis caused by exposure to the bacteria of the genus *Legionella*, hypersensitivity

pneumonitis caused by bioaerosol exposure, or eye irritation caused by exposure to formaldehyde. The other, SBS, usually involves buildings in which no single environmental constituent examined exceeds the generally accepted threshold. Assuming that the health-effects threshold data are correct, the problem is thought to be multifactorial but could be caused by a single component not detected by current sampling and analysis methods. In SBS, occupants complain of subchronic discomfort (eye irritation, headaches, lethargy, etc.) at a prevalence greater than that associated with occupants of "healthy" buildings (in which the prevalence is not well established, but might be around 20%). The symptoms characteristically diminish when the occupants leave the building (Molhave, 1987; Woods, 1988).

The multifactorial cause of SBS is believed to involve a complex interplay of indoor pollutant-source emissions, both chemical and bioaerosol, from building materials and furnishings, building systems (e.g., ventilation and humidification systems), and building use; physical factors (temperature, light, noise, etc.); human characteristics (race, sex, health status, sensitivity, etc.); and the group dynamics in the building. Except in rare instances, baseline information on those parameters is lacking for noncomplaint (healthy) buildings, so the basis for evaluating what is unique about a sick building is lacking (Berglund et al., 1987). The current situation is analogous to attempting to treat a sick patient without knowledge of normal physiology.

Carrying out accurate risk assessments and developing appropriate mitigation strategies to reduce adverse health outcomes in sick buildings are not possible without baseline information about the environmental characteristics of buildings without complaints, i.e., from healthy buildings, as well as similar data on sick buildings. Such information can come only from carefully executed epidemiological studies that include both healthy buildings and sick buildings. For example, Noma et al. (1988) have studies SBS through a statistical analysis of chemical concentrations in air samples collected from sick and healthy school buildings.

Many studies that could be classified as SBS studies have been reported, particularly in the proceedings of three international conferences on indoor air quality since 1981 (International Symposium on Indoor-Air-Pollution, Health and Energy Conservation, 1981; Third International Conference on Indoor Air Quality and Climate, 1984; and Fourth International Conference on Indoor Air Quality and Climate, 1987). Although the studies varied in size and quality, they shared a number of disturbing characteristics: they were not scientifically designed but rather were responses to complaints of building occupants; they were generally limited in their types of measurements, usually only monitoring for concentrations of contaminants near the occupational exposure limits; they seldom incorporated quality assurance plans; they generally

used no standardized protocols; and they were rarely designed to test clearly stated hypotheses.

Data from such studies are often characterized as anecdotal by scientists. Although such anecdotal data can be of use in the early development of a scientific discipline to assist in generating hypotheses, they are of little scientific value and, in fact, can do a disservice if they continue to be published in the scientific literature in the guise of results of studies.

It is important to distinguish between public health building investigations and SBS research studies. The primary objective of the former is to alleviate a problem or concern, and that of the latter is to test a hypothesis. The two objectives are not necessarily compatible. Therefore, regarding SBS, a sharp delineation should be made between anecdotal efforts and true research studies; efforts of the anecdotal type should be referred to simply as building-complaint investigations.

In recent years, a few studies have been conducted that can be considered SBS research studies, as opposed to building-complaint investigations. Finnegan et al. (1984) attempted to show a relation between symptoms and building ventilation type; their study was seriously flawed in that no environmental characteristics were measured—not even ventilation rates. Robertson et al. (1985) attempted a followup study in which some environmental measurements were made; it included only two buildings, and the measurements were limited to temperature, relative humidity, air velocity, and ion concentrations. Harrison et al. (1987) studied 2,587 workers in 27 buildings; but environmental measurements were limited to particulate matter, fungi, and bacteria. Hedge et al. (1987) correlated the symptoms of 4,373 office workers with types of building ventilation systems, but made no environmental measurements and reported no information on the age of the buildings, so their conclusions were tentative.

The Danish town-hall studies measured 29 environmental characteristics—including chemical, biological, and physical—and used detailed questionnaires regarding 4,369 employees (Skov and Valbjorn, 1987; Valbjorn and Skov, 1987). The study represents a definite advance in SBS study methods, but only 14 buildings were studied, so it is difficult to analyze the data on the many symptoms and environmental characteristics. This presents a clear dilemma to the investigator with limited resources; i.e., to understand the multifactorial causal relations of SBS, one must obtain data of many kinds, but adequate analysis requires covering many buildings.

Hypothesis and Study Design

This section discusses the various components that must be considered in the design of an SBS study. There is a very close relationship between the hypothesis and the study design. A hypothesis that states that "SBS is caused by multifactorial parameters" is too general and vague to be tested with limited resources. A good SBS hypothesis is one that requires reasonable resources, yet resolves a public health issue of concern. For example, a hypothesis that states that "there is a statistically significant relation among some symptoms (such as sensory irritation) and some environmental factors (such as chemicals, biological aerosols, temperature, relative humidity, and ventilation) or psychosocial situations, for clerical staff working in open environments in office buildings with specific characteristics (such as size and ventilation characteristics)" can be tested with more limited resources. The resolution of such a hypothesis will be of use in developing mitigation strategies. With that type of hypothesis in mind, we discuss here the major considerations for the components of a study. We will not discuss considerations common to most epidemiological studies, but will stress those peculiar to the SBS.

Measurement Techniques (Analytical and Sampling)

Because so little is known about SBS, any reasonable study will require a plethora of data of diverse categories, such as chemical, biological, physical (ventilation, relative humidity, temperature, noise, light, vibration), and psychosocial information and information on biological markers. Some data can be acquired through the use of questionnaires and time and activity reports, but a large amount must be obtained through costly microenvironmental measurements. It should be emphasized, however, that the techniques will have to be more sensitive than those typically used in industrial hygiene. Investigations to date usually have not indicated the presence of contaminants at concentrations approaching occupational exposure limits; that implies that the workplace is safe. However, it is obviously still a problem and the situation is complicated by the fact that there are no standards or guidelines to assist the exposure analyst in evaluating the significance of substances found. Clearly, a new approach that focuses on immunological toxicology and exposure-response research on the symptoms associated with sick buildings is necessary.

