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Epidemiologic Approaches for Assessing Health Risks from Complex Mixtures in Indoor Air

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Indoor air may be contaminated by diverse gaseous and particulate pollutants that may adversely affect health. As a basis for controlling adverse health effects of indoor air pollution, the presence of a hazard needs to be confirmed, and the quantitative relationship between exposure and response needs to be described. Toxicological, clinical, and epidemiological studies represent complementary approaches for obtaining the requisite evidence. The assessment of the effects of complex mixtures poses a difficult challenge for epidemiologists. Understanding the effects of exposure may require accurate assessment of concentrations and personal exposures to multiple agents and analytical approaches that can identify independent effects of single agents and the synergistic or antagonistic effects that may occur in mixtures. The array of epidemiological study designs for this task includes descriptive studies, cohort studies, and case-control studies, each having potential advantages and disadvantages for studying complex mixtures. This presentation considers issues related to exposure assessment and study design for addressing the effects of complex mixtures in indoor air.

Introduction

Indoor air in residential and nonresidential structures is typically contaminated by a complex mixture of gaseous and particulate pollutants. The sources are diverse and include building occupants and their activities, combustion, building materials and furnishings, biological agents, and entry of contaminated outdoor air and soil gas (*1,2*). The air of a home might contain nitrogen dioxide (NO_2) from unvented emissions from a gas stove or space heater, respirable particles from cigarette smoking, cooking, occupant activities, and outdoor air, formaldehyde from furnishings and plywood, tetrachloroethylene from recently dry-cleaned clothes, and allergens from a family cat. The potential health effects of indoor air pollution are equally diverse, spanning from short-term annoyance and discomfort to permanent disability, cancer, and even death.

Although the complexity of indoor air pollution is well recognized, most epidemiological studies of indoor air pollution and health have focused on the effects of single pollutants, e.g., NO_2, environmental tobacco smoke, and formaldehyde, or a single outcome measure in relation to several exposures, e.g., respiratory symptoms in children, NO_2, and environmental tobacco smoke. The restricted focus undoubtedly reflects, in part, the difficulty of accurately estimating personal exposures to multiple pollutants and multiple health outcomes. Furthermore, control strategies have tended to emphasize single pollutants and sources. However, even studies directed at a single pollutant inherently examine the effect of that pollutant on a background of exposure to other pollutants.

Nevertheless, a full understanding of the health effects of indoor air pollution will require information on effects of pollutant mixtures. This paper considers the epidemiological approaches applicable to studying the effects of multicomponent mixtures in indoor air. Relevant study designs and potential limitations are reviewed, as are approaches for exposure assessment and analytical approaches for assessing the effects of multiple exposures.

Concepts of Interaction

Studies of complex mixtures need to be designed with consideration of the potential patterns of combined effects of the component pollutants. The biological effect of one pollutant may be modified by the presence of other pollutants; this phenomenon, termed "effect modification" by epidemiologists, is more generally refered to as "interaction." Interactions may be synergistic (the effect of an exposure is increased by the presence of another factor) or antagonistic (the effect of an exposure is reduced by the presence of another factor). Interaction is assessed with statistical modeling approaches; for the purpose of public health protection, synergism is considered to be present if the combined effect of the multiple factors exceeds that expected on the basis of additivity of the independent effects (*3*). The results of statistical modeling or interaction should be interpreted with consideration of the measurement scale (additive or multiplicative) inherent in the selected model and of the limited statistical power of such analyses.

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Table 1. Examples of potential patterns of combined effects of indoor air pollutants in a multicomponent mixture.

Pollutants	Health outcome	Potential effect
Radon progeny, ETS[a]	Lung cancer	Increased exposure altered dosimetry
ETS, NO_2	Respiratory infection	Additive effects for incidence and severity
ETS, NO_2	Reduced lung function	Additive effects
Volatile organic compounds	Sick-building syndrome	Synergism
Allergens, ETS	Exacerbation of asthma	Additive effects or synergism

[a]ETS, environmental tobacco smoke.

