Introduction and Recommendations: Working Group on Indoor Air and Other Complex Mixtures

Jonathan M. Samet* and Frank E. Speizer

*Pulmonary and Critical Care Division, Department of Medicine; and the New Mexico Tumor Registry, Cancer Center, University of New Mexico, Albuquerque, NM 87131; The Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115

Air in indoor and outdoor environments typically contains many gaseous and particulate pollutants that may affect adversely any individual at sufficiently high concentrations and more sensitive individuals at lower concentrations. The public health relevance of addressing the effects of mixtures is becoming increasingly evident as we improve the concept of total personal exposure to pollution and obtain more data from personal monitoring. The papers within this volume represent the deliberations of a working group assembled with the goal of improving the epidemiologic approach to investigating the health effects of indoor air pollution and other complex mixtures. The group, composed of epidemiologists, human and animal toxicologists, and experts on biomarkers, comprehensively reviewed the methodologic issues involved in investigating complex mixtures. Members noted the deficiencies of current epidemiologic methodology for studying complex mixtures and called for broad-based advances in study design, exposure assessment, outcome assessment, and data analysis and interpretation. Understanding the health effects of complex mixtures will require multidisciplinary research using not only epidemiologic studies incorporating the new methods of exposure assessment but animal and clinical toxicology. — Environ Health Perspect 101(Suppl 4):143–147 (1993).

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Introduction

The gaseous and particulate pollutants that are typically present in the air of indoor and outdoor environments may have an adverse effect upon any individual at sufficiently high concentrations and upon more sensitive individuals at lower concentrations. The complexity and components of the pollutant mixture may vary as human activities influence the sources, as meteorology alters the distribution and dilution of the pollutants, and as components of the mixture undergo chemical transformation (1). For example, sources of indoor air pollution are diverse and include building occupants themselves and their activities, combustion, building materials and furnishings, biological agents, and entry of contaminated outdoor air and soil gas (2,3). The air of a home might contain nitrogen dioxide (NO₂) from the unvented emissions of a gas stove or space heater, respirable particles from cigarette smoking, cooking, and occupant activities, and outdoor air, formaldehyde from furnishings and plywood, tetrachloroethylene from recently dry-cleaned clothes, and allergens from a family cat. The contaminant levels would vary with occupant activities, such as cigarette smoking and cooking. For example, concentrations of environmental tobacco smoke components would be greatest during the smoking of cigarettes and the characteristics of the environmental tobacco smoke would change as the mixture aged (4,5). 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.

Similarly, pollutants in outdoor air are present in complex mixtures, although strategies for regulation and source control have tended to focus on single pollutants; adverse effects of concern span from short-term toxicity to chronic diseases reflecting long-term exposure. These mixtures of primary and secondary pollutants vary from urban to rural settings and across microenvironments.

Although the complex nature of air pollution is recognized, most epidemiologic studies of air pollution and health have focused on the effects of single pollutants or, at most, two specific pollutants such as total suspended particles and sulfur dioxide or on a single outcome measure in relation to several exposures such as respiratory symptoms in children, NO₂, and environmental tobacco smoke (6,7). Some pollutant mixtures, such as environmental tobacco smoke and photochemical pollution, have been investigated as though the mixture were a single agent, using a component of the mixture or indicators of source strength as indices of exposure in epidemiologic studies. The restricted focus undoubtedly reflects, in part, the difficulty of accurately estimating personal exposures to multiple pollutants and assessing multiple health outcomes. However, even studies directed at a single pollutant inherently examine the effect of that pollutant on a background of exposure to a complex mixture of other pollutants.