Developing a quality assurance program is more difficult for an SBS study than for most other environmental studies, because so many variables are involved and few standard methods or reference materials are available for

many chemical and biological species that appear to be of interest. Many of the standard methods used for outdoor or industrial environments require instruments too noisy and large to be used indoors. Thus, the investigator must validate the method either before (which is preferable) or during the study using procedures such as parallel sampling with different methods in selected buildings or splitting of collected air samples among other laboratories.

Biological Markers

Markers sometimes can be useful in BRI (building-related illness) studies, particularly in ensuring that an exposure has occurred. Understanding of the SBS problem is insufficient to be able to predict whether markers might be useful in SBS studies. Of course, the marker used depends on the suspect contaminants. Although markers have been used extensively in the industrial setting (e.g., blood lead), not many problem buildings have been studied with markers. That is partly because investigators usually have little information on what substances are causing the problem and marker methods are often invasive. Two notable exceptions are measurements of breath and urine, and it is recommended that these be considered for development and use whenever possible.

A spinoff of the use of biological markers is that building occupants tend to understand better and accept the meaning of measurements that describe their individual body burdens than measurements of the environment. The usefulness of markers was demonstrated in a California building that had a problem with pentachlorophenol eluted from interior wood treated with it. A combination of data on air and urine markers gave the investigators evidence that the building was the source of the problem and that mitigation efforts were fruitful, and also gave the building occupants some confidence that the problem was not out of control (Wesolowski et al., 1984). Many building problems, however, are multifactorial and thus do not lend themselves to such distinct monocontaminant resolution.

Biological markers, even noninvasive ones, should not be used unless they are needed to test a useful hypothesis, because their use requires that the persons tested be given clear explanations of what their test results imply about their present and future health. In many cases, particularly at the relatively low body burdens often encountered, such information is not known to the investigator. The same caution applies to indoor environmental measurements: occupants have a right to a clear interpretation of the health and discomfort implications of the data.

Questionnaires

Questionnaires are used in SBS studies to survey the nature and magnitude of health and comfort complaints, to determine the spatial and temporal distributions of complaints, to assess confounders of reported effects (such as current health status of respondents and demographics), and to obtain information on environmental factors that might be related to complaints. Questionnaires, when used to obtain information on environmental factors, can provide information on human exposures that could prove useful even if not accompanied by environmental measurements. They can also give information that helps to determine which environmental measurements should be used in a study.

When used specifically as an exposure assessment tool in SBS studies, questionnaires use the respondent as a sensor of the workplace environment to assess such important variables as odor, sound, lighting, comfort, and environment acceptability; to characterize potential sick building psychosocial factors (such as conflict at work, job satisfaction, and degree of control over work); and to provide surrogate measures of off-site (residence, outdoor, transportation, etc.) exposures to air contaminants in lieu of more expensive personal or microenvironmental monitoring.

Questionnaires have been used in SBS studies (Finnegan et al., 1984; Robertson et al., 1985; Gamble et al., 1986; Hedge et al., 1986; Leaderer et al., 1990a), but no standardized questionnaire is available. The lack of a standardized questionnaire makes it difficult to compare data collected in various studies. The questionnaires used so far have typically obtained information on only a few of the factors that affect exposure, and only one reported study attempted to obtain information on a wide range of psychosocial factors (Hurrell et al., 1990; Leaderer et al., 1990a). An effort is needed to develop and test a standardized questionnaire for use in SBS studies.

Several characteristics of administration of a questionnaire must be carefully chosen before a study begins. They include the sample selection method (building census, stratified sample based on air-handling systems, etc.), the method of distribution and collection of questionnaires (telephone, post office, in-building mail system, etc.), and the method and number of followup attempts to ensure a high response rate. The choices should be determined on the basis of the hypothesis being tested and the characteristics of the building and population involved in the study.

Models

The single-compartment and multicompartment mass-balance model discussed in Chapter 6 can be used to good purpose in designing and conducting a study to elucidate the relationship between health effects and exposures to airborne contaminants. Those models can provide a conceptual framework for designing the sampling strategy to be used in various buildings, can help to predict exposure concentrations from various sources or inferring source strengths from concentration measurements, and can be useful in designing controlled human exposure experiments in which concentrations of indoor contaminants are varied.

Empirical models constitute a second class of model that can often be used as hypothesis-generating and testing tools. Such models are typically multivariate. For an SBS study, some health end point would be related to environmental variables in a stepwise multiple regression.

Conclusions

The SBS problem has surfaced only in the last decade. Thus, the methods for understanding it have not had time or resources to be adequately developed by exposure analysts. However, the database obtained from investigations of BRI has suggested better approaches for the design of SBS studies and a need to develop measures to reduce exposure and the incidence of SBS. Issues of technique include the development of more refined hypotheses; the use of a broader range of physical, chemical, and biological measurements; more complete and standardized health and activity questionnaires; and the use of more sophisticated models of total exposure.

TOXICS RELEASE INVENTORY

Introduction

Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA), Public Law 99-499, is a free-standing statute titled "The Emergency Planning and Community Right-To-Know Act of 1986". In the development of SARA Section 313, it was acknowledged during discussions in Congress that the extent of human exposure to toxic chemicals released by industry was a major concern (*Congressional Record*, H11205, December 5, 1985). It was also expressed in Congress that much work is needed before human exposure

to toxic chemicals can be effectively managed and that acquisition of information is the next necessary step. Section 313 of SARA requires industrial facilities that manufacture, process, or use toxic chemicals to report annual environmental release information to the EPA. Initial requirements for submission of the information are specified by EPA in the Toxic Chemical Release Reporting Final Rule (*Fed. Reg.*, 1988a). The database resulting from the information reported to EPA is referred to as the Toxics Release Inventory (TRI). The TRI was seen as a means to gather information for three general objectives: (a) to identify the chemicals of the greatest concern; (b) to identify locations where the chemicals are manufactured, used, and released; and (c) to determine the quantities released into the environment (*Congressional Record*, S11772, September 19, 1985).