Interactions may reflect diverse biological phenomena (Table 1). For example, the effect of radon in causing lung cancer in nonsmokers might be modified by the presence of respirable particles generated by tobacco smoking. The increased concentrations of respirable particles tend to increase concentrations of radon progeny in inhaled air; the particles also alter the deposition of radon progeny in the airways of the lung. Thus, in this example, passive smoking not only affects exposure to radon progeny, but alters exposure–dose relations in the respiratory tract. For respiratory infection in children, the effects of exposures to NO_2 and environmental tobacco smoking might be additive; both agents potentially affect the host defense mechanisms against inhaled pathogens. Molhave (*4*), in discussing the sick-building syndrome, emphasizes the potential role of interactions among indoor air pollutants and other factors determining comfort and symptom responses of building occupants. A wide range of physical and biological interactions can be postulated. For example, increased temperature in a space may directly affect occupants by reducing thermal comfort and indirectly affect occupants by increasing emissions of formaldehyde and other volatile organic compounds.

Few generalizations can be offered concerning the likely directions or magnitudes of interaction among the components of complex, multicomponent mixtures. In a multistep disease process, agents acting at the same step tend to have a combined effect that is additive, whereas agents acting positively at different steps tend to have a combined effect that is multiplicative (*5*). However, the potential range of mechanisms of interaction among indoor air pollutants and other factors determining responses to indoor environments is broad, extending from physical interactions influencing exposure to interactions at the most proximal sites of disease causation.

Exposure Assessment

Evidence for interaction may be gained from appropriately designed experiments, including animal exposures or other types of toxicological investigation, controlled human exposures to mixtures, and epidemiological studies. To provide insight into patterns of interactions among pollutants, an epidemiological investigation needs to incorporate accurate estimates of exposure to the relevant pollutants and other factors.

Personal exposure refers to the air pollutant exposures experienced by an individual as the individual moves through various environmental settings. Thus, the link between the presence of a chemical contaminant in the environment and its contact with humans is complex, and in large part determined by patterns of human behavior. The portion of exposure that is adsorbed, ingested, or inhaled into the body is termed the "dose." The definition of dose can be refined further by introducing the concept of "biologically effective dose," referring to the quantity of material actually reaching the site of toxic action.

In many studies of air pollution and health, personal exposures to ambient pollutants were inferred from air pollution monitors sited in central locations and exposures to indoor pollutants assigned on the basis of the presence of sources, such as gas stoves or cigarette smoking. However, both of these approaches may introduce substantial misclassification of actual personal exposures. New personal monitoring instrumentation, which is small and unobtrusive, has recently been developed (*6*). The measurements from this new generation of monitors have clearly demonstrated the inaccuracy of basing estimates of personal exposures in indoor and transit environments on measurements made at outdoor sites.

Techniques for assessing personal exposure to air pollution can be divided into two major classes. The first approach measures the concentrations of the pollutant using monitors worn on the person or located in specific settings frequented by the person (i.e., home, workplace, or car), and the second estimates exposure from measurements of biological markers such as the pollutant concentrations in blood and breath samples. For example, in an investigation in Albuquerque, New Mexico (*7*), personal exposures of infants to NO_2 were directly measured by placing a sampler on the child. Personal exposures were also estimated by monitoring NO_2 concentrations in the rooms of the homes and then calculating an average exposure by weighing the concentrations with the time spent in each room. Biological markers of exposure are now available for many pollutants including tobacco smoke, carbon monoxide, some allergens, and various volatile organic compounds.

In studying the effects of exposure to a multicomponent mixture, the sampling strategy should provide estimates of personal exposure to the component pollutants considered relevant to the health outcome. The monitoring task is potentially large and expensive; strategies that incorporate more intensive monitoring for a sample of the study population have been recommended (*8*).

Epidemiological Study Designs

The health effects of multicomponent mixtures can be investigated using conventional epidemiological study designs: the cross-sectional study, the cohort study, and the case-control study. Each study design has potential advantages and disadvantages, depending on the exposures and health outcomes of concern.

