Assessing Exposures to Inhaled Complex Mixture

Brian P. Leaderer\textsuperscript{1}, Paul J. Lioy\textsuperscript{2}, and John D. Spengler\textsuperscript{3}

\textsuperscript{1}John B. Pierce Laboratory and Division of Environmental Health Sciences, Department of Epidemiology and Public Health, Yale University School of Medicine, 290 Congress Avenue, New Haven, CT 06519; \textsuperscript{2}Exposure Measurement and Assessment Division, UMDNJ-Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854; \textsuperscript{3}Department of Environmental Health, Harvard University School of Public Health, 665 Huntington Avenue, Boston, MA 02115

In the course of daily activities, individuals spend varying amounts of time in different spaces where they are exposed to a complex mixture of gas, vapor, and particulate contaminants. The term complex is used in this paper to refer to binary mixtures as well as truly complex mixtures of three or more constituents. The diversity of the environments where pollution may occur, the number of pollutants that may be present, and the nature of the activity in the environment combine to pose a challenge to investigators of the health effects of air pollutants. This article discusses several methods of measuring or assessing exposure to complex mixture air contaminants that include time-activity assessments, personal monitoring, biomarkers of exposure, and microenvironmental models that can be employed singly or in combination in a protocol for exposure assessment. The use of nested designs, involving more intensive data collection from samples or subjects, is also considered. — Environ Health Perspect 101(Suppl 4):167–177 (1993).

Key Words: Pollutant, complex mixture, exposure assessment, microenvironmental model, nested designs, time-activity assessment, biomarkers, monitoring

Introduction

Human activities routinely involve exposure to the complex mixtures of gases, vapors, and particulate matter that contaminate the air in most indoor and outdoor environments. The diversity of environments, where exposure may occur, and the number of pollutants that may be present pose a challenge in investigating the health effects of air pollutants. For example, in the course of a typical day, individuals spend time in a variety of both indoor and outdoor environments, such as residences, industrial and nonindustrial work places, automobiles, public buildings, and urban or rural outdoor locations. The many different activities of work and leisure time also affect the personal exposures. Although this paper focuses on inhaled pollutants, it is important to recognize that exposures also take place through media other than air and by routes of entry other than the respiratory tract.

The lack of information on the characteristics of the complex mixtures found in most environments makes investigation of the health effects difficult. Concentrations of the key compounds of many mixtures considered relevant to public health have not been quantified well, and even the identities of many mixture components are unknown.

Complex mixtures can be classified into three groups that a) originate from single sources (e.g., environmental tobacco smoke from active smoking), b) result from physical mixing of primary emissions from multiple sources (e.g., a range of volatile organic compounds [VOCs] emitted from building furnishings), or c) result from physical mixing of emissions from multiple primary sources with agents created by chemical transformations of those emissions (e.g., precursors of smog [like nitrogen oxides, hydrocarbons, and sulfur oxides] reacting to form ozone and acid particles mixed with other oxidants and metals). The term complex is used in the context of this paper to refer to binary mixtures as well as to truly complex mixtures of three or more constituents.

The methodologic challenge faced in assessment of exposure to each of these types of mixtures is evident. The components of mixtures, which are relevant to the health outcomes of interest, may not be known; and, therefore, the measurement of all components of mixtures in the context of an epidemiologic investigation is not possible for most mixtures of concern. In any case, such detailed information might not be readily interpretable without an adequate biologic framework.

As an alternative to full characterization of mixtures, marker components (also referred to as tracers, proxies, or surrogates) have been used to represent exposures to the mixtures. Markers or indicators may be speciesential elements, chemical compounds, size-fractionated airborne particles, metabolites in biologic specimens, variables derived from questionnaire responses, or model estimates. Ideally, a marker of exposure to a complex mixture should be unique to the mixture’s source, readily detectable in air at low concentrations, present in air in a consistent ratio to other components, and measured easily and accurately at an affordable cost (1). Unfortunately, exposure measures of a single marker for a complex mixture may not reflect toxicity from synergistic interactions among the components fully.

Tobacco combustion illustrates a single-source complex mixture found in indoor environments. Environmental tobacco smoke (ETS) is comprised of hundreds of different compounds in the particle and vapor phases (2). Many toxic and carcinogenic agents have been identified in ETS, and ETS has been linked to a wide range of acute and chronic health effects and to loss of comfort (2). Although it is not possible to measure all components of ETS, several specific air contaminants and categories of contaminants (nicotine, carbon monoxide, pyridine, aldehydes, and respirable particles) have been identified as markers for ETS (1-4). These markers have proved to be useful in studies of health.

---

This manuscript was prepared as part of the Environmental Epidemiology Planning Project of the Health Effects Institute, September 1990—September 1992.

*Author to whom correspondence should be addressed.
effects, for validation of questionnaires, and the development of exposure models (5).

Questionnaires have also been used to assess exposure to ETS by characterizing smoking in the environments where subjects spend time. Typical questions are directed to the smoking habits, especially locale and intensity, of family members or coworkers (4,6,7). Biologic markers of ETS exposure, including carbon monoxide level in exhaled air, carboxyhemoglobin level, and concentrations of nicotine and its metabolite cotinine in body fluids, have also been used to assess exposure (2).

Volatile organic compounds are a complex mix of contaminants resulting from multiple sources that exemplify the second class of mixtures. Hundreds of VOCs can be found in indoor and outdoor air. The many sources of indoor VOCs include industrial processes, consumer products, and home and office furnishings. Volatile organic compounds are suspected to be the cause of a wide range of adverse health and comfort effects (8). A particular VOC may be singled out as relevant to a specific health effect, for example, benzene and leukemia. However, no single compound has been identified as the causative agent of irritant and neuropsychologic effects. For example, no single marker compound has been identified for investigation of the hypothesized association of building-related symptoms with VOCs. For experimental human exposures, one investigator (9) has designed a mixture of 22 VOCs typically found in offices, while others use the total mass of VOCs as an exposure indicator.