The initial list of toxic chemicals for TRI reporting contains 308 specific chemical compounds and 20 chemical categories and can be modified only by a rule-making, such as the deletion of titanium dioxide (*Fed. Reg.*, 1988b). Information reported to the TRI includes routine releases (e.g., emissions from stacks) and accidental releases to air, land, and water. The first reports were filed on June 30, 1988. This case study examines the issues that should be addressed in the TRI to make it useful for assessing exposure to toxic chemicals.

The purpose of the TRI is to inform the public and government officials about total releases of toxic chemicals. Section 313 of SARA requires EPA to develop the TRI information into a computerized database for public access. The information is intended, among other purposes, to assist research and aid in the development of various regulations, guidelines, and standards (EPA, 1988c). There are no requirements to perform risk assessments or to regulate any TRI-listed chemicals. To minimize the burden of data-gathering on industry, Section 313 of SARA allows release reports to be based on estimates; monitoring data and other available information are not required, but can be reported if available.

Applications to Exposure Assessment

Although the TRI provides useful information on estimated mass quantities of chemical releases, it does little to assist in understanding the potential for human exposure to those releases and resulting impacts on public health. The inclusion of accidental and routine emissions in the total releases reported to the TRI makes estimation of downwind concentrations and exposures technically infeasible. The separate types of releases involve different exposure issues and require different analyses for determination of exposure and exposure

impact. The TRI database is useful in identifying chemicals of concern, which may, with further analysis, provide data needed for exposure assessment.

The TRI requires reporting of chemical quantities released directly into the environment or transferred to off-site locations, identity of releasing facility, geographical location (latitude and longitude), identity of all sites to which the reporting facility transports chemical wastes, how the reported chemicals are used, and types and efficiency of on-site methods to treat chemical wastes. The data, by themselves, are inappropriate for assessing either acute or chronic exposures, because they are not linked specifically to the potential concentrations and locations of exposure of the general population (Levin and Spence, 1989). TRI data are only one type of input data for air-dispersion models (see Chapter 6) used to estimate potential downwind concentrations, which are then linked with human time-activity data to assess potential exposures (see Chapter 5).

Even the simplest dispersion models cannot be used to estimate downwind concentrations of released toxic chemicals on the basis only of TRI data. The TRI provides some data useful in determining downwind concentrations, such as facility location, latitude and longitude (to assist in describing meteorological transport), and categorization of releases as either point sources (e.g., stack emissions) or fugitive releases. Additional data are needed for air-dispersion analyses. Values of various model parameters on individual sources are needed: release temperature and discharge velocity, orifice diameter and height of release; frequency and duration of releases; and nearby structure characteristics likely to affect small-scale air movements. Because the TRI does not collect those additional data, industry is not likely to obtain and store them, so they cannot be obtained simply by calling the TRI coordinator at each facility and requesting them. Some facilities have taken the initiative of estimating potential exposure concentrations of released chemicals reported to the TRI. Such information more fully prepares facilities to respond to inquiries from the public about impacts of their toxic chemical releases on public health and the environment.

Acute toxicity is the primary concern for assessment of exposure to accidental releases. To identify possible carcinogenic impacts, analysis of lifetime exposure to routine emissions is required. Even if all the necessary model data were provided for each release source, the results would be of little use for exposure assessment, because of the combination of data in the TRI on routine emissions and accidental releases.

For example, at low concentrations, hydrogen cyanide (HCN) gas, an acutely toxic agent, can be detoxified by the body. However, at high concentrations, HCN causes breathing loss and death. Reporting all emissions of HCN on an

annual basis could give a false impression of potential exposures that had acute health outcomes. The estimation of exposure on an annual basis might be acceptable for long-term effects, but even a single breath of HCN at more than 2,300 ppm(v) would result in death.

Only time will tell whether the TRI database will be applied incorrectly to exposure assessment activities. It is clear today, on the information submitted to the TRI database, that industry has committed resources to reduce emissions (Steyer, 1988) and EPA is expected to move more rapidly to develop regulations for several specific hazardous air pollutants.

Implications

The TRI reporting requirement will, in all probability, provide tangible environmental benefits. Data on releases to all media are important for understanding the impact of a chemical release on total human exposure and the global environment, but releases to air warrant special attention. Releases to air probably result in the most immediate, and perhaps the most important, exposures of the public living near an industrial facility that produces or uses toxic chemicals. Exposure to airborne toxic chemicals can occur directly through inhalation of contaminated air or through ingestion of food or water that contains contaminants deposited from the air.

In the future, acutely and chronically toxic chemicals should be reported separately to allow proper focus of resources on the most important exposure issues. A source and receptor database needed for the proper exposure assessment for both acutely and chronically toxic chemicals should be carefully considered for inclusion in the data-collection effort in any revision of SARA Section 313. Industry's burden of providing the additional information is an important aspect of the considerations.

Because the technology used for exposure assessment is changing rapidly, it would be appropriate to define data needs in regulations, rather than in specific laws. Regulations could then be changed as necessary to respond to advances in exposure assessment without the need to amend laws.