It should be noted that in the context of this collection of papers, the term complex mixture is used in several ways. Sometimes it is used to refer to binary mixtures of single compounds, sometimes to binary combinations of a complex mixture and a single compound such as environmental tobacco smoke and NO₂, and sometimes to mixtures of more than two compounds such as mixed volatile organic compounds. A more precise definition might well restrict the use of the term complex mixtures to mixtures of more than two constituents. Its broader use in this document is allowed on the grounds that in the context of epidemiologic research, a number of the problems encountered when trying to measure the effects of two factors are only compounded when the researcher is confronted with higher order mixtures (see Working Group, Recommendations, below).
The public health relevance of addressing the effects of mixtures is becoming increasingly evident as we refine the concept of total personal exposure to pollution and obtain more data from personal monitoring (1). Recognition of the complexity of pollutant mixtures in indoor and outdoor air has led to concern that synergism among the components of mixtures may produce adverse effects, even though effects would not be anticipated from the concentrations of individual components. For example, mixtures of volatile organic compounds, with individual compounds present below permissible exposure limits specific to the compounds, are a suspect cause of some outbreaks of sick-building syndrome (5). For protection of public health, identification of the specific components of mixtures that result in toxicity should lead to more specific and effective control strategies.

Difficult questions concerning the effects of mixtures, increasingly raised as we recognize the complexity of indoor and outdoor air pollution, pose new challenges to environmental epidemiology. The state of the art is largely reflective of study designs that have been tailored to studying single pollutants, although the data may be secondarily used to address other pollutants, sometimes to test hypotheses, but often only to control for a potentially confounding or modifying exposure. For example, the Harvard Six Cities Study was designed to assess the effects of sulfur oxide and particulate pollution; the original design assumed that a gradient of exposure to the same type of pollutants could be established across the six cities (8). Subsequently, the data were used to test hypotheses concerning indoor air pollution and additional outdoor pollutants (9,10). In a prospective cohort study in New Mexico of indoor nitrogen dioxide exposure and respiratory infections in infants, restriction has been used to remove the potential confounding or modifying effects of environmental tobacco smoke (11). By design, all subjects reside in homes having no adults who smoke.

In some investigations, data have been collected on indicators of exposures to multiple pollutants. Most of these studies have been cross-sectional in design and incorporated surrogates for indoor and outdoor exposures to complex mixtures. In those investigations that have attempted to address the effects of multiple pollutants, the most widely used approach for assessing joint effects has been multivariate regression analysis, incorporating variables for the main effects of the pollutants and often product terms for the interactive effects of the pollutants. Thus, for two exposures, an additive regression model would take the form:

\[ Y = f(a + b_1x_1 + b_2x_2 + b_3x_1x_2), \]

where \( x_1 \) and \( x_2 \) represent the two pollutants, \( b_1 \) and \( b_2 \) describe their independent effects, and the coefficient \( b_3 \) describes their joint effect.

Such regression methods now are used routinely for assessing the joint effects of multiple pollutants. Software for these methods is available and applied readily. However, regression alone does not offer a solution to the problem of understanding complex mixtures. Measures of exposure are used generally with the assumption that the surrogate measures of particles or specific gases are similarly applicable in different environments. Statistical models inherently simplify complex biological phenomena, and the relations assumed among exposures included in a model may represent inappropriately the underlying disease mechanism. Often understanding of causal pathways is insufficient for assuring that the model correctly represents biological mechanisms, and statistical considerations alone may direct model development.

Improvement in the state of the art for studying complex mixtures will require broad-based advances in study design, exposure assessment, outcome assessment, and data analysis and interpretation. Epidemiologic studies of indoor and outdoor air pollution have been almost exclusively observational in design. Experimental approaches might be designed to control variation in exposure to a complex mixture; hybrid designs combining observational approaches with controlled exposures o individuals may be evolving rapidly (12), but little consideration has been given yet to strategies that can be employed in epidemiologic studies of complex mixtures. Most outcome measures in studies of complex mixtures are nonspecific; newer approaches of assessing intermediate markers of outcome may augment sensitivity and possibly improve specificity. Epidemiologists use the term interaction in referring to interdependence of effect of multiple exposures (12,13). Approaches need to be designed for strengthening the links between toxicologic research and epidemiologic research to provide a common and biologically based framework for addressing interaction. The limitations of epidemiologic methods for addressing interaction also need further investigation, with emphasis on the consequences of the measurement error that inevitably affects studies of pollution.

