Assessment of Health Effects in Epidemiologic Studies of Air Pollution

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As we increasingly recognize the complexity of the pollutants in indoor and outdoor microenvironments, a broad array of inhaled mixtures has assumed scientific, public health, and regulatory importance. Few adverse effects of environmental pollutants are specific, that is, uniquely associated with a single agent; the adverse effects that might be considered in an investigation of the consequences of exposure to an inhaled complex mixture are generally nonspecific. In the context of this paper, we will refer to binary mixtures as complex, though we realize that a more precise definition of complexity would restrict the term to mixtures of three or more constituents. Their causes potentially include not only pollutant exposures through the medium of inhaled air but other environmental agents, such as infectious organisms and radiation, and inherent characteristics of the exposed persons, such as atopy. It is unlikely that any new investigational techniques will soon become available that will provide more specific indicators of pollutant effect. Thus, investigative approaches should be developed with acknowledgment of the nonspecificity of the usual outcome measures.

Past investigations of outdoor and indoor air pollution incorporated the outcome measures listed in Table 1 (1-3). Descriptive studies of community morbidity and mortality used such routinely collected data as death counts or death rates, hospitalization or emergency room visit rates, and absenteeism rates. In some investigations, categories of respiratory diagnoses were selected as outcome measures. Community-based epidemiologic studies of both cross-sectional and longitudinal design typically included assessment of respiratory symptoms using standardized questionnaires and of lung function using spirometry or peak flow measurement. A few investigations added measurements of nonspecific airways responsiveness, using challenge with a pharmacologic agent or cold air.

The extensive experience gained with these approaches for outcome assessment clearly documents the lack of specificity of the measures used at both the community and individual levels. Cause-specific mortality rates, for example, vary with disease prevalence and severity, patterns of medical care usage, and death certificate coding. Respiratory symptoms have multiple determinants. For example, a mother’s report that a child has a chronic cough might reflect the presence of underlying airways hyperresponsiveness, an effect of parental smoking, persistent symptoms after a recent

### Table 1. Health outcome measures in studies of indoor air and other complex mixtures.

| Category            | Respiratory                        | Neuropsychological                  |
|---------------------|------------------------------------|-------------------------------------|
| Overall mortality   | Acute and chronic symptoms         | Reduced performance on neurobehavioral testing |
| Morbidity index     | Acute infections                   | Neuropsychological syndrome         |
|                     | Chronic respiratory diseases       | Neuropsychological disease          |
|                     | Degree of nonspecific airways responsiveness |                                |
|                     | Reduced level of lung function     |                                     |
|                     | Increased rate of lung function decline |                              |
|                     | Decreased rate of lung function growth |                               |
|                     | Exacerbation of a chronic respiratory disease |                            |
|                     | Hospitalization for a chronic respiratory disease |                      |
|                     | Lung cancer                        |                                     |
|                     | Death secondary to a chronic respiratory disease |                    |

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This manuscript was prepared as part of the Environmental Epidemiology Planning Project of the Health Effects Institute, September 1990 – September 1992.
lower respiratory tract infection, and bias because the mother has a cough. Cross-sectionally measured reduction of lung function might be produced by obesity, cigarette smoking, or past occupational exposures.

In this paper, we review the outcome measures used in epidemiologic studies of the health effects of single pollutants and complex mixtures. In the context of this paper, we will refer to binary mixtures as complex, though we realize that a more precise definition of complexity would restrict the term to mixtures of three or more constituents. The emerging research on use of biomarkers is discussed elsewhere in these proceedings.

Conventional Outcome Measures

Introduction

This section reviews the outcome measures that might be used in assessing the health effects of complex mixtures of current concern. For the principal outcome measures, we briefly consider pathophysiologic mechanisms, accuracy, and potential sources of bias.

Overall and Cause-Specific Mortality

From the 1930s through the 1950s, episodes of excess mortality at times of extremely high outdoor air pollution provided dramatic evidence that air pollution can cause excess deaths (1). While overall mortality rates increased during these episodes, the excess deaths tended to be placed into cause-of-death categories for cardiovascular and respiratory diseases. Although such dramatic air pollution episodes are now infrequent in many developed countries, research continues on the effects of outdoor pollutants on overall and cause-specific mortality.

In investigations of air pollution and mortality, routinely collected vital statistics data for specific geographic areas are used as the health outcome measures, while air pollution exposure of the areas' residents is estimated from outdoor monitoring sites assumed to be representative for the populations. Association between mortality rates and pollutant levels is generally assessed using regression methods. For example, Schwartz and Dockery (4) examined variation in daily mortality rates in Steubenville, Ohio, in relation to daily levels of total suspended particles and sulfur dioxide. After controlling for season and temperature, the level of particles was significantly associated with the daily mortality counts in a regression model.