The third group of complex mixtures is illustrated by photochemical smog, which includes the primary pollutants sulfur dioxides, nitrogen oxides, and hydrocarbons, and diverse reactive species produced by atmospheric chemical reactions. Mixtures that concern health include photochemical oxidants and acidic gases and particles. Because identification and measurement of all the reaction by-products of this group are not possible, markers such as ozone, formaldehyde, and acid sulfates are used to assess exposure. These individual pollutants have also demonstrated adverse effects; for example, ozone is a criterion pollutant that causes transitory, and possibly long-term, effects at concentrations at or below the current standard of 0.12 ppm.

The challenge faced in assessing exposures in order to investigate the health effects of each of the three types of complex mixtures is evident. This article reviews the methods presently available for assessment and covers concepts of personal exposure, time-activity assessment, methods for measurement of contaminants, and the use of questionnaires and biomarkers. The article ends with a discussion of integrated approaches for exposure assessment and suggestions for further research.

Concepts of Exposure and Exposure Assessment

Concepts of exposure and exposure assessment evolved and matured during the 1970s and 1980s from studies involving large-scale measurements of the exposures of individuals and sample populations. The 1991 report of the Committee on Advances in Assessing Human Exposure to Airborne Pollutants of the National Research Council sets out these concepts and details approaches for using them in the context of epidemiologic studies (10). The committee defined exposure 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." Dose is defined as the amount of the pollutant absorbed or deposited in the exposed person over a particular period of time. These definitions must be considered in the context of the averaging time relevant to the biological response of concern. In an environmental epidemiology study, exposure assessment approaches should be based on an understanding of the biologically relevant time frame for the exposure-effect association under study. For example, exposures to radon in a study of lung cancer need to be assessed over periods of years rather than days or weeks. The time frame for assessing exposures to some single agents with well-characterized adverse effects may be evident; but for complex mixtures, however, it may be difficult to specify the biologically relevant time frame because the principal active components of the mix may be uncertain and the time course of the independent and combined effects unknown. The study of VOCs as a potential cause of sick-building syndrome exemplifies these problems. The mixture of VOCs indoors is diverse and variable over time, the health effects examined are varied, and exposures may take place in a number of different microenvironments over varying intervals.

The National Research Council committee provided a general framework for relating sources, media of exposure, exposure, dose, and health effects (Fig. 1). For air pollutants, a less complex microenvironmental model has been used to guide the development of exposure assessment approaches. This model is appropriate for pollutants for which air is the sole medium of exposure (e.g., carbon monoxide and ozone). A microenvironment is generally defined as a location where the concentration of a pollutant is considered to be spatially uniform during the time that individuals are exposed in that location. Integrated individual exposure from a medium or media to a pollutant can be estimated as the weighted average of the concentrations in the relevant microenvironments by using the time spent in the microenvironments as the weights (10–13).

![Figure 1. Contaminant sources and effects continuum (10).](image-url)
Table 1. Analytical method selection. \(^a\)

| 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 to 100% |  
| Cost              | Cost of sampling and analysis is not prohibitive; inexpensive, readily available components; few consumables; low maintenance |  
  
\(^{a}\)Data from the National Research Council (10)

Table 2. 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 |
|--------------------------|----------------|---------------------------|-----------------------------|----------------------|-----------------------|---------------------------|-----------------------|
| CO                       | D I            | D I                       | D I                         | D I                  | D I                   | D I                       | D I                   |
| NO\(_2\)                  | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| Vapor phase nicotine for ETS | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| Inhalable particles (<10 μm diameter) | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| Formaldehyde             | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| VOCs                     | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| Polar VOCs               | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| Pesticides               | NA             | √                         | √                           | √                    | √                     | √                         | √                     |
| Radon                    | √              | √                         | √                           | √                    | √                     | √                         | √                     |
| PAH                      | NA             | √                         | √                           | √                    | √                     | √                         | √                     |
| Biological aerosols      | NA             | √                         | √                           | √                    | √                     | √                         | √                     |
| House dust               | NA             | √                         | √                           | √                    | √                     | √                         | √                     |
| O\(_3\)                  | √              | √                         | √                           | √                    | √                     | √                         | √                     |

Abbreviations: D, direct readout; I, integrating collection of samples; NA, not applicable

\(^{a}\)Data from the U.S. Environmental Protection Agency (17)

Approaches to measuring personal exposures to air pollutants can be classified as direct or indirect (10). In the direct approaches for inhalation exposures in the microenvironments of interest, measurements of exposure are obtained by direct personal monitoring in the breathing zone or by the use of appropriate biological markers. Indirect approaches are based on the microenvironmental model. Measurements of a pollutant are made in the relevant microenvironments, and information is gathered on the human time and activity patterns and the weights for the concentrations in the exposure model. The measurements and the time and activity information are used to calculate integrated exposure. With this model, it is possible to apportion the contribution from various sources and locations.

Personal Monitoring

Of the approaches currently available for exposure assessment, personal monitors offer the most promise for minimizing uncertainty about the degree of contact with a contaminant (10). However, there are inherent difficulties involved in personal monitoring, including determination of the appropriate duration of monitoring, obtaining valid samples without altering the subject’s behavior or activities, and the development of small and reliable devices. The Committee on Advances in Assessing Human Exposure to Airborne Pollutants of the National Research Council has enumerated the factors to be considered in assessing monitoring devices (Table 1). Personal monitors appropriate for epidemiologic research should provide adequate instrumental specificity and a wide detection range for the biologically active or surrogate compounds of concern.

The use of a personal monitoring technique should be accompanied by simultaneous data collection on locations where time is spent and on activities in the locations (see below) (10,12,14–18). Data from a study that integrates assessment of sources and their locations with personal monitoring can be analyzed for the contribution of specific sources to exposures and can also provide a basis for developing exposure models (19,20).

In 1988, the U.S. Environmental Protection Agency (EPA) summarized the status of personal monitors (Table 2) (17). The status of the monitors varies widely among the pollutants. For some pollutants, the personal monitoring technology is available, but the devices still require improvement. The VOCs are particularly problematic, due in large part to the myriad of compounds that may be found indoors and outdoors. For some compounds, the time needed to collect an adequate personal sample may be too long to link exposure with an acute biologic response.