This group was assembled with the goal of improving the epidemiologic approach to investigating the health effects of indoor air pollution and other complex mixtures. Achieving this goal will require multidisciplinary research using not only epidemiologic studies incorporating the new methods of exposure assessment but animal and clinical toxicology. Working group participants thus included an animal toxicologist (JL Mauderly), a human toxicologist (WF McDonnell), experts on exposure assessment (BP Leaderer, PJ Liow, and JD Spengler), epidemiologists involved in air pollution research (DW Dockery, JM Samet, CM Shy, and PE Speizer), an expert on biomarkers (TC Wilcosky), and two epidemiologists with expertise in epidemiologic methods (S Greenland and NS Weiss). Similarly, broad expertise was provided by members of the Health Effects Institute Research Committee (C Harris, L Gordis, and M Urell). Additional observers included representatives of the sponsoring organizations (IH Billick, R Calderon, and RS Dyer). Working group participants were charged with considering the state of the art in their assigned areas, identifying barriers to research on complex mixtures, and proposing new research to reduce these barriers. Each member reviewed the status of his or her assigned area in a draft document that was circulated within the group. Subsequent discussion led to revision of these drafts, and the deliberations of the working group produced the overall recommendations of the participants.

The papers authored by the participants accompany this overview; they provide reviews and perspectives on various facets of the epidemiologic investigation of complex mixtures in inhaled air. Some of the authors provide useful research recommendations extending beyond those formally made by the whole group.

General epidemiologic concepts relevant to investigating complex mixtures are considered by Weiss (14). Weiss overviews circumstances under which observational studies are most informative and discusses threats to their validity, including selection bias and confounding. Investigation of the health effects of complex mixtures implies a research focus on the combined effects of the mixture's components. Greenland (15), in the Methodologic Issues document, reviews the general conceptual advances made in the epidemiologic literature in regard to distinguishing interaction among agents from the statistical, biological, and epidemiological perspectives. He illustrates
the problems of interaction assessment and points to evolving approaches for addressing these problems.

Two papers focus more specifically on research designs relevant to complex mixtures in inhaled air. Dockery (16) reviews the strengths and limitations of the conventional epidemiologic designs (cross-sectional surveys, cohort studies, and case–control studies) for investigating complex mixtures; he acknowledges that such research often is challenging because the agents of interest are ubiquitous and the anticipated levels of effect may be small. He suggests that no particular study design is optimal and calls for rigorous planning at the design stage. Outcomes other than adverse respiratory effects also may be associated with inhaled complex mixtures. Shy (17) addresses the investigation of neurotoxic, reproductive, and carcinogenic effects. He considers the data resources, such as registries, available for addressing these health outcomes and overviews research designs that might be used in investigating them.

In investigating the health effects of any environmental agent, exposure and outcome need to be accurately assessed if unbiased and informative results are to be obtained. Samet and Speizer (18) consider the approaches used to assess respiratory health effects; although standardized methods have been developed for measuring some of these health outcomes, nonspecificity limits interpretation of pollutant-outcome associations. Biological markers have been advanced as an approach for improving the sensitivity and specificity of outcome assessment. Wilcosky (19) reviews the biologic framework for applying biomarkers and specific markers that might be used for inhaled pollutants. As for the conventional outcome measures considered by Samet and Speizer (18), Wilcosky (19) points to lack of specificity as limiting current biomarkers of outcome.