All-cause mortality is not subject to error from assignment of cause of death. However, pathophysiologic considerations typically lead to research hypotheses focused on cause-specific mortality, such as ischemic heart disease or chronic obstructive lung disease. Exposure to pollutants might cause death in persons with underlying chronic obstructive lung disease by further incapacitating those with little functional reserve; for such patients, pollutant exposure, by diminishing the efficacy of host defenses, also might increase the incidence or severity of respiratory tract infections. Persons with ischemic heart disease are vulnerable to pollutants, such as carbon monoxide, that impair oxygen delivery to tissues (5).

Misclassification of the underlying cause of death by death certificate designation has been well documented (6); accuracy of cause-specific mortality data is influenced potentially by the extent of the population's contact with medical care, the diagnostic acumen of clinicians in the study areas, the accuracy of information on the death certificate, and the rate of error in coding the death certificate to a particular cause of death. Because of recent concern about increasing asthma mortality, the validity of death certificate designation of deaths as due to asthma has been examined in several countries (7). However, while the validity of death certificate data on respiratory cancer has been specifically evaluated (8), comprehensive assessments of the quality of death certificate data for other major chronic respiratory diseases and for acute respiratory infections have not been performed. Misclassification of the underlying cause of death in vital statistics data would be anticipated to occur randomly in relation to the level of pollutant exposure. Such random misclassification attenuates exposure-response relations and reduces the statistical power of an investigation to detect an effect of pollution.

All-cause and cause-specific mortality rates are also nonspecific outcome measures. Mortality rates vary with the background distribution of risk factors determining the incidence of disease and with the survival rate of those who have developed disease. Thus, assessments of the effects of air pollutants on mortality can be sharpened if these other factors can be considered in data analysis.

Indices of Morbidity

Epidemiologic studies of the health effects of air pollution have incorporated diverse indices of general morbidity, including absenteeism from school and work; days of restricted activity spent at home; and rates of utilization of outpatient medical facilities, of visits to emergency rooms, and of hospitalization (1,9). For example, in an investigation in Steubenville, Ohio, the relation between the numbers of visits made to the principal hospital's emergency room and daily air pollution levels was assessed (10). Like mortality rates, the general morbidity indices are nonspecific and subject to misclassification.

Respiratory Infections

Diverse microorganisms can cause respiratory tract infections, including mycoplasma, viruses, bacteria, and fungi (11). The spectrum of infecting organisms and of clinical manifestations varies from infants through the elderly (12). Research on air pollution and respiratory infection has focused largely on infants and younger children. Children, particularly infants, have been considered susceptible to inhaled pollutants because their lungs are maturing and rates of respiratory infection in this age group are the highest of any (12,13).

The occurrence of respiratory infections can be monitored using subject reports of symptoms or illnesses or by using inpatient and outpatient records of clinical facilities. The usual clinical respiratory illness syndromes include upper respiratory tract infections ("colds"), otitis media, and lower respiratory illnesses; the latter category includes group, tracheobronchitis, bronchitis, and pneumonia (11). Standardized and uniformly accepted clinical definitions have not been developed for these illnesses, and health care practitioners apparently develop their own operational criteria. In fact, a single unimpeachable gold standard for establishing the presence of a respiratory infection is unavailable; a clinical diagnosis and a positive culture for a pathogenic organism represent the most valid basis for documenting infection.

In some studies of children and of adults, illness histories have been obtained retrospectively by questionnaire. While such retrospective information can be collected readily, bias is likely, with subjects symptomatic or ill at the time of data collection more likely to report past illnesses (14). Prospective surveillance of illness avoids the potential problem of recall bias but requires a more elaborate system for ascertaining the occurrence of illness. Surveillance approaches using calendar diaries for recording of symptoms have been applied successfully in community-based studies on respiratory illnesses (15–17) but have been used in only a few studies of inhaled pollutants. For example, in a cohort study in progress in Albuquerque, New Mexico, on nitrogen
dioxide and respiratory infections, infants are enrolled shortly after birth and the occurrence of illness is ascertained by completion of a daily symptom diary and telephone contact every 2 weeks (18). To assess the validity of this system for illness ascertainment, a sample of ill children is evaluated by a nurse practitioner according to a standardized protocol.