Of the personal monitors now available, several are relevant to the example mixtures...
considered by the working group. Passive badges have been developed for exposures to NO₂ generated by combustion and for nicotine in tobacco smoke (10). Nicotine samples have been collected for periods as short as one day (10,22). Techniques for personal monitoring of radon, ozone, and NO₂ are not as well developed (10). Personal VOC samplers that use Tenax or a series of sorbents for passive and/or active collection are available, but these accurately detect only a limited number of compounds (10). The current efforts to employ multiple sorbents in a sampler have increased versatility by enabling the sampler to collect more compounds.

A personal dosimeter recently developed for radon was used in a personal exposure study conducted in New Jersey (22). Most epidemiological studies of radon have used microenvironmental measurements; however, these measurements do not capture the exposures that occur in microenvironments other than the home (23). The personal radon dosimeter is an example of a long-term personal monitor that should decrease uncertainty in individual exposure estimates in environmental epidemiological studies of lung cancer.

Personal monitors for ozone exposure are being developed (17,24). However, these monitors provide integrated exposure estimates over periods of several hours or days, depending on the concentration of ozone, and most of them do not measure biologically relevant short-term exposures between 1 and 4 hr.

Techniques for measuring reactive acidic particles and gases using a system of annular denuders and filter packs have been developed (25). The system has been employed as an indoor and outdoor monitor especially for acid sulfate and nitrate species. Some effort also has been made to develop a prototype personal monitor that measures a limited number of ionic species. All monitors, however, measure only total particle acidity, as hydrogen ion (H+), and do not speculate H₂SO₄ from NH₄HSO₄, which may be of greater biologic relevance (26,27).

In contrast to the estimation of other example pollutant exposures, estimation of exposures to ozone and acidic sulfate particles may not require personal monitoring because they are regional pollutants, and outdoor monitors may be sufficient for estimating the personal exposures sustained by a population (28,29). However, dose estimation of these compounds for individuals also requires valid questionnaire information on the amount of time the individuals spent outdoors and their level of participation in athletic activities and other activities that increase pulmonary ventilation (10).

For the mixtures addressed in these papers, representative personal and microenvironmental monitors are shown in Table 3 (30). Although these monitors hold promise, their sensitivity and time resolution may not be compatible with current research needs. In addition, the fixed samplers are not always available in a form that can be used in all microenvironments. An exception is the recent particle size selective samplers, which are integrating devices designed for operation within residential settings, outdoors, or in workplace settings (10,26,31,32). Real-time, continuous NO₂ and O₃ monitors are still unavailable for convenient operation in residential settings. The fixed-site outdoor sampler typically used in a trailer or similar location is still the only accurate instrument available for monitoring NO₂ and O₃, and these instruments are not incorporated readily into studies of the indoor residential environment.

**Time–Activity Assessment**

Time–activity patterns determine the duration of exposure to complex mixtures in relevant microenvironments. Three general categories of microenvironments can be used to describe most exposures to complex mixtures: a) environments where exposures to complex mixtures result from multiple sources emitting a class of contaminants (e.g., VOCs from building materials and furnishings); b) environments where exposures to complex mixtures occur because the source emits contaminants with dissimilar properties (e.g., gas and kerosene combustion can produce inorganic reactive gases, organic and inorganic particulate matter, organic vapors, and nonreactive inorganic compounds); and c) environments where exposures to complex mixtures occur because dissimilar source types are present (e.g., soil gas containing radon and cigarette smoke producing ETS).

The collection of time–activity data may be essential for estimating exposures to complex mixtures in each of these three types of environments. People integrate exposures to single-compound and complex mixtures through a range of common activities. These activities place people in specific microenvironments and determine their proximity to sources. In addition, activities relevant to the estimation of exposure may be diverse among individuals and highly variable for each individual. Activities vary among individuals because of age, ethnicity and race, socioeconomic status, health status, weather, and other factors. The variation in types and levels of activity probably is a strong determinant of variation in exposures to complex mixtures.

The application of time–activity information to estimation of exposures in an epidemiologic study requires in-depth consideration of the biologically relevant exposure measures. For short-term responses, it may be necessary to assess time–activity with a degree of temporal resolution that is not appropriate for long-term responses. The relevant microenvironments should also be determined in the analyses. As approaches to data collection are developed, emphasis should be placed on accurately measuring time in the microenvironments where subjects are exposed to the mixture being studied and on describing activities that may lead to contact with one or more components of the mixture.

Diary, recall, and observational approaches have been used to assess time and activity patterns (10,18,20). In the diary approaches, subjects are asked to complete a log of their activities that typically captures sequential information on each activity, its location, and its duration. An alternative approach asks subjects to account for each time interval of a given period in regard to activities and locations. Subjects may also be asked to supply information on time and activity patterns by recall. Direct observation of subjects has received little application in studies of human exposure.

Techniques for applying time–activity data to studies of total human exposure and the data sets that are available have been reviewed by Ott (20) and Robinson (18). Specifically, time–activity data from both the time budget and national travel surveys have been used to describe time spent in pollutant-relevant microenvironments for selected groups in the population (33,34). As new time–activity data have become available, researchers have updated and validated exposure models (35,36). Higher resolution time–activity data should improve predictions in the absence of personal exposure data.