RADON

Introduction

Exposure of the general public to radon and its decay products appears to constitute an important naturally occurring environmental health risk. Radon

decay products have clearly produced lung cancers in exposed underground miners (NRC, 1987a). However, there are considerable uncertainties in how the risks identified in the miner studies can be extrapolated to the general public. No clearly identified lung-cancer mortality in the general population can yet be specifically linked to exposure to radon decay products (NCRP, 1984a,b). Four relatively small case-controlled studies have suggested a possible relationship between lung cancer and building construction or residential radon exposure (Axelson et al., 1979; Edling et al., 1984; Lees et al., 1987; Svensson et al., 1987), but there are no unequivocal measurements of the lung-cancer risk associated with indoor radon. Because the estimated risks are higher than those associated with many other environmental agents suspected of having adverse health effects, there has been considerable interest in looking for clear evidence of radon-related lung cancer in the general population.

The problem of protecting the public health has been exacerbated by the uncertainties in the exposures and the corresponding risk estimates. Risk management decisions of EPA have suggested radon concentrations in indoor air that should trigger mitigation action, and those action concentrations if too low would result in unnecessary expenditures and concern. EPA reported in a September 1988 press conference that radon causes 20,000 lung-cancer deaths a year in the United States. However, that estimate is at the high end of the range estimated by the National Council on Radiation Protection and Measurements (NCRP, 1984a,b), so the risk estimates are not in good agreement. Major factors affecting the uncertainty in risk estimates are related to the measurement of the proportion of exposure that is environmental.

There are major difficulties in assessing exposure to natural airborne radioactivity, particularly to those radionuclides of greatest health-effect potential. It is universally agreed that the short-lived decay products of radon (^{218}Po, ^{214}Pb, ^{214}Bi, and ^{214}Po) cause the presumed health effects, but radon is generally measured as a surrogate for these other radionuclides, because it is reasonably easy and inexpensive to measure the indoor radon concentration. One must be careful in extrapolating short-term screening measurements made under nontypical conditions (e.g., in a basement in a closed house during winter) to annual average exposures, although these nontypical-condition measurements may represent a maximum exposure condition. Methods for measuring long-term, average exposure to radon require further development, and better communication is necessary to explain the risk uncertainties to the public.

The amount of airborne radon decay products in a room depends on several factors, including the amount of radon to produce them, the concentration of airborne particles to which they can become attached, and the aerodynamic

processes that contribute to the deposition of radioactivity on surfaces in the room (walls, ceilings, furniture, etc). Thus, the actual concentration of airborne radioactivity is a complicated function of several environmental variables.

The health effects of radon decay products also depend heavily on their aerodynamic behavior in the indoor atmosphere. Particularly for ^{218}Po, partitioning between the unattached state and the attached forms (i.e., combined with pre-existing aerosol particles) has an important impact on the calculation of the dose to the lung from a given airborne decay product concentration. In the dose models commonly used to relate tissue dose to airborne radioactivity concentrations (Jacobi and Eisfeld, 1980; James et al., 1980), a substantially increasing effective dose to the target tissue is predicted with decreasing particle size down to about 3 nm. The increase in dose is due to the increase in effective deposition through molecular diffusion as particle size approaches that of free molecules. Small changes in particle size in this range result in large changes in the diffusion coefficient and in depositional behavior, particularly in regard to the location of deposition in the tracheobronchial tree. These models of delivered dose of alpha radiation to lung tissue show radon to be a reasonable surrogate for exposure to the decay products because several of the opposing factors in the exposure cancel each other.

Hypothesis and Study Design

The hypothesis of interest is that increased exposure to radon decay products in the indoor environment increases the risk of induction of lung cancer. Exposure to tobacco smoke and differential residential mobility are substantial confounding factors in the estimation of health risk.

Two epidemiological studies are attempting to relate lung cancer to environmental radon and decay product exposure through retrospective measurement of indoor radon concentrations. One is being conducted by the state of New Jersey and the other by Argonne National Laboratory. Both are concerned with obtaining better risk estimates related to exposure of the general population to radon decay products and are using cases of lung cancer in white women as the subjects of case-controlled studies.

The New Jersey study (Schoenberg et al., 1987) is an earlier extension of a statewide population-based case-controlled interview study of New Jersey women. The cases include all of the female residents of New Jersey whose histologically confirmed primary cancers of the lung were newly diagnosed in the period from August 1982 to September 1983. For cancer patients who were interviewed, age- and race-matched controls were chosen from New

Jersey drivers-license files and from Health Care Financing Administration files for Medicare enrollees. For next-of-kin interviews, matched controls were selected from state death-certificate files. For the 1,306 cases identified, 994 patients or next-of-kin were interviewed; of the 1,449 controls chosen, 995 were interviewed. Some 53% of the interviews were with the patients, and the rest were with next-of-kin.

The study began without consideration of indoor radon, and residential housing information had been collected only on the towns in which the subjects lived. The subjects or next-of-kin were therefore recontacted to obtain street-address information. It was assumed that there is a minimal 10-year latency period between exposure and onset of cancer. Only one house was tested per subject because of resource limitations, so the study focused on subjects who lived for at least 10 years at an address in New Jersey during the period 1953—1972, about 10—30 years before the case diagnosis or control selection. It was found that 17% of the subjects had not lived in New Jersey for at least 10 years during 1953—1972 and that 10% had not lived at any address for at least 10 years during the critical period. In another 2% of the cases, it was not possible to determine specific street addresses. It was possible to obtain addresses for 1,216 subjects that met the criteria. Of those addresses, 82 no longer existed or were dwellings in upper floors of apartments, trailers, or other situations in which radon exposure would be expected to be negligible; that left 1,134 addresses. Short-term charcoal-canister measurements were made for a quick screening. For a better determination of the annual average concentrations, two alpha-track detectors were deployed in the 1,134 dwellings. In 10% of the dwellings, a third track-etch detector was collocated with one of the other detectors for quality assurance.