The occurrence of illness also can be documented by using diagnoses made by clinicians at the time of outpatient visits or hospital discharge diagnoses. However, illness rates based on contact with health care providers have potential determinants other than incidence, including patterns of access to health care, the severity of the illnesses, and diagnostic practices of the clinicians. More severe illnesses are likely to prompt contact with a health care provider, and thus illness rates based on clinical diagnoses are lower than those obtained by community-based surveillance. Therefore, in the United States, community-based surveillance studies show that children have about two lower respiratory tract illnesses during the first year of life (12); by contrast, from 20 to 30% of children receive a physician's diagnosis as having a lower respiratory tract illness during this same age range (19,20). Nevertheless, studies of both indoor and outdoor air pollution have used indices of respiratory infection derived from clinical encounters (11,21).

However, confounding may be introduced into studies using such clinical indices, because both pollution exposure and patterns of health care utilization may be associated with demographic and socioeconomic factors that also determine illness rates (11).

Respiratory Symptoms

Standardized respiratory symptom questionnaires, initially developed during the 1950s, are widely used in epidemiologic research for assessing the occurrence of the cardinal respiratory symptoms: cough, sputum production, wheezing, and dyspnea (22). The presently used questionnaires have evolved from the questionnaire originally developed by the British Medical Research Council; like the first questionnaire, the presently available instruments emphasize chronic symptoms and are insensitive for detecting acute symptom responses. Limited data have been published on the validity and reliability of individual questions (22,23). In the United States, an American Thoracic Society committee initially adopted the Medical Research Council questionnaire for adults in 1969. In 1978, the American Thoracic Society's Epidemiology Standardization Project published a revised questionnaire for adults and a new questionnaire for children (24). Proper use of these questionnaires reduces the potential for interviewer bias and assures comparability with data from other populations collected with the same techniques.

For pollutants with quickly changing concentrations and mechanisms of action associated with acute symptom responses, short-term longitudinal studies, often called "panel studies," may be carried out to examine the relation between pollutant levels and symptom occurrence on the time scale of a day or less. Typically, symptom status is tracked by asking subjects to complete a diary that covers such items as the occurrence of cough, sputum production, wheezing, sore throat, hoarseness, and fever (25). In studies involving controlled laboratory exposures, asthmatics are more susceptible to a number of inhaled pollutants than nonasthmatics (26). The diary approach has been applied to investigate the health effects of pollutant exposure on asthmatics and also on patients with chronic obstructive pulmonary disease in the community setting (27,28). In studies of asthmatics, medication pattern and use of health care services may be tracked in addition to symptom status. Standardized instruments for diary studies have not been published.

Pulmonary Function

Toxicologic considerations suggest that complex mixtures of current concern might have either irreversible or reversible effects on lung function. Permanent loss of function could reflect the development of emphysema, airways fibrosis, and interstitial fibrosis. Acute, reversible loss of function could be secondary to airways inflammation, bronchoconstriction, or other mechanisms. In a cross-sectional study, an irreversible loss of function would be reflected as a lower level of function in comparison with an unexposed "normal" population. In a longitudinal study, irreversible loss of function during childhood would be manifest as a reduced rate of lung growth, whereas during adulthood, accelerated decline of function would be expected. Acute adverse effects of pollutant exposure on lung function can be detected by longitudinal monitoring of function with comparison of preexposure to postexposure measurements.

Spirometry, involving the timed collection of exhaled air during the forced vital capacity maneuver, has been the most widely used technique for measuring lung function in epidemiologic studies of air pollution. Spirometers are available for field use and are inexpensive, portable, and durable. Standardization of spirometry has long been advocated and recommendations are available from the American Thoracic Society (24,29) and a Working Party of the European Coal and Steel Community (30). These recommendations cover specifications for spirometers, testing protocols, and test interpretation. Data collected following these recommendations and using proper equipment have small within-subject variability (23,31). In a few studies, other types of measurements have been made, including the single breath nitrogen test (31). However, these tests, as well as other types of testing used in clinical pulmonary function laboratories, have greater variability than spirometric measures of lung function, and the equipment is more complex and expensive than a simple spirometer.

Spirometry provides measurements of the forced vital capacity (FVC), the total amount of air exhaled, as well as the volume of air exhaled in the first second (FVC1) or at other time points. A spirometer integrated with a microprocessor can measure flow rates at various lung volumes. These spirometric measures are sensitive to processes impairing ventilatory function of the lung, but injury cannot be inferred at specific anatomic loci because of particular patterns of abnormality of spirometric parameters (32). However, abnormalities of flow rates at lower lung volumes are associated with adverse effects on the small airways of the lung (31).