Leaderer et al. (20) set out the concepts and methods of exposure assessment in relation to complex mixtures. They discuss the difficulties of measuring multiple contaminants for individual subjects in epidemiologic studies, in spite of the advances that have been made in personal monitoring techniques. Feasible approaches to assessing exposures to complex mixtures include selecting marker pollutants, employing passive personal samplers if available, collecting information by questionnaire on exposure to sources and time-activity patterns, and using nested designs that involve more intensive data collection for selected subjects.

In clinical studies, volunteer subjects are exposed to pollutants in the controlled circumstances of the laboratory. McDonnell (21) examines the potential uses of the clinical study approach for investigating complex mixtures. The clinical study design affords the opportunity of evaluating the effects of pollutants alone and in the form of a mixture. Animal studies also provide this same opportunity. Maunderly (22) comprehensively reviews toxicologic studies of complex mixtures. Surprisingly few studies have been directed at complex mixtures; barriers include the costs of such studies and the large numbers of experimental animals needed.

Several themes extend throughout these individual contributions. The authors emphasize the difficulties of approaching complex mixtures and the need for multidisciplinary investigative teams. None identified anticipated new techniques in methodology for exposure or outcome assessment that would rapidly advance our capabilities for investigating complex mixtures.

**Working Group Recommendations**

**Introduction**

The recommendations that follow are based on intensive discussions among the working group. Members were asked to consider investigative approaches to studying health effects of four complex mixtures of concern. The examples were intended to illustrate the range of challenges faced in testing hypotheses concerning the effects of complex mixtures. Subsequently, general recommendations were developed for new research methodology that would facilitate studies of complex mixtures.

**General Considerations**

For the purpose of the these proceedings, complex mixtures were considered to contain at least two pollutants potentially associated with the health effect of interest. While a mixture of only two pollutants might not be labeled as complex in other contexts, the methodologic issues raised in studying the joint effects of two pollutants merit designation from the epidemiologist's perspective. Working group participants also acknowledged that some pollutants that might be treated as a single agent in an epidemiologic study are complex mixtures themselves, such as environmental tobacco smoke and diesel exhaust.

Working group members noted that many of the methodologic issues faced in conducting studies of complex mixtures in inhaled air were equally challenging in studying single pollutants and, in fact, were inherent throughout environmental epidemiology. The group suggested that concepts and methodology already available needed to be applied more generally in studying indoor air and other complex mixtures. Laxity in applying these concepts and methods potentially extends from the initial step of hypothesis formulation to the final step of data interpretation. In regard to complex mixtures, hypotheses need to be specified with a level of clarity that is often lacking. The effect measure of interest should be determined, and the anticipated pattern of joint effects should be described, both in terms of direction (synergism or antagonism) on the measurement scale selected and in terms of quantitative magnitude. Such specification of the hypothesis of interest is needed to guide study design and sample size estimation. If this level of specification is not met, the resulting vague hypotheses concerning interaction, synergism, or antagonism cannot be tested rigorously.

The conceptual framework for considering joint effects of two or more agents has been the subject of numerous publications in the epidemiologic literature. A consensus has been achieved for using departure from the additive scale as indicating interaction of public health significance (12, 13). The pitfalls associated with using models that implicitly make assumptions concerning the underlying form of biologic interaction also have been well described. Working group members supported the development of biologically based analytic strategies, while recognizing that the needed understanding of pathogenetic mechanisms was lacking for many pollutants. The recommendation of the participants for interdisciplinary approaches to complex mixtures was prompted, in part, by the need for experimental data to support biologically driven data analysis. Errors in estimating exposures and in assessing outcomes also limit epidemiologic studies of complex mixtures. The consequences of measurement error and strategies for adjusting effect measures for error have been considered extensively in recent publications. Techniques for staged sampling of exposures, moving from less intensive and costly to more valid and more costly, have been described (1). This emerging literature also needs specific extension to inhaled complex mixtures.