Data from a recent statewide study of time–activity patterns of Californians over 11 years of age are used in Figure 2 to illustrate the activities and percent of time spent in a few generalized locations (37). A finer resolution of these patterns is required to quantify health effects, identify populations at risk, and formulate effective management strategies. For example, Jenkins et al. (37) were interested in identifying the duration, frequency, and location of exposures to specific indoor sources. Table 4, reprinted from Jenkins et al. (37), describes the frequency and duration of adult activities associated with exposures to...
Table 3. Monitoring equipment for particulate matter for indoor air quality studies.\textsuperscript{a,b}

| Pollutant sampler | Manufacturing company | Sensitivity and integrating time | Approximate cost |
|-------------------|-----------------------|----------------------------------|------------------|
| Radon: track etch | Terradex Corporation 460 N. Winnet Lane Walnut Creek, CA 94598 (415) 938-2545 | 1 to 3 month exposure 1 to 4 pCi/L | $20 to $60 depending on sensitivity desired |
| Radon: charcoal canister detector | RTCA 12 West Main Street Elmsford, NY 10523 (914) 347-5010 | 4 days 0.1 pCi/L | $35/canister includes shipment and analysis costs |
| Organic vapors | Industrial Scientific Corporation 355 Steubenville Pike Oakdale, PA 15071 (412) 758-4353 | | |
| Organic vapors: hydrocarbon chemical reaction tubes | National Draeger Inc. P.O. Box 120 Pittsburgh, PA 15230 (412) 787-8383 | 100 to 3000 ppm for 4 to 8 hr | $3/tube, $900 for pump and accessories |
| Organic vapors: charcoal badges | 3M Corporation Technical Service Department 3M Center St. Paul, MN 55144 (612) 733-1110 | Depends on vapors and sampling times; minimum level, 10/mg | $10/badge; $50 to $300 for analysis by GC or GC/MS |
| Formaldehyde: diffusion tube | Air Quality Research, Inc. 901 Grayson Street Berkeley, CA 94710 (415) 644-2097 | 5 to 7 days | $48/kit, includes 2 monitors, analysis and report |
| Formaldehyde: pro-tek adsorption badge | E.I. DuPont Company Applied Technical Division P.O. Box 110 Kennett Square, PA 19348 1 (800) 344-4900 | 1.6 to 54 ppm/hr up to 7 days or 0.2 to 6.75 ppm/8 hr TWA | $20/badge; $25 to $80 for analysis |
| Formaldehyde: diffusion monitor | 3M Corporation Technical Service Dept. Building 260-3-2 3M Center St. Paul, MN 55144 (612) 733-1110 | 0.1 ppm for 8 hr | $37/monitor and analysis |
| NO\textsubscript{2}, personal and alarm | MDA Scientific 405 Barclay Boulevard Lincolnshire, IL 60069 1 (800) 323-2000 | 2 to 3 ppm; 1/3 TLV electrochemical cell based 15 min to 8 hr TWA | $800/detector; $100/output; $2075/dosimeter; $1045/read-out unit |
| NO\textsubscript{2}, diffusion tubes | Environmental Sciences and Physiology Harvard School of Public Health 655 Huntington Avenue Boston, MA 02115 (617) 432-1000 | 500 ppb/hr integrated | $10/tube, research only |
| NO\textsubscript{2}, diffusion badge | Environmental Sciences and Physiology Harvard School of Public Health 655 Huntington Avenue Boston, MA 02115 (617) 432-1000 | 50 ppb/hr | $15/badge, research only |
| CO, passive badge | Lab Safety Supply Co. P. O. Box 1368 Janesville, WI 53547 (608) 754-2345 | 50 ppm for 8 hr produces color change | $3/holder; $12.75/10 indicating papers |

\textsuperscript{a} Sensitive and pollutants sampler.

\textsuperscript{b} Integrating time and approximate cost.
### Table 3. Monitoring equipment for particulate matter for indoor air quality studies \(^{a,b}\) (continued).

| Pollutant sampler | Manufacturing company | Sensitivity and integrating time | Approximate cost |
|-------------------|------------------------|----------------------------------|------------------|
| CO: detector tube integrated | National Draeger Inc. P.O. Box 120 Pittsburgh, PA 15230 (412) 767-8383 | 2.5 ppm for 8 hr | $255 pump and accessories; $3/tube |
| CO: detector tube grab | Sensidyne Inc. 12345 Sparkey Road Suite E Largo, FL 33543 (813) 530-3602 | 5 ppm/min | $130 pump; $2/tube |
| Nicotine for ETS diffusion monitor | John B. Pierce Laboratory 290 Congress Ave. New Haven, CT 06519 (203) 562-9901 | 0.01 μg sampling rate of 24 mL/min | $55/sample |
| Integrated gravimetric; particles <3.5 μm diameter | Cyclone separators with filter. Several manufacturers of cyclones, filters, and pumps | 1.7 L/min | Pumps $200 to $700; filters $2; cyclones $20 to $100 |
| Integrated gravimetric; particles between 10 and 3 μm and less than 3 μm diameters | National Bureau of Standards Under EPA Contract U.S. EPA Research Triangle Park, NC 27711 (919) 541-2350 | 6 L/min | Unknown |
| Instantaneous (2/10 sec); TSP or RSP; 0.1 to 10 μm forward light-scattering | GCA-Mini-RAM (personal aerosol monitor) GCA Corporation 213 Burlington Road Bedford, MA 01730 (617) 275-6444 | | $2500 |
| Continuous; RSP submicron light-scattering multi-sensor monitor | Handheld Aerosol Monitor (HAM) PPM Inc. 11428 Kingston Pike Knoxville, TN 37922 (615) 966-8796 | >10 μg/m\(^3\) mass concentrations; 1.5 L/sec | $3000 to $10,000 |

\(^a\)Particles can be measured using a variety of techniques. Using cyclone or impactor separators, smaller size fractions can be collected on filters. Mass can also be measured using the optical properties of particles. Measuring particles usually requires equipment costing several hundred to a few thousand dollars. Equipment using filters requires that they be preweighted and postweighted in a temperature- and humidity-controlled room.