Although spirometry has proven effective for community-based studies, it cannot be used readily in large numbers of subjects to track function on a day-to-day basis. In many studies investigating the relation between short-term variation in lung function and pollution exposure, peak expiratory flow rate (PEFR) has been measured using portable and inexpensive instruments that can be used by subjects themselves. Peak expiratory flow rate measurement takes only a few minutes and can be performed at multiple times throughout the day; measurements can be made before and after episodes of exposure. Accurate measurement of PEFR requires calibration of the peak flow meters and standardized protocols for subject training and data collection (33,34).

Non-specific Airways Responsiveness

Non-specific airways responsiveness refers to the extent of bronchoconstriction evoked by a nonantigenic stimulus (35). The pharmacologic agents most widely applied to assess non-specific airways responsiveness are methacholine and histamine; other
alternatives, including hypoactive and hyperactive aerosols, exercise, and hyperventilation with cold air, also have been used. Asthmatics, by definition, have airways hyperresponsiveness. In populations, the distribution of nonspecific airways responsiveness appears to be unimodal, with skewing towards hyperresponsiveness (35). In controlled exposure studies of asthmatics and healthy nonasthmatic subjects, nonspecific airways responsiveness often has been one of the monitored outcome measures (36). In the community setting, assessment of nonspecific airways responsiveness might provide a sensitive indicator of the effect of exposure to a complex mixture. The protocols for measuring nonspecific airways responsiveness are time consuming, however, and the possibility of adverse consequences of testing necessitates the presence of a physician. Thus, nonspecific airways responsiveness has not been used yet in large-scale epidemiologic research on the health effects of air pollutants.

Neuropsychological Responses

Exposure to mixtures of volatile organic compounds in indoor air can be postulated to have neurobehavioral consequences. In fact, volatile organic compounds have been postulated to be etiologic factors in the nonspecific sick-building syndrome. A variety of tests of neurobehavioral outcomes are available (37), and such tests have been applied in epidemiologic investigations (38,39). However, standardized approaches for assessing neurobehavioral outcomes have not been developed (37). Molfave (40) recently summarized symptomatology and commonly used tests for behavioral effects caused by volatile organic compounds. The tests are designed to assess sensory, cognitive, affective, and motor disorders. Although most of the tests have been used in the neurobehavioral field for a number of years, their applicability to field studies of indoor air health effects has been demonstrated only recently and standardization in such studies has not been achieved.

"Objective measures" of health impacts of indoor exposures to volatile organic compounds should relate to the patterns of reaction that can be anticipated (41). Acutely perceived reactions include odor, irritation of the skin, and the sensation of reduced air quality or the need for more ventilation. Subacute reactions manifest the beginning of the development of an inflammatory reaction with dilation of peripheral vessels: stinging, itching, or pain in the skin, and changes in skin temperature. Finally, subacute or chronic effects relate to discomfort, and complaints of headache, drowsiness, and changes in eye and nose liquids, odor threshold, performance, and mood. These latter signs can be assessed objectively with a variety of diagnostic techniques. For example, eye dryness can be assessed by the time required to clear a fluorescein dye placed in the eye (42). Change in pulmonary function over the course of the day, a commonly used measure in assessing occupationally related respiratory diseases, also has been used to assess the more toxic irritations seen in indoor air exposures.

Specific Examples

Environmental Tobacco Smoke and Nitrogen Dioxide

Environmental tobacco smoke and nitrogen dioxide (NO$_2$) are highly prevalent indoor exposures; slightly less than half of U.S. homes have gas cooking ranges and ovens, the principal sources of NO$_2$ indoors, and about 40% of U.S. homes have at least one adult smoker (2). Environmental tobacco smoke itself is a complex mixture, representing the combination of sidestream smoke with exhaled mainstream smoke (21,43). Its components include irritants, inflammatory agents, and carcinogens. Exposure to environmental tobacco smoke has been associated with increased lower respiratory tract infections in young children, increased respiratory symptoms and reduced lung growth in children, and lung cancer in adults who have never smoked (21,43). Nitrogen dioxide, an oxidant gas, also might increase rates of respiratory infection through adverse effects on respiratory defense mechanisms and, by causing airways inflammation, produce respiratory symptoms and reduce lung function (44). Thus, exposure to the combination of environmental tobacco smoke and NO$_2$ can be hypothesized to increase rates of respiratory infection and respiratory symptoms and to reduce lung function. Additive effects might be postulated because the effects might be mediated through similar pathways for the two agents.