**Specific Examples**

To illustrate problems encountered in investigating complex mixtures, the working group considered approaches for four
scenarios of exposure to complex mixtures of current concern: the combined effect of exposure to environmental tobacco smoke and nitrogen dioxide on respiratory infection in infants, the combined effect of indoor radon and environmental tobacco smoke on lung cancer in never-smokers, the combined effect of ozone and acid aerosols on respiratory morbidity, and the consequences of exposure to multiple volatile organic compounds indoors.

The first example addressed by the group was the combined effect of nitrogen dioxide and environmental tobacco smoke (Table 1). Environmental tobacco smoke has been associated with increased lower respiratory infections during the first two years of life; nitrogen dioxide exposure is a suspect cause of respiratory infection as well, although the evidence presently is less consistent. Both agents may act by reducing the efficacy of host defenses against infectious organisms. Thus, because the two agents may share the same step in a causal pathway, the additive scale was considered biologically appropriate for assessing the combined effect.

The case-control design was eliminated because all children have multiple episodes of illness and selection of controls would therefore be problematic. The proposed cohort design incorporates staged determination with sampling for both outcome and exposure. The resulting data would make possible the estimation of the degree of error and permit correction for error in the data analysis. The proposed analytic strategy would test for departure from additivity and then employ modeling to describe the pattern of joint effect across the range of the two exposures.

The second example was the combined effect of radon and environmental tobacco smoke. Radon, an occupational carcinogen, is found in the air of all homes, reaching concentrations as high in some homes as that found in underground mines. Exposure to environmental tobacco smoke also is a cause of lung cancer in never-smokers. Investigation of the combined effects of the two exposures might be motivated by the large numbers of persons exposed to both agents in their homes. Biologic rationale for investigating the joint effect can be found in the altered dosimetry of radon progeny in the presence of environmental tobacco smoke and the potential actions of the two agents at different points in a multistage carcinogenic process.

A case-control study was considered the only feasible approach. Three distinct design objectives were identified that might guide study design: testing the hypothesis that the combined effect is the same as observed in underground miners who smoked, comparing the additive with the multiplicative models, and obtaining sufficient data to describe the combined effect with specified precision. Exposure assessment would be accomplished by placing radon detectors in living areas in the present residence and, where possible, in previous residences, and using a questionnaire to classify exposure to environmental tobacco smoke. The cases would include persons with histologically diagnosed lung cancer; to potentially improve specificity, histologic type of lung cancer would be determined.

The analysis potentially would be limited by measurement error and missing data for radon exposure and misclassification of environmental tobacco smoke exposure. Misclassification also would likely affect the diagnosis of lung cancer. In this example, sampling strategies that apply more in-depth measurement approaches for samples would not be possible. Thus, the analysis would explore the sensitivity of the findings to varying degrees of error.

In the third example, a substantial proportion of the population is exposed to both acid aerosols and photochemical oxidants. Historical data link secondary ambient pollutants (sulfates and acid aerosols, and photochemical oxidants) with health effects. The air pollution disasters earlier in the century, such as Donora in 1948 and London in 1952, showed that acid aerosols were associated with excess mortality. For photochemical pollution, the evidence from controlled human exposure and studies of lung function during outdoor activities in the so-called camp studies shows that oxidant pollution can have short-term adverse effects on lung function (23). Recently developed monitoring techniques for acid have shown that acid aerosols and oxidant pollution, as indexed by level of ozone, commonly occur together and that levels may be especially high during the summer. Thus, an assessment of the combined effects of these two mixtures is needed for public health protection.

Because these pollutants generally undergo long-range transport, the monitoring strategy for assessing exposure could be based regionally and study designs might be based on comparing health status across regions rather than attempting to establish exposure gradients within regions. For example, morbidity has been compared across regions using hospital and health practitioner contacts as outcome measures. Other outcomes to be considered in an epidemiologic investigation include emergency room visits for respiratory diagnoses or status of patients with pulmonary disease, as assessed by symptoms or lung function. For a study of acute effects, daily concentrations of ozone and acids in the study communities might be used.