\(^b\)Data from Samet et al. (30)

### Table 4. Adult diary activity episodes with smokers present in locations with high frequencies or exposure times.

| Location of activities | Total number of activity episodes | Number of episodes with smoker present | Percent of episodes with smoker present | Average minutes per episode with smoker present |
|------------------------|----------------------------------|---------------------------------------|----------------------------------------|-----------------------------------------------|
| Own living room or family room | 4653 | 442 | 9 | 88 |
| Restaurants | 778 | 327 | 42 | 68 |
| Car | 5420 | 329 | 6 | 33 |
| Own kitchen | 4045 | 215 | 5 | 44 |
| Office building/bank | 841 | 188 | 22 | 153 |
| Industrial plants/factories | 340 | 125 | 37 | 173 |
| Shopping malls | 755 | 120 | 16 | 86 |
| Bars/nightclubs | 133 | 104 | 78 | 99 |
| Other public buildings | 245 | 62 | 25 | 135 |
| Playgrounds/parks | 248 | 51 | 21 | 120 |
| Hospitals/doctors' offices | 284 | 37 | 13 | 133 |
| Others' homes | 155 | 9 | 6 | 11 |
| Beauty parlors/barber shops | 49 | 9 | 18 | 138 |

\(^a\)Data from Jenkins et al. (37)
environmental tobacco smoke. Overall, the largest number of contacts with smokers occur inside the home environment, but the percentage of home activities associated with smokers is actually small. On the other hand, visits to restaurants, bars, and nightclubs are frequently associated with the presence of smokers. With a knowledge of the concentrations encountered in these microenvironments and of the potency of the complex mixture, the health risk to the population or to specific subgroups could be assessed.

Questionnaires

Questionnaires are the least expensive method for obtaining either retrospective or prospective information on the exposures of large populations, and they have been the method most commonly used for exposure assessment in epidemiologic studies. Questionnaires can be used to categorize exposures to sources and to describe the environmental characteristics that affect concentrations and activities, which, in turn, affect exposures and doses of inhaled pollutants. Questionnaires have been used extensively to provide a classification of potential exposures to sources and to obtain information on potential confounding and modifying factors. Questionnaires frequently ask simple questions such as "Do you live with a smoker?" or "Do you have a gas stove?" Others may be more specific, aimed at a particular source or pollutant.

In the indirect method of exposure assessment based on the microenvironmental model, the approach is to model the factors that govern the generation, dispersal, and removal of the air contaminant mix. Inputs to the models may include information collected by questionnaire, such as time-activity information, a source inventory, and patterns of source use. For example, in modeling NO₂ levels in a residential environment, questionnaires might ask for information on the sources (presence of a gas range and number of pilot lights, presence of a gas water heater, and presence of a gas dryer), source condition (age of the range), source use (number of burners used, length of time used, flame setting, and use of oven to heat the house), and the removal and dispersal of contaminants (use of outside-vented range hood and volume of home).

Questionnaires can play a major role in assessing exposure to complex mixtures. Exposures to ETS and NO₂, which are ubiquitous in indoor environments, can be assessed with sufficient accuracy in large-scale studies by using several different questionnaire approaches. For example, an initial screening instrument for sources might determine the smoking status of the household members and the presence of gas appliances in the home. The resulting source-based categories could be refined by questionnaires that assess the time spent in other environments, such as in day care, work, and outdoors, where exposures also may occur. The results could be further refined by questionnaire information related to the characteristics of the sources and the patterns of their use. For example, estimates of ETS exposure could incorporate the location of smoking in relation to the subject and the number of cigarettes smoked in the home. The questionnaire approach should be designed to assess exposures on a relevant time basis.

Questionnaire-based exposure measures can be made more accurate if supplemented by air monitoring—for example, passive monitoring for nicotine and NO₂ indoors and both passive and active monitoring for NO₂ outdoors—and by use of biomarkers such as urine cotinine. Leaderer et al. (38) have described nested approaches for applying the more costly and intensive techniques of air monitoring and measurement of biomarkers within an epidemiologic study population. The more accurate information obtained in the nested study can be used to estimate the error associated with the questionnaire method applied to the entire study population.

In the assessment of exposures to acidic aerosols and photochemical oxidants, another mixture considered by workshop participants, questionnaires would be of little value for estimating the concentrations in microenvironments. However, questionnaires would be useful for determining the time-activity patterns, the time spent outdoors, and the level of physical activity (29). Although acid aerosol and photochemical oxidants are primarily outdoor contaminants, there are indoor sources such as kerosene heaters, which may produce acid species, and malfunctioning air cleaners, which may emit ozone. The importance of these sources could be assessed by questionnaires. In addition, contaminants from outside can penetrate the building at a rate determined largely by the type of building and the air treatment equipment. Questionnaires can provide some information on these factors.

Questionnaires also have been used widely to provide retrospective assessment of exposures in the examination of the relationship between lung cancer and ETS and residential radon exposures in case-control studies. The questionnaires are used to assess ETS exposures in several microenvironments, to obtain residential histories, to estimate the time spent in each residence, and to determine other sources of exposure. This kind of questionnaire data is subject to both random and nonrandom sources of bias (39).

Exposures to VOCs, another example mixture, cannot be assessed readily by questionnaire. Volatile organic compounds are emitted from a large number of sources, and exposures occur in nearly all microenvironments. However, questionnaires can be used to assess the presence, absence, or use of potential sources such as cleaners, paints, new carpets, or dry cleaning, and indicate potential exposure. In studies of sick-building syndrome, such questionnaires form a major part of the exposure assessment component of the study (40).
Biomarkers of Exposure

Biomarkers show promise in epidemiologic studies as indicators of internal dose, biologically effective dose, early biological effects, altered function, and clinical disease (41,42). Within the context of assessment of exposure to air contaminants, biomarkers 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 human exposure to air contaminants (10). The markers are indicators of changes or events in human biological systems (10) and include indicators of both the internal dose and the biologically effective dose. A measure of internal dose indicates the amount of the contaminant absorbed into the body over a period of time. It is also a measure of the contaminant itself or its metabolites—for example, lead level in blood; cotinine or nicotine levels in urine, blood, or saliva; and concentrations of VOCs in exhaled air. The biologically effective dose refers to the amount of the contaminant or active metabolites delivered over a period of time to the target site. Some markers of biologically effective dose include protein adducts, DNA adducts, and sister chromatid exchange.

Recently, the use of biomarkers of exposure in epidemiologic studies has been discussed as offering methodology that may be useful in a) assessing the integrated exposure from all routes of entry (total exposure); b) reconstructing exposures; c) reducing error in respondent-provided exposure information resulting from biased recall, deliberate misinformation, inability to remember, and lack of knowledge; d) reducing exposure-associated misclassification and thereby enhancing study power; e) describing exposure–dose–response relationships, particularly when the target contaminant and its metabolic by-products can be identified and measured, for example, as with carbon monoxide or lead; f) identifying individuals or populations at risk through high exposure; and g) providing an independent measure of exposure for validating other measures (such as questionnaires or models).