In addition to selecting a study design, an investigator needs to specify the approach to studying the effects of a mixture. The alternative strategies are diverse. The range of exposures can be restricted to minimize the possible interactions. For example, we are conducting a longitudinal study of respiratory infections in infants and NO_2 exposure; households with any adult smokers are excluded. This strategy has the advantage of simplifying assessment of the independent effect of an exposure but does not provide information on combined exposures that may be experienced by broad segments of the population. For some mixtures, it may be possible to identify a surrogate for the overall

degree of pollution; for example, the concentration of total volatile organic compounds might serve as an exposure measure in studying the sick-building syndrome. If emphasis is to be placed on characterizing interactions, then balancing the distribution of the study population among the various exposure groups improves efficiency.

Cross-Sectional Studies

In a cross-sectional study, often termed a "survey," observations concerning health status and exposure are made at a single point in time. The cross-sectional approach is most appropriate for exposures having acute rather than chronic effects and for exposures that can be presumed to have remained stable over time. It is not appropriate for studying the effects of rapidly changing mixtures nor for studying diseases that occur only after a long period between onset of exposure and incidence, e.g., cancer.

This design has the advantages of feasibility and generally manageable costs and of permitting intensive monitoring of a number of pollutants at the time of study. For example, the cross-sectional approach has been widely used to investigate indoor air pollution and respiratory symptoms and lung function in children (*1*); outbreaks of building-related illness have also been investigated with this approach (*9*). Disadvantages include the potential for bias introduced by the tendency of persons adversely affected by exposure to be underrepresented in the study population and the limitations of cross-sectional data for describing longitudinal relationships between exposure and disease.

Cohort Studies

In cohort studies, subjects are selected on the basis of exposure status and followed over time for the development of disease. Cohort studies can be conducted prospectively or retrospectively. In a prospective cohort study, subjects are enrolled and then observed into the future, whereas in a retrospective cohort study, historical information is used to describe exposures and the occurrence of disease following entry into the cohort. The cohort design is particularly advantageous for assessing the effects of rare exposures.

For studies directed at complex multicomponent mixtures, the prospective cohort approach facilitates careful exposure assessment through the opportunity to prospectively plan and implement an optimal monitoring program. Similarly, longitudinal observations of health outcomes, such as respiratory symptoms or lunq function level can be made. Thus, a prospective cohort study of brief duration represents an appropriate design for exposures and health outcomes that vary on a short-term basis. For example, Lebowitz and colleagues (*10*) obtained daily measurements of peak expiratory flow rate (PEFR), a measure of lung function, in subjects with asthma and assessed the relationship between daily variation of PEFR and exposures to indoor and outdoor air pollutants.

The cohort design has the disadvantages of potentially high costs and of difficulty in maintaining followup of the study population. For health outcomes that occur infrequently, large numbers of subjects may be needed to attain adequate statistical power, particularly if the investigation is designed to assess interaction.

Case–Control Studies

The case–control design involves the identification of persons ("cases") with the health outcome of interest and a control series of persons without the disease who potentially would be selected as cases if they were to develop the disease. The exposure histories of the cases and controls are ascertained and compared to estimate the risk of disease associated with exposure. Case–control studies are particularly appropriate for investigating infrequent diseases or diseases that may follow a lengthy period of exposure. Hybrid designs that "nest" case–control studies within cohort studies offer an efficient approach for characterizing exposure–disease relationships (*11*).

The case–control design has been widely applied to investigating lung cancer and exposure to environmental tobacco smoke and to radon. Cohort designs are generally not practicable for lung cancer and these indoor pollutants. The case–control design has been used infrequently, however, for studying other indoor air pollutants and the effects of complex mixtures. The potential disadvantages include information bias, which may tend to increase or decrease associations, and selection bias, which occurs if methods for case and control selection affect the true relation between exposure and disease.