The Argonne study provides a good example of a potentially useful study design. The study population comprises white females born in Pennsylvania who lived in eastern and central Pennsylvania, excluding Philadelphia and Pittsburgh, and died of lung cancer between 1970 and 1987. Controls will be chosen from white females born in Pennsylvania in the same years as cases, selected by random-digit dialing and random selection from vital statistics. A large number of lung cancer cases are available (more than 6,000 through 1984) in an area where there are likely to be high indoor radon concentrations. Separate case series will be defined by histopathological type of lung cancer and by smoking status. The first case series of about 500 cases includes all lung cancers and categories of smokers. For each of the dwellings that the subjects have occupied and that can be identified, both short-term charcoal and long-term track-etch measurements will be made for all levels in the dwellings. When current occupants are willing, two sets of sequential 6-month track-etch samplers will be left and picked up by project personnel,

to ensure adequate response. Charcoal-canister measurements will be used to screen the dwellings to make preliminary assignments as to radon exposure. When current occupants are not willing to allow measurements, radon concentration will be based on the age and construction type of the dwelling and its geological setting. Although data on a number of dwellings already permit building of a predictive model for indoor radon, the results from the cooperative dwellings with occupants will improve the database on which the models are built.

The researchers also plan to measure radon-decay product concentrations to assess exposures to radon progeny more directly. There is no apparent plan to measure the radioactive particle size distributions. Thus, it will not be possible to assess the potential for deposition, and the analyses will have to include estimates of the effectiveness of the measured concentrations in producing specified doses.

Measurement Methods

Short-term charcoal and long-term track-etch detectors will be used. In both cases, it is assumed that current radon concentrations reflect past radon. If there have not been changes in the insulation, heating system, or general nature of a dwelling, the assumption should be reasonable. However, with the extensive energy-conservation efforts many homeowners made in the late 1970s and early 1980s, many homes might have been modified. Estimation of prior concentrations would then constitute a considerable problem.

Another important problem is the concentration of decay products relative to the radon concentration. If, for example, one or more occupants smoked and then quit, indoor particle concentrations might be much lower now than in the past. Higher particle concentrations result in higher decay product concentrations, but lower the concentrations of more diffusive unattached decay products and thus result in a lower average dose per unit of airborne radioactivity. Similarly, if a gas stove were traded for an electric unit, particle concentrations resulting from cooking would be lower; this could change the effective exposure to decay products. Air cleaners can substantially increase the unattached fraction, so EPA does not recommend the use of air cleaners to mitigate the effects of radon decay products.

Models

The choice of radon as the measured entity suggests the possibility of an

implicit use of dose models that make the following prediction: the inverse relationship between the concentration of airborne particles, the total decay products, and the unattached fraction cancels out the effects of particle concentration on dose (James, 1988). Therefore, exposure can be adequately measured by determining the integrated, average radon concentration. Such calculations have been presented by Vanmarcke et al. (1985).

The capability to predict indoor radon concentrations is central to the development of radon exposure models. Considerable effort is being devoted to the development of models of radon entry into houses as a function of soil characteristics (e.g., radium content and permeability), climatic conditions, and house characteristics (e.g., substructure type, type of heating system, and air-leakage area). Indoor radon concentrations are predicted by combining the models of radon entry into basements (Loureiro, 1987; Mowris and Fisk, 1988), generally with steady-state, two- or three-dimensional numerical codes that model the convective (pressure-driven) entry of soil gas (containing radon) through openings in the substructure. These models are being upgraded at Lawrence Berkeley Laboratory to account for diffusive entry of radon, spatial variability of soil properties, simultaneous transport of soil moisture, and transient effects. A smaller effort has been devoted to the entry of radon into houses with crawl spaces (Mowris and Fisk, 1988) and to the development of simplified closed-form or statistical models (Mowris and Fisk, 1988; Revzan, 1989). None of these models has been adequately validated, although a current experimental effort by Lawrence Berkeley Laboratory should provide critical data on radon entry into basements during the next few years.

Advances

Both of the large studies discussed here are making direct measurements in at least one of the dwellings occupied by each of many lung-cancer subjects over a long period and thus should yield a reasonable estimate of radon concentrations to which they have been exposed. In addition, information has been obtained on smoking behavior and mobility to try to account for these strongly confounding variables. The Argonne study will be partially supplemented by direct measurement of concentrations of radon decay products although the particle size distributions and their potential influence on dose are not explicit parts of either study.

New measurement methods have recently been developed that permit the determination of both concentrations and size distributions of radon decay products. The use of single screens in nonconventional diffusion batteries (graded screen arrays) and measurement of the radioactivity that passes

through each screen permit one to obtain size distribution over the range of 0.5-500 nm (Reineking and Porstendörfer, 1986; Holub and Knutson, 1987; Ramamurthi and Hopke, 1988). A new system can provide hourly measurements of concentrations and size distributions of each decay product, so it is now possible to measure directly the species that are responsible for health effects without resorting to assumptions and models (Ramamurthi, 1989). This system can be used soon to test the variability of concentrations in different size ranges directly so that a better understanding of the dynamics of indoor radon decay products will be possible.

Glossary

BIOLOGICAL MARKER. Indicators of changes or events in human biological systems. Biological markers of exposure refer to cellular, biochemical, or molecular measures that are obtained from biological media such as human tissues, cells, or fluids and are indicative of exposure to environmental contaminants.

BIOLOGICALLY EFFECTIVE DOSE. The amount of the deposited or absorbed contaminant that reaches the cells or target site where an adverse effect occurs or where an interaction of that contaminant with a membrane surface occurs.

DOSE. The amount of a contaminant that is absorbed or deposited in the body of an exposed organism for an increment of time—usually from a single medium. Total dose is the sum of doses received by a person from a contaminant in a given interval resulting from interaction with all environmental media that contain the contaminant. Units of dose and total dose (mass) are often converted to units of mass per volume of physiological fluid or mass of tissue.

ENVIRONMENT. Comprises air, water, food, and soil media. Regarding air, it refers to all indoor and outdoor microenvironments, including residential and occupational settings.