The relationship between the biomarker and exposure may be complex. It might vary with other environmental factors such as sources and activities and with the uptake, distribution, metabolism, location, and mode of action of the compound or compounds of interest. Biomarkers of exposure are indicators of dose and do not directly represent actual environmental exposures. Although external measurements and pharmacokinetic or pharmacodynamic models are needed to estimate quantitative exposure from measured biomarkers, biomarkers do provide an indication that exposure has occurred.

To be useful, a biomarker of exposure for an air contaminant should be chemically specific; detectable in trace quantities; measurable in samples obtainable by noninvasive techniques; inexpensive to collect, handle, and assay; and quantitatively associated with exposures encountered in the community setting (10). The utility of a biological marker in an epidemiologic study also depends on its biological relevance, the level of understanding of its pharmacokinetics and pharmacodynamics, the temporal relevance of the marker to the exposure of interest, its background levels, and the feasibility of its application. Additional considerations for using biomarkers for complex mixtures include the uniqueness of the marker for the mixture; the relation of the marker to concentrations of other components; and the relation of the marker to the uptake, distribution, metabolism, location, and mode of action of the other compounds.

Assessment of exposure to environmental tobacco smoke demonstrates the advantages and disadvantages of using biomarkers as indicators of exposure to complex mixtures. Many biomarkers have been proposed as indicators for ETS (2,3), including thiocyanate, carboxyhemoglobin, nicotine, cotinine, N-nitrosopropylene, aromatic amines, and protein or DNA adducts. Although these biomarkers indicate that exposure has taken place, they may not indicate the contaminants in the mixture that cause the adverse effect under study. Available biomarkers for ETS also show considerable variability between individuals, and most of them capture only short-term exposures. These markers have not been evaluated adequately in controlled conditions for sensitivity, specificity, reproducibility, and relation to air exposures at realistic environmental levels. Some of the markers, such as carboxyhemoglobin, thiocyanate, and DNA adducts, are not specific to ETS exposure, while others, such as thiocyanate and carboxyhemoglobin, are not sufficiently sensitive for the concentrations of ETS typically encountered. Nicotine and its metabolites, principally cotinine, are used widely as specific biomarkers of exposure to ETS. However, we lack data that relate the levels of these biomarkers to air exposures in different environments, such as the work place and the home, or to long-term exposures. Cotinine, however, has been useful for validating questionnaires and identifying high- and low-exposure groups.

Exhaled levels of specific VOCs recently have been explored for use as biomarkers of exposure to complex mixtures of VOCs (10). Measurements of exhaled VOCs can indicate that exposure to specific compounds has taken place. However, the relationships between levels of individual VOCs and the complex mixtures present in different microenvironments are undoubtedly complex and variable and depend on uptake, metabolism, and excretion of the compounds.

At present, biomarkers cannot be used alone as indicators of exposure to complex air contaminant mixtures in epidemiologic studies because they do not provide sufficient information on the frequency, duration, and magnitude of exposure. However, they may provide insights into dose–response relations in the population under study; and they can reduce misclassification of exposure to specific compounds. Biomarkers only provide an indirect measure of exposure and should be used in combination with direct measures, such as air sampling, questionnaires, and models.

Integration of Exposure Methods

The selection of one or more methods of assessing exposure for an epidemiologic study should consider the specificity of the stated hypothesis, identification of the complex mix of contaminants or sources, and the existing state of knowledge. When designing an exposure assessment protocol, it is important to consider many issues like the available resources (such as finances, work force, air sampling equipment, and laboratory analytical support), the size of the study population, the willingness of the subjects to participate, the time frame for completing the study, the suitability of the exposure methods available (biological markers, air monitors), and the acceptable level of uncertainty in the assessment of exposure.

No single method of assessing exposure to complex mixtures is without drawbacks. Personal monitors can provide only a measure of individual-compounds; they cannot determine the microenvironments in which the exposures take place or provide information on the factors controlling the concentration. They also represent a respondent burden. Biomarkers of exposure, although provided an indication of dose, may not be related readily to exposures, particularly exposures to complex mixtures. Biomarkers may also be limited by inadequate sensitivity and specificity, and they require costly and invasive approaches for specimen collection. Air monitoring of different microenvironments tends to be compound-specific and needs to be combined with time-activity
information to generate estimates of personal exposures. Questionnaires, as we have discussed, are subject to error and can introduce misclassification of exposure status.

The goal of any exposure assessment effort made in support of epidemiologic studies of the effects of complex mixtures is to provide sufficiently accurate and precise measures of exposure and dose in a cost-effective manner. Strategies are needed to integrate and utilize the strengths of the various exposure assessment methods. One such approach, the nested exposure assessment strategy (1,38), utilizes questionnaires to acquire an easily measured indicator of exposure on the whole population under study, while simultaneously obtaining more detailed exposure information by using more sophisticated and expensive measurement techniques such as personal monitoring and biomarkers, on ever-decreasing numbers of subjects (Fig. 3). In this strategy, the questionnaires provide a measure of exposure with a higher level of uncertainty; the more intensive measures provide a lower level of uncertainty. The more intensively monitored groups could be randomly selected or purposefully sampled to address specific exposure issues. Measures of exposure in the intensively monitored subgroups could then be used to model the exposure to the full population and to provide an estimate of the magnitude and direction of the uncertainty associated with exposures estimated from the questionnaires. Additional exposure issues which could be addressed in different nested studies include the generation, transport, and fate of compounds; the development and validation of predictive models; the evaluation of monitoring techniques; the relation between average and peak concentrations; and the evaluation of, or relation between, air exposures and biomarkers of exposure.