The investigation of chronic effects requires the estimation of cumulative exposure; such exposure estimates may be problematic because of lack of historical data and uncertainty with regard to the biologically appropriate exposure window. Outcome measures in a study of chronic effects might be chronic symptoms and cross-sectional differences in lung function levels. In adults, and to a lesser extent in children, confounding and modifying effects of other exposures would require consideration (e.g., cigarette smoking).

Finally, the need to study the effects of mixtures of volatile organic compounds is signaled by the occurrence of sick-building syndrome in the occupants of many buildings. The presence of many volatile organic compounds with irritant and neurophysiologic effects has led to the hypothesis that exposure to mixtures of volatile organic compounds may cause at least some outbreaks of sick-building syndrome. Barriers to planning

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**Table 1. Design features of a cohort study of the combined effect of environmental tobacco smoke (ETS) and nitrogen dioxide (NO₂) on respiratory infection in infants.**

| Study hypothesis | The incidence rate of respiratory infection in the jointly exposed subjects exceeds the value expected on the basis of additivity. |
|------------------|--------------------------------------------------------------------------------------------------|
| Outcome assessment | Prospective assessment of all subjects by periodic telephone follow-up. More detailed clinical evaluation for a sample of ill children. |
| Exposure assessment | Description of exposure sources for all children. More detailed assessment, possibly including monitoring of the homes for NO₂ and respirable particles, personal monitoring of the subjects for nicotine and NO₂, and use of biomarkers of ETS exposure. |
| Data analysis | Initial calculation of incidence rates and direct testing of departure from additivity. Subsequent modeling to describe the two-dimensional response surface of incidence rate versus measures of ETS and NO₂. Further modeling to take account of error in assessing outcome and exposure. |
a study include the lack of standard methods for measuring both exposure and outcome. The components of the mixture potentially responsible are unknown, and the outcome measures of interest are both nonspecific and not readily validated.

Any study would need a multidisciplinary team equipped to measure exposure and to assess outcomes. Cross-sectional, cohort, and case–control designs might be used. Comparisons of affected and nonaffected individuals might incorporate biomarkers of exposure and of response; for example, nasal lavage might be used to assess irritation. Observational studies should be designed to take advantage of the natural experiments that occur when buildings are altered. In fact, intervention designs could be implemented feasibly and ethically. Thus, concentrations of volatile organic compounds could be reduced by increasing the rate of exchange of indoor with outdoor air.

Hybrid designs that combine observational approaches with controlled human exposures would permit further characterization of affected and nonaffected subjects in an epidemiologic investigation. Blinded challenges to suspect volatile organic compounds could be performed to validate questionnaire reports of symptoms and to assess the effects of individual components of the mixture.

General Recommendations

Based on the presentations of individual participants and discussions involving the entire group, the following recommendations were made: a) The investigation of the health effects of complex mixtures needs multidisciplinary approaches involving epidemiology, exposure assessment, and toxicology. Mechanisms for promoting regular and sustained interaction among researchers in epidemiology, exposure assessment, and toxicology need to be developed. b) Methods should be developed to link controlled human and animal exposure studies to complex mixtures. c) Methods should be developed to link controlled human exposure studies and epidemiologic studies. d) Statistical methods should be developed to combine human and animal toxicologic data with epidemiologic data to obtain overall estimates of risk. e) Methods should be developed to use activity pattern data to quantify cumulative exposures to complex mixtures. f) Many already available statistical and epidemiologic techniques relevant for studying complex mixtures have not been utilized appropriately. Demonstrations of these techniques in relation to complex mixtures are needed. The development of user-friendly software would facilitate their application. g) Approaches for estimating measurement error for both exposures and outcomes should be developed further. h) Meta-analysis may provide a more powerful assessment of complex mixtures than can be achieved by the findings of single studies. Data should be published in a form that will facilitate the conduct of meta-analysis.

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