Respiratory infections are extremely common during childhood; active surveillance methods show that children have two or more episodes of lower respiratory tract infection during the first year of life and about twice as many upper respiratory tract infections (11). By contrast, only about 20% of children visit a physician for a lower respiratory tract infection during the first year of life, and hospitalization for such an illness is rare. Selection of an outcome measure for a study of environmental tobacco smoke and NO$_2$ needs to be made in light of the underlying hypothesis. If joint exposure is postulated to increase severity of infections, then physician visit or hospitalization should be selected. Alternatively, if joint exposure is postulated to increase incidence, then an active surveillance method for illness is appropriate. Recall of illnesses by a parent may not be adequate for describing incidence but may suffice for characterizing more severe illness occurrence.

To address the joint effect of exposure on respiratory symptoms and lung function in older children, conventional methods would include spirometry and completion of a standardized symptom and illness questionnaire by a parent. Symptoms and lung function level have multiple determinants, and the effects of the pollutant mixture cannot be assessed without controlling for these other factors, such as age, sex, and presence of asthma. The specificity of analysis might be improved by a priori identification of those symptoms and lung function measures of particular interest. Thus, for environmental tobacco smoke and NO$_2$, the symptom of chronic cough may be of greatest interest because of the temporal pattern of chronic and sustained exposure to the two agents; spirometric flows at low lung volumes might be selected for investigation because the dose of NO$_2$ may be greatest for the small airways, as suggested by the results of dosimetric analyses (45).

Environmental Tobacco Smoke and Radon

Environmental tobacco smoke is causally associated with lung cancer in never-smokers; radon exposure in underground mines causes lung cancer in both smokers and never-smokers, and active smoking and radon exposure interact in a synergistic manner (23,46). Thus, synergism between environmental tobacco smoke and radon exposure may be postulated. Environmental tobacco smoke potentially affects the dosimetry of radon progeny within the respiratory tract; tobacco smoking is a strong source of aerosol, and the presence of smoking may reduce the unattached fraction of radon progeny, thereby retarding removal through plateout and reducing the dose of alpha energy delivered to target cells (47). Points of interaction between the two agents that might affect lung cancer risk include altered exposure to radon progeny in the presence of environmental tobacco smoke, the effect on lung dosimetry of the inhaled progeny, and joint effects in the multistage process of carcinogenesis.
The outcome of concern, lung cancer, comprises a heterogeneous group of malignancies from the histologic perspective; four major types account for the majority of cases: squamous carcinoma (30%), adenocarcinoma (25%), small-cell carcinoma (20%), and large-cell carcinoma (15%) (48,49). In never-smokers, adenocarcinoma is the most common histologic type, but all types may occur. Radon-exposed underground miners have an increased frequency of small-cell, but this proportion declines as the interval since the start of exposure lengthens (46). Newer techniques of cellular and molecular biology have not provided more sensitive techniques for linking specific exposures to specific types of lung cancer yet.

A case–control study could be designed to address interaction between environmental tobacco smoke and radon. Interpretation might be clouded, however, by the present impossibility of assuring that some degree of disease misclassification is not present.

**Acid Aerosols and Ozone Outdoors**

Both acute and chronic effects of mixtures of acid aerosols and ozone can be anticipated from the known chemistry of these agents. Clinical chamber exposure studies suggest that physiologic changes suggestive of inflammation of the airway can occur after acute exposure to ozone (50). Animal studies of aerosols of H2SO4 suggest changes in clearance of particles, which increase as exposure increases (51). Most of the efforts to assess the combined exposure to ozone and H2SO4 have not shown synergistic effects; however, in some studies, a combined effect of the two agents is apparent (52).

To address these two agents in acute studies requires the use of panels of subjects exposed over time, with repeated studies of conventional outcomes, including symptoms and lung function, in conjunction with monitoring of exposure. In particular, potentially sensitive subgroups of subjects, as well as normal persons, need to be evaluated. Ideally, some measure of average minute ventilation during periods of exposure would be useful to assess delivered dose more quantitatively. For chronic exposure, prevalence of symptoms and level of pulmonary function, particularly in well-characterized groups of children, can be used as a measure of cumulative lifetime effects and compared among exposed and unexposed groups.

**Conclusions**

Epidemiologic studies of the health effects of air pollution have used an array of nonspecific outcome measures. The effects postulated to be associated with pollution exposure also are caused by other factors such as cigarette smoking, occupation, and subject characteristics. In interpreting effects attributed to pollutant exposure, careful control of confounding and assessment of joint effects is warranted by the nonspecificity of outcome measures. Moreover, the effects of pollution may vary with the background of other exposures.

Some of the outcome measures used in epidemiologic studies of air pollution, such as respiratory symptom questionnaires and spirometry, have been carefully standardized, and extensive data are available from pollutant-exposed and unexposed populations. Other outcome measures need similar standardization and modification to improve sensitivity and specificity for investigating the health effects of air pollution.

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