EXPOSURE. An event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time; the units of exposure are concentration multiplied by time.

EXPOSURE ASSESSMENT. Involves numerous techniques to identify the contaminant, contaminant sources, environmental media of exposure, transport through each medium, chemical and physical transformations, routes of entry to the body, intensity and frequency of contact, and spatial and temporal concentration patterns of the contaminant. An array of techniques can be employed, ranging from estimating the number of people exposed

	and contaminant concentrations to sophisticated methodology employing contaminant monitoring, modeling, and human biological marker measurement.
INTERNAL DOSE.	Refers to the amount of the environmental contaminant absorbed in body tissue or interacting with an organ's membrane surface.
MICROENVIRONMENT.	A three-dimensional space with a volume in which contaminant concentration is spatially uniform during some specific interval.
NUISANCE EFFECT.	A subjectively unpleasant effect (e.g., headache) that occurs as a consequence of exposure to a contaminant; it may be associated with some physiological response, but is not permanent.
POTENTIAL DOSE.	An exposure value multiplied by a contact rate (e.g., rates of inhalation, ingestion, or absorption through the skin) and assumes total absorption of the contaminant.
TOTAL HUMAN EXPOSURE.	Accounts for all exposures a person has to a specific contaminant, regardless of environmental medium or route of entry (inhalation, ingestion, and dermal absorption). Sometimes total exposure is used incorrectly to refer to exposure to all pollutants in an environment. Total exposure to more than one pollutant should be stated explicitly as such.

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Appendix A:

Basic Standard Environmental Inventory Questionnaire[1]

[1] Source: Lebowitz et al., 1989b.

Basic Standard Environmental Inventory Questionnaire*

Basic Household Characteristics

Name of designated head of household: _____

Name of Respondent: _____

Home address: _____

Home phone: _____ Zip code: _____

Date: ____/____/____

This is a questionnaire for you to complete, regarding your present living quarters. Most of the questions asked are about the materials, appliances and furniture that are used within your home.

To record your response(a) circle ( ), check [ ] or write *in* the responses to each question. Please follow the arrows pointing to the side questions inside of boxes. For most of the questions in bold print, a "no" response will instruct you to "skip to" the next bold printed question. You can reach us at _____ or _____ if you have any questions.†

We appreciate your assistance in this study.

Your answers will be kept confidential and used for research purposes only.

Thank you for your cooperation.

Identification/Core Module For Proposed Standard E.I.Q.

A. Location Data

State _____ County _____ (2)‡

Census tract _____ Block # _____ (5,5)

Street address: _____/_____ (20)
Apt./space #

City, zip _____/_____ (20,5-5)
Zip code

Name of respondent _____ (2)

B. Housing Characteristics

These questions are to determine the type of housing unit and living quarters in which your household lives. Circle one number only for each question.

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* Rev: EIQ, Final, 3/15/89

† Instructions refer to formats which are found on the original questionnaire. Further instructions for the Environmental Inventory Questionnaire are available from the authors.

‡ Numbers in parentheses indicate field lengths.

B1. How many rooms do you have in your living quarters?
(Do not count bathrooms, porches, balconies, foyers, halls, or half-rooms.)

Please Circle: 1 2 3 4 5 6 7 8 9+ (1)

B2. Are your living quarters—

1. Owned?
2. Rented?
3. Other? (1)

B3. Which best describes this building?
(Include all apartments, flats, etc., even if vacant.)

1. A mobile home or trailer
2. A one-family house detached from any other house
3. A one-family house attached to one or more houses
4. A building for 2 families
5. A building for 3 or 4 families
6. A building for 5 to 9 families
7. A building for 10 to 19 families
8. A building for 20 or more families
9. A boat, tent, van, etc.
10. Other, please specify: _____ (1)

B4. How many stories (floors) are in this building?
(Count an attic or basement as a story if it has any finished rooms for living purposes.)

1. 1 to 3
2. 4 to 6
3. 7 to 12
4. 13 or more stories (1)

B5. About when was this building originally built?
(Circle when the building was first constructed, not when it was remodeled, added to, or converted.)

1. 1986 to present
2. 1980 to 1985
3. 1970 to 1979
4. 1960 to 1969
5. 1950 to 1959
6. 1940 to 1949
7. 1939 or earlier
9. Don't Know (1)

B6. When did your household/family move into this house (or apartment)?

1. 1986 to present
2. 1980 to 1985
3. 1970 to 1979
4. 1960 to 1969
5. 1950 to 1969
6. 1940 to 1949
7. 1939 or earlier (1)

B7. How many bedrooms do you have?
(Count room used mainly for sleeping even if used also for other purposes.)

0. No bedroom
1. 1 bedroom
2. 2 bedrooms
3. 3 bedrooms
4. 4 bedrooms
5. 5 or more bedrooms (1)

B8. Where are cars/vehicles usually parked near your living quarters?
(Circle all that apply)

1. In an underground garage
2. In an attached garage
3. In an attached carport
4. On the street next to living quarters
5. Other (Specify): _____ (1)

C. Occupant Characteristics

The following questions describe the members of the household.

(b) Is your clothes dryer gas or electric?

1. Gas
2. Electric
3. Don't know (1)

(c) Where is the clothes dryer located?

1. In a room within the living quarters, such as the kitchen.
2. In a closet or storage room in part of the main living quarters.
3. In a utility or closet room separate from the main living quarters.
4. In the garage.
5. In the basement. (1)
6. Outside.

(d) Is the dryer vented?