The nested exposure assessment strategy could, for example, be utilized in assessing exposures to ETS and NO₂ in a study of the effect of these pollutants on respiratory infections in children. At the first level of exposure assessment, biweekly telephone questionnaires could be used for the whole study population to acquire respondent-estimated exposure to passive smoke and NO₂ in different environments. This would be accomplished by asking questions about the number of cigarettes smoked in the home, the location in the home where they are smoked, gas stove and kerosene heater use, and the time spent in the environments (outdoors, day care, school, and home). During one 2-wk period, a sample of respondents (second level of monitoring) could receive, in addition to the questionnaire, passive monitoring for vapor phase nicotine (an ETS marker) and NO₂ in one or several locations in the home. At this level, sampling might be conducted several times during the course of the study to as certain temporal variations. The third level of exposure assessment, conducted on a smaller sample, could include, in addition to the measures employed in the first and second levels, more detailed assessments such as personal passive monitors for nicotine and NO₂, passive monitoring in environments other than the home, and time and activity diaries. A fourth level of assessment, conducted on a still smaller sample, could employ yet a greater level of exposure assessment detail by acquiring urine samples for cotinine analysis, continuously monitoring NO₂ and respirable particles, collecting source-use diaries, counting or collecting cigarette butts, and measuring ventilation rates, all in addition to the measures obtained in levels one through three.

The example mixtures considered in these papers (VOCs, radon and ETS, ETS and NO₂, and photochemical smog and acidic aerosols) exemplify the types of mixtures that are of present public health concern as well as the difficulties of characterizing population exposures to complex mixtures. Exposure characterization studies have been conducted for individual components of complex mixtures, such as radon, ETS, NO₂, O₃ and a limited number of VOCs (3, 10, 23, 29, 30, 43, 44). The extent of the information is limited, and not all relevant microenvironments have been adequately assessed.

Population-based data are not available for any of the four mixtures. Further, few epidemiologic studies that involved comprehensive multiple-contaminant monitoring, particularly with personal monitoring, have been performed. The most comprehensive investigation to date is the Harvard Six Cities Study, and even in that study, selected participants wore monitors for only brief durations during the studies of short-term health responses. The exposure estimates in the Six Cities Study were based primarily on microenvironmental studies of the outdoor air (45).

Summary

During the last decade, substantial progress has been made in developing methodologies for assessing exposures to specific environmental contaminants in inhaled air. The newer techniques include personal monitoring, microenvironmental models, and biomarkers of exposure. We also have recognized that measurement error is inherent in most exposure measures used in epidemiologic research; approaches have been developed for minimizing this error and for evaluating its consequences.

While these advances have been incorporated effectively into studies of the health effects of single contaminants, the assessment of exposures to complex mixtures of air contaminants continues to present a formidable challenge. At present, no immediate and major advance in methodology that will offer resolution to the problems of estimating exposure to complex mixtures can be anticipated. We suggest that progress can be made through more effective application and continued evolution of already available methods, for example, a) development and validation of standardized questionnaires on

| Levels | Number | Exposure methods |
|--------|--------|------------------|
| 1      |        | Questionnaires   |
| 2      |        | Microenvironmental monitoring |
| 3      |        | Personal monitoring and time activity diaries |
| 4      |        | Biomarkers and continuous monitoring source use data |

Figure 3. Representation of "nested" exposure assessment strategy that utilizes questionnaires to acquire an easily acquired measure of exposure in the whole study population, while simultaneously obtaining more detailed exposure information by using more sophisticated techniques on ever-decreasing numbers of subjects.
sources, source use, building characteristics, and interactions of subjects with indoor environments; b) development and validation of prediction models for concentrations in the most frequently encountered microenvironments; and for personal exposure estimates; c) continued development and critical evaluation of personal monitors and biomarkers for complex mixtures; and d) development of efficient statistical designs for nested assessment of exposures using the more intensive and accurate techniques. The needed advances will be best achieved by interdisciplinary teams that include epidemiologists, statisticians, and persons with expertise in exposure assessment and monitoring.