Assessment of Interaction

Analytical Approaches

The assessment of interaction has been a subject of controversy in the epidemiological literature (*3,5*); the debate has been both semantic and conceptual. Nevertheless, some accord has been reached with regard to analytical methods and the interpretation of analyses directed at interaction.

Interaction is assessed by selecting a measurement scale on which to compare the individual and the combined effects of the multiple risk factors; available methods exclusively address the case of two interacting risk factors. Generally, the relative risk is the measure of effect used to assess interaction. On the additive scale, the combined effect is compared to the sum of the individual relative risks less unity. If the difference is zero, then interaction is not present. Positive differences represent synergism, whereas negative differences represent antagonism. On the multiplicative scale, the combined effect of the agents is compared to the product of the two relative risk estimates. Analysis methods have also been developed that flexibly fit the data on a continuum from less than additive to more than multiplicative (*11,12*).

The presence and degree of interaction depends on the measurement scale selected. A positive and hence synergistic interaction on an additive scale may be negative and hence antagonistic on a multiplicative scale. Because of this scale dependence in assessing interaction, the additive scale has been selected as most appropriate for determining interaction of public health significance (*13*).

In practice, interaction is generally assessed by adding product terms of the potentially interacting variables to a model that already includes individual variables for the factors. The coefficient for the product term describes the direction and magnitude of the interaction; the statistical significance of the coefficient can be tested on the null hypothesis of no interaction. Other measures of synergy have been proposed (*13*).

With regard to addressing complex, multicomponent mixtures in indoor air, applying these methods requires estimates of exposure or dose for the pollutants of concern. Methods for modeling beyond two independent factors have not been well developed, and additional limitations (see below) must be considered.

Barriers in Assessing Interaction

Misclassification and Confounding. Estimates of personal exposures to air pollutants, both in outdoor and indoor air, are subject to some degree of misclassification, potentially both random and nonrandom in relation to health status (*14,15*). Random misclassification tends to bias measures of association toward the null value (*14*). Both empiric and theoretical analyses indicate the potential for a strong bias toward the null (*16,17*). In assessing interaction, random misclassification would also tend to bias toward the null, whereas the consequences of nonrandom misclassification may be to increase or decrease effects.

Confounding refers to bias introduced by association between the risk factor of interest and another risk factor for the health outcome under investigation. The presence of uncontrolled confounding could potentially have complex consequences in assessing interaction, depending both on the direction of confounding and the pattern of interaction, synergistic or antagonistic.

Statistical Power. The statistical power of the usual methods for assessing interaction is limited (*18*). Power may be further compromised by misclassification of the estimates of the interacting exposures. Thus, failure to find statistically significant interaction does not exclude the presence of a significant degree of interaction, either from the biological or the public health perspectives. Confidence intervals for the parameters estimating interaction describe the range of interaction compatible with the data.

Model Specification. In assessing interaction, statistical models are used to represent potentially complex biological phenomena that may be incompletely characterized. Modeling approaches are determined largely by the availability of statistical software; most models inherently assume either an additive or a multiplicative scale for describing interaction. To the extent possible, models should be developed to be reflective of the underlying biological process, rather than chosen on the basis of convenience in modeling and the availability of software.

Flexible modeling strategies have been developed that do not require the direct specification of the model as additive or multiplicative (*10,11*). These approaches, however, also suffer from limited power in determining the pattern of interaction and should not replace *a priori* model specification on a biological basis.

Conclusions

A full understanding of the health effects of indoor air pollution will require the development of information on effects of pollutant mixtures. The usual epidemiological study designs can be used for this purpose, but the choice of design strategy merits particular consideration if interactions among pollutants are the focus of investigation. To provide insight into patterns of interactions among pollutants, an epidemiological investigation needs to incorporate accurate estimates of personal exposure to the relevant pollutants and other factors. Analytical methods are available for assessing interaction among pollutants, but in applying these methods, the limits posed by adequacy of statistical power and the biological relevance of the assumed statistical model need to be addressed.

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