1. Yes, always outside.
2. Yes, with an inside/outside switch.
3. Not vented to outside.
4. Don't know. (1)

E4. Heating System

(a) What is the main type of fuel used to heat your living quarters? (circle the one most often used)

1. Gas
2. Electric
3. Fuel oil
4. Kerosene
5. Coal
6. Wood
7. Solar
8. None → Skip to #E5
9. Other (Specify) _____ (1)

(b) What is the main type of furnace or heating system used to heat your living quarters? (circle one)

1. Forced air (central system with ducts that blow air into most rooms)
2. Wall furnace
3. Steam
4. Hot water
5. Floor furnace
6. Gravity furnace
7. Portable heater
8. Other (specify: _____) (1)
9. None

E5. Unvented Space Heaters:

(a) During the cold weather, do you use portable KEROSENE heaters in your living quarters?

1. Yes → How many? _____
2. No → skip to #E5(c) (2)

(b) How often do you use your KEROSENE heater during the cold weather?

1. Three or more days per week
2. One or two days per week
3. Only in the morning to take the chill off (for less than one hour) (1)

(c) Do you use any small GAS heaters in your living quarters?

1. Yes → How many? _____
2. No → skip to #E6 (2)

(d) How often do you use your GAS heater during the cold weather?

1. Three or more days per week
2. One or more days per week
3. Only in the morning to take the chill off (for less than one hour) (1)

(e) Is the flame visible?

1. Yes
2. No (1)

E6. Wood Stove and/or Fireplace

(a) During the cold weather, do you use a wood burning stove to help heat your living quarters?

1. Yes → How many? _____
2. No → skip to #E6(c) (1)

(b) How often do you use a wood burning stove during the cold weather?

1. Three or more days per week
2. One or two days per week
3. Only in the morning to take the chill off (for less than one hour) (1)

(c) During the cold weather, do you use any fireplaces in your living quarters?

1. Yes → How many? _____ (2)
2. No → skip to #F

(d) How often do you use your fireplaces during the cold weather?

1. Three or more days per week
2. One or two days per week
3. Only in the morning to take the chill off (for less than one hour) (1)

F. Radon

F1. Do you get water for general household use from a city or public system, a private well, or some other source?

1. city or public water system
2. private well supplying 1 or more homes
3. some other source (1)
[specify _____] (1)

F2. What months of the year are the living quarters closed completely because of heating or air conditioning? (ANSWER FOR BOTH HEATING AND AIR CONDITIONING)

1. none of the year (88)
2. all of the year (20)
3. part of the year → circle months below

JAN	FEB	MAR	APR	MAY	JUN
01	02	03	04	05	06

JUL	AUG	SEP	OCT	NOV	DEC
07	08	09	10	11	12

(2)

F3. Is there a crawl space or open space under any part of your living quarters? (Note: This is a space between the ground and the floor that cannot be occupied; it is not a basement or cellar.)

1. Yes 2. No (1)

F4. Is any part of the foundation or lower walls of your building built of concrete blocks or cinder blocks?

1. Yes 2. No (1)

F5. Do you have a full or partial basement, a cellar, or a level of the building for which one or more walls are completely or partially below the ground?

1. Yes 2. No (1)

C1. Number in household
(a) How many children under age 18 are there living in the Household?
_____ Number of Children (2)

(b) How many adults, ages 18 and older, are there living in the Household?
_____ Number ages 18–61 (2)
_____ Number age 62 or more (2)

For the designated head of the household
(Please identify one person as the head and answer the following questions for this individual)

C2. What ethnic group (race) does this person consider themself? (circle one only)

1. White, Non Hispanic
2. Hispanic
3. Black
4. Asian
5. Other (specify): _____ (1)

C3a. What is the highest grade (or year) of regular school this person has ever attended?
(For example, completion of high school = 12)

_____ Highest grade attended (2)

C4a. Does he/she have a paid job out of the home?

1. No, self employed in the home
2. No, full time homemaker
3. Yes, working full time
4. Yes, working part time
5. No, out of work just now but usually employed
6. No, a full-time student
7. Other, (specify): _____ (1)

C4b. Occupation
[ ] check here if this person has never worked outside of the home, and skip to next question.

1. What is or was his/her usual occupation? _____ (3)

2. What is his/her job title?: _____

For the respondent
(if not the Head of Household)

C5. What ethnic group (race) do you consider yourself? (circle one only)

1. White, Non Hispanic
2. Hispanic
3. Black
4. Asian
5. Other, (specify: _____) (1)

C6a. What is the highest grade (or year) of regular school that you have ever attended?
(For example, completion of high school = 12)

_____ Highest grade attended (2)

C7a. Do you have a paid job out of the home?

1. No, self employed in the home
2. No, full time homemaker
3. Yes, working full time
4. Yes, working part time
5. No, out of work just now but usually employed
6. No, a full-time student
7. Other, (specify): _____ (1)

C7b Occupation

[ ] Check here if you have never worked outside of the home, and skip to next question

1. What is or was your usual occupation? _____ (3)

2. What is your job title: _____

D. Smoking in the Home

1. Does anyone regularly smoke INSIDE OF YOUR LIVING QUARTERS?

1. Yes = Continue below
2. No = Skip to # E1 (1)

2. How many cigarettes, pipefuls, and/or cigars were smoked IN YOUR LIVING QUARTERS?

(a) During the most recent WEEK DAY:

_____ _____ (5)
cigarettes # pipes and/or cigars

(b) During the most recent WEEK-END DAY:

_____ _____ (5)
cigarettes # pipes and/or cigars

E. Cooking and Other Appliance Usage

E1. Cooking

(a) Do you have a gas range or oven?

1. Yes = continue below
2. No = skip to # E2 (1)

(b) Does your GAS range or oven have a continuously burning pilot light?

1. Yes 2. No (1)

(c) During the winter, do you ever use the range or oven to help heat the living quarters?

1. Yes, three or more days per week
2. Yes, one or two days per week
3. Yes, only in the morning to take the chill off (less than one hour) (1)
4. No

E2. Water Heater

(a) Is there a GAS water heater in your living quarters?