REFERENCES

1. Leaderer BP. Assessing exposures to environmental tobacco smoke. Risk Analysis 10:19–26 (1990).
2. U.S. Department of Health and Human Services. The health consequences of involuntary smoking, a report of the Surgeon General. DHHS PHS Publication No. (CDC) 87-8398. Rockville, MD: U.S. Government Printing Office, 1986.
3. National Research Council, Committee on Passive Smoking. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press, 1986.
4. Leaderer BP, Hammond SK. Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. Environ Sci Technol 25:770–777 (1991).
5. Repace JL, Lowrey AH. Indoor air pollution, tobacco smoke, and public health. Science 208:464–472 (1980).
6. Spengler JD, Tretimra RD, Tosteson T, Mage DT, Soczek ML. Personal exposures to respirable particulates and implications for air pollution epidemiology. Environ Sci Technol 19:700–707 (1985).
7. Oldaker GB, Ogden MW, Mialto KC, Conner JM, Conrad FW, DeLuca PO. Results from surveys of environmental tobacco smoke in restaurants, Washington, DC: National Academy Press, 1986.
8. Wallace LA. Volatile organic compounds. In: Indoor air pollution, a health perspective (Samet JM, Spengler JD, eds). Baltimore, MD: Johns Hopkins University Press, 1991; 252–272.
9. Molhave L. Indoor air quality in relation to sensory irritation due to volatile organic compounds. ASHRAE Trans. 32: Paper 2954 (1986).
10. National Research Council, Committee on Advances in Assessing Human Exposure to Airborne Pollutants. Human exposure assessment for airborne pollutants: advances and opportunities. Washington, DC: National Academy Press, 1991.
11. Ott WR. Total human exposure. Environ Sci Technol 19:880–886 (1985).
12. Liow PJ. Assessing total human exposure to contaminants, a multidisciplinary approach. Environ Sci Technol 24:938–945 (1990).
13. Duan N. Stochastic microenvironmental models for air pollution exposure. J Expo Anal Environ Epidemiol 1:235–257 (1991).
14. Liow PJ. Exposure analysis and assessment for low risk cancer agents. Int J Epidemiol 19 (Suppl):938–945 (1990).
15. Wallace LR, Ott WR. Personal monitors: a state-of-the-art survey. J Air Pollut Control Assoc 32:601–610 (1982).
16. Spengler JD, Soczek MC. Evidence for improved ambient air quality and the need for personal exposure research. Environ Sci Technol 8:268–280A (1984).
17. U.S. EPA. Research needs in exposure assessment: a comprehensive 5-year assessment (1989–1993). Final draft. Planning document of the Total Human Exposure Research Council (THERC). Washington, DC: U.S. Environmental Protection Agency, 1988.
18. Robinson JP. Time-diary research and human exposure assessment: some methodological considerations. Atmos Environ 22:2085–2092 (1988).
19. Sexton K, Ryan PB. Assessment of human exposure to air pollution: methods, measurements, and models. In: Air pollution, the automobile, and public health (Watson AT, Bates RE, Kennedy D, eds). Washington, DC: National Academy Press, 1988; 207–238.
20. Ott W. Human activity patterns: a review of the literature for estimating time spent indoors, outdoors, and in transit. Proceedings of the Research Planning Conference on Human Activity Patterns (Stark TH, ed) (EPA/600/4-89/004). Las Vegas, NV: U.S. Environmental Protection Agency, 1989.
21. Hammond SK, Leaderer BP. A diffusion monitor to measure exposure to passive smoking. Environ Sci Technol 21:494–497 (1987).
22. Litt BR, Waldman JM, Harley NH, Chittarporn P. Results from a pilot study to compare residential radon concentrations with occupational exposures using personal monitoring. Health Phys 61:727–735 (1991).
23. Neri AV, Schwab MB, Nazaroff WW, Revzan KL. Distribution of airborne radon–222 concentrations in U.S. homes. Science 234:992–997 (1986).
24. Koutrakis P, Wolfson JM, Slater JL, Mulik JD, Kronmiller K, Williams DD. Measurement of toxic and related air pollutants, VIP-17. Raleigh, NC: 1990; 48.
25. Spengler JD, Ryan PB, Schwab M, Billig IH, Colome SD, Becker E. An overview of the Los Angeles personal monitoring study. In: Proceedings of the First International Symposium on Total Exposure Assessment Methodology: A New Horizon, Las Vegas, NV, 1989. Pittsburgh, PA: Air and Waste Management Association.
26. Lippmann M. Health effects of ozone. A critical review. J Air Pollut Control Assoc 39:672–695 (1989).
27. Koutrakis P, Fasano AM, Slater JL, Spengler JD, McCarthy JF, Leaderer BP. Design of a personal annular denuder sampler to measure atmospheric aerosols and gases. Atmos Environ 23:2767–2773 (1989).
28. Waldman JM, Liow PJ, Thurston GD, Lippmann M. Spatial and temporal patterns in sulfate aerosol acidity and neutralization within a metropolitan area. Atmos Environ 24:115–126 (1990).
29. Liow PJ, Dyba RV. Tropospheric ozone: the dynamics of human exposure. J Toxicol Environ Health 5:493–504 (1982).
30. Samet JM, Marbury MC, Spengler JD. Health effects and sources of indoor air pollution. Part II. Am Rev Respir Dis 137: 221–242 (1988).
31. Marple V, Rubow KL, Turner W, Spengler JD. Low flow rate and impactor for indoor air sampling design and calibration. J Air Pollut Control Assoc 37:1303 (1987).
32. Liow PJ, Wainman T, Turner W, Marple V. An intercomparison of the indoor air sampling impactor and the dichotomous sampler for a 10 cm cut size. J Air Pollut Control Assoc 38:668–670 (1988).
33. Ott W. Exposure estimates based on computer generated activity patterns. Paper 81-37.6, presented at the 74th annual meeting of the Air Pollution Control Association, Philadelphia, PA, 1981.
34. Johnson T, Paul R. The NAAQS Exposure Model (NEM) applied to carbon monoxide. EPA-450/5-83-004. Research Triangle Park, NC: U.S. Environmental Protection Agency, 1983.
35. Ott WR, Thomas J, Mage DT, Wallace LA. Validation of the simulation of human activity and pollution exposure (SHAPE) model using paired days from the Denver, Colorado, carbon monoxide field study. Atmos Environ 22:2101–2113 (1988).
36. Johnson T. Human activity patterns in Cincinnati, Ohio. Report no EPRI EN-6204, project 940-6. Electric Power Research Institute, 1989.
37. Jenkins P, Phillips TJ, Mulberg EJ, Hui, SP. Activity patterns of Californians: use of and proximity to indoor pollutant sources. Atmos Environ 26A: 2141–2148 (1992).
38. Leaderer BP, Zagraniak RT, Berwick M, Stolwijk JA. Assessment of exposure to indoor air contaminants from combustion sources: methodology and application. Am J Epidemiol 124:275–289 (1986).
39. Lubin JH, Samet JM, Weinberg C. Design issues in epidemiologic studies of indoor exposure to radon and risk of lung cancer. Health Phys 59:807–817 (1990).
40. Leaderer BP, Wilcox T, Fidler A, Selfridge J, Hurrell J, Kollander M, Clickner R, Fine L, Teichman K. Protocol for a comprehensive investigation of building-related complaints. In: Indoor Air, 90: building and system assessment, vol 4 (Walkinshaw D, ed). Ottawa, Canada: Canada Mortgage and Housing Corporation, 1990; 609–614.

41. National Research Council and Committee on Biological Markers. Biological markers in environmental health research. Environ Health Perspect 64:3–9 (1987).

42. Hulka BS, Wilcosky TC, Griffith J, eds. Biological markers in epidemiology. New York: Oxford University Press, 1990.

43. Samet JM, Marbury MC, Spengler JD. Health effects and sources of indoor air pollution. Part I. Am Rev Respir Dis 136:1486–1508 (1987).

44. Wallace LA. The total exposure assessment methodology (TEAM) study: summary and analysis, vol 1, EPA 600/6–87/002a. Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency, 1987.

45. Ware HH, Ferris BG, Dockery DW, Spengler JD, Stram DO, Speizer FE. Effects of ambient sulfur oxides and suspended particles on respiratory health of children. Am Rev Respir Dis 133:834–892 (1986).