1. Yes = continue below # E2(b)
2. No = skip to Question # E3

(b) Where is your water heater located? (circle all that apply)

1. In a room within the living quarters, such as the kitchen.
2. In a closet or storage room in part of the main living quarters.
3. In a utility or closet room separate from the main living quarters.
4. In the garage.
5. In the basement.
6. Outside.
7. Other (please specify _____) (1)

E3. Clothes Dryer

(a) Is there a clothes dryer in your living quarters?

1. Yes = continue below # E3(b)
2. No = skip to # E4

F6. Which of the following best describes the construction of most of the lowest floor of the living quarters?

1. Concrete slab, uncovered
2. Tile, wood, or carpet over concrete
3. Earth, dirt, sand, or rock
4. Something else [SPECIFY _____] (1)

G. Organic Pollutants

G1. Have you worked with or used pesticides or herbicides outdoors for more than 1 hour at a time in the past 6 months?

1. Yes 2. No (1)

G2a. Did you or any member of the household, or a commercial applicator use pesticides in the living quarters in the past 6 months?

1. Yes
2. No → SKIP TO #G3a (1)
   b. Specify Brand Names _____ (2)

   _____

   _____

   c. Specifically, where are you using them?
   1. Living Room 4. Master Bedroom
   2. Dining Room 5. Other Bedrooms
   3. Kitchen 6. Other Rooms (6)

G3a. In the past 6 months, were the drapes, carpeting, or furniture in your home steam or dry cleaned?

1. Yes No (1)

G4a. Are you now using mothballs or moth crystals in your living quarters?

1. Yes
2. No → SKIP TO #G5 (1)

   b. Specifically, where are you using them?
   1. Living Room 4. Master Bedroom
   2. Dining Room 5. Other Bedrooms
   3. Kitchen 6. Other Rooms (6)

G5. Do you store cleaning supplies (e.g., chlorine bleaches, detergents) in the following places?

1. Kitchen (1)
2. Basement (1)
3. Utility Room (1)
4. Bathroom (1)
5. Other (SPECIFY) (1)

_____

Appendix B:

Exposure Assessment Workshop Participants and Presentations[1]

WORKSHOP PARTICIPANTS

GERALD AKLAND, U.S. Environmental Protection Agency

HARVEY CHECKOWAY, University of Washington

MARIA COSTANTINI, Health Effects Institute

ALISON DORRIES, Health Effects Institute

WILLIAM E. DUNN, University of Illinois

RICHARD FENSKE, Rutgers University

JOHN E. FRANKE, Peterson Associates

RICHARD GERBER, Agency for Toxic Substances and Disease Registry

WALTER JOHN, California Department of Health Services

GRAHAM KALTON, University of Michigan

JUDITH KLOTZ, New Jersey Department of Health

GERARD LANIAK, U.S. Environmental Protection Agency

JEFFREY D. LASKIN, UMDNJ—Robert Wood Johnson Medical School

MICHAEL LEBOWITZ, University of Arizona

WAYNE OTT, U.S. Environmental Protection Agency

DALE PAHL, U.S. Environmental Protection Agency

PETER ROMBOUT, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands

JOHN SCHAUM, U.S. Environmental Protection Agency

PAUL SCHULTE, National Occupational Safety and Health

LINDA SHELDON, Research Triangle Institute

ROBERT SPEAR, University of California at Berkeley

JOHN D. SPENGLER, Harvard School of Public Health

[1] The workshop was held on October 19 and 20, 1988, at the Peabody Museum of Natural History, Yale University, New Haven, Connecticut.

JAN STOLWIJK, Yale University School of Medicine
BRUCE STUART, Arthur D. Little, Inc.
GREG TRAYNOR, Lawrence Berkeley Laboratory
TUAN VO-DINH, Oak Ridge National Laboratory
PAUL WHITE, U.S. Environmental Protection Agency
MARSHA WILLIAMS, Browning-Ferris Industries
JANICE YAGER, University of California at Berkeley
TERRY YOSIE, American Petroleum Institute
CARRY YOUNG, Electric Power Research Institute
JAY ZEMEL, University of Pennsylvania

WORKSHOP PRESENTATIONS

Session I: Application of Methodology in Assessing Human Exposure to Air Contaminants

Environmental Epidemiology, Harvey Checkoway
Risk Assessment, Peter Rombout
Risk Management, Marsha Williams
EPA Risk Assessment, Peter Preuss

Session II: Biomarkers of Exposure

Pharmokinetics, Bruce Stuart
Analytical Techniques, Jeffrey Laskin
Applications, Janice Yager

Session III: Modeling

Stochastic, William Dunn
Indoor Sources, John Franke
Ventilation/Circulation, Robert Spear
Concentration Distribution, Greg Traynor
Exposure Models, Gerard Laniak

Session IV: Measurement Techniques

Volatile Organic Compounds, Linda Sheldon
Solid State Sensors, Jay Zemel
Luminescence and Raman Techniques, Tuan Vo-Dinh
Particles, Walter John

Session V: Time-Activity Patterns and Questionnaires

Inputs to Models, Wayne Ott
Questionnaire Design, Michael Lebowitz
Activity Patterns, John Spengler
Survey and Research Design Issues, Graham Kalton

Appendix C:

Commission on Physical Sciences, Mathematics, and Resources

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RICHARD S. NICHOLSON, American Association for the Advancement of Science, Washington, D.C.

JACK E. OLIVER, Cornell University, Ithaca

JEREMIAH P. OSTRIKER, Princeton University Observatory, Princeton

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FRANK L. PARKER, Vanderbilt University, Nashville

DENIS J. PRAGER, MacArthur Foundation, Chicago

DAVID M. RAUP, University of Chicago

ROY F. SCHWITTERS, Superconducting Super Collider Laboratory, Dallas

LARRY L. SMARR, University of Illinois at Urbana-Champaign

KARL K. TUREKIAN, Yale University, New Haven

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